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2021 ASCO ANNUAL MEETING PROCEEDINGS

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57th
Annual Meeting of the American Society of Clinical Oncology

June 4-8, 2021

2021 Annual Meeting Proceedings

(a supplement to *Journal of Clinical Oncology*)

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2021 ASCO ANNUAL MEETING PROCEEDINGS ABSTRACTS

Letter From the Editor

The *2021 ASCO Annual Meeting Proceedings* (a supplement to *Journal of Clinical Oncology*) is an enduring record of the more than 2,400 abstracts selected by the ASCO Scientific Program Committee for presentation as part of the ASCO Annual Meeting. Publication-only abstracts are included in the online supplement to the May 20 issue of *Journal of Clinical Oncology* at JCO.org. Abstracts can be also accessed online through the ASCO.org. Online abstracts include the full list of abstract authors and their disclosure information.

All abstracts carry *Journal of Clinical Oncology* citations, for example:

J Clin Oncol 39:18s, 2021 (suppl; abstr 1)

Should you have any questions or comments about this publication, we encourage you to provide feedback by contacting us at abstracts@asco.org.

Michael A. Carducci, MD, FACP, FASCO
Editor, *ASCO Annual Meeting Proceedings*

ASCO Abstracts Policy

Public Release of Abstracts

The abstracts published in the *2021 ASCO Annual Meeting Proceedings*, including those abstracts published but not presented at the Meeting, were publicly released by ASCO at 5:00 PM (EDT) on Wednesday, May 19, 2021. These abstracts are publicly available online through meetinglibrary.asco.org. Late-Breaking Abstracts, which include all Plenary Abstracts, will be publicly released at 5:00 p.m. (EDT) on Thursday, June 3, 2021.

In the unlikely event that ASCO publicly releases an abstract in advance of the scheduled time, the release will be publicly announced on am.asco.org.

Conflict of Interest Disclosure

As the CE provider for the Meeting, ASCO is committed to balance, objectivity, and scientific rigor in the management of financial interactions with for-profit health care companies that could create real or perceived conflicts of interest. Participants in the Meeting have disclosed their financial relationships in accordance with ASCO's Policy for Relationships with Companies; review the policy at asco.org/rwc.

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ABSTRACTS
American Society of Clinical Oncology
57th Annual Meeting
June 4-8, 2021

SPECIAL AWARD LECTURE ABSTRACTS

B.J. Kennedy Award and Lecture for Scientific Excellence in Geriatric Oncology

Treatment of advanced non-small cell lung cancer (NSCLC) in older patients: From best supportive care (BSC) to chemotherapy, targeted therapies, and immunotherapy.

Cesare Gridelli, MD, "S.G. Moscati" Hospital, Avellino, Italy

More than 50% of people with lung cancer are diagnosed over the age of 65 and about 40% over the age of 70. The majority of older patients tolerate chemotherapy poorly because of comorbidity and organ failure. At the end of the 1990s, considering the toxicity of cisplatin (CDDP)-based chemotherapy, best supportive care was considered the standard of care for advanced NSCLC in the elderly population. In a phase III trial (ELVIS-Elderly Lung Cancer Vinorelbine Italian Study), we showed that vinorelbine compared to BSC improved survival and quality of life in patients with advanced NSCLC age 70 or older. Then we ran a phase III trial (MILES-Multicenter Italian Lung Cancer in the Elderly Study) and demonstrated that gemcitabine and vinorelbine combination did not improve any outcome as compared to single-agent vinorelbine or gemcitabine. A French trial showed superiority of carboplatin plus paclitaxel chemotherapy, at doses usually used in younger patients, as compared to single-agent chemotherapy but with increased toxicity. Feasibility of CDDP-based polychemotherapy remained an open issue and was addressed by retrospective analyses of randomized trials without age limits, suggesting that advanced age alone should not preclude it to fit older patients. In a phase II randomized trial (MILES 02), we showed that CDDP-based regimens with reduced doses were feasible in older people. In the MILES 03-04, trial we demonstrated that CDDP plus gemcitabine or CDDP plus pemetrexed did not improve survival as compared to single-agent gemcitabine or pemetrexed but increased progression-free survival and response rate with higher toxicity. For patients with oncogene-addicted disease (EGFR or B-RAF mutations and ALK or ROS-1 rearrangements) the targeted therapies showed, in subset analyses of phase III randomized trials in general populations or dedicated phase II studies, similar tolerability and efficacy in older patients as compared to their younger counterparts. The same is for immunotherapy and for the chemotherapy plus immunotherapy combinations with no specific phase III trials in older patients.

Gianni Bonadonna Breast Cancer Award and Lecture

A Bronx tale: Pursuing progress, precision, and equity in cancer care.

Joseph A. Sparano, MD, FASCO, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY

Gianni Bonadonna ushered in the era of progress in cancer care through his pioneering work testing combination chemotherapy in rigorously conducted prospective clinical trials, both novel concepts at the time. His work provided a foundation for reducing mortality from breast cancer, Hodgkin lymphoma, and other cancers. For breast cancer, progress in reducing mortality has come with a price—broader use of adjuvant chemotherapy in those with early-stage disease who might have been adequately treated and perhaps cured without it. Moreover, declining cancer mortality rates have not been shared by all populations, even in circumstances where they may be equal access to care. This lecture will focus on three distinct challenges facing the field: 1) How can we continue to make progress? 2) How can biomarkers be used to more precisely guide the use of effective therapies? 3) How can we best address the inequities in outcomes?

LBA1 **Plenary Session**

OlympiA: A phase III, multicenter, randomized, placebo-controlled trial of adjuvant olaparib after (neo)adjuvant chemotherapy in patients with germline *BRCA1/2* mutations and high-risk HER2-negative early breast cancer. *First Author: Andrew Tutt, Breast Cancer Now, Toby Robins Research Centre, The Institute of Cancer Research, and The Breast Cancer Now Unit, Guy's Hospital Cancer Centre, King's College London, London, United Kingdom*

The full, final text of this abstract will be available at abstracts.asco.org at 5:00 PM ET on Thursday, June 3, 2021.

LBA2 **Plenary Session**

JUPITER-02: Randomized, double-blind, phase III study of toripalimab or placebo plus gemcitabine and cisplatin as first-line treatment for recurrent or metastatic nasopharyngeal carcinoma (NPC). *First Author: Rui-hua Xu, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

The full, final text of this abstract will be available at abstracts.asco.org at 5:00 PM ET on Thursday, June 3, 2021.

LBA3 **Plenary Session**

Adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The randomized phase III OUTBACK Trial (ANZGOG 0902, RTOG 1174, NRG 0274). *First Author: Linda R. Mileshkin, Department of Medical Oncology, Peter MacCallum Cancer Centre, Melbourne, Australia*

The full, final text of this abstract will be available at abstracts.asco.org at 5:00 PM ET on Thursday, June 3, 2021.

LBA4 **Plenary Session**

Phase III study of lutetium-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer (VISION). *First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY*

The full, final text of this abstract will be available at abstracts.asco.org at 5:00 PM ET on Thursday, June 3, 2021.

LBA5 **Plenary Session**

Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for patients with renal cell carcinoma: Randomized, double-blind, phase III KEYNOTE-564 study. *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, Boston, MA*

The full, final text of this abstract will be available at abstracts.asco.org at 5:00 PM ET on Thursday, June 3, 2021.

100 **Clinical Science Symposium**

Accrual of Black participants to cancer clinical trials following a five-year prospective initiative of community outreach and engagement. *First Author: Carmen E. Guerra, Abramson Cancer Center and Perelman School of Medicine, Philadelphia, PA*

Background: Accrual of Black participants to cancer clinical trials remains a major challenge across the country. Here, we report the outcomes of a five-year initiative of community outreach and engagement to improve enrollment of adult Black participants to clinical trials at the Abramson Cancer Center (ACC) at the University of Pennsylvania. **Methods**: Primary metrics were the percentage of Black patients among all cancer cases in our catchment area, the percentage of adult Black patients cared for at the ACC, and the percentage of adult Black participants enrolled on the three types of NCI-defined clinical trials. **Results**: In 2014, at baseline, Black residents comprised 19% of the population and 16.5% of cancer cases in our catchment area surrounding Philadelphia, but only 11.1% of ACC patients were Black. The percentages of Black participants accrued onto treatment, non-therapeutic interventional, and non-interventional trials were 12.2%, 8.3%, and 13.0%, respectively. We then established a center-wide program with community guidance to address these gaps. Key elements of the program included: 1) culturally tailored marketing strategies for cancer clinical trials; 2) plans for each protocol to facilitate Black participant enrollment; 3) new partnerships with faith-based organizations serving Black communities to conduct educational events about clinical trials; 4) pilot programs with Lyft and Ride Health to address transportation barriers; 5) patient education by nurse navigators regarding cancer and clinical trials; and 6) an improved informed consent process. These efforts reached more than 10,000 individuals in venues including churches, neighborhoods, community parks and centers, and health centers with formats ranging from educational forums to wellness fairs. Reassessing metrics in 2018, we found that the percentage of Black patients seen at ACC had increased to 16.2%, matching the percentage of Black cancer patients among all cancer cases in our catchment area (16.5%). Total cancer clinical trial accrual had increased from 9,308 participants in 2014 to 13,170 in 2018 (41.5% increase). The percentages of Black participants accrued onto treatment, non-therapeutic interventional, and non-interventional trials were 23.9%, 33.1%, and 22.5%, respectively – a 1.7- to 4.0-fold increase in five years and higher than the percentage of Black patients seen at the ACC. **Conclusions**: Our multifaceted, community-based engagement initiative to encourage clinical trial enrollment was associated with improved accrual of Black participants to cancer clinical trials. These findings also suggest that gaps in access to cancer centers are a key factor driving access to clinical trials. Medicaid expansion occurred concurrently in all states in our catchment area and its impact on accrual merits further research. Research Sponsor: U.S. National Institutes of Health.

101 **Clinical Science Symposium**

Effect of an antiracism intervention on disparities in time to lung cancer surgery. *First Author: Jacob Newton Stein, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: Racial disparities are well described in the management of early-stage lung cancer, with Black patients less likely to receive potentially curative surgery than non-Hispanic Whites. A multi-site pragmatic trial entitled Accountability for Cancer Care through Undoing Racism and Equity (ACCURE), designed in collaboration with community partners, eliminated racial disparities in lung cancer surgery through a multi-component intervention. The study involved real-time electronic health record (EHR) monitoring to identify patients not receiving recommended care, a nurse navigator who reviewed and addressed EHR alerts daily, and race-specific feedback provided to clinical teams. Timeliness of cancer care is an important quality metric. Delays can lead to disease progression, upstaging, and worse survival, and Black patients are more likely to experience longer wait times to lung cancer surgery. Yet interventions to reduce racial disparities in timely delivery of lung cancer surgery have not been well studied. We evaluated the effect of ACCURE on timely receipt of lung cancer surgery. **Methods:** We analyzed data of a retrospective cohort at five cancer centers gathered prior to the ACCURE intervention and compared results with prospective data collected during the intervention. We calculated mean time from clinical suspicion of lung cancer to surgery and evaluated the proportion of patients who received surgery within 60 days stratified by race. We performed a t-test to compare mean days to surgery and chi^2 for the delivery of surgery within 60 days. **Results:** 1320 patients underwent surgery in the retrospective arm, 160 were Black. 254 patients received surgery in the intervention arm, 85 were Black. Results are summarized in Table. Mean time to surgery in the retrospective cohort was 41.8 days, compared with 25.5 days in the intervention cohort ($p<0.01$). In the retrospective cohort, 68.8% of Black patients received surgery within 60 days versus 78.9% of White patients ($p<0.01$). In the intervention, the difference between Blacks and Whites with respect to surgery within 60 days was no longer significant (89.41% of Black patients vs 94.67% of White patients, p=0.12). **Conclusions:** Racial disparities exist in the delivery of timely lung cancer surgery. The ACCURE intervention improved time to surgery and timeliness of surgery for Black and White patients with early-stage lung cancer. A combination of real-time EHR monitoring, nurse navigation, and race-based feedback markedly reduced racial disparities in timely lung cancer care. Research Sponsor: U.S. National Institutes of Health.

Time to Lung Cancer Surgery.

	Black patients	White patients	p value	All patients	p value
Retrospective					
Mean (days)	47.7 (42.2-53.3)	41.0 (39.0-43.0)	p = 0.02	**41.8** (34.7-39.9)	
< 60 days	**68.8%**	**78.8%**	**p < 0.01**	**77.7%**	
Intervention					
Mean (days)	28.9 (22.9-34.9)	23.8 (20.7-26.9)	p = 0.10	**25.5** (22.6-28.4)	**p < 0.01***
< 60 days	89.4%	94.7%	p = 0.12	**92.9%**	**P < 0.01***

102 **Clinical Science Symposium**

Impact of the VA opioid safety initiative on pain management for cancer patients. *First Author: Mallika Marar, Department of Radiation Oncology, Stanford University, Stanford, CA*

Background: Limited research exists on how risk reduction policies in response to the opioid epidemic have impacted pain management among cancer patients. This study investigated the impact of the Veteran's Health Administration (VHA) Opioid Safety Initiative (OSI) on opioid prescribing patterns and opioid-related toxicity among patients undergoing definitive cancer treatment. **Methods:** This retrospective cohort study included 42,064 opioid-naïve patients receiving definitive local therapy for prostate, lung, breast, and colorectal cancer at the VHA from 2011-2016. Interrupted time series analysis with segmented regression was used to evaluate the impact of the OSI, which launched October 2013. The primary outcome was the incidence of new opioid prescriptions with diagnosis or treatment. Secondary outcomes included rates of high daily dose opioid (≥ 100 morphine milligram equivalent) and concomitant benzodiazepine prescriptions. Additional long-term outcomes included persistent opioid use, opioid abuse diagnoses, pain-related ED visits, and opioid-related admissions. **Results:** Prior to OSI implementation, the incidence of opioid prescriptions among new cancer patients increased from 26.7% (95% CI 25.0 – 28.4) in the first quarter (Q1) of 2011 to 50.6% (95% CI 48.3 – 53.0) in Q3 2013. There was a monthly increase in opioid prescription rate pre-OSI followed by a monthly decrease post-OSI (Table). High-dose opioid prescriptions were rare, and the monthly rate was stable before and after the OSI. Monthly incidence of concomitant benzodiazepine prescriptions was stable pre-OSI and decreased post-OSI. Persistent opioid use increased pre-OSI and decreased post-OSI. Pain-related ED visits had an incidence of 0.8% (95% CI 0.4 – 1.0) in Q1 2011, 0.3% (95% CI 0.1 – 0.6) in Q3 2013, and 1.8% (95% CI 0.9 – 2.7) in Q4 2016, with an increasing monthly rate after the OSI. At three years, the cumulative incidence of opioid abuse was 1.2% for both the pre- and post-OSI groups but opioid-related admissions were greater in the pre-OSI cohort than the post-OSI cohort (0.9% vs. 0.5%, $p < 0.001$). **Conclusions:** The OSI was associated with a decrease in new, persistent, and certain high-risk opioid prescribing as well as an increase in pain-related ED visits. Further research on patient-centered outcomes is required to optimize opioid prescribing policies for patients with cancer. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology., U.S. National Institutes of Health.

	Pre-OSI monthly change [95% CI]	Post-OSI monthly change [95% CI]
New opioid prescriptions	+ 3.3% [2.3, 4.2]; p < 0.001	- 0.3% [-0.4, -0.1]; p < 0.001
High-dose opioid prescriptions	+ 0.4% [-0.7, 1.5]; p = 0.49	- 0.8% [-2.2, 1.3]; p = 0.26
Concomitant benzodiazepine prescriptions	+ 0.3% [-0.1, 0.6]; p = 0.20	- 1.9% [-2.6, -1.1]; p < 0.001
Persistent opioid use	+ 1.8% [1.2, 2.4]; p < 0.001	- 3.1% [-3.8, -2.3]; p < 0.001
Pain-related ED visits	- 1.1 [-2.2, 0.0]; p = 0.05	+ 1.9% [0.4, 3.3]; p = 0.01

103 **Clinical Science Symposium**

Less is more: Postoperative pain management using restrictive opioid protocols in all surgical services in a comprehensive cancer center. *First Author: Jason Ricciuti, Department of Gynecologic Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Opioids are routinely given for postoperative pain management with limited evidence on the amount needed to be dispensed. Prescribed opioids increase the risk of chronic use, abuse, and diversion, which contribute to the opioid epidemic. We sought to demonstrate that postsurgical acute pain can be effectively managed across different surgical specialties with a markedly reduced number of opioids. **Methods:** A prospective case-control study of restrictive opioid prescription protocol (ROPP) was implemented in all surgical services from February 2019 through July 2019 at a tertiary comprehensive cancer center for all patients undergoing a surgery for which opioids would be routinely prescribed at discharge (n = 2,015). Data from surgeries performed by the same services from August 2018 through January 2019 were used for comparison (n = 2,051). At discharge, patients did not routinely receive opioids unless they had a maximally invasive procedure or if they required multiple doses of opioids during hospitalization (maximum 3-day supply). Compliance with the protocol was tracked by pharmacists daily. Patient demographics and surgical details were collected. State-run opioid prescription database was used to determine the number of opioids prescribed to all surgical patients within a 120-day surgical window. Validated patient satisfaction surveys were used at postoperative visits to assess patient experience. **Results:** After implementation of the ROPP, 45% less opioids were prescribed after surgery for all participating patients (323,674 morphine milligram equivalents (MME) vs 179,458 MME, $p < 0.001$). The majority of services complied with the ROPP in more than 95% of cases. There was no difference in postsurgical pain intensity between cohorts. Patients in the ROPP cohort had less refill requests compared to the control group (20.9% vs 17.9%, p value = 0.016). Surveys were completed by 338 patients in the control group (16.5%) and 360 in the ROPP group (17.9%). There was no significant difference in patient reported satisfaction with postoperative pain control or on the impact of pain on daily activities between the cohorts. **Conclusions:** Implementation of a ROPP by multiple surgical services at a tertiary cancer center was feasible and resulted in substantial decrease in the number of opioids prescribed while not compromising patient experience. Patients did not require more prescription refills despite being provided no opioids or a limited supply. This study provides evidence to support reducing the number of opioids routinely prescribed after surgery. Research Sponsor: Roswell Park Alliance Foundation.

Surgical service	Total MME Pre-protocol	Total MME Post-protocol	p value
Breast	35,319	8,683	< .001
Gastroenterology	45,642	38,595	< .001
Head and Neck	48,485	33,215	< .001
Neurosurgery	18,663	12,920	< .001
Soft Tissue Medicine	12,573	4,095	< .001
Thoracic	104,023	67,114	< .001
Urology	50,033	6,712	< .001

104 **Clinical Science Symposium**

Explainable prediction of survival using clinical, molecular, and radiomic profiles in recurrent high-grade glioma patients treated with CAR T-cell therapy. *First Author: Chi Wah Wong, City of Hope National Medical Center, Duarte, CA*

Background: High-grade glioma (HGG) is an aggressive heterogeneous primary CNS neoplasm with high recurrence rate and poor survival. Multiple ongoing clinical trials are leveraging targeted molecular and immunologic therapeutics (e.g., pembrolizumab, Chimeric Antigen Receptor [CAR] T-cell therapy) in effort to improve survival. Explainable predictive models have shown value in identifying biomarkers predictive of treatment response as well as informing prognosis. In this study, we developed an explainable machine learning model leveraging clinical, molecular and radiomic (imaging) features to predict overall survival in patients suffering from HGG treated with CAR T-cell therapy. **Methods:** In this IRB-approved phase 1 clinical trial, 60 patients (39 males, median age = 49) suffering from HGG underwent surgical resection and CAR T-cell therapy[1]. All patients underwent baseline MRI scans prior to both surgical resection and CAR T-cell administration in the resection cavity. Using contrast-enhanced T1-weighted MRIs, we segmented the enhancing tumor (ET) and generated radiomic features. For predictive modeling, we incorporated the following features: Age, gender, race, ethnicity, histology, tumor grade (WHO), IL-13 receptor alpha 2 (IL-13Rα2) expression (H score), unifocal or multifocal lesions, tumor location (lobe), shape-based radiomics (tumor volume, surface area, and sphericity). We utilized gradient-boosted tree models to classify whether survival is above or below 180 days with two-loop nested cross-validation. For the inner validation loop, we optimized the model with hyper-parameter tuning. For the outer validation loop, we tested the optimal model on the hold-out data and the predictions were used as survival scores (0 – 1). Larger scores imply better predicted survival. For prediction explanations, we adopted the Shapley additive explanation (SHAP) framework. **Results:** The outer validation loop Area Under the Receiver Operating Characteristic Curve and Area under the Precision-Recall Curve were 0.76 and 0.81, respectively. Among the top five most important features calculated from SHAP; patients with larger tumor surface area, tumor volume and age have reduced survival scores while patients with larger IL-13Rα2 and tumor sphericity have increased survival scores. We stratified the patients into two distinct prognostic sub-groups (30 patients each group) using the survival scores obtained from the outer loop, with a log-rank test $p < 0.01$. **Conclusions:** In patients with HGG treated with CAR T-cell therapy, we found that tumor surface area/volume and age are inversely related to survival while increased IL-13Rα2 expression and tumor sphericity were positive predictor of survival. Our model can potentially be used to optimize clinical trial enrollment through more precise patient screening and treatment planning. Research Sponsor: None.

105 **Clinical Science Symposium**

Imaging-based patient inclusion model for clinical trial performance optimization. *First Author: Michal R Tomaszewski, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: In the era of precision medicine, development of new cancer therapies relies strongly on effective selection of target patient population. We hypothesize that computational analysis of imaging data can be used for development of a quantitative population enrichment strategy in clinical trials and thus we aim to establish an appropriate framework for this analysis. **Methods:** This hypothesis was tested among soft-tissue sarcoma (STS) patients accrued into a randomized Phase III clinical trial (SARC021) that evaluated the efficacy of evofosfamide (Evo), a hypoxia activated prodrug, in combination with doxorubicin (Dox). Notably, SARC021 failed to meet its survival objective (PMC7771354). We tested whether an inclusion/exclusion model based on radiomic analysis and relevant clinical covariates could have been employed to result in a significant treatment benefit of the Evo+Dox combination compared to the standard Dox monotherapy. A total of 163 radiomics features were extracted from lung metastases of 303 patients from the SARC021 trial, divided into demographically matched training and test sets. Stability analysis identified the most reproducible features. Univariable and multivariable models were utilized to discriminate OS in the two treatment groups. **Results:** A bespoke enrichment framework was established for individualized patient selection, based on model-derived risk score threshold. A radiomic feature, Short Run Emphasis, was identified as the most informative. When combined with tumor histology and smoking history information, an enriched subset (42%) of patients had longer OS in Evo+Dox vs. Dox groups [p = 0.01, Hazard Ratio (HR) = 0.57 (0.36-0.90)], overperforming a clinical-only approach. Application of the same model and threshold value in an independent test set confirmed the significant survival difference (p = 0.002, HR = 0.29 (0.13-0.63), 38% patients included). The breakdown of Dox+Evo treatment benefit depending on proportion of patients included based on the model is shown in the Table. Notably, this process also identified patients most likely to benefit from doxorubicin alone. **Conclusions:** The study presents a first of its kind radiomic approach for patient enrichment in clinical trials based on a quantitative score. In particular, we have shown that had the novel model been used for selective patient inclusion into the SARC021 trial, it would have met its primary survival objective for patients with metastatic STS. Research Sponsor: U.S. National Institutes of Health., Dr. Fan was partially supported by funds from the Dept. Radiology, Tianjin Medical University, Tianjin, China.

	Training set	Dox+Evo vs. Dox		Test set	Dox+Evo vs. Dox	
Patients included (%)	p value	HR	HR 95% Conf. Int.	p value	HR	HR 95% Conf. Int.
100	0.61	1.09	(0.78 - 1.51)	0.25	0.74	(0.45 - 1.23)
80	0.63	0.92	(0.64 - 1.30)	0.11	0.64	(0.37 - 1.11)
60	0.24	0.79	(0.53 - 1.17)	0.11	0.61	(0.33 - 1.12)
50	0.12	0.71	(0.45 - 1.09)	0.04	0.50	(0.26 - 0.97)
42	0.017	0.57	(0.36 - 0.90)	0.010	0.37	(0.18 - 0.79)
40	0.013	0.55	(0.34 - 0.88)	0.011	0.37	(0.17 - 0.79)
30	0.007	0.47	(0.28 - 0.82)	0.003	0.27	(0.11 - 0.65)

106 **Clinical Science Symposium**

Artificial intelligence (AI)–powered pathologic response (PathR) assessment of resection specimens after neoadjuvant atezolizumab in patients with non-small cell lung cancer: Results from the LCMC3 study. *First Author: Sanja Dacic, Department of Pathology, University of Pittsburgh and UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: PathR is an efficacy endpoint in Phase II and III neoadjuvant trials and is proposed as a surrogate for disease-free survival (DFS) and overall survival. Machine learning (ML)–based, automated approaches standardize quantification of areas of tumor bed and residual viable tumor. Here we show that automation may provide a scalable alternative to or complementary tool for manual assessment. **Methods:** We determined inter-reader variability for PathR among pathologists in the LCMC3 (NCT02927301) study and developed an AI-powered digital PathR assessment tool in line with manual consensus recommendations. Study cases were reviewed for PathR by a local site pathologist and 3 central expert pathologists (n = 127). When determined manually, major PathR (MPR) was defined as ≤10% viable tumor averaged per case. ML models were trained and validated by the PathAI research platform using digitized H&E-stained tumor sections. The digital PathR model predicted percent viable tumor for each case as the sum of the cancer epithelium area from each slide divided by the sum of tumor bed area for each slide. DFS (clinical cutoff: Oct 23, 2020) was reported for patients with manual and digital PathR assessment (n = 135). For digital MPR, we used a prevalence-matched cutoff that maintained the same proportion of patients as manual MPR. **Results:** Inter-reader agreement among 1 local and 3 central pathologists for manual PathR was good (n = 127; ICC = 0.87; 95% CI: 0.84-0.90). Agreement was 91% (κ = 0.82) on manual MPR and 98% (κ = 0.88) on pathologic complete response (pCR). 6 patients had unanimous pCR. Digital and manual PathR were strongly correlated (n = 135, Pearson r = 0.78) and digital PathR demonstrated an outstanding predictability for manual MPR (AUROC = 0.975). The range was 0%-60% for digital PathR and 0%-100% for manual PathR with a regression line slope < 1.0 (m = 0.303) indicating systematic differences between the methods, consistent with digital PathR using a high-resolution segmentation of cancer epithelium from stroma across each slide. Longer DFS was observed for MPR yes vs no with both digital and manual assessment (Table). **Conclusions:** This analysis showed good inter-reader agreement for manual and strong correlation of AI-powered digital and manual PathR. Comparable DFS rates for manual MPR and digital MPR are encouraging in the preliminary data. These data support further studies of digital PathR as a standardized and scalable tool to determine PathR. Clinical trial information: NCT02927301. Research Sponsor: F. Hoffmann-La Roche.

	Manual MPR No	Manual MPR Yes	Digital MPR No	Digital MPR Yes
MPR, n	107	28[a]	107	28[a]
Events, n (%)	25 (23)	3 (11)	26 (24)	2 (7)
1-year DFS, %	82	93	82	93
1.5-year DFS, %	75	89	73	93

[a]23 patients were MPR Yes by both manual and digital.
Median DFS was not reached.

107 **Clinical Science Symposium**

HPV associated cancers in the United States over the last 15 years: Has screening or vaccination made any difference? *First Author: Cheng-I Liao, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*

Background: Human papillomavirus is a causative agent of many human cancers. This study aims to determine the incidence and trends of HPV-related cancers in the United States. **Methods:** HPV-associated cancers as classified by the CDC were included: oropharyngeal squamous cell carcinoma (SCC), anal & rectal SCC, vulvar SCC, vaginal SCC, cervical carcinoma, and penile SCC. Data were obtained from the United States Cancer Statistics program from 2001-2017. SEER*Stat 8.3.8 and Joinpoint regression program 4.8.0.1 were used to calculate incidence trends of HPV-associated cancers per 100,000. **Results:** The overall incidence of HPV related cancers for women was 13.68/100,000, more than half of which (52%) were cervical cancer, at 7.12/100,000 in the year 2017. Over the last 16 years, the incidence of cervical cancer has decreased at an annual percent change (APC) of 1.03% ($p < 0.001$). In contrast, oropharyngeal (APC = 0.77%, $p < 0.001$), anal & rectal (APC = 2.75%, $p < 0.001$), and vulvar SCC all increased significantly (APC = 1.27%, $p < 0.001$). For older women, the incidence of anal & rectal cancer approached that of cervical cancer. In those over 80, the incidence of cervical cancer was 6.95 (-2.90% APC, $p < 0.001$), compared to 6.36 for anal & rectal cancer (1.23% APC, $p < 0.001$). Using a projection model, incidence of anal & rectal cancer is expected to surpass that of cervical cancer by year 2025 for every age group over 55. For men, the incidence of all HPV-related cancers was 11.0/100,000 in the year 2017, 81% were associated with oropharyngeal cancer. Over the last 16 years, there was an overall annual increase in HPV related cancers at 2.36% per year ($p < 0.001$) with the highest increase in oropharyngeal (APC = 2.71%, $p < 0.001$) and anal & rectal SCC (APC = 1.71%, $p < 0.001$). Those at greatest risk of oropharyngeal cancer were older men aged 65-69 years with an incidence of 36.5/100,000 and annual percent increase of 4.24% ($p < 0.001$). The intersectionality of age and race showed that White men age 65-69 years had the highest incidence of oropharyngeal at 41.6/100,000. **Conclusions:** Overall, there was a decrease in cervical cancer incidence likely due to screening or vaccination. However, over 80% of men with HPV related cancers had oropharyngeal cancer, a nearly fivefold higher incidence compared to women. In contrast, there was a significant increase in non-screenable HPV-related cancers and anal & rectal SCC incidence is projected to surpass that of cervical cancer within 5 years for certain at-risk groups. Further resources and research should be conducted to address the lack of screening or vaccination in these preventable cancers. Research Sponsor: Fisher Foundation and Denise Cobb Hale.

108 **Clinical Science Symposium**

Finding the missing millions: Integrating automated viral hepatitis screening in a hospital with care and treatment in a primary care setting. *First Author: Ruth Brogden, Saint Barnabas Medical Center, Florham Park, NJ*

Background: Rates of hepatocellular carcinoma (HCC) are rising in the US. Patients at Saint Barnabas Medical Cancer Center (SBMC) present with late-stage HCC at higher rates (29%) compared to the national (16%). Chronic Hepatitis C (HCV) and Hepatitis B (HBV) are major drivers of liver cancer, yet screening rates are low. Finding these missing millions is important to reducing rates of HCC. An automated emergency department (ED) viral hepatitis (VH) screening program was initiated in 2018 at SBMC. In January 2020, it was expanded to the inpatient setting and HCV screening was modified from cohort screening (those born in 1945-65) to a one time test for anybody 18 years or over, per updated Centers for Disease Control (CDC) and USPSTF (US Preventive Services Taskforce) recommendations. **Methods:** The electronic medical record (EMR) was modified to automate screening. HBV testing is triggered by a patient's country of birth or race, and HCV testing is triggered by age over 18 and no previous testing. The automated HCV (HCV Ab with reflex to HCV RNA) or HBV (HBsAg) lab orders lead to an EMR notification to the nurses of patient eligibility and education is provided to patients. Alerts of positive results are sent to nursing staff, physicians, and the patient navigator (PN). The PN is sent a real-time secure text message and works individually with patients to arrange linkage-to-care (LTC) for evaluation and treatment. **Results:** From March 2018 - December 2020, 44,002 patients were screened for HCV and 884 (2.0%) were HCVAb+ and 242 (0.55%) HCV RNA+. For HBV, 21,328 patients were screened and 212 (0.99%) were HBsAg+. The expanded screenings accounted for 8,716 (19.8%) of the total HCV screenings. Individuals born outside the 1945-65 birth cohort (younger and older) made up 76.2% of those screened and 41% of the infected. The top 3 countries for HBV screenings were Haiti, Jamaica, and Ecuador. LTC rates, defined as attending first medical appointment or already in care, were 86.8% for HCV and 85.4% for HBV. Of those linked to care, 43 HCV+ patients were seen at a outpatient primary care practice part of SBMC, and of those, 39 initiated HCV cure therapy and 33 were cured (confirmed sustained virologic response at 12 weeks), and 35 HBV+ patients were seen and 6 initiated treatment. **Conclusions:** This automated program for VH has led to a significant scale up of screening with successful LTC and treatment of patients. Expansion to universal screening of all adults and to the inpatient setting found additional viral hepatitis patients who would have otherwise been missed. In addition to the automated screening, a multidisciplinary team including internists, pharmacists, and patient navigators were part of creating a primary care based program. Integration of viral hepatitis screening and care in a hospital system can be initial steps towards establishing liver cancer prevention program. Research Sponsor: Gilead Sciences.

109 **Clinical Science Symposium**

Identification of good and poor prognosis HPV associated oropharyngeal cancer based on CD103 immune cell expression in patients treated with cetuximab and radiotherapy on TROG 12.01 and De-ESCALaTE randomized trials. *First Author: Danny Rischin, Department of Medical Oncology, Peter MacCallum Cancer Centre and the Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia*

Background: Trials in human papilloma virus associated oropharyngeal squamous cell carcinoma (HPVOPSCC), substituting cetuximab (CETUX) for cisplatin (CIS) with radiotherapy (RT), resulted in decreased efficacy without improved toxicity or symptom burden. We reported that high intratumoral immune cell (ITIC) CD103 expression (> 30%), a marker of tissue-resident memory T cells, is associated with better prognosis in unselected patients with HPVOPSCC treated with CIS/RT. In this study our aim was to determine whether low risk HPVOPSCC patients treated with CETUX/RT with high CD103 have a superior prognosis. **Methods:** TROG 12.01 and De-ESCALaTE are randomised multicentre trials that compared 70Gy RT/CETUX with 70Gy RT/CIS (weekly in TROG 12.01, 3-weekly in De-ESCALaTE) in patients with HPVOPSCC, low risk by Ang criteria: AJCC 7^{th} Stage III (excluding T1-2N1) or stage IV (excluding N2b-c if smoking history > 10 pack years and/or distant metastases). In TROG 12.01 T4 and/or N3 patients were also excluded. Eligible patients required tumor samples available for immune cell quantification on immunohistochemistry. Data from the two trials were pooled, with analyses performed in eligible randomised patients who commenced treatment. The primary endpoint was failure-free survival (FFS) in patients receiving CETUX/ RT comparing CD103 ITIC > 30% (high) vs. < 30% (low). High/low CD103 were compared using Cox model adjusting for age, stage and trial. **Results:** Samples for CD103 testing were available in 159/182 patients on TROG 12.01 and 145/334 on De-ESCALaTE. ITIC CD103 expression was high in 26% of patients. The median follow-up was 3.2 years. The 3 -year failure-free survival rates in patients treated with CETUX/RT were 92% (95% CI: 78-97%) in high CD103 and 74% (95% CI: 64-82%) in low CD103, adjusted HR 0.25 (95% CI: 0.14-0.44); $p < 0.001$. The 3 -year overall survival (OS) in patients treated with CETUX/RT were 100% in high CD103 and 86% (95% CI: 76-92%) in low CD103, $p < 0.001$. Superior FFS in the high CD103 group was independent of stage. In patients treated with CIS/RT there was no significant difference in FFS (3-year 86% in high CD103 and 90% in low CD103; $p = 0.55$) or in OS (3-year 100% in high CD103 and 95% in low CD103; $p = 0.14$). The increase in failures in the low CD103 patients treated with CETUX/RT was evenly split between distant and locoregional failures. **Conclusions:** ITIC CD103 separates CETUX/RT treated low risk HPVOPSCC into excellent and poor prognosis subgroups. In a low risk population CIS/RT achieves excellent outcomes in both high and low ITIC CD103 groups. The high ITIC CD103 population is a rational target for future de-intensification trials. Research Sponsor: National Health and Medical Research Council (Investigator Grant GNT1175929).

110 **Clinical Science Symposium**

De-intensified chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma based on plasma EBV DNA: A phase 2 randomized noninferiority trial. *First Author: Hai-Qiang Mai, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The cisplatin-based chemoradiotherapy (CCRT), given at a dose of 100 mg/m^2 for 3 cycles during radiotherapy, is the major treatment for locoregionally advanced nasopharyngeal carcinoma (NPC). As several retrospective studies showed that receiving a cumulative cisplatin dose of 200 mg/m^2 can bring survival benefits to NPC patients, we sought to test the non-inferiority of 2-cycle concurrent cisplatin over 3-cycle in locoregionally advanced NPC with Epstein-barr virus (EBV) DNA levels < 4000 copies/ml. **Methods:** We did a non-inferiority, phase 2, randomised controlled trial. Patients were enrolled with stage III–IVB NPC, EBV DNA levels < 4000 copies/ml, aged 18–70 and adequate haematological, renal, and hepatic function. Eligible patients were randomly assigned (1:1) to receive 2 or 3 cycles of cisplatin-based CCRT. Patients in the 2-cycle group were scheduled to receive 100 mg/m^2 cisplatin given every 3 weeks concurrently with radiotherapy, and patients in the 3-cycle group received 100 mg/m^2 cisplatin given every 3 weeks for 3 cycles. Randomization was done by a computer-generated random number code with a block size of six, stratified by clinical stage III or IV. The primary endpoint was 3-year progression-free survival (PFS), with a non-inferiority margin of 10%. This study was registered with ClinicalTrials.gov, ID. NCT02871518. **Results:** Between September 2016 and October 2018, 342 patients were enrolled, of whom 332 were randomly assigned to receive 2 or 3 cycles of cisplatin. 314 (94.6%) patients completed protocol-defined cycles of chemotherapy. After median follow-up of 33.6 months, 20 (12.0%) patients in the 2-cycle group and 17 (10.2%) patients in the 3-cycle group had tumor progression, and the 3-year PFS rates were 88.0% and 90.4% respectively, with a difference of 2.4% (95%CI -4.3 to 9.1, $P_{non\text{-}inferiority} < 0.001$). In the per-protocol analysis, 3-year PFS was 88.5% in the 2-cycle group and 90.6% in the 3-cycle group, with a difference of 2.1% (95% CI –4.7 to 8.9; $P_{non\text{-}inferiority} = 0.001$). No significant difference was observed concerning OS, LRRFS and DMFS. The grade 3 or 4 acute adverse events were recorded in 113 (68.1%) patients in the 2-cycle group and 116 (69.9%) patients in the 3-cycle group. Patients in the 3-cycle group was observed to have significantly more hyponatremia. Besides, patients in the 3-cycle group presented with more grade 1 or 2 dry mouth, dysphagia, weight loss, fatigue, constipation, fever, mucositis and dermatitis. More grade 3 or 4 anorexia, mucositis and dermatitis were also recorded in the 3-cycle group. No patients died from treatment-related toxicities. **Conclusions:** IMRT plus 2 cycles of concurrent 100 mg/m^2 cisplatin could be an alternative option for patients with low-risk locoregionally advanced NPC. Further phase III studies are needed to validate the findings of this study. Clinical trial information: NCT02871518. Research Sponsor: None.

500 **Oral Abstract Session**

Outcome of patients with an ultralow risk 70-gene signature in the MINDACT trial.

First Author: Josephine Lopes Cardozo, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Gene signatures have proven successful in identifying patients with a low risk of distant recurrence who could forego chemotherapy (CT) and are currently included in international treatment guidelines for breast cancer. For the 70-gene signature (MammaPrint) an additional threshold was established within the low risk category to identify patients with an ultralow risk of distant recurrence. In independent cohorts, these patients had excellent breast cancer specific survival at 15 years, suggesting that ultralow risk cancers represent indolent disease (Esserman, JAMA Oncol 2017, Delahaye, BC Res Treat 2017). Here we evaluate survival of patients with an ultralow risk 70-gene signature who participated in the randomized phase 3 MINDACT trial (Piccart, Lancet Oncol 2021). **Methods:** Of the 6,693 patients enrolled in the MINDACT trial (EORTC 10041/BIG 3-04) between 2007-2011, profiling revealed an ultralow risk 70-gene signature in 1,000 patients (15%). We assessed 5- and 8-year distant metastasis free interval (DMFI) and breast cancer specific survival (BCSS) in patients stratified by 70-gene signature result (high, low, ultralow), and within the ultralow risk group stratified by clinical risk. For these exploratory analyses, we used Kaplan-Meier estimates for time to event endpoints and Cox-regression models to calculate hazard ratio's (HR). **Results:** Median follow-up was 8.7 years. Among the ultralow risk patients (n = 1,000), 67% were ≥50 years, 81% had tumors < 2cm, 80% were lymph node negative, 96% had grade 1 or 2 tumors and 99% were ER-positive. Systemic therapy was received by 83% of patients (69% endocrine therapy (ET), 14% ET + CT) and 16% received no adjuvant systemic treatment (AST). Survival estimates for all endpoints are shown in the table; 8-year DMFI was 97.0% (95% CI 95.8-98.1) for ultralow risk. The 8-year DMFI in ultralow risk patients who received no AST or ET only was 97.8% (95% CI 95.3-100) and 97.4% (95% CI 96.1-98.7), respectively. The HR for DMFI was 0.66 (95% CI 0.46-0.95) for ultralow vs low risk, after adjusting for tumor and treatment characteristics (preliminary results). **Conclusions:** In this prospective study, patients with an ultralow risk 70-gene signature have an excellent prognosis with 8-year BCSS above 99% regardless of clinical risk status, and with an 8-year DMFI of 95-98%. Research Sponsor: This research was supported by a grant from the EORTC Breast Group and from the Netherlands Cancer Institute.

70-gene signature	Events (N)	5-year DMFI (95% CI)	8-year DMFI (95% CI)	8-year BCSS (95% CI)
Ultralow risk (n = 1000)	36	98.1% (97.2-99.0)	97.0% (95.8-98.1)	99.6% (99.1-100)
Low risk* (n = 3295)	192	97.5% (97.0-98.1)	94.5% (93.6-95.3)	98.2% (97.7-98.7)
High risk (n = 2398)	273	92.5% (91.4-93.6)	89.2% (87.9-90.5)	93.7% (92.6-94.7)
Ultralow risk				
Clinical low risk (n = 741)	21	98.7% (97.8-99.5)	97.6% (96.4-98.8)	99.7% (99.3-100)
Clinical high risk (n = 259)	15	96.3% (94.0-98.7)	95.0% (92.3-97.8)	99.2% (98.0-100)

*Low risk excludes ultralow risk.

501 **Oral Abstract Session**

Breast Cancer Index (BCI) and prediction of benefit from extended aromatase inhibitor (AI) therapy (tx) in HR+ breast cancer: NRG oncology/NSABP B-42.

First Author: Eleftherios P. Mamounas, NSABP/NRG Oncology, and The Orlando Health Cancer Institute, Orlando, FL

Background: The BCI HOXB13/IL17BR ratio (BCI-H/I) has been shown to predict endocrine tx (ET) and extended ET (EET) benefit. We examined the effect of BCI-H/I for EET benefit prediction in NSABP B-42, evaluating extended letrozole tx (ELT) in HR+ breast cancer patients (pts) who completed 5 yrs of ET. **Methods:** All pts with available primary tumor tissue were eligible. Primary endpoint was recurrence-free interval (RFI). Secondary endpoints were distant recurrence (DR), breast cancer-free interval (BCFI), and disease-free survival (DFS). Stratified Cox proportional hazards model was used. Due to a non-proportional effect of ELT on DR, time-dependent secondary analyses (≤4y, >4y) were performed. Likelihood ratio test evaluated treatment by BCI-H/I interaction. **Results:** In 2,179 pts analyzed (60% N0; 62% AI only; 80% HER2-), 45% were BCI-H/I-High and 55% BCI-H/I-Low. ELT showed an absolute 10y benefit of 1.6% for RFI (HR=0.77, 95% CI 0.57-1.05, p=0.10) (BCI-H/I-Low: 1.1% [HR=0.69, 0.43-1.11, p=0.13]; BCI-H/I-High: 2.4% [HR=0.83, 0.55-1.26, p=0.38]; interaction p=0.55). There was no statistically significant ELT by BCI-H/I interaction for BCFI (BCI-H/I-Low: HR=0.53, 0.36-0.78, p=0.001; BCI-H/I-High: HR=0.85, 0.60-1.21, p=0.36; interaction p=0.07) or for DFS (BCI-H/I-Low: HR=0.75, 0.58-0.95, p=0.017; BCI-H/I-High: HR=0.81, 0.64-1.04, p=0.09; interaction p=0.62). Before 4y, there was no statistically significant ELT benefit on DR in either BCI-H/I group. After 4y, BCI-H/I-High pts had statistically significant ELT benefit on DR (HR: 0.29, 0.12-0.69, p=0.003), while BCI-H/I-Low pts were less likely to benefit (HR: 0.68, 0.33-1.39, p=0.28) (interaction p=0.14). **Conclusions:** BCI-H/I prediction of ELT benefit on RFI was not confirmed. In time-dependent DR analyses, BCI-H/I-High pts had statistically significant benefit from ELT after 4y, while BCI-H/I-Low pts did not. Observed ELT benefit on BCFI in BCI-H/I-Low pts was primarily driven by second primary breast cancers. Additional follow-up is needed to further characterize BCI-H/I predictive ability in this study. Support: U10CA180868, -180822, U24CA196067; Novartis; Biotheranostics. Clinical trial information: NCT00382070. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

		≤ 4 y			4 y		
	BCI-H/I	HR (95%CI)	4y abs. benefit (%)	P	HR (95%CI)	10y abs. benefit (%)	P
All	All	0.85 (0.51, 1.43)	0.4	0.55	0.47 (0.28, 0.81)	1.7	0.005
	L	0.47 (0.19, 1.17)	1.1	0.10	0.68 (0.33, 1.39)	0.4	0.28
	H	1.21 (0.63, 2.32)	-0.4	0.56	0.29 (0.12, 0.69)	3.6	0.003
N0	L	0.28 (0.03, 2.48)	0.7	0.22	1.05 (0.35, 3.14)	-1.0	0.93
	H	2.03 (0.62, 6.60)	-1.5	0.23	0.32 (0.06, 1.68)	1.8	0.16
N+	L	0.54 (0.19, 1.48)	2.4	0.22	0.49 (0.19, 1.28)	3.5	0.14
	H	0.94 (0.42, 2.09)	0.5	0.87	0.28 (0.10, 0.77)	5.6	0.009
AI Only	L	0.50 (0.15, 1.70)	0.8	0.26	0.70 (0.29, 1.68)	0.6	0.42
	H	1.06 (0.48, 2.37)	0.2	0.89	0.42 (0.15, 1.19)	3.2	0.09
Tam-AI	L	0.44 (0.11, 1.70)	1.7	0.22	0.63 (0.18, 2.24)	0.1	0.47
	H	1.56 (0.51, 4.76)	-1.5	0.43	0.16 (0.04, 0.76)	4.3	0.009

502 **Oral Abstract Session**

Utility of the 70-gene MammaPrint assay for prediction of benefit from extended letrozole therapy (ELT) in the NRG Oncology/NSABP B-42 trial.

First Author: Priya Rastogi, NSABP/NRG Oncology and the UPMC Hillman Cancer Center, Pittsburgh, PA

Background: The 70-gene MammaPrint (MP) assay predicts risk of distant recurrence (DR) in hormone-receptor positive early-stage breast cancer and classifies cancers as Low Risk or High Risk. NSABP B-42 evaluated ELT in patients (pts) who had completed 5 yrs of adjuvant endocrine therapy (tx). The primary objective was to determine the utility of MP to identify pts enrolled in NSABP B-42 who are likely to benefit from ELT. **Methods:** A total of 1,866 pts from B-42 had available MP results. Primary endpoint is DR. Secondary endpoints are disease-free survival (DFS) and breast cancer-free interval (BCFI). For the primary analysis, pts were classified as High Risk (MP-H) (MP score ≤0.000) or Low Risk (MP-L) (MP score > 0.000). Exploratory analyses were performed for MP-L subcategories: MP Ultralow Risk (MP-UL) (MP score > 0.355) and MP-L but not MP-UL (MP-LNUL) (MP score > 0.000, ≤0.355). Likelihood ratio test based on stratified Cox proportional hazards (PH) model was used for treatment by risk group interaction. Stratified log-rank test was used to compare treatment groups. Hazard ratios and 95% CI were computed based on the stratified Cox PH model. **Results**: Among 1,866 pts, 706 (38%) were MP-H and 1,160 (62%) were MP-L. Of the MP-L, 252 (22%) were MP-UL. There were no significant differences in the distribution of patient and tumor characteristics between the MP group and the rest of the B-42 cohort, except for HER2 status. ELT effect was more pronounced in the MP cohort than in the overall B-42 population. For DR, there was statistically significant ELT benefit in MP-L (HR = 0.43, 95% CI 0.25-0.74, p = 0.002), but not MP-H (HR = 0.65, 0.34-1.24, p = 0.19) (interaction p = 0.38). For DFS, there was statistically significant ELT benefit in MP-L, but not MP-H (interaction p = 0.015). Similar findings were observed for BCFI (interaction p = 0.006). Within subcategories of MP-L, there was statistically significant ELT benefit in MP-LNUL, but not in MP-UL for all three endpoints, however the power in MP-UL was limited due to low number of pts (Table). Clinical trial information: 00382070. **Conclusions:** Statistically significant ELT benefit was observed for MP-L, but not MP-H. The treatment by risk group interaction was not statistically significant for DR, but it was for DFS and BCFI. The benefit appears to be stronger in MP-LNUL than in MP-UL. NCT: 00382070. Support: U10CA180868, -180822, U24CA196067; Novartis; Agendia. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Endpoint	MP Risk Group	% of 10y event-free Letrozole	% of 10y event-free Placebo	HR (95%CI)	p
DR	L	96.5	92.8	0.43 (0.25,0.74)	0.002
	H	95.1	92.7	0.65 (0.34,1.24)	0.19
DFS	L	79.7	71.9	0.67 (0.52,0.85)	< 0.001
	H	71.2	72.8	1.10 (0.82,1.47)	0.55
BCFI	L	91.6	84.6	0.51 (0.35,0.74)	< 0.001
	H	85.4	88.4	1.15 (0.74,1.79)	0.53
DR	UL	97.1	94.2	0.53 (0.13,2.15)	0.37
	LNUL	96.4	92.4	0.42 (0.23,0.76)	0.003
DFS	UL	82.5	80.7	0.82 (0.45,1.48)	0.50
	LNUL	78.9	69.4	0.64 (0.49,0.83)	< 0.001
BCFI	UL	92.7	88.6	0.67 (0.28,1.65)	0.38
	LNUL	91.3	83.4	0.48 (0.32,0.73)	< 0.001

503 **Oral Abstract Session**

De-escalated neoadjuvant pertuzumab+trastuzumab with or without paclitaxel weekly in HR-/HER2+ early breast cancer: ADAPT-HR-/HER2+ biomarker and survival results.

First Author: Nadia Harbeck, Breast Center, Dept. Obstetrics & Gynecology, University of Munich (LMU) and CCCLMU and West German Study Group, Munich, Germany

Background: Optimal use of de-escalated, particularly chemotherapy(CT)-free, neoadjuvant regimens in HER2+ early breast cancer (EBC) is currently unclear as there are limited survival data so far. In ADAPT-HR-/HER2+, we previously showed an excellent pCR rate of 90% after 12-week neoadjuvant paclitaxel (Pac) +pertuzumab (P) +trastuzumab (T) and a substantial and clinically meaningful pCR rate of 34% after P+T alone in HR-/HER2+ EBC. Here, we present first survival data. **Methods:** The prospective multicenter WSG-ADAPT-HR-/HER2+ phase II-trial is part of the ADAPT-umbrella protocol. Patients with cT1-cT4c, cN0-3 HR-/HER2+ EBC (n = 134) were randomized to 4 cycles of P+T +/- pac d1,8,15 q3w. All tumors were HR-negative (ER and PR < 1%) and HER2-positive (central lab, i.e., 2+ FISH positive or 3+ by immunohistochemistry. Primary endpoint was pCR (ypT0/is/ypN0); omission of further CT was allowed in pts with pCR. Trial objective was to compare pCR in P+T+pac arm vs. early responders in P+T arm (defined as low cellularity and/or Ki67 decrease >30% after 3 weeks). The trial was stopped early due to the observed pCR superiority in the P+T+pac arm. Secondary endpoints included safety, 5-y (distant)-DFS, OS and translational research. Cox-regression analysis was applied. PAM50 subtype was assessed using the BC360 panel. **Results:** 134 patients were randomized to P+T (n = 92) or P+T+pac (n = 42). 60% of tumors were cT2-4, 42% clinically node-positive. After a median follow-up of 5 years, no significant differences between study arms were observed regarding DFS, dDFS, and OS; only 13 iDFS events (7 dDFS) were observed in the whole ITT population. pCR (vs. non-pCR) after the 12-week study treatment (irrespective of study arm) was strongly associated with improved iDFS (5y DFS 98.5% vs. 82%, HR = 0.14, 95% CI 0.03-0.64). Of the 69 patients with pCR, 39 (56.5%) received no further CT (P+T arm: n = 9, 29% vs. (P+T+pac arm n = 30, 79%); only 1 distant relapse (1.4%) was observed in these patients. In the CT-free P+T arm, no pCR was observed in patients with low HER2 expression (IHC 1+/2+ and FISH positive) and/or basal-like subtype by PAM50 (n = 17, 19%). In the total study population, low HER2 expression and/or no early response was strongly associated with worse dDFS (p = .029) and iDFS (p = .068). No new safety signals were observed. **Conclusions:** For the first time, we have shown both excellent pCR and survival in patients treated by de-escalated neoadjuvant CT+P+T irrespective of further CT use in a prospective multicenter study. Investigation of CT-free regimens may need to be focussed on selected patients only (e.g. with high HER2 expression/non-basal-like tumors). In ADAPT HR-/HER2+, early pCR after only 12 weeks of neoadjuvant P+T+pac was strongly associated with improved outcome and may thus serve as a predictive clinical marker for further treatment (de)-escalation. Clinical trial information: NCT01779206. Research Sponsor: Roche, AOK.

504 **Oral Abstract Session**

Prognostic impact of recurrence score, endocrine response and clinical-pathological factors in high-risk luminal breast cancer: Results from the WSG-ADAPT HR+/HER2- chemotherapy trial. *First Author: Oleg Gluz, West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and University Hospital Cologne, Cologne, Germany*

Background: In HR+/HER2- N0-1 early BC, postmenopausal patients (pts) with RS™ > 25 and a substantial proportion of premenopausal pts seem to benefit from addition of adjuvant chemotherapy (CT) to endocrine therapy (ET). However, the magnitude of absolute benefit from this treatment intensification seems to depend on clinical-pathological and biological prognostic factors. For the first time, we present outcome from the CT part of the prospective phase III WSG-ADAPT HR+/HER- trial combining both static (RS in baseline core biopsy (CB) and dynamic (Ki67 response) biomarkers to optimize adjuvant therapy in luminal EBC. **Methods:** Pts with clinically high-risk HR+/HER2- EBC (cT2-4 OR clinically N+ OR G3 OR Ki67>15%) were initially treated by 3 (+/-1) weeks of standard ET (postmenopausal: mostly AI; premenopausal: TAM) before surgery or sequential CB. Pts with cN2-3 or G3/Ki67>40% were randomized directly to the CT trial. pN0-1 pts with RS0-11 OR RS12-25/ET-response (central $Ki67_{postendocrine}$<10%) received ET alone; the remaining high-risk cohort was randomized to the CT trial: (neo)adjuvant dose-dense CT (4xPaclitaxelà4xEC q2w vs. 8xNab-Paclitaxel q1wà4xEC q2w) followed by ET. Primary endpoint is efficacy comparison of CT schedules for survival; secondary endpoints reported here involve impacts of key prognostic factors on survival. Kaplan-Meier and Cox proportional hazard models were used to estimate survival curves and hazard ratios. For this analysis, subgroups free of selection bias by RS/ET-response were defined. **Results:** 5625 pts were screened and 4621 (ITT) entered the trial. After 4.9y median follow-up, higher baseline and post-endocrine Ki-67 levels were associated with poorer iDFS (both $p < 0.001$). In the CT cohort (n = 2331), higher RS, nodal status, and tumor size were generally associated with poorer iDFS. However, iDFS differed between N1 and N0 status only among younger pts (<50 years). In pts with >4 positive LN (n = 390), lower RS was associated with improved iDFS (RS0-11 vs RS > 25: $p_{log-rank}$= 0.016, 5y-iDFS 90% vs. 64%). In pts with RS > 25 (n = 965), low $Ki67_{postendocrine}$, N0 status, and c/pT1 status were associated with improved iDFS. In particular, ET-responders had higher 5y-iDFS (84%) than ET-non-responders (77%; $p_{log-rank}$= 0.040). Younger patients (<50 years old) with N0-1 RS 12-25/ ET-non-responders treated by CT had non-significantly poorer 5-year iDFS (89%) compared to those with ET-response treated by ET only (92%) ($p_{log-rank}$= 0.249). **Conclusion**: First results from the prospective high risk cohort from a large prospective phase III ADAPT trial provide evidence for good prognosis in some pts with >4 positive LN and e.g. low RS. Moreover combination of lower post-endocrine Ki-67 and limited tumor burden may be a promising criterion for CT de-escalation strategies even in patients with high RS. Clinical trial information: NCT01779206. Research Sponsor: Genomic Health (Exact Science), Celgene, Amgen, AOK.

505 **Oral Abstract Session**

Neoadjuvant talazoparib in patients with germline *BRCA1/2* (g*BRCA1/2*) mutation-positive, early HER2-negative breast cancer (BC): Results of a phase 2 study. *First Author: Jennifer Keating Litton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Talazoparib (TALA) is a poly(ADP-ribose) polymerase inhibitor approved as monotherapy for treating adult patients (pts) with g*BRCA1/2*-mutated HER2-negative locally advanced or metastatic BC. **Methods:** This phase 2, non-randomized, single-arm, open-label study (NCT03499353) evaluated the efficacy and safety of TALA in the neoadjuvant setting for pts with early g*BRCA1/2*-mutated HER2− BC. Primary endpoint was evaluation of pathologic complete response (pCR) as assessed by Independent Central Review (ICR) after completing 24 weeks of neoadjuvant TALA monotherapy 1 mg QD (0.75 mg for moderate renal impairment) followed by surgery. Secondary endpoints included pCR by investigator (INV) and residual cancer burden (RCB) by ICR (RCB: 0 [pCR], I [minimal], II [moderate], III [extensive]). The evaluable population included pts who received at least 80% of the TALA dose prescribed at treatment start and underwent breast surgery and pCR assessment, plus those who progressed before pCR could be assessed. The intent-to-treat (ITT) population included all pts who received at least 1 dose of TALA. **Results:** Of 61 pts treated with TALA (ITT and safety populations), 48 comprised the evaluable population. All pts had triple-negative BC. 60 pts had adenocarcinoma and 1 had squamous cell histology, with the following staging: I=20, II=27, III=14. Mean age was 44.6 years, mean duration of 4.5 wks since disease onset, mean duration of treatment of 23.3 wks, and mean overall relative dose intensity of 84.5% (ITT population). pCR (assessed by ICR and INV) and RCB (by ICR) for the evaluable and ITT populations are shown in the table below. Ten (16.4%) patients discontinued treatment due to progressive disease. One pt had a disruption of treatment as a result of COVID-19 restrictions, 2 pts for other reasons: to undergo surgery early and consent withdrawal; 9 patients received <80% dose. Treatment-emergent adverse events (AEs) were reported in 98.4% of pts (27.9% grade [G] 1, 23.0% G2, 45.9% G3, 1.6% G4); the most common were fatigue (78.7%; G1 54.1%; G2 21.3%; G3 3.3%), nausea (68.9%; G1 54.1%; G2 13.1%; G3 1.6%), and alopecia (57.4%; G1 54.1%; G2 3.3%). Three (4.9%) pts discontinued treatment due to AEs (G3 anemia [n=2] and G3 vertigo [n=1]) and continued on study. **Conclusions:** TALA monotherapy in the neoadjuvant setting was active and showed pCR rates comparable to those observed with combination anthracycline and taxane-based chemotherapy regimens and was generally well tolerated. Clinical trial information: NCT03499353. Research Sponsor: Pfizer.

	Evaluable population (N=48)	ITT population (N=61)
pCR by ICR, n (%) [95% CI]	22 (45.8) [32.0, 60.6]	30 (49.2) [36.7, 61.6]
pCR by INV, n (%) [95% CI]	22 (45.8) [32.0, 60.6]	29 (47.5) [35.0, 60.1]
RCB by ICR, n (%) [95% CI]		
RCB 0	22 (45.8) [30.0, 62.6]	30 (49.2) [34.0, 64.5]
RCB I	0	1 (1.6) [0.2, 12.1]
RCB II	15 (31.3) [18.0, 48.5]	17 (27.9) [16.1, 43.7]
RCB III	0	0
Missing	11 (22.9) [11.8, 39.8]	13 (21.3) [11.2, 36.7]

506 **Oral Abstract Session**

Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). *First Author: Sibylle Loibl, German Breast Group (GBG), Neu-Isenburg, Germany*

Background: The GeparNuevo trial investigated the addition of durvalumab, an anti-PD-L1 checkpoint inhibitor (CPI), to standard neoadjuvant chemotherapy (NACT) in patients with early TNBC. Durvalumab increased the pathological complete response (pCR) rate particularly in patients treated with durvalumab alone before start of chemotherapy (Loibl et al. Ann Oncol 2019). **Methods:** GeparNuevo randomized patients with cT1b-cT4a-d tumors and centrally confirmed TNBC to durvalumab (D) 1.5 g i.v. or placebo every 4 weeks. D/placebo monotherapy (0.75 g i.v.) was given for the first 2 weeks (window phase), followed by D/placebo plus nab-paclitaxel 125 mg/m^2 weekly for 12 weeks, followed by D/placebo plus epirubicin/cyclophosphamide (EC) q2 weeks for 4 cycles. Randomization was stratified by stromal tumor infiltrating lymphocytes (sTILs) (low (≤10%), intermediate (11-59%), high (≥60%)). The primary objective was pCR (ypT0 ypN0). Secondary time-to-event endpoints included invasive disease-free survival (iDFS), distant disease-free survival (DDFS) and overall survival (OS). **Results:** A total of 174 patients were enrolled between June 2016 and September 2017. The pCR rate with durvalumab was 53.4% versus placebo 44.2% (OR 1.45, 95% CI 0.80–2.63, unadjusted Wald p = 0.224). Durvalumab effect was seen only in the window cohort (pCR 61.0% versus 41.4%, OR 2.22, 95% CI 1.06–4.64, p = 0.035; interaction p = 0.048). After a median follow-up of 42.2 months, 34 events occurred in 174 patients. 3-year iDFS in pCR vs non pCR was 92.0% vs 71.9% (log-rank p = 0.002). 3-year iDFS was 84.9% with durvalumab vs 76.9% with placebo (HR 0.54, 95%CI 0.27-1.09, stratified log-rank p = 0.0559); 3-year DDFS 91.4% vs 79.5% (HR 0.37, 95%CI 0.15-0.87, p = 0.0148); 3-year OS 95.1% vs 83.1% (HR 0.26, 95%CI 0.09-0.79, p = 0.0076). No difference was seen in iDFS, DDFS and OS between the window and no window cohort. **Conclusions:** Durvalumab added to neoadjuvant chemotherapy in TNBC significantly improved long-term outcome despite a small pCR increase and no continuation after surgery. It needs to be questioned whether adjuvant therapy with CPI is needed at all. Clinical trial information: NCT02685059. Research Sponsor: GBG Forschungs GmbH, Pharmaceutical/Biotech Company.

507 **Poster Discussion Session**

Usefulness of assessment of circulating tumor DNA(ctDNA) of cerebrospinal fluid(CSF) samples for early detection of brain metastasis (BrM) in patients with triple-negative breast cancer (TNBC). *First Author: Lucrezia Raimondi, U.O.C. Territorial Oncology of Aprilia, Sapienza University of Rome, Aprilia, Italy*

Background: Despite improvements in treatments, patients diagnosed with TNBC still have poor prognosis for a higher tendency of developing BrM. Identifying patients at high risk of BrM, enabling to predict who will take advantage from appropriate additional treatment, remains a critical problem. ctDNA represents a valuable tool associated with the outcome and the aggressiveness of breast cancer but no prognostic and predictive biomarker has been identified to predict the development of BrM in TNBC. We studied the usefulness of assessment of CSF-ctDNA for early identification of the risk of BrM in TNBC. **Methods:** Between January 2016 and December 2020, 323 newly diagnosed non-metastatic TNBC patients who underwent neoadjuvant therapy+surgery(NACT) with complete response(CR)were prospectively enrolled. After surgery, samples of CSF measuring ctDNA were obtained from all patients: CSF-ctDNA was extracted with the QIAamp Circulating Nucleic Acid Kit (Qiagen, Valencia, CA, USA) and ctDNA levels were measured. Survival curves were estimated using the Kaplan-Meier method and compared with the Log-rank test. Multivariate Cox regression was used to identify the risk of mortality at three years. **Results:** After NACT, CSF-ctDNA was detectable in 126/323 (39%) patients, 101/126 (80%) were diagnosed at III stage. 124 of 126 (98.4%) ctDNA+ patients subsequently developed BrM. In contrast, only 2 (2/197, 1%) ctDNA- patients subsequently developed BrM and the 195 other patients remain in a CR ($p < 0.001$, Fisher's exact test). CSF-ctDNA did associate with PFS and OS: undetectable ctDNA was associated with superior PFS (HR 0.3; p = 0.002) and OS (HR 0.2; $p < 0.01$), indicating survival is largely determined by the onset of BrM. With a median follow-up of 3 years, median PFS of ctDNA+ vs ctDNA- patients was 13 months vs not reach, p = 0.004 (by Log-rank test). Median OS for ctDNA+ vs ctDNA- patients was 16 months after NACT vs not reach, p = 0.0016 (by Log-rank test). At multivariate analysis detectable CSF-ctDNA emerged as the best predictor of the develop of BrM and 24-month mortality (HR:3.62; $p < 0.0001$). Age, stage, Ki67% and response to chemotherapy were not significantly associated with the prognosis. **Conclusions**: After NACT, detectable CSF-ctDNA significantly associates with PFS and OS, identifying early at-risk patients to develop BrM in TNBC. Research Sponsor: None.

508 **Oral Abstract Session**

Evaluation of intra-tumoral (IT) SD-101 and pembrolizumab (Pb) in combination with paclitaxel (P) followed by AC in high-risk HER2-negative (HER2-) stage II/III breast cancer: Results from the I-SPY 2 trial. *First Author: Amy Jo Chien, University of California, San Francisco, San Francisco, CA*

Background: I-SPY 2 is a multicenter, phase 2 trial using response-adaptive randomization within molecular subtypes defined by receptor status and MammaPrint (MP) risk to evaluate novel agents as neoadjuvant therapy for women with high-risk breast cancer. SD-101 is an investigational Toll-like receptor 9 (TLR9) agonist CpG-C class oligodeoxynucleotide that stimulates the production of IFN-α and interleukin (IL)-12, functional maturation of plasmacytoid dendritic cells, and production of cytotoxic antibodies. IT SD-101 was combined with systemic anti-PD-1 antibody Pb to investigate the antitumor and immunologic activity of this novel immunotherapeutic strategy. **Methods:** Women with tumors $\geq$ 2.5cm were eligible for screening. Only pts (pts) with HER2- disease were eligible for this treatment. Treatment included weekly P x 12 in combination with IT SD-101 2 mg/ml (1 ml for T2 tumors, 2 ml for >T3 tumors) weekly x 4, then q3 weeks x 2, and IV Pb q3 weeks x 4, followed by doxorubicin/cyclophosphamide (AC) q2-3 weeks x 4 (SD-101+Pembro 4). Pts in the control arm received weekly P x 12 followed by AC q2-3 weeks x 4. The I-SPY 2 methods have been previously published. This investigational arm was eligible for graduation (>85% chance of success in a 300-person phase 3 neoadjuvant trial) in 3 of 10 pre-defined signatures: HER2-, hormone receptor (HR)+/HER2- and HR-/HER2-. **Results:** 75 pts were randomized and evaluable in SD-101+Pembro 4 treatment arm. The control arm included 329 historical controls enrolled since April 2010. The study arm was stopped due to maximal patient accrual. Pt characteristics were balanced; 56% HR+, 44% HR-. The probability that SD-101+Pembro4 was superior to control exceeded 97% for all eligible tumor signatures, but did not reach the threshold for graduation in any of the signatures. However, it is notable that the rate of pCR/Residual Cancer Burden 1 (RCB1) in the HR+/HER2- signature was 51%. Preliminary safety events for SD-101+Pembro 4 include increased rates of fever, neutropenia, febrile neutropenia, transaminitis, and immune-related events, including adrenal insufficiency. **Conclusions:** The SD-101+Pembro 4 regimen was active but did not meet the pre-specified threshold for graduation in I-SPY 2. pCR/RCB 1 analysis suggests improved response in the HR+/HER-negative signature compared to control. The clinical significance of these findings needs to be weighed against the potential risk of immune-related toxicities. Clinical trial information: NCT01042379. Research Sponsor: Quantum Leap Healthcare Collaborative.

	Estimated pCR rate (95% prob interval)			
Signature	SD-101+Pembro 4	Control	Probability SD-101+Pembro 4 Superior to Control	Predictive Probability of Success in Phase 3
HER2–	0.34 (0.24-0.44) N= 75	0.20 (0.16-0.24) N= 329	0.99	0.72
HR-/HER2-	0.44 (0.28-0.60) N=29	0.28 (0.21-0.34) N=147	0.97	0.71
HR+/HER2-	0.26 (0.14-0.37) N=46	0.14 (0.09-0.18) N=182	0.99	0.68

509 **Poster Discussion Session**

Lisinopril or carvedilol in prevention of trastuzumab-induced cardiotoxicity in patients with HER2-positive early stage breast cancer: Longitudinal changes of left ventricular ejection fraction below normal levels (LVEF <50%). *First Author: Pamela N. Munster, University of California San Francisco, San Francisco, CA*

Background: Treatment of HER2-positive breast cancer patients with trastuzumab is highly effective. However, a trastuzumab-associated decline in the left ventricular ejection fraction (LVEF) and clinical heart failure often prompt interruption and discontinuation of treatment. We therefore evaluated the preventive impact of an ACE inhibitor or beta blockers on the left ventricular ejection fraction (LVEF) during treatment of trastuzumab and chemotherapy. **Methods:** In a prospective randomized study, women with early stage HER2 positive breast cancer undergoing (neo)adjuvant chemotherapy with trastuzumab were randomized to receive either once daily lisinopril (10mg), carvedilol (10mg) or placebo during treatment with trastuzumab and further stratified by anthracycline use (AC+T versus nonAC+T). In a follow up to the initially presented primary endpoint of overall cardiotoxicity, we measured the protective effects of lisinopril or carvedilol to prevent a trastuzumab induced LVEF decrease to less than 50% over the course of therapy as well as the impact on LVEF decrease by >10% within normal LVEF levels. **Results:** A total of 468 women (mean age was 51±10.7 years) with HER2 overexpressing early-stage breast cancer from 127 community-based oncology practices were enrolled, a prespecified minimum target of 189 (40%) patients were treated with AC+T and 279 (60%) with nonAC+T. Baseline cardiac risk factors of this study population included obesity and an elevated blood pressure. Patients in the anthracycline group were younger and without hypertension. A small, not clinically relevant decrease in LVEF was observed during trastuzumab therapy in all patients which was not significantly altered by any of the cardiac interventions. The rate of LVEF decline to <50% was much more frequent in patients treated with an anthracycline than those with a non-anthracycline containing regimen (21% vs 4.1%). Treatment with lisinopril averted the decline in LVEF in the AC+T group compared to placebo (10.8% vs 30.5%, p=0.045). A smaller but not significant effect was seen by carvedilol. The incidence of cardiotoxicity manifesting as LVEF decrease by $\geq$10% within the normal range was similar in both AC+T and the nonAC+T arms, and not affected by either lisinopril or carvedilol. **Conclusions:** In patients treated with trastuzumab without anthracyclines, the impact of trastuzumab on LVEF is small and infrequent. In contrast, patients treated with anthracyclines prior to trastuzumab, demonstrated a decrease in LVEF to below normal levels in a larger than previously reported number of women in this community based setting. The trastuzumab-anthracycline induced decline in LVEF could be prevented with concurrent treatment with lisinopril, which was tolerable even in patients without hypertension. Clinical trial information: NCT01009918. Research Sponsor: U.S. National Institutes of Health.

510 **Poster Discussion Session**

Cardiac safety of dual anti-HER2 blockade with pertuzumab plus trastuzumab (P+T) in the APHINITY trial. *First Author: Evandro de Azambuja, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B), Brussels, Belgium*

Background: Trastuzumab (T) increases the incidence of cardiac events (CEs) in patients (pts) with early breast cancer (BC). Dual blockade with P+T improves BC outcomes and is the standard of care for high-risk HER2-positive BC pts following the phase 3 APHINITY trial that evaluated the addition of P or placebo (Pla) to T and chemotherapy (CT). We analyzed the cardiac safety of P+T in APHINITY. **Methods:** APHINITY eligibility required a left ventricular ejection fraction (LVEF) $\geq$55% at study entry. LVEF assessment was performed every 3 months (mos) during treatment, every 6 mos up to month 36, and yearly thereafter. Primary CE was defined as heart failure (HF) class III/IV and a significant decrease in LVEF of at least 10 percentage points from baseline and to <50%, or cardiac death. Secondary CE was defined as a confirmed significant decrease in LVEF or CEs confirmed by the cardiac advisory board. **Results:** The safety analysis population consists of 4,769 pts. With 74 mos median follow-up (FU), CEs were observed in 159 pts (3.3%): 83 (3.5%) in the P+T and 76 (3.2%) in Pla+T arms, respectively. Most CEs occurred during anti-HER2 therapy: 123/159 (77.4%) and were asymptomatic or mildly symptomatic LVEF decrease (133/159; 83.6%) (Table 1). There were 2 cardiac deaths in each arm (0.1%). More CEs occurred in pts receiving an anthracycline-based CT compared to those receiving non-anthracycline CT (139 vs. 20 CEs, respectively). Acute recovery from a CE based on subsequent LVEF values was observed in 127/155 pts (81.9%). **Conclusions:** Dual blockade with P+T does not increase the risk of CE compared to Pla+T alone. The use of anthracycline-based CT increases the risk of a CE; hence non-anthracycline CT may be considered particularly in pts with other cardiovascular risk factors. Clinical trial information: NCT01358877. Research Sponsor: Roche/Genentech.

Incidence of cardiac events by time period.

CEs, type and timing	All patients N=4769 n (%)	P+T N=2364 n (%)	Pla+T N=2405 n (%)
Any cardiac event	159 (3.3)	83 (3.5)	76 (3.2)
Did not start anti-HER2 therapy	4 (0.1)	0 (0.0)	4 (0.2)
During anti-HER2 therapy	123 (2.6)	62 (2.6)	61 (2.5)
During FU	32 (0.7)	21 (0.9)	11 (0.5)
Time to first CE (mos) - median (range)	8.4 (0.4-61.3)	9.2 (2.3-61.3)	7.4 (0.4-53.7)
Cardiac deaths	4 (0.1)	2 (0.1)	2 (0.1)
During FU	4 (0.1)	2 (0.1)	2 (0.1)
Time to cardiac death (mos) - median (range)	30.2 (14.9-53.7)	29.4 (14.9-43.9)	35.1 (16.4-53.7)
HF class III or IV	22 (0.5)	16 (0.7)	6 (0.2)
Did not start anti-HER2 therapy	1 (0.0)	0 (0.0)	1 (0.0)
During anti-HER2 therapy	14 (0.3)	10 (0.4)	4 (0.2)
During FU	7 (0.1)	6 (0.3)	1 (0.0)
Time to HF class III or IV (mos) - median (range)	7.7 (0.4-61.3)	8.5 (4.8-61.3)	4.6 (0.4-15.8)
Asymptomatic or mildly symptomatic LVEF decrease	133 (2.8)	65 (2.7)	68 (2.8)
Did not start anti-HER2 therapy	3 (0.1)	0 (0.0)	3 (0.1)
During anti-HER2 therapy	109 (2.3)	52 (2.2)	57 (2.4)
During FU	21 (0.4)	13 (0.5)	8 (0.3)
Time to asymptomatic or mildly symptomatic LVEF decrease (mos) - median (range)	8.4 (1.9-49.9)	9.2 (2.3-49.9)	7.5 (1.9-38.2)

512 **Poster Discussion Session**

Discovery and validation of a genomic signature to identify women with early-stage invasive breast cancer who may safely omit adjuvant radiotherapy after breast-conserving surgery. *First Author: Martin Sjöström, University of California, San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Adjuvant radiotherapy (RT) is currently the standard of care for women with early-stage invasive breast cancer (BC) treated with breast conserving surgery (BCS). However, some women may have very low risk of recurrence and could safely be spared RT. This study aimed to identify these women using a molecularly-based approach. **Methods:** We performed an analysis of the SweBCG91-RT cohort, a trial randomizing women with node-negative stage I-II invasive BC +/- RT following breast conserving surgery, with sparse use of adjuvant systemic therapy. Only patients with ER+, HER2- tumors, and not treated with adjuvant systemic therapy, were included in this analysis. Transcriptome-wide profiling of tumors was performed using the Affymetrix Human Exon 1.0 ST microarray. The SweBCG91-RT cohort was divided into a training cohort of 243 patients and a validation cohort of 354 patients. Biological gene sets and individual genes related to locoregional recurrence in patients not receiving RT of the training set were identified, and a 16-gene signature was trained using elastic net regression. The signature, named Profile for the Omission of Local Adjuvant Radiation (POLAR), was locked prior to validation. **Results:** In the validation cohort, POLAR was prognostic for locoregional recurrence (LRR) in patients not treated with RT (multivariable Cox model adjusting for age, grade, tumor size, and luminal A vs luminal B: HR = 1.7 [1.2,2.3], p < 0.001). Patients categorized as POLAR low-risk had a 10-year locoregional recurrence rate of 7% in the absence of RT. Notably, there was no significant benefit from RT for these POLAR low-risk patients (HR = 1.1 [0.38,3.3], p = 0.83), whereas patients categorized as POLAR high-risk had a significant decreased risk of locoregional recurrence when treated with RT (recurrence rate without RT at 10-years 19%, HR = 0.43 [0.24,0.78], p = 0.0053). **Conclusions:** These data suggest that the novel POLAR genomic signature based on LRR biology can not only identify patients who have a low risk of LRR without adjuvant RT after BCS but who also would not benefit from RT, thus being prime candidates for RT omission. Research Sponsor: PFS Genomics, Other Foundation, Other Government Agency.

513 **Poster Discussion Session**

A novel biosignature identifies DCIS patients with a poor biologic subtype with an unacceptably high rate of local recurrence after breast conserving surgery and radiotherapy. *First Author: Frank Vicini, NRG Oncology, and 21st Century Oncology, Pontiac, MI*

Background: There is an unmet need to identify women diagnosed with DCIS who have a low recurrence risk and could omit radiotherapy (RT) after breast conserving surgery (BCS), or an elevated recurrence risk after treatment with BCS plus RT. DCISionRT and its response subtype (Rst) biosignature were evaluated in a contemporary cohort treated with BCS with or without RT to identify these risk groups. **Methods:** Pathology, clinical data, and FFPE tissue samples were evaluable for 485 women diagnosed with DCIS at centers in Sweden (1996-2004), the USA (1999-2008), and Australia (2006-2011). Patients were treated with BCS (negative margins) with or without whole breast RT. Ipsilateral breast tumor recurrence (IBTR) included DCIS or invasive breast cancer (IBC) that was local, regional, or metastatic. The patients were classified into Low and Elevated risk groups to assess IBTR and IBC rates. Patients in the Elevated risk group were categorized by two subtypes: a good response subtype (good Rst) or a poor response subtype (poor Rst) after BCS plus RT. Biosignatures were calculated using biomarkers (p16/INK4A, Ki-67, COX-2, PgR, HER2, FOXA1, SIAH2) assayed using IHC on FFPE tissue. Hazard ratios and 10-year risks were calculated using Cox proportional hazards (CPH) and Kaplan-Meier analyses. **Results:** In the DCISionRT Elevated risk group, RT was associated with significantly reduced recurrence rates, but only for those patients with a good Rst (Table, IBTR HR=0.18, p<0.001, IBC HR=0.15, p=0.003, n=241). For Elevated risk group patients with a poor Rst, no benefit to RT was noted (Table). Additionally, irrespective of RT, patients with a poor Rst had 10-year IBTR/IBC rates of 25%/16%, which were much higher than good Rst rates of 6.6%/4.5% (IBE HR=3.6, p=0.02, IBC HR=4.4, p=0.04, n=190). For patients in the Low risk group, there was no significant difference in 10-year IBTR/IBC rates with and without RT (Table, IBTR p=0.4, IBC p=0.9, n=177). The distribution of clinicopathologic risk factors (age <50 years, grade 3, size >2.5 cm) did not identify poor vs. good response subtypes, and multivariable analysis (n=485) indicated these traditional clinicopathologic factors and endocrine therapy were not significantly associated with IBTR (p≥0.22) or IBC (p≥0.34). **Conclusions:** Biosignatures identified a Low risk patient group with low 10-year recurrence rates with or without RT who may be candidates for omitting adjuvant RT. Biosignatures also identified an Elevated risk group receiving BCS plus RT with a poor response subtype that had unacceptably high recurrence rates, warranting potential intensified or alternate therapy. Research Sponsor: PreludeDx.

	Low Risk Group			Elevated Risk Group	
	n	%10-year Rate IBTR/IBC		n	%10-year Rate IBTR/IBC
BCS without RT	91	4.1/2.9	BCS without RT, all	118	29/18
BCS plus RT	86	6.3/2.7	BCS plus RT; good Rst	141	6.6/4.5
			BCS plus RT; poor Rst	49	25/16

514 **Poster Session**

Long-term results of simplified lymphatic microsurgical preventing healing approach (SLYMPHA) for the prevention of breast cancer-related clinical lymphedema after axillary lymph node dissection. *First Author: Tolga Ozmen, University of Miami, Miller School of Medicine, Division of Surgical Oncology, Miami, FL*

Background: Lymphedema (LE) is a serious complication of axillary lymph node dissection (ALND) with an incidence rate of 16%. SLYMPHA is a safe and relatively simple method, which decreases incidence of LE dramatically. Our initial study showed an 88% decrease in clinical LE rate after a median follow up of 15 months. The aim of this study was to confirm these results after a longer follow up period. **Methods:** All patients, undergoing ALND between January 2014 and November 2020 were included in the study. During follow-up visits, tape-measuring limb circumference method was used to detect clinical LE. The incidence of clinical LE was compared between patients with and without SLYMPHA. Univariate and multivariate analysis were used to assess the role of other factors in the appearance of clinical LE. **Results:** 580 patients were included in the study. 35% of cohort underwent SLYMPHA. Mean follow-up time was 44 ±31.9 months. Patients, who underwent SLYMPHA, had a significantly lower LE rate (10% vs 26%; p=0.002; OR 0.4 [0.31-0.77]). Diabetes and removing ^{3}22 lymph nodes also correlated with increased LE however this effect disappeared on multivariate analysis. **Conclusions:** SLYMPHA is a safe and relatively simple method, which continued its efficacy after 4-years follow up. It should be considered as an adjunct procedure to ALND for all patients during initial surgery. Research Sponsor: None.

Comparison of factors affecting lymphedema.

		No Lymphedema	Lymphedema	p (univariate)	p (multivariate)
Age		52.9 ± 11	53.2 ± 12	0.85	
Diabetes	No	290 (81)	70 (19)	0.035 OR 1.7 [1.04-2.85]	0.055
	Yes	70 (71)	29 (29)		
>= 22 Lymph nodes removed	No	333 (81)	80 (19)	0.038 OR 1.57 [1.02-2.4]	0.074
	Yes	114 (73)	43 (27)		
Radiotherapy	No	93 (82)	20 (18)	0.23	
	Yes	354 (77)	105 (23)		
SLYMPHA	No	277 (74)	98 (26)	0.002 OR 0.4 [0.31-0.77]	0.001
	Yes	174 (90)	30 (10)		

Categorical values reported as n(%). Continues values reported as mean ±SD.

515 **Poster Discussion Session**

Outcome of breast cancer patients treated with chemotherapy during pregnancy compared with non-pregnant controls. *First Author: Frederic Amant, University Hospitals Leuven, Leuven, Belgium*

Background: Overall a diagnosis of breast cancer during pregnancy (BCP) appears not to impact maternal prognosis if standard treatment is offered. However, caution is warranted as gestational changes in pharmacokinetics with respect to the distribution, metabolism and excretion of drugs may lead to reduced chemotherapy concentration in pregnant patients. This cohort study was designed to focus on the maternal prognosis of BCP patients that receive chemotherapy during pregnancy. **Methods:** The outcome of BCP patients treated with chemotherapy during pregnancy was compared to non-pregnant breast cancer patients treated with chemotherapy, diagnosed after 2000, excluding postpartum diagnosis and with an age limit of 45 years. The data was registered by two multicentric registries (the International Network of Cancer, Infertility and Pregnancy and the German Breast Cancer Group) that collect both retro-and prospectively breast cancer data. Cox proportional hazards regression was used to compare disease-free (DFS) and overall survival (OS) between both groups, adjusting for age, stage, grade, hormone receptor status, human epidermal growth factor 2 status and histology, weighted by propensity scoring in order to account for the differences in baseline characteristics between pregnant patients and controls. **Results:** In total, 662 pregnant and 2081 non-pregnant patients, were eligible for analysis. Median age at diagnosis was 34 (range 22-47) years for pregnant and 38 (range 19-45) years for non-pregnant patients. Pregnant patients were more likely to have stage II breast cancer (60.1% vs 56.1%, p = 0.035), grade 3 tumors (74.0% vs 62.2%, p < 0.001), hormone receptor-negative tumors (48.4% vs 34.0%, p < 0.001) or triple-negative breast cancer (38.9% vs 26.9%, p < 0.001). Median follow-up was 66 months. DFS and OS were comparable for pregnant and non-pregnant patients (DFS: HR 1.02, 95%CI 0.82-1.27, p = 0.83; OS: HR 1.08, 95% CI 0.81-1.45, p = 0.59). A subgroup analysis of 339 women that received more than 60% of chemotherapy during pregnancy (cut-off at median) revealed a comparable survival compared to non-pregnant women (DFS: HR 0.81, 95%CI 0.62-1.06, p = 0.13; OS: HR 0.85 95% CI 0.58-1.23, p = 0.39). **Conclusions:** Pregnancy-induced alternations in chemotherapy concentration do not seem to affect maternal prognosis in breast cancer patients. These results support initiation of chemotherapy for BCP where indicated for oncological reasons. Research Sponsor: European Research Council, Research foundation Flanders, Kom op tegen kanker.

516 **Poster Discussion Session**

Final analysis of the PROMISE-GIM6 phase III trial assessing GnRH agonist use during chemotherapy as a strategy to preserve ovarian function in premenopausal patients with early breast cancer. *First Author: Matteo Lambertini, U.O. Clinica di Oncologia Medica, IRCCS Ospedale Policlinico San Martino, Department of Internal Medicine and Medical Specialties (DiMI), University of Genova, Genoa, Italy*

Background: Current guidelines recommend GnRH agonist (GnRHa) use during chemotherapy (CT) as a strategy to reduce the risk of premature ovarian insufficiency (POI) in premenopausal patients with early breast cancer (EBC). However, no long-term safety data are available raising some concerns on concurrent use of GnRHa during CT in patients with hormone receptor-positive disease. In addition, there is no evidence on the protective role of this strategy in patients with germline *BRCA* mutations (*mBRCA*). Here, we report the final analysis of the PROMISE-GIM6 phase III randomized study, the largest trial addressing the role of GnRHa use during CT in premenopausal EBC patients (Del Mastro et al, JAMA 2011 & Lambertini et al, JAMA 2015). **Methods:** From October 2003 to January 2008, 281 premenopausal patients aged 18 to 45 years with stage I-III EBC candidates for (neo)-adjuvant CT were randomized to receive CT alone or combined with the GnRHa triptorelin. Primary endpoint was incidence of CT-induced POI (defined as amenorrhea and post-menopausal FSH/estradiol levels 1 year following CT). This final analysis reports on post-treatment pregnancies, disease-free survival (DFS) and overall survival (OS). An exploratory descriptive analysis in *mBRCA* patients is also reported. (ClinicalTrial.gov: NCT00311636) **Results:** Of the 281 randomized patients (CT+GnRHa arm = 148; CT alone arm = 133), 80% had hormone receptor-positive disease. At the time of this final analysis, 38 (13.5%) patients were lost to follow-up. Median follow-up was 12.4 years (IQR: 11.3-13.2 years). In the CT+GnRHa and CT alone arms, respectively, 9 (10-year cumulative incidence of pregnancy 6.5%, 95% CI 3.5%-12.3%) and 4 (10-year cumulative incidence of pregnancy 3.2%, 95% CI 1.2%-8.3%) patients had a post-treatment pregnancy (HR 2.14, 95% CI 0.66-6.92). No differences in 10-year DFS (72.4% in CT+GnRHa arm vs. 71.2% in CT alone arm: HR 1.16, 95% CI 0.76-1.77) nor in 10-year OS (82.0% in CT+GnRHa arm vs. 85.9% in CT alone arm: HR 1.17, 95% CI 0.67-2.03) were observed. There was no interaction between treatment effect and hormone receptor status. In patients with hormone receptor-positive disease, HR was 1.02 (95% CI 0.63-1.63) for DFS and 1.12 (95% CI 0.59-2.11) for OS. Out of 43 patients tested for *BRCA*, overall incidence of POI, irrespective of treatment arm, was 20% in *mBRCA* patients (n = 10) and 12% in patients without *mBRCA* (n = 33). In *mBRCA* patients, incidence of POI was 0% and 33% in the CT+GnRHa and CT alone arms, respectively. One post-treatment pregnancy was described in a patient with *mBRCA1* in the CT alone arm. **Conclusions:** The final analysis of the PROMISE-GIM6 trial at a median follow-up of 12.4 years provides reassuring evidence on the safety of GnRHa use during CT as a strategy to preserve ovarian function in premenopausal patients with hormone receptor-positive EBC. Clinical trial information: NCT00311636. Research Sponsor: AIRC - Italian Association for Cancer Research.

517 **Poster Discussion Session**

Abemaciclib combined with adjuvant endocrine therapy in patients with high risk early breast cancer who received neoadjuvant chemotherapy (NAC). *First Author: Miguel Martin, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Background: monarchE, a phase 3, open-label, randomized study evaluating abemaciclib combined with adjuvant endocrine therapy (ET) compared to ET alone in patients with HR+, HER2-, high risk early breast cancer (EBC), resulted in a statistically significant improvement in invasive disease-free survival (IDFS) (HR = 0.713; 95% CI: 0.583, 0.871). NAC is used in patients with HR+, HER2- EBC at higher risk of recurrence despite often limited response, suggesting a need for enhanced adjuvant ET. **Methods:** Patients with ≥4 positive notes (LNS), or 1-3 LNS and either Grade 3 disease, tumor size ≥5 cm, or central Ki-67 ≥20% were eligible. Prior chemotherapy (NAC, adjuvant, none) was one of the stratifications factors. Prior therapy and tumor characteristics prior to study entry were collected. Here, we present the results of the prespecified subgroup of patients who received NAC. **Results:** Out of 5,637 randomized patients, 2056 (36.5%) received NAC. For 84.8%, the chosen regimen included anthracycline + cyclophosphamide + taxane, for 4.4%, it included anthracycline + taxane. A total of 1044 (50.8%) patients who received NAC had a radiologic tumor size between 2-5 cm and 599 (29.1%) had tumors ≥5 cm at diagnosis. 6.2%, 49.4% and 36.7% of patients had tumors with histologic Grade 1, 2, 3 respectively. 55.2% of patients had LNS ≥4+ and 44.4% had 1-3+ LNS. Central Ki-67 prior to NAC was ≥20% in 64.8% of patients with available Ki-67 results (664 (32.3%) patients had missing Ki-67 results). Evaluation of clinical and pathological measures of response will be presented. A multivariate cox regression analysis of IDFS in the intent-to-treat (ITT) population, identified prior chemotherapy as prognostic, suggesting patients who received NAC were at risk of a worse outcome. Primary outcome efficacy data for patients who received NAC are shown in the table below. Abemaciclib + ET demonstrated treatment benefit in terms of IDFS vs ET alone (HR: 0.614 95% CI: 0.473, 0.797) with 2-year IDFS rates of 87.2% vs 80.6%, respectively. The addition of abemaciclib to ET resulted in an improvement in distant relapse-free survival (DRFS) (HR: 0.609, 95% CI: 0.459, 0.809), with 2-year DRFS rates of 89.5% and 82.8%, respectively. Safety profile was similar to the overall safety population. **Conclusions:** Patients with HR+, HER2- EBC who received NAC were noted to be at a higher risk of recurrence. In this subgroup, abemaciclib combined with ET demonstrated a clinically meaningful treatment benefit in IDFS and DRFS, which was numerically greater than in the ITT population. Safety data were consistent with abemaciclib safety profile. Clinical trial information: NCT03155997. Research Sponsor: Eli Lilly and Company.

Efficacy data.

		NAC Abemaciclib + ET N=1025	NAC ET Alone N=1031
IDFS	Events (n)	92	148
	HR (95% CI)	0.614 (0.473, 0.797)	
	2-year rate % (95% CI)	87.2 (84.1, 89.8)	80.6 (77.0, 83.6)
DRFS	Events (n)	77	125
	HR (95% CI)	0.609 (0.459, 0.809)	
	2-year rate % (95% CI)	89.5 (86.7, 91.8)	82.8 (79.3, 85.8)

518 **Poster Discussion Session**

Palbociclib combined with endocrine treatment in breast cancer patients with high relapse risk after neoadjuvant chemotherapy: Subgroup analyses of premenopausal patients in PENELOPE-B. *First Author: Frederik Marmé, Medical Faculty Mannheim, Heidelberg University, University Hospital Mannheim, Mannheim, Germany*

Background: PENELOPE-B assessed efficacy of the CDK4/6 inhibitor 1-year palbociclib versus placebo added to endocrine therapy (ET) as post-neoadjuvant treatment in a high-risk breast cancer population. Palbociclib did not improve invasive disease-free survival (iDFS) compared to placebo (3-year iDFS 81.3% vs 77.7%) (Loibl et al. J Clin Oncol 2021). Here we report results from the subpopulation of premenopausal women. **Methods:** Patients with hormone receptor positive, HER2-negative breast cancer without pathological complete response after taxane-containing neoadjuvant chemotherapy and at high risk of relapse (CPS-EG score ≥3 or 2 and ypN+) were randomized (1:1) to receive 13 cycles of palbociclib 125mg daily or placebo on days 1-21 in a 28d cycle in addition to standard endocrine treatment including tamoxifen (TAM) +/- gonadotropin-releasing hormone analogue (GnRH) and aromatase inhibitor (AI) +/- GnRH. Randomization was stratified by nodal status at surgery, age (< 50 vs ≥50 years), Ki-67, region, and CPS-EG score. **Results:** 616/1250 patients were premenopausal at the time of enrollment, 185 of these patients (30.0%) were younger than 40 years of age. 95.2% had ypN+ after surgery; 42.8% had ypT2 and 46.8% a CPS-EG score of 3. 23.1% of the premenopausal women had a Ki67 of > 15% in residual disease. 66.1% started with TAM alone; 19.3% with TAM and ovarian function suppression (OFS); and 13.6% received an AI+OFS. There was no difference in iDFS between palbociclib and placebo in the premenopausal women HR 0.948 (0.693-1.30). The 3-year iDFS was 80.6% and 78.3%, respectively. Palbociclib vs placebo in subgroups by endocrine treatment: TAM alone HR 1.05 (0.715-1.53) p = 0.817; TAM+GnRH HR 0.52 (0.267-1.02) p = 0.057 and AI+GnRH HR 1.58 (0.548-4.56) p = 0.397; $p_{interaction}$0.124. Hematologic toxicity was significantly more common with palbociclib. Non-hematological toxicity any grade palbociclib vs placebo were: fatigue 67.4% vs 51.3%; hot flushes 52.2% vs 54.8%; bone pain 15.6% vs 16.6%; and vaginal dryness 11.0% vs 11.5%. When receiving palbociclib fewer patients in the AI+GnRH group vs the TAM +/- GnRH cohort experienced anemia (54.1% vs 80.5%) and thrombocytopenia (37.8% vs 65.1%). Fatigue (75.7% vs 66.3%) and nausea (40.5% vs 24.9%) were more common with AI+GnRH than TAM +/-GnRH when palbociclib was added. Thromboembolic events were low with overall 9 events (4 vs 5; AI+GnRH 2.4% vs 1.3% TAM+/-GnRH). **Conclusions:** The addition of palbociclib to endocrine therapy did not improve iDFS in premenopausal women. These are the first safety results from a phase III study for the combination tamoxifen +/-GnRH and palbociclib. The addition of palbociclib to tamoxifen +/-GnRH in premenopausal women did not increase side effects compared to AI+GnRH and seems to be an alternative to AI+GnRH. Clinical trial information: NCT01864746. Research Sponsor: Pfizer.

519 **Poster Discussion Session**

Subgroup of post-neoadjuvant luminal-B tumors assessed by HTG in PENELOPE-B investigating palbociclib in high risk HER2-/HR+ breast cancer with residual disease. *First Author: Carsten Denkert, Institute of Pathology, Philipps-University Marburg and University Hospital Marburg, Marburg, Germany*

Background: About one third of patients with hormone-receptor-positive (HR+), HER2-primary breast cancer with residual invasive disease after neoadjuvant chemotherapy will relapse despite adjuvant endocrine therapy. Therapeutic inhibition of cyclin-dependent kinase 4 and 6 (CDK 4/6) by palbociclib combined with endocrine therapy demonstrated highly relevant efficacy in metastatic breast cancer. The phase III PENELOPE-B (NCT01864746) study did not show a significant benefit from palbociclib in women with centrally confirmed HR+, HER2- primary breast cancer without a pathological complete response after taxane-containing neoadjuvant chemotherapy and at high-risk of relapse (CPS-EG score ≥3 or 2 and ypN+) for the primary endpoint (Loibl et al. JCO 2021). **Methods:** After completion of neoadjuvant chemotherapy and locoregional therapy, PENELOPE-B patients were randomized (1:1) to receive 13 cycles (1 year) of palbociclib 125mg daily or placebo on days 1-21 in a 28d cycle in addition to standard endocrine therapy. Analysis of the primary endpoint of invasive disease-free survival (iDFS) was planned after 290 events. Secondary objective included iDFS in luminal-B group by treatment. Gene expression in post-neoadjuvant surgical residual tumor tissue samples was profiled using the HTG EdgeSeq Oncology Biomarker Panel targeting 2559 genes (HTG Molecular Diagnostics Inc.). Based on 91 genes of this panel the AIMS subtype (Paquet & Hallett, JNCI 2014) was calculated. **Results:** Gene expressions were measured in tumors from 906 of 1250 (72%) PENELOPE-B patients; 663 had LumA subtype, 64 LumB, 135 NormL, 16 BasalL, and 28 HER2E. Compared to LumA the LumB patients were older, had higher post-neoadjuvant Ki-67, higher risk status (CPS-EG), and higher grade; no significant correlation was found for the region of participating sites, cT, ypT, and ypN. Patients with LumB tumors had an estimated 3-year iDFS of 71.9% with palbociclib vs 44.8% with placebo HR = 0.50 (0.24-1.05); outcome was similar in patients with LumA tumors (3-year iDFS 83.9% vs 79.5%, HR = 0.93 (0.68-1.28), interaction p = 0.132); this was confirmed in multivariable analyses. Ki-67 by IHC and proliferation biomarkers from the HTG panel also showed no significant interaction with treatment. **Conclusions:** PENELOPE-B did not show a benefit from the addition of 1 year palbociclib to endocrine therapy compared to placebo in the total enrolled high-risk primary breast cancer population. However, the small group of luminal-B tumors (n = 64) derived benefit from palbociclib, although without a statistically significant interaction. Further investigation is required in a larger cohort to validate a palbociclib benefit that might be confined to this group. Research Sponsor: Pfizer.

520 **Poster Discussion Session**

Inflammatory cytokines and distant recurrence in HER2-negative early breast cancer in the ECOG-ACRIN 5103 trial. *First Author: Joseph A. Sparano, Montefiore Medical Center/Albert Einstein College of Medicine/ Albert Einstein Cancer Center, Bronx, NY*

Background: Systemic inflammation may contribute to cancer progression (PMC2803035), including recurrence of early breast cancer (PMC4828958). We hypothesized that inflammatory cytokines and/or chemokines may be associated with distant recurrence (DR). **Methods:** We performed a case:control study in women with stage II-III Her2-negative breast cancer, all of whom had surgery and adjuvant chemotherapy (doxorubicin/cyclophosphamide, then weekly paclitaxel) with/without bevacizumab, plus endocrine therapy if ER-positive (PMC6118403). Propensity score matching was used to identify approximately 250 case:control pairs (with/without DR). Serum samples obtained before adjuvant chemotherapy were analyzed using the MSD V-Plex Human Cytokine 36-Plex Kit for detection of human cytokines and chemokines involved in the Th1/Th2 pathway, chemotaxis, the Th17 pathway, angiogenesis, and immune system regulation. Conditional logistic regression analysis, with models fit via maximum likelihood, were used to estimate hazard ratios (HRs) and test for associations. Due to skewed nature of cytokines, HRs are reported on log base 2 scale. If adjusted for multiple testing including 36 markers, a p value of < 0.0014 would be required for statistical significance. **Results:** A total 249 matched pairs (498 patients) were identified. Covariates used for propensity score matching included age, menopausal status (post 54% vs. pre/peri 46%), ER/PR status (one/both pos 64% vs. both neg 36%) tumor size (< = 2cm 17%, > 2-5cm 67%, > 5cm 16%) nodal status (neg 15%,1-3+ 32%, 4+ 53%), and grade (low 3%, int. 31%, high 66%). The only biomarker associated with a significantly increased DR risk when adjusted for multiple testing was the proinflammatory cytokine IL-6 (HR 1.37, 95% confidence intervals [CI] 1.15, 1.65, p = 0.0006). Others associated with a 2-sided p value < 0.05 included the chemokine MDC(macrophage-derived chemokine/CCL22) (1.90, 95% CI 1.17, 3.1, p = 0.0098), the T helper cell inflammatory cytokine IL-17A (HR 1.36, 95% CI 1.10, 1.67, p = 0.0052), and the cytokine VEGF-A (HR 1.13 for, 95% CI 1.01, 1.27, p = 0.037). There was no statistical interaction between VEGF-A and bevacizumab benefit. The median and mean value for IL-6 was 0.95 and 7.5 pg/ml (range 0.04-2761.24 pg/ml). **Conclusions:** This analysis provides level 1B evidence indicating that higher levels of the cytokine IL-6 at diagnosis are associated with a significantly higher DR risk in high-risk stage II-III breast cancer despite optimal adjuvant systemic therapy. This provides a foundation for confirmatory validation of IL-6 as a prognostic biomarker, and potentially as a predictive biomarker for testing therapeutic interventions targeting the IL-6/JAK/STAT3 pathway. Supported by NCI U10CA180820,180794,180821; UG1CA189859,232760,233290, 233196; Komen Foundation; Breast Cancer Research Foundation. Clinical trial information: NCT00433511. Research Sponsor: U.S. National Institutes of Health, Breast Cancer Rsearch Foundation.

521 **Poster Session**

Predict the benefit of metronomic capecitabine maintenance in early-stage triple-negative breast cancer: Results from the SYSUCC-001 study. *First Author: Zhongyu Yuan, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Recent clinical trials and meta-analysis have suggested the benefit of adding capecitabine to standard chemotherapy in early-stage triple negative breast cancer (TNBC). We aimed to develop an individualized prediction model to quantify the clinical benefit of metronomic capecitabine maintenance in TNBC. **Methods:** Patients from the SYSUCC-001 trial, randomized to standard treatment with or without metronomic capecitabine maintenance, were pooled. Candidate covariates included age, tumor size, lymph node, histological grade, Ki-67 percentage, lymphovascular invasion, chemotherapy regimen and capecitabine medication. The primary endpoint was disease-free survival (DFS). The nonlinear effect of continuous covariate was modelled by restricted cubic spline. We developed a survival prediction model using the Cox proportional hazards model. **Results:** A total of 434 patients were recruited (306 in development cohort and 128 in validation cohort). The estimated 5-year DFS in the development cohort and validation cohort were 77.8% (95% CI, 72.9-82.7%) and 78.2% (95% CI, 70.9-85.5%), respectively. Age and lymph node had significant nonlinear effects on DFS. Four covariates significantly associated with DFS in the final prediction model were age, lymph node, lymphovascular invasion and capecitabine medication. The model demonstrated suitable calibration and fair discrimination ability with a C-index of 0.722 (95% CI, 0.662-0.781) and 0.764 (95% CI, 0.668-0.859) in the development cohort and validation cohort, respectively. We design an easy-to-use online calculator based on the model, capable of predicting capecitabine maintenance benefit. **Conclusions:** The evidence-based prediction model could identify those patients who most warrant metronomic capecitabine maintenance and thus help treatment decision making in daily clinical practice. Clinical trial information: NCT01112826. Research Sponsor: None.

522 **Poster Session**

Efficacy and safety analysis of Chinese patients in monarchE: Abemaciclib combined with adjuvant endocrine therapy for high risk HR+, HER2- early breast cancer. *First Author: Zhimin Shao, Department of Breast Surgery, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: In monarchE, abemaciclib (oral CDK4&6 inhibitor) plus endocrine therapy (ET) as adjuvant treatment for HR+, HER2- high risk early breast cancer (EBC), demonstrated a statistically significant improvement in invasive disease-free survival (IDFS) compared to ET alone. Here we present the efficacy and safety analysis of Chinese patients from monarchE. **Methods:** The overall study design was reported previously. Eligible patients were randomized to receive abemaciclib (150 mg BID for 2 years) combined with standard adjuvant ET or ET alone. The primary endpoint was IDFS per STEEP criteria. Secondary endpoints included distant relapse-free survival (DRFS), overall survival, and safety. Exploratory subgroup analyses were conducted among Chinese patients enrolled from Mainland China, Hong Kong, and Taiwan in the intent-to-treat (ITT) population. **Results:** A total of 501 Chinese patients were randomized to receive abemaciclib plus ET (259 patients) or ET alone (242 patients). At the time of data cutoff (July 8, 2020), 356 (71.1%) patients were still in the 2-year treatment period. A total of 26 IDFS events were observed (11 and 15 events in abemaciclib plus ET and ET arm, respectively). Comparing to ET alone, abemaciclib combined with ET reduced the risk of developing invasive disease or death by 34.3% (HR: 0.657, 95% CI: 0.301, 1.435) for Chinese patients, together with a clinically meaningful improvement in the 2-year IDFS rate (95.6% vs 92.1%). The addition of abemaciclib to ET also resulted in an improvement in DRFS (HR: 0.601, 95% CI: 0.245, 1.477) for Chinese patients, with the 2-year DRFS rate at 96.7% (ET alone: 93.4%). In the abemaciclib arm, the most frequent treatment-emergent adverse events (TEAEs) and grade ≥3 TEAEs: diarrhea (90.3% and 5.0%), leukopenia (76.8% and 21.2%), and neutropenia (76.4% and 23.9%), respectively. **Conclusions:** Abemaciclib combined with adjuvant ET demonstrated clinically meaningful IDFS and DRFS benefits among Chinese patients with HR+, HER2-, high risk EBC, which was consistent with the ITT population as reported previously. The safety profile of abemaciclib in Chinese EBC patients was consistent with global population and also with that observed in Chinese metastatic breast cancer patients. Clinical trial information: NCT03155997. Research Sponsor: Eli Lilly and Company.

523 **Poster Session**

Association of statin use with clinical outcomes in patients with triple-negative breast cancer. *First Author: Malgorzata Nowakowska, Baylor College of Medicine, Houston, TX*

Background: Statins have been shown to target pathways related to breast cancer carcinogenesis, specifically in more aggressive breast cancer subtypes such as triple negative breast cancer (TNBC). Given the limited toxicity profile, low cost, and ease of use of statins, an association between statin therapy and improved breast cancer outcomes, particularly in aggressive breast cancers with more limited treatment options, could have important public health implications. Here we examine the association of statin therapy with breast cancer outcomes in women with stage I-III breast cancer, specifically TNBC. **Methods**: We utilized Surveillance, Epidemiology, and End Results (SEER)-Medicare and Texas Cancer Registry (TCR)-Medicare data. We included women age 66 years or older with histologically confirmed stage I-III breast cancer diagnosed from 2008-2015. We used multivariable Cox proportional hazards regression models to examine the association of statin use with overall survival (OS) and breast cancer specific survival (BCSS) adjusting for age, race, education, state buy-in, residence area, stage, subtype, endocrine therapy, radiation, chemotherapy, surgery, baseline statin use, comorbidity, and baseline hypertension. For BCSS, we accounted for the competing risk of death using the Fine and Grey method. We required all individuals to survive until 12 months post-diagnosis, which we defined as the start of the follow-up period, to account for immortal time bias. **Results**: We identified 45,063 patients with stage I-III breast cancer meeting inclusion criteria, out of which 22,518 (50.0%) received a statin within one year following diagnosis (statin-users). The 5-year cumulative estimates of breast cancer specific deaths were 5.9% and 6.9% for statin-users and non-users ($P < .001$), respectively. In the overall cohort, adjusted models showed a statistically significant association between statin use and improved BCSS (subdistribution hazard ratio [SHR], 0.82; 95% CI, 0.70 to 0.97; $P = .021$), but no association with OS (hazard ratio [HR], 0.96; 95% CI, 0.90 to 1.03; $P = .23$). The association was strongest in patients with TNBC for BCSS (SHR, 0.60; 95% CI, 0.42 to 0.86; $P = .006$) and OS (HR, 0.76; 95% CI, 0.61 to 0.95; $P = .018$). Stratification by stage showed that the effect of statin therapy in TNBC was limited to patients with localized disease. Our results were consistent using propensity score matched models and when limiting our analysis to statin therapy initiated following breast cancer diagnosis. **Conclusions:** Among women with non-metastatic breast cancer, we found that statin use was associated with an OS and BCSS benefit among women with TNBC. Our data suggest that statins may have a role as an adjuvant therapy in select patients with breast cancer and supports further investigation, particularly among patients with TNBC, for whom effective treatment options are more limited. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency.

524 **Poster Session**

The prognostic performance of PREDICT+ in patients (pts) with HER2-positive (HER2+) early-stage breast cancer (EBC). *First Author: Elisa Agostinetto, Institut Jules Bordet and Université Libre de Bruxelles (U.L.B), Brussels, Belgium*

Background: PREDICT+ is a widely used, free, online tool based on traditional clinico-pathological features, including HER2, developed to predict individual mortality of EBC pts and to aid clinical decision making for adjuvant therapy. However, its prognostic role in HER2+ EBC pts treated with chemotherapy (CT) and anti-HER2 therapies remains unclear. We aimed to investigate the prognostic performance of PREDICT+ in HER2+ EBC pts enrolled in the ALTTO trial. **Methods:** ALTTO is a phase III study evaluating adjuvant lapatinib (L) +/- trastuzumab (T) vs. T alone in pts with HER2+ EBC. Pts enrolled in the ALTTO trial and receiving T-based therapy started concurrently with CT were eligible for this analysis. We calculated PREDICT+ estimates using variables extracted from ALTTO database, blinded to pts outcomes. The prognostic performance of PREDICT+ was evaluated by assessing its calibration and discriminatory accuracy. For calibration, median predicted 5-year (5-yr) overall survival (OS) was compared to observed 5-yr OS. For discriminatory accuracy, the area under the receiver-operator characteristic (AUC under the ROC) curve and corresponding 95% confidence intervals (CI) for predicted 5-yr OS were calculated. Subgroup analyses were performed according to type of anti-HER2 therapy, type of CT, age, hormone receptor (HR) status, nodal status and tumor size. **Results:** This analysis included 2,794 pts. After a median follow-up of 6.0 years (IQR, 5.8-6.7), 182 deaths were observed. Overall, PREDICT+ underestimated 5-yr OS by 6.7% (95% CI, 5.8-7.6): observed 5-year OS was 94.7% vs. predicted 88.0%. The underestimation was consistent across all subgroups (Table). For discriminatory accuracy, AUC under the ROC curve was 73.7% (95%CI 69.7-77.8) in the overall population, ranging between 61.7% and 77.7% across the analysed subgroups. **Conclusions:** In HER2+ EBC pts enrolled in the ALTTO trial, the PREDICT+ score highly underestimated OS. The low performance of this prognostic tool was consistent across all pts subgroups. PREDICT+ should be used with caution to give prognostic estimation in HER2+ EBC pts treated in the modern era with effective chemotherapy and anti-HER2 targeted therapies. Research Sponsor: Grant (number 2018-09) from Les Amis de l'Institut Bordet, submitted by P. Aftimos (title: The prognostic performance of PREDICT + in breast cancer patients with early-stage HER2-positive disease in the ALTTO trial).

Calibration according to subgroups.

		(Predicted – Observed) 5-yr OS (%) (95% CI)
Anti-HER2 Therapy	L + T	-7.0 (-8,5 -5,5)
	T alone	-6,3 (-7,8 -4,7)
	T → L	-6,8 (-8,3 -5,4)
CT	Non anthracycline-based	-8,1 (-10,3 -5,9)
	Anthracycline-based	-6,6 (-7,5 -5,6)
Age	≤40	-5,2 (-7,1 -3,4)
	41-64	-6,7 (-7,7 -5,7)
	≥65	-9,7 (-12,9 -6,6)
HR status	Negative	-13.0 (-14,4 -11,5)
	Positive	-2,7 (-3,7 -1,7)
Number of N+	0	-6,1 (-7,4 -4,9)
	1-3	-9.0 (-10,2 -7,8)
	3	-15,8 (-18,3 -13,3)
Tumor size (mm)	≤20	-6,2 (-7,1 -5,3)
	21-50	-7,3 (-8,7 -6.0)
	50	-15,3 (-20,4 -10,2)

525 **Poster Session**

Retrospective cohort study of estrogen receptor low positive early breast cancer using real world data. *First Author: Shahla Bari, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Estrogen receptor (ER) positive breast cancer (BC) is a heterogeneous disease, with ongoing debate on the optimal cut off point for clinically relevant ER expression. Tumors harboring ≤10% ER expression are associated with poor outcomes. We used a real-world database to assess prognostic and predictive value of an alternative ER expression cut points. **Methods**: This retrospective cohort study used the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. During the study period, the de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). We evaluated the association between ER expression (assessed locally by immunohistochemistry according to ASCO/CAP guidelines) with tumor characteristics, and treatment patterns of patients with early-stage BC (stage I-III) using descriptive statistics. Recurrence free survival and overall survival was defined as time in months from date of surgery until the data of documented cancer recurrence or death respectively. We used Kaplan Myer survival curves to calculate recurrence free (RFS) and overall survival (OS) of patients with ER low, ER intermediate and ER high tumors. To define an alternative ER expression cut point, the data set was divided into 2/3 training and 1/3 test data. A cut point analysis was performed on the training data set to find the optimum cut point of ER+ staining based on correlation with recurrence free survival as the outcome. **Results**: Among 4,697 ER positive early-stage BC patients, 83 (1.8%) had ER low (ER expression :1-10%) and 36 (0.8%) had ER intermediate BC (11-20%). Median follow up time was 63 months (range 24-84). ER low tumors were associated with higher tumor grade, larger size, and higher axillary tumor burden compared to ER high positive tumors ($>$ 20% ER expression). African American patients had a higher prevalence of both triple negative and ER low positive BCs compared to ER high tumors- 21%, 22%, and 8% respectively. No significant differences in patient- or tumor-associated characteristics were observed between Low ER and intermediate-ER positive BC patients. Both ER low and intermediate positive tumor patients had survival outcomes similar to patients with TNBC and worse than ER high positive tumors ($p < 0.001$). No significant correlations between endocrine therapy and RFS or OS were observed among patients with either ER low or intermediate BCs (HR 1.47 and 2.57, $p > 0.05$; respectively). Sensitivity analysis showed that tumors with ≤ 20% ER expression were associated with worse RFS in both univariate and multivariate analyses ($p < 0.05$). **Conclusions:** These findings suggest that patients with ER expression rates ≤ 20% have poor outcomes and derive minimal benefit from endocrine therapies. Research Sponsor: None.

526 **Poster Session**

Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: A subgroup analysis of the DESTINY-Breast01 trial. *First Author: Guy Heinrich Maria Jerusalem, Centre Hospitalier Universitaire du Sart Tilman Liège and Liège University, Liège, Belgium*

Background: Patients (pts) with HER2+ metastatic breast cancer (mBC) are at high risk of developing brain metastases (BMs), and treatment options are limited once BMs occur. T-DXd is an antibody-drug conjugate composed of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor payload. On the basis of findings of the phase 2 DESTINY-Breast01 trial (NCT03248492), T-DXd was approved for the treatment of adult pts with HER2+ unresectable or mBC who have received ≥2 prior anti-HER2–based regimens (US and Europe) or had prior chemotherapy and are refractory to or intolerant of standard treatments (Japan). Here we describe a subgroup analysis from DESTINY-Breast01 in pts with a history of BMs. **Methods:** DESTINY-Breast01 is an ongoing, 2-part, multicenter, open-label, phase 2 trial of T-DXd in adult pts with HER2+ unresectable or mBC previously treated with trastuzumab emtansine. Pts with baseline BMs that were treated, asymptomatic, and did not require therapy to control symptoms were eligible for enrollment. All treatment to control symptoms had to be completed ≥60 days before randomization. An MRI of the brain every 6 wks was only required for pts with BMs at baseline. Brain lesions were considered non-target lesions, and thus collection of diameter measurements was not required. This analysis includes pts with a history of BMs at baseline who received T-DXd at the approved dose of 5.4 mg/kg every 3 wks. **Results:** Twenty-four pts with a history of BMs were included (data cutoff, August 1, 2019). In these pts, the objective response rate (ORR), median progression-free survival (mPFS), and median duration of response (mDoR) per independent central review with T-DXd 5.4 mg/kg were 58.3% (95% CI, 36.6%-77.9%), 18.1 mo (95% CI, 6.7-18.1 mo), and 16.9 mo (95% CI, 5.7-16.9 mo), respectively, and were comparable to those in the total pt population (N = 184) treated at 5.4 mg/kg in the DESTINY-Breast01 study (ORR, 60.9%; mPFS, 16.4 mo; mDoR, 14.8 mo; median follow-up, 11.1 mo). The pattern of disease progression was similar in pts with and without BMs with 8 of 24 pts having progressed (33%; 2 in the brain) in the BMs subgroup and 40 of 160 pts (25%; 2 in the brain) in the non-BMs subgroup, suggesting durable systemic disease control. Baseline diameters of BMs were available for 14 of 24 pts (radiotherapy prior to study enrollment was reported in 12 of 14). Among the pts with information available on baseline BM diameter, the central nervous system response rate per investigators was 50% (7 of 14 pts). **Conclusions:** T-DXd showed strong clinical activity in both the overall population of pts with HER2+ mBC and the subgroup of pts with BMs. The demonstrable response of BMs to treatment and durable clinical activity of T-DXd in pts with a history of BMs at baseline are promising and warrant further investigation. Clinical trial information: NCT03248492. Research Sponsor: Daiichi Sankyo, Inc. and AstraZeneca.

527 **Poster Session**

Bone safety profile of steroidal aromatase inhibitor in comparison to non-steroidal aromatase inhibitors in postmenopausal women with breast cancer: A network meta-analysis. *First Author: Shanshan Chen, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Steroidal and non-steroidal aromatase inhibitors (AIs) provide better therapeutic response in comparison to other endocrine therapies in the adjuvant treatment of breast cancer (BC). They interfere with bone turnover which may lead to increased incidence of bone related safety events. There are no head-on studies comparing the incidence of bone safety events and hence we performed this network meta-analysis (NMA) to compare the incidence of bone safety events among patients treated with steroidal and non-steroidal AIs. **Methods:** Literature searches were performed in PubMed and Embase with key words to identify randomized controlled trials in BC patients treated with AIs in adjuvant settings compared against tamoxifen or other AIs, reporting any bone-related safety events. The study was designed as per PRISMA guidelines; publication bias was evaluated by comparison-adjusted funnel plots. Bayesian NMA was done by R software (ver 3.2), GemtC package. Odds ratio (OR) and the surface under the cumulative ranking curve (SUCRA) values were used to interpret the results. **Results:** 15 studies reporting 6 different bone-related endpoints were included. Treatment with steroidal AI, exemestane led to lower incidence of bone pain (OR Vs anastrozole and letrozole: 0.59, p=0.63; 0.54, p=0.75), fracture episodes (OR Vs anastrozole and letrozole: 0.84, p=0.41; 0.85, p=0.73), joint stiffness (OR Vs anastrozole: 0.55, p=0.73) and osteoporosis (OR Vs anastrozole and letrozole: 0.86, p=0.41; 0.74, p=0.29) (Table) in comparison to letrozole and anastrozole. Reduction in bone mineral density was also lesser in exemestane than anastrozole (mean reduction in hip: 1.08; lumbar spine: 1.34). SUCRA values suggested exemestane to be the drug with maximum likelihood for reducing the incidence of bone-related adverse events. **Conclusions:** This NMA suggested that bone-related safety events might be lower in early BC patients treated with exemestane in comparison to non-steroidal AIs, anastrozole and letrozole. Although there was no statistical significance, further head-on studies are required to substantiate our results. Research Sponsor: Pfizer ONC-2 Medical Affair.

Effect estimates and SUCRA values.

Events	No of studies	Exemestane (Exe) vs Anastrozole (Ana) (OR, 95% CrI, p value)	Exemestane vs Letrozole (Let) (OR, 95% CrI, p value)	SUCRA Values
Arthralgia	11	1.248 (0.575- 2.665, 0.58)	1.064 (0.344- 3.151, 0.92)	Ana:0.568 Let:0.382Exe:0.286
Bone pain	7	0.596 (0.062- 3.494, 0.63)	0.54 (0.011- 15.97, 0.75)	Exe:0.535Ana:0.276Let:0.297
osteoporosis	10	0.86 (0.593-1.185, 0.41)	0.74 (0.423-1.287, 0.29)	Exe:0.584 Ana:0.289 let:0.129
Joint stiffness	4	0.55 (0.04– 23.73, 0.73)	NA	Exe:0.31Ana:0.30
Fracture episodes	11	0.84 (0.56- 1.26, 0.41)	0.85 (0.318- 1.902, 0.73)	Exe:0.579Let:0.284Ana:0.227

OR: odds ratio, CrI: credibility interval.

528 **Poster Session**

The impact of COVID-19 on breast cancer stage at diagnosis. *First Author: Maxwell Lloyd, Beth Israel Deaconess Medical Center, Boston, MA*

Background: During the SARS-CoV-2 pandemic, routine screening mammography (SM) was stopped and diagnostic mammography (DM) was limited for several months across the United States in order to reduce patient exposure and redeploy medical personnel. We hypothesized that this delay would result in patients presenting with later-stage disease following the initial shutdown. **Methods:** Patients diagnosed with invasive breast cancers from 2016-2020 were identified using the Beth Israel Deaconess Medical Center Cancer Registry. Baseline patient characteristics, demographics, and clinical information were gathered and cross-referenced with our electronic medical record. Late-stage disease was defined as initial anatomic stage III-IV disease in the AJCC 8th edition staging system. The control cohort consisted of patients diagnosed from 2016-2019; patients diagnosed in 2020 were the test cohort. Chi-squared analysis was used to compare monthly distributions in stage at diagnosis between the control and test cohorts. Multivariate analysis was performed using a logistic regression model. **Results:** There were 1597 patients diagnosed with invasive breast cancer between 2016-2019 and 333 in 2020. Median age at diagnosis was 60 years; 99% were female, and 69.1% were white. Mammography was limited from 3/16/20-6/8/20, with 90% reduction in volume during this time. The number of screening studies performed in March, April, May, and June of 2020 were 987, 1, 4, and 721 compared to 2042, 2141, 2241, and 2142 in 2019. The volume of new diagnoses per month decreased substantially during the shutdown (see table). The proportion of patients diagnosed with late-stage disease was 6.6% in the control cohort compared to 12.6% in the 2020 test cohort ($p < 0.001$); 92.9% of late-stage diagnoses in 2020 occurred from June to December following the shutdown period. On multivariate analysis, year of diagnosis (2020 vs 2016-2019; OR = 4.25 95% CI 0.035-0.095, $p < 0.001$), lower income (<200% of the federal poverty level; OR = 2.73 95% CI 0.016-0.099, p = 0.006) and increased Charlson Comorbidity Index (OR = 12.01 95% CI 0.037-0.052, $p < 0.001$) were associated with later stage at diagnosis. **Conclusions:** Patients were more likely to be diagnosed with late-stage breast cancer following the global shutdown due to the SARS-CoV-2 pandemic. Patients with lower income and medical comorbidities were disproportionately affected. These data raise significant concerns regarding the impact of SARS-CoV-2 on cancer diagnoses and long-term outcomes, especially in vulnerable patient populations. Research Sponsor: None.

Proportion of patients with late disease by month of diagnosis.

Month	2016-2019	2020	Month	2016-2019	2020
Jan	7% (9/130)	0 (0/24)	Jul	9% (12/142)	7% (1/14)
Feb	5% (6/125)	10% (2/20)	Aug	9% (13/140)	21% (9/42)
Mar	7% (9/132)	3% (1/31)	Sep	5% (6/124)	15% (10/65)
Apr	6% (7/118)	0 (0/9)	Oct	7% (10/135)	19% (10/53)
May	7% (10/141)	0 (0/7)	Nov	7% (10/145)	12% (5/42)
Jun	7% (10/147)	21% (3/14)	Dec	3% (4/118)	8% (1/12)

529 **Poster Session**

Efficacy of epirubicin plus cyclophosphamide followed by taxanes versus carboplatin plus taxanes as adjuvant chemotherapy in triple-negative breast cancer: 8.1 years median follow-up on a randomized clinical trial. *First Author: Fangchao Zheng, National Cancer Centre/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Four cycles of adjuvant taxanes (paclitaxel or docetaxel) after four cycles of adjuvant doxorubicin plus cyclophosphamide (ECT) are considered a standard adjuvant treatment and improves survival outcomes of triple negative breast cancer (TNBC). The purpose of this analysis was to further assess whether adjuvant carboplatin plus taxanes (TP) was non-inferior to or superior to standard ECT chemotherapy in prolonging the survival time. **Methods:** This randomized, open-label, multicenter clinical trial conducted at three hospital in China from June, 2009 and October, 2015. Eligible early triple-negative breast cancer (TNBC) patients were randomized (1:1) to receive ECT (four cycles of epirubicin 90 mg/m2 + cyclophosphamide 600 mg/m2 followed by four cycles of docetaxel 75 mg/m2 or paclitaxel 175 mg/m2 every 3 weeks, ECT arm, n = 154) or receive TP (six cycles of docetaxel 75 mg/m2 or paclitaxel 175 mg/m2 + carboplatin AUC 5 every 3 weeks; TP arm, n = 154), which was then followed by surgery. **Results:** Three hundred and eight patients were recruited in this trial and final date of follow-up was January 20, 2021. Baseline characteristics were balanced between ECT arm and TP arm. Median follow-up was 97.6 months. Median disease free survival (DFS) was not reached; 8-year DFS rate was 78.35% with ECT arm and 81.73% with TP arm (hazard ratio [HR] = 0.84; 95% confidence interval [CI] = 0.50 - 1.40; P = 0.496). Median overall survival (OS) was also not reached; 8-year OS rate was 87.15% with ECT arm and 89.14% with TP arm (HR = 0.87; 95% CI = 0.44 - 1.70; P = 0.676). For TNBC patients with DFS $>$ 4 year, TP arm had a longer DFS than ECT (P = 0.01), and had a tendency with better OS (P = 0.4). In this subgroup analysis of SPARC $>$ 50%, TP arm had a longer DFS than ECT (P $<$ 0.05), and also had a tendency with better OS (P = 0.06). In subgroup analysis of PD-1 (-) and intravascular invasion (+), TP arm had a better DFS (P = 0.02) and OS (P = 0.03) than ECT arm. DFS or OS had no significant differences in ECT and TP arm with BRCA mutation or BRCA wild (all P values $>$ 0.05). **Conclusions:** TP chemotherapy showed significant non-inferiority for PFS and OS versus ECT in the first-line adjuvant treatment of early TNBC. For some particular subgroup of TNBC, TP may be a more effective chemotherapy than ECT. TP may be considered an effective alternative to early TNBC. Clinical trial information: NCT01150513. Research Sponsor: None.

530 **Poster Session**

Use of a novel convolutional neural network-based mammographic evaluation to assess response to adjuvant endocrine therapy in women with early-stage breast cancer. *First Author: Julia Elizabeth McGuinness, Columbia University Irving Medical Center, New York, NY*

Background: The standard of care for early-stage hormone receptor (HR)-positive breast cancer (BC) is 5-10 years of adjuvant endocrine therapy (ET), which leads to a 50-60% relative risk reduction in BC recurrence. However, 10-40% of patients may relapse up to 20 years (y) after diagnosis, and there is a need for biomarkers of response to ET. We developed a novel, fully-automated convolutional neural network (CNN)-based mammographic evaluation that accurately predicts BC risk, which is being evaluated as a pharmacodynamic response biomarker to adjuvant ET. **Methods:** We conducted a retrospective cohort study among women with HR-positive stage I-III unilateral BC diagnosed at Columbia University Irving Medical Center from 2007-2017, who received adjuvant ET and had at least 2 mammograms of the contralateral breast (baseline and annual follow-up). Demographics, clinical characteristics, BC treatments, and relapse status were extracted from the electronic health record and New York-Presbyterian Hospital Tumor Registry. We performed CNN analysis of mammograms at baseline (start of ET) and annual follow-up. Our primary endpoint was change in CNN risk score, expressed as a continuous variable (range, 0-1). We used two-sample *t*-tests to assess for differences in mean CNN scores between patients who relapsed or remained in remission. We evaluated if CNN score at baseline and change from baseline were associated with relapse using logistic regression, with adjustment for known prognostic factors. **Results:** Among 870 evaluable women, mean age at diagnosis was 59.5y (standard deviation [SD], 12.4); 60.3% had stage I tumors, 72.6% underwent lumpectomy, and 45.8% received chemotherapy. With a median follow-up of 4.9y, there were 68 (7.9%) breast cancer relapses (36 distant, 26 local, 6 new primary). Median number of evaluable mammograms per patient was 5 (range, 2-13). Mean baseline CNN risk scores were significantly higher among women who relapsed compared to those in remission (0.258 vs 0.237, p = 0.022), which remained significant after adjustment for known prognostic factors. There was a significant difference in mean absolute change in CNN risk score from baseline to 1y follow-up between those who relapsed vs. remained in remission (0.001 vs. -0.022, p = 0.027), but this was no longer significant in multivariable analysis. **Conclusions:** We demonstrated that higher baseline CNN risk score was an independent predictor of BC relapse. A greater decrease in mean CNN risk scores at 1-year follow-up after initiating adjuvant ET was seen among BC patients who remained in remission compared to those who relapsed. Therefore, baseline CNN risk scores may identify patients at high-risk for breast cancer recurrence to target for more intensive adjuvant treatment. Early changes in CNN risk scores may be used to predict response to long-term ET in the adjuvant setting. Research Sponsor: Herbert Irving Comprehensive Cancer Center Velocity Pilot Award.

531 **Poster Session**

Breast Cancer Index and prediction of benefit from extended endocrine therapy based on treatment compliance: An IDEAL study. *First Author: Gerrit-Jan Liefers, Leiden University Medical Center, Leiden, Netherlands*

Background: The IDEAL trial randomized hormone receptor-positive (HR+) breast cancer patients to 5 vs 2.5y of extended letrozole after completion of 5y of adjuvant endocrine therapy. In the parent trial, approximately 60% of patients overall were compliant with endocrine treatment (59% vs 74% compliance in 5y and 2.5y arms, respectively), with patient experiences as the most significant factors leading to treatment discontinuation. Breast Cancer Index is a gene expression-based signature that predicts which HR+ patients are likely to benefit from extended endocrine therapy (EET) vs those unlikely to benefit [BCI (H/I)-High and -Low, respectively]. The current study examined EET compliance and outcome by BCI (H/I) status in patients treated in the IDEAL trial. **Methods:** Patients with available primary tumor specimens were eligible for this blinded study. Primary endpoint was recurrence-free interval (RFI), including locoregional and distant recurrences. Kaplan-Meier and Cox proportional hazards regression analysis were used to analyze the benefit of EET. Non-compliance was defined as completion of $\leq$60% of treatment duration ($\leq$3y for 5y arm; $\leq$1.5y for 2.5y arm) for any reason other than disease events. Overtreatment was defined as % compliant BCI (H/I)-Low patients in the 5y arm; undertreatment was % noncompliant BCI (H/I)-High patients in the 5y arm. **Results:** 908 HR+ patients (73% pN+, 59y, 45% pT1, 48% pT2) were included. 78% (n = 708) of patients were compliant, of which 48% (n = 338) were BCI (H/I)-High and 52% (n = 370) were BCI (H/I)-Low. In non-compliant patients (22%, n = 200), 45% (n = 91) were BCI (H/I)-High and 55% (n = 109) were BCI (H/I)-Low. BCI (H/I)-Low patients irrespective of compliance status did not derive significant benefit from EET (P = 0.922, compliant subset; 0.894 non-compliant subset). Compliant BCI (H/I)-High patients showed significant benefit from EET (HR 0.35, 95% CI 0.16-0.79; absolute benefit 11.7%; P = 0.008) whereas non-compliant BCI (H/I)-High patients did not (HR 0.75, 95% CI 0.17-3.35; absolute benefit 2.1%, P = 0.704). In this study, 38% of patients in the 5y EET arm were BCI (H/I)-Low and compliant and thus were overtreated, while 13% of patients in the 5y EET arm were BCI (H/I)-High and non-compliant and thus were undertreated. **Conclusions:** Patients that were BCI (H/I)-Low did not derive significant benefit from 5 vs 2.5y of EET even when compliant, and thus may be considered for treatment de-escalation. Importantly, BCI (H/I)-High patients with endocrine responsive disease showed significant improvements in outcome when compliant and should be guided to continue treatment. BCI may serve as an important genomic tool to increase EET compliance and identify patients that may be candidates for increased side effect management and support to potentially improve outcomes. Clinical trial information: NTR3077; BOOG 2006-05; Eudra-CT 2006-003958-16. Research Sponsor: Biotheranostics, Inc, Leiden University Medical Center Institutional Grant; Novartis.

532 **Poster Session**

A validated model to predict low recurrence risk distinguished by 21-gene recurrence score in hormone receptor-positive invasive breast cancer patients. *First Author: Yasue Tsuchida, Department of Breast Surgical Oncology, St. Luke's International Hospital, Tokyo, Japan*

Background: In the prospective TAILORx and RxPONDER trials, the 21-gene Recurrence Score (RS) showed endocrine therapy alone was non-inferior to chemo-endocrine therapy in the analysis of invasive disease-free survival in postmenopausal hormone-receptor (HR)-positive breast cancer patients with RS $<$ = 25. They also indicated chemotherapy was associated with benefit for women 50 years or younger with RS 11 to 25. However, in Japan, the test is not conventionally available because of non-coverage by national insurance. We aimed to develop and validate a model to predict RS using clinicopathological factors that identify patients who would have low risk shown by testing the 21-gene RS and can avoid chemotherapy. **Methods:** Four hundred patients, including 187 N0/1 postmenopausal, and 213 N0 premenopausal women who underwent surgery and had the RS from St. Luke's International Hospital, Tokyo, Japan, were included in derivation cohort. Derivation cohort was divided into 2 groups by RS 25; patients with RS of 0 to 25 (n = 321) and with RS over 26 (n = 79). Multivariate logistic regression analysis was performed using candidate factors for all patients and pre- or postmenopausal patients. The prediction model was validated using an external cohort of 70 patients from Showa University School of Medicine, Tokyo, Japan. **Results:** Nuclear grade (NG) (adjusted OR, 5.28, 95% CI, 2.47–11.30), high Progesterone receptor (PgR) expression (Allred score 7-8) (adjusted OR, 10.62, 95% CI, 5.34–21.13) and low Ki67 level ($<$ = 20%) (adjusted OR, 5.29, 95% CI, 2.33-12.01) were significant independent predictors of RS of 0 to 25. With these factors could predict RS of 0 to 25 (AUC of 0.848, 95% CI, 0.803-0.893) with the highest probability of low-RS for 100%. The prediction model of the validation cohort had same discriminatory ability having an AUC of 0.812 (95% CI, 0.701-0.923). In postmenopausal patients, NG (adjusted OR, 4.81, 95% CI, 1.72–13.42), high PgR expression (adjusted OR, 10.62, 95% CI, 4.52–37.72), and low Ki67 level (adjusted OR, 4.94, 95%CI, 1.87-13.04) were significantly associated with RS of 0 to 25 in multivariate analysis. A regression model with these 4 factors could predict RS of 0 to 25 (AUC of 0.842, 95%CI, 0.782-0.902). In premenopausal patients, NG (adjusted OR, 8.76, 95% CI, 1.14–67.40), high PgR expression (adjusted OR, 3.22, 95% CI, 1.61–6.43), and low Ki67 level (adjusted OR, 2.87, 95% CI, 1.20–6.87) were significantly associated with RS of 0 to 10 in multivariate analysis. These factors could predict RS of 0 to 10 (AUC of 0.811, 95% CI, 0.731-0.891). However, the highest probability of low-RS provided this model for premenopausal women was 46.8%. **Conclusions:** Our validated model could provide useful information to distinguish low-RS especially for postmenopausal patients with high reproducibility. However, for premenopausal women, the 21-gene RS is warranted. Research Sponsor: None.

533 **Poster Session**

Clinical trial testing superiority of combination plinabulin (Plin) and pegfilgrastim (Peg) versus peg alone in breast cancer treated with high-risk febrile neutropenia risk chemotherapy (chemo): Final results of the phase 3 protective-2 in chemo-induced neutropenia (CIN) prevention. *First Author: Douglas W. Blayney, Stanford University, Stanford, CA*

Background: Peg is standard of care (SoC) for the prevention of CIN. Peg's mechanism of action leaves patients vulnerable to FN in week 1 of the chemo cycle(C), as the absolute neutrophil count (ANC) does not normalize until week 2. Plin is a first-in-class, non-G-CSF small molecule agent, which received breakthrough designation from FDA in CIN. It prevents CIN by protecting progenitor cells in bone marrow from chemo assault and has normal ANC in week 1 (Blayney JAMA Onc 2020). Phase 2 testing showed the combination of Plin and Peg achieved CIN protection throughout the entire cycle vs Peg alone (Blayney: St Gallen 2019, ASCO 2019). **Methods:** Plin is given on Day (D)1 after Chemo, has a favorable safety profile, and also has anticancer activity. A separate phase 3 study evaluating Plin as an anticancer agent (DUBLIN-3; NCT02504489) in NSCLC pts is underway, with anti-cancer results in OS expected in 2021. In PROTECTIVE-2 (Study 106; NCT0329457), we added Plin (on D1) to Peg (on D2), testing superiority of the combination for CIN prevention vs Peg alone. Study 106, is a global multicenter randomized (1:1) double-blind study to evaluate Plin 40 mg + Peg 6mg (Arm 1) versus Peg 6mg + Placebo (Plac) (Arm 2) in preventing Severe Neutropenia (N), (defined as ANC $<$0.5 cells $\times$ 10E9/L) in early-stage BC (node positive or node negative with a high risk of recurrence) pts. 221 pts with ECOG status 0 or 1 received Docetaxel (75 mg/m2), Doxorubicin (50 mg/m2), and Cyclophosphamide (500 mg/m2) (TAC) on D1 for four 21 D cycles and study treatment. Central laboratory ANC was assessed at Covance in Cycle 1 (C1) on D 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, and 15. Primary objective was to compare the percentage (%) of pts with a Duration of Severe Neutropenia (DSN) of 0 days [that is % of pts with no Grade (Gr) 4 neutropenia (N)] in C1 in each arm. Key secondary endpoints were DSN and ANC Nadir in C1. We also evaluated safety (AE frequency and Grade). **Conclusions:** Adding Plin to Peg offers superior CIN protection compared to Peg alone and also has a superior safety profile by lowering over 20% of grade 4 AE. The effect size of the CIN protection in the combination is also correlated to clinical meaningful FN reduction compared to peg alone. Clinical trial information: NCT03531099. Research Sponsor: BeyondSpring Pharmaceuticals,Inc.

	C1 pts with no Gr4 N (%)	C1 DSN Day 1- 8 (days)	C1 DSN (days)	C1 mean ANC Nadir (cells x10E9/L)	C1-4 pts with worst AE grade of Gr4 (%)	C1-4 pts with Febrile Neutropenia (%)
Plin/Peg (n=111)	31.5%	1.1	1.2	0.538	58.6%	3.60%
Peg/Plac (n=110)	13.6%	1.4	1.5	0.308	80%	6.36%
p-value	0.0015	0.0065	0.03	0.0002	0.0006	0.36

534 **Poster Session**

Cost-effectiveness of the Oncotype DX Breast Recurrence Score test in postmenopausal women with node-positive early breast cancer based on the RxPONDER trial. *First Author: Vladislav Berdunov, PHMR Ltd, London, United Kingdom*

Background: The Oncotype DX test is a predictive and prognostic multigene assay used to guide adjuvant chemotherapy in HR+/HER2- early breast cancer. The ability of the Oncotype DX test to predict the benefit of chemotherapy in node-positive early breast cancer was demonstrated in SWOG-8814. This evidence, in combination with findings from a bespoke analysis of the TransATAC study, informed an economic evaluation of the Oncotype DX test by the National Institute for Health and Care Excellence in the UK. This study examined the impact of new evidence from the RxPONDER trial on the cost-effectiveness of the Oncotype DX test in postmenopausal women with node-positive early breast cancer. **Methods:** The cost-effectiveness of the Oncotype DX test compared to clinical risk tools only in postmenopausal HR+/HER2- early breast cancer was estimated using a model in Microsoft Excel. The pre-RxPONDER analysis using the old cut points (RS 0-17, RS 18-30, RS 31-100) was informed by TransATAC and SWOG-8814. The model was updated with 5-year probability of distant recurrence as first site estimates based on new RS cut points (RS 0-25, RS 26-100) from RxPONDER. The impact on incremental lifetime costs and quality-adjusted life-years (QALYs) gained was examined based on the list price for the Oncotype DX test in the UK. **Results:** The impact of adding data from RxPONDER into the cost-effectiveness analysis is summarized in the table below. **Conclusions:** The RxPONDER trial demonstrated that the addition of chemotherapy to endocrine therapy had no benefit for distant recurrence in postmenopausal women with RS 0-25, regardless of clinical features, which suggests that most patients with 1-3 positive nodes can be safely spared adjuvant chemotherapy. In the model this was reflected in reduced cost of chemotherapy and higher QALYs from avoiding short and long-term adverse effects of chemotherapy. Targeted chemotherapy of a minority (17%) of patients with RS 26-100 reduced the cost of distant recurrence and improved survival based on the model results. RxPONDER provides direct evidence to inform the probability of distant recurrence with endocrine and chemo-endocrine therapy, whilst previous models have had to synthesize multiple sources of DRFI and chemotherapy treatment effect. Future studies should examine the impact of the RxPONDER findings on chemotherapy treatment decision-making in routine clinical practice. Research Sponsor: Exact Sciences.

Summary of cost-effectiveness results (in 2020 pound sterling).

Category	Pre-RxPONDER model	Model with RxPONDER
Incremental cost	-£451	-£1,525
Multigene assay	£2,580	£2,580
Chemotherapy (incl. AEs)	-£3,153	-£3,958
Local and distant recurrence	£143	-£53
Follow-up	-£2	£4
Terminal care	-£38	-£91
Incremental QALYs	0.01	0.19
Incremental life-years	-0.01	0.21
Incremental cost-effectiveness ratio	The Oncotype DX test dominant	The Oncotype DX test dominant

535 **Poster Session**

Outcome and immune landscape of HER2-positive invasive lobular carcinoma in the North Central Cancer Treatment Group (NCCTG) N9831 (Alliance) trial. *First Author: Saranya Chumsri, Mayo Clinic, Jacksonville, FL*

Background: Invasive lobular carcinoma (ILC) is a rarer form of breast cancer, accounting for 10% of the disease cases. HER2 overexpression in ILC is infrequent and limited data exist regarding clinical characteristics and outcome of HER2-positive (HER2+) ILC patients (pts) treated with adjuvant trastuzumab. **Methods:** Patient characteristics were compared between ILC and invasive ductal carcinoma (IDC) using Wilcoxon rank sum test for continuous variables and Chi-square test for categorical variables. Kaplan-Meier (KM) method was used to estimate the freedom from mortality and recurrence. Cox regression model was used to evaluate the association between ILC and outcomes adjusted for other characteristics. NanoString technology was used to quantify mRNA to develop immune-related gene signatures. **Results:** From a total of 3,304 pts, 122 (3.7%) pts had ILC. Pts with ILC were significantly older (median age 54 vs. 49 years), had larger tumors, lower grade, more ER and PR positive tumors, and more lymph node involvement (25.4% had N3 disease compared to 12.7% in IDC). Overall, with KM analysis, pts with ILC had significantly worse overall survival (OS, p = 0.005) and recurrence-free survival (RFS, p = 0.046) compared to IDC. The 15-year freedom from recurrence was merely 57.67% in ILC compared to 72.68% in IDC. A significant number of hormone receptor-positive (HR+) ILC pts developed late recurrence with cumulative event rates increasing from 23% at 5 years to 42% at 15 years. Nevertheless, in multivariate Cox regression analysis adjusting for other clinical characteristics, including age, tumor size, grade, ER/PR, and lymph node status, lobular histology was not significantly associated with worse outcome for OS (HR = 1.19, 95%CI 0.67-2.1, p = 0.55) and RFS (HR = 1.5, 95%CI 0.9-2.5, p = 0.12), as compared with IDC. However, ILC pts appeared to have similar degree of benefit from trastuzumab, with RFS HR = 0.58 compared to HR = 0.67 in the entire population. For immune landscape, there was no significant difference in gene signatures related to CD45, CD8, B cells, or cytotoxic cells. However, ILC had more enrichment in mast cell gene signature and fewer macrophage, NK CD56dim, and regulatory T cell signatures compared to IDC ($p < 0.05$). **Conclusions:** HER2+ ILC has distinct clinical characteristics and immune landscape compared to IDC. ILC pts appeared to have worse outcome compared to IDC likely because ILC pts often presented with more locally advanced disease. However, similar benefit of trastuzumab was observed in ILC pts. Due to high risk of late relapse in HR+ HER2+ ILC, extended adjuvant endocrine therapy should be considered in this group of high-risk pts. Clinical trial information: NCT00005970. Research Sponsor: U10CA180821, U24CA196171, Other Foundation.

536 **Poster Session**

Dose escalation for mitigating diarrhea: Ranked tolerability assessment of anti-diarrheal regimens in patients receiving neratinib for early-stage breast cancer. *First Author: Gavin M. Marx, University of Sydney, Sydney, Australia*

Background: The primary tolerability concern with neratinib (NERLYNX®; N), an irreversible pan-HER tyrosine kinase inhibitor, is diarrhea. Data from the multi-cohort, open-label, phase 2 CONTROL trial [Barcenas et al. Ann Oncol 2020] demonstrated significant improvement in grade 3 diarrhea and diarrhea-related discontinuations vs the ExteNET trial, which did not mandate anti-diarrheal prophylaxis. We report a systematic analysis of tolerability in CONTROL and ExteNET. **Methods:** Patients (pts) ≥18y with stage I–IIIc HER2+ breast cancer received N (240 mg/d po for 1y) after trastuzumab-based adjuvant therapy and were enrolled sequentially into cohorts assessing different modalities to mitigate diarrhea. Cohorts with complete data were included: loperamide (L); L+budesonide (BL); L+colestipol (CL); CL as needed (CL-PRN); and N dose escalation (DE; 120 mg/d on d1–7, 160 mg/d on d8–14, and 240 mg/d thereafter). Integrated ranking (IR) analysis was performed on 13 endpoints in 4 domains (exposure, diarrhea, adverse events [AEs], quality of life [QoL]) identified with input from clinicians; cohorts were ranked from 1 (best) to 5 (worst). Index scores (IS) based on individual pt data from CONTROL were calculated as supportive analysis to confirm selection of the regimen with best overall tolerability, which was then compared with ExteNET. **Results:** Of the 5 CONTROL cohorts evaluated, DE ranked best for most endpoints. Average ranks per IR method: L 3.4; BL 3.2; CL 3.0; CL-PRN 3.3; DE 2.0. The IS analysis supported DE as the cohort with best overall tolerability. Comparison of CONTROL DE vs ExteNET showed improvement in tolerability in all domains (table). **Conclusions:** These analyses suggest superiority of weekly DE vs other anti-diarrheal strategies. A lower rate of grade 3 diarrhea was observed with CONTROL DE vs ExteNET (13.3 vs 39.9%, respectively), as well as a comparable or improved AE profile. The data also reveal greater compliance with N (fewer early discontinuations, longer treatment duration, higher cumulative dose) and reduced impact on QoL with DE, suggesting improved tolerability. Clinical trial information: NCT02400476. Research Sponsor: Puma Biotechnology Inc.

ExteNET vs CONTROL DE.

	ExteNET (n=1408)	CONTROL DE (n=60)
Exposure		
Treatment duration 25th percentile, months	2.5	11.1
Mean cumulative dose, mg	54,193.9	67,364.0
Diarrhea, n (%)		
Grade 3 diarrhea*	562 (39.9)	8 (13.3)
Discontinuation due to diarrhea during first 3m of treatment	1204 (14.5)	2 (3.3)
Incidence of all-grade diarrhea	1343 (95.4)	59 (98.3)
AEs, n (%)**	388 (27.6)	8 (13.3)
TEAEs leading to treatment discontinuation	47 (3.3)	1 (1.7)
Grade 3 vomiting	26 (1.8)	0
Grade 3 nausea	24 (1.7)	0
Grade 3 abdominal pain	23 (1.6)	1 (1.7)
Grade 3 fatigue	3 (0.2)	0
Grade 3 decreased appetite	0	0
Grade 3 constipation		
QoL	–4.6	–3.0
FACT-B mean change from baseline at month 1		

*1 pt had grade 4 diarrhea in ExteNET; no grade 4 diarrhea in CONTROL DE. **No grade 4 events observed.

537 **Poster Session**

Clinical validation of EndoPredict in premenopausal women with estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2-) primary breast cancer. *First Author: Anastasia Constantinidou, The Institute of Cancer Research and The Royal Marsden Hospital, London, United Kingdom*

Background: The EndoPredict 12-gene prognostic assay is validated to predict distant recurrence-free survival (DRFS) and response to chemotherapy in post-menopausal women with ER+, HER2- breast cancer. This study evaluated the performance of EndoPredict in pre-menopausal women. **Methods:** Stored tumor samples from women with ER+, HER2- primary breast cancer who were pre-menopausal at the time of diagnosis and were systemically treated with endocrine therapy alone were obtained from two sites (University of Nottingham and University of Cyprus). These samples were tested with EndoPredict to produce a 12-gene molecular score (EP). Pathologic tumor size and nodal status were algorithmically combined with the EP score to produce the clinicomolecular EPclin score. Cases with tumors > pT3, which were treated with chemotherapy, or for whom the EPclin score was missing or invalid were excluded. Associations of EP and EPclin with 10-year DRFS were evaluated in terms of hazard ratios (HRs) from Cox proportional hazards models stratified by cohort. 10-year DRFS was estimated for EPclin high-risk and low-risk women by Kaplan-Meier analysis. **Results:** Out of 411 eligible cases, 385 had a valid EPclin score and were included in the analysis. Mean age at breast cancer diagnosis was 46.5 years (standard deviation 4.7). Most women (N = 239, 62.6%) had grade II tumors and 16.1% (N = 62) had node-positive disease. Over the observation period (median 9.7 years, interquartile range 6.6-13.9 years), 35 women had a distant recurrence within 10 years. Both the molecular EP score and the molecular-clinicopathologic EPclin score were associated with increased risk of distant recurrence [HR 1.3, 95% confidence interval (CI) 1.2-1.5; $p < 0.001$ and HR 3.6, 95% CI 2.3-5.7; $p < 0.001$, respectively]. Of these patients, 249 (64.7%) were categorized as low risk by EPclin score while the remaining 136 (35.3%) were categorized as high risk. Compared to EPclin low-risk women, EPclin high-risk patients were more likely to experience distant recurrence (HR 4.6, 95% CI 1.4-15.2; p = 0.004). At 10 years post-diagnosis, EPclin low-risk women who received endocrine therapy alone had a DRFS of 97% (95% CI 93-99%). Conversely, EPclin high-risk women had a DRFS of only 76% (95% CI 67-82%). **Conclusions:** The EPclin score is highly associated with DRFS in pre-menopausal women who received adjuvant endocrine therapy alone. Based on these data, pre-menopausal women with EPclin low-risk breast cancer may safely forgo adjuvant chemotherapy in addition to endocrine therapy. Research Sponsor: Myriad Genetics, Inc.

538 **Poster Session**

De-escalation of five years adjuvant endocrine therapy duration in patients with ER-low positive (immunohistochemical 1% to 10%) early-stage breast cancer: A propensity-matched analysis from the prospectively maintained database. *First Author: Keda Yu, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: There are limited data on endocrine therapy benefits for patients with estrogen receptor (ER)-low positive breast cancer (staining 1% to 10% of tumor nuclei by immunohistology). We aimed to compare the effect of short-term 2-3 years versus standard 5 years of adjuvant endocrine therapy on survival outcomes in patients with ER-low positive early breast cancer. **Methods:** We used data from the prospectively maintained Breast Surgery Database of Fudan University Shanghai Cancer Center for this propensity-matched analysis. Women with ER-low positive, operable, and unilateral early-stage invasive ductal breast cancer were enrolled in this study. Patients with advanced disease, having received neoadjuvant chemotherapy or ovarian function suppression, or with unknown duration or longer than 5 years of adjuvant endocrine therapy were excluded. Enrolled patients were divided into three groups: received no endocrine therapy; received 2-3 years of endocrine therapy; and received approximately 5 years of endocrine therapy. The primary endpoint was disease-free survival (DFS). Multivariate Cox regression analysis and propensity score matching were performed to minimize bias. Hazard ratios (HR) with 95% CIs were calculated. **Results:** From 2012 to 2017, 634 patients with ER-low positive breast cancer in the database met the inclusion criteria. At a median follow-up of 60 months (interquartile range, 46-74), the 5-year DFS of the whole cohort was 84.9%, with 77.6% for patients who received no endocrine therapy (N = 89), 83.7% for patients who received 2-3 years endocrine treatment (N = 185), and 87.5% for patients who received 5 years endocrine therapy (N = 360). When compared with those receiving no endocrine therapy, patients receiving 5 years treatment was associated with a significantly improved DFS (HR, 0.55; 95% CI 0.32-0.95; P = 0.03); however, there was no significant difference in DFS between patients receiving 2-3 years and 5 years endocrine therapy (HR, 0.79; 95% CI, 0.48-1.28; P = 0.33). In the multivariate Cox regression analysis of the propensity score-matched samples of 360 patients, the DFS was not significantly better for patients who received 5 years of endocrine therapy than 2-3 years treatment (HR, 0.74; 95% CI 0.41-1.34; P = 0.32). An exploratory analysis of re-biopsy of the recurrence lesions indicated more than half of relapsed disease displayed ER-negative, and less than 5% lesions were proved to be ER ≥10% positive. **Conclusions:** Our data did not support the necessity of 5 years duration of endocrine therapy for patients with ER-low positive breast cancer. Short-term 2-3 years duration might be an alternative option. Further translational research on identifying endocrine-sensitive cases within ER-low positive patients is needed. Research Sponsor: Chinese NSFC.

539 **Poster Session**

Comprehensive genomic profiling (CGP) of 275 male breast cancer (BC) tissue (TBx) and liquid (LBx) biopsies: Comparative analysis to a female cohort (FBC) and therapeutic considerations. *First Author: Arun Kadamkulam Syriac, Dana Farber Cancer Institute/St. Elizabeth Hospital, Boston, MA*

Background: Male BC accounts for < 1% of all BC and is often diagnosed at later stage, which can result in higher mortality. Due to the rarity of this diagnosis, limited data exist on genomic alterations and prevalence of cancer susceptibility genes (CSG). We aimed to comprehensively describe the genomics of male BC and compare these to a FBC cohort across subtypes to provide insight on tumor biology and opportunities for targeted therapies. **Methods:** 275 male BC TBx or LBx were sequenced by Foundation Medicine (FM) using hybrid capture-based CGP. Both TBx and LBx were evaluated for all classes of genomic alterations (GA). Histological subtype, receptor status, and biopsy site were extracted from pathology reports. Paired samples with both TBx and LBx were available in 7 cases. The male BC TBx cohort with known receptor status (n = 253) was compared to a FBC cohort (n = 2855). Mutational prevalence in 5 breast CSG *(ATM/BRCA1/BRCA2/CHEK2/PALB2)* were compared along with their associated genomic LOH (gLOH) values. **Results**: Among male BCs, subtype distribution was: ER+/HER2- n = 210 (83%), ER+/HER2+ n = 22 (9%), TNBC n = 20 (8%). ER+/HER2+ male BC cases had higher rates of *ERBB2* SV *(*22.7% v. 0.62%, $p < 0.0001$), *PIK3CA* (68.2% vs. 34%, p = 0.01), *MDM2* amplifications (36% v. 4%, $p < 0.0001$) and *GATA3* (36.6% v. 6.2%, p = 0.0002) than ER+/HER2+ FBC. In the ER+/HER2- cohort, male BC had more alterations in *BRCA2* (13.8% v. 5.3%, $p < 0.0001$) and *GATA3* (26% vs. 15%, p = 0.0004) and less alterations in *TP53* and *ESR1* ($p < 0.0001$ both). 28.6% of male BC v. 16.6% of FBC (p = 0.004) had one or more variants in one of 5 CSG of potential germline origin with a higher % of *BRCA* mutations in male BC vs. FBC (17.5% v. 9.9%, p = 0.0006). In the paired male BC Bx's we saw genomic heterogeneity in a case showing 5 unique *ESR1* alts and a *PIK3CA* SV unique to LBx done at the same time as TBx. We saw evidence of resistance with a shared *BRCA1* alteration and several reversion mutations unique to LBx taken 471 days later, and a longitudinal pair with unique *ESR1,PIK3CA* and *MTOR* mutations in a LBx 547 days apart. **Conclusions**: Although male and female BC share some common alterations, our study revealed potentially important findings that may explain biological differences and provide treatment opportunities. Despite HR+/HER2+ male BC being rare, it was notable for increased co-mutations with *ERBB2* SV, *PIK3CA* SV, and *GATA3* SV, which can be associated with a worse prognosis but perhaps allow more novel combinations. *ESR1* mutations appear more common in ER+/HER2- FBC reflective of treatment with aromatase inhibitors versus tamoxifen for male BC. *TP53* mutations were more common in all subtypes of FBC. *BRCA2* mutations and other potential germline CSG variants were more common in male BC, suggesting an opportunity for PARP inhibitors. LBx identified additional biomarkers and resistance mutations not seen in TBx. Research Sponsor: None.

540 **Poster Session**

Association between treatment duration and overall survival in early-stage HER2+ breast cancer patients receiving extended adjuvant therapy with neratinib in the ExteNET trial. *First Author: Beverly Moy, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Completion of planned treatment has been shown to improve clinical outcomes. In the ExteNET trial (NCT00878709), where diarrhea prophylaxis was not mandated, 17% of patients (pts) discontinued neratinib early due to diarrhea. This compares with 3.3% of pts from the CONTROL trial (NCT02400476) who used a neratinib dose-escalation strategy. Prior analyses have shown improved invasive disease-free survival (iDFS) in pts who completed planned duration of neratinib therapy in ExteNET (Table). Here we assess outcomes, including overall survival (OS), for pts who completed planned therapy in 3 groups from ExteNET: intent-to-treat (ITT) population; pts with hormone receptor-positive (HR+) disease who initiated neratinib within 1y after prior trastuzumab (HR+/≤1y, the population neratinib is approved for in the EU); and HR+/≤1y with residual disease post-neoadjuvant therapy (no pathologic complete response [pCR]). **Methods:** Pts with early-stage HER2+ breast cancer received oral neratinib 240 mg/d or placebo after trastuzumab-based (neo)adjuvant therapy. Pts who completed neratinib therapy (defined as ≥11m or cessation of neratinib if recurrence occurred prior to 11m) were compared with placebo (all randomized pts). iDFS and OS were analyzed using Kaplan-Meier methods; hazard ratios (HR) with 95% confidence intervals (CI) were estimated using Cox proportional-hazards models. Data cutoff: July 2019. **Results:** There were 2840 pts in the ITT population. The table shows iDFS and OS in the overall population and in pts who completed planned duration of neratinib therapy. Completion of planned neratinib was associated with improvements in iDFS and OS in all groups evaluated. **Conclusions:** These descriptive findings suggest that pts who receive the recommended duration of treatment of 1y with neratinib may have improved outcomes. Clinical trial information: NCT00878709. Research Sponsor: Puma Biotechnology Inc.

	N		5-y iDFS rate, %				8-y OS rate, %			
	Neratinib	Placebo	Neratinib	Placebo	Δ[a]	HR (95% CI)	Neratinib	Placebo	Δ[a]	HR (95% CI)
ITT population	1420	1420	90.2	87.7	+2.5	0.73 (0.57–0.92)[b]	90.1	90.2	–0.1	0.95 (0.75–1.21)[b]
Completed therapy[c]	872	1420	91.0	87.7	+3.3	0.68 (0.52–0.90)	92.2	90.2	+2.0	0.78 (0.58–1.04)
HR+/≤1y[d]	670	664	90.8	85.7	+5.1	0.58 (0.41–0.82)	91.5	89.4	+2.1	0.79 (0.55–1.13)
Completed therapy[c]	402	664	93.1	85.7	+7.4	0.44 (0.28–0.68)	95.2	89.4	+5.8	0.49 (0.29–0.78)
HR+/≤1y[d] no pCR[e]	131	164	85.0	77.6	+7.4	0.60 (0.33–1.07)	91.3	82.2	+9.1	0.47 (0.23–0.92)
Completed therapy[c]	92	164	89.5	77.6	+11.9	0.42 (0.20–0.87)	95.4	82.2	+13.2	0.29 (0.01–0.68)

[a]Difference (neratinib vs placebo); [b]Stratified by stratification factors; [c]Defined as ≥11m of therapy or ended treatment due to disease recurrence in neratinib arm, and all randomized subjects in placebo arm; [d]HR+ and ≤1y after prior trastuzumab; [e]Residual disease post-neoadjuvant therapy.

541 **Poster Session**

PD-L1 expression and TOP3A mutation as prognostic factors for adjuvant chemotherapy in triple negative breast cancer. *First Author: Xue Wang, National Cancer Center/National Clinical Research Center for Cancer/ Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Triple negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer that is markedly heterogeneous and lacks specific targets. The aim of this study is to explore potential predictors and therapeutic targets based on clinical and genetic characteristics. **Methods:** 138 patients with triple-negative breast cancer after surgical treatment were 1:1 randomly assigned to the paclitaxel combined with carboplatin (TCb) group or the epirubicin combined with cyclophosphamide sequential paclitaxel (EC-T) adjuvant chemotherapy group. PD-L1 was retrospectively analyzed by surgically resected specimens, and 733 cancer-related genes were detected by NGS. Pathway enrichment analysis was performed using DAVID for functional enrichment genetic alterations. Cox regression models and Kaplan-Meier were used to evaluate disease-free survival (DFS). **Results:** In this study, there was no significant difference in DFS between the TCb and EC-T groups. 31 (22.5%) of 138 TNBC patients were positive for PD-L1 expression, including 15 (10.9%) patients positive for PD-L1 in tumor cells (TCs) and 29 (21.0%) patients positive for PD-L1 in tumor-infiltrating immune cells (TICs). Patients with positive PD-L1 expression, either in TCs or TICs, achieved better DFS [HR=0.13 (95% CI: 0.02-0.93), p=0.016], the difference was also shown in the EC-T group [HR=0 (95% CI: 0- inf), p=0.037], but not in the TCb group [HR=0 (95% CI: 0.04-2.1), p=0.189]. In addition, we identified 7 patients with mutations in DNA topoisomerase IIIα(TOP3A), a homologous recombination (HR)-related gene, and patients with mutations in this gene had worse DFS than those without mutations [HR=4]. However, there was no statistically significant association between BRCA mutation and response to either therapeutic regimens. **Conclusions:** In this TNBC patient population, immunohistochemistry (IHC) and NGS analyses identified potential prognostic markers. PD-L1 positive and TOP3A mutation were significantly associated with early triple-negative breast cancer prognosis. Research Sponsor: Capital Health Development Research Project (2018-2-4023).

542 **Poster Session**

Final five-year median follow-up safety data from a prospective, randomized, placebo-controlled, single-blinded, multicenter, phase IIb study evaluating the use of HER2/neu peptide GP2 + GM-CSF vs. GM-CSF alone after adjuvant trastuzumab in HER2-positive women with operable breast cancer. *First Author: Snehal Patel, Greenwich LifeSciences, Stafford, TX*

Background: The final analysis of the GP2 prospective, randomized, placebo-controlled, single-blinded, multicenter Phase IIb trial investigating GP2+GM-CSF administered in the adjuvant setting to node-positive and high-risk node-negative breast cancer patients with tumors expressing any degree of HER2 (immuno-histochemistry [IHC] 1-3+) (*NCT00524277*) is now complete with 5 year follow-up. The trial enrolled HLA-A02 patients randomized to receive GP2+GM-CSF versus GM-CSF alone. It was previously reported that completion of the GP2+GM-CSF Primary Immunization Series (PIS) reduced recurrence rates to 0% over a 5 year follow-up period in HER2 3+ patients, who received a standard course of trastuzumab after surgery. **Methods**: Each enrolled and consented patient was randomly scheduled to receive a total of 6 GP2+GM-CSF (500 mcg GP2: 125 mcg GM-CSF) or GM-CSF only intradermal injections every 3-4 weeks as part of the PIS for the first 6 months and 4 GP2+GM-CSF or GM-CSF only booster intradermal injections every 6 months thereafter. Boosters were introduced during the trial, thus some patients did not receive all 4 boosters. Injection sight reactions were measured. **Results:** Safety data was analyzed to assess local and systemic toxicity of each treatment arm. Most subjects completed the planned PIS, 81 (91.0%) GP2+GM-CSF and 86 (94.5%) GM-CSF only. In addition, 77 GP2+GM-CSF and 80 GM-CSF only subjects received all 4 booster injections. The most common local toxicities were erythema, induration and pruritis and they occurred with similar frequency in the two treatment arms. Local reactions were reported by almost all subjects over the course of vaccinations. Occurring in a smaller percentage of subjects, the most common systemic toxicities were fatigue, headache, and myalgia/arthralgia, again with similar incidence by treatment group. The majority of all events reported were of Grade 1 mild severity (GP2+GM-CSF 92.5%, GM-CSF only 90.6%). Only 5 events in 4 subjects were considered Grade 3: induration and maculopapular rash/pruritis, in two GP2+GM-CSF subjects and chest pain and hypersensitivity reaction in two GM-CSF only subjects. The incidence of local reactions minimally increased with subsequent vaccinations however, the types of events remain unchanged. No serious adverse events were reported over the full 5 year treatment and follow-up periods. **Conclusions:** The study confirms the finding from the Phase I trial evaluating GP2+GM-CSF that the vaccine is safe and well-tolerated. The majority of patients experienced only mild local and systemic toxicities. Importantly, toxicities in the GP2+GM-CSF group were comparable to those seen in the GM-CSF only group, suggesting the toxicities are attributable to GM-CSF. Clinical trial information: NCT00524277. Research Sponsor: Greenwich LifeSciences.

543 **Poster Session**

Survival following locoregional recurrence in breast cancer by clinical subtype. *First Author: Kirsten Allen, BC Cancer-Kelowna, Kelowna, BC, Canada*

Background: We sought to explore the impact of locoregional recurrence (LRR) on survival in breast cancer (BC) patients in British Columbia treated in the modern era. **Methods:** A retrospective cohort study design identified patients diagnosed with stage I-III BC from 04/2005-12/2013 treated with surgery and who had a subsequent LRR. Exclusions were death or distant metastasis within 120 days of LRR, bilateral previous/synchronous BC, and other invasive cancers. After LRR, overall survival (OS) and factors associated with OS, including clinical subtype and adjuvant therapy (AdTx), were examined. We defined clinical subtypes as: Luminal (Lum) A-estrogen receptor (ER) and progesterone receptor (PR) positive, HER2 negative, and grade 1 or 2; Lum B-as Lum A but grade 3, or as Lum A but only one of ER or PR positive; triple negative (TNBC)-ER and PR and HER2 negative; and HER2 positive (with any ER, PR). In the absence of earlier LRR, we defined adequate AdTx as: (a) TNBC: >=50% of planned chemotherapy (Chx), (b) HER2 positive: >=50% of planned Chx and >=8 cycles of anti-HER2 therapy, (c) Lum A, B: >=4 years of endocrine therapy and (d) after partial mastectomy or positive final margins: >=50% of radiation therapy dosage. **Results:** The final cohort had 492 patients with a median follow-up of 7.2 years from LRR and 11.8 years from diagnosis. LRR was local in 69.3% (n=341) and regional +/- local in 30.7% (n=151). Compared with local only, regional recurrences were associated with higher T and N stage, grade, and Lum status (p<=0.01). Biomarkers were re-evaluated at LRR in 82% and changed from initial diagnosis in 32% of those tested: ER expression 3.8% gain, 6.1% loss; PR expression 9.1% gain, 15.1% loss; HER2 overexpression 3.7% gain and 4.8% loss. Over half of patients (n=255, 52%) did not receive adequate AdTx, either by choice or recommendation. A similar proportion with local vs. regional recurrence had inadequate AdTx. Time to death from 1st LRR did not vary significantly between local vs. regional recurrences (median 2.7 years). OS after LRR was lowest in TNBC (median 3.1 years, 24.2% 10-year OS) and longest in Lum A (median not reached, 64.7% 10-year OS) (Table). **Conclusions:** Our data provide rates of OS after LRR in the era of modern adjuvant therapy. OS after LRR varied by clinical subtype, with TNBC faring the worst, and Lum A the best. Over half had not received adequate AdTx. Despite similar treatment options, OS after LRR was significantly longer for Lum A than B subtypes, underscoring the need for therapy tailored to biology. OS was low in all other subtypes, emphasizing the importance of avoiding LRR. Research Sponsor: Centre Priorities Advisory Group (CPAG) through BC Cancer Foundation.

Overall survival (OS) by clinical subtype (from date of first locoregional recurrence).

n	10 year OS Estimate (%) & 95% CI	Median OS (years), &95% CI	p-value
Luminal A 174	64.7 (55.5, 72.5)	Not reached	<0.001
Luminal B 145	26.8 (17.1, 37.5)	4.8 +/- 0.5	<0.001
HER2+ 85	43.7 (31.2, 55.5)	7.3 +/- 0.4	<0.001
Triple Negative 75	24.2 (13.9, 36.0)	3.1 +/- 0.7	<0.001

544 **Poster Session**

Potential non-drug cost differences associated with the use of the fixed-dose combination of pertuzumab and trastuzumab for subcutaneous injection (PH FDC SC) in the treatment of HER2-positive early breast cancer patients in Western Europe and the United States. *First Author: Federico Manevy, F. Hoffmann-La Roche Ltd., Basel, Switzerland*

Background: In patients with HER2-positive early breast cancer (BC), pertuzumab (P) added to trastuzumab (T) and chemotherapy has been recognized as a standard-of-care, improving the risk of recurrence. P and T treatments can be given intravenously (PT IV) or, more recently, subcutaneously – via PH FDC SC. Both methods are comparable in terms of efficacy and safety profiles. However, PH FDC SC allows for a faster infusion than that of PT IV, and this can be associated with lower costs. The aim of this study is to estimate the incremental difference in non-drug costs between PH FDC SC and PT IV for a typical patient receiving treatment for HER2-positive early BC in Western Europe and the United States. **Methods:** A model-based cost-minimization analysis was performed to quantify mean non-drug cost differences per patient over a full course of therapy (18 cycles). Western Europe: costs in the analysis are based on an archetypal country, and explicitly include estimates for costs for patient chair time, active healthcare professional (HCP) time, usage of non-drug consumables, port-a-cath placement surgeries and patients' productivity losses. Costs are calculated by multiplying the resource use by its corresponding unit price. Costing data were obtained from literature sources on T SC time and cost savings for Western European countries, and assumptions on PH FDC SC and PT IV times and costs. United States: non-drug costs for the two strategies were estimated using average net reimbursement amounts for relevant procedure codes for intravenous and SC therapy administration among commercial payers in the MarketScan databases. **Results:** PH FDC SC is estimated to reduce non-drug costs by 73% – 80% in Western Europe, and 75% in the United States. Total monetary non-drug savings per patient over 18 cycles of treatment are estimated in the range of €2,474 – €8,975 in Western Europe, and at $10,138 in the United States. In Western Europe, where the analysis allows for a disaggregation by cost category, cost savings related to savings in patient chair time (excluding patients' productivity losses) are estimated to account for up to 62% of overall non-drug cost savings. Patients' productivity losses are estimated to explain up to 11% of non-drug cost differences. **Conclusions:** The use of PH FDC SC for the treatment of HER2-positive BC can potentially result in substantial non-drug cost savings. These savings could easily derive in overall net cost savings to the healthcare system, contributing to the long-term sustainability of the healthcare spending, while still providing a safe and effective therapy. Research Sponsor: F. Hoffmann-La Roche Ltd.

	Western Europe	United States
Non-drug cost savings per patient – full course of therapy (18 cycles)	€2,474 (73%) – €8,975 (80%)	$10,138 (75%)

545 **Poster Session**

Impact of endocrine therapy on overall survival in ER negative/PR positive locoregional breast cancer: An analysis of the National Cancer Database. *First Author: Vidya Kollu, Gundersen Health System, Lacrosse, WI*

Background: Breast cancer expressing PR, but not ER (ER-/PR+) are uncommon, comprising 2–8% of breast cancers, with less known about their characteristics and responsiveness to therapy. The role of adjuvant endocrine therapy (ET) in ER-/PR+ locoregional breast cancer is unclear as these patients have been largely excluded from prospective clinical trials. Despite a lack of data patients are often treated with adjuvant ET due to perceived possible benefit. We used the National Cancer Data Base (NCDB) to assess role of adjuvant ET in ER-/PR + breast cancer. **Methods:** Using the NCDB, we included adults ≥ 18 and ≤ 70 years old in order to minimize the non-cancer related deaths. We selected only female patients with stage I, II, and III. Patients have received definitive surgery (lumpectomy with radiation or mastectomy) with negative margins. Systemic therapy (ST) was defined as receipt of chemotherapy and/or immunotherapy. We excluded those who had unknown ST status, unknown ET status, unknown HER 2 status, who did not receive definitive surgery and those whose survival time was missing. Patients were stratified into four groups based on HER2 status and receipt of ET. Both Multivariable Cox proportional hazards regression modeling was utilized to determine predictors of overall survival (OS). A propensity score matched cohort was developed based on relevant demographic and clinical factors. The primary endpoint assessed was OS. All analyses were performed using SAS 9.4. **Results:** We identified 5344 patients (74% were Caucasian, 20% were African American and 6% were others) with ER-/PR+(74% were HER2 - and 26% were HER2 +) locoregional breast cancer (51% were Stage I, 38 % were stage II and 11% were stage III). Grade 1 cancer was seen in 2%, grade 2 in 18%, and majority being grade 3 in 80%. Of which 3093 (58%) patients received ET and 4462 (83%) received ST. Majority of patients were in age group 50-70 comprising of 69% patients, 8 % in age 18—39, 23% in age 40-49 with Charlson-Deyo Score of 0 in 83%, 1 in13%, 2-3 in 4%. In a propensity matched cohort (N=3980), ET was not significantly associated with OS among HER2 negative (HER2-) patients (HR=1.05, 95% CI 0.86-1.28, p=0.63). In HER2+ patient ET was associated with significantly improved OS (HR=0.65, 95% CI 0.42-0.99, p=.047). **Conclusions:** Receiving ET was not associated with improved OS in locoregional ER-/PR+/HER2- breast cancer based on our study using a propensity matched cohort in the NCDB. However, was frequently administered. Interestingly, improved OS was seen in locoregional ER-/PR+/HER2+ breast cancer with adjuvant ET. Research Sponsor: None.

546 **Poster Session**

Chemotherapy induced profound neutropenia (PN) in patients (pt) with breast cancer (BC) after chemotherapy and plinabulin (Plin) plus pegfilgrastim (Peg) combination versus (vs) peg alone: Final phase 3 results from protective-2 (BPI-2358-106). *First Author: Yuankai Shi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: PN [absolute neutrophil count (ANC) of <0.1 cells x 10E9/L)] is the most severe form of chemotherapy (Chemo)-induced neutropenia (CIN), and is associated with severe adverse clinical outcome. According to literature, PN leads to 80% death in first week of infection[1], 48% FN and 50% Infection[2]. Peg is standard of care for the prevention of CIN. Peg has a slow onset of action with absolute neutrophil count (ANC) recovery occurring in week 2 of the cycle (C), leaving patients (pts) vulnerable in the first week of the Cycle (C), which >75% of negative clinical consequences occur. Plin, which received breakthrough designation from FDA, is a novel, non-G-CSF small molecule agent for the prevention of CIN and has CIN protection in week 1 (Blayney JAMA Onc 2020), which is the rationale for adding Plin to Peg to achieve superior protection against CIN throughout the entire cycle vs Peg alone (Blayney, St Gallen 2019; ASCO 2019). **Methods:** Plin is given on Day (D)1 after the last Chemo, has a favorable safety profile, and also has anticancer activity. A phase 3 study evaluating Plin as an anticancer agent (DUBLIN-3; NCT02504489) in NSCLC pts, is fully enrolled, with anti-cancer OS results expected in 2021. In PROTECTIVE-2 (Study 106; NCT0329457), we compare the CIN preventive effects of Plin (on D1) added to Peg (on D2) vs Peg alone. Here we report on PN results. Study 106 is a global multicenter randomized (1:1) double-blind study to evaluate Plin 40 mg + Peg 6mg (Arm 1) versus Peg 6mg + Plac (Arm 2) in early-stage BC (node positive or node negative with a high risk of recurrence) pts (n=221) with ECOG status 0 or 1, receiving docetaxel (75 mg/m2), doxorubicin (50 mg/m2), and cyclophosphamide (500 mg/m2) (TAC). Primary objective was to compare the prevention of severe (Gr 4) neutropenia between Plin+-Peg and Peg+Plac. As an exploratory objective in C1, we evaluated PN between the Plin/Peg and Peg/Plac. ANC (Covance Central Laboratory) was assessed in Cycle 1 (C1) on D 1, 2, 3, 6, 7, 8, 9, 10, 11, 12, 13, and 15. **Results:** Shown in the table below. **Conclusions:** In conclusion, Peg still cannot protect patients with the most severe form of neutropenia, PN, at 46.4% in this study. Adding Plin to Peg offers superior protection for the prevention of profound neutropenia by reducing > 50% of PN, and its clinical sequelae in FN and hospitalization as compared to Peg alone. References: 1. Bodey et al. Ann Intern Med 64(2): 328 (1966); 2. Bodey et al. Cancer 41(4): 1610 (1978). Clinical trial information: NCT03531099. Research Sponsor: BeyondSpring Pharmaceuticals,Inc.

	Pts with PN (%)	Mean duration of PN (days)	Pts with PN and Febrile Neutropenia (%)	Pts with PN and Hospitalizations (%)
Plin/Peg (n=111)	21.6%	0.34	4.2	8.3
Peg/Plac (n=110)	46.4%	0.63	13.7	11.8
p-value	0.0001	0.0004	0.21	0.66

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Head-to-head comparison of single agent (SA) plinabulin (Plin) versus pegfilgrastim (Peg) for the prevention of chemotherapy-induced neutropenia (CIN) in the phase 3 trial PROTECTIVE-1. *First Author: Douglas W. Blayney, Stanford University, Stanford, CA*

Background: Peg is the current standard of care (SoC) for the prevention of CIN, with a low absolute neutrophil (N) count (ANC) week 1 after chemotherapy (chemo) with normalization in week 2. Breakthrough designation agent from FDA, Plin, a novel, non-G-CSF agent for the prevention of CIN, produces a normal ANC in week 1 of cycle (C) 1 by potentially protecting progenitor cells in bone marrow from chemo assault, and also has anticancer activity (Blayney, St Gallen 2019; ASCO 2019). Here we report data from a pre-specified interim analysis from PROTECTIVE-1 (Study 105; NCT03102606). **Methods:** Breast cancer (BC), lung (NSCLC) and prostate cancer (HRPC) pts with at least 1 risk factor as per NCCN, received docetaxel (Doc) 75 mg/m2 with either Peg 6mg (n=53) or Plin 40 mg (n=52) over 4 cycles, and had ANC blood draws on Day (D) 1, 2,6,7,8,9,10,15 in C1 (Covance Central Laboratory). Plin was given on D1, as a 30 min IV infusion, 30 min after Doc, and Peg, 24 hrs after Doc. Primary objective was to demonstrate non-inferiority (NI) of SA Plin vs SA Peg for duration of severe neutropenia (DSN) in C1. NI of Plin vs Peg would be declared if the upper limit of 95% confidence interval for the mean DSN difference between Plin and Peg would be <0.65 day. Other endpoints included C1 platelet count, C1 bone pain scores (validated questionnaire), C1-4 clinical sequelae of CIN through [febrile neutropenia (FN), infection, antibiotic and hospitalization rate, and Doc discontinuation (Discont) and delays], and safety (AEs, hematology and chemistry, vital signs) **Results:** Predefined DSN NI criterion between SA Plin and SA Peg was met. C1 Grade 4 toxicity was not different between Plin and Peg (p=NS). Clinical sequelae of CIN were comparable or slightly better for Plin vs Peg (see Table). Plin caused less bone pain (p=0.01) and less thrombocytopenia (p<0.0001 on D15) vs Peg. AE frequency and overall safety was comparable for SA Plin and SA Peg. **Conclusions:** SA Plin has efficacy for Doc CIN prevention non-inferior compared to SoC Peg, and accordingly has comparable (or numerically better) profile for clinical sequelae of CIN. Plin has an advantage for bone pain, platelet counts, convenience of use (same day vs next day dosing) over SoC Peg and has anticancer activity. Clinical trial information: NCT03102606. Research Sponsor: BeyondSpring Pharmaceuticals,Inc.

	FN	Infection	Antibiotics	Hospitalization	Doc Discont	Doc Delay
Plin (n=52)	0%	7.69%	15.4%	3.84%	13.5%	3.85%
Peg(n=53)	1.89%	15.1%	13.2%	1.89%	26.4%	5.66%

548 **Poster Session**

Long-term outcomes of patients with node-negative (N0), triple-negative breast cancer (TNBC) who did not receive adjuvant chemotherapy according to stromal TILs (sTILs). *First Author: Roberto Antonio Leon-Ferre, Mayo Clinic, Rochester, MN*

Background: sTILs are a well-established prognostic and predictive biomarker in patients with operable TNBC receiving pre or postoperative systemic therapy. We[1] and others[2,3] have also shown that sTILs are prognostic in patients who did not receive adjuvant chemotherapy. Here, we detail the outcomes of systemically untreated patients with N0 TNBC according to sTIL score. We focused on the N0 subset as a group of patients who may be candidates for future prospective therapy de-escalation trials. **Methods:** From a clinically annotated cohort of 605 patients with centrally confirmed TNBC (ER/PR < 1% and HER2 negative) with long-term outcomes data, we identified 182 patients treated with locoregional therapy only (breast surgery +/- radiation therapy and no chemotherapy). The clinicopathological characteristics of this cohort have previously been published[1]. In this analysis, we report the 5- and 10-year invasive disease-free survival (iDFS) and overall survival (OS) rates of patients with N0 TNBC according to sTIL levels. IDFS and OS were defined as per the STEEP classification and estimated using the Kaplan–Meier method. Comparisons of the survival distributions between groups were assessed by the log-rank test. sTILs were assessed as a continuous parameter according to the International TIL Working Group guidelines. For comparisons of outcomes between groups, tumors were classified as lymphocyte-predominant TNBC (defined as containing ≥50% sTILs) vs non-lymphocyte-predominant (< 50% sTILs). **Results:** Of 182 systemically untreated patients, 149 (82%) were N0 and most (78%) were post-menopausal. T stage distribution was T1: 68%, T2: 28%, T3/4: 4%. Among N0 patients, 31 (21%) had lymphocyte-predominant TNBC, and in this group the 5-year iDFS and OS were 89% (95% CI 76-100) and 96% (95% CI 89-100), while the 10-year iDFS and OS were 89% (95% CI 76-100) and 87% (95% CI 73-100), respectively. In contrast, outcomes for patients with non-lymphocyte predominant TNBC were significantly worse. For this group, 5-year iDFS and OS were 62% (95% CI 53-73) and 78% (95% CI 71-86) while the 10-year iDFS and OS were 45% (95% CI 36-58) and 66% (95% CI 68-76), respectively (log-rank p = 0.02 for iDFS and log-rank p = 0.03 for OS). **Conclusions:** sTIL quantification identifies a subset of patients with early-stage N0 TNBC with an exceedingly good prognosis, even in the absence of adjuvant chemotherapy. These data provide support for the evaluation of sTILs as part of prospective investigation of systemic therapy de-escalation strategies in N0 TNBC. References:[1]Leon-Ferre et al, Breast Cancer Res Treat (2018) 167:89-99 [2]Park et al, Ann Oncol (2019) 12:1941-1949 [3]De Jong et al, ESMO 2020 Research Sponsor: U.S. National Institutes of Health.

549 Poster Session

Validation of the RSClin risk calculator using the National Cancer Database (NCDB). *First Author: Frederick Howard, Section of Hematology/Oncology, Department of Medicine, University of Chicago, Chicago, IL*

Background: Clinical practice guidelines recommend the use of genomic assays to aid decision making regarding the use of adjuvant chemotherapy (CT) for hormone receptor-positive, HER2-negative (HR+/HER2-) early breast cancer (EBC). Recently, the RSClin clinical tool, which integrates the 21-gene recurrence score (RS) and clinicopathologic features, was developed using data from the TAILORx trial. By integrating clinical and genomic risk, RSClin demonstrated greater precision in guiding adjuvant CT use in HR+/HER2- EBC than the 21-gene RS alone. As outcomes differed by race and ethnicity in TAILORx, further validation in real world datasets of diverse populations is needed. **Methods:** This study includes patients (pts) from the NCDB who were diagnosed with HR+/HER2- EBC from 2010-2017 and received adjuvant endocrine therapy (ET) with or without CT. RSClin provides a predicted absolute reduction in distant recurrence at 10 years with CT, while the NCDB database only provides overall survival (OS) metrics. While OS underestimates distant recurrence, we correlated RSClin predictions with survival differences between pts receiving ET versus those who received ET plus CT. Inverse probability of treatment weighting was used to correct for differences in age, comorbidity index, insurance, and race/ethnicity. OS benefit of CT was assessed in pts with low ($< 2\%$), intermediate (2-5%), and high ($>5\%$) absolute CT benefit (ACB) per RSClin using the log-rank test. **Results:** 150,268 pts with EBC were included. Average (avg) age was 59 yrs; 84% were white, 8% black, 4% Hispanic, and 4% Asian/Pacific Islander. Avg tumor size was 1.7 cm, avg RS 17, and 82% had lymph node (LN) negative disease. A significant OS benefit with CT was seen in the intermediate (HR 0.70) and high (HR 0.66) RSClin predicted ACB in the LN negative pts. When analyzed by racial / ethnic subgroup, all pts with a high RSClin ACB had improvement in survival with CT; in pts with an intermediate RSClin ACB, only white pts demonstrated significantly higher OS with CT (HR 0.72). **Conclusions:** Although developed to predict distant recurrence rates, the RSClin tool also correlates with OS in pts receiving ET with or without CT, which can aid in clinical decision making in pts with HR+/HER2- EBC. Predictive accuracy of RSClin differs by race/ethnicity. Accurate risk stratification in diverse populations is essential in ensuring equitable treatment and mitigating disparities in breast cancer outcomes in different racial/ethnic groups. Research Sponsor: U.S. National Institutes of Health.

550 Poster Session

Molecular characterization of luminal breast tumors in African American women. *First Author: Yael Simons, University of Illinois at Chicago College of Medicine, Division of Medical Oncology, Chicago, IL*

Background: Racial disparities in breast cancer (BC) mortality are attributed to later stage diagnoses and a higher incidence of triple-negative BC among African American (AA) women. In previous work, we showed that AA women with ER+ BC are more likely to develop biologically aggressive disease and are more likely to die from early stage, ER+ BC than non-Hispanic White women (Hoskins et al, JAMA Oncol, 2021). The underlying molecular drivers of this disparity are unknown. Here we report the molecular characterization of a series of luminal BC from AA women. **Methods:** Consecutive breast tumor specimens received in the Pathology Department underwent next generation sequencing (NGS). Unstained FFPE tissue sections were macrodissected to isolate tumor cells, and nucleic acids were extracted using commercially available kits. DNA and RNA sequencing libraries were prepared with the Oncomine Comprehensive Assay v3 (OCAv3) (Thermo Fisher), which includes 161 driver genes and detects SNVs, CNVs, INDELs and gene fusions. Sequencing was performed on the Ion S5XL sequencer. Sequencing reads were mapped to the UCSC human genome build GRCh37/hg19 using Torrent Suite™ software (version 5.10; Thermo Fisher). Data analysis and variant calling was performed using the Ion Reporter analysis tool. **Results:** We identified 60 somatic driver gene alterations in luminal tumors from 35 AA patients (primary tumors, n = 26; metastatic tumors, n = 9). Recurrently altered genes identified in $> 5\%$ of tumors are listed in the Table. The most frequently altered gene was *PIK3CA* (42% of tumors). *ESR1* gene fusions were seen in 25% of tumors. Interestingly, an equal frequency of *ESR1* fusions were detected in primary (27%) and metastatic (22%) tumors, in contrast to activating mutations which are found in recurrent tumors following treatment with aromatase inhibitors. *ARID1A* alterations were identified in 17% of primary tumors. *ARID1A* encodes a subunit of the SWI/SNF chromatin remodeling complex. Alterations in *ARID1A* confer endocrine resistance, and are enriched in recurrent tumors in the literature. We also found a high number of CNVs in members of the *FGF* gene family (36% of tumors), which are also associated with resistance to endocrine therapy. An *in silico* analysis comparing our findings with publicly available datasets will be presented. **Conclusions:** This study of somatic driver gene alterations in a consecutive series of luminal breast tumors from AA patients found a higher than expected frequency of alterations in genes associated with endocrine resistance in untreated primary tumors, suggesting a partial explanation for racial disparities in survival. Research Sponsor: None.

Recurrent somatic alterations in driver genes.

Gene	Number of tumors with alteration (%)
ARID1A	6 (17%)
ATM	4 (11%)
CCND1	5 (14%)
ERBB2	7 (20%)
ESR1	2 (6%)
ESR1-AKAP12	3 (8%)
ESR1-ARMT1	2 (6%)
ESR1-CCDC170	4 (11%
FGF19	4 (11%)
FGF3	4 (11%)
FGFR1	5 (14%)
PIK3CA	15 (42%)
PTEN	4 (11%)
SLX4	4 (11%)
TP53	4 (11%)

551 Poster Session

Population-based estimates of the age-specific cumulative risk of breast cancer for pathogenic variants in *CHEK2*: Findings from the Australian Breast Cancer Family Registry. *First Author: Tu Nguyen-Dumont, Monash University, Clayton, Australia*

Background: Case-control studies of breast cancer have consistently shown that pathogenic variants in *CHEK2* are associated with about a 3-fold increased risk of breast cancer. Information about the recurrent protein truncating variant *CHEK2*c.1100delC dominates this estimate. There have been no formal estimates of age-specific cumulative risk of breast cancer for all *CHEK2* pathogenic (including likely pathogenic) variants combined. **Methods:** We conducted a genetic screen of *CHEK2* in an Australian population-based case-control-family study of breast cancer. This study is focused on disease at an early age and participants were unselected for family history. The age-specific cumulative risk (penetrance) of breast cancer was estimated using segregation analysis. **Results:** The estimated hazard ratio for carriers of pathogenic *CHEK2* variants (combined) was 4.9 (95% CI 2.5-9.5; $p < 0.0001$) relative to non-carriers. The HR for carriers of the *CHEK2* c.1100delC variant was estimated to be 3.5 (95% CI 1.02-11.6) and the HR for carriers of all other *CHEK2* variants combined was estimated to be 5.7 (95% CI 2.5-12.9). The age-specific cumulative risk of breast cancer was estimated to be 18% (95% CI 11-30%) and 33% (95% CI 21-48%) to age 60 and 80 years, respectively. **Conclusions:** These findings provide important information for the clinical management of breast cancer risk for women carrying pathogenic variants in *CHEK2*. Research Sponsor: National Breast Cancer Foundation Australia, Monash University.

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Use of a high-sensitivity anti-Mullerian hormone (AMH) assay to determine ovarian function after chemotherapy for early breast cancer. *First Author: Florian Clatot, INSERM U1245, IRON Group, Centre Henri Becquerel, University Hospital, University of Normandy, Rouen, France*

Background: It is now well established that AMH can indicate the extent of chemotherapy-induced damage on the ovarian reserve. Very low AMH levels in women after chemotherapy for early breast cancer (eBC) may indicate treatment-induced premature ovarian failure (POI), but the evidence to implement its routine clinical use remains limited. **Methods:** AMH was measured (Roche cobas autoanalyser) in 197 women aged 40-45 years at diagnosis treated with anthracycline/cyclophosphamide/taxane based chemotherapy for eBC, with no previous endocrine therapy and no subsequent aromatase inhibitor exposure or ovarian suppression. 76% were ER positive and received tamoxifen. The primary objective was to assess the relationships between AMH levels at 6 months after chemotherapy (AMH6) with subsequent ovarian function at 30 months. This included accuracy of prediction of loss of ovarian function at 30 months (E30) after chemotherapy by AMH levels at 6 months (AMH6) and the value of other endocrine/clinical factors pretreatment and at 6 months. Multivariate analysis was performed with data were split into 70% training and 30% testing sets with results reported for model performance on the test set. **Results:** AMH fell from a median of 0.62 (IQR 0.21-1.31) ng/ml pretreatment to become undetectable (< 0.01ng/ml) in 137 (70%) of women at 6 months. AMH showed very little recovery, being undetectable in 115 women at 18 months and 119 at 30 months. In those with detectable AMH at 30 months, it remained very low, median 0.07ng/ml, max 0.82ng/ml but nevertheless it reflected ovarian function. Thus median estradiol at 30 months (E30) was 50 pmol/l (IQR 34-68) in women with undetectable AMH at that time, vs 313 pmol/l (IQR 102-1052) in the 80 women with detectable AMH. AMH at 6 months was predictive of ovarian function at 30 months, as E30 was 56 pmol/l (IQR 40-104) in women with undetectable AMH6 vs 258pmol/l (IQR 69-780; $p < 0.0001$) in women with detectable AMH6, and the positive predictive value (PPV) of AMH being undetectable at 6 months and remaining so at 30 months was 77%. Random forest analysis identified BMI as a non-endocrine predictive factor of E30. Using a stringent cutoff of $\leq$50pmol/l (13.6 pg/ml) and adding 1:9 weighting to improve PPV gave a test validated PPV of 79.0% while maintaining AUC at 83.7% for prediction of E30. Other classifiers performed less well than random forests. **Conclusions:** Measurement of AMH at 6 months after chemotherapy has predictive value for later ovarian function, and combining this with other endocrine and baseline data improves discriminative ability. This approach indicates the potential role of multivariate analysis based on AMH measured shortly after chemotherapy to helping optimise subsequent endocrine therapy. Research Sponsor: Institutional funds, Pharmaceutical/Biotech Company.

553 **Poster Session**

A gp78/AMFR protein-driven gene signature that predicts breast cancer outcome. *First Author: Sandeep K Singhal, Department of Pathology, School of Medicine and Health Sciences, University of North Dakota, Grand Forks, ND*

Background: gp78, also known as the autocrine motility factor receptor (AMFR) or RNF45, is a polytopic RING-type E3 ubiquitin ligase resident to the endoplasmic reticulum (ER) that plays major role in the cellular response to stress by regulating ER homeostasis and signaling through its participation in the unfolded protein response (UPR) and ER associated degradation. We used machine learning (ML) and statistical modeling (SM) to assess gp78 as a protein biomarker that is an independent predictor of breast cancer (bc) survival exclusively in women of self-reported African descent as opposed to European ancestry. **Methods:** We examined a cohort of racially diverse 555 BC bc patients who underwent surgery for their primary BC in Greenville, NC using ML and SM approach. We leveraged the availability of RNA-seq gene expression data on a portion of our bc cohort (N=136 of 555) to construct gene expression signatures. **Results:** Using antibodies developed in the Weissman lab and established methods for quantitative IHC, we have found that gp78 expression is significantly increased in the tumors of bc patients compared to normal breast epithelia. In addition, we found that gp78 is expressed at significantly higher levels in bc of non-Hispanic black women (NHB) compared to non-Hispanic white women (NHW) (p=0.0038), and that bc subtypes known to be more aggressive and associated with higher grades like, Basal (p=1.6e-12), Luminal B (p=2.3e-4) and HER2(8.3e-4), display significantly higher levels of gp78 compare to Luminal A. Moreover, Kaplan-Meier survival curve analyses show that gp78 protein expression is more significantly associated with poor survival in NHB women (HR:1.65, p=0.073) compared to NHW women (HR:2.01, p=0.004). Finally, multivariate analysis reveals that gp78 protein expression, based on quantitative IHC, is an independent predictor of poor bc survival exclusively in women of African (NHB) ancestry (HR:1.99, p=0.017). We leveraged the availability of RNA-seq gene expression data on a portion of our bc cohort to construct gene expression signatures or gene modules. An analysis of pooled publicly available data from 845 patients that underwent neoadjuvant chemotherapy for bc (primarily taxane and anthracycline based), reveals that gp78 gene modules are highly predictive of patient response to therapy. gp78-derived gene modules show both high fold difference and significance in predicting response to therapy (AUC:0.72) which is very similar to other multi-gene panels that are currently in clinical use including Prosigna, MammaPrint, and Oncotype Dx. **Conclusions:** Our results show that gp78/AMFR is an independent predictor of bc survival and response to therapy, based on race, thus implicating a role for this protein, and potentially the UPR, as underlying biological differences in tumor properties linked to genetic ancestry. Research Sponsor: None.

554 **Poster Session**

Neoadjuvant talazoparib (TALA) in patients (pts) with germline *BRCA1/2* (g*BRCA1/2*) mutation-positive, early HER2-negative breast cancer (BC): Exploration of tumor *BRCA* mutational status and zygosity and overall mutational landscape in a phase 2 study. *First Author: Melinda L. Telli, Stanford University School of Medicine, Stanford, CA*

Background: TALA is a poly(ADP-ribose) polymerase inhibitor approved as monotherapy for adult pts with g*BRCA1/2*-mutated HER2-negative locally advanced/metastatic BC. We report biomarker analyses from a phase 2, nonrandomized, single-arm, open-label study (NEOTALA; NCT03499353) evaluating the efficacy and safety of TALA in the neoadjuvant setting for pts with early g*BRCA1/2*-mutated HER2− BC. Efficacy and safety results are presented separately. **Methods:** The biomarker analysis population was all pts treated with TALA for whom biomarker results are available. To support molecular eligibility, blood was tested using BRCAnalysis CDx (Myriad Genetics). Baseline tumor tissue was retrospectively tested using FoundationOne CDx, with *BRCA1/2* zygosity assessed using somatic-germline-zygosity (SGZ; Sun et al. JCO PO, 2018). Germline mutational status of 14 non-*BRCA* DNA damage response (DDR) genes was retrospectively assessed in baseline saliva samples using Ambry CustomNext-Cancer. Mutations were defined as known/likely pathogenic/deleterious variants, including copy number alterations (CNAs). Association between mutational status of *MYC* or *RAD21* and primary endpoint pathological complete response (pCR) as per Independent Central Review was investigated with logistic regression. **Results:** Of 52 evaluable tumor samples from 61 treated pts, 39 (75%) and 13 (25%) pts exhibited *BRCA1* and *BRCA2* mutations, respectively; 1 (2%) pt exhibited mutations in both genes, and 1 (2%) pt had mutations in neither. *BRCA* loss of heterozygosity (LOH) was seen in 42/43 (98%) evaluable *BRCA*-mutant tumors. Of 45 pts evaluable centrally for both germline and tumor, 44/45 (98%) pts exhibited the same *BRCA* mutation in tumor as originally detected in germline, with the remaining pt exhibiting a g*BRCA1* mutation, but lacking a tumor *BRCA* mutation. None of 49 saliva-evaluable pts exhibited non-*BRCA* germline DDR mutations. *TP53* (51 [98%] pts) was the most frequently mutated gene in tumors. *MYC* and *RAD21* (each 14 [27%] pts) were the most frequent CNAs. No evidence of association between mutational status of *MYC* or *RAD21* and pCR was found (odds ratio=0.39, 95% CI 0.12-2.30). Based on a cutoff of ≥16%, genomic LOH was elevated in 24/27 (89%) tumors evaluable for both gLOH and pCR, precluding assessment of the potential association of gLOH high/low status with pCR. **Conclusions:** Tumor *BRCA* mutations were evident in nearly all pts in the biomarker analysis population, with *BRCA* LOH evident in all but 1 *BRCA*-mutated tumor. No pts had non-*BRCA* germline DDR gene mutations; tumor *TP53* mutations were near-universal. *MYC* and *RAD21* each exhibited CNAs in 27% of tumors, with no association with pCR. These results support the central role of *BRCA* mutations in tumor pathobiology in this indication. Clinical trial information: NCT03499353. Research Sponsor: Pfizer Inc.

555 **Poster Session**

ER and immune-related signatures define benefit to palbociclib, trastuzumab, pertuzumab +/- fulvestrant in ER+/HER2+ breast cancer patients in the NA-PHER2 trial. *First Author: Giampaolo Bianchini, IRCCS Ospedale San Raffaele, Milan, Italy*

Background: In the NA-PHER2 study we assessed the association between biological pathways with pathological complete response (pCR) and Ki67 down-regulation **Methods:** Patients with centrally confirmed ER+ (> 10%) HER2+ breast cancer (BC) were treated in two independent, non-randomized cohorts with neoadjuvant trastuzumab, pertuzumab, palbocilib with (Fulv, n = 30) or without (NoFulv, n = 28) fulvestrant (+/-LHRH analogues). We assessed RNA-seq on core-biopsies obtained pre-treatment [n = 53/58 (91.4%)], at day 14 [n = 49/58 (84.5%)], and on residual disease at surgery [n = 42/45 (93.3%)]. We investigated biomarker dynamics and association with pCR or Ki67 down-regulation (centrally evaluated) at day 14 and at surgery. In the overall population and in each cohort, we primarily assessed three pre-defined biomarkers (ER-metagene [from OncotypeDX], a CD8-metagene and ERBB2 expression), and secondarily we explored a pre-defined list of genesets. Continuous and categorical (median cut-point) variables were evaluated. **Results:** In the biomarker population, pCR rate was 22.5% (28.6% and 16.0% in Fulv and NoFulv cohorts). At baseline, continuous CD8-metagene (OR 1.85 [1.12-3.06], p = 0.016) and ER-metagene (OR 0.56 [0.34-0.90], p = 0.016) associated with higher and lower pCR rate, respectively. High ERBB2 (above median) was marginally associated with pCR (OR 3.83 [0.90-16.3], p = 0.068). Only ER- and CD8-metagenes retained significance in multivariate analysis and were similarly predictive in both cohorts. Combining categorical variables, the groups with high-CD8/low-ER and low-CD8/high-ER had 61.5% and 0% pCR rate respectively, whereas low-CD8/low-ER and high-CD8/high-ER had similar 15% pCR (p = 0.001). The association was significant in both cohorts (p = 0.019 Fulv; p = 0.028 NoFulv). Dynamic assessment of the same biomarkers at day 14 did not improve prediction. Higher ER-metagene at baseline, but not CD8 and ERBB2, was associated with robust down-regulation of Ki67 at day 14 (Ki67 < 2.7%, complete cell cycle arrest) only in Fulv cohort (p = 0.016). ER-metagene also associated with retained Ki67 down-regulation (Ki67 < 10%) at surgery (p = 0.002). Alternative ER- and immune-related signatures provided very similar results. The comprehensive landscape of complex molecular dynamics and exploratory association with outcome will be presented. **Conclusions:** In ER+/HER2+ BC, low expression of ER-related and high expression of immune-related genes identified patients with very high likelihood of achieving pCR with a chemo-free regimen. In the fulvestrant cohort, the group with high ER-metagene, despite a lower pCR rate, had higher Ki67 down-regulation at day 14, which has been associated with long-term benefit in luminal tumors. These findings provide a potential tool for tailored de-escalation strategies. Research Sponsor: Associazione Italiana per la Ricerca sul Cancro (AIRC), Breast Cancer Research Foundation (BCRF), Fondazione Michelangelo, Supported in part by unrestricted grants from Hoffman-La Roche and Pfizer.

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Dysregulation of soluble immune checkpoint proteins in newly-diagnosed early breast cancer patients. *First Author: Bernardo Leon Rapoport, Department of Immunology, Faculty of Health Science, University of Pretoria, Pretoria, South Africa*

Background: Checkpoint proteins regulate the immune system. Breast cancer (BC) cells exploit the up-regulation or down-regulation of these proteins to evade anti-tumor immune responses. Soluble forms of immune checkpoint molecules (ICM) can be measured in human plasma, however their biological and clinical significance remains essentially unknown. The aim of the present analysis was to measure the pre-treatment ICM in newly- diagnosed BC patients (pts) and compare them to healthy controls. **Methods:** Soluble forms of ICM, as well as cytokines and chemokines, were measured using Multiplex bead array and ELISA technologies. Plasma samples from 98 BC pts and 45 healthy controls were analyzed for each protein. Data was prospectively obtained. Measured levels were compared between BC pts and healthy controls using a non-parametric test (Mann-Whitney). P-values below 0.05 were considered statistically significant. **Results:** Soluble stimulatory molecules GITR ($p < 0{,}000002$), GITRL ($p < 0{,}007$), CD27 ($p < 0{,}002$), CD28 ($p < 0{,}003$), CD40 ($p < 0{,}003$), CD80 ($p < 0{,}009$), ICOS ($p < 0{,}0006$), as well as inhibitory molecules PD-L1 ($p < 0.0000001$), CTLA-4 ($p < 0{,}005$), TIM-3 ($p < 0{,}00006$), HVEM ($p < 0{,}00002$) TLR-2 ($p < 0{,}05$), levels were significantly lower in early BC pts compared to healthy controls. When analyzed according to BC characteristics (TNBC vs. non-TNBC, tumor size, stage, nodal status and age) no significant difference was detected between the soluble levels of these ICM between the different subsets. Additionally, serum CXCL5 ($p < 0{,}000001$), CCL23 ($p < 0{,}04$), IL-16 ($p < 0{,}00005$), interferon-α ($p < 0{,}03$) and IL1-RA ($p < 0{,}03$) were significantly lower compared to healthy controls. Serum CX3CL1 or fractalkine ($p < 0{,}024465$) was significantly higher compared with healthy controls. Serum interferon-γ ($p < 0{,}2$), IL-6 ($p < 0.6$) and IL-2 ($p < 0.6$) levels were not significantly different between the BC pts and the healthy controls. **Conclusions:** We identified low levels of both the stimulatory and inhibitory immune checkpoint molecules, in newly-diagnosed, non-metastatic BC pts compared to healthy controls. These results indicate that early BC is associated with a down-regulation of both soluble stimulatory and inhibitory immune-checkpoint pathways. Newly-diagnosed early BC pts have a generalized immune-suppression independent of subtype (TNBC vs non-TNBC) and stage, which, to our knowledge, is the first study to describe soluble immune checkpoints in early BC pts. Research Sponsor: CANSA Cancer Association of South Africa.

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Genomic characteristics of breast cancer to predict response of neoadjuvant chemotherapy and long-term prognosis. *First Author: Ji-Yeon Kim, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: To precisely predict neoadjuvant chemotherapy (NAC) response and long-term prognosis, we developed prediction model with clinical and genomic characteristics of breast cancer (BC). **Methods:** We included early and locally advanced BC that would be scheduled to receive standard NAC (four cycles of anthracycline and cyclophosphamide and four cycles of docetaxel or docetaxel plus trastuzumab for HER2+ BC) followed by curative surgery. For each patient, tumor tissue and matched blood were prospectively collected three times: at diagnosis (T1), three weeks after the first cycle of chemotherapy (T2), and curative surgery (T3). Whole exome sequencing (WES) was performed to detect somatic mutation, mutational signature and tumor mutational burden (TMB) while RNASeq with PAM50 prediction was to classify intrinsic subtype. In terms of clinical variables, clinical stage and IHC subtype at diagnosis, residual cancer burden (RCB) class and distant recurrence free survival (DRFS) were used. Logistic regression was used for predicting RCB class with clinical and genomic variables at T1. Univariate and multivariate Cox regression were performed to identify prognostic factors for DRFS. **Results:** In total, 210 patients were enrolled and treated with NAC as scheduled. We successfully conducted WES in 231 BC tissues (T1:117, T2:101 and T3:13) from 117 patients. In NAC response, 13 patients were in RCB class 3, 39 in class 2, 14 in class 1 and 46 in class 0. Median follow up duration was 44months and distant recurrence was observed in 13 patients. *TP53* mutation (68%) was the most commonly detected genetic alteration. *ARID1A*, *CDH1*, *CSMD3*, *LRP1B*, *PIK3CA*, *RUNX1* and *TP53* were significantly mutated genes in driver gene analysis. Median TMB was 87 (range, 14-570) and signature 3 was most frequently observed. Among genetic characteristics, high TMB was significantly associated with better NAC response compared with low TMB (hazard ratio[HR] for RCB class III: 0.11, 95% confident interval[CI]: 0.01, 0.74, p = 0.05). In prediction model, combination of seven variables: intrinsic subtype, TMB, *LRRK1*, *OPLAH*, and *PIK3CA* hotspot mutation, *ERBB2* amplification, and clinical stage had 0.83 in area under curve (AUC) and 0.75 in accuracy. High clinical stage, *PTEN* and *PIK3CA* hotspot mutation negatively affected to DRFS while high TMB had protective effect (all ps < 0.05). Prediction model made with five variables: intrinsic subtype, TMB, *PTEN* mutation, *PIK3CA* hotspot mutation and clinical stage had 0.88 in c-index (95% CI: 0.81, 0.95). **Conclusions:** TMB, *PIK3CA* hotspot mutation and clinical stage showed predictive roles on NAC response and distant recurrence of BC in NAC setting. In prediction model, intrinsic subtype, TMB, *LRRK1*, *OPLAH*, and *PIK3CA* hotspot mutation, *ERBB2* amplification, and clinical stage affected to RCB class while intrinsic subtype, TMB, *PTEN*, *PIK3CA* hotspot mutation and clinical stage did to DRFS. Clinical trial information: NCT02591966. Research Sponsor: None.

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MamaPred: A new and innovative approach to determine recurrence risk in HR+/HER2- early-stage breast cancer using HTG EdgeSeq technology. *First Author: Jose Antonio Lopez Guerrero, Department of Pathology, Medical School, Catholic University of Valencia, Valencia, Spain*

Background: Genomic platforms, such as Mammaprint (Agendia) (MP) and OncoType (Genomic Health) (OT), have been validated to determine the risk of relapse in therapeutic decision-making in early-stage hormone receptor positive (HR+), epidermal growth factor receptor 2 (HER2) negative breast cancer (BC). Discordances in risk allocation between these platforms affect up to 30% of patients. This study aims to develop the MamaPred test to improve the diagnostic performance of recurrence risk in HR+/HER2- early-stage BC. **Methods:** A total of 606 HR+/HER2- early-stage BC previously tested with OT [n = 287; Low Risk (LR) = 165, Intermediate Risk (IR) = 103 and High Risk (HR) = 19] and MP (n = 319; LR = 217 and HR = 102) were included. A retrospective independent series of 144 HR+/HER2- early-stage BC [median follow-up: 10.53 years (range: 3.1-23.1 yrs); age (median = 62.9 yrs (33-89 yrs); systemic relapse 10.5% (n = 15)] was used as validation set.The expression levels of 2560 cancer-related mRNAs were evaluated from one 5 μm thin-section of a FFPE block (15 mm2 tumor area) using the Oncology Biomarker Panel (OBP) and the HTG EdgeSeq System (HTG Molecular Diagnostics. Inc) and quantified by NGS on a NextSeq550 sequencer (Illumina). A predictive model was built from normalized and logarithmically transformed values (rescaled to [0, 1]) using as response a binary metavariable constructed by taking the values -1 (for LR of MP and OT together the OT IR) and 1 (for HR MP and OT). Differential expression, GSEA and visualization were performed with DESeq2, gage and pathview packages respectively in R v4.0.1. **Results:** MamaPred consists of a logistic regression classifier with an elastic net penalty (mix of L1 and L2 priors as regularizer) where the mixing parameter is optimized along with regularization strength by selecting the ones that minimize the area under the precision and recall curve over a validation split for each training fold. Metrics of MamaPred were: balanced accuracy, 80.5%; Kappa, 0.562; specificity, 80.7%; and NPV, 91.4%. GSE analysis on differentially expressed genes ($q < 0.1$) showed four KEGG pathways overrepresented in HR ($p < 0.05$): *adherens junction*, *tight junction*, *glutathione metabolism* and *focal adhesion*; and two underrepresented: *DNA replication* (p = 0.0765) and *pyrimidine metabolism* (p = 0.086).The prognostic prediction of MamaPred was validated on the independent retrospective series, distant disease-free survival for HR and LR being 88.63% (95% IC: 78.72%-99.78%) and 98.1% (95% IC: 95.6%-100%) respectively (p = 0.00603). Correlation between the probabilities assigned to any given sample and its replicas was extremely high ($r > 0.9$ $p <$ 1e-5). **Conclusions:** MamaPred identifies HR+/HER2- early-stage BC patients with high-risk of distant relapse improving the prognostic value of those studies that compare MP and OT, suggesting a more precise risk classification. Research Sponsor: HTG Molecular Diagnostics, Own resources.

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Gene expression associated with lymphovascular invasion and genomic risk in early-stage breast cancer. *First Author: Nina D'Abreo, Perlmutter Cancer Center at NYU Langone Hospital-Long Island, NYU Long Island School of Medicine, Mineola, NY*

Background: Lymphovascular invasion (LVI), the passage of carcinoma cells through lymphatic and blood vessels, is an important early step in metastasis; however, LVI is excluded from most breast cancer (BC) clinical risk assessments. Previous studies assessed the prognostic value of LVI to estimate clinical outcomes. To gain understanding of the molecular basis of LVI, we evaluated differentially expressed genes (DEGs) between tumors with LVI *versus* those without LVI, stratified by the 70-gene signature (MammaPrint/MP) and 80-gene molecular subtyping signature (BluePrint/BP). **Methods:** The prospective, observational FLEX Study (NCT03053193) includes stage I-III BC patients who receive MP/BP testing and consent to full transcriptome and clinical data collection. Patients with LVI (n=581) and without LVI (n=600, randomly selected), enrolled from 2017 to present, were included. LVI was assessed by local pathology laboratories. Differential gene expression analysis of 44k Agilent microarray data was performed with R limma package. DEGs were compared within all samples, BP Luminal subtype, MP risk groups (Low Risk [LR]/Luminal A and High Risk [HR]/Luminal B), and by lymph node (LN) status. DEGs with FDR<0.05 were considered significant. **Results:** Of tumors with LVI (LVI+), 66% were MP HR; notably, 51% of tumors without LVI (LVI-) were MP HR. LVI was associated with larger T stage, LN involvement, high grade, negative ER status by IHC, and younger patient age (LVI+ vs. LVI-, $p<0.05$ for all comparisons). Patient ethnicity, obesity, and tumor type did not differ by LVI status; however, prevalence of type 2 diabetes trended higher in patients with LVI+ HR tumors (21%), compared with LVI- HR (15%, p=0.09) and LVI+ LR (11%, p=0.004). There were significant transcriptomic differences between LVI+ and LVI, *with most DEGs evident in the Luminal B subset.* DEGs in LVI+, LN-negative (LN-) tumors overlapped substantially with the overall Luminal group analysis. Functional enrichment analysis showed dysregulation of cell cycle, extracellular matrix (ECM) organization, cell adhesion, and cytokine receptor pathways. Gene sets related to insulin growth factor pathways were also enriched in LVI+ tumors. **Conclusions:** DEGs associated with LVI were primarily found in MP HR Luminal, LN-negative tumors; enrichment analysis suggested dysregulation of ECM organization and cell adhesion pathways, consistent with previous reports. DEGs were not associated with LVI presence in LN+ tumors, suggesting that LVI assessment may be less relevant in LN+ breast cancer. Future studies will assess clinical outcomes, as well as LVI-associated gene expression in BP Basal- and HER2-type tumors. However, the current analysis indicates few DEGs in LVI+ MP LR tumors; thus, the potential prognostic information gained from LVI-associated gene expression is likely already captured by the MP and BP signatures. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

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Race, subjective social status and metabolic syndrome in women with breast cancer. *First Author: Giampaolo Greco, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Metabolic syndrome (MS) is associated with worse breast cancer prognosis. Black women have higher rates of advanced breast cancer, as well as MS, diabetes and obesity. As socioeconomic status is associated with MS, we asked whether the subjective perception of social status (SSS), might influence this association in black and white women with a new breast cancer (BC) diagnosis. **Methods:** We surveyed, obtained serum and conducted anthropometric measures of 1206 women with a new BC diagnosis. Triglycerides, systolic blood pressure (SBP), waist circumference (cm), HDL and glucose were used to calculate a severity index of MS (MS-Zscore: mean=0; sd=1). Women reported their SSS on the 10 rung McArthur US social status ladder, their household income, education attained, diet quality (5 point scale), and exercise measured with metabolic equivalents (METS). Data were analyzed with multivariable generalized linear models. Missing data were imputed with multiple imputation. **Results:** Average age was 58 yrs of 295 black and 911 white women. BC stage > II was in 11.6% of black and 2.4% of white women. On average black women had higher BMI (31.5 vs 26.6; p<0.001), waist circumference (103 vs 93; p<0.001) glucose (96 vs 92; p<0.001) and SBP (132 vs 126; p<0.001); lower triglycerides (92 vs 104; p<0.001) and HDL (59 vs 68; p<0.001). Black women were more likely than white women to live in poverty (23.7% vs 4.6%; p<.001); report poor diet (32.4% vs 10.4%; p<.001) and less exercise (29.7% v 23.6% in the 25th %ile), and less likely to graduate college (30.3% vs 70.4%). MSZ-score was positively associated with age (.02 per year; p<.001) and black race (0.35; <.001) and negatively with better diet (-.20 per point in 4 point scale); p<.001), exercise (-.11 per quartile increase in METS; p<.001) and SSS (-.04 per ladder rung; p=.004). SSS was lower in black women within the same levels of income and education). **Conclusions:** Race, age, diet, exercise and subjective social status all impact metabolic syndrome, a risk factor for breast cancer. Of concern, among breast cancer patients, black women are more likely to rate their SSS below white women, within each education or income level. Subjective social status among women with a new breast cancer diagnosis is associated with MS and may be important to address as a risk factor among breast cancer patients. Research Sponsor: U.S. National Institutes of Health.

U.S. ladder by income and education.

		WHITE	BLACK	P value
INCOME	POVERTY	6.2 ± 0.4	5.3 ± 0.3	<.001
	≤$50,000	6.6 ± 0.2	6.1 ± 0.2	
	$50,000-75,000	7.0 ± 0.2	6.6 ± 0.3	
	-$75,000	7.7 ± 0.1	6.9 ± 0.2	
EDUCATION	Up to High School	6.5 ± 0.2	6.0 ± 0.2	<.001
	Some college Vocational School	6.9 ± 0.2	6.1 ± 0.2	
	College Graduate	7.7 ± 0.1	6.6 ± 0.2	

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Association of allograft rejection response score with biological cancer aggressiveness and with better survival in triple-negative breast cancer (TNBC). *First Author: Masanori Oshi, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Although the importance of immunity in the progression of breast cancer was widely reported, the clinical relevance of enhanced immune response is still unclear. We hypothesized that the enhanced immune response is associated with better breast cancer patient survival. **Methods:** We used 6,245 breast cancer patient sample data from publicly available data sets (METABRIC, GSE96058, TCGA cohorts). To elucidate the function of immunity in breast cancer, we calculated the immune function score using hallmark allograft rejection gene sets by Gene Set Variation Analysis algorithm. **Results:** The immune response score correlated most with cytolytic activity among hallmark immune-related gene sets in both cohorts (Spearman's rank correlation (r) = 0.892 and 0.860, respectively, both $p < 0.01$). The score reflected the amount of infiltrating immune cells, including several anti-cancer immune cells (CD8+ T cells, CD4+ memory T-cells, T helper Type 1 cells, M1 macrophages, plasmacytoid dendritic cells), T helper Type 2 cells, and B cells. The score also correlated with expression levels of immune checkpoint molecule genes (all $r > 0.500$). A high score was significantly associated with high intratumor heterogeneity, homologous recombination deficiency (HRD), and mutation rate in the TCGA cohort (all $p < 0.001$). A high score was significantly associated with advanced Nottingham histological grade, advanced stage, and lymph node metastasis. High score breast cancer enriched not only immune-related gene sets but also pro-cancer-related gene sets, such as epithelial-mesenchymal transition (EMT) and p53 pathway, in both ER-positive/HER2-negative breast cancer and TNBC. The score was highest in TNBC compared to other subtypes, and TNBC with high score was significantly associated with better survival. **Conclusions:** The counterbalance between malignant biology and the enhanced immune response is an important factor in clinical outcomes. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

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Association of changes of pro-inflammatory markers with physical function in women with breast cancer receiving chemotherapy. *First Author: Nikesha Gilmore, University of Rochester Medical Center, Rochester, NY*

Background: Chemotherapy adversely affects the immune system and physical function. Inflammation is independently associated with functional decline. Compared to the individual cytokines [e.g., interleukin-6 (IL-6)], the pro-inflammatory index, IL-6/IL-10 ratio, is a better predictor of poor outcomes and mortality in many diseases. Other markers of inflammation such as soluble tumor necrosis factor (sTNFR) I, and sTNFRII have also been shown to be predictive of poor outcomes. We have previously reported a significant increase in sTNFRI/II with chemotherapy in patients with breast cancer. However, it is not yet understood if chemotherapy-related changes to inflammatory makers is associated with physical function after treatment. In this study, we assessed the relationship between changes of pro-inflammatory markers during chemotherapy with physical function after completing chemotherapy. **Methods:** This was a secondary analysis of a large nationwide cohort study in women with stage I-III breast cancer (NCT01382082). Serum levels of IL6, IL10, sTNFRI, and sTNFRII were measured $\leq$7 days before chemotherapy (T1) and $\leq$1 month after chemotherapy (T2), and the IL6/IL10 ratio was calculated. Absolute changes (T2-T1) of sTNFR-I and sTNFRII (reported in pg/mL) and the IL6/IL10 ratio were calculated. Physical function was measured by the Functional Assessment of Cancer Therapy: General – physical well being (FACT-PWB) at T1 and T2 and contains 7-items, each using a 5-point rating scale ranging from 0 (Not at all) to 4 (Very much), with a total score ranging from 0-28; higher scores represent higher physical function. ANOVA was used to compare means of FACT-PWD scores and mean changes of pro-inflammatory markers. Multivariate linear regressions were used to determine if increased pro-inflammatory markers were associated with lower FACT-PWD at T2, controlling for baseline FACT-PWD, age, race, education, and marital status. **Results:** We included 580 patients (mean age=53 years, range 22-81). Physical function significantly and clinically declined from T1-T2 (mean=22.2, SE=0.23 vs mean=19.4, SE=0.25; $p<0.001$). From T1-T2, there was a significant increase in IL6/IL10 (average change = 0.32, SE=0.09; p=0.004). A greater increase in pro-inflammatory markers from T1 to T2 was associated with lower FACT-PWD score at T2; sTNFRI (β=-3.92, SE=1.4), sTNFRII (β=-14.9, SE=7.1), and IL6/IL10 (β=-0.17, SE=0.06); all $p<0.05$. **Conclusions:** Serum pro-inflammatory markers increased from pre-chemotherapy to post-chemotherapy in patients with breast cancer. Greater increases in pro-inflammatory markers are associated with lower physical function within one month of the completion of chemotherapy. Pro-inflammatory markers; sTNFRI, sTNFRII, and IL6/IL10, may serve as useful biomarkers to help identify patients at risk of reduced physical function after chemotherapy. Research Sponsor: U.S. National Institutes of Health.

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Molecular profiles of genomically high risk ER+ HER2- breast cancer tumors classified as functionally basal or luminal B by the 80-gene signature. *First Author: Joyce O'Shaughnessy, Texas Oncology-Baylor Sammons Cancer Center, US Oncology, Dallas, TX*

Background: The 80-gene signature (BluePrint/BP) classifies early-stage breast cancers based on functional molecular pathways as luminal, HER2, or Basal-type. In the NBRST study, 13% of immunochemistry (IHC) defined ER+ HER2- cancers reclassified as Basal-type by the BP assay (ER+ Basal), and these had worse prognosis but responded better to neoadjuvant chemotherapy than ER+ HER2- cancers classified as genomically luminal-type. The 70-gene risk of recurrence signature (MammaPrint/MP) further stratifies luminal-type cancers into low risk luminal A or high risk (HR) luminal B. HR cancers can be further stratified into High 1 (H1) or High 2 (H2), and the I-SPY2 trial has shown higher pCR rates in ER+ cancers classified as H2. Here, we investigated biological differences among ER+ Basal, ER- Basal, H1 luminal B, and H2 luminal B cancers by full transcriptome analysis. **Methods:** From the FLEX Study (NCT03053193), 1501 breast cancers with known IHC ER status were classified by MP and BP: 103 ER+ Basal, 210 ER- Basal and 1188 luminal B (H1 n=1034, H2 n=154). Clinical factors were assessed by either the Chi-square or Fisher's exact tests; ANOVA or *t* test were used to analyze age. Differentially expressed genes (DEGs) were detected using Limma and pathway analyses were performed with GSEA. DEGs with a fold change >2 and FDR < 0.05 were considered significant. **Results:** Basal-type cancers (ER+/ER-) were larger and higher grade than luminal B cancers. Clustering analysis showed similar transcriptional profiles between ER+ Basal and ER- Basal cancers, distinct from luminal B cancers. Few DEGs were detected between ER+ Basal and ER- Basal cancers, and significantly more DEGs were found between ER+ Basal and luminal B cancers. Only three upregulated genes were detected in ER+ Basal compared to ER- Basal cancers: *ESR1* and two immune-related genes (*FDCSP* and *LTF*). Enrichment analysis of DEGs indicated increased immune activation and cell proliferation in ER+ Basal and ER- Basal cancers, and decreased estrogen response between ER+ Basal and luminal B cancers. Enrichment analysis between luminal B H1 and H2 cancers showed H2 cancers had higher immune activation and cell proliferation and lower estrogen response. **Conclusions:** Reclassification by BP of IHC defined ER+ HER2- cancers identified a subgroup of ER+ cancers that are biologically closer to ER- Basal than luminal-type cancers. Significant differences in response to neoadjuvant chemotherapy that have been seen between ER+ Basal and luminal B breast cancers lend support to the clinical importance of these findings. These data explain the poor prognosis observed in patients with ER+ Basal cancers and suggest that optimized chemotherapy, such as that for triple negative cancer, might be of benefit. BP provides clinically actionable information beyond pathological subtyping, which may guide neoadjuvant treatment recommendations. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

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Characterization of the tumor immune microenvironment of triple-negative breast cancer (TNBC) patients who self-identify as African American (AA) or non-African American (NonAA). *First Author: Kim Blenman, Yale University, New Haven, CT*

Background: What tumor biological differences, if any, contribute to the higher incidence and worse prognosis of triple negative breast cancer (TNBC) in African American (AA) compared to NonAA patients are unknown. We hypothesized that differences in the tumor immune microenvironment may contribute to the outcome disparities. The purpose of this study was to characterize and compare the immune microenvironment of TNBC between patients self-identified as NonAA or AA. **Methods**: Formalin fixed paraffin embedded surgically resected cancer and paired normal tissues collected before any systemic therapy and the corresponding clinical data were collected for NonAA (n = 56) and AA (n = 54) stage I-III TNBC treated at Yale Cancer Center between 2000-2017. The two cohorts were matched for clinical stage, age of diagnosis, and year of diagnosis. We performed somatic and germline whole exome sequencing (WES), bulk RNA sequencing, and immunohistochemistry to assess PD-L1 expression (SP142). Stromal tumor infiltrating lymphocytes (sTILs) were assessed on H&E slides. Mutation load, mutation frequencies, and gene expression differences were compared at gene and pathway level. Immune cell composition was estimated through gene expression deconvolution analyses (TIDE). **Results**: Tumor mutational burden was similar between the two cohorts. At gene level, few genes had significantly different somatic mutation frequencies, or differential mRNA expression between AA and NonAA samples. Pathway level alterations showed inflammation, immunity (adaptive; innate), antigen presentation, and allograft rejection pathways were more affected by somatic mutations in AA samples. The affected genes differed from cancer to cancer and were not recurrent and therefore were missed at gene level analysis. Gene set enrichment and co-expression analysis also showed higher immune related pathway expression in AA samples. Unsupervised co-expression cluster analysis confirmed coordinated overexpression of genes involved in immunity, inflammation, and cytokine/chemokine signaling in AA patients. Two immunotherapy response predictive signatures, immune inflamed and the IFNG as well as sTILs score and PD-L1 positivity were also higher in AA samples. These findings raise the possibility that immune checkpoint inhibitors might be particularly effective in AA patients. In NonAA samples, the EMT transition, angiogenesis, adipogenesis, myogenesis, fatty acid metabolism, TGFβ signaling, UV-response, and hypoxia pathways were overexpressed. TIDE analysis suggested higher levels of TAM M2, overall TIDE score, and the Immune Exclusion score in NonAA samples. **Conclusions**: TNBC in AA patients more frequently harbor somatic mutations in genes involved with immune functions and overexpress immune and inflammatory genes compared to NonAA patients. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

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Whole transcriptome analysis comparing HR+ HER2- breast cancer tumors from patients < 50 years and >50 years. *First Author: Cathy Graham, Emory University School of Medicine, Atlanta, GA*

Background: Recent prospective clinical trials have demonstrated a differential chemotherapy effect based on age (≤ 50 vs. > 50 years) or menopausal status (pre- vs. post-) in a genomic low risk group. Whether this is a direct anti-tumor effect of chemotherapy or a secondary ovarian function suppression effect caused by chemotherapy is unclear. We aimed to compare the biological characteristics of breast cancer tumors from patients aged ≤ 50 years and from patients aged > 50 years using whole transcriptome analysis to provide insights into this differential chemotherapy response. **Methods:** The FLEX Registry (NCT03053193) enrolls stage I-III breast cancer patients who receive 70-gene signature (MammaPrint/MP) test with or without 80-gene signature (BluePrint/BP) test and consent to clinically annotated transcriptome data collection. 3868 patients with HR+HER2- tumors were evaluated, of whom 808 were aged ≤ 50 years and 3060 were aged > 50 years. Clinical risk was assessed based on the MINDACT algorithm. MP classified tumors as low risk (LR) or high risk (HR). HR was stratified to H1 or H2; H2 exhibits a greater chemotherapy response. BP and MP classified tumors as luminal A-, luminal B-, HER2-, or basal-type. Differences in MP, BP, and clinical features were assessed by chi-squared or *t* test. For gene expression analysis, older patients were randomly selected to obtain an equal sample size as younger patients. Differentially expressed genes (DEGs) were detected using limma and considered significant with FDR <0.05 and fold change ≥ 2. **Results:** Approximately 70% of patients aged ≤ 50 were pre or peri-menopausal, whereas 90% of patients aged > 50 were post-menopausal. A higher proportion of patients aged ≤ 50 had tumors of high clinical risk (54%) compared to patients aged > 50 (39%) (p < 0.001). Approximately 53% of patients aged ≤ 50 had a HR tumor, of whom 25% classified as H2, while patients aged > 50 had a lower frequency (44%) of HR tumors (p<0.001). Additionally, younger patients had more tumors that classified as BP Luminal B and Basal-type than older patients (p<0.001). Principal component analysis of the top 500 genes with the highest variance revealed no distinct clustering by age group. Accordingly, only 5 DEGs were detected in tumors from patients aged ≤ 50 compared to patients aged > 50, and even fewer DEGs were detected when adjusting for MP risk and BP subtype group. **Conclusions:** Whole transcriptome analysis identified no substantial differences in gene expression between tumors, including Low Risk Luminal-type tumors, from women aged ≤ 50 (mostly pre or peri-menopausal) and women aged > 50 (mostly post-menopausal). These data support the likely explanation that the observed age-dependent difference in chemotherapy benefit in women ≤ 50 or >50 years of age is not due to intrinsic biological differences in breast cancers due to age, but rather to differences in the effect of chemotherapy on the host. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

566 **Poster Session**

Adding carbon nanoparticles to dual-tracers for the sentinel node evaluation after neoadjuvant chemotherapy in patients with pretreatment node-positive breast cancers: The TT-SLNB trial. *First Author: Jie Chen, Department of Breast Surgery, West China Hospital, Sichuan University, Chengdu, China*

Background: This study measures the feasibility and accuracy of sentinel lymph node biopsy (SLNB) with triple-tracers (TT-SLNB) which combines carbon nanoparticles (CNS) with dual tracers of radioisotope and blue dye, hoping to achieve an optimized method of SLNB after neoadjuvant chemotherapy (NAC) in ycN0 breast cancer patients with pretreatment positive axillary lymph nodes. **Methods:** Clinically node-negative invasive breast cancer patients with pre-NAC positive axillary lymph nodes who received surgeries from November 2020 to January 2021 were included. CNS was injected at the peritumoral site the day before surgery. Standard dual-tracer (SD)-SLNs were defined as blue-colored and/or hot nodes, and TT-SLNs were defined as lymph nodes detected by any of hot, blue-stained, black-stained, and/or palpated SLNs. All patients received subsequent axillary lymph node dissection. Detection rate (DR), false-negative rate (FNR), negative predictive value (NPV) and accuracy of SLNB were calculated. **Results**: Seventy-six of 121 (62.8%) breast cancer patients converted to cN0 after NAC and received TT-SLNB. After NAC, 28.95% (22/76) achieved overall (breast and axilla) pCR. The DR was 94.74% (72/76), 88.16% (67/76) and 96.05% (73/76) for SLNB with single-tracer of CNS (CNS-SLNB), SD-SLNB, and TT-SLNB, respectively. The FNR was 22.86% (8/35) for CNS-SLNB and 10% (3/30) for SD-SLNB. The FNR of TT-SLNB was 5.71% (2/35), which was significantly lower than those of CNS-SLNB and SD-SLNB. The NPV and accuracy was 95.0% and 97.3% for TT-SLNB, respectively. Moreover, a significant relation was seen between the pretreatment clinical T classification and the DR of TT-SLNB (Fisher's exact test, $p = 0.010$). **Conclusions**: TT-SLNB revealed ideal performance in post-NAC ycN0 patients with pretreatment node-positive breast cancers. The application of TT-SLNB reached a better balance between more accurate axillary evaluation and less intervention. Clinical trial information: ChiCTR2000039814. Research Sponsor: This study is supported by the funding from the National Natural Science Foundation of China (32071284 and 81902686) and the Program of the Science and Technology Bureau of Sichuan (2019YFS0338).

	Final axillary nodal status						
Method of lymphatic mapping	Positive	Negative	Total	DR (%)	FNR (%)	NPV (%)	Accuracy (%)
SD-SLNB				88.16	10.0	92.5	95.5
Positive	27	-	27				
Negative	3	37	40				
CNS-SLNB				94.47	22.9	82.2	88.9
Positive	27	-	27				
Negative	8	37	45				
TT-SLNB				96.05	5.7	95.0	97.3
Positive	33	-	33				
Negative	2	38	40				

DR, detection rate; FNR, false-negative rate; NPV, negative predictive value; CNS-SLNB, sentinel lymph node biopsy with single tracer of carbon nanoparticles; SD-SLNB, standardized sentinel lymph node biopsy with dual tracers of radioisotope and blue dye; TT-SLNB, triple-tracer sentinel lymph node biopsy with carbon nanoparticles, radioisotope and blue dye.

567 **Poster Session**

Clinicopathologic features of breast cancers diagnosed in females treated with prior radiation therapy for Hodgkin lymphoma: Results from a population-based cohort. *First Author: Stephanie M Wong, McGill University, Jewish General Hospital Stroll Cancer Prevention Centre, Montréal, QC, Canada*

Background: Childhood and young adult survivors of Hodgkin Lymphoma are at an increased risk of developing breast cancer, although little data exist on the characteristics and biologic subtype of breast cancers that develop in this high-risk population. **Methods**: The Surveillance, Epidemiology, and End Results (SEER) database was used to identify all histologically confirmed breast cancers diagnosed between 1990-2016 in women treated with prior radiation therapy for Hodgkin Lymphoma ≤ 30 years of age. Clinicopathologic features of subsequent breast cancers (BC-HL) were examined and compared to breast cancers diagnosed in women with no prior malignancy (BC-NPM). The association between prior chemotherapy use and biologic subtype of BC-HL was evaluated. **Results**: We identified 321 breast cancers diagnosed in 257 women with a history of radiation therapy for Hodgkin Lymphoma. The median age at Hodgkin Lymphoma diagnosis was 22 years (range, 12-30 years), and nearly all BC-HL (97.9%) were diagnosed 8 or more years after radiation therapy. Overall, 56 (21.8%) BC-HL patients developed bilateral breast cancer, of which 28 (50%) were synchronous. When compared to women with BC-NPM, women with BC-HL were significantly younger at time of diagnosis (median age, 43 years vs. 60 years, p<0.001) and less likely to present with ductal carcinoma *in situ* (8.4% vs. 14.9%, p=0.001). Patients with invasive BC-HL were more likely to have high grade (43.8% vs. 32.9%, p<0.001), estrogen receptor (ER) negative breast cancer (27.7% vs. 18.2%, p<0.001), although pathologic tumor size, nodal status, and stage were not significantly different from those with BC-NPM. Compared to women with BC-NPM, the majority of operable BC-HL patients underwent surgical management with mastectomy (86.5% vs. 42.5%, p<0.001). In subset analysis of 102 women for which HER2 status was available, BC-HL were HER2+ in 18.7% of patients. Distribution of biologic subtype between BC-HL and BC-NPM are shown in the table below. In BC-HL patients, prior chemotherapy exposure was not associated with substantial differences in the proportion of ER+HER2- breast cancers (65.8% vs. 63.5%, p=0.82). **Conclusions:** Breast cancers in women treated with radiation therapy for Hodgkin Lymphoma are characterized by earlier onset and more aggressive biologic features, although the majority remain estrogen sensitive and early stage at presentation. Further studies are warranted to evaluate the use of preventive strategies in this high-risk patient population. Research Sponsor: None.

	BC-HL (n = 102)		BC-NPM (n = 327,335)	
Biologic Subtype	% BC-HL	95% CI	% BC-NPM	95% CI
ER+HER2-	63.7%	(53.6-73.0)	72.7%	(72.6-72.9)
ER+HER2+	12.8%	(7.0-20.8)	11.2%	(11.0-11.3)
ER-HER2+	5.9%	(2.2-12.4)	4.8%	(4.7-4.9)
TNBC	17.7%	(10.8-26.5)	11.3%	(11.2-11.4)

568 **Poster Session**

Impact of patient, tumour and treatment factors on psychosocial outcomes in invasive breast cancer. *First Author: David W Lim, Women's College Hospital, Toronto, ON, Canada*

Background: In breast cancer, clinicians aim to improve survival while patients value quality of life. We aim to delineate the impact of patient, tumour and treatment factors on psychosocial outcomes after treatment. **Methods:** A prospective cohort of women with unilateral stage I-III breast cancer were recruited at University Health Network in Toronto, Canada between 2014-2017. Validated questionnaires (BREAST-Q, Impact of Event, Hospital Anxiety & Depression Scales) were completed pre-operatively, and 6 and 12 months after surgery. Change in psychosocial scores over time by surgical procedure was assessed using linear mixed models, controlling for age, pathologic stage, hormone (HR) and HER2 receptor, and treatments. Predictors of psychosocial outcomes at 12 months were assessed using multivariable linear regression models. *P* values < .05 were significant. **Results:** 413 women underwent unilateral lumpectomy (48%), unilateral mastectomy (36%) and bilateral mastectomy (16%). Pathologic stage were: 18 *yp*T0/Tis (4%), 201 stage I (49%), 136 stage II (33%) and 58 stage III (14%). Receptor profiles were as follows: 277 HR+/HER2- (68%), 59 HR+/HER2+ (14%), 31 HR-/HER2+ (8%) and 39 HR-/HER2- (10%). Over time, women having unilateral lumpectomy had the highest scores of breast satisfaction ($P < .01$), psychosocial ($P < .01$) and sexual ($P < .01$) well-being, with no difference between unilateral versus bilateral mastectomy groups. Age was inversely related with distress ($P < .01$), psychosocial ($P < .01$) and physical ($P = .001$) well-being. Radiotherapy was associated with worse breast satisfaction (-8.1, $P < .01$), psychosocial (-6.9, $P < .01$) and physical (-5.8, $P < .01$) well-being, while chemotherapy was associated with worse sexual well-being (-5.5, $P = .04$). Endocrine therapy was associated with worse distress (6.7, $P < .01$), physical (-5.2, $P < .01$) and sexual (-6.4, $P = .03$) well-being. Women with a pathologic complete response had less anxiety compared to stage I (-2.0, $P = .03$). Women with triple-negative disease had worse breast satisfaction (-8.0, $P = .03$), distress (8.0, $P = .01$), anxiety (2.4, $P < .01$) and psychosocial (-7.5, $P = .047$) well-being than HR+/HER2- disease. In our regression model at 12 months, surgical procedure was a significant predictor of breast satisfaction ($P < .01$), psychosocial ($P < .01$), physical ($P < .01$) and sexual ($P < .01$) well-being. HER2 positivity predicted worse satisfaction ($P = .045$), psychosocial ($P = .047$), physical ($P = .02$) and sexual ($P = .01$) well-being. Income level ($P = .01$) predicted breast satisfaction and physical well-being. Ethnicity ($P < .01$) and education level ($P = .04$) predicted distress scores. **Conclusions:** Psychosocial functioning after breast cancer is influenced by an interplay between patient, tumour and treatment factors. Delineating these influences identifies potentially modifiable factors with de-escalation therapy and enhancing psychosocial support. Research Sponsor: None.

569 **Poster Session**

Survival in male breast cancer (MaBC) over the past three decades. *First Author: Jose Pablo Leone, Dana-Farber Cancer Institute/Harvard Medical School, Boston, MA*

Background: Breast cancer mortality in women has declined significantly over the past several years. In men, it is unclear whether survival has changed over time. The aim of this study was to evaluate changes in breast cancer-specific survival (BCSS) and overall survival (OS) in MaBC over the past three decades. **Methods:** We evaluated men diagnosed with breast cancer between 1988 and 2017, with known cause of death reported in the Surveillance, Epidemiology, and End Results registry. Patients were categorized into 3 groups by year of diagnosis: 1988-1997, 1998-2007 and 2008-2017. BCSS and OS were estimated by Kaplan-Meier and differences between groups were compared by log-rank test. Cox proportional hazards regression was used to evaluate the independent association of tumor and patient characteristics with BCSS and OS. **Results:** We included 8,412 men diagnosed between 1988-1997 (N = 1,033), 1998-2007 (N = 2,938) and 2008-2017 (N = 4,441). Median age for the overall population and within each decade of diagnosis was 68 years. Median follow-up was 23.6 years, 14.3 years and 4.5 years in periods 1988-1997, 1998-2007 and 2008-2017, respectively. Overall, BCSS at 5 years was 83.5%, 83.6% and 84.3% in periods 1988-1997, 1998-2007 and 2008-2017, respectively; p = 0.8. There was no significant difference in BCSS between the three periods of diagnosis within each stage of breast cancer (stage I, II, III and IV). Among all patients, OS at 5 years was 64.7%, 67.2% and 69.3% in periods 1988-1997, 1998-2007 and 2008-2017, respectively; p = 0.01. In multivariate Cox models, older age at diagnosis, black race, grade 3 disease, increasing stage, hormone receptor negative status and no surgery were all independently associated with worse BCSS and OS. In these adjusted Cox models, each additional year of diagnosis had no significant association with BCSS (hazard ratio, 1.0; 95% CI, 0.99 – 1.01; p = 0.78), and a significant improvement in OS (hazard ratio, 0.99; 95% CI, 0.98 – 0.99; p = 0.01). **Conclusions:** Over the past three decades, there has been no significant improvement in BCSS in MaBC. The changes in OS over time suggest increasing life expectancy. Efforts to improve BCSS in MaBC are warranted. Research Sponsor: None.

571 **Poster Session**

Role of 21- gene recurrence score in patients age ≥70 with T1N0 ER/PR+ HER2- breast cancer treated with breast-conserving surgery and endocrine therapy. *First Author: Neil Chandrabhan Chevli, The University of Texas Medical Branch, Department of Radiation Oncology, Galveston, TX*

Background: Based on the results of the CALGB 9343 trial, patients age ≥70 with T1N0 ER/PR+ HER2- breast cancer who are treated with breast conserving surgery (BCS) and endocrine therapy (ET) are candidates for omission of radiotherapy (RT). This trial predated the 21- gene RT-PCR recurrence score (RS) test, which is an assay now available for patients with hormone receptor positive, HER2 negative, node negative breast cancer to determine who will benefit from chemotherapy. Whether the RS can predict for patients most likely to benefit from radiation therapy (RT) following BCS has not been previously examined. The purpose of this study was to use a large database of patients age ≥70 with T1N0 ER/PR+ HER2- disease to determine if RS could predict who would benefit from RT following BCS. **Methods:** The National Cancer Database (NCDB) was queried (2004-2017) for female patients age ≥70 with pT1N0 ER+ PR+ HER2- breast cancer treated with BCS and ET and who had an available RS. Patients were stratified based on their RS (low risk [LR] = 1-10, intermediate risk [IR] = 11-25, high risk [HR] = 26-99). For survival analysis, propensity score matching (PSM) was conducted overall and for each group to create 1:1 matched cohorts of patients who received radiotherapy and patients who did not. Kaplan-Meier analysis with log-rank testing was used to evaluate overall survival (OS). Univariable (UVA) and multivariable (MVA) analysis were conducted using Cox proportional hazard models to determine which clinical and treatment factors were prognostic for OS. **Results:** A total of 13,614 patients met the selection criteria: 3,840 in the LR cohort, 8,383 in the IR cohort, and 1,391 in the HR cohort. A total of 79% received RT: 77% in the LR cohort, 79% in the IR cohort, and 85% in the HR cohort. Because PSM could not be efficiently performed in the HR cohort alone, the IR and HR cohort were merged (IRHR) for matching. After PSM, overall the 5-year OS was 90% for those who received RT and 88% for those who did not (p = 0.03). The 5-year OS in the LR cohort was 89% for those who received RT and 89% for those who did not (p = 0.517). In the IRHR cohort, the 5-year OS was 93% for those who received RT and 88% for those who did not (p = 0.004). On MVA in the overall cohort, RT (p = 0.037) was predictive of improved OS while increasing age ($p < 0.001$) and CDCC comorbidity score ($p < 0.001$) were predictive of worse OS. On MVA in the LR cohort, RT (p = 0.602) was not predictive of improved OS. However, on MVA in the IRHR cohort, RT (p = 0.004) was a positive prognostic factor for OS. **Conclusions:** This is the first study investigating the role of RS in this subset of patients eligible for omission of radiotherapy. There is an OS benefit with the use of RT in patients with IRHR RS, but not in patients with LR RS. Pending prospective evaluation, assessment of RS in this older subset of patients is recommended with consideration of RT when RS is ≥11. Research Sponsor: None.

572 **Poster Session**

Trends in breast cancer mortality according to molecular subtypes: A population-based study. *First Author: Yunan Han, Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, MO*

Background: Breast cancer is the second leading cause of cancer death in U.S. women. On the molecular level, breast cancer is a heterogeneous disease. Heterogeneous expressions of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) are etiologically and clinically meaningful, as they map to distinct risk factors and different treatment strategies. Although breast cancer mortality has been declining since 1990, little is known about mortality trends according to molecular subtypes at the population level. **Methods:** We examined the incidence-based mortality rates and trends among women who were diagnosed with invasive breast cancer from 2010 through 2017 using the Surveillance, Epidemiology, and End Results (SEER) database. We defined incidence-based mortality using a moving 5-year calendar period starting in 2014. We further assessed mortality according to breast cancer molecular subtypes: luminal A (ER and/or PR positive, HER2 negative), luminal B (ER and/or PR positive, HER2 positive), HER2-enriched (HER2 over-expressed or amplified, ER and PR negative) and triple-negative (ER and PR negative, HER2 negative) tumors. We calculated annual percent changes (APC) in incidence-based mortality using joinpoint regression models. **Results:** Overall, incidence-based mortality for breast cancer significantly decreased by 1.5% annually from 2014 through 2017 (APC, -1.5%; 95% coefficient interval [CI], -2.3% to -0.7%; $p<0.001$). Incidence-based mortality decreased annually by 2.0% for luminal A breast cancer (APC, -2.0%; 95% CI, -3.7% to -0.3%; $p<0.001$), 2.1% for luminal B breast cancer (APC, -2.1%; 95% CI, -5.4% to 1.4%; p=0.1), 1.1% for triple-negative breast cancer (TNBC) (APC, -1.1%; 95% CI, -2.1% to -0.0%; $p<0.001$). However, incidence-based mortality for HER2-enriched breast cancer increased 2.3% annually during the study period (APC, 2.3%; 95% CI, -2.4% to 7.2%; p=0.2). **Conclusions:** Between 2014 and 2017, incidence-based mortality for luminal A, luminal B, and TNBC decreased among U.S. women, with a larger decrease observed for luminal tumors. However, incidence-based mortality for HER2-enriched breast cancer increased. The favorable incidence-based mortality trends for luminal tumors and TNBC are likely due to the continuing improvement in treatments and early detection. The increasing trend of incidence-based mortality for HER2-enriched breast cancer constitutes a priority for cancer control activities and further research. Research Sponsor: None.

574 **Poster Session**

Pyrotinib as neoadjuvant therapy for HER2+ breast cancer: A multicenter, randomized, controlled, phase II trial. *First Author: Xiaowen Ding, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Institute of Cancer and Basic Medicine (ICBM), Chinese Academy of Sciences, Hangzhou, China*

Background: Pyrotinib is a new irreversible tyrosine kinase inhibitor (TKI) which significantly improved the progression-free survival (PFS) of patients with HER2+ metastatic breast cancer (MBC). In this study we aim to investigate the efficacy and safety of pyrotinib in neoadjuvant therapy. **Methods**: This is an open-label, multicenter, randomized controlled trial. Eligible patients (pts) aged 18–70 years with invasive carcinoma, $cT_{2\text{-}3}N_{0\text{-}3}M0$ stage, HER2-positive breast cancer were included. We randomized 34 pts into the treatment group and 33 into the controlled group from 2019-2021. Pts in the treatment group received 6 cycles of pyrotinib 400mg + trastuzumab 6mg/kg (LD 8mg/kg) + docetaxel 75mg/m^2 + carboplatin (AUC = 6mg/ml·min) (TCbH+Py) treatment while the controlled group received 6 cycles of trastuzumab 6mg/kg (LD 8mg/kg) + docetaxel 75mg/m^2 + carboplatin (AUC = 6mg/ml·min) (TCbH). Total pathologic complete response (tpCR) was defined as no invasive or in situ disease in the breast or axilla (ypT0/Tis, ypN0) and was assigned to be the primary outcome (NCT03756064). **Results**: 51 cases had completed 6 cycles of neoadjuvant therapy and successfully underwent operation (21 in the treatment group and 30 in the controlled group). In the treatment group, 6 cases have not complete neoadjuvant therapy, 6 cases quitted because of poor compliance and 1 patient has not receive operation yet. For controlled group, 3 patients have not complete neoadjuvant therapy. The tpCR rate in the treatment group is 71.4% (15/21) versus 36.7% (11/30) in the controlled group. A significant difference was determined between the two groups ($p < 0.05$). All pts achieved an objective response in the treatment group while in the controlled group for about 83.3% (25/30). 4 cases showed stable disease (SD) and 1 case was evaluated as progressive disease (PD) in the controlled group. The most common AE in the treatment group is diarrhoea with grade 3 occurred in 6 cases (28.6%), most of this event limited in the first treatment cycle. In the controlled group 3 pts (10%) occurred grade 3 diarrhoea. **Conclusions**: In this study TCbH+Py neoadjuvant therapy significantly improved the tpCR rate of HER2+ breast cancer pts for about twice higher than TCbH with a manageable safety. Clinical trial information: NCT03756064. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

575 **Poster Session**

Racial differences and trends in pathologic complete response following neoadjuvant chemotherapy for breast cancer. *First Author: Sung Jun Ma, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Given improvements in systemic therapy, pathologic complete response (pCR) rates following neoadjuvant chemotherapy were over 60% in breast cancer patients in recent clinical trials, especially in human epidermal growth factor receptor 2 (HER2)-positive and triple negative cases. While racial minority groups were associated with worse survival outcomes despite receiving standard of care in prospective studies, they were under-represented in clinical trials. To address this knowledge gap, we performed an observational cohort study to evaluate pCR and survival outcomes stratified by racial and ethnic groups. **Methods:** The National Cancer Database (NCDB) was queried for female patients with stage I-III breast cancer diagnosed between 2010 and 2017 treated with neoadjuvant chemotherapy followed by surgery. Cochran-Armitage test was used to analyze the trend of pCR over time. Logistic multivariable analysis (MVA) was used to identify variables associated with pCR defined as ypT0/isN0. Cox MVA was used to analyze the overall survival (OS) benefit. **Results:** A total of 105,804 patients (n = 72,631 for non-Hispanic white [NHW], n = 7,632 for Hispanic white [HW], n = 19,505 for black, n = 4,393 for Asian or Pacific Islander [API], n = 1,643 for other race) were included for analysis. Median follow up was 49.2 months (interquartile range 32.7-71.3). Overall pCR rate increased from 15.1% in 2010 to 27.2% in 2017, largely driven by API women (15.7% to 31.6%) and hormone receptor (HR)-HER2+ tumors (28.6% to 53.1%; all trend $p < 0.001$). On logistic MVA, when compared to NHW women, HW women were more likely to have pCR for HR-HER2+ (adjusted odds ratio [aOR] 1.18, p = 0.02) and HR+HER2+ tumors (aOR 1.29, p = 0.005), while black women were more likely to have pCR for HR+HER2- tumors (aOR 1.13, p = 0.01) and less likely for HR-HER2+ (aOR 0.80, $p < 0.001$) and triple negative tumors (aOR 0.82, $p < 0.001$). API women were more likely to have pCR for HR-HER2+ tumors compared to NHW women (aOR 1.17, p = 0.04). On Cox MVA, when compared to NHW women, HW (ypT+N0: adjusted hazards ratio [aHR] 0.75, $p < 0.001$; ypN+: aHR 0.79, $p < 0.001$) and API women (ypT0/isN0: aHR 0.52, p = 0.005; ypT+N0: aHR 0.63, $p < 0.001$; ypN+: aHR 0.86, p = 0.03) were associated with improved OS, while black women were associated with worse OS for ypN+ only (aHR 1.18, $p < 0.001$). **Conclusions:** To our knowledge, this is the largest study using a nationwide oncology database suggesting the improving trend of pCR rate over time for all racial cohorts. In our study, when compared to NHW, HW and API women were more likely to have pCR for select HER2+ tumors, while black women were less likely to have pCR for HR-HER2+ and triple negative tumors but not for HR+HER2- tumors. HW and API women were associated with improved survival in the setting of any residual disease compared to NHW women, while black women were associated with worse survival only for residual nodal disease. Research Sponsor: None.

576 **Poster Session**

Evaluation of risk-stratification using gene expression assays in patients with breast cancer receiving neoadjuvant chemotherapy. *First Author: Sung Jun Ma, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Among patients with hormone receptor-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer, several prospective studies investigated various gene expression assays, such as 21-gene recurrence score (21 RS) and 70-gene signature (70 GS), to identify a subgroup of patients with pathologic complete response (pCR) from neoadjuvant chemotherapy. However, in the absence of large prospective trials to validate such findings, the National Comprehensive Cancer Network guideline does not recommend the routine adoption of such assays in the setting of neoadjuvant therapies. To address this knowledge gap, we performed an observational cohort study to compare pCR and survival outcomes based on these assays. **Methods:** The National Cancer Database (NCDB) was queried for female patients diagnosed between 2010 and 2017 with stage I-III breast cancer who underwent neoadjuvant chemotherapy and either 70 GS or 21 RS. Logistic multivariable analysis (MVA) was performed to identify variables associated with pCR. Cox MVA was performed to evaluate overall survival (OS). Subgroup analyses were performed among patients with favorable hormone receptor status (hormone receptor-positive, HER2-negative) and with RS $\geq$26 instead of RS $\geq$31. **Results:** A total of 3,009 patients met our inclusion criteria, with 2,075 (n = 1,287 for RS $<$ 31, n = 788 for RS $\geq$31) and 934 (n = 175 for low risk, n = 759 for high risk) patients who underwent 21 RS and 70 GS, respectively. The median follow up was 48.0 months (interquartile range 32.2-66.7). On logistic MVA for all patients, those with a high risk from 70 GS or with RS $\geq$31 were more likely to have pCR. When compared to RS $\geq$31, a high risk from 70 GS was not associated with pCR. However, among those with favorable hormone receptor status, similar findings were noted, except that those with a high risk group from 70 GS were less likely to have pCR compared to those with RS $\geq$31. On Cox MVA for all patients, pCR was associated with improved OS. While RS $\geq$31 was associated with worse mortality, a high risk from 70 GS was not. No interaction was observed between pCR and risk groups for OS in both groups (interaction p = 0.23 for 70 GS, p = 0.66 for 21 RS). When analyses were repeated using a high risk group from 21 RS defined as RS $\geq$26, similar findings were noted, except that having favorable hormone receptor status and RS $\geq$26 was not associated with pCR when compared to the high risk from 70 GS. **Conclusions:** To our knowledge, this is the largest study using a nationwide oncology database suggesting that high recurrence risk groups in both assays were associated with pCR and that pCR was associated with improved survival. For those with favorable hormone receptor status, RS $\geq$31 may be a more selective prognostic marker. Further studies would be warranted to investigate the role of gene expression assays in the setting of neoadjuvant chemotherapy. Research Sponsor: None.

577 **Poster Session**

Evaluation of pharmacodynamic (PD) and biologic activity in a preoperative window-of-opportunity (WOO) study of giredestrant (GDC-9545) in postmenopausal patients (pts) with estrogen receptor-positive, HER2-negative (ER+/HER2–) operable breast cancer (BC). *First Author: Heather M. Moore, Genentech, Inc., South San Francisco, CA*

Background: Modulation of ER activity and/or estrogen synthesis is the mainstay therapeutic strategy in ER+ BC treatment. Giredestrant is a highly potent, nonsteroidal oral selective ER degrader (SERD) that achieves robust ER occupancy and is effective regardless of *ESR1* mutation status. The first short-term preoperative WOO study (NCT03916744) of giredestrant in ER+/HER2– operable BC was designed for dose selection, while providing an early readout of PD as measured by traditional immunohistochemistry (IHC) and transcriptional profiling by assessing treatment effects in paired tumor tissue pre/posttreatment. We present an interim analysis. **Methods:** Pts were assigned to 14 days' preoperative treatment with 10, 30, or 100 mg PO giredestrant QD. Pts had newly diagnosed, stage I–III operable, ER+/HER2– untreated BC $\geq$1.5 cm in diameter (by ultrasound). Modulation of ER signaling and cell proliferation were assessed using paired formalin-fixed paraffin-embedded tumor specimens collected before and after ~14 days of study treatment. ER, progesterone receptor (PR), and Ki67 protein levels were analyzed by IHC. Change from baseline in tumor cell proliferation by Ki67 was the primary endpoint. Gene expression analysis was performed using the Illumina TruSeq RNA Access method. **Results:** From Jul 26, 2019 to Oct 15, 2020, 46/75 biomarker-evaluable pts were enrolled across three dose cohorts (10 mg: n = 15; 30 mg: n = 18; 100 mg: n = 13). Pt demographics and tumor characteristics were similar across cohorts. Baseline PAM50 analysis classified tumors as Luminal A (77%) or B (23%). Giredestrant treatment resulted in robust and indistinguishable PD and biologic activity at all doses. Geometric mean posttreatment proportional reduction of Ki67 was 79% (95% CI: 69–89; 10 mg: 80%; 30 mg: 76%; 100 mg: 80%), and 51% of tumors exhibited complete cell cycle arrest, defined as Ki67 $\leq$2.7%. Mean posttreatment proportional reductions of ER and PR H-scores were 71% (95% CI: 67–75) and 60% (95% CI: 51–70), respectively. An analysis of a predefined, experimentally derived set of 38 ER target genes (the 'ER activity signature'), was completed for 42 paired tumor specimens. Forty-one of 42 pts (98%) showed a posttreatment reduction in ER activity with a mean proportional decrease of 79% (95% CI: 70–88). A wide range of baseline ER activity was observed with no correlation to baseline ER or PR H-score, or Ki67. There were no discontinuations due to adverse events (AEs). A single grade 3 serious AE was reported in each cohort (all assessed as unrelated to giredestrant). No grade 4 or 5 AEs were reported. **Conclusions:** Giredestrant was well tolerated in the preoperative setting in ER+/HER2– operable BC, and PDs were consistent with the 30 mg dose achieving maximal ER inhibition. Clinical trial information: NCT03916744. Research Sponsor: Genentech, Inc.

578 **Poster Session**

A phase 2 trial of talimogene laherparepvec (TVEC) in combination with neoadjuvant chemotherapy for the treatment of nonmetastatic triple-negative breast cancer. *First Author: Hatem Hussein Soliman, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: TVEC is a modified oncolytic herpes simplex 1 (HSV1) virus currently FDA approved for the treatment of unresectable cutaneous and nodal melanoma. TVEC is designed to preferentially lyse tumor cells over normal tissue to release tumor associated antigens, produces GM-CSF to activate dendritic cells, and stimulates T cells to infiltrate the tumor (TILs). TILs in breast cancer are associated with better response to neoadjuvant chemotherapy (NAC), so we hypothesized that intratumoral TVEC may enhance response to NAC. We report results of a phase 2 trial combining NAC with TVEC in stage 2-3 TNBC. **Methods:** Stage II-III TNBC pts (N = 37) were to be enrolled into a single arm, optimal Simon 2 stage phase 2 trial with TVEC (10^6 PFU 1st dose then 10^8 PFU x 4 doses) weeks 1,4,6,8,10 + weekly paclitaxel (80mg/m2) IV x 12, followed by dose dense AC (doxorubicin/cyclophosphamide 60/600 mg/m2) IV q2weeks x 4 alone given preoperatively. Primary endpoint was residual cancer burden 0 rate (RCB0). Trial meets primary endpoint with $\geq$15 RCB0 responses out of 37 evaluable pts, assuming p1 = 45% vs. p0 = 30% with one sided type I error rate at 0.10 and power at 70%. **Results:** Forty pts were enrolled at Moffitt (5/2018 – 4/2020) and evaluable for safety with 3 pts non-evaluable for efficacy due to incomplete treatment. Study demographics: median age 49 (27-66), 67.5% White, 10% Black, 15% Hispanic, clinical stage II 83% and III 17%, node + 42%. The RCB0 rate = 16/37 (43%, 95% CI 27-61%) and additional 9 pts with RCB-1 (RCB0/1 rate 68%, 95% CI 50-82%). Toxicities did not differ significantly from expected NAC toxicities except for increased brief G1-2 fevers, chills, injection site pains. Four pts had G2-3 thromboembolic events (10%) slightly greater than expected 6% rate on NAC. **Conclusions:** Addition of TVEC to NAC increased RCB0 rates with manageable toxicities and warrants additional investigation in TNBC. Immune correlates and updated survival data will be presented at the meeting. Clinical trial information: NCT02779855. Research Sponsor: Amgen.

579 **Poster Session**

Pathological complete response rate and survival in patients with *BRCA*-associated triple-negative breast cancer after 12 weeks of de-escalated neoadjuvant chemotherapy: Translational results of the WSG-ADAPT TN randomized phase II trial (NCT01815242). *First Author: Lisa Katharina Katharina Richters, Center for Familial Breast and Ovarian Cancer and Center for Integrated Oncology (CIO), Medical Faculty, University Hospital Cologne, Cologne, Germany*

Background: The phase II trial WSG-ADAPT TN randomized triple-negative breast cancer (TNBC) patients to receive 12 weeks of neoadjuvant nab-paclitaxel (nab-pac) combined with carboplatin (carbo) vs gemcitabine (gem) and showed a substantial improvement of pathological complete response (pCR: ypT0/is, ypN0) with carbo (45.9% vs 28.7%). pCR had a strong favorable impact on iDFS after 3-year follow-up. Distribution of tumor mutations in BC-associated genes and impact of *BRCA* mutation status on pCR and outcome are analyzed here. **Methods:** NGS-based mutational analysis of *BRCA1/2* and 18 further (potentially) BC-associated genes was performed on DNA derived from pretreatment FFPE samples (gem: n = 158, carbo: n = 108) using a customized gene panel. Variants with a variant fraction of ≥5% were included and classified according to IARC and ENIGMA guidelines. **Results:** In 42 of the 266 analyzed samples, at least one deleterious *BRCA1/2*-variant was found (15.8%; *BRCA1* n = 37, *BRCA2* n = 3, *BRCA1+BRCA2* n = 2) one of which displayed an additional *STK11*-mutation. In the *BRCA1/2*-negative cohort, a mutation in one of 14 further analyzed (potential) BC-risk genes was found in 19 samples (7.1%; *BARD1* n = 3, *CHEK2* n = 2, *CDH1* n = 2, *FANCM* n = 3, *PALB2* n = 5, *RAD50* n = 1, *RAD51C* n = 1, *RAD51D* n = 1, *XRCC2* n = 1; no deleterious mutations were found in *ATM*, *BRIP1, MRE11A, NBN*). At least one deleterious variant in *TP53*, *PIK3CA*, *PTEN* or *MAP3K1* was seen in 89.1% (n = 237; *TP53* n = 233, *PIK3CA* n = 22 *PTEN* n = 15, *MAP3K1* n = 1). In 22 samples (8.3%) no deleterious mutation was identified in the analyzed genes. Overall, patients with tumor *BRCA* mutation (carbo n = 14, gem n = 28) had 45.2% vs 34.4% pCR (OR = 1.58, 95%-CI: 0.81-3.07, p = .18) without a mutation. pCR in the small group with mutation receiving carbo (n = 14) was 64.3% vs. 34.5% in all others (OR = 3.41, 95%-CI: 1.11-10.50; p = .03); direct comparison to *BRCA*-positive patients receiving gem (n = 28, 35.7%, OR = 3.2, 95%-CI: 0.85-12.36, p = 0.079) did not reach statistical significance. The results suggest that the strong favorable impact of pCR on iDFS is preserved even among *BRCA*-positive patients (n = 42, p = .07), as well as in the *BRCA*-negative subgroup (p < .001). No evidence for a predictive impact of *BRCA* mutation on efficacy of 4xEC additional chemotherapy was seen overall or within pCR subgroups. **Conclusions:** Twelve weeks of neoadjuvant nab-pac/carbo is a highly effective anthracycline-free regimen that leads to an excellent pCR-rate of 64% in tumor *BRCA1/2*-mutated cases. *BRCA1/2* mutation status could support this de-escalation strategy in early TNBC, but further prospective validation of survival impacts in larger cohorts and with longer follow up is needed. More detailed survival analyses will be presented at the meeting. Clinical trial information: NCT01815242. Research Sponsor: Celgene, Teva.

580 **Poster Session**

Evaluation of sensitivity to endocrine therapy index (SET2,3) for response to neoadjuvant endocrine therapy (NET) and subsequent prognosis. *First Author: William Fraser Symmans, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients (pts) in Cohort A of the American College of Surgeons Oncology Group Z1031 (Alliance) trial of NET for cStage II-III breast cancer were randomized to anastrozole [ANA], letrozole [LET] or exemestane [EXE] for 16-18 weeks (wks). In Cohort B, pts chose between ANA and LET and switched to chemotherapy or surgery if a tumor biopsy after 2-4 wks of NET had Ki67 >10%. Treatments after surgery were not defined by the trial protocol. SET2,3 measures nonproliferation gene expression related to estrogen and progesterone receptors adjusting for a baseline prognostic index that combines clinical tumor and nodal stage and a 4-gene molecular subtype (RNA4) defined by *ESR1*, *PGR*, *ERBB2* and *AURKA*. High SET2,3 in a pre-treatment biopsy using cStage information is defined as SET2,3 >1.77. **Methods:** 379 pts had gene expression data from a research tumor biopsy prior to NET (Agilent 44K microarrays). A bioinformatician blinded to pt treatment and clinical outcomes determined SET2,3. The trial statistician then examined the association between SET2,3 and pharmacodynamic response at 2-4 wks (N=141, Cohort B): Ki67 ≤10% and complete cell cycle arrest (CCCA Ki67 ≤2.7%); pathologic outcomes in pts who completed NET: ypStage 0/1 (N=329, Cohorts A&B), PEPI-0 rate (N=155, Cohort B); and event-free survival (EFS) post-registration (N=244, Cohorts A&B). We used Fisher's exact tests to assess whether responses, and Cox modeling to evaluate whether EFS, differed with respect to SET2,3 status. **Results:** High SET2,3 in 48% of pts (183/379) was associated with older age (median: 66 vs 63 years; p=0.012); cStage II (95% vs 75%; p <0.001); and pre-NET Ki67 ≤10% (37% vs 20%; p< 0.001) in pts with low SET2,3. In Cohort B, pts with high SET2,3 had a higher rate of pharmacodynamic response in their tumor at wk 2-4 than pts with low SET2,3 (Table). In the subset of Cohort B pts with wk 2-4 Ki67 ≤10%, pre-treatment SET2,3 trended numerically higher in pts who achieved PEPI-0 score (p=0.049) but the proportion achieving PEPI-0 did not differ by SET2,3 high/low status (Table). EFS was significantly longer for pts with high SET2,3 than pts with low SET2,3 (HR[H/L]: 0.52; 95% CI: 0.34-0.80; p=0.003). **Conclusions:** An exploratory analysis of Z1031 data demonstrated that the rate of pharmacodynamic suppression of proliferation by NET at 2-4 wks was greater and EFS was longer for pts with breast cancer expressing high SET2,3 disease than pts with low SET2,3. Support: U10CA180821, U10CA180882, U24CA196171; https://acknowledgments.alliancefound.org; Clinical trial information: NCT00265759. Research Sponsor: Breast Cancer Research Foundation, U.S. National Institutes of Health.

Response endpoints: Rate of attainment (%) by SET2,3 status.

		SET2,3 Status		
Response	**Frequency % (ratio)**	**Low**	**High**	**P =**
Pharmacodynamic at 2-4 wks				
Ki67 ≤ 10%	74 (104/141)	57	88	< 0.001
Ki67 < 2.7% (CCCA)	38 (54/141)	25	50	0.003
Pathologic at Surgery				
***yp* Stage 0-I**	26 (85/329)	25	27	0.710
PEPI-0	19 (29/155)	16	22	0.414

581 **Poster Session**

Effect of moderate physical exercise on the immune system modulation in patients with breast cancer during preoperative chemotherapy: The NEORUNNER study. *First Author: Ornella Garrone, Breast Unit AO S. Croce e Carle Teaching, Cuneo, Italy*

Background: The link between physical activity (PA) and the immune system (IS) is known. However, it is not yet fully understood the immune mechanisms activated by PA. We investigated the immune effect of moderate PA (MPA), nordic or fit walking, during neoadjuvant chemotherapy (NACT) in patients (pts) with breast cancer. **Methods:** Pts received sequential epirubicin and cyclophosphamide for 4 cycles followed by paclitaxel for 12 weeks. Blood samples from pts underwent MPA (TR) were collected before starting chemotherapy (CT) at baseline (T0), at day 1 of week 6 of paclitaxel (before starting MPA) (T1), before surgery (S) (T2) and after S (T3). Samples were also collected in a group of pts who declined MPA (UN) at the same time points and in 15 healthy volunteers (HV). MPA consisted of 3 workouts per week, 1 hour each, in the 9 weeks before S. At each time point the level of 17 cytokines (IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12, IL-13, IL-15, CCL-2, CCL-4, CXCL-10, CCL-22, IFN-γ, TGF-β, TNF-α, VEGF) was measured. The difference among the median value of cytokines was analyzed using non parametric Mann Whitney *U* test. Principal component analysis (PCA) was computed to compare the best discriminating cytokine, identified by ROC analysis, of pts at T1, T2, T3 and in HV. Each patient was distributed in the PCA. Pts having similar cytokine values were plotted in the near position. Normalized values of 8 cytokines (IL-2, IL-4, IL-5, IL-6, IL-13, IL-15, CCL-2, VEGF) were used in PCA. **Results:** Data from 27 pts are available: 10 TR and 17 UN. A significant increase of IFN-γ, IL-5, IL-8, CCL-2 and CXCL-10 between T0 and T1 (P = 0.004, P = 0.013, P = 0.032, P = 0.046, P = 0.046, respectively) was found in the whole population. CXCL-10 significantly increased also between T1 and T2 in UN pts (P = 0.033). TR pts showed a significant lower level of IL-6, IL-13, CCL-2 at T2 (P = 0.012, P = 0.038, P = 0.023) and higher IL-15 level at T3 (P = 0.047) compared to UN pts. Moreover, a significant decrease of IL-5 was observed between T2 and T3 (P = 0.031). PCA showed that TR and UN pts were mixed at T1. HV were clustered all together and distinct from pts. At T2 TR pts moved toward HV and mixed with them while UN remained separated. TR pts tended to separate from HV at T3, while UN pts still remained distinct. **Conclusions:** NACT upregulated median values of IFN-γ, IL-5, IL-8, CCL-2 and CXCL-10; CXCL-10 value continues to increase during CT only in UN pts supporting the inflammatory effect of CT. On the contrary, during MPA the level of IL-6, IL-13, CCL-2 decreases in TR compared to UN pts. All together these data suggest that MPA damps the inflammatory response to NACT. Our results show that the majority of TR pts reach an immune profile similar to that of HV in PCA. However, at T3 the effect of MPA is dampened, suggesting a potential negative effect of S. Research Sponsor: ARCO Foundation.

582 **Poster Session**

Independent validation of simbiosys tumorscope to predict response to neoadjuvant chemotherapy (NACT) in early breast cancer (EBC). *First Author: Gong He, University of Chicago Medical Center, Chicago, IL*

Background: Despite substantial advances in the understanding of breast cancer biology, the decision to use NACT for EBC is based on tumor size, lymph node status, and subtype. Even with aggressive therapy, the majority of women will not achieve a pathologic complete response (pCR). Investigational treatment regimens, including immunotherapy, can increase pCR rates, but are associated with irreversible immune-related toxicities. Being able to accurately predict pCR could identify candidates for intensification or de-escalation of NACT, allowing for personalized medicine. SimBioSys TumorScope (TS) is a biophysical model that utilizes baseline MRI, receptor status, and planned treatment regimen to simulate response to NACT over time. TS has demonstrated accurate prediction of pCR in prior studies. Here, we describe an independent external validation of TS. **Methods:** We conducted a retrospective study of University of Chicago patients (pts) who received NACT for EBC from Jan 2010 - March 2020. Pts must have had a pretreatment breast MRI. Tumors were analyzed using TS by investigators who were blinded to response data. TS predicted pCR was predefined as a residual tumor volume < 0.01 cm^3 or a 99.9% or greater reduction in tumor volume. Performance metrics of TS were calculated. **Results:** 144 tumors from 141 pts were analyzed. Average age was 52 yrs; 65% had stage II and 19% had stage III disease. Sensitivity and specificity of TS for predicting pCR were 90.4% and 92.4%, respectively. Of the 7 patients who were predicted to achieve a pCR but did not, 5 had a tumor cellularity < 5%. With a median follow-up of 4.7 yrs, the 4-yr distant disease free survival (DDFS) was 100% for patients predicted to achieve pCR, versus 81.5% for those predicted to have residual disease. Results were generally robust for all subgroups analyzed (Table). **Conclusions:** TS accurately predicts pCR and DDFS from baseline MRI and clinicopathologic data. Given the high sensitivity and specificity of this assay across breast cancer subtypes, TS can be used to aid in escalation/de-escalation strategies for EBC. Research Sponsor: None.

Sensitivity and specificity of TS prediction for pCR for select subgroups.

Subgroup	**n**	**Accuracy (%)**	**Sensitivity (%)**	**Specificity (%)**
Total	144	92	90	92
TNBC	59	92	91	92
HER2-/HR+	36	92	83	93
HER2+	49	92	91	92
Anthracycline-containing NACT	103	90	92	90
Anthracycline-free NACT	41	95	88	100

583 **Poster Session**

Phase II prospective open label study of neoadjuvant pertuzumab, trastuzumab, and nab-paclitaxel in patients with HER-2 positive advanced breast cancer. *First Author: Sayeh Moazami Lavasani, City of Hope National Medical Center, Duarte, CA*

Background: HER2 overexpression occurs in 20-25% of breast cancers (BC) and is associated with poor prognosis. The addition of trastuzumab (trast) to chemotherapy significantly improves disease-free (DFS) and overall survival (OS) in the adjuvant setting. Pertuzumab (pert) inhibits ligand-activated signaling and in combination with trast has synergistic inhibition of BC cells overexpressing HER2. In the neoadjuvant therapy (NT) setting, the combination of trast, pert, and docetaxel can improve the pCR rate. PCR may predict for improved DFS and OS. De-escalation with weekly paclitaxel combined with trast and pert appeared to be safe and efficacious but requires steroid premedication, whereas nab-paclitaxel (nab) does not require steroid premedication. To decrease treatment-associated toxicity in patients with HER2+ BC, we utilized a non-anthracycline regimen with pert, trast, and nab as NT. The objectives of this study were to evaluate the safety and efficacy of pert added to trast and nab in HER2+ locally advanced BC (LABC) to determine the pCR, as well as DFS and OS. **Methods:** A total of 45 patients with biopsy-confirmed HER2+ LABC or inflammatory BC were enrolled from 2013-2017, and were treated with 6 cycles of neoadjuvant pert (840 mg loading dose, then 420 mg IV day 1 every 21 days), weekly trast (4 mg/kg loading dose, then 2 mg/kg), and weekly nab (100 mg/m^2 IV). Patient characteristics, including age, race, menopausal status, grade, stage, and prior surgery and radiation were recorded. Median treatment cycles determined, and events (AE) were identified for each arm. PCR rate, DFS and OS were calculated. **Results:** Median age was 56 (31-78) years. 1/45 (2%) was stage I, 30/45 (67%) were stage II, 14/45 (31%) were stage III. pCR rate was 29/45 (64.4%). The initial primary tumor size was similar in pCR and non-pCR patients (mean 4.1 cm vs. 3.2 cm, respectively). Median follow-up was 36.1 months (95% CI [27.1, 41.8]). Median treatment cycles completed was 6 (1-6). A total of 4/45 (9%) patients had >1 cycle delayed, and 32/45 (71%) patients had >1 cycle modified. For the patients achieving pCR, the DFS (95% CI) at 3 years was 85.9% (66.7%, 94.4%) and for those without pCR, it was 87.5% (58.6%, 96.7%). OS was not reached (95% CI [NR, NR]). Grade 3 AEs (> 2 patients) included 7/45 (16%) of patients with hypertension; 4/45 (9%) with anemia; and 2/45 (4%) with diarrhea, ALT, fatigue, or rash. **Conclusions:** This anthracycline-free regimen which included nab achieved great pCR rate of 64.4% in HER2+ BC patients with fewer treatment-related toxicities. The pCR rate is comparable with docetaxel, carboplatin, trast, and pert (TCHP) therapy in NT setting, but without the treatment-associated toxicities. This suggests we may be able to safely avoid anthracyclines and carboplatin for NT in HER2+ BC patients. The improved pCR did not translate into DFS benefit. Clinical trial information: NCT01730833. Research Sponsor: Genentech, Inc., Bristol Myers Squibb, City of Hope.

584 **Poster Session**

Computational features of tumor-infiltrating lymphocyte architecture of residual disease after chemotherapy on H&E images as prognostic of overall and disease-free survival for triple-negative breast cancer. *First Author: Germán Corredor, Case Western Reserve University, Cleveland, OH*

Background: Approximately 30% of all breast cancers are characterized as triple-negative (TNBC). TNBC typically occurs in younger women and is associated with a poorer prognosis relative to other breast cancer subtypes. High levels of tumor-infiltrating lymphocytes (TILs) in residual disease after Neoadjuvant chemotherapy (NACT) have previously been shown to be associated with better prognosis in TNBC. In this work, we sought to evaluate the prognostic value of computationally derived measures of TIL spatial architecture in residual TNBC after NACT. **Methods:** H&E-stained samples from 92 patients (pts) with TNBC (41 died, 45 had disease recurrence) and residual disease after NACT were retrospectively collected from 2 sites: Instituto Nacional de Enfermedades Neoplásicas (S1) and University Hospitals (S2). 45 pts (16 deaths, 23 recurrences) from S1 formed the training set and 47 pts (25 deaths, 22 recurrences) from S2 formed the independent validation cohort. Samples were digitized at 20x. Computerized algorithms automatically identified 2 types of nuclei (TILs and non-TILs) and built clusters for each nuclei type based on cell proximity. The spatial arrangement of these clusters was then quantified using network graph metrics. The top 5 features, determined by least absolute shrinkage and selection operator, were used to train a Cox regression model that assigned a risk of death and recurrence to each patient on the training set. The percentile 33 risk score was used as a threshold for stratifying pts on the validation set as either low or high risk. For comparison, we also employed a model based on TIL density alone. Survival analysis was used to evaluate the performance of both approaches on disease-free survival (DFS) and overall survival (OS). **Results:** Pts in S2 (n=47) identified as "high risk" by the model based on spatial architecture of residual TILs had a significantly shorter survival time. The median OS for pts at high risk was 25 months vs. 55 months for low-risk pts. The median DFS for pts at high risk was 32 months vs 51 months for low-risk pts. Univariable analysis showed this model was prognostic for both OS (Hazard Ratio (HR) = 2.57, 95% Confidence Interval (CI): 1.07-6.16, p=0.03) and DFS (HR=2.38, CI: 1.01-5.62, p=0.04). In contrast, the model based on TIL density was not prognostic for OS (HR=1.24, CI: 0.33-4.63, p=0.73) nor DFS (HR=1.19, CI: 0.32-4.34, p=0.78). **Conclusions:** A computerized image analysis model based on measurements of spatial arrangement of residual TILs and surrounding cells was found to be prognostic in TNBC pts who received NACT. This method appears to be more prognostic than TIL density alone. Additional multisite validation and multivariable analysis is needed to further establish the independent prognostic utility of TIL based image biomarkers in the post-NACT TNBC. Research Sponsor: U.S. National Institutes of Health, Other Government Agency, Ohio Third Frontier, Wallace H. Coulter Foundation, Case Western Reserve University.

585 **Poster Session**

Impact of dendritic cell vaccines added to neoadjuvant CT on pathological complete responses in early breast cancer patients according to PD-L1 expression. *First Author: Ignacio Ortego, Clínica U. Navarra, Pamplona, Spain*

Background: Breast cancer (BC) in early stages exhibit a naïve and competent immune system that translates into a more prominent TIL infiltration and higher PD-L1 expression as compared to the advanced BC scenario were immunoescape and exhaustion are more prevalent. Expression of PD-L1 has been related to a better pCR when immune checkpoint inhibitors (IPI) have been added to neaodjuvant chemotherapy (NACT) in triple negative BC (TNBC). Our prior results shown dendritic cells vaccines (DCV) increased pCR in both TNBC and luminal B subtypes, with an absolute gain of 20% (p = 0.03) and a safe tolerance. **Methods**: Eighty-three HER2 negative BC patients with untreated stage II-III were included: 39 patients from the NCT01431196 trial that combine NACT with autologous DCV and 44 patients from a historic control group treated with the same NACT alone. NACT consists of dose dense Epirubicin plus Cyclophosphamide for 4 cycles sequenced to Docetaxel for 4 cycles. PD-L1 expression was measured in the membrane of tumoral cells with monoclonal rabbit anti PD-L1 28.8 pharmaDX (DAKO, Agilent Technologies) in FFPE samples at diagnosis. Primary endpoint was pathologic complete response (pCR) stratified by PD-L1 expression (positive or negative), while secondary endpoints were event-free survival (EFS) and overall survival (OS), also stratified by PD-L1 expression. **Results**: Both cohorts were well balanced in most of the features. Thirty-three percent of the tumors in the experimental group were PD-L1 positive, whereas 50% of them in the CG expressed PD-L1 (p = 0.06). Pathological CR was observed in 50% of the PD-L1 positive population, in contrast to a 2.8% in the PD-L1 negative in the NACT cohort ($p < 0.01$) as compared to the patients assigned to the DCV group (33.4% in PD-L1 positive vs 23.1% in PD-L1 negative population; p = 0.16). Among PD-L1 positive population, more pCR were seen in the CG than in the DCV group (50% vs 33.4%; p = 0.06). Within the PD-L1 negative population, more pCR were observed in the DCV group than in the CG (23.1% vs 2.8%; $p < 0.05$). With a median follow-up of 7 years, no significant differences were observed between the different subgroups neither in EFS (HR = 1.7; 0.42-6.8; p = 0.19) nor in OS (HR = 2.5; 0.56-11, p = 0.43). At 7 years, 20% and 14.4% of the patients relapsed according to the PD-L1 positive versus negative status respectively, and 10.78% versus 13.33% were dead. **Conclusions**: The benefit of DCV seems to be outstanding in the PD-L1 negative tumors that have a basal immune appropriate milieu. PD-L1 expression implies a more suppressed niche in which DCV are not able to stimulate antigen presentation and cell cytotoxic activity. PD-L1 positive population reach higher responses with both NACT±DCV than PD-L1 negative group, although the benefit seem to be higher in the NACT alone cohort. Further studies combining DVC+IPI together with NACT are needed. Clinical trial information: NCT01431196. Research Sponsor: 1. Principal investigator of the project: Estudio prospectivo fase II de la vacunación con células dendríticas autólogas en pacientes con cáncer de mama triple negativo en estadios II-III". Ministerio de Sanidad y Política Social en la.

586 **Poster Session**

Impact of different sequencing strategies of talazoparib and carboplatin combination upon efficacy and toxicity in BRCA-wild type and BRCA-mutant triple-negative breast cancer models. *First Author: Michele Beniey, Universite de Montreal, Montreal, QC, Canada*

Background: PARP inhibitors (PARPi) such as talazoparib and olaparib, have demonstrated an improvement in progression-free survival (PFS) amongst metastatic HER2-negative breast cancer patients with germline mutations in BRCA1/2 (BRCA-MUT). Clinical trials have evaluated PARPi in combination with carboplatin, but with mixed results. Earlier trials studied the combination of carboplatin and a low-dose PARPi of low potency, veliparib. The concomitant combination of carboplatin and talazoparib, a higher-potency PARPi, was also evaluated in solid tumors, using a heavily pretreated population. Here, we perform a comparative evaluation of different sequencing strategies of talazoparib and carboplatin to determine efficacy and toxicity in BRCA-MUT and BRCA wild-type (WT) TNBC models. **Methods:** We used three orthotopic xenograft models in NSG (NOD scid gamma) mice, with 7-14 mice in each treatment group: MDAMB231 (BRCA-WT), HCC1806 (BRCA-WT), and MX1 (BRCA-MUT). We treated mice with carboplatin (C) (35 mg/kg intraperitoneally) in combination with talazoparib (T) (0.33 mg/kg oral gavage) using 2 dosing strategies: a) concomitant administration of C + T; and b) T first, followed by C three days later, each compared to vehicle control. We evaluated primary tumor inhibition and hematologic toxicity. Kruskal-Wallis test and Dunn's multiple comparison test was used to assess statistical significance. **Results:** Using the MDAMB231 xenograft, we found the T-first approach led to a 66.7% ($P < 0.0001$), and the concomitant approach resulted in a 51.4% decrease in primary tumor volume, (P = 0.08), in comparison to control. In HCC1806, the T-first approach resulted in a 62.0% decrease in tumor volume ($P < 0.0001$), whereas the concomitant combination showed a 54.4% decrease (P = 0.002). In MX1, the T-first and concomitant approaches resulted in 72.7% ($P < 0.0001$) and 81.4% ($P < 0.0001$) decrease in tumor volume, respectively. With regards to neutrophil counts, T-first approach decreased neutrophils by 66.2% and 43.0% in MDAMB231 and HCC1806 xenografts respectively, similar to the trend with concomitant T + C: 61.4% and 38.0%. In the MX1 cohort, the T-first approach resulted in a 66.2% decrease in neutrophils (P = 0.001), and the concomitant approach led to a 77.5% decrease in neutrophils (P = 0.006). **Conclusions:** Our results demonstrate that the talazoparib-first approach is effective in two BRCA-WT models with no statistically significant neutropenia. While the concomitant combination approach demonstrated greater tumor inhibition in the BRCA-MUT model, this was also associated with significant neutropenia. This is suggestive that sequencing of talazoparib and carboplatin may have differential effect in BRCA-WT and BRCA-MUT tumors and may play an important role in improving efficacy in BRCA-WT tumors. Research Sponsor: Pfizer Canada, Fonds de recherche de Quebec - Santé.

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Treatment Efficacy Score (TES), a continuous residual cancer burden-based metric to compare neoadjuvant chemotherapy efficacy between trial arms in the I-SPY 2 trial. *First Author: Michal Marczyk, Silesian University of Technology, Gliwice, Poland*

Background: Residual cancer burden (RCB) is a continuous score that captures the amount of residual cancer after neoadjuvant chemotherapy and predicts disease recurrence and survival across all breast cancer subtypes. RCB score 0 corresponds to pathological complete response (pCR; ypT0, ypN0). We hypothesize that comparison of the distributions of RCB scores between randomized treatment arms of a trial could predict treatment effect on recurrence free survival better than comparison of pCR rates only. **Methods:** The cancer Treatment Efficacy Score (TES) compares efficacies of two treatments using non-continuous RCB results. We examined (i) area between cumulative distribution (ABC) functions; (ii) density ratio of RCB scores; and (iii) density difference of RCB scores from two treatments, to select the most efficient metric to compute TES. A random permutation procedure was used to estimate the p-value from each test. These methods were applied to data from the durvalumab/olaparib arm and corresponding controls of the I-SPY2 trial, separately by molecular subtype. In subsampling and simulation experiments we assessed robustness of results including power and false positive rate control under variable sample sizes to select the most robust TES metric. The other 11 experimental arms of I-SPY2 were used to assess the performance of the final metric. We calculated correlation between TES and (i) pCR rate difference, and 3- and 5-year (ii) event-free (EFS) and (iii) distant recurrence free survivals (DRFS). **Results:** RCB scores are multimodal and do not follow normal distribution.In simulated data ABC provided more stable results than the other methods, had good power, performed well with small sample sizes, resulted in low false positive rate, required the least computational time, and therfore was selected as the TES metric for validation in 11 arms of I-SPY2. We found a high correlation between difference in pCR rate and TES value across all molecular subtypes in each of the 11 trial arms ($r = 0.92$, $p = 1.7e-8$). There was also significant linear relationship between TES and survival estimates in EFS ($r = 0.58$, $p = 9.3e-3$ for 3-years survival; $r = 0.62$, $p = 4.8e-3$ for 5-years survival) and DRFS ($r = 0.56$, $p = 1.2e-2$ for 3-years survival; $r = 0.54$, $p = 1.8e-2$ for 5-years survival). Statistically significant TES score correlated significantly with higher benefit in 3-years survival ($p = 9.7e-4$ for EFS; $p = 5.7e-3$ for DRFS) and 5-years survival ($p = 9.7e-4$ for EFS; $p = 3.0e-3$ for DRFS). In most instances, this correlation with survival was higher than seen with pCR difference. **Conclusions:** TES is a novel more optimal metric to identify the more effective cytotoxic neoadjuvant regimen from the entire distribution of pathologic response that significantly correlates with event and recurrence free survival and may serve as a better surrogate than pCR rate difference. Research Sponsor: The I-SPY Trials. Quantum Leap Healthcare Collaborative.

589 **Poster Session**

Does timing of chemotherapy impact breast satisfaction after breast conservation therapy and mastectomy with immediate reconstruction? *First Author: Kate R. Pawloski, Breast Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Receipt of chemotherapy is associated with decreased postoperative breast satisfaction, but whether timing as neoadjuvant (NAC) versus adjuvant (AC) affects this outcome after breast conservation therapy (BCT) and mastectomy with immediate reconstruction (M-IR) is unclear. **Methods:** We retrospectively identified patients treated with chemotherapy and breast surgery (BCT and M-IR), from 1/2017-12/2019, who completed ≥ 1 BREAST-Q survey through 12/2020. Mean (standard deviation [SD]) Q-scores for satisfaction with breasts (SATBR) were compared between NAC versus AC groups in BCT and M-IR cohorts, respectively. Higher Q-scores on a 0-100 scale indicate superior satisfaction. A minimum 4-point difference was considered clinically important. Chemotherapy timing and significant covariates on univariate analyses were entered in multivariable linear regressions of 1- and 2-year SABTR. **Results:** 640 patients had BCT and 602 had M-IR; 210 (33%) BCT patients and 294 (49%) M-IR patients had NAC. Compared with M-IR, SATBR was higher after BCT in both NAC and AC groups, at all postoperative timepoints (Table). Following BCT, SABTR was highest in both NAC and AC groups at 6 months and returned to baseline in the NAC group by year 3. In the M-IR cohort, 331 (55%) patients had radiation and 120 (20%) had complications requiring re-operation or hospitalization. Compared with baseline, mean (SD) Q-scores were substantially lower at 6 months but improved to near baseline at 3 years in both NAC and AC groups. On multivariable analysis, radiation was associated with decreased SABTR at 1 year (Beta, -11; 95% CI, -17, -5.0; $p<0.001$) and 2 years (Beta, -12; 95% CI, -19, -5.5; $p<0.001$), as were complications at 1 year (Beta, -6.1; 95% CI, -12, -0.34; $p=0.038$) but not 2 years (Beta, -5.5; 95% CI, -12, 0.92; $p=0.09$). After multivariable adjustment, NAC was not significantly associated with 1- or 2-year SABTR after M-IR or BCT. **Conclusions:** SABTR was higher in BCT compared with M-IR cohorts, independent of chemotherapy timing. Following BCT, SABTR was lower in the NAC group at years 2-3 but remained at baseline or higher at all timepoints. In the M-IR cohort, both groups endorsed lower than baseline SABTR in years 0-2 but returned to near baseline at 3 years. Radiation and complications were independent predictors of decreased SABTR, but our findings suggest that patients who experience complications after M-IR can expect return to baseline breast satisfaction by 2 years. Research Sponsor: U.S. National Institutes of Health.

Mean (SD) of SABTR Q-scores among BCT and M-IR cohorts.

	BCT			M-IR		
Variable	Overall (N = 640)	NAC (N = 210)	AC (N = 430)	Overall (N = 602)	NAC (N = 294)	AC (N = 308)
Preoperative	65 (23)	65 (23)	65 (23)	63 (21)	63 (22)	63 (21)
6 months	78 (21)	78 (19)	77 (22)	33 (30)	25 (31)	38 (28)
1 year	75 (21)	73 (21)	76 (21)	52 (25)	51 (24)	52 (26)
2 years	72 (23)	67 (23)	74 (23)	55 (22)	55 (22)	55 (22)
3 years	70 (23)	65 (23)	72 (23)	61 (20)	59 (21)	64 (19)

590 **Poster Session**

The impact of gut microbial composition on response to neoadjuvant chemotherapy (NACT) in early-stage triple negative breast cancer (TNBC). *First Author: Nour Abuhadra, MD Anderson Hematology/Oncology Fellowship, Houston, TX*

Background: The impact of gut microbiome on tumor biology, progression and response to immunotherapy has been shown across cancer types. However, there is little known about the impact of gut microbial composition on response to chemotherapy. We have previously shown that the gut microbiome remains unaltered during NACT in a cohort of 32 patients. Here we investigate the association between gut microbiome and response to NACT in a larger cohort of early-stage TNBC. **Methods:** Longitudinal fecal samples were collected from 85 patients with newly-diagnosed, early-stage TNBC patients enrolled in the ARTEMIS trial (NCT02276443). Patients all received standard NACT with adriamycin/cyclophosphamide (AC); volumetric change was assessed using ultrasound and patients with < 70% volumetric reduction (VR) after 4 cycles of AC were recommended to receive targeted therapy in addition to standard NACT to improve response rates. We performed 16S sequencing on bacterial genomic DNA extracted from 85 pre-AC fecal samples using the 2x250 bp paired-end read protocol. Quality-filtered sequences were clustered into Operational Taxonomic Units and classified using Mothur method with the Silva database version 138. For differential taxa-based univariate analysis, abundant microbiome taxa at species, genus, family, class, and order levels were analyzed using DESeq2 after logit transformation. Alpha-diversity indices within group categories were calculated using phyloseq. Microbial alpha diversity (within-sample diversity) was measured by Simpson's reciprocal index. β-diversity was measured using weighted UniFrac distances between the groups. The association between microbiota abundance and pathologic complete response (pCR) or residual disease (RD) was assessed using DESeq2 analysis. **Results:** Pre-AC fecal samples from 85 patients were available for analysis. Amongst them, there were 46 patients with pCR and 39 patients with RD. There was no significant difference in alpha diversity ($p = 0.8$) or beta-diversity ($p = 0.7$) between the pCR and RD groups. However, relative to patients with RD, the gut microbiome in patients with pCR was enriched for the Bifidobacterium longum species ($p = 0.03$). The gut microbiome in patients with RD was enriched for Lachnospiraceae ($p = 0.03$) at the genus level and the Bacteroides thetaiotaomicron species ($p = 0.02$). **Conclusions:** We have demonstrated significant differences in the gut microbial composition in patients with pCR as compared to patients with RD. Further investigation in larger studies is needed to support therapeutic exploration of gut microbiome modulation in TNBC patients receiving chemotherapy such as probiotic supplementation or fecal microbiota transplant. Research Sponsor: MD Anderson Cancer Center Moonshots Program, the Springwater Foundation and a CPRIT Multi-Investigator Research Award (MIRA).

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Multi-gene prognostic assays and age-related differences in prediction of pathologic complete response to neoadjuvant chemotherapy and survival in breast cancer. *First Author: Kent Hanson, University of Illinois at Chicago, Chicago, IL*

Background: Multi-gene testing of primary breast tumors in early-stage breast cancer is used to classify the risk of developing distant metastases and predict the benefit of adjuvant chemotherapy. The association between the tumor genomic prognostic score (GPS) and response to neoadjuvant chemotherapy (NACT) and survival is not well characterized. Our objective was to describe the association between GPS and rates of pathologic complete response (PCR) and subsequent overall survival among women with or without PCR. **Methods:** We utilized the National Cancer Database to perform a hospital-based, retrospective cohort study of breast cancer patients ages 18 years and older. We included women diagnosed with first primary stages I-III hormone receptor positive (HR+), HER2 negative (HER2-) breast cancer who received NACT and surgery between 2010 and 2017. Women were categorized as having low (0-10 or 200), intermediate (11-25 or 300), or high-risk (25-199 or 400) GPS based on OncotypeDX or MammaPrint scores. Multivariable modified Poisson regression models with robust error variance were used to estimate the crude and adjusted relative risk and 95% confidence intervals (CI) for PCR associated with GPS groups. Multivariable Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) and 95% CI for associations between the GPS and overall survival (OS) in women who did and did not have PCR. **Results:** A cohort of 3,446 women (mean [SD] age, 56.7 [12.0] years; median [interquartile range] follow-up of 47 [31-68] months) who received genomic testing and neoadjuvant chemotherapy were included in our analysis, of which 935 (27%) were low risk, 1,357 (39%) intermediate risk, and 1,154 (34%) high risk GPS. The relative risk of PCR for all women with high GPS was 1.81 (95% CI, 1.47-2.22; $p < 0.001$) in crude models and 1.49 (95% CI, 1.16-1.92; $p = 0.002$) after full adjustment compared to low GPS. Across all models, having a high GPS was significantly associated with achieving PCR in younger women (< 65 years). In women ages ≥65 years, the association between GPS and PCR was not predictive nor statistically significantly. Among women with no response or partial response to NACT, high GPS was associated with a significantly increased risk of overall mortality (HR 2.41; 95% CI, 1.61-3.60; $p < 0.001$) compared to low GPS. Conversely, in women who did achieve PCR, GPS was not predictive of overall mortality across all age groups. **Conclusions:** In women with HR+/HER2- breast cancer, high risk GPS was predictive of PCR following NACT, primarily in younger women (< 65 years). Our findings also indicated GPS was associated with lower OS in high-risk patients who do not achieve PCR and unpredictive of OS in those without PCR. The utility of tumor genomic testing in the neoadjuvant setting needs further investigation. Research Sponsor: None.

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Neoadjuvant atezolizumab (atezo) and nab-paclitaxel (nab-p) in patients (pts) with triple-negative breast cancer (TNBC) with suboptimal clinical response to doxorubicin and cyclophosphamide (AC). *First Author: Clinton Yam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Neoadjuvant anti-PD-(L)1 therapy confers an improvement in pathological complete response (pCR) rate in unselected TNBC. However, given the potential for long-term morbidity from immune related adverse events (irAE), it is important to optimize the risk-benefit ratio for the use of these novel agents in the curative neoadjuvant setting. Suboptimal clinical response to neoadjuvant therapy (NAT) by sonography is associated with low rates of pCR rate (2-5%, GeparTrio and Aberdeen trials). Here, we report the results of a single arm phase II study of atezo and nab-p as the second phase of NAT in pts with TNBC with suboptimal clinical response to AC (NCT02530489). **Methods:** Pts with stage I-III TNBC showing suboptimal response to 4 cycles of doxorubicin and cyclophosphamide (AC), defined as disease progression or a <80% reduction in tumor volume by sonography, were eligible. Pts received atezo (1200mg IV, Q3 weeks x 4), and nab-p (100mg/m2 IV, Q1 week, x 12) as the second phase of NAT before undergoing surgery followed by adjuvant atezo (1200mg IV, Q3 weeks, x 4 cycles). This single arm, two-stage Gehan-type study was designed to detect an improvement in pCR from 5% to 20% in order to deem the regimen worthy of further study in a large, randomized, phase II/III trial; success was defined as pCR in 8 out of 37 pts enrolled. In a subset of pts, sufficient baseline tumor tissue was available for stromal TIL assessment (n=29). **Results:** 34 pts were enrolled from 2/2016-12/2020. Among the 33 pts who have completed NAT, the pCR rate was 30% (10/33, 95% CI: 16-49%) and the pCR/RCB-I rate was 42% (14/33, 95% CI: 25-61%). Clinicopathological characteristics are described in the table below. Treatment-related adverse events (all grades) occurring in ≥ 20% of pts include fatigue (73%), anemia (55%), peripheral sensory neuropathy (55%), neutropenia (48%), rash (42%), ALT elevation (39%), AST elevation (33%), nausea (30%), anorexia (24%), diarrhea (21%), myalgia (21%). Discontinuation of atezo due to irAEs occurred in 4 pts (12%, nephritis [n=2]; adrenal insufficiency [n=1]; hepatitis [n=1]); 2 of these pts had pCR. **Conclusions:** This study met its primary endpoint, demonstrating a promising signal of activity in this high risk pt population (pCR=30% vs 5% in historical controls). The 12% discontinuation rate due to irAEs confirms that further evaluation of a strategy administering immunotherapy only to pts with high risk disease not responding to AC warrants further investigation. Exploratory genomic and immunological correlative studies are ongoing. Clinical trial information: NCT02530489. Research Sponsor: Genentech, Conquer Cancer Foundation of the American Society of Clinical Oncology, MD Anderson Breast Cancer Moon Shots Program.

	pCR (n=10)	Non-pCR (n=23)
Median age – years (IQR)	58 (52-64)	46 (36-61)
	n (%)	
T stage		
T1	1 (10)	2 (9)
T2	9 (90)	10 (43)
T3	0	6 (26)
T4	0	5 (22)
Nodal status		
Positive	8 (80)	16 (70)
Negative	2 (20)	7 (30)
Histologic grade		
1/2	3 (30)	3 (13)
3	7 (70)	20 (87)
Stromal TIL		
<20%	3 (38)	16 (76)
≥20%	5 (63)	5 (24)

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Automated, IHC/FISH-free, H&E histopathology image-based HER2 amplification, tumor infiltrating lymphocyte (TIL) and tumor heterogeneity profiling in breast cancer. *First Author: Satabhisa Mukhopadhyay, 4D Path Inc., Newton, MA*

Background: Digital pathology has fostered the development of automated diagnostic solutions. However, current technologies in breast cancer remain unable to determine HER2 amplification status, which is established by immunohistochemistry (IHC) and/or fluorescent in situ hybridization (FISH). These ancillary tests carry a significant cost, prolong diagnostic time and fail to capture HER2 tumor heterogeneity and tumor infiltrating lymphocyte (TIL) burden, both of which determine the effectiveness anti-HER2 targeted therapy. **Methods:** This study describes the real-life clinical context development and validation of a patented novel, universal, automated, white-box, scanning platform agnostic solution that determines HER2 amplification status, prognostically significant TIL levels and tumor heterogeneity index (HI) from hematoxylin and eosin (H&E) stained malignant breast biopsy whole slide images (WSIs) alone. Unlike conventional artificial intelligence-based approaches, the underlying proprietary algorithm's prediction criteria are explainable and are based on deterministic, hard-coded observational relationships of scale constructed from image morphological features mapped to observables representing underlying tumor-related perturbations in biological pathways/mitotic checkpoints.This includes G1/S deregulation signatures reflecting oncogenic HER2-neu. **Results:** Blinded validation of HER2 status prediction (n = 197 WSIs; 118 independent cases/patients) showed excellent diagnostic performance (κ = 0.85) relative to existing standard-of-care methodologies. This was independent of WSI file format, background histology, tumor subtype/grade or hormone receptor status. The device also displayed good accuracy (92%) in determining TIL profiles, and its combined HER2-TIL and HER2-HI prediction scales both exhibited a significant association with progression-free survival (CoxPH hazard ratio: 1.856; 95% CI: 1.002-3.438; p = 0.049 and CoxPH hazard ratio: 3.45; 95% CI: 0.95-12.55; p = 0.060). **Conclusions:** This technology opens up the future possibility of bypassing existing ancillary HER2 profiling investigations, thus potentially reducing laboratory workloads/healthcare costs while accelerating diagnostic turnaround times for patient benefit. In the interim, if used as an adjunct tool, this device could provide an objective HER2 testing reference scale while the robustness of its prediction of patient response to anti-HER2 targeted therapy is fully explored. Research Sponsor: 4D Path Inc.

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Investigating survivin as a novel target in black women with breast cancer. *First Author: Andrea Walens, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Black women with breast cancer have higher mortality than White women. Differences in tumor biology contribute to racial disparities in breast cancer outcomes. BIRC5 gene encodes survivin, an inhibitor of apoptosis protein, and an independent marker of poor prognosis in breast cancer. Cancer patients have anti-survivin antibodies and circulating survivin-specific T cells, suggesting that survivin may be targetable. Several ongoing antibody-mediated, vaccine strategies that target survivin are being developed. Nevertheless, most survivin studies were conducted in cohorts of White women. To date, the prevalence and/or role of survivin expression in breast tumors from Black women has not been studied. **Methods:** Associations between BIRC5 expression, clinicopathological and molecular features were measured in the population-based Carolina Breast Cancer Study (CBCS) and The Cancer Genome Atlas (TCGA) breast cancer cohort. Gene expression was measured by Nanostring RNA counting and split into BIRC5 high (4^{th} quartile) and low categories based on log2 gene expression values. Relative frequency differences (RFD) for the association between BIRC5 high and clinicopathologic features were estimated. RNA based p53 mutant status and homologous recombination deficiency (HRD) status were included in RFD analysis. Receiver operating characteristic (ROC) curves were used to illustrate the potential of BIRC5 expression to distinguish patients who achieved pathological complete response (pCR) after receiving neoadjuvant chemotherapy in CBCS (133 Black, 49 non-Black). **Results:** BIRC5 gene expression was significantly increased in tumors from 966 Black patients compared to 1,497 non-Black ($p < 0.00001$), adjusting for stage and subtype. BIRC5 high tumors were significantly more expressed in higher stage and basal-like breast cancer subtypes. BIRC5 high tumors were also significantly enriched for expression of genes involved in p53 loss and HRD. Furthermore, in an analysis of 182 CBCS patients, BIRC5 gene expression alone predicted pCR with similar overall AUC to ROR-PT multigene signatures (AUC 0.62 vs 0.64). **Conclusions:** Our study shows that survivin expression is particularly high in breast tumors from Black women. This was associated with more aggressive clinicopathological features in addition to p53 mutant and HRD status. Black women with breast cancer represent an area of unmet clinical need and could potentially benefit from anti-survivin targetable treatment strategies. Further studies are needed to help close this gap which constitutes the largest disparity among cancer-specific diseases. Research Sponsor: U.S. National Institutes of Health.

	BIRC5 Category		
	High n = 675	Low n = 1797	Total n = 2472
PAM50 Subtype	n (%)	n (%)	
Luminal	200 (12.2)	1443 (87.9)	1643
HER2	68 (34.2)	131 (65.8)	199
Basal-like	356 (61.6)	222 (38.4)	578
Race			
Non-Black	313 (20.9)	1184 (79.1)	1497
Black	345 (35.7)	621 (64.3)	966

TPS595 **Poster Session**

A011801 (CompassHER2 RD): Postneoadjuvant T-DM1 + tucatinib/placebo in patients with residual HER2-positive invasive breast cancer. *First Author: Ciara Catherine Maria O'Sullivan, NCI/NIH, Bethesda, MD*

Background: Patients (pts) with HER2+ early breast cancer (EBC) and invasive residual disease (RD) after neoadjuvant therapy (NAT) have a higher risk of relapse than pts with a pathologic complete response (pCR). Post neoadjuvant T-DM1 has improved invasive disease-free survival (iDFS), but pts with estrogen receptor (ER)-negative or nodal RD have suboptimal outcomes and recurrences in the central nervous system are a problem. More effective treatment strategies are needed. The CompassHER2 trials, EA1181 and A011801, leverage pCR to tailor post neoadjuvant therapy in HER2+ EBC. EA1181 is a NAT de-escalation trial of a taxane, trastuzumab and pertuzumab (THP) in clinical stage II-III HER2+ EBC; pts with a pCR complete HP +/- adjuvant radiation (RT) +/- endocrine therapy (ET). A011801 is an escalation trial for pts with high risk HER2+ RD after NAT, examining addition of the HER2 selective tyrosine kinase inhibitor (TKI) tucatinib to adjuvant T-DM1. **Methods:** Eligibility and Intervention: Pts. with high-risk HER2+ RD (e.g. ER- ,node-positive, or both) *after* a predefined course of neoadjuvant HER2-directed treatment are randomized 1:1 to adjuvant T-DM1+ placebo (pb), vs. T-DM1 and tucatinib with adjuvant RT +/- ET. Eligibility criteria include completion of ≥ 6 cycles of NAT, including ≥ 9 weeks of T and H +/- P. All chemotherapy (CT) must be completed preoperatively unless participating in EA1181 (~15-30% enrollees); these pts must receive postoperative CT to complete ≥ 6 cycles prior to enrollment on A011801. Pts who received prior HER2-targeted TKIs or antibody-drug conjugates are ineligible. Objectives: The primary objective is to determine if iDFS is higher with addition of T-DM1 to tucatinib in pts with HER2+ EBC with RD after NAT; secondary endpoints include overall survival, breast cancer free survival, distant recurrence-free survival, brain metastases-free survival and disease-free survival. Correlative objectives include the association of i) tumor infiltrating lymphocyte (TILs) levels in the primary tumor and RD with iDFS, ii) TILs with tucatinib benefit, iii) iDFS and circulating tumor cells (CTC) at serial timepoints and iv) the magnitude of benefit of tucatinib (iDFS) in pts with/without detectable pretreatment CTCs. Quality of life and pharmacokinetic endpoints will also be evaluated. Statistics: A011801 is a prospective, double-blind, randomized, phase III superiority trial; stratified by i) receipt of postoperative CT (Y/N), ii) hormone receptor-status (+/-),and iii) pathologic lymph node status (+/-). The study targets an absolute difference of 5% in iDFS (control vs. experimental arm 82% & 87%, HR = 0.7), with a two-sided alpha of 0.05 and power of 80%. The sample size is 981; target accrual = 1031 pts; activation and completion dates are 01/6/21 and ~ 01/2028. Support: U10CA180821, U10CA180882; Seagen Inc; ClinicalTrials.gov Identifier: NCT04457596 Clinical trial information: NCT04457596. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company, U.S. National Institutes of Health, U24CA196171,U10CA180821, U10CA180882.

TPS596 **Poster Session**

eMonarcHER: A phase 3 study of abemaciclib plus standard adjuvant endocrine therapy in patients with HR+, HER2+, node-positive, high-risk early breast cancer. *First Author: Sara M. Tolaney, Dana-Farber Cancer Institute, Boston, MA*

Background: Hormone receptor positive (HR+), human epidermal growth factor receptor 2-positive (HER2+) breast cancer (BC) with high-risk characteristics has a high risk of disease recurrence. Novel therapeutic options for this population are urgently needed. Abemaciclib is an oral, selective, and potent CDK4 & 6 inhibitor administered on a continuous schedule which is approved for HR+, HER2- advanced BC (ABC) as monotherapy and in combination with endocrine therapy (ET). Abemaciclib combined with ET demonstrated a statistically significant improvement in invasive disease-free survival (IDFS) in participants (pt) with HR+, HER2-, node-positive, high risk early breast cancer (EBC) and also clinical activity in HR+, HER2+ ABC. The eMonarcHER trial investigates whether abemaciclib plus ET will improve IDFS in pts with HR+, HER2+, node-positive, high risk EBC. **Methods:** eMonarcHER is a phase 3 global, randomized, double-blinded, placebo (PB)-controlled trial in participants with HR+, HER2+, node-positive, high risk EBC who have completed adjuvant HER2-targeted therapy (tx). Eligible participants are randomized 1:1 to receive either abemaciclib 150 mg twice daily or PB, plus standard ET. Study intervention period will be ≤26 cycles (approximately 2 years) followed by ≤8 years of ET as medically indicated. Participants must have undergone definitive surgery of the primary breast tumor and have high-risk disease. High-risk disease is defined as (i) detection of residual axillary nodal disease at the time of definitive surgery in participants with prior neoadjuvant (neoadj) tx; or (ii) in patients not receiving neoadj tx, must have either ≥4 pathologically positive axillary lymph nodes (pALNs), or 1-3 pathological pALNs and either: histologic Grade 2-3 and/or primary invasive tumor size ≥5 cm. Participants must have received either adjuvant pertuzumab plus trastuzumab with chemotherapy or adjuvant T-DM1. Stratification factors include treatment with neoadj tx, menopausal status, and region. The study is powered at approximately 80% to detect the superiority of abemaciclib plus ET over PB plus ET in terms of IDFS (as defined by the STEEP system) at a 1-sided α = .025 using a log-rank test. Assuming a hazard ratio of 0.73, this requires approximately 324 events at final IDFS analysis. Key secondary objectives include overall survival, distant relapse free survival, safety, pharmacokinetics, and patient-reported outcomes. The study is planned to start in March 2021. Approximately 525 centers in 23 countries plan to enroll ~2450 participants. Clinical trial information: NCT04752332. Research Sponsor: Eli Lilly and Company.

TPS597 **Poster Session**

ALEXANDRA/IMpassion030: A phase 3 study of standard adjuvant chemotherapy with or without atezolizumab in patients with early-stage triple-negative breast cancer. *First Author: Shigehira Saji, Fukushima Medical University School of Medicine, Fukushima, Japan*

Background: Early stage triple negative breast cancer (TNBC) is associated with a high risk of distant relapse. Because TNBC does not currently have specific targeted agents approved for use in the early setting, it is treated primarily with chemotherapy. TNBC may be more immunogenic than other subtypes of breast cancer. Atezolizumab (an anti–PD-L1 antibody), in combination with nab-paclitaxel has been approved in >70 countries for the treatment of PD-L1-positive unresectable locally advanced or metastatic TNBC based on the results of the randomized phase 3 IMpassion130 trial. The phase 3 IMpassion031 study, evaluating atezolizumab in combination with chemotherapy (nab-paclitaxel followed by doxorubicin and cyclophosphamide) in comparison to placebo plus chemotherapy as neoadjuvant treatment demonstrated a statistically significant and clinically meaningful improvement in pCR in both PD-L1 positive and PD-L1 negative tumors. ALEXANDRA/IMpassion030 is a global, prospective, randomized, open-label, phase 3 trial currently investigating the efficacy, safety and pharmacokinetic profile of adjuvant atezolizumab plus standard anthracycline/taxane adjuvant chemotherapy versus chemotherapy alone in early stage TNBC. **Methods:** ALEXANDRA/IMpassion030 will randomize 2300 patients with operable stage II-III TNBC, confirmed by central pathology review. Patients are stratified by type of surgery, nodal status, and centrally assessed PD-L1 status. Adjuvant chemotherapy consist of weekly paclitaxel 80 mg/m^2 for 12 weeks followed by dose dense anthracycline (epirubicin 90 mg/m^2 or doxorubicin 60 mg/m^2) and cyclophosphamide 600 mg/m^2 for 4 doses every 2 weeks or the same chemotherapy regimen (T-EC/AC) given concomitantly with atezolizumab 840 mg every 2 weeks followed by maintenance atezolizumab 1200 mg every 3 weeks until completion of 1 year of atezolizumab. The primary endpoint is invasive disease-free survival (iDFS) and secondary endpoints include, iDFS in the PD-L1 selected tumour status (IC1/2/3) and node-positive subpopulations, overall survival, safety, patient functioning and health related quality of life (HRQoL). Tumor tissue and blood samples will be collected for biomarker research. The first site was activated on May 4 2018, and approximately 373 sites in 30 countries are currently participating in this trial. This trial is sponsored by F. Hoffmann-La Roche Ltd and conducted in partnership with the Breast International Group, Frontier Science and Technology Research Foundation, Institute Jules Bordet and Alliance Foundation Trials. Clinical trial information: NCT03498716. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS598 **Poster Session**

ADAPTlate: A randomized, controlled, open-label, phase III trial on adjuvant dynamic marker—Adjusted personalized therapy comparing abemaciclib combined with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy in (clinical or genomic) high-risk, HR+/HER2- early breast cancer. *First Author: Oleg Gluz, West German Study Group and Ev. Hospital Bethesda, Breast Center Niederrhein, Moenchengladbach, Germany and University Hospital Cologne, Cologne, Germany*

Background: The WSG ADAPT trial program addresses the individualization of (neo)adj. decision-making in EBC. The ADAPT umbrella trial established early predictive molecular surrogate markers for response after a 3-wk endocrine treatment (ET) to omit chemotherapy (CT) in a cohort of early high-risk HR+/HER2- pts. ADAPTlate seeks to improve adj. therapy for pts. at high risk for late disease recurrence, who completed definite locoregional therapy (with / without (neo-)adj. CT) and are under adj. ET. This high-risk population does not derive optimal benefit from standard ET, develops secondary ET resistance, and late recurrences. **Methods:** Prospective, multi-center, interventional, two-arm, open, randomized, controlled adj. phase III trial (NCT04565054) to investigate additional benefit from 2 years of the CDK4/6-inhibitor abemaciclib combined with ET compared to ET alone in pts. with high-risk HR+/HER2- EBC. Abemaciclib demonstrated to improve outcome in metastatic BC and even in EBC when given as part of primary therapy. Primary objective is to demonstrate superiority of iDFS of abemaciclib + ET vs. standard ET. Secondary objectives include OS, dDFS, occurrence of CNS metastases, QoL, and translational research. Recruitment started in 9/2020 to screen 1250 pts. and to randomize 903 pts. in a ratio 3:2 . Until date of submission, 33 pts. were screened and 22 randomized. Pre-/postmenopausal pts. with histologically confirmed invasive HR+/HER2- EBC, 2-6 y after primary diagnosis, with either known high clinical risk (c/pN 2-3 OR high CTS score in pN 0-1 OR non-pCR after neoadj. CT in cN 1 or G3 tumors OR G3 and Ki-67 ≥ 40% in pN 0-1) or known high genomic risk (RS >25 in c/pN 0, RS >18 in c/pN 1 OR high risk Prosigna, EPclin or Mammaprint in pN 0-1) or intermediate clinical, but unknown genomic risk (luminal B-like (G3 or Ki-67 ≥20%) in c/pN 0-1 AND either RS >25 in c/pN 0 or RS >18 in c/p N1 in screening) will be eligible. Treatment duration is 2 years for the abemaciclib + ET (premenopausal: AI + GnRH) arm, followed by at least 3-6 years ET alone. Pts. in control arm will receive 5-8-years ET at investigator's choice. ePROs are collected using CANKADO. Translational analyses: Exploratory tissue biomarker research to assess alterations in molecular markers. Liquid biopsies (CTC/ctDNA/ctRNA) will be assessed for mutations and gene expression relevant for HR+/HER2- EBC using an appropriate technology at time of testing. Conclusions: ADAPTlate seeks to evaluate whether Abemaciclib + ET is superior to ET alone in pts. with clinical or genomic high-risk EBC even 2-6 years after initial diagnosis. Translational research aims at assessing potential mechanisms of resistance to endocrine and/or CDK4/6 targeted therapy. Clinical trial information: NCT04565054. Research Sponsor: Lilly; Exact Sciences.

TPS599 **Poster Session**

Optima: Optimal personalised treatment of early breast cancer using multiparameter analysis, an international randomized trial of tumor gene expression test-directed chemotherapy treatment in a largely node-positive population. *First Author: Rob C. Stein, National Institute for Health Research University College London Hospitals Biomedical Research Centre, London, United Kingdom*

Background: Multi-parameter tumor gene expression assays (MPAs) are validated tools to assist adjuvant chemotherapy decisions for post-menopausal women with luminal-type node-negative breast cancer. Currently there is less certainty for women with 1-3 involved axillary lymph nodes and no information on MPA use for patients with higher level nodal involvement. Three RCTs with available data report chemotherapy benefit for premenopausal women; with limited use of ovarian function suppression (OFS) for non-chemotherapy treated participants, chemotherapy-induced menopause may explain these results. **Methods:** OPTIMA is an international academic, partially-blinded RCT of test-directed chemotherapy treatment with an adaptive design. Women and men aged 40 or older with resected luminal-type breast cancer may participate if they fulfil one of the following stage criteria: pN1-2; pN1mi with pT ≥20mm; pN0 with pT ≥30mm. Consenting patients are randomized between standard treatment with chemotherapy followed by endocrine therapy or to undergo Prosigna testing; those with high-Prosigna Score (> 60) tumors receive standard treatment whilst those with low-score tumors are treated with endocrine therapy alone. Patients are informed only of their treatment; test details, and randomization for chemotherapy-treated patients are masked. Clinical choice of chemotherapy is declared at randomization from a menu of standard regimens. Endocrine therapy must be for at least 5 years. Women postmenopausal at trial entry should receive an AI; men, tamoxifen; and premenopausal women, either an AI or tamoxifen, and OFS for 3 or more years; OFS initiation may be deferred because of post-chemotherapy amenorrhea. OPTIMA aims to randomize 2250 patients in each arm to demonstrate non-inferiority of test directed treatment, defined as not more than 3% below the estimated 85% 5-year IDFS for the control arm with a one sided 5% significance level. Power is 81% assuming recruitment over 96-months from January 2017 and 12 months minimum follow-up. OPTIMA also has at least 80% power to demonstrate 3.5% non-inferiority of IDFS for patients with low Prosigna Score tumors (estimated 65% of participants). Cox proportional hazards models will be used to explore important prognostic factors including menopausal status. Additional secondary endpoints include DRFI. A cost-effectiveness analysis of protocol specified MPA driven treatment against standard clinical practice will be conducted. At 31/01/2021, 2004 patients had been randomized. The DMC reviewed the trial in December 2020 with knowledge of related trial results and suggested that the trial continues as planned. OPTIMA is registered as ISRCTN42400492 and funded by the UK NIHR Health Technology Assessment Programme, award number 10/34/501. Clinical trial information: ISRCTN42400492. Research Sponsor: UK National Institute for Health Research (Health Technology Assessment programme), Local academic funding to support country-specific recruitment; support in kind from Veracyte Inc towards cost of Prosigna testing.

TPS600 **Poster Session**

Axillary management in T1-3N1M0 breast cancer patients with needle biopsy proven nodal metastases at presentation after neoadjuvant chemotherapy (ATNEC). *First Author: Amit Goyal, Royal Derby Hospital, Derby, United Kingdom*

Background: Neoadjuvant chemotherapy (NACT) results in eradication of cancer in the axillary nodes in 40% to 70% of patients. This raises questions about the benefit of further axillary treatment in those patients with no evidence of residual nodal disease (ypN0) after NACT. **Methods:** *Design:* ATNEC is a phase 3, randomised (1:1), multi-centre trial, with embedded economic evaluation, comparing standard axillary treatment (axillary lymph node dissection [ALND] or axillary radiotherapy [ART]) with no further axillary treatment in T1-3N1M0 breast cancer patients with needle biopsy proven axillary nodal metastases, who after NACT have no residual nodal disease (ypN0) on dual tracer sentinel node biopsy (SNB) and removal of at least 3 nodes (sentinel nodes and marked involved node). *Stratification:* Institution, type of surgery (breast conserving surgery vs mastectomy), receptor status (triple negative vs HER2 positive vs ER positive and/or PR positive and HER2 negative). *Inclusion criteria* are**:** Age ≥ 18, Male or female, T1-3N1M0 breast cancer at diagnosis (pre-NACT), FNA or core biopsy confirmed axillary nodal metastases at presentation, ER and HER2 status evaluated on primary tumour, received standard NACT as per local guidelines, ultrasound of the axilla at completion of NACT, dual tracer SNB after NACT and at least 3 nodes removed (sentinel nodes and marked node), no evidence of nodal metastases post NACT (ypN0). *Exclusion criteria* are: bilateral invasive breast cancer, SNB prior to NACT, marked node not removed *except* where at least one node removed shows evidence of down-staging with complete pathological response e.g. fibrosis/scarring and at least 3 nodes removed, previous ipsilateral axillary surgery, previous cancer within last 5 years or concomitant malignancy *except* basal or squamous cell carcinoma of the skin, in situ carcinoma of the cervix, in situ or stage 1 melanoma, contra- or ipsilateral in situ breast cancer. *Aims:* To assess whether, omitting further axillary treatment (ALND and ART) for patients with early stage breast cancer and axillary nodal metastases on needle biopsy - who after NACT have no residual nodal disease on SNB (ypN0) - is non-inferior to axillary treatment in terms of disease free survival, and reduces the risk of lymphoedema at 5 years. *Statistical methods:* All analyses will be carried out on an intention-to-treat basis to preserve randomisation, avoid bias from exclusions and preserve statistical power. *Radiotherapy quality assurance:* Study has in-built radiotherapy QA programme that will be co-ordinated by National Radiotherapy Trials QA (RTTQA) group. *Target accrual:* 1900. *Trial status:* Recruiting. *Number of sites:* 100. Clinical trial information: NCT04109079. Research Sponsor: UK National Institute for Health Research - Health Technology Assessment Programme (NIHR128311).

TPS601 **Poster Session**

A single-arm confirmatory study to evaluate the efficacy of nonsurgical therapy for HER2-positive early breast cancer with clinical complete response after primary systemic therapy (JCOG1806: AMATERAS-BC study). *First Author: Tomomi Fujisawa, Department of Breast Oncology, Gunma Prefectural Cancer Center, Gunma, Japan*

Background: The surgical treatment is a standard therapy for early breast cancer (EBC) after primary systemic therapy (PST). In more than half of HER2 positive (HER2(+)) breast cancer, pathological complete response (pCR) is achieved by PST with HER2 inhibitors and chemotherapy. In addition, hormone receptor (HR) negative HER2(+) (HR(-)HER2(+)) subtype has higher concordance between pCR and clinical complete response (cCR) before surgery than other subtypes, especially in EBC. However, non-surgical therapy is not an option for EBC with cCR after PST because of few evidence. We planned single arm confirmatory study to evaluate the efficacy and safety of the non-surgical therapy for HR(-)HER2(+) EBC with cCR after PST. **Methods:** The key eligibility criteria are as follows: 1) Histologically confirmed as invasive ductal carcinoma of breast, HR(-)HER2(+). 2) cT1-2, N0, M0 (UICC 8th). 3) No ipsilateral BC. 4) Women aged 20-74 years. 5) ECOG performance status 0 or 1. 6) Written informed consent. HER2 inhibitors (trastuzumab and pertuzumab) and cytotoxic drugs as PST are administered for all patients (pts). After completion of PST, cCR is diagnosed by breast imaging and physical examination. cCR is defined as 1) Not palpable breast mass by physical examination, 2) No enhanced breast mass by enhanced MRI, 3) No breast mass by sonography. After diagnosis of cCR, conventional radiotherapy for whole breast and boost radiation for tumor bed are mandatory, followed by pertuzumab and trastuzumab every 3 weeks during 9 months. In non-cCR cases, surgical resection is performed and adjuvant therapy are not specified. The primary endpoint is a distant metastasis-free survival (DMFS) at 3 year, the secondary endpoints are DFS, OS, RFS, proportion of local recurrence, and cosmetics outcome. Given that the threshold and expected of DMFS at 3-year is 93% and 98% with a significance level 2.5% (one sided) and 80% power, 170 cCR cases are required. Assuming half of HER2 pts reach to cCR, 350 pts are required as sample size started PST. Enrollment launched January, 2020 and 57 pts are enrolled as of January 12, 2021. Recent reports found that HR positive HER2(+) subtype has higher concordance between pCR and cCR by adding needle biopsy in the diagnosis, so we are planning to include HR positive subtype in this trial. This clinical trial has been registered at Japan Registry of Clinical Trials as jRCTs031190129 and conducted by the Japan Clinical Oncology Group (JCOG) Breast Cancer Study Group under public fund (National Cancer Center Research and Development Fund). Clinical trial information: jRCTs031190129. Research Sponsor: National Cancer Center Research and Development Fund.

TPS602 **Poster Session**

Phase III postneoadjuvant study evaluating sacituzumab govitecan, an antibody drug conjugate in primary HER2-negative breast cancer patients with high relapse risk after standard neoadjuvant treatment: SASCIA. *First Author: Frederik Marmé, Medical Faculty Mannheim, Heidelberg University, University Hospital Mannheim, Mannheim, Germany*

Background: Women with triple-negative breast cancer (TNBC) having residual disease after neoadjuvant chemotherapy (NACT) as well as HR-positive/HER2-negative breast cancer (BC) with a CPS (clinical and post treatment pathological stage) +EG (estrogen receptor status and grade) score ≥ 3 or score 2 and nodal involvement after NACT (ypN+) are at high risk of recurrence. Sacituzumab govitecan is approved for the treatment of patients with metastatic TNBC who received at least two prior therapies for metastatic disease and has shown activity in heavily pretreated patients with metastatic HR-positive/HER2-negative BC. Therefore, sacituzumab govitecan may represent a new option against the resistant residual disease after standard NACT. **Methods:** SASCIA is a phase III, prospective, international, multicenter, randomized, open label, parallel group study in patients with HER2-negative BC with residual disease after NACT (NCT04595565). Eligible patients must have received taxane-based NACT for 16 weeks, including at least 6 weeks of a taxane. Patients should be at high risk of recurrence after treatment, defined as having centrally confirmed HER2-negative BC (IHC score 0-1 or FISH negative according to ASCO/CAP guideline) assessed preferably on tissue from postneoadjuvant residual invasive disease of the breast and either HR-negative (<1% positive stained cells), with any residual invasive disease > ypT1mi after NACT or HR-positive (≥1% positive stained cells), with a CPS+EG score ≥ 3 or CPS+EG score 2 and ypN+ using local ER and grade assessed on core biopsies taken before NACT. Radiotherapy should be delivered before the start of study treatment. Patients are randomized 1:1 to receive either sacituzumab govitecan 10 mg/kg body weight (days 1, 8 q3w for eight cycles) or treatment of physician's choice (capecitabine 2000 mg/m^2 day 1-14 q21 or platinum-based chemotherapy i.e. carboplatin AUC 5 q3w or AUC 1.5 weekly for eight 3 weekly cycles or observation). Randomization is stratified by HR status (HR-positive vs negative) and nodal involvement after NACT (ypN+ vs ypN0). In patients with HR-positive BC, endocrine-based therapy will be administered according to local guidelines. The primary endpoint is invasive disease-free survival (iDFS). Secondary endpoints include comparison of overall survival (OS, key secondary endpoint), distant disease-free survival, locoregional recurrences-free interval, safety, compliance, iDFS and OS according to stratified and - predefined subgroups, patient reported outcome, and quality of life between treatment arms. As of February 2 2021, 7/1200 patients have been randomized in Germany. International study groups will join soon. Clinical trial information: NCT04595565. Research Sponsor: Gilead Sciences, Inc.

TPS603 **Poster Session**

TRIO-US B-12 TALENT: Phase II neoadjuvant trial evaluating trastuzumab deruxtecan with or without anastrozole for HER2-low, HR+ early stage breast cancer. *First Author: Sara A. Hurvitz, University of California Los Angeles, Jonsson Comprehensive Cancer Center, Los Angeles, CA*

Background: Although patients with hormone receptor-positive (HR+)/HER2-negative breast cancer (BC) frequently respond clinically to neoadjuvant treatment, fewer than 10% achieve a pathologic complete response (pCR) with standard chemotherapy or endocrine therapy, even in combination with targeted agents such as CDK4/6 inhibitors. Thus, finding more effective therapies for this disease remains an area of unmet need. *HER2* amplification is a known driver of endocrine resistance and HER2 protein may be expressed at a low level (IHC 1+ or 2+) in up to 60% of HR+ BC. Trastuzumab deruxtecan (DS-8201a, T-DXd) is a novel HER2-targeting antibody drug conjugate (ADC) that is FDA approved for HER2-positive metastatic BC and has demonstrated promising clinical efficacy in HER2-low BC with an objective response rate of ~37%. The aim of TALENT (TRIO-US B-12) is to evaluate the clinical activity and toxicity of neoadjuvant T-DXd either alone or in combination with endocrine therapy in patients with HR+/HER2-low early BC. **Methods:** TRIO-US B-12 TALENT (NCT04553770) is an ongoing randomized, multicenter, open-label, two-stage, phase II neoadjuvant trial for participants with early stage, HR+, HER2-low expressing (1+ or 2+ by IHC) BC. Eligible participants include men and women with previously untreated, operable invasive BC greater than 2.0 cm (cT2) in size. Pts with recurrent or metastatic BC, or inflammatory BC are excluded. Pts are randomized 1:1 to receive six cycles of T-DXd (5.4 mg/kg IV q21 days) either alone or in combination with anastrozole (1 mg PO QD). Men and pre/peri menopausal women randomized to the anastrozole arm also receive standard of care GnRH agonist. Stratification factors include HER2 expression (1+ or 2+) and menopausal status. Tumor tissue is taken at baseline, cycle 1 day 17-21, and at surgery. Blood samples are taken at four time points for biomarker analysis. The primary endpoint is pCR rate (breast and lymph node) at definitive surgery. In stage I, 58 participants will be randomized (29/arm). If >2 participants in an arm achieve pCR, that arm will expand (stage II) to enroll an additional 15 participants (total of 44/arm). A pCR rate of >10% (5/44) would be considered favorable, warranting further evaluation of the treatment in a larger trial. Other endpoints include safety, changes in Ki67 expression, Residual Cancer Burden index, biomarker analysis (including serial cfDNA analysis), and health-related quality of life. As of January 2021, four participants have enrolled. **Conclusions:** To our knowledge this is the only ongoing study evaluating T-DXd with or without endocrine therapy for HR+, HER2-low breast cancer in the neoadjuvant setting. The study will shed light on clinical activity and biomarkers, which may guide larger confirmatory studies for patients with HR+, HER2-low early breast cancer. Clinical trial information: NCT04553770. Research Sponsor: Daiichi Sankyo.

TPS604 **Poster Session**

A prospective, randomized, multicenter, double-blinded, placebo-controlled phase III trial of the HER2/neu peptide GP2 + GM-CSF versus bacteriostatic saline/WFI placebo as adjuvant therapy after any trastuzumab-based therapy in HER2-positive women with operable breast cancer. *First Author: Snehal Patel, Greenwich LifeSciences, Stafford, TX*

Background: GP2 is a biologic nine amino acid peptide of the HER2/*neu* protein delivered in combination with an FDA-approved immunoadjuvant Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF, sargramostim, leukine) that stimulates an immune response targeting HER2/neu expressing cancers. In a prospective, randomized, single-blinded, placebo-controlled, multicenter Phase IIb clinical trial completed in 2018, no recurrences were observed in the HER2/neu positive adjuvant setting after median 5 years of follow-up, if the HLA 2+ patient received the 6 primary intradermal injections over the first 6 months ($p = 0.0338$) in a pre-specified subgroup analysis. Furthermore, the GP2 immunotherapy elicited a potent immune response measured by local skin tests and immunological assays. Of the 138 patients that have been treated with GP2 to date over 4 clinical trials, GP2 treatment was well tolerated and no serious adverse events were observed related to the GP2 immunotherapy. This Phase III trial aims to reproduce the Phase IIb study and will explore the use of GP2 + GM-CSF as adjuvant therapy to prevent the recurrence of breast cancer in HER2/neu positive and HLA 2+ patients, post-surgery and following the first year treatment with any trastuzumab-based therapy. **Methods:** This phase III trial is a prospective, randomized, double-blinded, multi-center study. After 1 year of trastuzumab-based therapy or an approved biosimilar, treatment with GP2 + GM-CSF or placebo (bacteriostatic saline/WFI) will be administered intradermally for the 6 primary immunization series over the first 6 months and 5 subsequent boosters over the next 2.5 years for a total of 11 injections over 3 years of treatment. The participant duration of the trial will be 3 years treatment plus 2 years follow-up for a total of 5 years following enrollment. An interim analysis is planned and patients will be stratified based on prior and current treatments, among other factors. Eligibility Criteria: The majority of breast cancer patients will be HER2/*neu* positive and HLA 2+, disease-free, conventionally treated node-positive, post breast tumor removal surgery and following the first year treatment with trastuzumab-based therapy. Trial Objectives: 1. To determine if GP2 therapy reduces recurrence in HER2/*neu* positive breast cancer patients. 2. To monitor the in vitro and in vivo immunologic responses to GP2 therapy and correlate these responses with the clinical outcomes. 3. To monitor for any unexpected adverse events and toxicities related to GP2 therapy. Accrual: The target enrollment is up to approximately 500 patients. Contact information: snehal.patel@greenwichlifesciences.com Funding: This trial is supported by Greenwich LifeSciences. Research Sponsor: Greenwich LifeSciences.

605 **Oral Abstract Session**

A randomized phase III post-operative trial of platinum-based chemotherapy (P) versus capecitabine (C) in patients (pts) with residual triple-negative breast cancer (TNBC) following neoadjuvant chemotherapy (NAC): ECOG-ACRIN EA1131 *First Author: Ingrid A. Mayer, Vanderbilt University, Nashville, TN*

Background: Pts with TNBC who have residual invasive disease (RD) after completion of NAC have a very high risk for recurrence, which is reduced by adjuvant capecitabine (C). Pre-clinical models support the use of platinum agents (P) in the TNBC basal subtype. EA1131 tested the hypothesis that invasive disease-free survival (iDFS) would not be inferior but improved in pts with basal subtype TNBC after NAC with the adjuvant use of a P instead of C (primary objective). **Methods:** Pts with clinical stage II/III TNBC post neoadjuvant taxane +/- anthracycline-based chemotherapy with at least 1 cm RD in the surgical specimen were randomized (1:1) to receive P (carboplatin or cisplatin once every 3 weeks for 4 cycles) or C (14/7d every 3 weeks for 6 cycles). TNBC subtype (basal vs. non-basal) was analyzed in the surgical specimen by PAM50. A non-inferiority design (non-inferiority margin of hazard ratio [HR] of 1.154) with superiority alternative (alternative HR of 0.754) was chosen, assuming a 4-year iDFS of 67% for the C arm. Non-inferiority was tested first. If non-inferiority was shown, a formal test for superiority of P compared to C would be conducted. **Results:** 401 participants were randomized to P or C between 2015 and 2020 (recruitment goal, 775), 310 (77%) had TNBC basal subtype disease (primary analysis population). Pts' median age was 52 years, 71% were White and 19% Black. At diagnosis, most tumors were high grade (78%), T2 (59%), 47% N0, and 40% N1. Residual tumors were 37% ypT1, 44% ypT2, and 47% ypN0. Overall incidence of any toxicity was similar (83% with P, 80% with C), but grade 3 and 4 toxicities (no grade 5) were more common with P (25% vs 15%). After median follow-up of 18 months, 113 iDFS events (58% of full information) had occurred. 3-year iDFS for P arm was 40% (95%CI, 29%-51%) and 44% (95%CI, 32%-55%) for C arm. The HR for arms P/C was 1.09 (95% Repeated Confidence Interval, 0.62-1.90) and the probability of eventually rejecting the null of inferiority (i.e., conditional power) was 6%. The Data Safety and Monitoring Committee recommended stopping the trial at the 5th interim analysis in March 2021 since it was unlikely that the trial would be able to show non-inferiority or superiority of the P arm. **Conclusions:** Participants with TNBC with RD after NAC had a lower than expected 3-year iDFS regardless of study treatment. Available data show that it is very unlikely that the study would be able to establish non-inferiority of P to C. In addition, severe toxicities were more common with P. In pts with TNBC, particularly basal subtype, with at least 1 cm RD after NAC and high-risk of recurrence, adjuvant P use does not improve outcomes. Correlative analyses of RD tissue (NGS), circulating markers (ctDNA and CTC pre/post treatment), and patient-reported outcomes (PRO) questionnaires will now occur. Clinical trial information: NCT02445391. Research Sponsor: U.S. National Institutes of Health.

1000 **Oral Abstract Session**

Overall survival (OS) with palbociclib (PAL) + fulvestrant (FUL) in women with hormone receptor–positive (HR+), human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): Updated analyses from PALOMA-3. *First Author: Massimo Cristofanilli, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Feinberg School of Medicine, Chicago, IL*

Background: In PALOMA-3, a randomized, double-blind, placebo-controlled, phase 3 study, PAL+FUL significantly prolonged progression-free survival (PFS) compared with placebo (PBO) + FUL (1-sided $P<0.0001$). The final protocol-specified OS analysis, which was conducted with a median follow-up of 44.8 months (mo), showed improved OS with PAL+FUL vs PBO+FUL (median OS, 34.9 vs 28.0 mo; hazard ratio, 0.814 [95% CI, 0.644–1.029]; 1-sided $P=0.0429$). Here, we report the results from an OS analysis with a longer median follow-up of 73.3 mo. **Methods:** A total of 521 patients (pts) with HR+/HER2– ABC who had progressed on prior endocrine therapy were randomized 2:1 to PAL (125 mg/d orally, 3/1 week schedule) + FUL (500 mg intramuscular injection) or PBO+FUL. Investigator-assessed PFS was the primary endpoint; OS was a key secondary endpoint. An ad hoc OS analysis was performed when 393 events (75% of the total population) were observed. Circulating tumor DNA (ctDNA) analysis was conducted among pts who consented for this study. **Results:** Improvement in OS continues to be observed with longer follow-up, with a hazard ratio of 0.806 (95% CI, 0.654–0.994; 1-sided nominal $P=0.0221$). The 5-year OS rate was 23.3% (95% CI, 18.7–28.2) with PAL+FUL and 16.8% (95% CI, 11.2–23.3) with PBO+FUL. Favorable OS with PAL+FUL vs PBO+FUL was observed in most subgroups except among pts who were endocrine resistant or had prior chemotherapy for ABC. No new safety signals were identified. Eighteen pts remain on study treatment, including 15 (4.3%) on PAL+FUL and 3 (1.7%) on PBO+FUL. A post-study cyclin-dependent kinase 4/6 inhibitor was received by 20 pts (7.5%) in the PAL+FUL arm and 32 pts (22.2%) in the PBO+FUL arm. ctDNA analyses of tumor mutation profiles (ie, *ESR1*, *PIK3CA*, *RB1*) at the end of treatment and their effect on OS will also be presented. **Conclusions:** The clinically meaningful improvement in OS with PAL+FUL was maintained with >6 years of median follow-up in pts with HR+/HER2– ABC who had progressed on prior endocrine treatment. Pfizer (NCT01942135) Clinical trial information: NCT01942135. Research Sponsor: Pfizer Inc.

Updated OS in the ITT population and by subgroup.

Subgroup	n (%)	Hazard Ratio (95% CI)	PAL+FUL median OS (95% CI)	PBO+FUL median OS (95% CI)	1-sided *P* value
ITT population	521 (100)	0.81 (0.65–0.99)	34.8 (28.8–39.9)	28.0 (23.5–33.8)	0.0221
Sensitivity to prior endocrine therapy					
Yes	410 (78.7)	0.76 (0.60–0.96)	39.7 (34.4–45.7)	29.5 (23.5–36.3)	0.011
No	111 (21.3)	0.97 (0.62–1.5)	19.9 (17.4–26.4)	26.2 (17.5–31.8)	0.440
Prior chemotherapy in ABC					
Yes	177 (34.0)	0.97 (0.69-1.4)	24.6 (21.3-30.0)	24.3 (18.9-36.3)	0.432
No	344 (66.0)	0.72 (0.55-0.94)	39.3 (34.5-44.4)	29.7 (23.8-35.5)	0.008

ITT=intent-to-treat.

1001 **Oral Abstract Session**

Updated overall survival (OS) results from the phase III MONALEESA-3 trial of postmenopausal patients (pts) with HR+/HER2- advanced breast cancer (ABC) treated with fulvestrant (FUL) ± ribociclib (RIB). *First Author: Dennis J. Slamon, David Geffen School of Medicine, University of California Los Angeles, Santa Monica, CA*

Background: The Phase III MONALEESA-3 trial (NCT02422615) previously demonstrated a statistically significant improvement in OS with RIB, a cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), plus FUL compared with placebo (PBO) plus FUL as first-line (1L) or second-line (2L) treatment in postmenopausal pts with HR+/HER2– ABC (median, not reached vs 40.0 mo; hazard ratio [HR], 0.72; 95% CI, 0.57-0.92, P = .00455). This analysis was final per the protocol; following the unblinding of the study, pts still on study treatment in the PBO arm were allowed to cross over to the RIB arm. We report an exploratory analysis of OS after an additional median 16.9 mo of follow-up, allowing for further characterization of long-term survival benefits of RIB. **Methods:** Postmenopausal pts with HR+/HER2– ABC were randomized 2:1 to receive RIB + FUL or PBO + FUL in 1L and 2L settings. Updated OS was evaluated by Cox proportional hazards model and summarized using Kaplan-Meier methods. Additional postprogression endpoints such as progression-free survival 2 (PFS2), time to chemotherapy (CT), and CT-free survival were also evaluated and summarized. **Results:** At the data cutoff (Oct 30, 2020), the median follow-up was 56.3 mo (min, 52.7 mo) and 68 (14.0%) and 21 (8.7%) patients were still on treatment in the RIB vs PBO arms, respectively. With this extended follow-up, RIB + FUL continued to demonstrate an OS benefit vs PBO + FUL (median, 53.7 vs 41.5 mo; HR, 0.73; 95% CI, 0.59-0.90). RIB + FUL had prolonged OS vs PBO + FUL in the 1L (median, not reached vs 51.8 mo; HR, 0.64; 95% CI, 0.46-0.88) and 2L subgroups (median, 39.7 vs 33.7 mo; HR, 0.78; 95% CI, 0.59-1.04). Subgroup analyses also showed a consistent OS benefit compared with the intent-to-treat (ITT) population for most subgroups. PFS2, time to CT, and CT-free survival for the ITT population favored RIB + FUL (Table). Among pts who discontinued study treatment, 81.9% and 86.4% received a next-line subsequent antineoplastic therapy, while 14.0% and 30.0% received a CDK4/6i as any subsequent line in the RIB vs PBO arms, respectively. No new safety signals were observed. **Conclusions:** The previously demonstrated robust and clinically meaningful OS benefit with RIB + FUL compared with PBO + FUL was maintained after almost 5 years of follow-up in postmenopausal pts with HR+/HER2– ABC. The OS benefit of RIB was observed in the 1L and 2L subgroups, which further supports the use of RIB in these populations. The results also demonstrated a significant delay in the use of subsequent CT with RIB vs PBO. Clinical trial information: NCT02422615. Research Sponsor: Novartis Pharmaceuticals Corporation.

	RIB + FUL (n = 484)		PBO + FUL (n = 242)
PFS2, events, n (%)	265 (54.8)		163 (67.4)
Median, mo	37.4		28.1
HR (95% CI)		0.69 (0.57-0.84)	
Time to first CT, events, n (%)	215 (44.4)		131 (54.1)
Median, mo	48.1		28.8
HR (95% CI)		0.70 (0.57-0.88)	
CT-free survival, events, n (%)	287 (59.3)		178 (73.6)
Median, mo	32.3		22.4
HR (95% CI)		0.69 (0.57-0.83)	

1002 **Oral Abstract Session**

Dalpiciclib versus placebo plus fulvestrant in HR+/HER2- advanced breast cancer that relapsed or progressed on previous endocrine therapy (DAWNA-1): A multicenter, randomized, phase 3 study. *First Author: Binghe Xu, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Dalpiciclib (SHR6390), a novel CDK4/6 inhibitor, as monotherapy has demonstrated tolerability and preliminary antitumor activity in pretreated HR+/HER2– advanced breast cancer (ABC). Here we evaluated dalpiciclib with fulvestrant in ABC. **Methods:** In this randomized, double-blind, phase 3 trial, patients (pts) with HR+/HER2– locally advanced or metastatic breast cancer who had relapsed or progressed on previous endocrine therapy were enrolled. Eligible pts were randomized 2:1 to receive dalpiciclib (dalp; 150 mg po qd, d1-21, q4w) or placebo (PBO) with fulvestrant (fulv; 500 mg im, cycle 1 d1, d15, then d1 q4w). The primary endpoint was investigator (INV)-assessed PFS. As of Nov. 15, 2020, 162 (71.4% of total projected) events of disease progression or death had occurred and a preplanned interim analysis was done. The corresponding superiority boundary was 1-sided P = 0.0080 (Lan-DeMets [O'Brien-Fleming] boundary). **Results:** Overall, 361 pts were randomized to receive dalp-fulv (n = 241) or PBO-fulv (n = 120). With a median follow-up of 10.5 mo, dalp-fulv significantly improved INV-assessed PFS versus PBO-fulv (median, 15.7 [95% CI 11.1-NR] vs 7.2 [95% CI 5.6-9.2] mo; HR, 0.42 [95% CI 0.31-0.58]; P < 0.0001). PFS per IRC were consistent with INV assessment (Table). The benefit of dalpiciclib extended beyond initial study treatment based on time to first subsequent chemotherapy (TFSCT; HR, 0.47 [95% CI 0.32-0.69]; P < 0.0001). OS data were not mature with a total of 25 deaths documented. Median duration of exposure was 9.4 (IQR, 4.3-11.4) mo with dalpiciclib and 9.9 (4.7-11.9) mo with fulvestrant in the dalp-fulv group and was 6.1 (3.7-11.0) mo with fulvestrant in the PBO-fulv group. The most common (incidence ≥3%) grade 3 or 4 AEs with dalp-fulv were neutropenia (84.2%; vs 0% with PBO-fulv) and leukopenia (62.1%; vs 0%). Treatment discontinuation due to AE was reported for 2.5% of pts with dalp-fulv vs 3.3% with PBO-fulv. The incidence of SAE was 5.8% with dalp-fulv vs 6.7% with PBO-fulv. **Conclusions:** The study met its primary endpoint, demonstrating that dalpiciclib plus fulvestrant significantly improved PFS versus placebo plus fulvestrant, with a manageable safety profile. Our findings support dalpiciclib plus fulvestrant as a new treatment option in pts with HR+/HER2- ABC who relapsed or progressed on endocrine therapy. Clinical trial information: NCT03927456. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

		Per INV dalp-fulv (n = 241)	Per INV PBO-fulv (n = 120)	Per IRC dalp-fulv (n = 241)	Per IRC PBO-fulv (n = 120)
PFS	Median (95% CI), mo	15.7 (11.1-NR)	7.2 (5.6-9.2)	13.6 (11.3-NR)	7.7 (5.6-10.9)
	HR (95% CI)	0.42 (0.31-0.58)	-	0.45 (0.32-0.64)	-
	Log-rank P*	< 0.0001	-	< 0.0001	-
TFSCT	Median (95% CI), mo	NR (NR-NR)	14.2 (9.7-NR)	-	-
	HR (95% CI)	0.47 (0.32-0.69)	-	-	-
	Log-rank P*	< 0.0001	-	-	-
ORR	% (95% CI)	27.0 (21.5-33.0)	20.0 (13.3-28.3)	30.3 (24.6-36.5)	15.8 (9.8-23.6)
	CMH P	0.0727	-	0.0015	-

*1-sided stratified

1003 **Oral Abstract Session**

Trastuzumab plus endocrine therapy or chemotherapy as first-line treatment for metastatic breast cancer with hormone receptor-positive and HER2-positive: The sysucc-002 randomized clinical trial. *First Author: Zhongyu Yuan, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: For metastatic breast cancer with hormone receptor-positive and HER2-positive, no evidence showed that which first-line regimens were preferred, either anti-HER2 therapy plus endocrine therapy or anti-HER2 therapy plus chemotherapy. This study aimed to determine whether trastuzumab plus endocrine therapy is as efficacious as trastuzumab plus chemotherapy and with decreased toxic effects. **Methods:** We conducted an open-label, non-inferiority, phase 3, randomized, controlled trial at nine hospitals in China. Patients with hormone receptor-positive and HER2-positive histologically confirmed advanced breast cancer were randomly assigned (1:1) to receive trastuzumab plus chemotherapy (CT group) or endocrine therapy (ET group). The primary endpoint was progression-free survival with a non-inferiority upper margin of 1.35 for the hazard ratio (HR). This trial is registered with ClinicalTrials.gov, number NCT01950182. **Results:** Between Sep 16, 2013, and Dec 28, 2019, 392 patients were enrolled and randomly assigned to receive trastuzumab plus endocrine therapy (n = 196) or trastuzumab plus chemotherapy (n = 196). In the intention-to-treat population, the median PFS was 14.8 months (95% CI 12.8-16.8) in the CT group and 19.2 months (95% CI 16.7-21.7) in the ET group (HR 0.88, 95% CI 0.71-1.09; $P_{\text{non-inferiority}} < 0.0001$). Significantly higher frequency of toxicities were observed in CT group compared with ET group, including: leucopenia (98 [50%] vs 13 [6.6%]), nausea (93 [47%] vs 24 [12%]), fatigue (47 [24%] vs 31 [16%]), vomiting (45 [23%] vs 12 [6%]), headache (65 [33%] vs 24 [12%]) and alopecia (125 [64%] vs 8 [4%]). No patients died from treatment-related causes. **Conclusions:** Trastuzumab plus endocrine therapy was non-inferior to and had decreased toxicities to trastuzumab plus chemotherapy in patients with metastatic breast cancer with hormone receptor-positive and HER2-positive. Trastuzumab plus endocrine therapy could provide more convenient treatment and allow better treatment tolerance. Clinical trial information: NCT01950182. Research Sponsor: None.

1004 **Oral Abstract Session**

Results from VERONICA: A randomized, phase II study of second-/third-line venetoclax (VEN) + fulvestrant (F) versus F alone in estrogen receptor (ER)-positive, HER2-negative, locally advanced, or metastatic breast cancer (LA/MBC). *First Author: Geoffrey J Lindeman, Peter MacCallum Cancer Centre/Walter and Eliza Hall Institute, Melbourne, Australia*

Background: For patients (pts) with ER-positive, HER2-negative MBC, CDK4/6 inhibitors + endocrine therapy (ET) is standard first-line treatment, with single-agent ET considered for second-line. Nevertheless, most pts progress. A novel therapeutic target is the antiapoptotic protein BCL2, which is overexpressed in ~85% of primary ER-positive breast cancers. VEN is a potent, selective BCL2 inhibitor that has shown promising clinical activity in pts with ER-positive and BCL2-positive MBC who have received prior ET. We report the prespecified primary and updated (for overall survival [OS]) analysis of VERONICA (NCT03584009), a phase II study of VEN + F vs F in ER-positive, HER2-negative LA/MBC. **Methods:** Pts were ≥18-year-old women with ER-positive, HER2-negative LA/MBC, who received ≤2 prior lines of ET and no prior chemotherapy in the LA/MBC setting and experienced disease recurrence/progression during/after CDK4/6 inhibitor therapy (received ≥8 weeks prior). Pts were randomized 1:1 to VEN (oral; 800 mg daily) + F (intramuscular; 500 mg day 1 and 15 of cycle 1; day 1 of subsequent 28-day cycles) or F, and were treated until disease progression, unacceptable toxicity, withdrawal of consent, death, or predefined study end. Pts were stratified by prior lines of therapy in the LA/MBC setting (1 vs 2) and BCL2 status (high vs low). Primary endpoint was clinical benefit rate (CBR; complete response, partial response, and stable disease ≥24 weeks). Secondary endpoints included progression-free survival (PFS) and OS; safety and exploratory subgroup analyses were also conducted. **Results:** At primary analysis (cutoff: Aug 5, 2020), 103 pts had been randomized (intention-to-treat [ITT] population). Median age was 58.0 and 59.5 years in the VEN + F and F arms, respectively. CBR was similar between arms (VEN + F: 11.8% [n = 6/51; 95% confidence interval (CI) 4.44–23.87]; F: 13.7% [7/51; 5.70–26.26]; risk difference: -1.96% [95% CI -16.86–12.94]). Median PFS was 2.69 months (95% CI 1.94–3.71) in the VEN + F vs 1.94 months (1.84–3.55) in the F arm (stratified hazard ratio: 0.94 [95% CI 0.61–1.45]). Results for CBR and PFS were similar in the BCL2-high and -low subgroups vs the ITT population. More grade 3–4 adverse events (AEs) were observed in the VEN + F vs F arm (n = 13/50 [26%] vs 6/51 [11.8%]). AEs observed with VEN + F were consistent with their individual safety profiles. At updated analysis (cutoff: Oct 22, 2020), OS data were not mature (35.0% event/pt ratio); median OS was 16.99 months in the VEN + F vs not reached in the F arm (stratified hazard ratio: 2.06 [1.04–4.09]). **Conclusions:** From the primary analysis, VERONICA did not show an improved CBR or PFS with VEN + F, vs F alone, in pts with endocrine- and CDK4/6 inhibitor-refractory LA/MBC. Biomarker analysis is ongoing. Clinical trial information: NCT03584009. Research Sponsor: F. Hoffmann-La Roche Ltd.

1005 **Oral Abstract Session**

Treatment-related side effects and views about dosage assessment to sustain quality of life: Results of an advocate-led survey of patients with metastatic breast cancer (MBC). *First Author: Anne L Loeser, Patient-Centered Dosing Initiative, Salt Lake City, UT*

Background: Metastatic breast cancer (MBC) is generally incurable and the majority of patients with MBC will remain on treatment indefinitely. Patients usually begin each new treatment at the Recommended Starting Dose (RSD) on the FDA-approved label based on results from clinical trials. However, patients' ability to tolerate the RSD in the real-world may differ from the clinical trial setting. While the importance of patient reported outcomes is recognized, understanding tolerability from the patient's perspective is lacking and patients' willingness to discuss individualized doses for MBC therapy has not been evaluated. **Methods:** Patient advocates from the Patient-Centered Dosing Initiative distributed a confidential online survey to patients with MBC via social media groups, organizational newsletters, and online support forums. The survey was developed by patients and medical oncologists to ascertain the prevalence and impact of patients' treatment-related side effects, quality of patient-physician communication, management of side effects, and interest in alternative approaches to the RSD when a new treatment is initiated or adverse side effects are experienced. **Results:** 1,221 patients with MBC completed the survey within 15 days. The median number of lines of MBC therapy was 2.5 (range 1 - ≥5) and 46% (n = 564) of patients received their MBC diagnosis within two years of taking the survey. 86% (n = 1,051) reported experiencing at least one significant treatment-related side effect, and of these, 20% (n = 213) visited the Emergency Room/hospital and 43% (n = 454) missed at least one treatment. 98% (n = 1,026) of patients with side effects discussed them with their doctors and 82% (n = 838) were helped by their physicians. The most common (non-exclusive) mitigation strategies were dosage reductions (66%, n = 556) and prescription medications (59%, n = 494). Of the 556 patients given a dosage reduction, 83% (n = 459) reported feeling better. Notably, 92% (n = 1,127) of patients expressed willingness to discuss alternative dosing options with their physicians based upon their personal characteristics and individual preferences. **Conclusions:** Given that 86% of patients with MBC experienced at least one significant treatment-related side effect and 83% improved after dosage reduction, innovative dosage-related strategies are warranted to sustain Quality of Life. Patient-physician discussions in which the patient's physical attributes and circumstances are periodically assessed may determine the right dose for the patient upon treatment initiation and afterwards, and the vast majority of patients would be receptive to such discussions. Research Sponsor: Anne Loeser.

1006 **Oral Abstract Session**

The tumor microenvironment (TME) and atezolizumab + *nab*-paclitaxel (A+nP) activity in metastatic triple-negative breast cancer (mTNBC): IMpassion130. *First Author: Leisha A. Emens, University of Pittsburgh Medical Center Hillman Cancer Center, Pittsburgh, PA*

Background: IMpassion130 was the first randomized phase 3 study to show clinical benefit of cancer immunotherapy (CIT) in untreated PD-L1+ mTNBC. Enhanced A + nP efficacy vs placebo (P) + nP was seen in pts with a richer immune TME but was confined to PD-L1 IC+ pts (PD-L1–expressing immune cells on ≥1% of tumor area; Emens JNCI 2021). While TNBC molecular subtyping and CD8 localization are prognostic in early TNBC, it is unknown whether these features are associated with CIT benefit in mTNBC. This exploratory analysis aimed to identify TME components associated with A + nP efficacy in IMpassion130. **Methods:** IHC was used to assess PD-L1 status (VENTANA SP142) and immune phenotypes (inflamed/excluded/desert per CD8 stromal/intratumoral localization; Mariathasan Nature 2018). RNA-seq was used for molecular subtyping (Burstein CCR 2015) and pathway analyses (MSigDB Hallmark). Cox regression was used to compare PFS/OS between A + nP vs P + nP, adjusted for prior taxanes, liver mets. **Results:** Sample classification and PD-L1 distribution are shown (Table). Improved PFS with A + nP vs P + nP was seen in PD-L1 IC+ inflamed and excluded tumors, but improved OS was limited to PD-L1 IC+ inflamed tumors. PD-L1 IC+ basal-like immune activated (BLIA) and immune suppressed (BLIS) subgroups derived PFS benefit, but OS benefit was limited to PD-L1 IC+ BLIA subgroups. In PD-L1 IC+ pts, pathway analysis identified proliferation/DNA damage repair (basal-like tumor features) and angiogenesis/ER response (higher in luminal androgen receptor [LAR]/ mesenchymal [MES] tumors) were associated with improved and reduced PFS, respectively. **Conclusions:** PD-L1 IC+ immune-inflamed tumors and PD-L1 IC+ BLIA tumors show highest CIT sensitivity, and LAR tumors may be resistant to CIT. These data warrant further study and validation. Clinical trial information: NCT02425891. Research Sponsor: F. Hoffman-La Roche Ltd.

Subgroup (% of biomarker-evaluable pts)	All		PD-L1 IC+			PD-L1 IC−		
	PFS HR (95% CI)	OS HR (95% CI)	% PD-L1 IC+	PFS HR (95% CI)	OS HR (95% CI)	% PD-L1 IC−	PFS HR (95% CI)	OS HR (95% CI)
Immune phenotype (n=802): Inflamed (36)	0.63 (0.49, 0.81)	0.71 (0.54, 0.95)	63	0.58 (0.42, 0.80)	0.61 (0.42, 0.88)	37	0.74 (0.49, 1.10)	0.94 (0.60, 1.50)
Excluded (47)	0.76 (0.61, 0.95)	0.86 (0.68, 1.10)	41	0.72 (0.51, 1.00)	0.72 (0.50, 1.10)	59	0.80 (0.60, 1.10)	0.97 (0.71, 1.30)
Desert (16)	1.10 (0.79, 1.60)	1.10 (0.74, 1.60)	8	0.25 (0.04, 1.50)	0.14 (0.02, 0.99)	92	1.20 (0.83, 1.80)	1.10 (0.76, 1.70)
Molecular subtype (n=836): BLIA (27)	0.54 (0.40, 0.72)	0.61 (0.44, 0.85)	74	0.49 (0.34, 0.69)	0.54 (0.36, 0.80)	26	0.59 (0.31, 1.10)	0.91 (0.46, 1.80)
BLIS (42)	0.85 (0.68, 1.10)	0.99 (0.78, 1.20)	32	0.66 (0.44, 0.98)	0.92 (0.60, 1.40)	68	0.98 (0.74, 1.30)	1.00 (0.76, 1.40)
LAR (26)	0.86 (0.64, 1.20)	0.90 (0.66, 1.20)	31	0.91 (0.53, 1.60)	0.75 (0.39, 1.40)	69	0.86 (0.60, 1.20)	1.00 (0.70, 1.50)
MES (5)	1.10 (0.58, 2.20)	1.00 (0.49, 2.10)	28	3.40 (0.66, 18.00)	0.70 (0.17, 2.80)	72	0.93 (0.42, 2.00)	0.98 (0.38, 2.50)
ITT N=902								

1007 **Oral Abstract Session**

Combination of famitinib with camrelizumab plus nab-paclitaxel as first-line treatment for patients with immunomodulatory advanced triple-negative breast cancer (FUTURE-C-PLUS): A prospective, single-arm, phase 2 study. *First Author: Li Chen, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Camrelizumab (anti-PD-1 antibody) and nab-paclitaxel (nab-P) have demonstrated promising anti-tumour activity in patients with immunomodulatory (IM) subtype metastatic triple negative breast cancer (TNBC), with 52.6% of ORR observed in heavily pretreated patients in our previous umbrella trial (FUTURE). As antiangiogenic agents were known to enhance the response to immune checkpoint inhibitors, we assessed the efficacy and safety of novel triplet combination of famitinib (tyrosine kinase inhibitor targeting VEGFR-2, PDGFR and c-kit), camrelizumab and nab-paclitaxel in patients with IM subtype advanced TNBC. **Methods:** In this prospective, single-arm, phase 2 study, eligible patients were 18-70 years and had treatment-naive IM subtype unresectable locally advanced or metastatic TNBC. IM subtype was defined as CD8+ by immunohistochemistry. Eligible patients received camrelizumab (200 mg iv, d1, 15, q4w) with nab-P (100 mg/m^2 iv, d1, 8, 15, q4w) and famitinib (20 mg po qd, d1-28, q4w). Treatment was continued until disease progression, patient withdrawal, or unacceptable toxic effects. In the absence of intolerable toxicity, nab-P was to be administered for a minimum of 6 cycles. Primary endpoint was objective response rate according to RECIST v1.1. We explored the predictive biomarkers using targeted sequencing with a 484-gene panel. **Results:** From Oct 2019 to Oct 2020, 48 patients were enrolled. Confirmed objective responses were achieved in 39 (81.3%; 95% CI 70.2%-92.3%) of 48 patients in the intention-to-treat population and in 39 (84.8%; 95% CI 74.4%-95.2%) of 46 patients in the per-protocol population. Median time to response was 1.8 months (95% CI 1.8-2.0 months). With a median follow-up of 9.0 months, progression-free survival (PFS) and duration of response data were not mature. Thirty patients (62.5%) are still on the study treatment. The 9-month PFS rate was 60.2% (95% CI, 43.2% to 77.3%). Grade 3 or 4 adverse events were neutropenia (33.3%), anaemia (10.4%), febrile neutropenia (10.4%), thrombocytopenia (8.3%), hypertension (4.2%), hypothyroidism (4.2%), proteinuria (2.1%), septicemia (2.1%) and immune related myocarditis (2.1%). Adverse events that led to the discontinuation of any agent occurred in 6.3% of the patients. Two patients had treatment-related serious adverse events. No treatment-related deaths were reported. Biomarker analysis showed that somatic mutations of *GSK3A* may have the potential to predict immunotherapy response. **Conclusions:** Addition of famitinib to camrelizumab and nab-paclitaxel showed promising antitumour activity as first-line therapy with manageable toxicity profile for IM subtype advanced TNBC patients. Results from ongoing randomized controlled trial FUTURE-SUPER (NCT 04395989) are eagerly awaited. Clinical trial information: NCT04129996. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

1008 **Oral Abstract Session**

Randomized multicenter trial of 3 weekly cabazitaxel versus weekly paclitaxel chemotherapy in the first-line treatment of HER2 negative metastatic breast cancer (MBC). *First Author: Amit Bahl, University Hospitals Bristol and Weston NHS Foundation Trust, Bristol, United Kingdom*

Background: Paclitaxel is commonly used as first line chemotherapy for HER2 negative MBC. However, with response rates of 21.5-53.7% and a significant risk of peripheral neuropathy there is a need for more effective and better tolerated chemotherapy (CCT). **Methods:** This open label randomised (1:1) phase 2 trial compared 6 cycles of cabazitaxel (25 mg/m^2) every 3 weeks, with weekly paclitaxel (80mg/m^2) over 18 weeks as first line CCT. HER2 negative and performance status ≤1 patients were eligible. Patients on cabazitaxel received GCSF prophylaxis. Primary endpoint was Progression Free Survival (PFS) with 127 events required to detect a hazard ratio (HR) of 0.65 with 85% power. Secondary endpoints included objective response rate (ORR; RECIST 1.1), time to response (TTR), overall survival (OS), safety and tolerability and quality of life (QoL). **Results:** 158 patients were recruited from 14 UK hospitals (79 in each arm). Median age (range) was 56(34-81) in the cabazitaxel arm and 61(34-79) in the paclitaxel arm. 61% of patients were performance status 0. Median time on treatment was 15 weeks for both arms, but more patients on paclitaxel had a treatment delay (61% vs 39%) or dose reduction (37% vs 24%). Comparing cabazitaxel to paclitaxel after 146 PFS events, median PFS was 6.7 vs 5.8 months (HR 0.84; 95%CI 0.60–1.18, P = 0.3). There was no difference in OS, median 19.3 vs 20.0 months (HR 0.94; 95%CI 0.63-1.40, P = 0.7), ORR (42% vs 37%) or TTR (HR 1.09; 95%CI 0.68–1.74, P = 0.7). Grade ≥3 adverse events occurred in 42% of patients on cabazitaxel and 48% on paclitaxel. Diarrhoea, febrile neutropenia and nausea were the most common grade ≥3 events in the cabazitaxel arm with rates of 11%, 11% and 10% respectively compared to 1%, 1% and 0% in the paclitaxel arm. In the paclitaxel arm the top grade ≥3 events were lung infection and peripheral neuropathy, 6% and 5% respectively compared to 2.5% and 0% in the cabazitaxel arm. Peripheral neuropathy of any grade was reported by 55% of patients treated with paclitaxel vs 17% on cabazitaxel. Alopecia occurred in 41% of patients on paclitaxel compared to 27% on cabazitaxel. Adverse events leading to discontinuation were more frequent with paclitaxel (22%) than cabazitaxel (14%). Over the course of treatment, mean EQ5D single index utility score (+0.05; 95%CI 0.004-0.09, P = 0.03) and visual analogue scale score (+7.7; 95%CI 3.1-12.3, P = 0.001) were higher in the cabazitaxel arm compared to paclitaxel suggestive of better QoL on Cabazitaxel. **Conclusions:** 3 weekly cabazitaxel as first line chemotherapy in HER2 negative MBC does not significantly improve PFS compared to weekly paclitaxel, though it has a lower risk of peripheral neuropathy with better patient reported overall health outcomes. Cabazitaxel is safe and well tolerated for MBC and requires fewer hospital visits, an important consideration in the COVID pandemic and beyond. Clinical trial information: NCT03048942. Research Sponsor: Sanofi, NIHR portfolio support.

1009 **Clinical Science Symposium**

Disparities within luminal breast cancer: Clinical and molecular features of African American and non-Hispanic white patients. *First Author: Kent Hoskins, University of Illinois at Chicago College of Medicine, Division of Medical Oncology, Chicago, IL*

Background: African American breast cancer patients (AA) are diagnosed younger, have more high-risk features, and poorer clinical outcomes than non-Hispanic White patients (NHW), despite similar treatments. Although comorbidities such as obesity and metabolic syndrome may contribute to differences, ancestry-specific factors and effects of structural violence that disproportionately afflict AA individuals may influence tumor biology and outcomes. We previously reported differentially expressed genes (DEGs) associated with tumor aggressiveness in Basal tumors from AA compared with NHW (Sharma et al., 2020). Here, we compare DEGs in luminal tumors between AA and NHW. **Methods:** The prospective, observational FLEX study (NCT03053193) includes stage I-III breast cancer patients who receive 70-gene signature (MammaPrint/MP)/80-gene signature (BluePrint/BP) testing and consent to full transcriptome and clinical data collection. AA (n=364) and NHW (n=400, random selection) with BP luminal tumors, enrolled from 2017 to present, were included. Race/ethnicity was self-reported. AA were younger than NHW (mean, 59 vs. 62 years, p=0.001); thus, an age-matched subset (n= 360 AA, NHW) was compared. Differential gene expression analysis was performed with R limma package. Comparisons were made between AA and age-matched or randomly selected NHW in: (1) all, (2) luminal A, (3) luminal B, and (4) luminal B, obese. DEGs with FDR<0.05 were significant. Different fold change (FC) thresholds were evaluated. **Results:** Compared with age-matched NHW, AA were similar in menopausal status, T stage, grade, and tumor type; obesity, T2DM status, and nodal stage were significantly different ($p<0.01$). Tumors from AA were more often MP high risk ($p<0.001$), regardless of age matching. Luminal B AA vs. age-matched NHW comparison resulted in more DEGs (n=1070) than other comparisons; however, most were FC<2. Notably, 5/6 DEGs (*PSPH*, *NOTCH2NL*, *POLR1A*, *MAP1LC3P* and *RPS26P10*) in basal tumors (Nunes et al. 2019) were also identified here. Of 9 DEGs (FC>1.7) in the luminal B age-matched comparison, 2 (*PSPH* and *LINC01139*) were also found in the luminal B, obese subset. Consistently upregulated DEGs in AA were associated with metabolism, translation, and cellular stress response pathways. **Conclusions:** We found significant transcriptomic differences between luminal tumors from AA and NHW, when controlling for age, obesity, and genomic classification. A subset of DEGs in luminal B tumors were consistent with those in Basal tumors, suggesting that similar race-associated factors drive DEGs regardless of tumor subtype. DEGs that may be unique to AA luminal tumors were also found. This study suggests that some biological differences in breast tumors may result from patient ancestry or shared adverse socioeconomic exposures and underscores the need for inclusion of diverse patient groups in clinical trials. Clinical trial information: NCT03053193. Research Sponsor: Agendia, Inc.

1010 **Clinical Science Symposium**

Impact of African ancestry on the relationship between BMI and survival in early stage breast cancer: Retrospective analysis from E5103. *First Author: Tarah J. Ballinger, Indiana University, Indianapolis, IN*

Background: Both Black race and obesity are associated with worse survival in early stage breast cancer. Obesity disproportionately affects Black women; however, the degree this contributes to racial disparities in breast cancer remains unclear. Prior work evaluated heterogeneous populations or used self- reported race, rather than genetic ancestry. African ancestry is associated with higher BMI and worse survival in breast cancer; however, the intersection between genetic ancestry and obesity on survival outcomes remains unknown. **Methods:** We analyzed data from the adjuvant trial E5103. Patients with high risk, HER2 negative breast cancer received doxorubicin/cyclophosphamide x 4, followed by weekly paclitaxel x 12, with or without bevacizumab. Genetic ancestry was determined on the 2,854 patients with available germline DNA, BMI, and outcome data using principal components from a genome-wide array. The primary objective assessed impact of BMI on DFS and OS by ancestry. Multivariate Cox proportional hazard models evaluated correlation between continuous or binary BMI and survival in African (AA) and European (EA) Americans. **Results:** 13.4% of patients were genetically classified as AA and 86.6% as EA. Higher continuous BMI was significantly associated with worse DFS and OS only in AAs (DFS: HR = 1.25 95% CI 1.07-1.46, p = 0.004; OS: HR = 1.38 95% CI 1.10-1.73, p = 0.005); not in EAs (DFS HR = 0.97 95% CI 0.90-1.05, p = 0.50; OS HR = 1.03 95% CI 0.93-1.14, p = 0.52). By disease subtype, BMI was associated with worse outcomes only in AAs with ER+, and not TNBC. By categorical BMI, WHO class III obesity (^{3} 40) significantly associated with worse DFS and OS only in AAs (DFS HR = 1.98, p = 0.010; OS HR = 2.07, p = 0.064), not in EAs (DFS HR = 0.97, p = 0.86; OS HR = 1.28, p = 0.30). Proportion of African ancestry (proAA) was associated with higher BMI and worse outcomes in the total population; however, within AAs there was no significant interaction between proAA and BMI on DFS (HR = 0.36, p = 0.06) or OS (HR = 0.38, p = 0.24). In AAs, BMI remained associated with DFS (HR = 2.78, p = 0.019), suggesting higher BMI is associated with worse DFS regardless of proAA. Coefficients for the interaction term indicate that as proAA increases the impact of BMI on outcome is lessened. **Conclusions:** Higher BMI is significantly associated with worse breast cancer outcomes in women of African ancestry in E5103, but not in those of European ancestry. Categorically, this association was significant only for severe obesity, indicating the relationship may depend on the degree of obesity. As proAA increased in AAs, the impact of BMI on outcome was lessened, suggesting other host factors may contribute more to obesity's influence on outcome than genetics. Determination of the optimal populations for weight loss interventions will advance precision medicine efforts to impact racial disparities and outcomes in early stage breast cancer. Research Sponsor: None.

1011 **Clinical Science Symposium**

Outcomes in patients (pts) aged ≥65 years in the phase 3 ASCENT study of sacituzumab govitecan (SG) in metastatic triple-negative breast cancer (mTNBC). *First Author: Kevin Kalinsky, Winship Cancer Institute, Emory University, Atlanta, GA*

Background: Approximately 20% of pts diagnosed with TNBC are aged ≥65 y. Often, older pts are less fit for chemotherapy due to a greater rate of comorbidities, increased use of medications, and pre-existing frailty or functional loss. SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. The landmark phase 3 ASCENT study (NCT02574455) showed improved outcomes with SG vs single-agent chemotherapy of physician's choice (TPC) in pts with relapsed/refractory mTNBC (median progression-free survival [PFS], 5.6 vs 1.7 mo; median overall survival [OS], 12.1 vs 6.7 mo). Here we assess the impact of age on the efficacy and safety of SG in ASCENT. **Methods**: Pts with mTNBC refractory/relapsing after ≥2 prior chemotherapies were randomized 1:1 to receive SG (10 mg/kg IV on days 1 and 8, every 21 days) or TPC (capecitabine, eribulin, vinorelbine, or gemcitabine) until disease progression/unacceptable toxicity. Primary endpoint was PFS per RECIST 1.1 by independent review in brain metastases-negative (BMNeg) pts. Safety outcomes were assessed in all treated pts. This prespecified subgroup analysis assessed the impact of age (pts ≥65 y) on PFS, OS, and safety. **Results:** Of 529 pts enrolled, 468 were BMNeg (median age, 54 y); of these, 44/235 pts (19%) who received SG and 46/233 pts (20%) who received TPC were aged ≥65 y. SG treatment improved median PFS vs TPC in pts ≥65 y (7.1 vs 2.4 mo; HR, 0.22; 95% CI, 0.12-0.40). SG vs TPC treatment also improved median OS in pts ≥65 y (15.3 vs 8.2 mo; HR, 0.37; 95% CI, 0.22-0.64). Treatment with SG vs TPC resulted in higher ORR (50% vs 0%) and clinical benefit rate (CBR, 61% vs 9%) in pts ≥65 y. Of the 7 pts ≥75 y who received SG, 2 had partial response, 4 had stable disease [SD], and 1 had SD > 6 mo as best response. In pts < 65 y, median PFS for SG vs TPC was 4.6 vs 1.7 mo (HR, 0.46; 95% CI, 0.35-0.59), and median OS was 11.2 vs 6.6 mo (HR, 0.50; 95% CI, 0.40-0.64), respectively; the ORR and CBR were 31% vs 6% and 41% vs 9%, respectively. Pts ≥65 y treated with SG vs TPC had similar rates of all grade and grade ≥3 treatment-emergent adverse events (TEAEs). TEAEs leading to dose reduction were similar in pts ≥65 y in the SG vs TPC arms (35% vs 33%) and were lower in pts < 65 y (19% vs 24%). Key treatment-related TEAEs leading to dose reduction in pts ≥65 y in the SG vs TPC arms were neutropenia (including febrile neutropenia; 14% vs 25%), fatigue (10% vs 4%), diarrhea (6% vs 0%), and nausea (4% vs 0%). TEAEs leading to treatment discontinuation with SG vs TPC were low in pts ≥65 y (2% vs 2%) and < 65 y (5% vs 6%). There were no treatment-related AEs leading to death in any SG-treated age group. **Conclusions:** Irrespective of age, pts who received SG had a significant survival benefit vs TPC, with a tolerable safety profile. Proactive AE monitoring and management will allow optimal therapeutic exposure to SG in older pts. Clinical trial information: NCT02574455. Research Sponsor: Immunomedics, Inc. a subsidiary of Gilead Sciences, Inc.

1012 **Clinical Science Symposium**

PALOMAGE, a French real-world cohort of elderly women beyond age 70 with advanced breast cancer receiving palbociclib: Baseline characteristics and safety evaluation. *First Author: Philippe Caillet, Hôpital Européen Georges Pompidou, Paris, France*

Background: Advanced breast cancer (ABC) is common in older patients, resulting from the high incidence of breast cancer beyond age 70. This population is often limited in clinical trials. Endocrine therapy (ET) combined with a CDK4/6 inhibitor is the standard of care in ABC overexpressing hormonal receptors (HR+). Data specific to older patients are scarce in the literature, deserving further research. **Methods:** PALOMAGE is an ongoing French prospective study evaluating palbociclib (PAL) + ET in real life setting in women aged ≥70 with HR+ HER2- ABC, split in 2 cohorts: ET sensitive patients with no prior systemic treatment for ABC (cohort A), and ET resistant patients and/or with prior systemic treatment for ABC (cohort B). Data collected include clinical characteristics, quality of life (EORTC QLQ-C30 and ELD14) and geriatric description [G8 and Geriatric-COre DatasEt (G-CODE)]. This analysis reports on baseline characteristics and safety data for the whole population. **Results:** From 10/2018 to 10/2020, 400 and 407 patients were included in cohort A and B, respectively. The median age was 79 years (69-98), 15.1% with an age > 85. ECOG performance status (PS) was ≥2 in 17.9% patients, 68.3% had a G8 score ≤14 suggesting frailty, 32.1% had bone only metastasis, and 44% had visceral disease. 35.8% of patients in cohort B had no prior treatment for ABC. Safety data were available for 787 patients. The median follow-up was 6.7 months (IC95% = 6.1-7.6). At start of treatment, full dose of PAL (125 mg) was used in 76% of the patients: 62.6%, 68.7% and 71.6% of patients aged ≥ 80, those with ECOG PS ≥2 and those with a G8 score ≤14, respectively. In the safety population, 70% had ≥1 adverse event (AE), including 43.1% grade 3/4 AE, and 22.9% ≥ 1 serious AE. Most frequent AE reported were neutropenia (43.2%), anemia (17.5%), asthenia (16.3%) and thrombocytopenia (13.6%). Grade 3/4 neutropenia was observed in 32.3% of patients, with febrile neutropenia in 1.1%. Grade 3/4 AE PAL-related were reported in 40.1%, 31.4% of patients aged < 80, ≥80, respectively. Regarding PAL, 23.4% of patients had a dose reduction and 41.8% had a temporary or permanent discontinuation due to AE. Safety data were similar in both cohorts. Geriatric data and impact on safety will be presented. **Conclusions:** PALOMAGE is a unique large real-world cohort focusing on older patients treated with PAL in France. These preliminary data do not suggest any new safety signal, matching data derived from PALOMA trials. The occurrence of less grade3/4 AE related to PAL in patients aged 80 and beyond might reflect the 30% decrease of PAL dose upfront. Effectiveness analyses are eagerly awaited. Clinical trial information: EUPAS23012. Research Sponsor: Pfizer.

1013 **Poster Discussion Session**

Prospective longitudinal multi-omics study of palbociclib resistance in hormone receptor+/HER2- metastatic breast cancer. *First Author: Yeon Hee Park, Samsung Medical Center, Seoul, South Korea*

Background: The development of CDK4/6 inhibitors represents a significant advance in the treatment of metastatic breast cancer (MBC). To better understand the impact of treatment and drug resistance at the molecular level, we performed multi-omics profiling of matched pre-treatment, on-treatment, and post-progression tumor biopsies from patients treated with palbociclib combined with endocrine blockades (AIs and fulvestrant). The purpose of the study was to identify biomarkers of palbociclib resistance as well as to assess molecular changes during treatment, and those appearing at disease progression. **Methods:** Patients with Hormone Receptor positive (HR+)/HER2- MBC treated with palbociclib in combination with endocrine therapies were prospectively enrolled from July 2017 to June 2020. Of the 89 patients enrolled, we obtained tumor biopsies and matched blood samples, taken at pre-treatment, on-treatment (6 weeks or 12 weeks) and progressive disease (PD) from 71 patients (first line: 55, second line or later: 16 pts.) who had agreed to informed consent form. Tumor biopsies were profiled using whole-exome sequencing (WES) and whole-transcriptome sequencing (RNA-Seq). **Results:** Median follow-up duration was 20 (3-48) months and median age of the patients was 45 (range 30-71) years. The median progression free survival (PFS) of 71 patients was 15 (0.7-39.8) months. The Luminal B subtype is associated with shorter PFS compared to Luminal A (8.6 m vs 19.3 m, p=0.03, HR=1.96). The Luminal B subtype along with multiple cell cycle regulatory genes such as CCNE1 (8.3 m, p=0.015, HR=2.07), CCNE2 (8.5 m, p=8.5e-3, HR=2.2), CDK2 (8.45 m, p=0.05, HR=1.79) are associated with shorter PFS while estrogen response signatures (20.9 m, p=4.6e-3, HR=0.43) and PGR gene expression (20.2 m, p=6.2e-2, HR=0.56) are associated with more favorable prognosis. A Cox-regression multivariate model (p=5.17e-5, C-Index=0.72) was developed and revealed that PFS is independently associated with *BRCA1/2* (HR=1.44; CI=[0.49, 4.29]), *TP53* mutation statuses (HR=3.58; CI=[1.58, 8.13]), the HRD mutation signature (HR=1.40; CI=[1.09, 1.81]) and the proliferative index (HR=1.53; CI=[1.00, 2.34]), an expression signature of cell proliferation. Tumors classified as Luminal A at baseline frequently switched into Luminal B or Her2-enriched subtypes at PD, along with up-regulation of cell cycle markers and proliferation signatures. Further, tumor mutation burden (TMB) and HRD index, a DNA-based measure of genomic instability, significantly increased from baseline to PD in patients with *TP53* and *BRCA1/2* wild-type tumors. **Conclusions:** Our longitudinal multi-omics study identified prognostic biomarkers as well as post-treatment enrichment of HRD related genomic scars and frequent switching into molecular subtypes with aggressive and estrogen independence characteristics. Clinical trial information: NCT03401359. Research Sponsor: Oncology Research & Development, Pfizer.

1014 **Poster Discussion Session**

CCNE1 mRNA and cyclin E1 protein expression as predictive biomarkers for efficacy of palbociclib plus fulvestrant versus capecitabine in the phase III PEARL study. *First Author: Javier Pascual, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom*

Background: The randomized PEARL trial found no superiority of palbociclib plus endocrine therapy over capecitabine in patients (pts) with metastatic HR-positive, HER2-negative breast cancer resistant to prior aromatase inhibitors (Martin M, Ann Oncol 2020). Gene expression analysis showed high *CCNE1* mRNA (*CCNE1*) conferring relative resistance to palbociclib in the PALOMA-3 trial (Turner N, JCO 2019), but further validation is needed. Cyclin E1 protein (cyclin E1) expression in this context has not been studied in randomized trials. We explored *CCNE1* and cyclin E1 as predictive biomarkers in tumor samples from the PEARL study. **Methods:** Formalin-fixed paraffin-embeded tumor samples were retrieved from pts enrolled in PEARL cohort 2 (palbociclib (PAL) + fulvestrant (FUL) vs capecitabine (CAPE)). We measured *CCNE1* using the HTG EdgeSeq Oncology Biomarker Panel (HTG Molecular Diagnostics). Cyclin E1 immunohistochemistry (IHC) staining was performed using specific mouse monoclonal antibody HE12 (Abcam) and scored as percentage of invasive nuclei stained (0-100%). *CCNE1* and cyclin E1 correlations were explored using Pearson coefficients. Cox regression models were used for progression free-survival (PFS) analyses using expression levels split by median, to define high (> median values) vs. low expression. Site of disease and prior chemotherapy were used as confounders in multivariate models. **Results:** Analyses were conducted in 219 pts (47% receiving PAL + FUL and 53% CAPE) with available tumors, with the analysed patients representative of the overall study. Most samples were from the archival primary (72%), obtained > 5 years before this analysis° (74%). *CCNE1* and cyclin E1 were only moderately correlated (r = 0.5). Median *CCNE1* was higher in metastatic vs primary (7.37 vs 6.94, p < 0.01), and in luminal B and non-luminal subtypes compared to luminal A (p < 0.001). In patients with high *CCNE1* expression, median PFS on CAPE was 10.35 and PAL + FUL was 5.68 (HR = 1.63, 95% CI 1.02-2.59, p = 0.042). In patients with low *CCNE1* expression, median PFS on CAPE was 9.43 and PAL + FUL was 8.97 (adjusted HR = 0.93, 95% CI 0.59-1.48, p = 0.762, interaction p = 0.072). Median cyclin E1 protein was higher in luminal B and non-luminal subtypes compared to luminal A (p < 0.01). Cyclin E1 protein expression was not predictive of treatment effect (high cyclin E1 expression CAPE vs PAL + FUL HR = 1.17, low cyclin E1 expression CAPE vs PAL + FUL HR = 1.21, interaction p = 0.977). **Conclusions:** High tumor *CCNE1* mRNA expression identified patients with relative resistance to palbociclib plus fulvestrant, validating prior observations although without statistical significance for interaction. Assessment of Cyclin E1 protein expression did not show predictive value. Investigation treatments to enhance CDK4/6 inhibitor efficacy in tumors with high CCNE1 expression is warranted. Clinical trial information: NCT02028507. Research Sponsor: Pfizer and AstraZeneca.

1015 **Poster Discussion Session**

Characterizing demographics, clinical, and genomic characteristics for U.S. patients with HR+, HER2- metastatic breast cancer following progression on a CDK4 and 6 inhibitor. *First Author: Fabrice Andre, Gustave Roussy, Villejuif, France*

Background: Cyclin-dependent kinases 4 and 6 inhibitors (CDK4 & 6i) have advanced the therapeutic landscape for patients with hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (MBC). However, there is an unmet need for treatment strategies following progression on CDK4 & 6i +/- endocrine therapy (ET). The objective of this analysis is to aid in the development of post-progression treatment by characterizing genomic profiles of tumor biopsies after progression on a CDK4 & 6i +/- ET. **Methods:** This is a retrospective study comparing two cohorts of US patients (pts) diagnosed with HR+, HER2- MBC since January 2011. One cohort underwent biopsy following progression on a CDK4 & 6i +/- ET (Cohortpost) while the second cohort underwent biopsy with no evidence of CDK4 & 6i treatment (Cohortpre). Tumor tissue was analyzed using the next generation sequencing Tempus xT assay that analyses 595 cancer-related genes. Of 595 molecularly profiled pts, 369 had sufficient medical record data to be eligible for this analysis. Patient characteristics at metastatic diagnosis and CDK4 & 6i initiation were described. For genomic profile comparison, Mann-Whitney *U*-test was used for continuous variables such as tumor mutation burden (TMB) with significance at P < 0.05; Chi-square or Fishers' exact test was used as appropriate for categorical variables including mutation frequency, with significance at false discovery rate (FDR) < 0.2. **Results:** Of 369 pts, 177 (48%) were in Cohortpre and 192 (52%) were in Cohortpost. Overall, the mean age at the time of MBC diagnosis was 59 and 55 years, respectively; 47% and 66% of patients had evidence of prior chemotherapy or ET; and 30% and 25% had de novo stage IV MBC. The most common biopsy site was liver, occurring in 38% of pts overall (Cohortpre, 23%; Cohortpost, 52.6%). The xT assay results indicated that pts in Cohortpost had significantly higher TMB compared to patients in Cohortpre (median 2.92 vs 1.67, P < 0.0001). A subset of patients with liver mets across both cohorts (n = 141) showed a similar, but nonsignificant trend (median 2.92 vs 2.08, P = 0.0565). Additionally, pts in Cohortpost had a higher *ESR1* alteration frequency compared to Cohortpre (mutations: 32.29% vs 9.60%, FDR < 0.0001; fusions: 7% vs 3%, P = 0.1420). No significant differences were noted in *TP53*, *CCNE1*, *CCND1*, *RB1*, *CDK4*, and *CDK6* between cohorts. **Conclusions:** These findings describe clinical characteristics and specific genomic alterations noted after progression on CDK4 & 6i +/- ET. Further analyses will evaluate timing of resistance, mutational and transcriptomic signatures. This may aid in understanding mechanisms of progression associated with CDK4 & 6i +/- ET, ultimately contributing to development of treatment options post progression. Research Sponsor: Eli Lilly and Company.

1016 **Poster Discussion Session**

Predictors of non-receipt of first-line CDK 4/6 inhibitors (CDK4/6i) among patients with metastatic breast cancer (MBC). *First Author: Kimberley T Lee, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: CDK4/6i improve survival outcomes for first-line treatment of patients with hormone receptor positive (HR+), human epidermal growth factor-2 negative (HER2-) MBC. Yet, not all eligible patients (pts) receive a first-line CDK4/6i. We sought to describe factors associated with not receiving a first-line CDK 4/6i among MBC pts treated at our institution. **Methods:** Retrospective cohort of pts with HR+, HER2- MBC diagnosed between May 1, 2015 and June 30, 2019 treated at Johns Hopkins clinic sites in Baltimore City (BCi), Baltimore County (BCo), and Washington DC (DC). Primary outcome was receipt of a first-line CDK 4/6i. Clinical and demographic factors were abstracted from the electronic medical record. Patient zip-code was used to define a low-income neighborhood (LIN) as an area where >10% of households have median income below the federal poverty level. Univariate and multivariable logistic regression models (determined using a stepwise model selection approach) were performed to identify factors associated with not receiving a first-line CDK 4/6i. **Results:** Of the 211 pts in the cohort, 203 (96.2%) were female, 133 (63%) were White, and 53 (25%) were Black. Median age was 58 yrs (range 25-90 yrs). 26% of pts had de novo MBC and 44% had visceral disease at diagnosis. About half, 104 (49%), were privately insured, 83 (49%) had Medicare, and 15 (7.1%) had managed care plans including Medicaid. 118 (56%), 43 (20%), and 50 (24%) pts were treated in BCi, BCo, and DC respectively. 60% (n=126) of pts received a first-line CDK 4/6i and there was a trend of increased utilization over time with 39% of pts receiving first-line CDK4/6i in 2015 and 67% in 2019. On univariate analysis, LIN, clinic site, and year of MBC diagnosis (2015-2017 vs 2018-2019) were associated with first-line CDK4/6i use. The multivariable model included age, race, clinic site, LIN, and year of MBC diagnosis. In this model, pts treated in BCi were 58% less likely to receive first-line CDK 4/6i compared to those treated in BCo (OR 0.42, 95% CI 0.18-0.95). Those diagnosed with MBC in 2017 or later were 2.6 times more likely to receive first-line CDK4/6i than those diagnosed prior (OR 2.63, 95% CI 1.45-4.83). Those who lived in a LIN were 39% less likely to receive first-line CDK4/6i vs those in a non-LIN, though this was no longer statistically significant (OR 0.61, 95% CI 0.32-1.13). **Conclusions:** We identified disparities in the use of CDK4/6i for first-line treatment of MBC. Lower use was observed among pts who received care at our urban Baltimore city site with a trend towards lower use among pts from lower-income neighborhoods. These findings highlight potential barriers with accessing oral cancer therapies - cost, patient distrust, and/or systemic bias. Further work is needed to delineate the multi-level factors contributing to these disparities and to develop resources to overcome these barriers and achieve equitable utilization of these drugs. Research Sponsor: Pfizer.

1017 **Poster Discussion Session**

Safety and activity of single-agent giredestrant (GDC-9545) from a phase Ia/b study in patients (pts) with estrogen receptor-positive (ER+), HER2-negative locally advanced/metastatic breast cancer (LA/mBC). *First Author: Komal L. Jhaveri, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Targeting ER activity and/or E synthesis is a mainstay of ER+ BC treatment, but many pts relapse during/after adjuvant endocrine therapy (ET) or develop resistance via *ESR1* mutations that drive E-independent transcription and proliferation. Most tumors remain ER signaling-dependent and pts may respond to second-/third-line ET after disease progression (PD) on prior therapies (Di Leo 2010; Baselga 2012). Giredestrant, a highly potent, nonsteroidal oral selective ER degrader, achieves robust ER occupancy, is active despite *ESR1* mutations, and was well tolerated ± palbociclib with encouraging antitumor activity in the nonrandomized, open-label, dose-escalation and -expansion, phase Ia/b GO39932 study (NCT03332797; Jhaveri 2019; Lim 2020). We present updated interim data from the dose-escalation and -expansion single-agent giredestrant cohorts. **Methods:** Pts had ≤2 prior therapies in the LA/mBC setting with disease recurrence/PD while being treated with adjuvant ET for ≥24 mo and/or ET in the LA/mBC setting, and derived a clinical benefit (CB) from therapy (tumor response/stable disease [SD] ≥6 mo). Pts received 10, 30, 90/100, or 250 mg PO giredestrant QD on D1–28 of each 28-day cycle. Pts were postmenopausal (medical menopause on LHRH agonists was allowed with ≥100 mg giredestrant). **Results:** Clinical cutoff: Jul 31, 2020; median prior therapy lines in the LA/mBC setting: 1; mean dose intensity: 98%. Safety/activity: see the table below. No adverse events (AEs) led to study drug withdrawal. No dose-limiting toxicities (DLTs) occurred; maximum tolerated dose was not reached. Most common AEs in 107 pts: fatigue (22; 21%), arthralgia (18; 17%), and nausea (17; 16%); largely grade 1/2. Related grade 3 AEs were infrequent (5; 5%); none were grade 4/5 per investigator assessment (grade 5 duodenal perforation occurred with 90/100 mg after stopping giredestrant due to PD). 8 (7%) had bradycardia (none with 10 mg or the 30 mg phase 3 dose; all grade 1 except one grade 2 at 250 mg; no treatment interruptions/dose reductions were required). Objective responses and CB were observed at all doses. **Conclusions:** Single-agent giredestrant was well tolerated at all doses, with no DLTs. AEs were generally low grade and in keeping with expected AEs for ETs. Clinical activity was observed at all doses. Updated data, including biomarker and correlative data, will be presented. Clinical trial information: NCT03332797. Research Sponsor: Genentech, Inc.

Pts (%) unless specified	10 mg n=6	30 mg n=41	90/100 mg ± LHRH n=51	250 mg ± LHRH n=9
AEs, pts with ≥1:				
Grade ≥3	1 (17)	4 (10)	14 (27)	1 (11)
Serious	0	2 (5)	6 (12)	0
Leading to dose reduction	0	1 (2)	2 (4)	0
Activity				
Median progression-free survival, mo (95% CI)	5.3 (1.7–15.6)	7.2 (3.5–13.6)	7.9 (5.3–16.7)	5.4 (1.7–not evaluable)
CB rate: complete + partial response (PR) + SD ≥6 mo	1/6 (17)	13/27 (48)	27/51 (53)	3/9 (33)
PR	1 (17)	2 (5)	5 (10)	0
SD	2 (33)	20 (49)	28 (55)	5 (56)

1018 **Poster Discussion Session**

Phase I/II study of H3B-6545, a novel selective estrogen receptor covalent antagonist (SERCA), in estrogen receptor positive (ER+), human epidermal growth factor receptor 2 negative (HER2-) advanced breast cancer. *First Author: Erika P. Hamilton, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: H3B-6545, a selective, small molecule covalent antagonist of ERα demonstrated preclinical and preliminary clinical activity against ER+ breast cancer (Hamilton EP, SABCS, 2020). This study evaluated the activity and tolerability of H3B-6545 in patients (pts) with metastatic ER+, HER2-, breast cancer refractory to endocrine therapy. **Methods:** Patients received H3B-6545 once daily at the recommended phase II dose of 450 mg. The primary objective of the phase II is to estimate the objective response rate (ORR), progression-free survival (PFS), clinical benefit rate (CBR) and secondary objectives include safety. **Results:** 83 pts were treated with 450 mg in the phase II part of the trial. Additionally, 11 pts were treated with 450 mg in the phase I part of the trial and are included in this analysis. Median age was 62 years (range: 38 to 87 years), 81% had liver and/or lung metastases, and the median number of prior therapies for metastatic disease was 3 (range: 1 to 8). Prior CDK4/6 inhibitors, aromatase inhibitors, fulvestrant, and chemotherapy were received by 85%, 80%, 72%, and 50% of the pts, respectively. 58 pts (62%) had detectable *ESR1* mutations in liquid biopsies, including 10 (11%) and 19 pts (20%) who had clonal Y537S and clonal D538G mutation, respectively. As of January 29, 2021, grade (gr) 2 or higher adverse events (AE) reported in ≥10% were anemia (19%), fatigue (16%), nausea (17%), and diarrhea (12%). Laboratory gr 2 or higher abnormalities reported in ≥10% pts were creatinine clearance decrease (38%), hemoglobin decrease (37%), bilirubin increase (12%), ALT increase (14%), AST increase (13%), and creatinine increase (11%). AE of gr 1 sinus bradycardia (asymptomatic) was reported in 34% and gr 2 (symptomatic, no intervention needed) was reported in 5%. Gr 2 and 3 QTcF prolongation were reported in 2 and 3 pts, respectively. There were no treatment-related deaths. Efficacy estimates are presented in the table below. Responses were observed in heavily pretreated pts, pts with visceral metastases and in pts who received prior fulvestrant, CDK4/6 inhibitor, and/or chemotherapy in the metastatic setting. **Conclusions:** H3B-6545 has a manageable safety profile and demonstrated single-agent anti-tumor activity in heavily pretreated ER+, HER2-mBC patients. Clinical activity was observed in pts with *ESR1* mutations. Clinical trial information: NCT03250676. Research Sponsor: H3 Biomedicine / Eisai.

Efficacy estimates.

Efficacy endpoint	All pts (N = 94)	Pts with clonal Y537S (N = 10)	Pts with clonal D538G (N = 19)
ORR (n, %)	12 (17%)[1]	3 (30%)	0 (0%)
Median duration of response (mo, 95% CI)	7.6 (5.4, NE)	–[2]	–
CBR (%)	30 (32%)	6 (60%)	6 (32%)
Median PFS (mo, 95% CI)	5.1 (3.2, 6.2)	7.3 (0.8, 11.2)	5.4 (1.7, 7.2)

CI: Confidence interval
[1] Based on 72 pts who are response-evaluable. All 12 pts had confirmed partial responses.
[2] Not estimated due to small number of responders.

1019 **Poster Discussion Session**

A phase Ib study of proxalutamide (GT0918) in women with androgen receptor-positive metastatic breast cancer. *First Author: Huiping Li, Beijing Cancer Hospital, Beijing, China*

Background: Androgen receptor (AR) is an emerging prognostic marker and therapeutic target in breast cancer. AR is expressed in 60% to 80% of breast cancers. Recent studies have shown the association between AR signaling and tumor carcinogenesis in breast cancer, suggesting AR pathway as a potential target for breast cancer treatment. However, no AR targeting therapies have been approved for treating breast cancer. GT0918 is a new chemical entity of AR antagonist with possible AR down-regulation. We had finished the phase I study and submitted the paper. Here we present a multicenter, open-label phase Ib trial assessing the safety and efficacy of GT0918 in women with AR positive metastatic breast cancer. The primary objective is to evaluate the efficacy of GT0918. The secondary objectives are to assess its safety and to explore the relevant biomarkers. **Methods:** This is an expansion study of a phase I dose-escalation trial. In this phase Ib study, only patients with AR positive metastatic breast cancer were enrolled. All eligibled patients would take GT0918 orally once a day, of a 28 -day cycle. After 2 cycles' safety and tolerability assessment, patients could choose to continue their treatment until they experience disease progression, intolerable toxicities, death, or withdrew consent. The primary efficacy endpoints were 8-week disease control rate (DCR) and 16-week DCR. The secondary efficacy endpoint was progression free survival (PFS). **Results:** In total, 45 patients were enrolled in the study at 200mg (n = 30) and 300mg (n = 15) doses. The most common (≥10%) treatment-related adverse events (AEs) were asthenia (42.2%), aspartate aminotransferase increased (26.7%), blood cholesterol increased(17.8%), alanine aminotransferase increased (17.8%), decreased appetite (17.8%), blood triglycerides increased (13.3%), blood lactate dehydrogenase increased (13.3%), anaemia (13.3%), blood alkaline phosphatase increased (11.1%), gamma-glutamyltransferase increased (11.1%), urinary tract infection (11.1%). Grade 3/4 AEs were reported in 9 patients (20%). No treatment-related deaths occurred. The 8-week and 16-week DCR were both 22.2% (n = 10) (95% CI 10.08%, 34.37%). The median PFS was 1.8 months (95% CI 1.8, 1.9) in all patients. 12 out of 45 (26.7%) were triple negative breast cancer cases. The median PFS was 1.9 months (95% CI 1.7, 9.1), 4 out of 12 patients (33.3%) > 6 months, 2 out of 12 patients (16.7%) > 9 months. **Conclusions:** GT0918 has been shown to be well tolerated and may provide potential clinical benefits to AR positive metastatic breast cancer patients. This study demonstrated triple negative in AR positive patients had more benefit. Clinical trial information: NCT04103853. Research Sponsor: the National Science and Technology Major Project of the Twelfth Five--Year Plan and the National Science and Technology Major Project of the Thirteenth Five-Year Plan.

1020 **Poster Discussion Session**

Efficacy of enobosarm, a selective androgen receptor (AR) targeting agent, correlates with the degree of AR positivity in advanced AR+/estrogen receptor (ER)+ breast cancer in an international phase 2 clinical study. *First Author: Carlo Palmieri, Clatterbridge Cancer Centre NHS Foundation Trust, Wirral, United Kingdom*

Background: The AR is expressed in up to 90% of ER+ breast cancer where it acts as a tumor suppressor. Historically, therapy with synthetic androgens had efficacy, but virilizing side effects and toxicity limited their use. Enobosarm is a selective AR activating agent that does not cause masculinization and has positive attributes such as promotion of bone and improvement of physical function. In a phase 2 study, correlation between the degree of AR staining and antitumor activity in AR+/ER+ patients with metastatic breast cancer (MBC) was examined. **Methods:** A phase 2, open label, parallel design randomized study was conducted in 136 patients to evaluate the efficacy and safety of enobosarm in heavily pretreated women with AR+/ER+ MBC. Patients were randomized to 9 mg (n=72) or 18 mg (n=64) of oral daily enobosarm. AR expression (%AR nuclei staining) in breast cancer samples was determined centrally by immunohistochemistry. The correlation between %AR staining and clinical outcomes was examined with a focus on the 9mg dose, selected for the phase 3 study and the optimal %AR staining established. **Results:** Tumor objective outcomes correlated with percent AR staining (Table). Further, using a 40% AR staining cutoff in patients with measurable disease, the clinical benefit rate (CBR) for ≥40% AR is 80% and <40% is 18% (p<0.0001). Best objective tumor response (BOR) in patients with ≥40% AR is 48% and <40% is 0% (p<0.0001). At ≥40% AR, median radiographic progression free survival (rPFS) is 5.47 and mean is 7.15 months vs <40% AR where the median rPFS is 2.72 and mean is 2.7 months. Similar %AR staining correlation was observed in the 18mg cohort. Enobosarm treatment was well tolerated with significant positive effects on quality of life measurements. **Conclusions:** Enobosarm is a novel oral selective AR activating agent in which a higher % AR staining correlates with a greater antitumor activity. By targeting and activating AR, enobosarm may represent a new hormone treatment approach for AR+/ER+ MBC. The phase 3, ARTEST trial will commence in early 2021 and randomize patients with AR+/ER+/HER2- heavily treated MBC that have progressed on a non-steroidal aromatase inhibitor, fulvestrant and CDK 4/6 inhibitor to receive enobosarm or standard endocrine therapy. Clinical trial information: NCT02463032. Research Sponsor: Veru Inc.

AR %	n	Median rPFS (months)	Average rPFS (months)	Objective Responses (CR+PR)	Objective Response Rate	Clinical Benefit Response Rate
<20	13	2.70	2.83	0	0%	15%
20-40	9	2.77	2.51	0	0%	22%
40-60	7	2.93	4.62	3	43%	86%
60-80	10	5.60	8.10	6	60%	80%
≥80	8	6.23	8.18	3	38%	75%
<40	**22**	**2.72**	**2.70**	**0**	**0%**	**18%**
≥40	**25**	**5.47**	**7.15**	**12**	**48%**	**80%**

1021 **Poster Discussion Session**

Prevalence of HER2 low in breast cancer subtypes using the VENTANA anti-HER2/neu (4B5) assay. *First Author: Marietta Scott, AstraZeneca R&D, Cambridge, United Kingdom*

Background: Breast cancer patients with HER2 low expression by immunohistochemistry (IHC), defined as IHC1+ or IHC2+ without gene amplification (ISH-) do not respond to conventional anti-HER2 therapies such as trastuzumab or pertuzumab. The HER2-targeted antibody-drug conjugate (ADC) trastuzumab deruxtecan (T-DXd) showed efficacy in late line HER2-overexpressing patients, with some responses in patients with low HER2 expression. Two of the market leading IHC IVDs are Dako Herceptest and Ventana 4B5. T-DXd is being investigated in HER2 low patients as determined by the VENTANA anti-HER2/neu (4B5) assay in the phase III DESTINY-Breast04 study. There is a paucity of information on prevalence of IHC1+/2+ in different breast cancer subtypes, which this study aims to address. **Methods:** HER2 status was calculated from 3750 consecutive primary or metastatic breast cancer patient samples successfully stained using the 4B5 assay and scored locally according to ASCO/CAP 2018 guidelines. Samples were obtained from 3 anatomic pathology labs that support networks of US community hospitals. 500 additional breast cancer samples, pre-selected to include a range of IHC staining (concordance cohort), were stained with both 4B5 and HercepTest (Dako/Agilent) and scored (IHC0, IHC1+, IHC2+, IHC3+) at a central laboratory. **Results:** Prevalence of HER2 categories in 3750 consecutive breast cancer samples is presented in the table below. >50% of estrogen-receptor positive (ER+ve) and progesterone receptor positive (PR+ve) subtypes are HER2 low. In the 500 sample concordance cohort, 28.0% were IHC1+/2+ using the 4B5 assay compared with 11.6% using HercepTest. HercepTest identified IHC1+/2+ staining in 21.6% [95%CI:15.1,29.4] of the patients classified as IHC1+/2+ by 4B5. 98.3% [95%CI: 96.2, 99.5] of samples IHC0 by 4B5 were also IHC0 by Herceptest. **Conclusions**: HER2 IHC1+/2+ (ISH-) by Ventana 4B5 represent a significant proportion of breast cancer patients and more than 50% of ER+ve and PR+ve subtypes. The 4B5 assay classed several patients as IHC1+/2+ that are IHC0 by Herceptest, but almost all patients IHC0 by 4B5 were also IHC0 by Herceptest. Research Sponsor: AstraZeneca.

Subtype (n)	Prevalence IHC0 % [95% CI]	Prevalence IHC1+/2+ (ISH-) [HER2 low] % [95% CI]	Prevalence IHC2+ (ISH+)/IHC3+ % [95% CI]
Total breast cancer (3727)	35.9 [34.4, 37.5]	51.1 [49.5, 52.8]	13.0 [11.9, 14.1]
ER+ve (3028)	34.1 [32.5, 35.9]	55.4 [53.6, 57.2]	10.4 [9.4, 11.6]
ER-ve (588)	43.9 [39.0, 48.0]	29.8 [26.1, 33.6]	26.4 [22.8, 30.1]
PR+ve (2671)	34.6 [32.8, 36.4]	55.9 [54.0, 57.8]	9.5 [8.4, 10.7]
PR-ve (945)	39.0 [35.9, 42.2]	38.0 [34.9, 41.2]	23.0 [20.3, 25.8]
ER or PR+ve (3086)	34.1 [32.4, 35.8]	55.2 [53.4, 57.0]	10.7 [9.6, 11.8]
ER/PR-ve (530)	45.3 [41.0, 49.6]	28.1 [24.3, 32.1]	26.6 [22.9, 30.6]
Triple negative (389)	61.7 [56.7, 66.6]	38.3 [33.4, 43.3]	Not applicable

1022 **Poster Discussion Session**

RC48-ADC, a HER2-targeting antibody-drug conjugate, in patients with HER2-positive and HER2-low expressing advanced or metastatic breast cancer: A pooled analysis of two studies. *First Author: Jiayu Wang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Currently, there are no standard ≥3 line regimens recommended for HER2-positive (IHC 3+, or IHC 2+/FISH+) advanced or metastatic breast cancer, and no recommended HER2-targeting treatment for HER2-low expressing (IHC 2+/FISH-, or IHC 1+) population. RC48-ADC is an innovative HER2-targeting antibody-drug conjugate with a cleavable linker and a potent microtubule inhibitor payload MMAE that has a bystanding effect in tumor cell killing. **Methods:** C001 CANCER (NCT02881138) was a dose-escalation phase I study (0.5, 1.0, 1.5, 2.0, and 2.5 mg/kg) with the 3+3 design among HER2-positive patients. C003 CANCER (NCT03052634) was a phase Ib study with 1.5, 2.0, and 2.5 mg/kg doses in the HER2-positive subgroup and 2.0 mg/kg dose in both IHC 2+/FISH-, and IHC 1+ HER2-low expressing subgroup. C003 CANCER is currently ongoing for IHC 1+ patients. Pooled analysis of the two studies was conducted for the efficacy and safety of RC48-ADC in HER2-positive or HER2-low expressing subgroups. **Results:** At the time of data cutoff (December 31, 2020), 118 female breast cancer patients were enrolled and treated with RC48-ADC. 70 patients (59.3%) were HER2-positive and 48 patients (40.7%) were HER2-low expressing. At baseline, 77 patients (65.3%) had liver metastases, 50 patients (42.4%) were ECOG PS 1, 47 patients (39.8%) had received ≥3 prior chemotherapy regimens. In the HER2-positive subgroup, ORRs for 1.5, 2.0, and 2.5 mg/kg doses were 22.2% (95% CI: 6.4%, 47.6%), 42.9% (95% CI: 21.8%, 66.0%), and 40.0% (95% CI: 21.1%, 61.3%). mPFSs for 1.5, 2.0, and 2.5 mg/kg cohorts were 4.0 months (95% CI: 2.6, 7.6), 5.7 months (95% CI: 5.3, 8.4) and 6.3 months (95% CI: 4.3, 8.8). In the HER2-low expressing subgroup, the ORR and mPFS were 39.6% (95% CI: 25.8%, 54.7%) and 5.7 months (95% CI: 4.1, 8.3). ORR and mPFS for IHC2+/FISH- patients were 42.9% (15/35) and 6.6 months (95% CI: 4.1, 8.5). For IHC1+ patients, even though the COVID-19 pandemic led to treatment postpone for some patients, ORR and mPFS reached 30.8% (4/13) and 5.5 months (95% CI: 2.7, 11.0). The common treatment-related adverse events (TRAEs) were AST increased (64.4%), ALT increased (59.3%), hypoesthesia (58.5%), white blood cell count decreased (48.3%), and neutrophil count decreased (47.5%); most were grade 1-2 in severity. Neutrophil count decreased (16.9%), GGT increased (12.7%), and fatigue (11.9%) were the grade 3 and above TRAEs occurring in ≥ 10% of the overall population. **Conclusions:** RC48-ADC showed consistent efficacy in HER2-positive and HER2-low expressing subgroups. The 2.0 mg/kg Q2W showed a more favorable benefit-risk ratio than other dose levels. No new safety signals were observed. Further studies are initiated to evaluate the efficacy and safety of RC48-ADC in various settings. Clinical trial information: NCT02881138; NCT03052634. Research Sponsor: Remegen.

1023 **Poster Discussion Session**

BEGONIA: Phase 1b/2 study of durvalumab (D) combinations in locally advanced/metastatic triple-negative breast cancer (TNBC)—Initial results from arm 1, d+paclitaxel (P), and arm 6, d+trastuzumab deruxtecan (T-DXd). *First Author: Peter Schmid, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom*

Background: Chemotherapy with immune checkpoint inhibitors can improve outcomes vs chemotherapy alone in patients (pts) with metastatic TNBC; however, many still have poor clinical outcomes. BEGONIA is an ongoing 2 part, multicenter, multiarm, open-label platform study evaluating safety and efficacy of D (anti–PD-L1)+P and D±P combined with novel therapies as first-line (1L) treatment for metastatic TNBC (NCT03742102). We report initial results from Part 1 of Arm 1, D+P, and Arm 6, D+T-DXd, an antibody-drug conjugate comprising an anti-HER2 antibody, tetrapeptide-based cleavable linker, and topoisomerase I inhibitor payload. **Methods:** Eligible pts had untreated unresectable locally advanced or metastatic TNBC. Pts with HER2-low–expressing tumors (IHC 2+/ISH–, IHC 1+/ISH–, or IHC 1+/ISH untested) per local testing were assigned to the D+T-DXd arm. Pts received D (1500 mg IV Q4W)+P (90 mg/m^2 IV Day 1, 8, 15 Q4W) in Arm 1 and D (1120 mg IV)+T-DXd (5.4 mg/kg IV) Q3W in Arm 6, until progression or unacceptable toxicity. Primary objectives are safety and tolerability. Secondary endpoints include objective response rate (ORR), duration of response (DoR), and progression-free survival (PFS). Tumors were assessed Q8W (D+P) or Q6W (D+T-DXd). The first 6 pts treated with D+T-DXd were evaluated for dose-limiting toxicities (DLTs), with additional pts enrolled if D+T-DXd was tolerated. Study arms are noncomparable due to differing eligibility criteria, treatments, and data maturity. **Results:** Arm 1 D+P (data cutoff Sep 2020): 23 pts received D+P (7 ongoing); 2 discontinued D+P due to AEs. Median follow-up time was 16.6 (range 8.5–19.8) mos. Any Grade 3/4 AEs and SAEs were experienced by 10 (44%) and 1 (4%) pts, respectively. D dose was delayed for 7 (30%) pts. Confirmed ORR was 13/23 (57%) with 54% of those remaining in response at 12 mos (median DoR not reached). Median PFS was 7.3 (95% CI 5.4–13.8) mos in the D+P arm. Arm 6 D+T-DXd (data cutoff Nov 2020): 11 pts received D+T-DXd to date (all ongoing). Median follow-up time was 2.3 (0–6) mos. Any Grade 3/4 AEs and SAEs were experienced by 4 (36%) and 1 (9%) pts, respectively. Pts who received D+T-DXd had no DLTs and 1 had a Grade 1 troponin increase. D dose was delayed and T-DXd dose reduced for 2 (18%) pts each. Confirmed ORR was 4/4 (100%; only 4 pts had the opportunity to complete 2 on-treatment disease assessments) with all 4 remaining in response at data cutoff (median DoR not reached). **Conclusions:** D+P demonstrated a tolerable safety profile and response rate as expected for a 1L TNBC IO/taxane combination. D+T-DXd showed promising early safety and efficacy in 1L HER2-low–expressing TNBC; pt evaluation and enrollment for D+T-DXd are ongoing. D+T-DXd data will be updated and the impact of PD-L1 expression in both arms will be examined. Clinical trial information: NCT03742102. Research Sponsor: AstraZeneca, Pharmaceutical/Biotech Company.

1024 **Poster Discussion Session**

Phase I study of A166 in patients with HER2-expressing locally advanced or metastatic solid tumors. *First Author: Xichun Hu, Department of Medical Oncology, Fudan University Cancer Hospital, Shanghai, China*

Background: A166 is an antibody-drug conjugate composed of a novel cytotoxic drug (Duo-5, anti-microtubule agent) site-specifically conjugated to an anti-HER2 antibody (transtuzumab) via a stable protease-cleavable valine citrulline linker. In a phase I trial in US patients (pts) with relapsed or refractory advanced solid tumor, A166 had an acceptable toxicity profile and best objective response rate (ORR) of 36% at efficacious dose levels (Yongheng Liu et al. ASCO 2020). Here we report a phase I study of A166 in Chinese pts with locally advanced or metastatic solid tumors (CTR20181301). **Methods:** KL166-I-01-CTP is a single arm, open-label, dose-escalation and dose-expansion phase I study evaluating A166 in pts with HER2-expressing locally advanced or metastatic solid tumors. Pts received A166 at doses of 0.1, 0.3, 0.6, 1.2, 2.4, 3.6, 4.8, 6.0 mg/kg IV Q3W. Dose cohorts were expanded at 4.8 and 6.0 mg/kg Q3W. The objectives were to determine the safety and tolerability, pharmacokinetics and antitumor activity of A166. **Results:** 57 pts (median age 53 [range 26-74], 50 female, 7 male) enrolled from Aug 1, 2018 to Nov 30, 2020. HER2 expression was available for all 57 pts: 51 HER2-positive (3+ or 2+/ISH+), 6 HER2-low (1+ or 2+/ISH-). 61.4% (35/57) had received ≥5 prior lines of therapy. No DLTs were observed in all dose groups. Any grade treatment-related AEs (TRAEs) were documented in 96.5% (55/57) of pts, with 31.6% (18/57) being grade 3 or higher. Common TRAEs were corneal epitheliopathy (73.7%), vision blurred (59.6%), peripheral sensory neuropathy (26.3%), dry eye (21.1%), anemia (19.3%), hyponatremia (19.3%). Most common grade ≥3 TRAEs were corneal epitheliopathy (17.5%), hypophosphatemia (5.3%), and dry eye (5.3%). Four pts had serious AEs, two of which were possibly related to the study drug, including thrombosis and fatigue. TRAEs led to 5.3% (3/57) dose reduction and 5.3% (3/57) treatment discontinuation. One death occurred during the treatment due to progressive disease. At the doses of 0.3-6.0 mg/kg, the exposure of ADC in serum were dose dependent and the mean half-life was found to be 1.17-11.04 days. Serum free toxins was about 0.1% and 0.2% of total A166 (ADC) on a molar basis with the Cycle 1 C_{max} and AUC, respectively. At efficacious dose, 36 HER2-positive breast cancer pts with measurable disease were assessed for efficacy, best ORR were 59.1% (13/22) and 71.4% (10/14) in 4.8 and 6.0 mg/kg cohort, respectively. Median progression-free survival (PFS) was not reached, and one patient in 4.8 mg/kg cohort has undergone the treatment for more than 19 months. **Conclusions:** A166 had a manageable safety profile and high stability in the circulation with much lower acute hematological and gastrointestinal toxicities in terms of incidence rate and grade. It demonstrated promising antitumor activity with clinically meaningful responses in heavily pretreated subjects with HER2-positive breast cancer. Clinical trial information: CTR20181301. Research Sponsor: Sichuan Kelun-Biotech Biopharmaceutical Co., Ltd.

1025 **Poster Session**

Serial circulating tumor DNA samples from patients with metastatic breast cancer and *BRCA1/2* mutations. *First Author: Katharine Collier, Division of Medical Oncology, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: Analysis of circulating tumor DNA (ctDNA) over time allows non-invasive evaluation of tumor genomic evolution. We characterize changes in tumor fraction (TFx), somatic copy number alterations (SCNAs), and somatic mutations (muts) over time in patients (pts) with *BRCA1/2* muts and metastatic breast cancer (mBC) who received a PARP inhibitor (PARPi) or platinum chemotherapy. Specifically, we seek to identify the frequency of *BRCA1/2* reversion muts. **Methods:** Pts with mBC and germline or somatic *BRCA1/2* muts were identified on a banking protocol of prospectively-collected serial samples of blood and plasma. Control pts without a *BRCA1/2* mut were matched 2:1 by age and hormone receptor (HR) status. Ultra-low-pass whole genome sequencing (ULPWGS) with 0.1x depth was performed on all plasma samples (n = 103) and the ichorCNA algorithm was used to determine TFx and SCNAs. Targeted panel sequencing (TPS) of 402 cancer-related genes was performed at 10,000x depth on plasma samples, and one blood sample per pt. The panel includes *BRCA1/2* and 38 other DNA damage repair (DDR) genes. Somatic muts were identified by joint calling with Mutect2 across plasma timepoints with paired pt normal blood. Germline variant calling from TPS on blood with HaplotypeCaller was used to confirm germline muts in *BRCA1/2*.**Results:** We identified 10 pts with mBC with a germline (n = 7) or somatic (n = 3) *BRCA1* (n = 2) or *BRCA2* (n = 8) mut and banked blood and plasma samples at 3-9 timepoints at a median of 8 weeks apart (range 1-43). The control cohort of 20 pts with mBC and wildtype *BRCA1/2* was well matched by age and HR status. All pts with *BRCA1/2* muts received a PARPi and/or platinum chemotherapy at some point during sample collection. Half of control pts received platinum chemotherapy. Germline *BRCA1/2* muts were confirmed in all 7 pts with known germline muts. Among the *BRCA1/2* mut cohort, median TFx was 0.04 (range 0-0.57) with 20% of samples having TFx > 0.10. A median of 1.5 (range 0-39) somatic muts per pt were found in DDR genes. Four pts (40%) had secondary non-reversion muts in *BRCA1/2*. A reversion mut of a germline *BRCA2* mut, restoring the open reading frame of *BRCA2*, was discovered at the last timepoint from 1 pt while receiving carboplatin. A germline *BRCA1/2* reversion mut in this cohort occurred in 2.3% of samples, 14.3% of pts. There was no significant difference in the percent of genome with a SCNA between the first and last time point, nor before and after PARPi/platinum. The somatic mut landscape and clonal evolution of TPS using PyClone will be presented. **Conclusions:** Evaluation of serial ctDNA samples for TFx, SCNAs, and somatic muts from banked plasma and blood from pts with mBC is feasible. The frequency of reversion muts in *BRCA1/2* was low, suggesting that either their incidence is low or ctDNA TPS is not sensitive enough to detect them. Secondary non-reversion muts in *BRCA1/2* and other somatic DDR muts were more common. SCNAs were stable over time. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health.

1026 **Poster Session**

Favorable prognostic factors of oligometastatic breast cancer: A subset analysis of OLIGO-BC1. *First Author: Kun Wang, Department of Breast Cancer, Cancer Center, Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: The Federation of Asian Clinical Oncology (FACO) conducted an international retrospective cohort study of oligometastatic breast cancer (BC) (OLIGO-BC1) (UMIN No.000030047). At ASCO2020, we demonstrated that locoregional and systemic therapy prolonged overall survival (OS) for patients with oligometastatic BC, especially for cases with some type of systemic therapy, younger age, ECOG performance status 0, stage I BC, non-triple negative subtype, fewer metastatic sites, local recurrence and longer disease-free interval from a multivariate analysis (#1025). Although BC is heterogeneous and a retrospective dataset has many kinds of bias, we attempted a subset analysis based on intrinsic subtype and several prognostic factors. **Methods:** Oligometastatic BC patients diagnosed from 2007 to 2012 were registered from CSCO, KSMO and JSCO. OS period was measured from the diagnosis of oligometastases to the latest follow-up. ER, PgR and HER2 status were determined by immunohistochemistry and/or in situ hybridization. A hazard ratio (HR) of OS was calculated by using a univariate analysis. **Results:** In 1200 eligible cases, one oligometastatic site was found in 578 cases, two in 289, three in 154, four in 102 and five in 77. Bone metastases were recorded in 301 cases, visceral metastases in 387, locoregional recurrence in 25, local recurrence in 83 and multiple metastatic sites in 404. Luminal subtype was recorded in 526 cases (44%), luminal-HER2 in 189 (16%), HER2 in 154 (13%), triple-negative in 166 (14%) and others in 165 (13%). In any subtype, locoregional and systemic therapy and ECOG performance status 0 were beneficial for OS. Stage I BC, one oligometastatic site and longer disease-free interval were also related to favorable prognosis in luminal and HER2 subtype. However, triple-negative subtype had no survival advantage with these 3 factors. On the other hand, pathological negative or micrometastatic lymph nodes at primary BC and one oligometastatic site of lymph node, lung, liver and bone were favorable prognostic factors. In addition, cases treated locally with surgical resection and conventional radiation therapy were expected to prolong OS. Discussions: Locoregional therapy for oligometastatic BC may be considered in luminal and HER2 subtype with some conditions. As reported in ASCO2020, triple-negative BC should be managed with systemic therapy. **Conclusions:** Oligometastatic BC is diagnosed by chance, but some cases seem to survive with multidisciplinary treatment. It is worthwhile to consider locoregional therapy in oligometastatic BC after evaluating favorable prognostic factors. Research Sponsor: The Federation of Asian Clinical Oncology.

1027 **Poster Session**

Refining neutropenia risk assessment in patients treated with first-line endocrine therapy (ET) and cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) for metastatic breast cancer (MBC) through a cell-free DNA workflow (cfDNA). *First Author: Lorenza Palmero, Department of Medical Area, University of Udine; Department of Medical Oncology, IRCCS, CRO of Aviano, Udine, Italy*

Background: The combination of ET and CDK4/6i is the current standard of care for hormone receptor (HR)-positive/HER2-negative MBC (luminal MBC), with neutropenia being the main dose limiting toxicity. We previously observed the potential association between leucocyte count (WBC) and different fractions of cell free circulating DNA (cfDNA) (Bortot et al 2020). The present study aimed to evaluate the feasibility of a cfDNA-based workflow as a new tool to assess the risk of treatment induced neutropenia. **Methods:** The study analyzed a prospective cohort 83 luminal MBC patients (pts) treated with first line ET and CDK4/6i in the CRO-2018-56 multicenter study from 2018 to 2021. cfDNA was characterized through droplet digital PCR (ddPCR) based on different *ACTB* DNA fragments lengths: short (s), medium (m) and long (l). Blood samples were collected before treatment start (BL) and at the first clinical evaluation after 3 months (E1). Associations between clinical characteristics, neutropenia and cfDNA were explored through Kruskal Wallis, time to G3 neutropenia (NG3) (TTN) was analyzed through log-rank and Cox regression. **Results:** Neutropenia was G3 in 44 out of 83 pts (53%) and G4 in 2 pts (2%). Median TTN was 1.8 months, 60% of NG3 occurred within 3.7 months. Overall, 74 pts (89%) resolved toxicity within 7 days, 10 pts (12%) reduced CDK4/6i dose after NG3. BL neutrophils count (Neu) and WBC were significantly lower in pts that developed NG3 (P = 0.0013 and P = 0.0020 respectively). *De novo* metastatic pts had numerically higher Neu (median 4825 vs 3895), but only a numerically lower risk of NG3 was observed (HR 0.53 P = 0.064). Although bone involvement was not associated with risk of developing NG3, the total number of metastatic lesions was associated with higher NG3 (P = 0.0016). In particular, > 5 metastatic lesions were associated with higher NG3 risk (p = 0.013). E1 *ACTB*_m was significantly lower with respect to BL in pts that experienced NG3 (median 100% vs 16%, P = 0.0136 in NG3 no vs yes) with a consistent impact on the risk of NG3 (HR: 2.81, P = 0.025). No associations were observed for the other *ACTB* fragment length fractions. BL Neu and *ACTB*_m dichotomized at the median were then combined to describe 4 distinct TTN risk groups (P = 0.0006). Interestingly, pts with low BL Neu and low E1 *ACTB*_m had a median TTN of 0.9 months, while pts with high BL Neu and high E1 *ACTB*_m have not experienced NG3 after a median follow-up of 16.1 months. **Conclusions:** The present study proofed the concept of using cfDNA to provide clinically meaningful data not only about tumor biology, but also for a comprehensive patient assessment. Based on these results, a prospective study focused on a multiparametric neutropenia risk assessment will be started. Research Sponsor: Ricerca Finalizzata Italian Ministry of Health.

1028 **Poster Session**

Identification of pathogenic *CDK12* alterations in cell-free DNA (cfDNA) from patients with breast cancer. *First Author: Mary Love Taylor, Duke University Medical Center, Durham, NC*

Background: Cyclin dependent kinase 12 (*CDK12*) has both tumor suppressive and proto-oncogenic potential in metastatic breast cancers (MBC). *CDK12* may be an important biomarker and target in MBC. However, a comprehensive genomic analysis of *CDK12* alterations from cfDNA in MBC has not been investigated and the genomic impact of *CDK12* alterations across the MBC spectrum is unknown. The purpose of this study was to identify the incidence of *CDK12* genomic alterations occurring in cfDNA from patients with MBC and elucidate which *CDK12* alterations may impact *CDK12* kinase activity. **Methods:** We queried 13,070 MBC samples from the Guardant Health database between April 2019 – November 2020 to identify the incidence of *CDK12* alterations detected in cfDNA. We classified each alteration type as: missense mutations, indels, or truncations. Amino acid changes occurring at conserved regions across multiple species were identified. Three-dimensional biochemical *in silico* analyses with ChimeraX were used to determine which *CDK12* alterations may impact *CDK12* kinase activity. To gain further biologic insights into *CDK12* altered MBC we made associations with *CDK12* alterations and co-occurring mutated genes. **Results:** Nonsynonymous *CDK12* alterations from the Guardant Health database were found in 317 samples from a cohort of 13,070 patients indicating an overall incidence of 2.43%. Alterations included: 239 (75.4%) missense mutations; 26 (8.2%) indels; and 52 (16.4%) truncations. We identified 62 alterations within the kinase domain with all occurring at highly conserved regions across species. The most frequent hotspot mutation identified was I76M/T, occurring in 11 unique breast cancers. Three-dimensional analyses indicate that *CDK12* alterations within the hinge, HRD, DFG, catalytic spine, and regulatory spine may impact *CDK12* kinase activity. The significantly co-occurring mutations from the Guardant Health breast cancer database in samples with *CDK12* alterations were *ARID1A, APC, RB1*, and *PTEN*. **Conclusions:** A modest incidence of *CDK12* genomic alterations occur in cfDNA from patients with breast cancer. Novel somatic alterations in *CDK12* were identified from Guardant Health that were not detected in the public domain. A portion of these occurred at highly conserved regions across species suggesting these specific *CDK12* mutations may impact *CDK12* kinase expression and be actionable therapeutic targets in breast cancers. Three dimensional analyses of the *CDK12* gene further illustrate which specific alterations may induce *CDK12* kinase expression or lead to inactivation. Co-occurring mutations reveal a unique genotype associated with *CDK12* alterations that may play a biologic role in *CDK12*-mediated breast cancer pathogenesis. Preclinical studies to determine the prognostic and therapeutic implication of *CDK12* alterations in MBC are warranted. Research Sponsor: METAvivor Early Career Investigator Award: Triangle Metsquerade Presented In Memory of Kristie Godwin Rolan.

1029 **Poster Session**

Characterization of long-term responders following treatment with talazoparib (TALA) or physician's choice of chemotherapy (PCT) in the phase 3 embraca trial. *First Author: Johannes Ettl, Department of Obstetrics and Gynecology, Klinikum rechts der Isar, Technische Universität München, Munich, Germany*

Background: In the EMBRACA trial (NCT01945775), the poly(ADP-ribose) polymerase inhibitor (PARPi) TALA significantly improved progression-free survival (PFS) versus PCT in patients (pts) with germline *BRCA1/2*-mutated HER2-negative locally advanced/metastatic breast cancer (BC) (8.6 vs 5.6 months [mo]; hazard ratio [HR, 95% CI] 0.54 [0.41-0.71]; $P < 0.0001$). Predictive markers for response to PARPi, other than germline *BRCA1/2* mutational status, are largely unknown. A previous analysis investigated biomarkers associated with long and short responders in EMBRACA. Here, we report the clinical characteristics of long and short responders. **Methods:** Pts were randomized 2:1 to TALA or PCT. In this retrospective analysis, pts in the intent-to-treat (ITT) population were mapped into two groups based on response: LONG (pts in TALA arm with overall survival [OS] ≥30 mo and duration of treatment ≥24 mo; pts in PCT arm with OS ≥30 mo); SHORT (pts in either arm with a PFS event [progressive disease by Independent Radiological Facility or death] ≤12 wks). Data cutoff date was Sept 30, 2019. **Results:** Of 431 pts randomized, 412 pts were treated (286 received TALA; 126 received PCT). In the ITT population, 37 pts receiving TALA and 34 pts receiving PCT were identified as LONG responders; 40 pts receiving TALA and 32 pts receiving PCT were SHORT responders. The Table shows a summary of pt characteristics for LONG and SHORT responders. More pts with HR+ BC and no prior CT for ABC were associated with LONG response; more pts with TNBC and ≥2 prior CT regimens or platinum were associated with SHORT response (Table). Median treatment duration for LONG responders (n = 37, TALA; n = 31, PCT) was 33.5 (24.0-61.4) mo for TALA and 7.6 (1.1-36.3) mo for PCT; 51.4% receiving TALA and 91.2% receiving PCT had subsequent therapy. In SHORT responders, median treatment duration was 2.0 (0.1-5.5) mo (TALA) and 1.4 (0.2-5.6) mo (PCT); 67.5% and 68.8% received subsequent therapy following TALA or PCT, respectively. **Conclusions:** In this clinical characterization of responders from the EMBRACA study, a higher number of LONG responders had HR+ BC and received no prior CT for ABC. A greater proportion of SHORT responders had TNBC and received ≥2 prior CT regimens or platinum. Further investigation is warranted in a larger number of pts. Clinical trial information: NCT01945775. Research Sponsor: Pfizer.

	TALA – LONG (n = 37)	PCT – LONG (n = 34)	TALA – SHORT (n = 40)	PCT – SHORT (n = 32)
Median age, y	50.0	50.5	42.5	45.5
No. (%)				
TNBC	17 (45.9)	10 (29.4)	25 (62.5)	20 (62.5)
HR+ BC	20 (54.1)	24 (70.6)	15 (37.5)	12 (37.5)
***BRCA1* status**	16 (43.2)	7 (20.6)	25 (62.5)	18 (56.3)
***BRCA2* status**	20 (54.1)	25 (73.5)	12 (30.0)	14 (43.8)
No prior CT for ABC	21 (56.8)	20 (58.8)	8 (20.0)	6 (18.8)
1 prior CT for ABC	12 (32.4)	8 (23.5)	14 (35.0)	13 (40.6)
≥2 prior CT for ABC	4 (10.8)	6 (17.6)	18 (45.0)	13 (40.6)
Prior platinum	5 (13.5)	4 (11.8)	11 (27.5)	10 (31.3)
Postbaseline olaparib	1 (2.7)	18 (52.9)	0	5 (15.6)

1030 **Poster Session**

Deep proteomic analysis of plasma exosomes in patients with advanced, hormone receptor-positive breast cancer treated with palbociclib and tamoxifen. *First Author: Xiuyuan Ma, University of Illinois at Chicago, Chicago, IL*

Background: Combining a CDK4/6 inhibitor (CDK4/6i) with endocrine therapy (ET) in advanced, hormone receptor (HR)-positive, HER2-negative breast cancer (BC) doubles median progression-free survival, but eventually drug resistance and disease progression occur. For most patients, the mechanism of resistance is unknown. Exosomes are membrane-bound extracellular vesicles that contain lipids, proteins, and nucleic acids, and are released from tumors as a form of intercellular communication. Exosomes can be recovered from plasma, and analysis of their cargo provides a dynamic read-out of biological pathways that are activated in cancer cells. Proteomic analysis of plasma exosomes may provide insight into mechanisms of resistance that emerge during treatment with CDK4/6i-ET. **Methods:** The Big Ten Cancer Research Consortium conducted a single arm, phase II trial of palbociclib plus tamoxifen as first line therapy for advanced, HR+/HER2- BC (NCT02668666). Whole blood was collected in Streck tubes from study participants (n = 49) at baseline, at disease progression, and at time points during study treatment. Plasma was separated and stored at -80C within 48 hours of collection. Exosomes were isolated from thawed plasma using commercially available kits and ultracentrifugation. Exosome extraction and purification was optimized for protein recovery. Purified exosomes were processed for proteomic analysis and labeled with TMT10 (tandem mass tag 10plex) and quantified with the QExactive HF mass spectrometer. Ultrasensitive mass spectrometry provided deep proteomic coverage of exosomal proteins and detected various post-translational modifications (PTM). Data were analyzed with a pipeline developed in our lab using an improved SEQUEST/ProLuCID database search engine and Percolator data filtering toolchain. Exosome protein expression was determined at baseline, at best response and at the time of progression. **Results:** With our ultrasensitive proteomic method, we detected more than 500 exosome proteins from as little as 100 ng of purified exosomes. A significant enrichment of exosome specific markers was observed when comparing patient samples with healthy donor samples. Enrichment of surface glycoproteins (e.g. CD44) was seen in BC patient samples, as in previous reports. Ultrasensitive proteomics also detected PTM including phosphorylation, methylation, oxidation, deamidation, and glycosylation. Differential proteomic and PTM profiles comparing samples collected from responding patients at baseline vs. at progression will be presented. **Conclusions:** Our innovative method provided an unparalleled portrait of the proteomic landscape of plasma exosomes during treatment with CDK4/6i-ET. This powerful approach may provide novel insights into mechanisms of resistance that emerge during treatment. This study was funded by Pfizer. Clinical trial information: NCT02668666. Research Sponsor: Pfizer, inc.

1031 **Poster Session**

A retrospective study of characteristics and survival in patients with breast cancer brain metastases classified by subtype using NCI SEER registry. *First Author: Monika Devanaboyina, The University of Toledo College of Medicine and Life Sciences, Toledo, OH*

Background: Breast cancer brain metastasis (BCBM) de novo is associated with the worst prognosis among all types of metastases in breast cancer (BC). Analysis of factors associated with BCBM stratified by subtype of BC could lead to earlier identification of metastasis. **Methods:** 1,268 patients with BCBM at the time of BC diagnosis and known clinical subtype (580 HR+/HER2-, 225 HR+/HER2+, 176 HR-/HER2+, and 287 HR-/HER2-) who were ≥ 20 years of age from 2010 to 2017 were identified using the NCI's Surveillance, Epidemiology, and End Results (SEER) Program 18 registry. Baseline characteristics and survival were analyzed using Chi-Square and Kaplan-Meier methods. **Results:** Patients with HR-/HER2+ BC were the most likely to present with BCBM, compared to all BC patients (prevalence of 13.9% vs. 4.7%; $p<0.001$). Further analysis demonstrated that HER2+ patients had an odds ratio of presenting with BCBM of 2.52 (95% CI: 2.24-2.84) compared to HER2- patients. Interestingly, in patients ages 20-39 with HR-/HER2+ BC, higher rates of brain metastases are noted within the BCBM group compared to all HR-/HER2+ breast cancer cases (28% vs. 7.6%; $p<0.001$). The same trend is seen within the HR-/HER2+ African American population, with those in the BCBM group experiencing higher rates of brain metastases compared to all BC cases with the same subtype (14.3% vs. 5.9%; $p<0.001$). Upon exploring insurance demographics, uninsured patients with HR-/HER2+ BCBM had much higher rates of brain metastases compared to all HR-/HER2+ BC cases (14.8% vs 6.4%; p=0.001). When examining TNM status, significant associations were noted between brain metastases and increased tumor and nodal status. Patients with T4 or N3 status with HR-/HER2+ BCBM exhibited much higher rates of metastasis compared to all BC cases with the same subtype ($p<0.001$). Analysis of survival outcomes showed a median overall survival of 12 months for patients with HR-/HER2+ BCBM. The results displayed in the table below show that HR-/HER2- BCBM patients had the lowest 5-year percent survival, while HR+/HER2+ BCBM patients had the highest 5-year survival. **Conclusions:** This SEER database study provides insight into the demographics, clinical variables, and outcomes for BC clinical subtypes, specifically HR-/HER2+, from 2010 to 2017 in the United States. HR-/HER2+ breast cancer patients within the noted high-risk populations should be made aware of the increased rates of brain metastases compared to the general BC population, as earlier identification of brain metastases within the HR-/HER2+ cohort could improve patient survival. Research Sponsor: None.

5-year percent survival analysis (95% CI).

	BCBM (n=1,413)	All BC (n=389,696)
HR+/HER2-	9.8 (6.9-13.3)	86.3 (86.2-86.5)
HR+/HER2+	21.9 (16.0-28.4)	85.6 (85.1-86.0)
HR-/HER2+	14.3 (8.5-21.5)	79.7 (79.0-80.4)
HR-/HER2-	3.6 (1.6-6.9)	71.9 (71.4-72.4)
All subtypes	**11.3 (9.2-13.6)**	**84.3 (84.1-84.4)**

1032 **Poster Session**

Overcoming the breast tumor microenvironment by targeting MDSCs through CAR-T cell therapy. *First Author: Saisha Abhay Nalawade, Baylor College of Medicine, Houston, TX*

Background: Successful targeting of solid tumors such as breast cancer (BC) using CAR T cells (CARTs) has proven challenging, largely due to the immune suppressive tumor microenvironment (TME). Myeloid derived suppressor cells (MDSCs) inhibit CART's function and persistence within the breast TME. We generated CAR T cells targeting tumor-expressed mucin 1 (MUC1) (Bajgain P et al, 2018) for BC. To potentiate expansion and persistence of MUC1 CARTs and modulate the suppressive TME, we developed a novel chimeric co-stimulatory receptor, TR2.4-1BB, encoding a ScFv derived from a TNF-related apoptosis-inducing ligand receptor 2 (TR2) mAb followed by a 4-1BB endodomain. We hypothesize that engagement with TR2 expressed on TME-resident MDSCs, will lead to both MDSC apoptosis and CART co-stimulation, promoting T cell persistence and expansion at tumor site. **Methods:** Function of the novel TR2.4-1BB receptor, was assessed by exposing non-transduced (NT) and TR2.4-1BB transduced T cells to recombinant TR2 and nuclear translocation of NFκB was measured by ELISA. Functionality of in vitro generated MDSCs was determined by the suppression assay. In vitro CART/costimulatory receptor T cell function was measured by cytotoxicity assays using MUC1+ tumor targets in presence or absence of MDSCs. In vivo anti-tumor activity was assessed using MDSC enriched tumor-bearing mice using calipers to assess tumor volume and bioluminescence imaging to track T cells. **Results:** Nuclear translocation of NFκB was detected only in TR2.4-1BB T cells. MDSCs significantly attenuated T cell proliferation by 50±5% and IFNγ production by half compared with T cells cultured alone. Additionally, presence of MDSCs, diminished cytotoxic potential of MUC1 CARTs against MUC1+ BC cell lines by 25%. However, TR2.4-1BB expression on CAR.MUC1 T cells induced MDSC apoptosis thereby restoring the cytotoxic activity of CAR.MUC1 against MUC1+ BC lines in presence of TR2.4-1BB (67±8.5%). There was an approximate two-fold increase in tumor growth due enhanced angiogenesis and fibroblast accumulation in mice receiving tumors + MDSCs compared to tumors alone. Treatment of these MDSC-enriched tumors with MUC1.TR2.4-1BB CARTs led to superior tumor cell killing and significant reduction in tumor growth (24.54±8.55 mm^3) compared to CAR.MUC1 (469.79.9±81.46mm^3) or TR2.4-1BB (434.86±64.25 mm^3) T cells alone (Day 28 after T cell injection). The treatment also improved T cell proliferation and persistence at the tumor site. Thereby, leading to negligible metastasis demonstrating ability of CARTs to eliminate tumor and prevent dissemination. We observed similar results using HER2.TR2.4-1BB CARTs in a HER2+ BC model. **Conclusions:** Our findings demonstrate that CARTs co-expressing our novel TR2.4-1BB receptor have higher anti-tumor potential against BC tumors and infiltrating MDSCs, resulting in TME remodeling and improved T cell proliferation at the tumor site. Research Sponsor: CPRIT (Cancer Prevention and Research Institute of Texas).

1033 **Poster Session**

Uncovering the differential impact of *ESR1* and *PIK3CA* codon variants on the clinical phenotype of metastatic breast cancer (MBC) through circulating tumor DNA (ctDNA) next-generation sequencing (NGS). *First Author: Lorenzo Gerratana, Department of Medicine-Hematology and Oncology, Feinberg School of Medicine, Northwestern University; Department of Medicine (DAME), University of Udine, Chicago, IL*

Background: The exposure to endocrine therapy (ET) can induce the onset of *ESR1* gene alterations that have an impact on not only treatment resistance but also clinical phenotype. We previously demonstrated the potential of liquid biopsy in describing the metastatic behavior of MBC. The aim of this study was to explore the different clinical phenotype across the main *ESR1* and *PIK3CA* codon variants. **Methods**: The study retrospectively analyzed a cohort of 501 MBC patients (pts) characterized for ctDNA through NGS before treatment start at Northwestern University (Chicago, IL), Massachusetts General Hospital (Boston, MA), CRO National Cancer Institute (Aviano, IT) and ASUFC Hospital (Udine, IT) between 2014 and 2020. Associations between clinical characteristics and *ESR1* and *PIK3CA* codon variants were explored through logistic regression corrected for sites and *ESR1*/*PIK3CA* status. Survival was tested through Cox regression both for progression-free survival (PFS) and overall survival (OS). **Results**: Of the total 501 pts, 289 (58%) were diagnosed with hormone-receptor positive (HRpos) MBC, 114 (23%) with HER2-positive MBC, and 93 (19%) with triple-negative MBC. *ESR1* mutations were detected in 71 pts (14%) and *PIK3CA* in 154 pts (31%). The most represented *ESR1* gene mutations were found in codons 380 (9%), 536 (23%), 537 (34%), and 538 (34%), while alterations in codons 542 (19%), 545 (21%), and 1047 (60%) were the most common for *PIK3CA*. As expected, *ESR1* mutations were found only in HRpos pts previously exposed to ET ($P < 0.001$). No significant differences were observed for *PIK3CA*. After multivariable analysis, *ESR1*mutations were confirmed as highly associated with liver and bone metastases (OR 3.31, $P < 0.001$ and OR 5.09, $P < 0.001$). Moreover, an association with lung (OR 2.07, $P = 0.010$) was observed in this cohort. After multivariable analysis, codon 537 mutations were associated with bone involvement (OR 12.97, $P = 0.014$), codon 538 with liver (OR 4.73, $P = 0.010$), and codon 536 with soft tissue (OR 5.84, $P = 0.006$) and liver (OR 4.06, $P = 0.048$). *PIK3CA* mutations were associated with bone (OR 2.61, $P < 0.001$) and lung metastases (OR 1.62, $P = 0.044$). Specifically, codon 1047 mutations were the primary driver (OR 3.14, $P = 0.001$ and OR 1.97, $P = 0.019$). In HRpos MBC, baseline mutations in *ESR1* codon 537 and 538 had a negative impact on OS (HR 3.73, $P < 0.010$ and HR 2.99, $P < 0.021$), while 380 and 536 had a negative impact on PFS (HR 18.98, $P < 0.001$ and HR 2.60, $P = 0.015$). No impact was observed across *PIK3CA* gene variants. **Conclusions**: This study showed the different tumor biology across *ESR1* and *PIK3CA* gene variants. As novel selective estrogen receptor degraders (SERDS) and *PIK3CA* inhibitors are gaining momentum as new ET options in MBC, these results highlight the future pivotal role of ctDNA NGS in refining tumor biology characterization. Research Sponsor: Lynn Sage Breast Cancer Foundation, OncoSET, Ricerca Finalizzata - Italian Ministry of Health.

1034 **Poster Session**

Molecular characterization of the Ras-MAPK pathway in metastatic breast cancer. *First Author: Justin Wayne Wong Tiu-Iim, USC Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: The Ras-MAPK pathway is a known driver of tumorigenesis and therapeutic target in a variety of cancers. Alterations in this pathway have been linked to decreased tumor immunogenicity. However, molecular alterations in the Ras-MAPK are rare in breast cancer (BC) and their clinical implications remain unclear. As mutational status does not accurately correlate with transcriptional activity, a MAPK pathway activity score (MPAS, Wagle et al., 2018, npj Precision Medicine) is indicative of MAPK activation and correlates with response to MEK (MEKi) or BRAF inhibition (BRAFi). Our goal was to determine the frequency of molecular alterations in the Ras-MAPK and correlate to MAPK pathway activation in MBC. **Methods:** A total of 6464 BC samples underwent comprehensive molecular profiling at Caris Life Sciences. Analyses included next generation sequencing of DNA (592 Gene Panel, NextSeq; whole exome sequencing, NovaSEQ), RNA (NovaSeq, whole transcriptome sequencing, WTS) and IHC. MPAS and immune cell fraction (ICF, Quantiseq) were assessed by mRNA analysis. Wilcoxon, Fisher's exact, or Dunnett's test was used. All results shown were statistically significant ($p < 0.05$). **Results:** The predominant alteration of RAS genes was mutation followed by amplification, no fusions were detected (Table). Only 0.17% of all tumors harbor KRAS G12c mutations. The highest MPAS scores were found in KRAS mutants (mut), HRAS mut (Q61, G1213), BRAF V600 (class 1) mut and NRAS Q61 mut (Table) and therefore used to define Genomic MAPK Activated Tumors (GMAT). GMAT compared to wild type (WT) had significantly higher PD-L1 expression, TMB and MSI/dMMR. GMAT had less B cells (3.4% vs 4.4%), more M1 Macrophages (4.4% vs 3.4%) and neutrophils (5.5% vs 2.7%) regardless of HR status but less NK cells (2.3% s 3.0%), MSDCs (0.9% vs 3.0%) only in HR- tumors with respect to WT. GMAT tumors showed more frequent mutation rate (mr) of PIK3CA (HR+: 57.3% vs 40%; HR-: 41.9% vs 17.9%). HR+ tumors had a higher mr of MSH3 (11.8% vs 0.6%) while HR- tumors had higher mr of PIK3R1 (9.6% vs 3.8%), RhoA (5.3% vs 0.5%), DNA repair genes (TERT, 18.2% vs 1.0%; ARID1A, 18.2% vs 5.9%; PRKDC, 3.9% vs 0) and lower TP53 mr (54.5% vs 85.8%) compared to WT. **Conclusions:** Our study demonstrates that RAS, BRAF and MEK1 mutations are associated with MAPK pathway activation indicative of benefit from MEKi or BRAFi. GMAT warrant further investigation for combinations targeting the RAS-MAPK pathway and immune checkpoint inhibitors. Research Sponsor: U.S. National Institutes of Health.

Ras-MAPK pathway mutations and MPAS in the BC cohort.

	KRAS				NRAS				MEK1	
	Q61	G1213	other	CNV	Q61	G1213	other	CNV	Mut	CNV
N (%)	6 (0.10)	71 (1.15)	16 (0.26)	47 (0.78)	3 (0.05)	5 (0.08)	8 (0.13)	–	3 (0.05)	8 (0.13)
MPAS	2.16	1.31	0.99	0.52	3.56	0.65	-0.65		1.21	0.52
p	<0.0001			0.39	0.1				0.74	

	HRAS				BRAF					
	Q61	G1213	other	CNV	class1	class2	class3	Other	CNV	WT
N (%)	10 (0.16)	18 (0.29)	25 (0.40)	–	13 (0.21)	6 (0.10)	9 (0.15)	4 (0.06)	4 (0.06)	4173
MPAS	3.52	1.55	-0.18		2.49	-0.66	0.04	-0.44	-0.44	-0.1
p	<0.0001				<0.0001					

1035 **Poster Session**

Cyclin-dependent kinase 4/6 (CDK4/6) inhibitor SHR6390 combined with pyrotinib and letrozole in patients with human epidermal growth factor receptor 2-positive (HER2+), hormone receptor positive (HR+) metastatic breast cancer (MBC): Phase Ib study results. *First Author: Jian Zhang, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: The combining of HER2 targeted therapy and endocrine therapy (ET) has been demonstrated to be a reasonable therapeutic approach and recommended for highly selected patients (pts) with HR+/HER2+ MBC. CDK4/6 inhibitors could sensitize HER2 targeted therapies in multiple patient-derived xenograft models and delay tumor recurrence in a transgenic model of HER2+ breast cancer. The aim of this phase Ib/II study was to investigate the safety and efficacy of adding a CDK 4/6 inhibitor to the combination. Primary phase Ib results were reported. **Methods:** Patients with HR+/HER2+ MBC who were eligible for first- or second-line treatment were enrolled, and orally received letrozole, pyrotinib, and a novel CDK4/6 inhibitor SHR6390. In the "3+3" dose-exploring phase, letrozole was given at a fixed dose of 2.5mg/d. Pyrotinib and SHR6390 were initially given at a dose of 400mg/d and 125 mg/d respectively (Level $_{I}$). If the initial dose level could be tolerated, subsequent pts were assigned to the higher level (Level $_{H}$) with pyrotinib 400 mg/d and SHR6390 150mg/d; otherwise, simultaneously to Level $_{L1}$ with pyrotinib 400 mg/d, and SHR6390 100 mg/d, or Level $_{L2}$ with pyrotinib 320mg/d, and SHR6390 125 mg/d. Primary endpoints of phase Ib included dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), safety and efficacy. **Results:** As of 4 Jan 2021, a total of 15 pts (Level $_{I}$ 5 pts, Level $_{L1}$ 6 pts, and Level $_{L2}$ 4 pts) were enrolled in phase Ib and received the study treatment. 6 of them had received systemic therapies in the advanced stage, and 10 of them had been previously treated with trastuzumab. The most frequent grade 3/4 adverse events included neutrophil count decreased (n = 6), white blood cell count decreased (n = 4), stomatitis (n = 4) and diarrhea (n = 3). 3 pts (2 in Level $_{I}$, and 1 in Level $_{L1}$) had experienced DLTs, all of which were grade 3 stomatitis. Of the 15 pts evaluable for response, 7 pts (46.7%) had achieved confirmed partial responses (1 in Level $_{I}$, 3 in Level $_{L1}$, and 3 in Level $_{L2}$) and 7 pts (46.7%) had stable disease. Based on DLTs and clinical efficacy, pyrotinib 320mg/d, SHR6390 125mg/d, and letrozole 2.5mg/d was declared as RP2D. **Conclusions:** Data from phase Ib showed the triplet combination of pyrotinib, letrozole, and SHR6390 had an acceptable safety profile and encouraging preliminary efficacy, potentially offering a chemotherapy sparing treatment option for patients with HR+/HER2+ MBC. Enrollment on phase II is ongoing. Clinical trial information: NCT03772353. Research Sponsor: None.

1036 **Poster Session**

Concordance of HER2+ status by IHC/ISH and *ERBB2* status by NGS in a real-world clinicogenomic database and analysis of outcomes in patients (pts) with metastatic breast cancer (mBC).

First Author: Cheryl D. Cho-Phan, Flatiron Health, San Francisco, CA

Background: HER2 overexpression/amplification measured by IHC or ISH is a predictive biomarker for HER2-targeted therapies. Next-generation sequencing (NGS) can identify *ERBB2* amplification (amp) and mutations. We examined clinical characteristics, NGS testing patterns, and outcomes of pts treated with 1L HER2 therapy with HER2+ mBC based on *ERBB2* amp status using a real-world (RW) clinico-genomic database (CGDB). **Methods:** Pts with mBC (HER2+ by IHC and/or ISH) treated with 1L HER2 therapy who had undergone NGS and were treated within the Flatiron Health (FH) network were eligible. Clinical characteristics and HER2 testing results were obtained via technology-enabled abstraction of clinician notes and radiology/pathology reports and linked to genomic data from Foundation Medicine (FMI) in the nationwide (US-based), de-identified FH-FMI CGDB. Demographic, clinical and genomic characteristics were summarized and stratified by concordance between HER2+ (IHC 3+ or ISH amp+) and *ERBB2*amp+ status [copy number (CN) ≥ 5]. NGS testing patterns and 1L HER2 therapy were characterized and stratified by concordance status. Concordance was assessed based on contemporaneous timing of paired test specimen collection dates (FMI NGS ≤ 30 days of HER2+ status). RW overall survival (rwOS) stratified by HER2+/*ERBB2* amp concordance was estimated with Kaplan-Meier analysis and adjusted Cox proportional hazards models. **Results:** Among 268 eligible pts, HER2+/*ERBB2*amp+ concordance was 66% (176/268); concordance among contemporaneous paired specimens was 73% (106/145). Demographic and clinical features were overall well-balanced with most pts treated at community sites [94%, (252/268)]; the discordant (HER2+/*ERBB2*amp-) group (95/268) had more pts with hormone receptor positive disease (73% vs 62%). Concordance by assay type varied; IHC+ only, IHC+/ISH+, and ISH+ only agreement was 72% (95/132), 76% (26/34) and 52% (50/96), respectively. A higher proportion of discordance (35% vs 19%) was seen in pts treated at community vs. academic sites. Median rwOS was 32.9 months (IQR 25.9-38.9) among concordant (HER2+/*ERBB2*amp+) and 15.5 months (IQR 8.9-30.1) among discordant (HER2+/*ERBB2*amp-) pts, aHR = 0.71 [95% CI: 0.48-1.03; p = 0.073]. **Conclusions:** Among RW pts with HER2+ mBC receiving 1L HER2 therapy, discordance between *ERBB2*amp and IHC/ISH HER2 testing methods was observed. Pts with tumors HER2+ by IHC and/or ISH but negative for *ERBB2*amp had a trend towards worse rwOS following receipt of HER2 therapy compared to concordant cases. Contemporaneous timing of specimen collection was associated with greater concordance. Future analyses on the additive value of *ERBB2* CN as a predictive marker, and assessing factors that may affect discordance such as intratumor HER2 heterogeneity, tumor content, and biopsy site are warranted. Research Sponsor: None.

1037 **Poster Session**

Pyrotinib plus capecitabine for HER2-positive metastatic breast cancer patients with brain metastases (PERMEATE): A multicenter, single-arm phase II study.

First Author: Min Yan, Breast Cancer Center, Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, Henan, China

Background: HER2-positive metastatic breast cancer (BC) has a high risk of brain metastases (BM), leading to poor survival. Small molecule tyrosine kinase inhibitor (TKI) with enhanced penetrability to the blood brain barrier combined with capecitabine have demonstrated promising clinical outcomes in HER2-positive metastatic BC patients with untreated (such as lapatinib) or previously treated (such as neratinib) BM. The randomized phase III PHOEBE trial has proved better efficacy of pyrotinib, an irreversible pan-HER receptor TKI, versus lapatinib when in combination with capecitabine in HER2-positive local relapsed or metastatic BC. This study was conducted to investigate the efficacy and safety of pyrotinib plus capecitabine in HER2-positive metastatic BC patients with BM. **Methods:** In this multicenter phase II trial (NCT03691051), eligible patients received pyrotinib 400 mg orally once daily without breaks and capecitabine 1000 mg/m^2 orally twice daily for 14 days followed by 7 days off. Treatment was continued until disease progression or intolerable toxicity. Prior HER2 TKIs were not allowed. Cohort A included patients with radiotherapy-naive BM, and cohort B included those with progressive BM after whole brain radiotherapy or stereotactic conformal radiotherapy. The primary endpoint was confirmed central nervous system (CNS) objective response rate (ORR), as assessed according to the Response Evaluation Criteria In Solid Tumors version 1.1. **Results:** Between January 2018 and July 2020, a total of 78 female patients were included (Table). For cohort A (n = 59), the CNS ORR was 74.6% (95%CI: 61.6%-85.0%). For cohort B (n = 19), the CNS ORR was 42.1% (95%CI: 20.3%-66.5%). By the cutoff date on 25 January 2021, the median progression-free survival was 12.1 months (95%CI: 9.0-14.7) in cohort A and 5.6 months (95%CI: 3.4-10.7) in cohort B. The most common grade ≥3 adverse events were diarrhea (23.1% [18/78]), neutrophil count decreased (12.8% [10/78]), white blood cell count decreased (12.8% [10/78]), anemia (9.0% [7/78]), hand-foot syndrome (7.7% [6/78]), hypertriglyceridemia (6.4% [5/78]), and hypokalemia (5.1% [4/78]). **Conclusions:** Pyrotinib plus capecitabine resulted as an effective and safe treatment for HER2-positive BC patients with radiotherapy-naive BM, but the efficacy was modest in those with radiotherapy-treated BM. Clinical trial information: NCT03691051. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

	Cohort A (n = 59)	Cohort B (n = 19)
Age (years), median (range)	49 (31-67)	47 (33-68)
Prior trastuzumab, n (%)	53 (89.8)	18 (94.7)
Prior brain surgery, n (%)	2 (3.4)	0
Best central nervous system response, n (%)		
Complete response	9 (15.3)	1 (5.3)
Partial response	35 (59.3)	7(36.8)
Stable disease	11 (18.6)	4 (21.1)
Progressive disease	2 (3.4)	5 (26.3)
Not evaluable	2 (3.4)	2 (10.5)

1038 **Poster Session**

Safety and unique pharmacokinetic profile of ARX788, a site-specific ADC, in heavily pretreated patients with HER2-overexpresing solid tumors: Results from two phase 1 clinical trials.

First Author: Sara A. Hurvitz, David Geffen School of Medicine, University of California, Los Angeles/ Jonsson Comprehensive Cancer Center, Los Angeles, CA

Background: ARX788 is a site-specific, homogeneous, and highly stable ADC. The payload AS269 is conjugated to the synthetic amino acids para-acetylphenylalanine (pAF) in a humanized anti-HER2 mAb. ARX788 demonstrated promising activity in HER2-positive, HER2-low, and T-DM1 resistant tumors in preclinical studies. Here we present the phase 1 clinical data evaluating the safety, antitumor activity, and PK of ARX788 in advanced solid tumors. **Methods:** The standard 3+3 design (0.33 - 1.5 mg/kg; Q3W or Q4W) is used to determine the MTD and/or RP2D in two phase 1 studies in HER2-positive solid tumors in U.S. and Australia (ACE-Pan tumor-01) and in HER2-positive breast cancers in China (ACE-Breast-01). The efficacy endpoints include ORR and DCR. Intensive PK sampling in first 3 cycles is performed to characterize serum PK profiles of ARX788, total Ab, and pAF-AS269. **Results:** 69 and 34 heavily pretreated patients received ARX788 monotherapy in the ACE-Breast-01 (median 6 prior lines of therapy) and ACE-Pan tumor-01 trial (including breast, gastric/GEJ, NSCLC, ovarian, urothelial, biliary track, endometrial, and salivary gland cancer) respectively. Dose escalation for both studies have been completed with no DLT reported. MTD has not been reached. ARX788 was generally well tolerated with most AEs being grade 1 or 2. The most common grade >3 AEs include ocular AEs (5.7 %) and pneumonitis (4.3%) in the ACE-Breast-01 trial; pneumonitis (2.9%) and fatigue (2.9%) in the ACE-Pan tumor-01 trial. Low systemic toxicities in terms of the incidence rate and grade (as shown in table). No treatment-related death. In the 1.5 mg/kg cohort, ORR was 74% (14/19) and 67% (2/3) for ACE-Breast-01 and ACE-Pan tumor-01, respectively. DCR was 100%. Median DOR or median PFS has not been reached. PK profiles for total antibody and ARX788 were generally comparable across all dose levels. Mean T1/2 for ARX788 and total antibody had approximately 100 hours at the dose of 1.5 mg/kg. Serum pAF-AS269 concentrations peaked with a median time of 168 h. Serum exposure of pAF-AS269 was low with the Cmax and AUC at cycle 1 being approximately 0.1% and 0.18% of those for ARX788 on a molar basis, respectively. **Conclusions:** High stability of ARX788 and low serum exposure of pAF-AS269 may underlie the low systemic toxicity, which differentiates it from other ADCs. Clinical trial information: NCT032550070. Research Sponsor: Ambrx, Inc.

Low Systemic toxicity of ARX788.

	ACE-Breast-01 (N=69)		ACE-Pan tumor-01 (N=34)	
n,%	All Grades	Grade 3 or 4	All Grades	Grade 3 or 4
Nausea/ Vomiting	3 (4.3)/4 (5.8)	0/0	5 (14.7)/2 (5.9)	0/0
Constipation/ Diarrhea	6 (8.7)/3 (4.3)	0/0	5 (14.7)/6 (17.6)	0/0
Neutropenia	14 (20.3)	0	1 (2.9)	0
Decreased WBC	12 (17.4)	0	1 (2.9)	0
Thrombocytopenia	9 (14.3)	1 (1.4)	3 (8.8)	0
Anemia	6 (8.7)	0	4 (11.8)	0
Fatigue	20 (29.0)	0	12 (35.3)	1 (2.9)
Neuropathy	0	0	2 (5.9)	0

1039 **Poster Session**

Safety of trastuzumab emtansine (T-DM1) in patients (pts) with HER2-positive locally advanced or metastatic breast cancer (mBC): Final results from KAMILLA Cohorts 1 (global) and 2 (Asia).

First Author: Rachel Wuerstlein, University Hospital Munich, Department of Obstetrics and Gynecology, Breast Center and CCC Munich, LMU, Munich, Germany

Background: KAMILLA is an open-label, single-arm, phase 3b safety study of T-DM1 in pts with HER2-positive advanced BC (NCT01702571). The treated (safety) population of KAMILLA comprises 2 cohorts: a larger global Cohort 1 (n=2002) and a smaller Asia Cohort 2 (n=181 [China, n=154; Thailand, n=15; Indonesia, n=12]). Here we report results from Cohort 2 in the context of those previously reported for Cohort 1. **Methods:** Pts had HER2-positive, locally advanced or mBC with progression after chemotherapy and anti-HER2 therapy or ≤6 months (mo) of completing adjuvant therapy. T-DM1 3.6 mg/kg was given intravenously every 3 weeks until disease progression, consent withdrawal, or unacceptable toxicity. Primary endpoints were grade ≥3 (G≥3) adverse events of primary interest (AEPIs), specifically hepatic events, allergic reactions, thrombocytopenia (TCP), and hemorrhage events; all other G≥3 treatment-related AEs (TRAEs); and all-grade pneumonitis. **Results:** As of 31 July 2019,KAMILLA enrolled 2185 pts (Cohort 1, n=2003; Cohort 2, n=182), of which 2002 and 181 in each cohort, respectively, received ≥1 study dose and were included in the safety population. Baseline characteristics were generally similar between cohorts. Median (range) T-DM1 exposure was 5.6 mo (0–46) for Cohort 1 and 5.0 mo (0–31) for Cohort 2. The overall G≥3 AEPI rate was higher in Cohort 2 vs Cohort 1 (Table), mostly driven by a higher G≥3 TCP rate in Cohort 2. In Cohort 2, G≥3 TCP (the most frequently reported G≥3 AEPI) did not appear to be associated with G≥3 hemorrhagic events — the majority of G≥3 TCP events (128/138) fully resolved, with a duration of ≤15 days for 98/138 of these events. G≥3 TRAE rates were 18.4% in Cohort 1 and 48.6% in Cohort 2, the latter mainly due to TCP and platelet count decreased; any-grade pneumonitis rates were 1.0% and 2.2%, respectively. No other safety signals were identified. Median progression-free survival and overall survival were similar for both cohorts (Table). **Conclusions:** These data confirm prior observations in an Asian subgroup of the phase 3 EMILIA trial of T-DM1 in pts with previously treated mBC. Although the G≥3 TCP rate was higher in the Asia cohort, the majority of these events resolved fully. OS and PFS were similar in both cohorts. These data reinforce the favorable T-DM1 benefit-risk profile in mBC. Clinical trial information: NCT01702571. Research Sponsor: F. Hoffmann-La Roche/Genentech.

	Cohort 1 (Global; n = 2002)	95% CI	Cohort 2 (Asia; n = 181)	95% CI
G≥3 AEPIs, n (%)	462 (23.1)	21.2, 25.0	93 (51.4)	43.9, 58.9
Hepatic events	139 (6.9)	5.9, 8.1	22 (12.2)	7.8, 17.8
Allergic reactions	46 (2.3)	1.7, 3.1	2 (1.1)	0.1, 3.9
TCP	74 (3.7)	2.9, 4.6	66 (36.5)	29.5, 43.9
Hemorrhage events	46 (2.3)	1.7, 3.1	3 (1.7)	0.3, 4.8
Any-grade pneumonitis, n (%)	21 (1.0)	0.7, 1.6	4 (2.2)	0.6, 5.6
G≥3 TRAEs, n (%)	368 (18.4)	16.7, 20.1	88 (48.6)	41.1, 56.1
Median PFS, mo	6.8	5.8, 7.6	5.7	5.5, 7.0
Median OS, mo	27.2	25.5, 28.7	29.5	21.1, non-estimable

1040 **Poster Session**

Comparison of therapy benefit from standard anti-HER2 directed approaches in metastatic breast cancer (MBC) between initially HER2-positive patients and patients initially HER2-negative with switch to HER2-positive. *First Author: Hans-Christian Kolberg, Marienhospital, Bottrop, Germany*

Background: Metaanalyses have demonstrated that 5% of initially HER2 negative breast cancer patients switch to HER2 positive during the course of the disease. Whether there is a difference in benefit from standard HER2 targeted therapies between patients initially HER2 positive and patients switching from negative to positive is unclear. We used data from the PRAEGNANT registry to compare the outcome of those patients. **Methods:** PRAEGNANT is a prospective advanced breast cancer registry (NCT02338167) focusing on molecular biomarkers. Patients in all therapy lines receiving any kind of treatment are eligible. This analysis compared progression-free survival (PFS) with standard HER2 targeted therapies between patients with tumors initially HER2 negative and switched to HER2 positive and patients with tumors that were initially HER2 positive adjusted for age and hormone receptor status. **Results:** At the time of this analysis 4061 patients with MBC were included in the PRAEGNANT registry, 49 of which met the requirements for this analysis. Median age was 56 (IQR 48-64) years and 87.8% of the patients were hormone receptor positive. At first diagnosis 15 patients were HER2 negative and 34 patients were HER2 positive. Within a median observation time of 9 months (95%CI: 3.8, 23.7) 35 PFS events occurred. Median observation time was 9 months (95% CI: 3.8, 23.7). Initially HER2 positive patients had a longer progression-free survival (HR = 0.49, 95% CI (0.24, 1.03), p = 0.07) as compared to initially HER2 negative patients switched to HER2 positive. The 1- and 2-year-PFS rates were also higher for patients initially HER2 positive: 1-year-PFS: 52% (95% CI: 36%, 73%) versus 26 % (95% CI: 12%, 52%); 2-year-PFS: 44% (95% CI: 29%, 67%) versus 19% (95% CI: 7%, 50%). **Conclusions:** Median PFS and 1- and 2-year PFS rate seem to be better in patients HER2 positive at initial diagnosis receiving standard HER2 directed therapies. Although our result has to be interpreted with caution because of the small cohort and the retrospective nature of our analysis, it justifies prospective research including the group of initially HER2 negative patients switched to HER2 positive as a distinct entity. Clinical trial information: NCT02338167. Research Sponsor: None.

1041 **Poster Session**

Impact of extracranial disease status on survival after initial central nervous system (CNS) involvement and radiation therapy in HER2+ breast cancer brain metastases (BCBM). *First Author: Laura Noteware, Duke University School of Medicine, Durham, NC*

Background: BCBMs are very common in metastatic HER2+ breast cancer. CNS-directed local therapy is the gold standard for treatment, followed by systemic HER2-targeted therapies. In patients with HER2+ BCBM and stable extracranial disease (ECD), consensus guidelines recommend continuing current systemic therapy after local therapy. Our goal was to determine the implications of ECD status at time of HER2+ BCBM first CNS involvement on outcomes including intracranial progression-free survival (PFS1) and overall survival (OS). **Methods:** Retrospective analysis was performed on data extracted from 77 patients with HER2+ BCBM who received CNS radiation at Duke between 2006 and 2020 following initial documentation of CNS involvement. Demographics, dates of metastatic and intracranial diagnosis, ECD status at first CNS involvement, systemic therapy, and outcomes were collected. The primary endpoint was PFS1 defined as the time from first CNS radiation to the subsequent documentation of intracranial progression (RANO-BM). OS was defined as time from first CNS radiation and first metastatic disease to date of death or last known alive. ECD status was defined by RECIST1.1 from systemic staging scans within 30 days of first CNS involvement. **Results:** In this patient cohort of HER2+ BCBMs undergoing CNS radiation at first CNS involvement, >50% of patients had extracranial disease control: no ECD (25%) or stable/responding disease (31%). 52% of patients' tumors were ER+. Median age was 50 years (range 27 – 75). Most patients (58%) developed first CNS involvement during adjuvant or first/second line metastatic therapy. For first CNS radiation, 49% received SRS and 48% WBRT. All patients with no ECD presented with isolated CNS disease as first metastatic presentation. Median OS in this cohort from initial metastatic disease to death was markedly worse for patients with no ECD (25.3m, 95% CI: 16.8 to 35.3) compared to those with progressive or stable/responding ECD (48.8m, 95% CI: 28.1 to 65; and 52.9 months, 95% CI: 43.7 to 73.3, respectively; p=0.03). Median OS from first CNS involvement to death was not statistically different amongst groups. This analysis did not detect median PFS1 differences based on ECD after first CNS radiation: progressive ECD (6.3m), no ECD (8.7m), or stable/responding ECD (10.6m) (p=0.13), though clinically meaningful differences were observed. **Conclusions:** Patients with isolated HER2+ BCBM with no ECD at the time of their initial CNS involvement (25% of population) have substantially worse OS compared to patients who present with ECD and develop CNS metastases later in their disease course. This population with isolated CNS disease at metastatic presentation deserves investigation of novel treatment algorithms, including earlier introduction of brain penetrable HER2-targeted agents. Research Sponsor: None.

1042 **Poster Session**

Phase I study of LZM005, a HER2 antibody, as monotherapy or in combination with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer. *First Author: Cong Xue, Department of Medical Oncology, Sun Yat-sen University Cancer Center; State Key Laboratory of Oncology in South China; Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: LZM005 is a novel anti-HER2 antibody that binds with elevated affinity to the domain II of HER2. This phase I study assessed the safety, tolerability, pharmacokinetics (PK) and activity of LZM005, as monotherapy or combined with trastuzumab and docetaxel in patients with HER2-positive metastatic breast cancer. **Methods:** The phase I trial included phase Ia and Ib. Phase Ia was the monotherapy dosage escalation design. LZM005 was administered intravenously with 5mg/kg, 10mg/kg, 15mg/kg and 20mg/kg. The endpoints were dose limited toxicity (DLT) and maximum-tolerated dose (MTD), safety, tolerability and PK analysis. In phase Ib, LZM005 was combined with trastuzumab and docetaxel with MTD. The endpoints included safety and tolerability, response, PK and biomarker analysis. **Results:** From Jan 2017 to Feb 2020, 35 patients received LZM005 (15 monotherapy, 20 combination). No DLT was observed from 5mg/kg to 20mg/kg. In phase Ib two arms were set: 420mg arm and 525mg arm. The pharmacokinetics of LZM005 were similar to pertuzumab (Table). Common adverse events included increased transaminases, diarrhea and anemia in monotherapy and combination therapy. The common AE in phase Ia trial included diarrhea (21.4%), anemia (14.3%), elevated transaminase (14.3%). The common AE in phase Ib trial included anemia (44.1%), diarrhea (41.2%), fatigue (26.5%), elevated transaminases (23.5%), nausea (20.6%), rash (17.6%) and asymptomatic urinary tract infection (11.7%). All adverse events were manageable. No treatment-related death occurred. The clinical benefit rate and objective response rate was respectively 42.90% (6/14) and 7.14% (1/14) with monotherapy, with combination cohort was 100% (8/8) and 62.5% (5/8) in trastuzumab-naive, 83.3% (11/12) and 41.7% (5/12) in trastuzumab-pretreated patients. The median progression free survival was 22.5 weeks. **Conclusions:** LZM005 was well tolerated and showed potent activity in patients with HER2-positive metastatic breast cancer. Further evaluation was warranted. Clinical trial information: CTR20191921. Research Sponsor: Livzon Mabpharm Inc, Other Foundation.

PK parameters of LZM005 in Chinese patients.

	average±SD (%CV)			
Group	**5 mg/kg (N=1)**	**10 mg/kg (N=4)**	**15 mg/kg (N=3)**	**20 mg/kg (N=6)**
AUC 0-21d(h*μg/ml)	22598.296±-(-)	37026.958±6856.2857(18.517)	57284.723±4943.5427(8.63)	59894.118±13138.0635(21.935)
Cmax (μg/ml)	132.385±-(-)	219.402±39.0606(17.803)	345.502±36.8012(10.652)	340.037±40.5673(11.930)
t1/2(h)	211.122±-(-)	374.983±63.2312(16.862)	244.263±57.0101(23.34)	215.294±72.6508(33.745)
CL(ml/h)	10.433±-(-)	8.989±2.1178 (23.56)	11.576±3.8161(32.965)	16.279±5.4647 (33.568)
Vss(ml)	3382.474±-(-)	4508.610±430.9516(9.558)	3708.281±354.6646(9.564)	4609.199±599.7108(13.011)
Vz(ml)	2922.609±-(-)	4543.860±349.47 (7.691)	3855.877±770.0037(19.970)	4537.133±733.7645(16.172)
Ctrough(mg/ml)	0±-(-)	0±-(-)	0±-(-)	0±-(-)

1043 **Poster Session**

Updated results of tucatinib versus placebo added to trastuzumab and capecitabine for patients with pretreated HER2+ metastatic breast cancer with and without brain metastases (HER2CLIMB). *First Author: Giuseppe Curigliano, Istituto Europeo di Oncologia, Milan, IRCCS and University of Milano, Milan, Italy*

Background: Tucatinib (TUC) is an oral tyrosine kinase inhibitor (TKI) highly specific for HER2. TUC is approved for use in combination with trastuzumab (T) and capecitabine (C) in patients (pts) with and without brain metastases (BM) who have received 1 or more prior anti-HER2–based regimens in the metastatic setting. In the primary analysis from the pivotal HER2CLIMB trial, the addition of TUC to T and C in pts with HER2+ metastatic breast cancer showed a statistically significant and clinically meaningful prolongation of progression-free (PFS) (HR = 0.54 [95% CI: 0.42, 0.71]; P < 0.001) and overall survival (OS) (HR = 0.66 [95% CI: 0.50, 0.88]; P = 0.005) (Murthy, et al. NEJM 2020). TUC in combination with T and C was well tolerated with few discontinuations other than for disease progression. Based on these data, the protocol was amended for unblinding of sites to treatment assignment to allow for crossover from the placebo arm to receive TUC in combination with T and C. **Methods:** HER2CLIMB (NCT02614794) is a global, randomized, double-blind, placebo-controlled trial in pts with unresectable locally advanced or metastatic HER2+ breast cancer previously treated with T, pertuzumab, and T-emtansine (T-DM1), including pts with untreated, treated stable, or treated and progressing BM. Overall 612 pts were randomized 2:1 to receive TUC 300 mg BID or placebo, each in combination with T and C. Randomization was stratified by BM, ECOG performance status, and geographic region. Protocol prespecified analysis of OS, PFS (by investigator assessment) and safety in the total study population will be performed at approximately 2 years from the last patient randomized. **Results:** Updated Kaplan-Meier time-to-event analysis of OS and PFS with hazard ratios and 95% confidence intervals for TUC arm vs placebo arm will be presented overall, as well as for OS in the prespecified subgroups reported previously (Murthy, et al. NEJM 2020). Safety and tolerability assessments will include frequency of adverse events by severity, dose modifications and discontinuation of study medications. **Conclusions:** Conclusions will be presented in the presentation. Clinical trial information: NCT02614794. Research Sponsor: Seagen Inc.

1044 **Poster Session**

Pharmacokinetic (PK) analyses in CSF and plasma from TBCRC049, an ongoing trial to assess the safety and efficacy of the combination of tucatinib, trastuzumab and capecitabine for the treatment of leptomeningeal metastasis (LM) in HER2 positive breast cancer. *First Author: Erica Michelle Stringer-Reasor, University of Alabama at Birmingham, Birmingham, AL*

Background: Tucatinib is a potent and highly selective HER2-targeted tyrosine kinase inhibitor approved for use in combination with trastuzumab and capecitabine for patients with metastatic HER2+ breast cancer (MBC) who have received ≥1 prior HER2-based regimen in the metastatic setting, including patients with brain metastases (BM). TBCRC049 (NCT03501979) is an investigator-initiated phase 2 single-arm study currently enrolling to evaluate the safety and efficacy of tucatinib, trastuzumab and capecitabine in HER2+ BC with newly diagnosed LM. Here, we report the pre-specified pharmacokinetic (PK) analysis for the first 15 patients to determine bioavailability of tucatinib and its predominant metabolite, ONT-993, in the CSF. **Methods**: Eligible patients included adults with HER2+ MBC, KPS > 50, and newly diagnosed, untreated LM (defined as positive CSF cytology and/or radiographic evidence of LM, plus clinical signs/symptoms). Patients with treated or concurrent/new BM were allowed. The primary endpoint is overall survival with an accrual goal of 30 pts. Parallel PK samples were collected in plasma and CSF via Ommaya reservoir on day 1 of cycles 1 and 2 at 0h (baseline), 2-3h, 5-7h and 24h (optional) following initiation of tucatinib 300 mg BID. Tucatinib and ONT-993 were quantified in plasma (n=15) and CSF (n=13) using validated liquid chromatography-mass spectrometry methods. **Results**: Tucatinib and ONT-993 plasma concentrations were consistent with previous studies and exhibited high interindividual variability. Tucatinib and ONT-993 were detectable in the CSF within 2 hours post tucatinib administration; concentrations ranged from 0.57 to 25 ng/mL for tucatinib (IC_{50} for tucatinib against HER2 is 3.3 ng/mL) and 0.28 to 4.7 ng/mL for ONT-993. Tucatinib concentrations in the CSF per timepoint were in a similar range to unbound plasma ($plasma_{ub}$) tucatinib. CSF to $plasma_{ub}$ ratios were generally consistent over time; the steady-state (cycle 2) median tucatinib CSF to $plasma_{ub}$ ratio was 0.83 (0.19 to 2.1). ONT-993 CSF to $plasma_{ub}$ ratios were similar to tucatinib CSF to $plasma_{ub}$ ratios. **Conclusions**: In patients with LM from HER2+MBC who were treated with tucatinib, trastuzumab, and capecitabine, tucatinib and ONT-993 were detectable in the CSF of all patients at median levels similar to $plasma_{ub}$ tucatinib. This is the first documented evidence of tucatinib distributing into the CSF in patients with HER2+MBC. Efficacy and safety of tucatinib, trastuzumab, and capecitabine in patients with HER2+ LM will be reported upon completion of TBCRC 049 accrual. Clinical trial information: NCT03501979. Research Sponsor: SeaGen, Translational Breast Cancer Research Consortium.

1045 **Poster Session**

68Ga-HER2 affibody PET/CT imaging as an option in patients whose HER2 status of any tumor in the body needs to be deciphered. *First Author: Haitao Miao, Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Anti-HER2 targeted agents are standard of care for HER2 positive patients with either early or advanced breast cancer. Determination of tumor HER2 status helps diagnosing and treating breast cancer. In any tumor which required this biological information, we used a novel ^{68}Ga-NOTA-MAL-MZHER2 (^{68}Ga-HER2) affibody PET/CT to differentiate HER2 status of each lesion in the patient body. **Methods:** ^{68}Ga-HER2 affibody PET/CT was performed in breast cancer patients if HER2 status of any lesions in the patient body remained to be determined. **Results:** Twenty-four patients were enrolled. ^{68}Ga-HER2 affibody PET/CT was requested by physicians due to the following reasons: 6 with multiple primary cancers (including patients who harbored two primary breast malignancies but with different HER2 status, and patients who had at least another non-breast primary other than HER2-positve breast cancer), 13 with metastases inaccessible for biopsy or repeated biopsy, 6 with inconsistent HER2 status between the primary and metastatic lesions, and 4 with different HER2-status within metastases (ICH ranging from 0-3+). Assessment report showed that the ^{68}Ga-HER2 affibody tumor uptake was considered positive in 16 patients, negative in 7 patients, and equivocal in one patient. In 11 lesions which was pathological-confirmed HER2-positivity, 100% of the tumors were also positive with this PET/CT. The heterogeneity of ^{68}Ga-HER2 affibody uptake was obvious, with a maximal 8.5-fold difference within one patient and a maximal 11-fold difference among patients. **Conclusions:** ^{68}Ga-HER2 affibody PET/CT imaging is a valuable tool if HER2 status of any tumor needs to determined. We are now evaluating the ^{68}Ga-HER2 affibody PET/CT imaging as a non-invasive approach to classify the molecular subtype of metastatic breast cancer, and its potential application in the dynamic surveillance of anti-HER2 therapies. Research Sponsor: None.

1046 **Poster Session**

Clinicopathological characteristics of exceptional responders who achieve durable remissions beyond five years (DR5) in HER2+(H+) metastatic breast cancer (MBC). *First Author: Darko Skrobo, St Vincent's University Hospital, Dublin, Ireland*

Background: The introduction of anti-H2 targeted therapies has resulted in substantially improved outcomes for patients (pts) with H+MBC, yet despite survival prolongation, most patients so-treated will still ultimately die from MBC. Some patients do however, achieved prolonged remissions. In this report we outline the long-term outcomes of patients with H+MBC who were treated in our institution, with at least five-year follow-up from the diagnosis of MBC. **Methods:** As part of our larger single-institution "Thousand Patient HER-2 Database", we conducted a retrospective review of all patients in whom a diagnosis of H+MBC was made prior to December 2015 (range 2000-2015 years). The DR5 category included only those who had never experienced relapse or progression following initial anti-H2 therapy for MBC, and who were alive at 5 years. Patients were designated as (1) DR5, defined as never relapse with an overall survival (OS) > 5 years; (2) nonDR, which included those who had no or shorter remission, but also included nine pts who did achieve a 5 year CR, but who subsequently relapsed. OS was calculated from the date of diagnosis of MBC. The frequency distribution was assessed by Fisher's Exact Test or Chi-Square Test, as appropriate. OS and PFS were calculated according to Kaplan Meier method, and evaluated by Log-rank test. Univariate and multivariate Cox proportional hazards regression analysis was used to evaluate the effect of clinicopathological features on OS and PFS. **Results:** A total of 245 patients diagnosed with advanced H+MBC were identified. The median survival was 38 months, (range 0.3 – 248 months). Among these, 85 patients (35%) experienced an OS > 5 years, with 34 designated as DR5. The median OS for DR5 was 117 months, whereas nonDR (n = 211) had median OS of 33 months. The median age was similar between groups (DR5 53 yrs vs nonDR 56 yrs). A higher incidence of visceral disease was present in nonDR compared to DR5 (69% vs 44%). Of all patients diagnosed with *de novo* H+MBC, 23% achieved DR5. Presence of visceral disease, number of metastases and site of metastases were statistically significant negative predictors of achieving DR5 ($P < 0.05$). Presence of ER positive disease was not associated with OS. **Conclusions:** A meaningful subset of patients (14%) with advanced H+MBC achieve prolonged remission beyond five years with H2 targeted therapy. Nearly one quarter of those with *de novo* H+MBC achieve DR5. As *de novo* H+MBC now constitutes a higher proportion of all H+MBC than it did in the pre-trastuzumab era, an increasing proportion of H+MBC may now be achieving DR5. Prospective identification of variables to predict DR5 could assist in the stratification of patients for whom additional therapy is needed. Research Sponsor: Cancer Clinical Research Trust.

1047 **Poster Session**

Efficacy of CDK4/6i in the visceral crisis setting: Result from a real-world database. *First Author: Shaheenah S. Dawood, Mediclinic City Hospital, Dubai, United Arab Emirates*

Background: The combination of the CDK4/6 inhibitors(CDK4/6i) and endocrine therapy has improved overall survival(OS) in patients(pts) with either endocrine sensitive or resistant disease who are not in visceral crisis. The goal of this retrospective analysis of a real world database was to look at the efficacy of CDK4/6i among pts with hormone receptor positive (HR+ve)/HER2-ve metastatic breast cancer(MBC) who present with visceral crisis at diagnosis. **Methods:** For this analysis, we utilized a federated network of de-identified health data representing approximately 64 million patient lives available through the TriNetX Platform. We identified 5966 pts who had HR+ve/HER2-ve MBC diagnosed between 2015 and 2020. OS was computed using the Kaplan Meier product limit method. Propensity score matching was performed on all comparisons of survival. Visceral crisis was defined as either liver metastases with liver dysfunction, lymphangitis with dyspnea or the presence of pancytopenia. **Results:** 906(15%) pts received CDK4/6i. OS any time after treatment among pts who did and did not receive CDK4/6i was significantly different (p=0.0002) favoring the group receiving CDK4/6i, with median OS at 59.6 months and 46.2 months and 2-year OS at 71.6% and 61.4% respectively. Among pts who received CDK4/6i versus another treatment as first line therapy, OS was significantly different(HR 0.7, 95%CI 0.57 – 0.86, p<0.0001), and median OS was 59.6 months and 41.5 months respectively. 336 pts with HR+ve mbc presented with visceral crisis at the time of diagnosis of whom 61(18%) received CDK4/6i therapy as first line therapy. Median OS among pts who did and did not have visceral crisis at diagnosis and received treatment was 8.1 months and 210 months respectively. OS any time after initial treatment was significantly different among pts with visceral crisis who did and did not receive CDK4/6i (p=0.01), with 2-year OS at 26.1% and 8.1% and median OS at 11 months and 6 months respectively **Conclusions:** The use of CDK4/6i in the presence of visceral crisis at diagnosis was associated with a 5 month improvement in OS compared to chemotherapy. Future clinical trials should explore the use of CDK4/6i in the setting of visceral crisis. Research Sponsor: None.

1048 **Poster Session**

Real-world cost-effectiveness of pertuzumab (P) with trastuzumab + chemo (T+Chemo) in patients (pts) with metastatic breast cancer (MBC): A population-based retrospective cohort study by the Canadian Real-world Evidence for Value in Cancer Drugs (CanREValue) collaboration. *First Author: Wei Fang Dai, University of Toronto, Toronto, ON, Canada*

Background: Addition of P to T+chemo for MBC pts has been shown to improve overall survival (OS) in a pivotal randomized trial (hazard ratio [HR] = 0.66, 95% CI: 0.52, 0.84) (Baselga et al., NEJM 2012). In Canada, the manufacturer submission to the health technology assessment agency estimated that P produced 0.64 life years gained (LYG) with an incremental cost-effectiveness ratio (ICER) of $187,376/LYG over 10 years (CADTH-pCODR, 2013). This retrospective cohort analysis aims to determine the comparative real-world population-based effectiveness and cost-effectiveness of P among MBC pts in Ontario, Canada. **Methods:** MBC pts were identified from the Ontario Cancer Registry and linked to the New Drug Funding Program database to identify receipt of treatment between 1/1/2008 and 3/31/2018. Cases received P-T-chemo after universal public funding of P (Nov 2013) and controls received T-chemo before. Demographic (age, socioeconomic, rurality) and clinical (comorbidities, prior adjuvant treatments, prior breast cancer surgery, prior radiation, stage at diagnosis, ER/PR status) characteristics were identified from linked admin databases balanced between cases and controls using propensity score matching. Kaplan-Meier methods and Cox regressions accounting for matched pairs were used to estimate median OS and HR. 5-year mean total costs from the public health system perspective were estimated from admin claims databases using established direct statistical methods and adjusted for censoring of both cost and effectiveness using inverse probability weighting. ICERs and 95% bootstrapped CIs were calculated, along with incremental net benefit (INB) at various willingness-to-pay values using net benefit regression. **Results:** We identified 1,823 MBC pts with 912 cases and 911 controls (mean age = 55 years), of which 579 pairs were matched. Cases had improved OS (HR = 0.66; 95% CI: 0.57, 0.78), with median 3.4 years, compared to controls median OS of 2.1. P provided an additional 0.63 (95% CI: 0.48 – 0.84) LYG at an incremental cost of $196,622 (95% CI: $180,774, $219,172), with a mean ICER = $312,147/LYG (95% CI: $260,752, $375,492). At threshold of $100,000/LYG, the INB was -$133,632 (95% CI: -$151,525, -$115,739) with < 1% probability of being cost-effective. Key drivers of incremental cost increase between groups included drug and cancer clinic costs. **Conclusions:** The addition of P to T-chemo for MBC increased survival but at significant costs. The ICER based on direct real-world data was higher than the initial economic model due to higher total costs for pts receiving P. This study demonstrated feasibility to derive ICER from person-level real-world data to inform cancer drug life-cycle health technology reassessment. Research Sponsor: Canadian Institute for Health Information, Other Government Agency.

1049 **Poster Session**

A phase 1b study of chemoimmunotherapy with pegylated liposomal doxorubicin and pembrolizumab in estrogen receptor-positive, endocrine-resistant breast cancer. *First Author: Alberto A. Gabizon, The Oncology Institute, Shaare Zedek Medical Center, Jerusalem, Israel*

Background: This is a single center phase 1b study of a regimen of pembrolizumab (PBZ) and pegylated liposomal doxorubicin (PLD) in endocrine-resistant breast cancer. PLD was chosen as chemotherapy component because it is mildly myelosuppressive and non-immunosuppressive and contains doxorubicin, a strong immunogenic cell death inducer. **Methods:** Patients with estrogen receptor positive, HER2 negative, metastatic breast cancer, whose disease progressed on hormonal and biological therapy and up to 2 chemotherapy lines were eligible for enrollment. PLD, 30 mg/m^2, and PBZ, 200 mg flat dose, were infused on day 1 of every 3-week cycles. The main study objectives were safe dose clearance, characterization of dose-limiting toxicities (DLT), tumor response, and pharmacokinetic analysis of PLD and PBZ during the first 3 cycles of treatment in a 1st cohort of 6 patients and a 2nd confirmatory cohort of 6-9 patients. Patients with partial response (PR) or stable disease (SD) continued on the extended phase of the study consisting of 9 additional cycles during which further safety information was collected. All patients were followed-up for survival. **Results:** 12 patients were recruited (median age 61 y, range 45-91). 9 patients had received prior doxorubicin treatment. 82 treatments have been administered (median: 7, range 2-13). Overall, treatment was well tolerated. DLT including infusion reactions, grade ≥2 myelosuppression, hair loss and mucocutaneous toxicity were not observed in the first 3 cycles. Subsequently, skin toxicity (grade 2-3 palmar-plantar erythema) was observed forcing treatment delays of 1-2 weeks. Except for 2 cases of subclinical hypothyroidism, there were no other apparent PBZ-related side-effects. There was no evidence of cardiac toxicity. There were 2 early deaths (days 25 and 45) probably related to disease progression. Upon reevaluation on week 9, we observed: 2 patients with PD, 4 with SD, 2 with PR (15+ and 5+ mth), 1 with no measurable disease, and 1 early to evaluate. Three out of 5 patients responded well to post-study chemotherapy with durable improvement or stabilization (range, 5 to 11+ mth). Median follow-up is 14 mth. Median survival has not been reached with 4 deaths and a longest survivor of 19+ mth. Median progression-free survival is 6.0 mth. The clearance of PLD was slow with high Cmax, long T$^1/_2$ and small Vd. There was a significant increase in the AUC of PLD between the 1st and 3rd cycle (median: 2,649 vs 3,422 mg*h/l, p = 0.039). Analysis of PBZ plasma levels is ongoing. **Conclusions:** The combination of PLD and PBZ is well tolerated and feasible for extended treatment. Dose interval of PLD should be lengthened to 4 weeks after 2-3 cycles to prevent skin toxicity. The late appearance of skin toxicity is probably related to a delay in PLD clearance after 2 treatment cycles with PLD and PBZ. Clinical trial information: NCT03591276. Research Sponsor: Merck.

1050 **Poster Session**

A first-in-human phase 1a/b trial of LY3484356, an oral selective estrogen receptor (ER) degrader (SERD) in ER+ advanced breast cancer (aBC) and endometrial endometrioid cancer (EEC): Results from the EMBER study. *First Author: Komal L. Jhaveri, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Novel degraders and antagonists of ER are under evaluation in aBC, to overcome both ER mediated resistance and the bioavailability and dosing limitations of fulvestrant, the only approved SERD. ER is also overexpressed in ~80% of EEC and endocrine therapy (ET) is utilized for these patients (pts). LY3484356, a novel, orally bioavailable SERD with pure antagonistic properties results in sustained inhibition of ER-dependent gene transcription and cell growth. Preclinically, LY3484356 shows favorable efficacy and pharmacokinetic (PK) properties, including antitumor activity in *ESR1* mutants. Here we present the initial clinical data from EMBER, an ongoing first-in-human phase 1a/b trial of this novel agent. **Methods:** Phase 1a evaluated LY3484356 dose escalation (i3+3 design) in women with ER+, HER2- aBC (≤3 prior therapies for aBC following protocol amendment; prior ET sensitivity) and ER+ EEC (prior platinum therapy). Premenopausal women received a concomitant GnRH agonist. Key endpoints included determination of the recommended phase 2 dose, safety and tolerability, PK, and objective response rate and clinical benefit rate per RECIST v1.1. **Results:** As of the data cut (November 9, 2020), 28 pts (n = 24 aBC, n = 4 EEC) were enrolled at doses ranging from 200-1200 mg QD. Median age was 59 years (range, 35-80). Median number of prior therapies for aBC was 2 (range, 1-8; 6 pts enrolled prior to protocol amendment had received ≥4 prior therapies), including prior fulvestrant (46%), a CDK4/6 inhibitor (83%), and chemotherapy (33%). No dose-limiting toxicities were observed. Treatment-emergent adverse events (TEAEs) were mostly grade 1-2, including nausea (32%), fatigue (25%), and diarrhea (18%). The only grade 3 treatment-related AE was diarrhea (n = 1). TEAEs of bradycardia and QTc prolongation were not observed despite intensive central ECG monitoring. Dose-proportional increases in LY3484356 exposures were observed across all evaluated doses and $t_{1/2}$ was 25-30 hours. At the starting dose level (200 mg QD), unbound LY3484356 exposures exceeded those achieved with fulvestrant. 16 of 28 pts were efficacy evaluable, with the remaining 12 pts ongoing prior to first scan. Among 16 evaluable pts, 11 (8 aBC, 3 EEC) had stable disease (10 pts ongoing), and 5 had progressive disease. RECIST responses were observed after the data cut and will be detailed at the meeting. Plasma ctDNA analysis indicated decreases in mutant allele frequencies, including mutant *ESR1* in 9/12 (75%) evaluable pts across all dose levels. **Conclusions:** LY3484356 QD dosing shows favorable safety and PK properties, along with preliminary efficacy in pts with heavily pretreated ER+ aBC and EEC. Updated data will be presented at the meeting. Clinical trial information: NCT04188548. Research Sponsor: Loxo Oncology at Lilly.

1051 **Poster Session**

Correlation between work productivity loss (WPL) and European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) domains from the MONALEESA-7 (ML-7) trial of premenopausal women with HR+/HER2- advanced breast cancer (ABC). *First Author: Debu Tripathy, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The international, randomized, double-blind, placebo-controlled, Phase III ML-7 trial (NCT02278120) assessed ribociclib + endocrine therapy (ET) vs ET alone in premenopausal women with HR+/HER2– ABC. To our knowledge, the relationship between WPL and domains of the EORTC QLQ-C30 and the tumor-specific module for breast cancer (QLQ-BR23) has not been explored in ABC. In this post hoc analysis (data cutoff, November 30, 2018) of all patients (pts) enrolled in ML-7, we assessed the correlation between the WPL component of the Work Productivity and Activity Impairment: General Health (WPAI:GH) questionnaire and domains of the EORTC QLQ-C30/BR23. **Methods**: We analyzed EORTC and WPAI:GH data from all pts enrolled in ML-7 who were employed at any point during the trial (N = 329 of 672 total pts). Domains of the EORTC QLQ-C30 and QLQ-BR23 that had the greatest correlation (pairwise Pearson correlation) with WPL were prioritized for analysis. Separate univariable mixed-model repeated-measures regression models were fitted for each domain, with WPL as the dependent variable and each EORTC domain as a single fixed-effect covariate. Linear and quadratic relationships were considered. Model selection was based on the Akaike information criterion (AIC). **Results**: Linear models were favored over quadratic models. WPL was negatively correlated with global health status (GHS) and the physical, role, social, and emotional functioning domains and was positively correlated with the fatigue and pain domains of the QLQ-C30 ($P < .001$; Table). The coefficients indicated the estimated mean change in WPL was associated with a 1-unit increase in each QLQ-C30 domain. For example, a 10-point increase in GHS was associated with an estimated mean decrease of 7.8% (95% CI, 7.1%-8.5%) in WPL. **Conclusions**: Greater WPL was associated with higher levels of fatigue and pain and with lower levels of overall quality of life and physical, role, social, and emotional functioning among pts with HR+/HER2− ABC in ML-7. Further investigation of the correlation with QLQ-BR23 and multivariable analysis could determine which EORTC domains and items independently drive these findings. Clinical trial information: NCT02278120. Research Sponsor: Novartis Pharmaceuticals Corporation.

Domain	AIC (Linear)	AIC (Quadratic)	Regression Coefficient (Linear Model) (95% CI)	*P* Value
Fatigue	19,475.96	19,486.02	0.61 (0.54 to 0.67)	< .001
Pain	19,469.70	19,470.45	0.53 (0.47 to 0.59)	< .001
Physical functioning	19,383.55	19,389.79	−0.98 (−1.07 to −0.88)	< .001
Global health status	19,291.10	19,303.40	−0.78 (−0.85 to −0.71)	< .001
Role functioning	19,359.71	19,373.50	−0.65 (−0.71 to −0.60)	< .001
Social functioning	19,443.55	19,457.02	−0.59 (−0.65 to −0.53)	< .001
Emotional functioning	19,557.42	19,570.86	−0.49 (−0.56 to −0.42)	< .001

1052 **Poster Session**

The association of HER2 low expression with the efficacy of CDK4/6 inhibitor in hormone receptor positive HER2 negative metastatic breast cancer. *First Author: Kelvin K H Bao, Department of Clinical Oncology, Queen Elizabeth Hospital, Kowloon, Hong Kong*

Background: Markers for the efficacy of CDK4/6 inhibitor in estrogen receptor (ER) positive, HER2 negative advanced breast cancer are limited. The bidirectional crosstalks that exist between ER and HER2 pathways contribute to endocrine resistance. We investigated the association between low levels of HER2 expression and the clinical outcome of patients with ER+ HER2- metastatic breast cancer (MBC) treated with CDK4/6 inhibitors. **Methods:** We identified consecutive patients with ER+ HER2- MBC who received CDK4/6 inhibitor plus either letrozole or fulvestrant between Mar 2017 - Jun 2020 from an institutional cancer registry. HER2-low expression was defined as IHC score 1+, or 2+ with a negative ISH. Progression-free survival (PFS) was defined as the time from the initiation of CDK4/6 inhibitor to the date of radiological or clinical progression, or death. The relationship between HER2 expression levels and PFS was evaluated using log-rank test and multivariable Cox regression modelling. **Results:** 106 women with MBC were eligible for analysis. Median age at treatment was 58 (23.0-91.4). The majority received palbociclib (84%) while the rest received ribociclib. CDK4/6 inhibitor was used as first-line treatment in 50.9% of cases. Most tumors were of ductal histology (83%) and progesterone receptor (PgR) positive (84.9%), and 22.6% of the patients had bone-only disease. 77.3% of cases were considered HER2-low expressing. HER2-low expression was associated with a significantly shorter PFS compared with HER2 IHC 0 counterpart (median, 8.9 vs 18.8 months, p= 0.014). In multivariate analysis, HER-2 low expression remained significantly associated with an inferior PFS (HR 1.96, 95%CI 1.03-3.75, p= 0.041) after adjusting for the line of treatment, PgR status and disease extent (bone only vs extra-osseous disease). **Conclusions:** In patients with ER+ HER2- MBC treated with CDK4/6 inhibitors, HER2-low expression was associated with an inferior PFS, and may serve as a potential marker candidate for CDK4/6 inhibitor efficacy. As novel anti-HER2 antibody-drug conjugates demonstrated efficacy in HER2-low expressing MBC, coupled with the emerging evidence for the combination of CDK4/6 inhibitors with anti-HER2 agents, this HER2-low expression subgroup warrants prospective evaluations in future trials. Research Sponsor: None.

1053 **Poster Session**

Resistance to CDK4/6 inhibitors (CDK4/6i): The clinical usefulness of liquid biopsy in metastatic breast cancer (mBC). *First Author: Lucrezia Raimondi, U.O.C. Territorial Oncology of Aprilia, Sapienza University of Rome, Aprilia, Italy*

Background: Palbociclib (P) in combination with fulvestrant (F) or letrozole (L), is used globally to treat metastatic breast cancer but despite therapeutic improvements most patients acquire resistance to CDK4/6i. *KRAS* tumor mutations (^{mut}KRAS) have been associated with worse PFS in several tumor types but have not been analysed extensively in breast cancer. To understand the molecular mechanisms of resistance to CDK4/6i and their clinical behavior, using liquid biopsy, we evaluated the opportunity to reveal the onset of resistance to CDK4/6i detecting ^{mut}KRAS ctDNA. **Methods**: We studied the KRAS mutation status of 211 patients with mBC treated with CDK4/6i plus L or F as first-line metastatic therapy. Using Bio-Rad QX200 droplet digital polymerase chain reaction (ddPCR) system we determined *KRAS* ctDNA levels in plasma. Using logistic and Cox regression, a predictive model for objective response (OR), progression-free survival (PFS) and overall survival (OS) was constructed. The PFS and the OS were estimated by the Kaplan–Meier method and compared with use of the log-rank test. **Results**: In 38% (81 patients, 24 in treatment with L and 57 in treatment with F) we observed ^{mut}KRAS ctDNA before starting CDK4/6i: the detection of ^{mut}KRAS significantly correlated with the onset of resistance to CDK4/6i within 6months from the evidence of *KRAS* mutation and worse PFS ($p<0.001$). OR was seen in 84 of 130 KRAS wild-type (WT) patients versus 0 of 81 in KRAS mutants. At 24-month follow up, median PFS was significantly better in KRAS WT versus mutants (3.1 [range: 1-6months,95%CI 0.9-3.6] versus NA months; $p<0.001$). Correlating the results of liquid biopsy both to tumoral burden and patients clinical features, we observed a higher ^{mut}KRAS circulating copies-number in those patients with two or more metastatic sites($p<0.001$). **Conclusions**: Despite the study's limitations, our data suggest ^{mut}KRAS ctDNA status leads to CDK4/6i resistance acquisition within 6 months from the detection and provide critical information for the prediction of therapeutic responses in mBC. Monitoring *KRAS* status with liquid biopsy, we could predict who will take advantage from CDK4/6i, decreasing wastes of resources ensuring the best patients' quality of life. Research Sponsor: None.

1054 **Poster Session**

Long-term (LT) disease control in patients (pts) with hormone receptor-positive (HR+), *PIK3CA*-altered advanced breast cancer (ABC) treated with alpelisib (ALP) + fulvestrant (FUL). *First Author: Dejan Juric, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: *PIK3CA* mutations, present in ~40% of HR+, HER2– ABC, are associated with therapeutic resistance and shorter survival. Alpelisib (ALP) + fulvestrant (FUL) demonstrated efficacy in this population for which achieving long-term (LT) disease control is challenging. Here, we report on pts with HR+, *PIK3CA*-altered ABC who achieved LT disease control with ALP + FUL. **Methods:** SOLAR-1 was a phase 3, randomized, double-blind study of ALP (or placebo) + FUL in HR+, HER2– ABC that progressed on/after an aromatase inhibitor. CBYL719X2101 (X2101) was a phase 1, open-label study of escalating ALP doses ± FUL in advanced solid tumors that progressed on/after anti-estrogen therapy (ET) or relapsed after adjuvant anti-ET. A cut-off ≥ median (progression-free survival [PFS] + 2 SE) was chosen based on Kaplan-Meier curves from SOLAR-1 to define LT disease control as PFS (SOLAR-1) or time on treatment (X2101) ≥18 mo. **Results:** In SOLAR-1, 51 of 169 pts (30.2%) randomized to ALP + FUL achieved LT disease control with a median PFS of 33.5 mo (95% CI, 27.4 mo-not reached). Baseline characteristics of pts in SOLAR-1 are in the table below. In pts with LT disease control, adverse events (AEs) of special interest (combined preferred terms) of GI toxicity were observed in 47 pts (92.2%; grade ≥3: 11.8%, n=6), of hyperglycemia in 41 pts (80.4%; grade ≥3: 39.2%, n=20), and of rash in 28 pts (54.9%; grade ≥3: 19.6%, n=10). Median ALP relative dose intensity was 79.9% and 82.1% for pts with LT disease control (n=51) and the overall population (n=168), respectively. In X2101, 7 of 52 pts (13.5%) with ABC who received ALP+FUL achieved LT disease control up to 47.8 mo. **Conclusions:** In this subset of pts with hard-to-treat, endocrine-resistant disease, LT disease control ≥18 mo is meaningful considering median PFS of 4.6-9.3 mo or 9.5-16.4 mo with FUL alone or with cyclin-dependent kinase 4/6 inhibitors, respectively. Here, LT disease control was observed in 2 studies of HR+, *PIK3CA*-altered ABC, including in pts with poor prognosis, diabetes/pre-diabetes at baseline, and heavy pretreatment. AE profile was consistent with prior reports and did not preclude LT disease control. Further work is needed to better understand factors influencing LT disease control. Clinical trial information: NCT01219699, NCT02437318. Research Sponsor: Novartis Pharmaceuticals Corporation.

Baseline characteristics (SOLAR-1).

Characteristics, n (%)	Pts with LT disease control (n=51)	Overall population[a] (n=169)
Age, median (range), yr	62 (35-79)	63 (25-87)
Eastern Cooperative Oncology Group performance status ≥1	12 (23.5)	56 (33.1)
Diabetic or pre-diabetic[b]	31 (60.8)	104 (61.5)
Number of metastatic sites ≥3	9 (17.6)	48 (28.4)
Lung and/or liver metastasis	22 (43.1)	90 (53.3)
Endocrine resistance (primary/secondary)	3 (5.9) / 34 (66.7)	23 (13.6) / 119 (70.4)

[a]Pts with *PIK3CA*-mutated ABC in the ALP + FUL arm; [b]based on American Diabetes Association guidelines.

1055 **Poster Session**

Overall survival in patients with breast cancer treated with a CDK 4/6 inhibitor plus fulvestrant: A U.S. Food and Drug Administration pooled analysis. *First Author: Jennifer J Gao, US Food and Drug Administration, Silver Spring, MD*

JJG, JC, TMP contributed equally. JAB, LAK contributed equally. **Background:** Cyclin dependent kinase 4/6 inhibitors (CDKIs) are oral targeted agents approved for use in combination with endocrine therapy as first or secondline treatment of hormone-receptor positive (HR+), human epidermal growth factor receptor 2 (HER2)-negative advanced or metastatic breast cancer. We previously reported the pooled analyses of progression-free survival of patients in certain clinicopathologic subgroups, and results showed a consistent benefit from the addition of a CDKI to endocrine therapy. Here, we report the pooled overall survival (OS) results in patients treated with a CDKI plus fulvestrant. **Methods:** We pooled individual patient data (n=1948) from three phase III randomized breast cancer trials of a CDKI plus fulvestrant submitted to the FDA in support of marketing applications. All analyzed patients received at least one dose of a CDKI or placebo, plus fulvestrant. The median OS was estimated using Kaplan-Meier (KM) methods, and hazard ratios (HR) with corresponding 95% confidence intervals (CIs) were estimated using Cox regression models. **Results:** Results of OS analyses, including all pooled patients, patients treated in the first-line setting, and patients treated in the second line and later settings, are summarized in the table below. Additional subgroup analyses of OS by progesterone receptor status, site of metastases, breast cancer histology, ECOG performance status, race, and de novo metastatic presentation all favored adding a CDKI to fulvestrant. In patients age < 40, the estimated OS HR favored fulvestrant alone, but this subgroup had a small sample size (n=89), so this result must be interpreted with caution. All results are considered exploratory and hypothesis-generating. **Conclusions:** Addition of CDKIs to fulvestrant appears to confer a consistent survival benefit across all pooled patients and within most clinicopathological subgroups of interest. Research Sponsor: None.

	n	# Events CDKI/N (%)	# Events Placebo/N (%)	HR (95% CI)	HR Range, individual trials
All trials	1948	586/1296 (45)	349/652 (54)	0.77 (0.68, 0.88)	0.73, 0.79
First-Line Setting*	396	74/262 (28)	49/134 (37)	0.74 (0.52, 1.07)	0.74, 0.79
Second-Line and Later Setting	1552	512/1034 (50)	300/518 (58)	0.77 (0.67, 0.89)	0.72, 0.79

* Majority (n=353) from one trial. MNE = median not estimable.

1056 **Poster Session**

A single-arm phase II trial of palbociclib in combination with tamoxifen as first-line therapy for metastatic hormone receptor-positive breast cancer.

First Author: Oana Cristina Danciu, University of Illinois at Chicago, Chicago, IL

Background: Palbociclib is a CDK4/6 inhibitor used to treat metastatic hormone receptor-positive (HR+) breast cancer (MBC) in combination with endocrine therapy. Tamoxifen is an effective treatment for HR+ MBC, with different toxicity profile compared with aromatase inhibitors (AI) and fulvestrant. Preclinical data demonstrated synergy for the combination of tamoxifen and palbociclib, being effective in a model of acquired tamoxifen resistance. **Methods:** We conducted an open-label, single-arm, multicenter phase II trial of palbociclib in combination with tamoxifen in patients with HR+/HER2 - advanced BC, with no prior therapy for MBC. Ovarian suppression was recommended for pre-menopausal women, but not required. Primary objective was progression free survival. Secondary objectives: objective response rate (CR or PR) based on RECIST 1.1 or MDA Criteria (for patients with bone only disease); safety and tolerability (using CTCAE v4); clinical benefit rate (CR, PR or SD lasting min 24 weeks); 2-year overall survival. Correlative objectives: proteomic analysis of plasma exosomes to identify mechanisms of primary and secondary resistance to tamoxifen/palbociclib. **Results**: Between 6/30/2016 and 7/02/2019, we enrolled 49 patients (47 evaluable): 23 pts with de-novo metastatic disease and 24 pts with recurrent BC (12 pts were on adjuvant treatment with AI at time of recurrence and 12 pts on surveillance). As of 1/5/21 data cut-off, 7 pts were still on treatment. Median follow-up time was 24 months (range 8-42). Median age was 60 (range 39-82). The median PFS was 14.6 months with 95% CI (7-41) for pts with de-novo MBC and 6 months (2-12) for pts with recurrent BC. The ORR was 30% overall, 39% for pts with de novo MBC, 21% for pts with recurrent BC. CBR was 64% overall, 78% for pts with de novo MBC and 50% for pts with recurrent BC. CBR was 65% for white pts and 55% for African American pts. Best response per RECIST1.1: 14 pts (34%) had PR, 18 pts (44%) had SD, 9 pts (22%) had PD. All 6 pts with bone only disease had SD. The most common drug related grade ≥ 3 AE was neutropenia (51%), transient and manageable by dose modifications, no cases of febrile neutropenia. Four patients developed thromboembolic events (1 grade 2, 2 grade 3, 1 grade 4). One patient died while on treatment from PD. **Conclusions**: The combination of palbociclib and tamoxifen showed tolerable, expected safety profile. This may be an alternative approach for selected patients in first line treatment of HR+ MBC, especially those who are intolerant to AI, although this small study indicates a lower PFS. Clinical trial information: 02668666. Research Sponsor: Pfizer.

Baseline demographics (N 47).

Parameter	N	%
Sex		
Female	47	100
Race		
White	31	66
Black or African American	11	23
Asian	1	2
American Indian or Alaska Native	1	2
Unknown	3	6
Ethnicity		
Hispanic or Latino	3	6
Non-Hispanic	44	94
ECOG Performance status		
0	31	66
1	15	32
2	1	2
Menopausal status		
Post-menopausal	38	81
Pre-menopausal	9	19

1057 **Poster Session**

A phase Ib study of xentuzumab plus abemaciclib and fulvestrant in patients (pts) with advanced hormone receptor-positive (HR+), HER2-negative breast cancer (BC) with visceral or non-visceral disease.

First Author: Douglas Yee, Masonic Cancer Center, University of Minnesota, Minneapolis, MN

Background: Cyclin-dependent kinase (CDK) 4 & 6 inhibitors plus endocrine therapy (ET) are standard of care for advanced HR+ BC. Combining xentuzumab, an insulin-like growth factor (IGF) ligand-neutralizing antibody, with ET and everolimus, suggested progression-free survival (PFS) benefit in pts with advanced HR+ BC and non-visceral disease. Activation of the IGF pathway leads to an increase in cyclin D1, providing a rationale for combining IGF and CDK4 & 6 inhibition. This prospective, open-label study is investigating xentuzumab plus abemaciclib, a CDK4 & 6 inhibitor, with fulvestrant. In dose-finding cohorts, the recommended phase II dose (RP2D) was determined as xentuzumab 1000 mg weekly intravenously plus abemaciclib 150 mg every 12h orally (Q12h). Here, we report preliminary data on disease control rate (DCR) from two expansion cohorts in pts with advanced HR+ BC with visceral (D1) or non-visceral disease (D2). **Methods:** Postmenopausal women with advanced/metastatic HR+ BC that had progressed on or after ET (including adjuvant ET) were enrolled. Pts could not have received >1 line of ET or any chemotherapy for metastatic disease. No prior CDK4 & 6 inhibitor therapy was permitted. Pts had to have ≥1 documented visceral metastasis in D1 and no visceral metastases in D2. Pts received xentuzumab weekly plus abemaciclib Q12h (at RP2D) plus fulvestrant 500 mg per label. Protocol primary endpoint was PFS rate at 18 months (mos). Secondary endpoints included DCR (complete response [CR], partial response [PR] and non-CR/non-progressive disease [PD] or stable disease [SD] lasting ≥24 weeks [wks]). **Results:** In D1/D2, 33/31 pts were treated: median age 60/53 years. 19 pts in D2 had bone-only, non-measurable disease. At data cut-off (Jan 2021), median treatment duration was 7.5/9.2 mos in D1/D2; 40 pts remain on treatment. In D1, DCR was 64%: 17 (52%) pts had PR and 4 (12%) had SD lasting ≥24 wks. In D2, DCR was 55%: 5 (16%) pts had PR, 10 (32%) had non-CR/non-PD lasting ≥24 wks and 2 (7%) had SD lasting ≥24 wks. Median duration of disease control was 10.9 mos in each cohort. Some pts had not reached 24 wks; full DCR data will be presented. Most common AEs are shown in the table (≥33% all-grade in either cohort). No hypo/hyperglycemia was reported. **Conclusions:** Xentuzumab plus abemaciclib and fulvestrant demonstrated encouraging disease control in pts with advanced HR+ BC with visceral and non-visceral disease. The safety profile was manageable, and consistent with the known profiles of the three agents. Clinical trial information: NCT03099174. Research Sponsor: Boehringer Ingelheim.

	D1 n=33		D2n=31	
AE, %	**All**	**Grade ≥3**	**All**	**Grade ≥3**
Diarrhea	28 (85)	1 (3)	28 (90)	3 (10)
Nausea	20 (61)	0	20 (65)	2 (7)
Neutrophil count decreased	17 (52)	12 (36)	12 (39)	10 (32)
Asthenia	12 (36)	0	9 (29)	1 (3)
Anemia	11 (33)	1 (3)	11 (36)	1 (3)
Muscle spasms	11 (33)	0	4 (13)	0
Platelet count decreased	10 (30)	0	13 (42)	1 (3)
Vomiting	9 (27)	0	13 (42)	2 (7)

1058 **Poster Session**

AMEERA-1: Phase 1/2 study of amcenestrant (SAR439859), an oral selective estrogen receptor (ER) degrader (SERD), with palbociclib (palbo) in postmenopausal women with ER+/ human epidermal growth factor receptor 2-negative (HER2-) metastatic breast cancer (mBC).

First Author: Sarat Chandarlapaty, Memorial Sloan Kettering Cancer Center, New York, NY

Background: AMEERA-1 (NCT03284957) investigates amcenestrant, an oral SERD, as monotherapy and combined with targeted therapies in ER+/HER2– mBC. Here we report data from dose escalation (Part C) and dose expansion (Part D) of amcenestrant + palbo. **Methods:** Patients (pts) were postmenopausal women with ER+/HER2– mBC and ≥ 6 mos prior advanced endocrine therapy (ET) or adjuvant (adj) ET resistance (relapse on adj ET started ≥ 24 mos ago or < 12 mos after completing adj ET). Prior chemotherapy (≤ 1) for advanced disease was allowed; targeted therapies were not except ≤ 1 CDK4/6i in Part C. Part C assessed dose-limiting toxicities (DLTs) and aimed to establish the recommended phase 2 dose (RP2D) for amcenestrant (200 or 400 mg once daily [QD], in 28-day cycles) in combination with palbo (125 mg QD for 21 days on/ 7 days off). Safety (treatment-emergent adverse events [TEAEs] and lab abnormalities per CTCAE v4.03) and pharmacokinetics (PK) were evaluated. Antitumor activity at the RP2D for amcenestrant + palbo was evaluated in a subset of Part C pts and Part D, according to RECIST v1.1, determined locally by investigators. **Results:** Feb 8, 2021 data cutoff. In Part C (n = 15; 200 mg: 9; 400 mg: 6), no DLTs occurred and amcenestrant 200 mg QD was selected as the RP2D with palbo, based on PK and safety data. In the pooled safety population at the RP2D (n = 39; Part C: 9; Part D: 30), median (range) age was 59 y (33–86) with ECOG PS 0 (74.4%) or 1 (25.6%) and 2 (1–6) organs involved. Immediate prior therapy was neo/adj (41.0%, all ET resistant) or advanced (59.0%, range 1–4 lines). Median (range) exposure was 32 wks (1–66) with 59.0% pts on ongoing therapy. No amcenestrant dose reductions occurred; 25.6% had ≥ 1 palbo dose reduction. Most common non-hematological TEAEs related to amcenestrant were Grade 1–2 nausea and fatigue (17.9% each), asthenia and hot flush (10.3% each); to palbo were fatigue (30.8%), nausea (25.6%), asthenia and dysgeusia (10.3% each). Two pts discontinued due to AEs. The majority (94.9%) had neutrophil count decrease (53.8% Grade ≥ 3). Preliminary antitumor activity after at least 6 cycles of therapy (unless early treatment discontinuation) is reported in the table below. **Conclusions:** In pts with ER+/HER2– mBC, safety at the RP2D of amcenestrant + palbo was favorable, with no safety signals of bradycardia or eye disorders. Preliminary antitumor activity was observed (ORR: 31.4% and CBR: 74.3%). Clinical trial information: NCT03284957. Research Sponsor: Sanofi.

	Pooled C*+D (n = 35)
Best Overall Response, n (%)	
Complete Response	1 (2.9)
Partial Response	10 (28.6)
Stable Disease†	23 (65.7)
Progressive Disease	1 (2.9)
Objective Response Rate, % (90% CI)	31.4 (18.7–46.6)
Clinical Benefit Rate, % (90% CI)	74.3 (59.4–85.9)

*Response-evaluable pts with no prior mTORi or CKD4/6i †Including 1 pt with PR to be confirmed at next assessment

1059 **Poster Session**

Systematic review and meta-analysis of post-progression outcomes in ER+/HER2- metastatic breast cancer after treatment with endocrine therapy and CDK 4/6 inhibitors within randomized clinical trials.

First Author: Elisabetta Munzone, European Institute of Oncology, Milan, Italy

Background: CDK4/6 inhibitors combined with endocrine therapy (ET) deeply transformed the treatment landscape of HR+/HER2− advanced breast cancer. After progression with the combination, there are no established guidelines for an optimal sequencing of the various therapeutic options. Data from randomized clinical trials (RCT) suggest that subsequent progression free survival (PFS2) was not compromised by the use of these drugs and time to subsequent chemotherapy (TTC) may be delayed. Therefore, we performed a meta-analysis to evaluate the benefit of such treatments on PFS2 and on delaying the TTC. **Methods:** We conducted a systematic literature search using PubMed to select all available randomized clinical trials of CDK4/6-inhibitors and ET reporting PFS2 or TTC data in first- or second-line therapy of HR+/HER2- pre- or postmenopausal metastatic breast cancer. We also reviewed abstracts and presentations from all major conference proceedings. We calculated the pooled hazard ratios (HR) for PFS2 and TTC with 95% confidence intervals (CI) using fixed-effects models. The pooled HRs for PFS and OS were also calculated. I^2 was used to quantify heterogeneity between studies' results. **Results:** Seven studies (PALOMA 1-2-3, MONALEESA 3-7, MONARCH 2-3) were included in our analyses (n = 3912 patients). A clear PFS2 benefit was observed in patients who received CDK 4/6 inhibitors + ET (pooled HR = 0.67, 95% CI = 0.61 to 0.74, I^2 = 0.0%) and also a delay in subsequent TTC (pooled HR = 0.63, 95% CI = 0.58 to 0.70, I^2 = 0.0%). As previously reported, the benefit in terms of PFS (pooled HR = 0.54, 95% CI = 0.50 to 0.59, I^2= 0%) and OS (pooled HR = 0.77, 95% CI = 0.68 to 0.86, I^2= 0%) was also confirmed. **Conclusions:** CDK4/6-inhibitors plus ET compared with ET alone improve PFS2, and TTC. The delay of chemotherapy can spare the patients toxicities, potentially improving the quality of life. Thus, the observed benefit in PFS2 may postpone the onset of endocrine resistance and may offer an additional therapeutic advantage in this setting. Research Sponsor: None.

1060 **Poster Session**

Impact of duration of prior cyclin-dependent kinase 4/6 inhibitor (CDK4/6i) therapy on alpelisib (ALP) benefit in patients (pts) with hormone receptor–positive (HR+), human epidermal growth factor receptor-2–negative (HER2–), *PIK3CA*-mutated advanced breast cancer (ABC) from BYLieve. *First Author: Stephen K. L. Chia, British Columbia Cancer Agency, Vancouver, BC, Canada*

Background: Mutations in *PIK3CA* (encoding PI3Kα) are present in ~40% of HR+, HER2– ABC tumors and are associated with relative endocrine resistance and poor prognosis. ALP inhibits and degrades PI3Kα. Primary analyses of Cohorts A and B from the phase 2 BYLieve study demonstrated that ALP + endocrine therapy (ET; fulvestrant [FUL] or letrozole [LET]) is effective and safe in pts with HR+, HER2– *PIK3CA*-mutated ABC with prior CDK4/6i therapy. Here, we evaluate if duration of prior CDK4/6i-based therapy impacts benefit of ALP + ET in these 2 cohorts. **Methods:** Cohorts A and B of BYLieve included pre/postmenopausal women who received CDK4/6i + AI or FUL, respectively, as immediate prior therapy. Cohort A received ALP 300 mg PO QD + FUL 500 mg IM Q28D + C1D15; Cohort B received ALP 300 mg PO QD + LET 2.5 mg PO QD. Within each cohort, pts were divided into 2 subgroups per duration of prior CDK4/6i therapy ("high"/"low," above/below median duration of therapy) and the association of progression-free survival (PFS) with this covariate was analyzed using stratified log-rank test and Cox PH model. This analysis included pts for whom duration of prior CDK4/6i therapy was known, and efficacy was assessed in pts with centrally confirmed *PIK3CA* mutation in tumor tissue. **Results:** Of the 126 pts in Cohort A with duration of prior CDK4/6i available, 120 had centrally confirmed *PIK3CA*-mutated disease; 60 were exposed to CDK4/6i for $>$ 380 days (high) and 60 for $<$ 380 days (low), with similar demographics/disease characteristics between subgroups. There was no significant difference in PFS between the high vs low subgroups (HR 1.03; 95% CI, 0.64-1.64; P= 0.927; median 8.0 vs 7.0 mo). Grade $\geq$3 adverse events (AEs) were experienced by 66.9% (n = 85) of all pts in Cohort A and 66.7% (n = 42)/68.3% (n = 43) in the high/low subgroups, respectively. Of the 123 pts in Cohort B with duration of prior CDK4/6i available, 113 had centrally confirmed *PIK3CA*-mutated disease; 57 were exposed to CDK4/6i for $>$ 305 days (high) and 56 for $<$ 305 days (low), with similar demographics/disease characteristics between subgroups. There was no significant difference in PFS between high vs low subgroups (HR 1.20; 95% CI, 0.78-1.84; P= 0.400; median 5.4 vs 5.9 mo). Grade $\geq$3 AEs were experienced by 69.8% (n = 88) of all pts in Cohort B and 71.0% (n = 44)/68.9% (n = 42) in the high/low subgroups, respectively. **Conclusions:** This analysis demonstrates that the benefit and safety profiles of ALP + ET are similar in pts with HR+, HER2– *PIK3CA*-mutated ABC who achieved relatively shorter duration of disease control with prior CDK4/6i vs those with longer duration of disease control, and suggests that ALP overcomes acquired resistance to CDK4/6i in these pts. Clinical trial information: NCT03056755. Research Sponsor: Novartis Pharmaceuticals Corporation.

1061 **Poster Session**

Results from CONTESSA 2: A multinational, multicenter, phase 2 study of tesetaxel (T) plus a reduced dose of capecitabine (C) in patients (pts) with hormone receptor + (HR+), HER2- metastatic breast cancer (MBC) not previously treated with a taxane. *First Author: Lee S. Schwartzberg, West Cancer Center, Memphis, TN*

Research Funding: Odonate Therapeutics, Inc. **Background:** T is a novel, oral taxane with unique properties, including: oral administration with a low pill burden, a long (8-day) half-life in humans, once-every-3-weeks dosing, no observed hypersensitivity reactions and significant activity against chemotherapy (CT)-resistant breast cancer cell lines. T had encouraging monotherapy activity in a phase 2 study in 38 pts with HR+, HER2- MBC, with a confirmed objective response rate (ORR) per RECIST 1.1 of 45% (Seidman, 2018 ASCO Annual Meeting, Abstract 1042). In CONTESSA, a randomized phase 3 study in 685 pts with HR+, HER2- MBC previously treated with a taxane, T plus a reduced dose of C improved progression-free survival (PFS) as assessed by the Independent Radiologic Review Committee (IRC) vs. the approved dose of C alone: median of 9.8 months (mo) vs. 6.9 mo, an improvement of 2.9 mo (HR=0.716; p=0.003) (O'Shaughnessy, SABCS 2020, GS4-01). **Methods:** CONTESSA 2 is a multinational, multicenter, phase 2 study of T (27 mg/m^2 on day 1 of a 21-day cycle) plus a reduced dose of C (1,650 mg/m^2/day for 14 days of a 21-day cycle) in pts with HR+, HER2- MBC previously treated with 0-1 prior CT regimens for MBC and not previously treated with a taxane. The primary endpoint is ORR as assessed by the IRC. The secondary efficacy endpoints are duration of response (DoR), PFS and disease control rate (DCR) as assessed by the IRC, and overall survival (OS). **Results:** 150 pts were enrolled and treated. 80% had visceral disease, 46% had de novo MBC, 52% were previously treated with a CDK 4/6 inhibitor and 33% were $\geq$65 years old. At the prespecified interim analysis approx 4 mo after the last patient enrolled, the confirmed ORR was 51% (95% CI: 42%-60%), and the unconfirmed ORR was 63% (95% CI: 54%-71%). The median DoR was 9.5 mo (95% CI: 5.4-11.5 mo), the median PFS was 12.9 mo (95% CI: 8.1 mo-NR) and the DCR was 71% (95% CI: 62%-79%). OS data are immature. Grade (Gr) $\geq$3 treatment-emergent adverse events (TEAEs) occurring in $\geq$5% of pts were: neutropenia (74.0%), leukopenia (10.7%), hypokalemia (7.3%), anemia (6.7%), hand-foot syndrome (6.0%) and diarrhea (5.3%). Gr 2 alopecia occurred in 11.3% of pts, febrile neutropenia occurred in 4.7% of pts and Gr $\geq$3 neuropathy occurred in 2.0% of pts. Discontinuation of T and C due to any adverse event occurred in 13.3% of pts. **Conclusions**: An all-oral regimen of T plus a reduced dose of C demonstrated a high level of antitumor activity in pts with HR+, HER2- MBC not previously treated with a taxane. The confirmed ORR was 51%, median DoR was 9.5 mo and median PFS was 12.9 mo. Neutropenia was the most frequent Gr $\geq$3 TEAE; the rate of febrile neutropenia was 4.7%. Rates of clinically significant alopecia and neuropathy were low. Clinical trial information: NCT03858972. Clinical trial information: NCT03858972. Research Sponsor: Odonate Therapeutics, Inc.

1062 **Poster Session**

Endocrine therapy-based strategies with different endocrine sensitivity statuses for hormone receptor positive/HER2 negative metastatic breast cancer: A network meta-analysis. *First Author: Jiani Wang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Novel endocrine therapies (ETs) and targeted therapeutic regimens have been developed to dramatically improve the outcome of hormone receptor-positive (HR+), HER2-negative (HER2-) metastatic breast cancer (MBC). Since the absence of direct head-to-head comparisons for all regimens, decision-making guidelines are urgently needed for different endocrine sensitivity statuses. This study is to evaluate the efficacy of ET-based regimens in patients with HR+/HER2- MBC and to assess the heterogeneity among different compounds with a particular focus on their ability to improve survival outcomes. **Methods:** This network meta-analysis of phase II/III randomized controlled trials (RCTs) with at least one ET in HR+/HER2- MBC were enrolled. Based on the endocrine responses, participants were stratified into endocrine therapy sensitivity (ETS) and endocrine therapy resistance (ETR) groups. Primary endpoints, including progression-free survival (PFS) and overall survival (OS), were assessed by bayesian algorithms and primarily measured as surface under the cumulative ranking curve (SUCRA). **Results:** A total of 42 trials (22917 patients) were included. Regarding PFS, cyclin-dependent kinases 4/6 inhibitors (CDK4/6i) +fulvestrant 500mg (F500) was recommended for the ETS group (SUCRA = 76.92%), while chemotherapy was considered as the most effective option for the ETR group (SUCRA = 73.47%). For visceral metastases, CDK4/6i +aromatase inhibitors (AIs) could provide the extreme efficacy for the ETS group (SUCRA = 63.27%) while the CDK4/6i +F500 (SUCRA = 76.17%) as the prior regimen for the ETR group. For bone-only disease, CDK4/6i+F500 was preferred for both the ETS (SUCRA = 67.04%) and the ETR (SUCRA = 70.24%) group. Concerning OS, CDK4/6i+tamoxifen was estimated as the first-rank regimen for the ETS subgroup (SUCRA = 67.04%) and chemotherapy for the ETR subgroup (SUCRA = 60.02%). Regarding resistance category, abemaciclib +F500 was likely the best option with PFS, for both primary (SUCRA = 69.19%) and secondary ETR (SUCRA = 69.09%) settings, as well as primary ETR associated with OS improvement (SUCRA = 67.67%). Pictilisib +F500 could be the optimal treatment with OS for secondary ETR (SUCRA = 60.50%)group. **Conclusions:** The results showed that CDK4/6i + F500 was probably the most promising option in ETS, visceral ETR and bone-only disease settings in terms of PFS. OS subgroup analysis showed that different endocrine sensitivity statuses required various optimal treatment strategies. Research Sponsor: None.

1063 **Poster Session**

Rintodestrant (G1T48), an oral selective estrogen receptor degrader, in combination with palbociclib for ER+/HER2– advanced breast cancer: Phase 1 results. *First Author: Marina Maglakelidze, LLC Arensia Exploratory Medicine, Tbilisi, Georgia*

Background: Rintodestrant, a potent, oral selective estrogen receptor degrader, competitively binds and degrades the estrogen receptor (ER), thus blocking ER signaling in tumors resistant to other endocrine therapies (ET). Results from parts 1 and 2 dose-escalation/expansion indicate that once-daily (QD) rintodestrant has a favorable safety profile and antitumor activity in patients (pts) with heavily pretreated ER+/HER2– advanced breast cancer (ABC), including those with *ESR1* variants (Aftimos et al. SABCS 2020 [PS12-04, PD8-07]). The optimal dose of rintodestrant was 800 mg. Here, we present part 3, combining rintodestrant with the CDK4/6 inhibitor palbociclib. **Methods:** This open-label study evaluated rintodestrant in pts with ER+/HER2– ABC after progression on ET (NCT03455270). Part 3 assessed rintodestrant 800 mg QD + palbociclib 125 mg QD for 21 days every 28 days. Key eligibility criteria included $\leq$1 line of chemotherapy and/or $\leq$1 line of ET in the advanced setting, with $\geq$6 months of ET in the advanced setting and/or $\geq$24 months in the adjuvant setting. Prior CDK4/6 inhibitor therapy was not allowed. Primary objectives included safety and efficacy. Secondary objectives included pharmacokinetics and antitumor activity (RECIST v1.1). Exploratory objectives included mutation profiling (cell-free DNA) at baseline and cycle 1 day 15. **Results:** Enrollment occurred Jul–Oct 2020. As of Dec 9, 2020, 40 pts were treated, with a median age of 58 years (35–76) and ECOG PS of 0 (70%) or 1 (30%); 20% had de novo stage 4 disease, 10% bone-only, and 68% visceral metastases. Median number of visceral sites was 1 (0–3): 30% of pts with lung and 40% with liver involvement. Median number of prior lines in the advanced setting was 1 (0–2), including chemotherapy (48%), fulvestrant (15%), and aromatase inhibitors (50%). Most recent ET was given in the adjuvant and metastatic settings in 28% and 73% of pts, respectively. Rintodestrant-related adverse events (AEs) were reported in 8% of pts—all nonserious and grade 2—and included nausea (3%), vomiting (3%), and neutropenia (3%). The most common ($\geq$10%) treatment-related AEs (rintodestrant and/or palbociclib) were neutropenia (88%), leukopenia (45%), anemia (10%), and thrombocytopenia (10%); grade 3/4 neutropenia was 38%/15%, in line with the safety profile of palbociclib. No deaths or treatment discontinuations due to AEs were reported. At data cutoff (median treatment duration of 3 months [1.5–4.6]), 28 pts (70%) remained on study treatment, 2 (5%) had a confirmed partial response, and 27 (68%) had stable disease. Additional efficacy and pharmacodynamic data will be presented. **Conclusions:** Rintodestrant, as monotherapy or combined with palbociclib, continues to demonstrate an excellent safety/tolerability profile with promising antitumor activity in pts with ER+/HER2– ABC, including those with *ESR1* variants. Clinical trial information: NCT03455270. Research Sponsor: G1 Therapeutics, Inc.

1064 **Poster Session**

Alpelisib and fulvestrant efficacy in HR-positive HER2-negative *PIK3CA*-mutant advanced breast cancer: Data from the French early access program. *First Author: Diana Bello, Institut Curie, Saint-Cloud, France*

Background: In 11.2018, the PIK3CA-inhibitor alpelisib was made available in France through an early access program (EAP), in combination with fulvestrant in pre-treated PIK3CA-mutant, HR-positive, HER2-negative advanced breast cancer (ABC) patients. Patients had to received two or more prior systemic treatments for ABC, including an aromatase inhibitor and a CDK4/6 inhibitor in the absence of contraindications. This retrospective real-life, EAP-based study aimed to assess the efficacy and safety of alpelisib/fulvestrant combination in the post CDK4/6 inhibitor setting. **Methods:** The IRB-approved protocol and call for data were sent on 10.2020 to the cancer centers which participated the most in the EAP prospective registry. Eligible patients were women who started alpelisib/fulvestrant between 11. 2018 and 10.2020 as part of the EAP (which excluded patients with visceral crisis or inflammatory BC). Alpelisib and fulvestrant were used at standard doses. Primary endpoint was PFS by local investigators using RECIST1.1. Secondary endpoints included objective response rate and safety (NCI CTCAE v5.0). **Results:** 10 centers provided individual data regarding 209 consecutive patients. Patients had received a median number of 4 (1-14) previous systemic treatments for ABC, including CDK4/6 inhibitors, chemotherapy, fulvestrant (alone or in combination) and everolimus for 206 (98.8%), 159 (76.1%), 163 (78%) and 123 (58.8%) patients, respectively. With a median FU of 7.0 months, median PFS was 4.0 months (95%CI [3.5;5.0]) and 35.4% of 164 evaluable patients had an objective response. After stratification on the number of prior lines of treatment, prior exposure to everolimus had no impact on PFS (mPFS in the 123 patients pretreated with everolimus: 4.0m, 95%CI [3.5-5.5]). Of note, this population was enriched in patients who had a long disease control by everolimus (median time spent on everolimus: 7.0m, range (6.5-9.0)). In multivariable analysis, characteristics significantly associated with longer PFS were PS < 3 (HR = 0.03, 95%CI [0.02-0.29]) and prior treatment with fulvestrant (HR = 0.53, 95%CI [0.32-0.89]). N = 81(38.8%) patients discontinued alpelisib due to adverse events (AEs). Most frequent grade 3/4 AEs were hyperglycemia, skin rash, diarrhea and fatigue occurring in 13.4, 8.1, 4.8 and 1.9 % of patients, respectively. **Conclusions:** Despite heavy pre-treatments, alpelisib +fulvestrant had a clinically relevant efficacy in the French EAP population. Interestingly, prior treatment with either everolimus or fulvestrant did not overtly impair alpelisib-fulvestrant efficacy. The best treatment sequence for PI3KCA/mTOR inhibitors could be examined in future trials in PIK3CA-mutant ER+/HER2- ABC patients. Research Sponsor: None.

1065 **Poster Session**

Landscape of *GATA3* mutations identified from circulating tumor DNA clinical testing and their impact on disease outcomes in estrogen receptor-positive (ER+) metastatic breast cancers treated with endocrine therapies. *First Author: Marko Velimirovic, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: The *GATA3* gene encodes for a transcription factor (TF) that plays a pivotal role in the development of breast tissue. Breast tumors with lower *GATA3* expression have worse prognosis compared to tumors with higher expression. However, the consequences of somatic *GATA3* mutations ($GATA3^{mut}$) on clinical outcomes in metastatic breast cancer (MBC) remain poorly understood. Further, *GATA3* TF interferes with *FOXA1* and *ER* to enhance transcription of *ER*-responsive genes, but the role of $GATA3^{mut}$ in altering downstream transcriptional activity and its effects on response to anti-estrogens remains unclear. **Methods:** We retrospectively identified ctDNA next-generation sequencing results from 101 ER+/HER2- patients with MBC treated with either selective estrogen receptor degraders (SERDs) alone or a combination of SERDs and CDK4/6 inhibitors at Massachusetts General Hospital (Boston, MA) and Northwestern University (Chicago, IL). Associations between $GATA3^{mut}$, patient and tumor characteristics, and prior treatments were assessed using logistic regression. Clinical outcomes were estimated through Cox proportional hazards regression. **Results:** $GATA3^{mut}$ were observed in 13 patients (13%), each with a single *GATA3* variant. These mutations were detected in exon 4 (M294K), exon 5 that includes Zn-finger-2 motif (T327fs, R331fs, N334K, D336fs, c.925-3_925-2del splice acceptor variant), and exon 6 (K358fs, P409fs, M416fs, G431fs, M439fs, V440fs). All mutations except for M294K were insertion/deletion frameshift mutations that result in either elongation or truncation of the protein, potentially with heterogenous downstream effects. $GATA3^{mut}$ were the only detectable alteration in 4 patients. The most commonly co-occurring mutations with $GATA3^{mut}$ were $ESR1^{mut}$ in 7/13 (53.8%) and $PIK3CA^{mut}$ in 6/13 (46%) patients. Presence of $GATA3^{mut}$ was associated with prior exposure to chemotherapy (OR = 1.09, 95%CI [1.01 - 1.10], p = 0.03). Patients with $GATA3^{mut}$ tumors had shorter PFS compared to $GATA3^{wild}$ tumors (4.1 vs. 6.7 months, in both univariate and multivariate analysis controlled for presence of $ESR1^{mut}$: HR = 2.22 95%CI [1.12 – 4.38], p = 0.02). OS was also significantly shorter in patients harboring $GATA3^{mut}$ compared to $GATA3^{wild}$ (14.1 vs. 27.1 months, multivariate analysis: HR = 2.30 95%CI [1.04 – 5.11], p = 0.04). **Conclusions:** $GATA3^{mut}$ in breast cancer tend to be grouped within exons 5 and 6, and they likely contribute to acquired resistance to endocrine-based therapies in MBC. Our study showed that patients with $GATA3^{mut}$ ER+ MBC have worse prognosis compared to those who were $GATA3^{wild}$. Larger studies are needed to further stratify and ascertain functional effects of different *GATA3* mutations and explore *GATA3* gene or its translational product as a possible druggable target. Research Sponsor: None.

1066 **Poster Session**

On-treatment derived neutrophil-to-lymphocyte ratio and response to palbociclib and letrozole: Analysis of a multicenter retrospective cohort and the PALOMA-2 study. *First Author: Chang Gon Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Relevant predictive biomarkers for cyclin dependent kinase 4 and 6 (CDK4/6) inhibitors have not been identified in hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer (ABC). We investigated whether dynamic changes in the peripheral immune cells can predict therapeutic response to CDK4/6 inhibitors in ABC with translational relevance. **Methods**: Postmenopausal women who received palbociclib and letrozole for HR-positive, HER2-negative ABC from tertiary referral centers were analyzed (n = 221; exploratory cohort). Pre- and on-treatment leucocyte, neutrophil, lymphocytes counts, neutrophil-to-lymphocyte ratio (NLR), and derived NLR (dNLR; neutrophil/[leucocyte-neutrophil]) were correlated with survival outcomes. Patients from the PALOMA-2 study (NCT01740427) treated with letrozole with or without palbociclib (n = 410 and 209, respectively) were analyzed for validation (validation cohort). Prospectively enrolled patients were subjected to immunophenotyping with flow cytometry to explore the immune cell dynamics after CDK4/6 inhibitor treatment. **Results**: In the exploratory cohort, palbociclib administration significantly reduced leucocyte, neutrophil, and lymphocyte counts on cycle 2 day 1. Not baseline, but on-treatment neutrophil and lymphocyte counts were associated with superior and inferior outcomes, providing predictive significance to on-treatment NLR and dNLR for progression-free survival (PFS; HR = 1.64 and 2.52; all $P< 0.001$). In the validation cohort, higher on-treatment dNLR was associated with inferior PFS in patients treated with palbociclib and letrozole (HR = 1.50 and $P= 0.009$ with 1.04 cut-off), whereas not correlated with outcome in placebo and letrozole-administered patients. Exploratory analysis revealed that CDK4/6 inhibitor prevented T cell exhaustion and diminished relative frequencies of myeloid-derived suppressor cells, both of which trigger antitumor immunity. **Conclusions**: On-treatment dNLR significantly predicted treatment outcome in HR-positive, HER2-negative ABC treated with palbociclib and letrozole, allowing early prediction of treatment response with mechanistic insights. Clinical trial information: NCT01740427. Research Sponsor: None.

1067 **Poster Session**

Phase I safety and efficacy study of autophagy inhibition with hydroxychloroquine to augment the antiproliferative and biological effects of preoperative palbociclib plus letrozole for estrogen receptor-positive, HER2-negative metastatic breast cancer (MBC). *First Author: Akshara Singareeka Raghavendra, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Endocrine therapy with a CDK4/6 inhibitor is standard of care for patients (pts) with estrogen-receptor-positive (ER+), HER2-negative MBC, yet resistance ultimately develops. We have shown that low doses of palbociclib activates autophagy, which reverses initial G1 cell cycle arrest. High concentrations of palbociclib induce senescence, but these are off target effects of the drug. The autophagy inhibitor hydroxychloroquine (HCQ) induces senescence at a lower (i.e. on-target) continuous dosing of palbociclib, in *in vitro* and *in vivo* models. This strategy is being tested in a phase I/II trial (NCT03774472). Results from the phase I portion are reported here. **Methods:** The phase I part of this study uses a dose escalation 3+3 design testing HCQ, 400, 600 and 800 mg daily (6 pts at 800 mg) with continuously dosed palbociclib at 75 mg and letrozole 2.5 mg daily. Dose limiting toxicity (DLT) includes any study drug-related grade $\geq$ 3 nonhematological (lab) toxicity. Responding pts may continue on therapy beyond 8 weeks for up to 52 weeks. Primary objective is to determine safety, tolerability and the recommended phase 2 dose (RP2D) of HCQ. Secondary objectives are overall tumor response and time to progression. Eligible pts are $\geq$18 years of age, postmenopausal (ovarian suppression allowed) with ER+/HER2-negative MBC, ECOG performance status score of $\leq$1 and with adequate renal, hepatic, and hematologic function. Response is assessed per RECIST v1.1. **Results:** Between 9/24/18 and 12/15/20, 14 pts were evaluable for safety. Median age was 41 with Asian (1, 7.1%), Black (2, 14.3%) White (11, 78.6%) patients enrolled. No DLTs were observed. One pt progressed during the DLT period and 2 withdrew consent (one during the DLT period); two pts were replaced for DLT assessment. Reasons for coming off study were grade 3 skin toxicity (1), per protocol at 8 weeks (non-measurable or pt/physician preference, 9), and (2) full duration treatment at 50 and 52 weeks. Adverse events (AEs) of grade $\geq$3 were hematologic (29), metabolism/nutrition (2), musculoskeletal/ connective tissue (1), and skin/subcutaneous tissue (3), with no serious AEs reported. The percent of palbociclib doses held per pt due to neutrophil level ranged from 0-37.5% with no apparent relation to HCQ dose. Best response was partial (2) stable (11); and progression (1). For measurable disease, tumor decreases of 11%, 12%, 21%, 26%, 30%, 55% and increase in 1 pt by 55% were seen. **Conclusions:** This phase I study showed acceptable safety and no HCQ dose-toxicity relationship. The RP2D of HCQ is 800 mg/day with continuous dosing palbociclib at 75 mg/day and letrozole at 2.5 mg/day. The phase 2 trial will proceed in the neoadjuvant setting, with Ki67 proliferative index response as the primary endpoint. Clinical trial information: NCT03774472. Research Sponsor: U.S. National Institutes of Health.

1068 **Poster Session**

Real-world (rw) clinical outcomes on alpelisib (ALP) in patients (pts) with breast cancer (BC) and *PIK3CA* mutations (PIK3CAm). *First Author: Hope S. Rugo, University of California, San Francisco, San Francisco, CA*

Background: ALP was approved by the FDA for treatment of HR+/HER2- advanced BC with activating PIK3CAm based on the phase 3 SOLAR-1 trial. Enrollment used 11 PIK3CAm (SOLAR1m) in *PIK3CA* exons 7, 9 and 20. We report the prevalence of SOLAR1m and other predicted activating mutations elsewhere in the *PIK3CA* gene (OTHERm) in pts with BC, as well as rw clinical outcomes of ALP treatment in these pts. **Methods:** Comprehensive genomic profiling (CGP) results from 31,765 tissue and 4,147 liquid biopsies from pts with BC were analyzed. Clinical characteristics and treatment history were available for 1,579 pts with PIK3CAm in a de-identified Flatiron Health-Foundation Medicine clinico-genomic database (data obtained from ~800 US sites, 1/2011 - 9/2020, via technology-enabled abstraction of clinician notes and radiology/pathology reports). 3 cohorts were considered. Cohort A: HR+/HER2- pts receiving fulvestrant (FUL) alone (n = 124) or ALP/FUL (n = 111) in treatment line ≥2L were considered in survival analysis. Rw progression-free survival (rwPFS) from start of treatment was estimated with Kaplan-Meier analysis and hazard ratios from Cox proportional hazards models adjusted for survival bias. Cohort B: 627 HR+/HER2- pts who received a clinical report with ALP listed (report date after 5/2019) Cohort C: 36 pts with OTHERm only, any receptor subtype, treated with ALP in any combination. **Results:** Among 31,765 BC tissue biopsies, 10,869 (34%) had PIK3CAm. 8,750 (28%) had SOLAR1m, and of these 1,146 had ≥1 additional OTHERm. 2,119 pts (6.7%) had ≥1 OTHERm without any SOLAR1m. OTHERm more common in the presence of a SOLAR1m were: E726K, E418K, E365K, E453Q, and H1048R ($p < 0.0001$). OTHERm more common in absence of a SOLAR1m were: N345K, G1049R, Q546K, and indels disrupting PIK3R1 binding ($p < 0.0001$). Among 4,147 liquid biopsies, detection rates were comparable to tissue: 1,391 (34%) had PIK3CAm and 1159 (28%) had SOLAR1m. In Cohort A, median rwPFS was 4.1 mo on FUL [95%CI: 3-6.2] versus 6.5 mo on ALP/FUL [95%CI: 4.8-9.5] ($p = 0.027$). In Cohort B, 202/524 (39%) pts with a SOLAR1m were treated with ALP, compared to 28/103 (27%) pts who had OTHERm only. Pts with SOLAR1m received ALP treatment earlier: median [interquartile range] 4L [3-6] versus 5.5L [4-8]. In Cohort C, rwPFS > 6 months was observed in 5 pts bearing: N345K, Q75E, R38C, G106_108del, and N345K/N1044K. **Conclusions:** This study validates the activity of ALP among a diverse real world population, showing pts with *PIK3CA* mutations have longer rwPFS on ALP/FUL than FUL alone. Pts with SOLAR1m were more likely to be treated with ALP- and tended to be treated in earlier line settingthan pts with OTHERm. No consistent effect in a small subset of pts with OTHERm treated with ALP was observed, but there is evidence that OTHERm may differ in their degree of PI3K activation, oncogenicity, and ALP sensitivity. Liquid biopsy CGP detected PIK3CAm at similar rates to tissue biopsy. Research Sponsor: Foundation Medicine.

1069 **Poster Session**

Stereotactic radiosurgery (SRS) for brain metastasis (BM) in hormone receptor positive (HR+) HER2 negative breast cancer (BC). *First Author: Akshara Singareeka Raghavendra, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: With the increase of the utilization of SRS for the treatment of oligometastatic BM over surgical reaction or whole brain radiation therapy (WBRT), we sought to evaluate the impact of SRS on overall survival in HR+Her2- BC and prognostic factors associated with SRS. **Methods**: We reviewed prospectively collected data in the electronic data bases of the breast medical, surgical and radiation oncology departments at MD Anderson cancer center. We aimed at identifying HR+HER2- BC patients who received upfront SRS for BM's between 08/10/2009 and 02/27/2018.Overall survival was defined as the time from the first SRS to last follow-up/death. Multivariate analysis by the Cox proportional hazards regression analysis was performed to evaluate the prognostic factors (age at BM, stage, Karnofsky performance score (KPS), symptomatic BM, BM at 1stdistant metastatic presentation, extracranial Disease, treatment history, salvage therapy, number of brain lesion treated) of SRS that influenced survival. **Results:** A total of 125 patients were identified, and we are reporting on 68 with completed analysis. Median age at time of first SRS was 53.86 years. 51 patients of the 68 were deceased at the time of this analysis and 17 patients were alive at the time of last follow-up. 49 patients (72.06 %) presented with radiation necrosis after SRS; 36 patients (52.94 %) presented with BM as 1st distant metastasis including metastasis to other sites. Number of BM's lesions <4 was 60 (88.2%) and >=4 was 7 (10.3%). The median follow-up from time of first SRS for survivors was 10.84 months. 24 (35.29%) received two or more sessions of SRS and the mean time between first and second SRS sessions for these patients was 14.24 months. Median time from first SRS to second SRS for ER+HER2− patients was 10.84 months (n = 24); on multivariable analysis, higher Karnofsky performance score (KPS) was associated with better survival compared to no salvage therapy. Patients with KPS>90 (p=0.005) had better survival and reduced the hazard by a factor of 0.33 (or 67%). Receiving SRS (p=0.0003) or SRS+WBRT (0.0001) as salvage therapy reduced the hazard (risk of death) by 86% and 85%, respectively. **Conclusions:** SRS is an effective treatment modality for HR+HER2- BM from BC. Patients who received SRS or SRS and WBRT, KPS >90 had better survival than patients who didn't receive any salvage therapy. Updated data will be available at the time of the presentation. Research Sponsor: None.

Types of initial and salvage treatments for BM.

Type of Initial treatment for BM	68	%
SRS alone	55	88.88
SRS + Surgery	10	14.71
SRS + WBRT	3	4.41
Type of Salvage after initial SRS		
None	33	48.53
SRS alone	8	11.76
WBRT	11	16.18
SRS + LITT	1	1.47
SRS + Surgery	1	1.47
SRS + WBRT	9	13.24
SRS + Surgery + LINAC	1	1.47
SRS + Surgery + WBRT	3	4.41
SRS + WBRT + LINAC	1	1.47

1070 **Poster Session**

Efficacy of AI and palbociclib in ER+ HER2- advanced breast cancer patients relapsing during adjuvant tamoxifen: An exploratory analysis of the PADA-1 trial. *First Author: François-Clément Bidard, Institut Curie, Paris, France*

Background: In PADA-1 (NCT03079011), a phase III trial testing the clinical utility of $ESR1_{mut}$ detection, ER+ HER2- advanced breast patients (ABC pts) received Aromatase Inhibitor (AI) and Palbociclib (Pal) +/- LHRH agonist as first line therapy. PADA-1 was open to "AI-sensitive" pts, including those with de novo stage IV disease or metastatic relapse after adjuvant endocrine therapy but also pts with metastatic relapses during adjuvant tamoxifen (TAM). In this subsidiary analysis, we report the efficacy of AI+PAL as first line therapy in patients relapsing on adjuvant TAM. **Methods:** Main inclusion criteria in PADA-1 are: pre- or post-menopausal pts with ER+ HER2- ABC, who did not receive any prior therapy for ABC and who had no adjuvant AI or completed adjuvant AI for > 12 months or who had disease recurrence while on adjuvant TAM. **Results:** From 04/2017 to 01/2019, 1017 ABC pts have been included in PADA-1, of which 115 (11.3%) had a metastatic relapse while on adjuvant TAM (TAM only (N = 112) or TAM+GnRH agonist (N = 3)). Median age at inclusion was 46 years (range 25-81), and 58 (50.4%) patients had visceral disease. The median PFS under AI+PAL was 20.4 months (95%CI16.1;27.8) in patients relapsing during adjuvant TAM. In contrast, median PFS in patients with de novo metastatic disease and metastatic relapses after the completion of adjuvant endocrine therapy were 30.6 months (95%CI26.7;Not reached) and 27.8 months (95%CI24.1;30.)], respectively. A subgroup analysis among patients relapsing on adjuvant TAM showed that those relapsing during the first two years of adjuvant TAM had a shorter PFS (11.4 months 95%CI[8.7;20.7]) than those relapsing after 2 years of adjuvant TAM (23.8 months 95%CI[20.2;Not reached]). **Conclusions:** To our knowledge, these are the first data on first line AI+CDK4/6 inhibitor in patients relapsing on adjuvant TAM. While PFS on AI + PAL appears primarily driven by endocrine resistance status, our data show that AI+PAL is a valuable option also in patients relapsing during adjuvant TAM. Clinical trial information: NCT03079011. Research Sponsor: Pfizer.

1071 **Poster Session**

Real-world quality of life (QoL) in black, indigenous and people of color (BIPOC) treated with palbociclib (PAL) and endocrine therapy for hormone receptor–positive (HR+)/human epidermal growth factor receptor 2–negative (HER2–) advanced breast cancer (ABC): A subgroup analysis from POLARIS. *First Author: Gabrielle Betty Rocque, University of Alabama at Birmingham, Birmingham, AL*

Background: Racial disparities in breast cancer incidence, mortality, and care are well documented. PAL plus endocrine therapy is indicated for patients (pts) with HR+/HER2− ABC. Findings from the PALOMA clinical trials have shown that pts receiving PAL maintained stable QoL; however, limited QoL data are available from real-world settings for BIPOC receiving PAL. **Methods:** POLARIS is a noninterventional, prospective, primarily US-based study in pts with HR+/HER2− ABC receiving PAL. QoL was assessed with the European Organisation for Research and Treatment of Cancer Quality-of-Life Questionnaire Core 30 (EORTC QLQ-C30) at baseline, monthly for the first 3 mo of treatment (Tx) with PAL, and then every 3 mo. In this interim analysis, we report Tx patterns and QoL assessments at baseline and at 6 mo and 12 mo in BIPOC from POLARIS. **Results:** Of 1280 pts treated with PAL as November 10, 2020, 233 were included in the BIPOC subgroup of whom 159 (68.2%) completed PAL Tx for ≥6 mo and 112 (48.1%) for ≥12 mo. In the BIPOC cohort, 59.2% of pts were black, 35.2% Hispanic, 3.4% American Indian or Alaskan native, 2.1% Pacific Islander. PAL in combination with letrozole/anastrozole was received by 116 pts, 94 received PAL plus fulvestrant, 13 received PAL plus exemestane, and 10 received PAL plus another Tx; 175 pts (75.1%) received PAL as first-line Tx. Mean EORTC QLQ-C30 global health QoL and functional scales scores remained stable over the first 12 mo of PAL Tx, without any changes at or above the 10-point threshold considered clinically meaningful, and were similar to those previously reported in an earlier analysis of the entire POLARIS population (Table and Rocque et al SABCS 2019). Symptom scales scores, including nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, and diarrhea, also remained stable over 12 mo. **Conclusions:** In this subgroup analysis, PAL had no significant adverse impact on QOL in BIPOC with HR+/HER2− ABC, consistent with previous findings from the total POLARIS study population. Pfizer (NCT03280303). Clinical trial information: NCT03280303. Research Sponsor: Pfizer Inc.

EORTC QLQ-C30*	Baseline	6 Months	12 Months
Global health/QoL			
n (missing)	211 (22)	121 (78)	78 (93)
Mean (SD) score	62.0 (23.6)	71.0 (21.4)	68.1 (22.8)
Functional scales score, mean (SD)			
Physical	73.2 (25.5)	75.4 (23.5)	73.0 (23.0)
Role	70.0 (33.9)	72.3 (31.0)	71.2 (29.6)
Emotional	73.5 (24.9)	78.1 (23.0)	74.8 (25.7)
Cognitive	79.3 (23.8)	78.2 (23.8)	80.8 (24.9)
Social	73.7 (30.6)	77.7 (25.5)	75.6 (30.5)

*Higher scores indicate a better level of functioning.

1072 **Poster Session**

Relative risk of pneumonitis or interstitial lung disease (ILD) associated with the use of cyclin-dependent kinase inhibitors (CDK4/6i): A systematic review and meta-analysis of phase 3 randomized controlled trials. *First Author: Nusrat Jahan, Texas Tech University Health Sciences Center, Lubbock, TX*

Background: All three currently approved cyclin-dependent kinase 4/6 inhibitors (CDK4/6i) such as palbociclib, abemaciclib, and ribociclib are reported to cause significant pulmonary toxicities including fatal pneumonitis or interstitial lung disease (ILD). We conducted a systematic review and meta-analysis of phase 3 randomized controlled trials (RCTs) to determine the relative risk of pneumonitis or ILD associated with CDK4/6i. **Methods:** We conducted a systematic search using PRISMA guidelines in PubMed, EMBASE, American Society of Clinical Oncology and San Antonio Breast Cancer Symposium meeting abstracts from inception through Jan 30, 2021. Phase 3 RCTs using CDK4/6i in the intervention arm and reporting the number of events for pneumonitis or ILD were included in the analysis. The Cochran-Mantel-Haenszel method and random effects model were used to calculate the pooled risk ratio (RR) with 95% confidence interval (CI). Heterogeneity was tested by Cochran's Q test and I^2 value. **Results:** Five phase 3 RCTs — MONALEESA-3, MONALEESA-7, MONARCH plus, monarchE, and PALLAS — reported the number of events for any grade pneumonitis or ILD and were included in the final analysis. A total of 13,191 patients — 6,758 in the CDK4/6i arm and 6,433 in the control arm — were analyzed. Following regimens were used in CDK4/6i arms — MONALEESA-3: ribociclib + fulvestrant; MONALEESA-7: ribociclib + tamoxifen or a non-steroidal aromatase inhibitor + goserelin; MONARCH plus: in cohort A, abemaciclib + anastrozole or letrozole, and in cohort B, abemaciclib + fulvestrant; MonarchE: abemaciclib + standard-of-care adjuvant endocrine therapy (ET); PALLAS: Palbociclib + ET. In the control arms, all studies used placebo and respective endocrine therapies. Any grade pneumonitis or ILD was reported in 1.64% of patients in the CDK4/6i arm versus 0.68% of patients in the control arm. The pooled RR of any grade pneumonitis or ILD was 2.26, 95% CI: 1.60-3.19, $P < 0.00001$, $I^2 = 0\%$. Grade 3/4 pneumonitis or ILD was reported in 0.28% of patients in the CDK4/6i arm and 0.06% of patients in the control arm with pooled RR of 2.35, 95% CI: 0.37-15.08, $P = 0.37$, $I^2 = 34\%$. One grade 5 pneumonitis was reported in the monarchE. **Conclusions:** Cyclin-dependent kinase 4/6 inhibitors are associated with increased risk of any grade pneumonitis or ILD. Early detection and prompt initiation of appropriate interventions are vital to reduce the morbidity and mortality associated with CDK4/6i induced pneumonitis or ILD. Research Sponsor: None.

1073 **Poster Session**

Confirmed tumor response by molecular subtype in patients with metastatic breast cancer: Sub-analysis from a phase 3 clinical study comparing oral paclitaxel and encequidar to IV paclitaxel. *First Author: Gerardo Antonio Umanzor Funez, Liga Contra El Cancer, San Pedro Sula, Honduras*

Background: Paclitaxel, a foundation treatment in MBC, is hydrophobic and must be formulated for IV administration with Cremophor EL, increasing the risk of infusion reactions and necessitating pre-treatment with corticosteroids and antihistamines. Paclitaxel cannot be administered orally because it is a substrate for P-gp. The oral bioavailability of paclitaxel is improved when administered 1 hour after the highly selective, potent, and minimally absorbed P-gp inhibitor encequidar. As oral paclitaxel is Cremophor-free there is no need for pretreatment for infusion reactions. While targeted therapies have improved outcomes in patients with HER2+ tumors there is still an unmet need for therapies that prolong survival with reduced toxicity across all tumor subtypes. **Methods:** A phase 3, open-label, randomized, multicenter study in women with histologically- or cytologically-confirmed MBC for whom treatment with IV paclitaxel monotherapy had been recommended by their oncologist randomized 402 patients 2:1 to either oral paclitaxel and encequidar (oPac+E) or IV paclitaxel (IVPac). Oral paclitaxel 205 mg/m^2 was administered once daily for 3 consecutive days, weekly. Encequidar 12.9 mg was administered 1 hour before each dose of oral paclitaxel. IV paclitaxel 175 mg/m^2 was infused over 3 hours on day 1 of every 3 weeks. **Results:** In the ITT population oPac+E was superior to IV paclitaxel with a confirmed tumor response rate of 35.8% vs 23.4% for IVPac: a difference of 12.4% ($p = 0.0107$). A post-hoc subgroup efficacy analysis was conducted based on tumor subtypes, however, the study was not powered to detect statistical differences within these subgroups. Patients in the HR+/HER2- subgroup had a better tumor response to oPac+E (44.8% vs 21.4% IVPac-response rate difference of 23.4%) as did patients in the TNBC (30.5% vs 20.2%-response rate difference of 10.3%) subgroup. Responses were similar (49% vs 47.4% IVPac) in the HER2+ subgroup. Patients with unknown HER2 status receiving oPac+E had a 58.8% response rate vs 14.3% with IVPac (response rate difference of 44.5%). **Conclusions:** oPac+E is the first oral taxane to demonstrate superiority in radiologically confirmed tumor response rate compared to IVPac in a group of 402 women with metastatic breast cancer. Patients with HR+/HER2-, TNBC, and Unknown subtypes responded considerably better to oPac+E vs IVPac—especially the HR+/HER2- subtype which represented 63% of the patients treated with oPac+E and 55% of the patients treated with IVPac. Clinical trial information: NCT 02594371. Research Sponsor: Athenex Inc.

1074 **Poster Session**

A phase Ib study of TQB2450 plus anlotinib in patients with advanced triple-negative breast cancer. *First Author: Jiayu Wang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: TQB2450 is a humanized monoclonal antibody targeting programmed death-ligand 1 (PD-L1). Anlotinib is an antiangiogenic small molecule, multi-target tyrosine kinase inhibitor that has improved clinical outcomes in various solid tumors. This phase 1b study aims to evaluate the safety and efficacy of TQB2450 plus anlotinib for patients with advanced triple-negative breast cancer (TNBC) after the failure of standard therapy. **Methods:** This ongoing study included a dose-escalation phase and an expansion phase. Advanced TNBC patients with prior anthracyclines and/or taxanes treatment and failed at least first-line therapy were enrolled. In the dose-escalation phase, eligible patients received anlotinib (8mg, 10mg, and 12mg, qd, days 1-14; 21 days per cycle) plus TQB2450 (1200mg, day 1; 21 days per cycle) following the conventional 3+3 design. If the starting dose of 10mg anlotinib led to ≥2 dose-limiting toxicities (DLTs), 8mg anlotinib would be administered. After the dose-escalating phase, eligible patients were enrolled into the expansion cohort. The primary endpoint was objective response rate (ORR), and the secondary endpoints were overall survival (OS), disease control rate (DCR), progression-free survival (PFS), and safety. **Results:** Between May 29, 2019, and December 31, 2020, in the dose-escalation phase, three patients receiving 10mg anlotinib plus 1200mg TQB2450 had no DLTs in the first cycle, neither did three patients with 12mg anlotinib plus TQB2450. Next, 28 patients with advanced TNBC received 12 mg anlotinib plus TQB2450 in the expansion phase. Finally, a total of 34 patients were included with median age of 49.5 (32-70) and median prior lines of 2 (1-6). Numbers of patients with prior platinum therapy: 16, prior anthracycline therapy: 32. The ORR was 26.47% (9/34) and DCR was 82.35% (28/34). The median PFS was 8.57 months. Seventeen patients experienced grade 3 treatment-related AEs (TRAEs). Most frequently occurring (>5%) grade 3 TRAEs were QT interval prolongation (17.65%), hypertension (14.71%), diarrhea (8.82%), hand-foot syndrome (HFS) (8.82%), and hypertriglyceridemia (5.88%). **Conclusions:** TQB2450 plus anlotinib showed an acceptable safety profile with promising activity for previously anthracyclines and/or taxanes-treated advanced TNBC patients. Clinical trial information: NCT03855358. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

List of grade 3 TRAEs.

Grade 3 TRAEs, n (%)	Anlotinib + TQB2450 n=34	Grade 3 TRAEs, n (%)	Anlotinib + TQB2450 n=34
QT interval prolongation	6 (17.65)	Neutrophil count decreased	1 (2.94)
Hypertension	5 (14.71)	Higher LDL-C levels	1 (2.94)
Diarrhea	3 (8.82)	Hyperbilirubinemia	1 (2.94)
Hand-foot syndrome	3 (8.82)	Weight loss	1 (2.94)
Hypertriglyceridemia	2 (5.88)	Hypercholesterolemia	1 (2.94)
AST elevation	1 (2.94)	Oral mucositis	1 (2.94)
White blood cell decreased	1 (2.94)		

1075 **Poster Session**

Apatinib plus vinorelbine versus vinorelbine for advanced triple-negative breast cancer with failed first or second-line treatment: The NAN trial. *First Author: Doudou Li, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: No standard treatment exists for triple negative breast cancer (TNBC) with failure of multi-line therapies. Apatinib is a small-molecule tyrosine kinase inhibitor that has promising anti-angiogenesis and antitumor activity for TNBC. We aimed to evaluate the safety and efficacy of adding apatinib to chemotherapy in patients with metastatic TNBC with failed first/second-line treatment. **Methods:** This randomized, open-label, phase 2 trial recruited patients with advanced TNBC who failed to receive first or second-line treatment. A total of 66 patients were randomly assigned, in a 1:1 ratio, to receive vinorelbine 25 mg/m^2 (days 1, 8, 15) or vinorelbine 20 mg/m^2 (days 7, 14, 21) with apatinib (250 mg once daily, days 1-5, 8-12, 15-19, if tolerable, the second cycle started with 500 mg per day) in 28-day cycles. The efficacy was evaluated every two treatment cycles (8 weeks ± 3 days). According to the RECIST criterion, patients with CR, PR and SD continued treatment until disease progression or unacceptable toxicity or withdrawal of consent. The primary end point was progression-free survival (PFS). Secondary end points included overall survival (OS), overall response rate (ORR) and safety. **Results:** Between Sep 14, 2017 and Dec 08, 2020, 66 patients underwent randomization. Median follow-up was 21.3 months. 33 received apatinib plus vinorelbine and 32 received vinorelbine (1 was withdrawal of consent). Median PFS was significantly longer in the apatinib plus vinorelbine group than in the vinorelbine group (3.8 months vs. 1.9 months; hazard ratio for disease progression or death, 1.76; 95% confidence interval [CI], 1.02 to 3.05; P= 0.039). Median OS was 14.6 months with apatinib plus vinorelbine and 14.1 months with vinorelbine (HR,1.34; 95% CI, 0.60 to 3.00; P= 0.469). The ORR was 48.5% in the apatinib plus vinorelbine group and 31.3% in the vinorelbine group (P= 0.156). The most common treatment-related hematologic grade 3–4 adverse events in those treated with apatinib plus vinorelbine versus vinorelbine, respectively, were leukopenia (42.4% vs. 34.4%), granulocytopenia (57.6% vs. 28.1%), anemia (9.1% vs. 12.5%) and thrombocytopenia (3.1% vs. 3.0%). The most frequent grade 3 nonhematologic toxicities were hand–foot syndrome (21%), proteinuria (9%), hypertension (9%) and increased ALT (9%) and which only occurred in apatinib plus vinorelbine group. No treatment-related nonhematologic grade 4 adverse events or treatment-related deaths were observed. **Conclusions:** Collectively, among patients with advanced TNBC with failed first/second-line treatment, apatinib plus vinorelbine show a promising benefit in PFS compared to vinorelbine monotherapy. Apatinib plus vinorelbine regimen shows promising efficacy and manageable toxicity, which might be a previously unappreciated therapeutic option for advanced TNBC. Clinical trial information: NCT03254654. Research Sponsor: None.

1076 **Poster Session**

Romidepsin (HDACi) plus cisplatin and nivolumab triplet combination in patients with metastatic triple negative breast cancer (mTNBC). *First Author: Priyanka Sharma, University of Kansas Medical Center, Westwood, KS*

Background: Histone deacetylase inhibitors (HDACi) upregulate genes involved in antigen presentation machinery and increase expression of natural killer group 2, member D ligands (NKG2DL), thus resulting in enhanced tumor cell recognition and response to PD-1/CTLA-4 blockade. Cisplatin and HDACi combination synergistically induces cytotoxicity, apoptosis, and DNA damage. This phase I-II trial investigated combination of romidepsin (HDACi) plus cisplatin and nivolumab (PD-1 inhibitor) in mTNBC. **Patients and Methods:** Eligible patients had mTNBC with any number of prior chemotherapies. Phase I was 3+3 dose-escalation design with three dose levels of romidepsin (8, 10, 12mg/m^2, D2, 9) plus cisplatin 75mg/m^2 D 1 every 21 days. Phase II treatment included romidepsin plus cisplatin plus nivolumab 360mg every 21 days and was designed according to Simon's two stage minimax design. Primary endpoints were recommended phase 2 dose (RP2D) and objective response rate (ORR). Additional endpoints included safety, PFS, and pharmacokinetics. **Results:** 51 patients were enrolled (N=13 phase I, N=38 phase II) between 2015-2020. 69% had received ≥1 prior metastatic chemotherapy, 47% had prior platinum, 53% had liver metastasis, 12% had *BRCA1/2* mutation, and 11% had PD-L1 positive disease. There were no dose limiting toxicities in phase I. The RP2D was romidepsin 12mg/m^2 D2,9 + cisplatin 75mg/m^2 D1 + nivolumab 360mg D1 every 21 days. Thrombocytopenia (G3:27%, G4:0%), neutropenia (G3:25%, G4:0%), anemia (G3:22%, G4:0%), nausea (G3:22%, G4:0%), and vomiting (G3:20%, G4:0%) were the most common grade 3/4 adverse events. 21% of patients had immune AEs (G3-4:8%). Among 34 evaluable phase II patients, ORR was 44% (Table), median PFS was 4.4 months, and 1-year PFS was 23%. Median OS was 10.3 months and 1-year OS was 43%. No pharmacokinetic interactions were detected with co-administration of romidepsin-cisplatin-nivolumab. **Conclusions:** The triplet combination of romidepsin plus cisplatin and nivolumab was well tolerated and shows encouraging efficacy in pretreated mTNBC, including in patients with PD-L1 negative disease and in those with liver metastasis. Correlative biomarker work is ongoing. This combination warrants further evaluation in larger studies. Clinical trial information: NCT02393794. Research Sponsor: Celgene and Bristol Myers Squibb.

Objective response (phase II).

		Prior lines of metastatic chemotherapy			Liver metastasis		PD-L1[a] status		
Response - N (%)	N=34	0 (N=10)	1 (N=12)	≥2 (N=12)	Yes (N=22)	No (N=12)	Positive (N=4)	Negative (N=19)	Unknown (N=11)
ORR	15 (44%)	7 (70%)	5 (42%)	3 (25%)	9 (41%)	6 (50%)	3 (75%)	9 (47%)	3 (27%)
CR	1 (3%)	1 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (8%)	0 (0%)	0 (0%)	1 (9%)
PR	14 (41%)	6 (60%)	5 (42%)	3 (25%)	9 (41%)	5 (42%)	3 (75%)	9 (47%)	2 (18%)
SD >18 weeks	7 (21%)	1 (10%)	4 (33%)	2 (17%)	5 (23%)	2 (17%)	0 (0%)	3 (16%)	4 (36%)
Clinical benefit rate (ORR + SD >18 weeks)	22 (65%)	8 (80%)	9 (75%)	5 (42%)	14 (64%)	8 (67%)	3 (75%)	12 (63%)	7 (64%)

[a] Ventana SP142 or 22C3 PharmDx.

1077 **Poster Session**

Assessment of sacituzumab govitecan (SG) versus treatment of physician's choice (TPC) cohort by agent in the phase 3 ASCENT study of patients (pts) with metastatic triple-negative breast cancer (mTNBC). *First Author: Joyce O'Shaughnessy, Texas Oncology-Baylor Sammons Cancer Center, US Oncology, Dallas, TX*

Background: In pts with pretreated mTNBC, standard-of-care chemotherapy is associated with low objective response rates (ORRs) and short median progression-free survival (PFS). SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. SG received accelerated FDA approval for treatment of pts with mTNBC who have received ≥2 prior therapies for metastatic disease. The confirmatory phase 3 ASCENT study (NCT02574455) in pts with relapsed/refractory mTNBC demonstrated a significant survival benefit of SG over TPC (median PFS: 5.6 vs 1.7 mo, HR 0.41, $P< 0.0001$; median overall survival [OS]: 12.1 vs 6.7 mo, HR 0.48, $P< 0.0001$) with a tolerable safety profile. Here we summarize efficacy results for SG vs each TPC agent in ASCENT to examine how each TPC agent performed individually. **Methods**: Pts had mTNBC refractory to or progressing after ≥2 prior standard chemotherapy regimens. Pts were randomized 1:1 to receive SG (10 mg/kg intravenously on days 1 and 8, every 21 days) or single-agent TPC (eribulin, vinorelbine, capecitabine, or gemcitabine). Primary endpoint was PFS per RECIST 1.1 by independent review in brain metastases-negative (BMNeg) pts. Secondary endpoints were ORR per RECIST 1.1, duration of response, OS, and safety. Outcomes for each of the agents in the TPC arm were analyzed and compared with SG. **Results**: Of 529 pts enrolled, 468 were BMNeg. Among pts in the TPC cohort (n = 233), eribulin was the most commonly chosen chemotherapy (n = 126), followed by vinorelbine (n = 47), capecitabine (n = 31), and gemcitabine (n = 29). Treatment with eribulin, vinorelbine, capecitabine, and gemcitabine resulted in shorter median PFS vs SG (2.1, 1.6, 1.6, and 2.7 vs 5.6 mo, respectively); similar results were observed for median OS (6.9, 5.9, 5.2, and 8.4 vs 12.1 mo), ORR (5%, 4%, 6%, and 3% vs 35%), and clinical benefit rate (CBR; 8%, 6%, 10%, and 14% vs 45%). Key grade ≥3 treatment-related adverse events (TRAEs) with TPC overall vs SG included neutropenia (33% vs 51%), leukopenia (5% vs 10%), fatigue (5% vs 3%), and anemia (5% vs 8%). Key grade ≥3 TRAEs with eribulin vs SG included neutropenia (30% vs 51%), leukopenia (5% vs 10%), fatigue (5% vs 3%), anemia (2% vs 8%), and peripheral neuropathy (2% vs none), respectively. The safety profiles of vinorelbine, capecitabine, and gemcitabine combined were consistent with that of TPC overall and with eribulin. One treatment-related death was reported for the TPC arm (eribulin) and none with SG. **Conclusions**: The efficacy benefit observed with SG vs TPC in pts with mTNBC was retained when evaluating each TPC chemotherapy agent individually. These results confirm that SG should be considered as a new standard of care in pts with pretreated mTNBC. Clinical trial information: NCT02574455. Research Sponsor: Immunomedics, Inc. a subsidiary of Gilead Sciences, Inc.

1078 **Poster Session**

A phase I/IB study of ipatasertib in combination with carboplatin or carboplatin/paclitaxel or capecitabine and atezolizumab in patients with metastatic triple-negative breast cancer. *First Author: Yuan Yuan, City of Hope National Medical Center, Duarte, CA*

Background: Ipatasertib (ipat) is an AKT inhibitor which has shown efficacy in combination with paclitaxel and atezolizumab in patients with triple negative breast cancer (TNBC). In previous trials, ipat was given 21 days on 7 days off due to gastrointestinal toxicities. The current trial was designed to test the safety and efficacy of ipat continuous dosing in combination with carboplatin (carbo) or carboplatin/paclitaxel (carbo/taxol). The trial was later amended to include an additional arm using ipat 21 days on 7 days off with capecitabine/atezolizumab (cape/atezo) to explore the safety of the combination. **Methods:** Patients with metastatic TNBC and up to 2 lines of prior chemotherapy were enrolled to receive the following: Arm A, ipat 400 mg daily, carbo AUC 2 and taxol 80 mg/m2 IV days 1, 8, 15, every 28 days; Arm B, ipat 400 mg daily, carbo AUC 2 IV days 1, 8, 15, every 28 days; Arm C, ipat 300 mg daily 21 days on 7 days off, cape 750 mg/m^2 7 days on 7 days off, atezo 840 mg IV every 28 days. Ipat continuous dosing was used for Arms A and B. Ipat 21 days on 7 days off dosing was used for Arm C. The primary endpoint is safety and recommended phase II dose (RP2D). Secondary endpoints are response rate (RR) and overall survival (OS). **Results:** Twenty-three patients with median age 49 (29-75) were enrolled from 04/2019 to 12/2020, with 9 in Arm A, 10 in Arm B, and 4 in Arm C. A total of 15/23 (65%) had dose delay and 10/23 (43%) had dose modification. 3/4 (75%) of patients in Arm A had dose limiting toxicities (DLT) including diarrhea and gastric pain, which led to de-escalation to dose -1 with ipat (300 mg daily). 5 more patients were treated at dose -1 of Arm A with only 1 DLT (maculo-papular rash). No DLTs were observed in Arm B. Of the 4 patients treated in Arm C, 1 had DLT (maculo-papular rash). The RP2D for Arms A and B are: ipat 300 mg/carbo AUC2/taxol 80 mg/m2; ipat 400 mg/carbo AUC2. RP2D for Arm C has not been determined and accrual is ongoing. There were no clinically significant G4 toxicities in Arm A; G3 toxicities included 4/9 (44%) diarrhea, 1/9 (11%) hypertension, 1/9 (11%) stomach pain, and 1/9 (11%) neutropenia. For Arm B, G3 toxicities included 2/10 (20%) diarrhea, 1/10 (10%) anemia, 1/10 (10%) maculo-papular rash, and 1/10 (10%) hyperglycemia. For Arm C, there was 1/4 (25%) G3 maculo-papular rash. Best overall responses for Arm A were: 2/9 (22%) PR, 4/9 (44%) SD, and 3/9 (33%) PD. Best responses for Arm B were 2/10 (20%) PR, 6/10 (60%) SD, and 2/10 (20%) PD. For Arm C, best responses were 3/4 (75%) SD, and 1 not evaluable (repeat biopsy showed HER2+ disease). With a median follow up of 8.1 months, the median PFS was 4.0 months (95% CI [2.6, 5.3]). **Conclusions:** Continuous dosing of ipatasertib in combination with carbo or carbo/taxol is well-tolerated with modest efficacy. Clinical trial information: NCT03853707. Research Sponsor: Genentech, Inc, City of Hope.

1079 **Poster Session**

A phase II trial of stereotactic radiation therapy and *in situ* oncolytic virus therapy in metastatic triple-negative breast cancer (mTNBC) patients followed by pembrolizumab (STOMP). *First Author: Kai Sun, Houston Methodist Cancer Center, Houston, TX*

Background: Pembrolizumab, stereotactic body radiotherapy (SBRT), and viral vector-based gene therapy such as adenovirus-mediated expression of herpes simplex virus thymidine kinase (ADV/HSV-tk) plus ganciclovir have each shown antitumor immune activity. The combination of those modalities may represent a window of opportunity to enhance pembrolizumab efficacy in mTNBC patients. **Methods:** In this single-arm, open-label phase II trial, mTNBC patients were treated with *in situ* oncolytic ADV/HSV-tk (5 x 10^{11} vp) intratumoral injection, followed by SBRT to the injected tumor site, then pembrolizumab until progression or intolerable toxicity. Response was assessed in non-irradiated metastatic sites. The primary end point was clinical benefit rate (CR, PR and SD per RECIST version1.1). Secondary endpoints included duration on treatment (DoT) and safety. Immune correlative analysis with peripheral blood CYTOF (D1 baseline, D7 and D38), and tissue imaging mass cytometry (IMC) with 35 cell surface markers was performed on paired biopsies (D1 baseline and D17). **Results:** 28 mTNBC patients were enrolled; 18 (64.3%) had PD-L1 negative tumors. Median age was 54 years (range 34-78). Median prior lines of chemotherapy were 2 (range 0-6), with 8 (28.6%) having received >3. 3 (10.7%) had brain metastases. Clinical benefit was seen in 6 (21.43%) patients; 2 CR (7.1%),1 PR (3.57%) and 3 SD (10.7%). Patients who had clinical benefits had durable responses, with median DoT of 383 days (range 195-1195). One patient who had CR, but discontinued pembrolizumab due to Grade 3 pneumonitis, has remained disease free without any systemic therapy for 39 months. The combination was well tolerated; 9 (32.1%) patients had Grade 3- 4 AEs. Pre- and post-therapy CYTOF analysis showed significant association between immune biomarkers with clinical responses (AUC 0.75, Cohen's Kappa 0.364). Tumor PDL1 was independently associated with response (AUC 0.70, Cohen's Kappa 0.347); AUC for PDL1 together with immune biomarkers is 0.85. **Conclusions:** ADV/HSV-tk gene therapy followed by radiation therapy and then pembrolizumab is a well-tolerated promising treatment in heavily pretreated mTNBC patients. Early detection of increased effector and effector memory CD8 T cells and nonclassical monocytes correlates with response and non-response respectively. Clinical trial information: NCT03295916. Research Sponsor: Merck.

	Breast (n = 28)
Best overall response – no. (%)	
Confirmed CR	2 (7.14)
Confirmed PR	1 (3.57)
Stable disease	3 (10.71)
Progressive disease	22 (78.57)
Clinical benefit (CR, PR and SD)	6 (21.43)

1080 **Poster Session**

Assessment of sacituzumab govitecan (SG) in patients with prior neoadjuvant/adjuvant chemotherapy in the phase 3 ASCENT study in metastatic triple-negative breast cancer (mTNBC). *First Author: Lisa A. Carey, University of North Carolina, Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: mTNBC is a heterogenous disease with few treatment options and poor outcomes. Pts who recur ≤ 12 mo after completing (neo)adjuvant chemotherapy may represent a subset with more aggressive disease. SG is an antibody-drug conjugate composed of an anti–Trop-2 antibody coupled to the cytotoxic SN-38 payload via a proprietary, hydrolyzable linker. SG received accelerated approval for pts with mTNBC who received ≥ 2 prior therapies for metastatic disease; clinical benefit for SG over treatment of physician's choice (TPC) was confirmed in the phase 3 ASCENT study (NCT02574455) for median progression-free survival (PFS; 5.6 vs 1.7 mo), median overall survival (OS; 12.1 vs 6.7 mo), objective response rate (ORR; 35% vs 5%), clinical benefit rate (CBR; 45% vs 9%), and median duration of response (6.3 vs 3.6 mo). This ASCENT subanalysis of pts with mTNBC who recurred ≤ 12 mo after (neo)adjuvant chemotherapy and then only received 1 line of therapy in the metastatic setting assessed the benefit of SG in this subgroup vs the overall trial population. **Methods:** In ASCENT, pts with mTNBC refractory/relapsing after ≥ 2 prior chemotherapies were randomized 1:1 to receive SG (10 mg/kg IV on days 1 and 8, every 21 days) or TPC (capecitabine, eribulin, vinorelbine, or gemcitabine). Per protocol, a pt was eligible after only 1 prior regimen in the metastatic setting if their disease recurred within 12 months of completing (neo)adjuvant therapy. Primary endpoint was PFS per RECIST 1.1 by independent review in brain metastases-negative (BMNeg) pts. Efficacy and safety was assessed in a subset of pts who recurred ≤ 12 mo after (neo)adjuvant chemotherapy and then received 1 line of therapy in the metastatic setting. **Results:** In total, 33 and 32 BMNeg pts with a median age of 49 and 51 yrs received SG and TPC in this subgroup, respectively. In this subgroup, treatment with SG (vs TPC) improved PFS (median 5.7 vs 1.5 mo; HR, 0.41; 95% CI, 0.22-0.76; P = 0.0049) and OS (median 10.9 vs 4.9 mo; HR, 0.51; 95% CI, 0.28-0.91; P = 0.0227). We also observed higher ORR (30% vs 3%) and CBR (42% vs 6%) with a median response duration of 6.7 mo with SG vs not calculable with TPC. The efficacy results from this subgroup are similar to those for SG vs TPC in the overall BMNeg population. The safety profile of SG in pts in this subgroup was consistent with prior reports. There were no treatment-related deaths with SG. **Conclusions:** Pts with mTNBC who recurred ≤ 12 mo after (neo)adjuvant therapy and then had 1 line of prior therapy in the metastatic setting may represent a subset with more aggressive disease. In this subgroup, pts had superior outcomes with SG vs TPC in the second-line metastatic setting, consistent with the benefit seen in the overall BMNeg population. Studies are ongoing (NeoSTAR, NCT04230109; SASCIA, NCT04595565) to evaluate SG as an earlier-line treatment option for TNBC. Clinical trial information: NCT02574455. Research Sponsor: Immunomedics, Inc. a subsidiary of Gilead Sciences, Inc.

1081 **Poster Session**

Efficacy of DAN-222, a novel investigational polymeric nanoparticle with topoisomerase I inhibitor, as monotherapy in breast cancer models and when combined with PARP inhibitor. *First Author: Ashley P Wright, Dantari, Inc., Thousand Oaks, CA*

Background: Patients with BRCA-positive HER2-negative breast cancer benefit from PARP inhibitor therapy, but additional benefit is still desired. PARP inhibition alone does not prevent all mechanisms for repairing damage to DNA such as homologous recombination repair. An attractive combination for treating such patients would be combining a topoisomerase I inhibitor with a PARP inhibitor given the dual mechanism this would provide for DNA damage and inhibited repair, leading to tumor cell death. This combination has been tried in multiple phase 1 studies, but myelotoxicity prevented the combination from being evaluated further. DAN-222 is a novel investigational polymeric nanoparticle conjugated with camptothecin, a topoisomerase I inhibitor, that provides significant accumulation of drug in tumor tissues *via* the enhanced permeability and retention (EPR) effect and significantly reduced bone marrow exposure compared to native chemotherapy. These observations underscore the potential advantages of DAN-222 alone as well as in combination with other agents such as PARP inhibitors in solid tumors. Here, we report the effects of DAN-222 monotherapy and in combination with a PARP inhibitor on the growth inhibition in an HRD+ TNBC breast cancer (MDA-MB-436) and an HRD- ovarian (OVCAR3) xenograft mouse model. **Methods:** HRD+ breast cancer tumor cells (MDA-MB-436) were implanted into female NCr nu/nu mice and HRD- ovarian cancer tumor cells (OVCAR3) were implanted into female CB.17 SCID mice. Mice were randomized to vehicle or treatment arms until tumors reached 2000 mm^3 or day 45 (MDA-MB-436) or 1000mm^3 or day 45 (OVCAR3). The groups evaluated include multiple dose levels of DAN-222 as monotherapy and those also combined with niraparib. **Results:** Results were consistent in both the HRD+ and HRD- tumor models with profound dose-response of DAN-222 monotherapy inhibiting tumor growth. Additionally, synergy was demonstrated when DAN-222 was combined with niraparib, clearly evident with low doses of both products when used in combination. The table below highlights the synergy of the combination of DAN-222 at 0.3 mg/kg and niraparib at 25 mg/kg above each agent alone on the tumor growth inhibition in the MDA-MB-436 xenograft. **Conclusions:** Combining a PARP inhibitor with a topoisomerase I inhibitor delivered *via* this polymeric nanoparticle delivery system (DAN-222) has synergistic efficacy in both HRD+ and HRD- xenograft tumor models. These data support continued development of DAN-222 to treat solid tumors and its combination use with PARP inhibitors. Research Sponsor: Dantari, Inc.

Treatment	Dose (mg/kg)	Day 21 TGI (%)	Day 34 TGI (%)
DAN-222	0.3	75	82
DAN-222	1	91	98
DAN-222	3	95	99
Niraparib	25	51	59
DAN-222 + Niraparib	0.3, 25	91	97
DAN-222 + Niraparib	1, 25	94	98
DAN-222 + Niraparib	3, 25	97	99

1082 **Poster Session**

Control arm heterogeneity in trials for unselected advanced triple-negative breast cancer (aTNBC). *First Author: Kinisha Gala, The Larvol Group, LLC, San Francisco, CA*

Background: Primary endpoints of clinical trials frequently include subgroup-analyses. Several solid cancers such as aTNBC are heterogeneous, which can lead to unpredictable control arm performance impairing accurate assumptions for sample size calculations. We explore the value of a comprehensive clinical trial results repository in assessing control arm heterogeneity with aTNBC as the pilot. **Methods:** We identified P2/3 trials reporting median overall survival (mOS) and/or median progression-free survival (mPFS) in unselected aTNBC through a systematic search of PubMed, clinical trials databases and conference proceedings. Trial arms with sample sizes ≤25 or evaluating drugs no longer in development were excluded. Due to inconsistency among PD-L1 assays, PD-L1 subgroup analyses were not assessed separately. The primary aim was a descriptive analysis of control arm mOS and mPFS across all randomized trials in first line (1L) aTNBC. Secondary aims were to investigate time-to-event outcomes in control arms in later lines and to assess time-trends in aTNBC experimental and control arm outcomes. **Results:** We included 33 trials published between June 2013-Feb 2021. The mOS of control arms in 1L was 18.7mo (range 12.6-22.8) across 5 trials with single agent (nab-) paclitaxel [(n)P], and 18.1mo (similar range) for 7 trials including combination regimens (Table). The mPFS of control arms in 1L was 4.9mo (range 3.8-5.6) across 5 trials with single-agent (n)P, and 5.6mo (range 3.8-6.1) across 8 trials including combination regimens. Control arm mOS was 13.1mo (range 9.4-17.4) for 3 trials in first and second line (1/2L) and 8.7mo (range 6.7-10.8) across 5 trials in 2L and beyond. R^2 for the mOS best-fit lines across control and experimental arms over time was 0.09, 0.01 and 0.04 for 1L, 1/2L and 2L and beyond, respectively. **Conclusions:** Median time-to-event outcomes of control arms in 1L aTNBC show considerable heterogeneity, even among trials with comparable regimens and large sample sizes. Disregarding important prognostic factors at stratification can lead to imbalances between arms, which may jeopardize accurate sample size calculations, trial results and interpretation. Optimizing stratification and assumptions for power calculations is of utmost importance in aTNBC and beyond. A digitized trial results repository with precisely defined patient populations and treatment settings could improve accuracy of assumptions during clinical trial design. Research Sponsor: None.

Control arm mPFS and mOS in 1L aTNBC (Pac: paclitaxel).

Trial	NCT ID	Drugs	N	mPFS	mOS
IMpassion130	NCT02425891	Nab-Pac	451	5.5	18.7
IMpassion131	NCT03125902	Pac	220	5.6	22.8
PAKT	NCT02423603	Pac	70	4.2	12.6
LOTUS	NCT02162719	Pac	62	4.9	16.9
COLET	NCT02322814	Pac	43	3.8	19.6
KEYNOTE-355	NCT02819518	(Nab-)Pac/carboplatin-gemcitabine	281	5.6	-
CBCSG006	NCT01287624	Pac-gemcitabine	118	6.1	18.1
TnAcity	NCT01881230	Carboplatin-gemcitabine	66	6	12.6

1083 **Poster Session**

miR-503-5p induces doxorubicin resistance in triple-negative breast cancer. *First Author: Iris Garrido-Cano, Biomedical Research Institute INCLIVA, Valencia, Spain*

Background: Triple-negative breast cancer (TNBC) is an aggressive breast cancer (BC) subtype comprising approximately 15% of BC. Conventional cytotoxic chemotherapies continue to be the mainstay for treatment of this BC, which lacks targetable markers. In this context, microRNAs have been described to have an important role. The aim of this work was to elucidate the function of miR-503-5p in doxorubicin resistance in TNBC. **Methods:** miR-503-5p expression was evaluated in the TNBC cell line with acquired resistance to doxorubicin (MDA-MB-231R) and its parental cell line (MDA-MB-231), by qRT-PCR. Studies of gain/loss of function of miR-503-5p were carried out in MDA-MB-231 and MDA-MB-231R cells by transient transfection of mimics and inhibitors. Cells were treated with doxorubicin, and viability was measured by flow cytometry and MTT assay. The role of miR-503-5p was also evaluated *in vivo* by Chicken Chorioallantoic Membrane (CAM) assay. MDA-MB-231 cells transfected with miR-503-5p mimic or scramble miRNA were inoculated onto the CAM of fertilized chicken eggs. After 48 hours, tumours were treated with doxorubicin or supplemented media for 48 hours and tumour growth was measured. miR-503-5p expression was quantified by qRT-PCR in a retrospective cohort of 74 TNBC patients treated with anthracycline + taxane regimens. Overall survival analysis for miR-503-5p in TNBC patients from METABRIC dataset was evaluated by the KM plotter online tool. **Results:** miR-503-5p was significantly upregulated in the resistant MDA-MB-231R TNBC cell line when compared to its parental cell line MDA-MB-231 (~3.5-fold; $p< 0.0001$). Then, gain/loss function assays showed that upregulation of miR-503-5p in MDA-MB-231 cells increased resistance to doxorubicin ($p< 0.0001$) and its downregulation in MDA-MB-231R cells had the opposite effect ($p< 0.0001$). Moreover, the role of miR-503-5p was also confirmed in the CAM assay *in vivo* model, where miR-503-5p overexpression inhibited the effect of doxorubicin. In our cohort of patients, miR-503-5p expression levels in core biopsies sampled before preoperative chemotherapy were associated with residual cancer burden (RCB). miR-503-5p expression was significantly higher in patients with poor response to chemotherapy (RCB II and III; median, 95% CI: 0.00055, 0.00024 - 0.00136) than in patients with good response (RCB 0 and I; median, 95% CI: 0.00018, 0.00011 - 0.00034; $p = 0.036$). Moreover, we confirmed that TNBC patients with high expression of miR-503-5p had worse overall survival than patients with low expression ($p= 0.016$). **Conclusions:** We identified miR-503-5p as a modulator of doxorubicin resistance in TNBC. Our *in vitro* findings are supported by the clinical data of TNBC patients and *in vivo* assays. Hence, the inhibition of miR-503-5p may be a promising strategy to improve chemotherapeutic efficacy. Moreover, the expression levels of miR-503-5p may be used as a biomarker for therapy response in TNBC. Research Sponsor: None.

1084 **Poster Session**

Distant metastases after diagnosis: Racial disparities in breast cancer outcomes. *First Author: Julia Blanter, Division of Internal Medicine, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Black women diagnosed with breast cancer are more likely to have a poor prognosis, regardless of breast cancer subtype. Despite having a lower incidence rate of breast cancer when compared to white women, black women have the highest breast cancer death rate of all racial and ethnic groups, a characteristic often attributed to late stage at diagnosis. Distant metastases are considered the leading cause of death from breast cancer. We performed a follow up study of women with breast cancer in the Mount Sinai Health System (MSHS) to determine differences in distant metastases rates among black versus white women. **Methods:** Women were initially recruited as part of an NIH funded cross-sectional study from 2013-2020 to examine the link between insulin resistance (IR) and breast cancer prognosis. Women self-identified as black or white race. Data was collected via retrospective analysis of electronic medical records (EMR) between September 2020-January 2021. Distant metastases at diagnosis was defined as evidence of metastases in a secondary organ (not lymph node). Stage at diagnosis was recorded for all patients. Distant metastases after diagnosis was defined as evidence of metastases at any time after initiation of treatment. Univariate analysis was performed using Fisher's exact test, multivariate analysis was performed by binary logistic regression, and results expressed as odds ratio (OR) and 95% confidence interval (CI). A p value <0.05 was considered statistically significant. **Results:** We identified 441 women enrolled in the IR study within the MSHS (340 white women, 101 black women). Median follow up time for all women was 2.95 years (median = 3.12 years for white and 2.51 years for black women (p=0.017)). Among these patients, 11 developed distant metastases after diagnosis: 4 (1.2%) white and 7 (6.9%) black (p=0.004). Multivariate analysis adjusting for age, race and stage at diagnosis revealed that black women were more likely to have distant metastasis (OR 5.8, CI 1.3-25.2), as were younger women (OR for age (years) 0.9, CI 0.9-1.0), and those with more advanced stage at diagnosis. **Conclusions:** Black women demonstrated a far higher percentage of distant metastases after diagnosis even when accounting for age and stage. These findings suggest that racial disparities still exist in the development of distant metastases, independent from a late-stage diagnosis. The source of existing disparities needs to be further understood and may be found in surveillance, treatment differences, or follow up. Research Sponsor: U.S. National Institutes of Health.

1086 **Poster Session**

The impact of radiological assessment schedules on progression-free survival in metastatic breast cancer: A systemic review and meta-analysis. *First Author: Dor Reuven Dabush, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel*

Background: The impact of the interval of radiological assessment on the magnitude of benefit observed in randomized trials (RCTs) in metastatic breast cancer is undefined. **Methods:** All RCTs investigating anti-neoplastic drugs for metastatic breast cancer published between 2006 and 2019 were identified. Intervals for restaging were categorized as short (<9 weeks) or long ($\geq$9 weeks). Hazard ratios (HRs) and 95% confidence intervals for progression-free survival (PFS) and overall-survival (OS) were pooled in a meta-analysis and compared between trials employing short and long restaging intervals assessed as subgroup analyses. Analyses were repeated for pre-specified subgroups according to disease subtype, drug type, whether experimental therapy was added to or replaced standard treatment and whether HR for PFS was <1 or $\geq$1. **Results:** Eighty-nine studies comprising 95 comparisons and 44,901 patients were included. The magnitude of PFS benefit was non-significantly larger in trials which employed short compared to long restaging intervals (HR 0.79 vs. 0.86, p = 0.15). Short restaging interval was associated with significantly higher magnitude of effect on PFS in pre-specified subgroups including non-first line studies (HR 0.78 vs. 0.92, p = 0.04), studies with drugs replacing standard treatment (HR 0.86 vs. 1.04, p = 0.02) and studies performed exclusively in human epidermal growth factor receptor 2 (HER2) positive disease (HR 0.72 vs. 0.90, p = 0.02). Restaging interval was not associated with OS for all included studies (HR 0.92 vs. 0.93, p = 0.66) or for any of the pre-specified subgroups. **Conclusions:** Shorter restaging intervals are associated with a higher magnitude of effect of PFS, but not OS. Awareness of the impact of the restaging interval on quantification of intermediate endpoints such as PFS is important for the design and interpretation of RCTs. Research Sponsor: None.

1087 **Poster Session**

A phase 2 study of pamiparib in the treatment of patients with locally advanced or metastatic HER2-negative breast cancer with germline *BRCA* mutation. *First Author: Tao Sun, Liaoning Cancer Hospital & Institute, Shenyang, China*

Background: Breast cancer is the most common cancer among women, with up to 37% of patients (pts) harboring germline *BRCA1/2* mutations (g*BRCA1/2*m) that appear to be sensitive to poly (ADP-ribose) polymerase proteins 1 and 2 (PARP1/2) inhibition. Pamiparib is an orally administered selective PARP1/2 inhibitor that has the potential to cross the blood-brain barrier. This study evaluated the efficacy and safety of pamiparib in pts with locally advanced/metastatic human epidermal growth factor receptor 2-negative (HER2-) breast cancer, with deleterious or suspected deleterious g*BRCA1/2*m, who received $\leq$ 2 prior lines of chemotherapy. **Methods:** In this open-label, phase 2, multi-center study in China (NCT03575065), pts with locally advanced/metastatic HER2- breast cancer with deleterious or suspected deleterious g*BRCA1/2*m triple negative breast cancer (TNBC cohort) or hormone receptor-positive (HR+)/HER2- breast cancer (HR+ cohort) were enrolled. Pts received pamiparib 60 mg orally twice daily in 28-day cycles. The primary endpoint was objective response rate (ORR; RECIST v1.1) by independent review committee (IRC). Secondary endpoints included duration of response (DOR) and progression free survival (PFS) by IRC, overall survival (OS), safety and tolerability. **Results:** 88 pts were enrolled (median age 45.5 years), 76 pts (TNBC cohort n = 55; HR+ cohort n = 21) had measurable disease at baseline per IRC. 60 pts (68.2%) received 1 or 2 prior lines of chemotherapy; 42 pts (47.7%) were treated with platinum previously. Median follow-up was 13.77 months (TNBC cohort, 10.87 months; HR+ cohort, 18.45 months). In the TNBC cohort: confirmed ORR was 38.2% (95% CI: 25.4–52.3); median DOR (mDOR) was 6.97 months (95% CI: 3.94–not estimable[NE]); median PFS (mPFS) was 5.49 months (95% CI: 3.65–7.33); median OS (mOS) was 17.08 months (95% CI:13.70–NE). In the HR+ cohort: confirmed ORR was 61.9% (95% CI: 38.4–81.9); mDOR was 7.49 months (95% CI: 5.55–14.75); mPFS was 9.20 months (95% CI: 7.39–11.93); mOS was not reached (NR; 95% CI 18.10–NE). $\geq$ Grade 3 treatment emergent adverse events (TEAEs) occurred in 54 pts (61.4%); anemia was the most common TEAE, occurring in 77 pts (87.5%). Dose reduction due to TEAEs occurred for 57 pts (64.8%); discontinuations due to TEAEs occurred for 2 pts (2.3%). **Conclusions:** Pamiparib showed a promising response in pts with locally advanced/metastatic HER2- breast cancer with a g*BRCA1/2*m. The safety profile of pamiparib was considered acceptable and was generally consistent with therapies in the same class. Clinical trial information: NCT03575065. Research Sponsor: This trial is sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Yasmin Issop, PhD, and Shannon Galgani, MSci, of Ashfield Medcomms, an Ashfield Health company, and was funded by BeiGene, Ltd.

Efficacy by cohort.

	TNBC (N = 62)	HR(+)/HER2(-) (N = 26)
Efficacy Evaluable Analysis Set, N	55	21
ORR by IRC, n (% [95% CI])	21 (38.2% [25.4–52.3])	13 (61.9% [38.4–81.9])
mDOR by IRC, months (95% CI)	6.97 (3.94–NE)	7.49 (5.55–14.75)
mPFS by IRC, months (95% CI)	5.49 (3.65–7.33)	9.20 (7.39–11.93)
mOS, months (95% CI)	17.08 (13.70–NE)	NR (18.10–NE)

1088 **Poster Session**

Survival time in urban center breast cancer patients with CNS metastasis with or without visceral metastasis. *First Author: Miriam Pearl Klahr, Albert Einstein College of Medicine, Bronx, NY*

Background: There is limited data about the role of isolated central nervous system (CNS) metastasis (mets) in patients with breast cancer (BC), since prior studies evaluated BC patients with CNS plus visceral mets. Furthermore, though Black race is associated with worse BC outcomes, there are few studies on CNS mets that predominantly included racial and ethnic minorities in their cohorts. Our study compares overall survival (OS) in BC patients with CNS involvement with and without visceral mets in an underrepresented patient population. **Methods:** This is a retrospective case series study. We used Montefiore's Clinical Looking Glass software to identify patients. Inclusion criteria were females age $\geq$18 years at our institution with the diagnosis of BC and CNS mets between 3/31/1997 to 3/31/2019. Chart review was conducted to obtain clinical-pathological features, including date of diagnosis, treatment, clinical course, and survival status. Patients with BC and CNS mets were divided into two cohorts, those with additional mets limited to bone and lymph nodes but without further visceral spread (CNS-NV), and those with CNS mets plus visceral mets (CNS-V). Kaplan-Meier methods were used to analyze the median OS. **Results:** Our study included a high proportion of underrepresented minorities (n=177); 46.3% were Black, 10.7% were White, and 34.5% were Other Race; besides, 28% were Hispanic. Mean age at diagnosis of CNS mets was 58 years (SD = 12.9). 62.1% were estrogen receptor (ER) and/or progesterone receptor (PR) positive, 27.1% were HER2 positive; and 19.8% were ER, PR and HER2 negative. Mean number of chemotherapy and endocrine therapy lines before CNS mets were 2 (IQR = 1-2) and 1 (IQR = 1-2), respectively. CNS-NV and CNS-V cohorts included 35 and 142 patients, respectively. Patients with CNS-NV had longer OS than CNS-V (2118 vs. 1120 days, p=0.02). Further subgroup analysis for group CNS-NV was performed based on treatment modality. In this cohort, OS was not significantly different between patients who did and did not receive chemotherapy (n =35, mean OS 1509 vs. 960 days, p = 0.49). In addition, OS was not significantly different between patients who received and did not receive endocrine therapy (n = 24, mean OS 857 vs. 1394 days, p = 0.4). Finally, OS did not significantly differ between patients who did and did not receive anti HER2 treatment (n = 11, 1753 vs. 849 days, p = 0.15). **Conclusions:** Minimal research has been conducted on breast cancer patients with CNS mets and distal involvement limited to the bones or lymph nodes. In a heterogenous racial and ethnic population, patients with BC and CNS mets have prolonged OS if the extent of distal involvement is limited to the bones or lymph nodes, compared to those with visceral mets. More research with larger sample sizes is needed to confirm our findings, which may help to de-escalate and tailor treatment for patients with CNS mets. Research Sponsor: None.

1089 **Poster Session**

Clinical and pathological characteristics of breast cancer with resected brain metastasis. *First Author: Shiyuan Anabeth Liu, Washington University School of Medicine, St. Louis, MO*

Background: Breast cancer brain metastasis (BCBM) has poor prognosis and limited therapeutic options. Studies have shown that BCBM may differ from their matched primary tumors in receptor subtypes and genomic characteristics. However, studies have been limited by the tissue availability of BCBM. Taking advantage of our institutional database of resected BCBM with matched primary breast samples, this study aimed to investigate the clinical and pathological characteristics of patients with resected BCBM. **Methods:** We performed retrospective chart review for all breast cancer patients who had resected BCBM samples at our institution over the last 20 years. Hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status of the primary breast and BCBM samples, location of BCBM, and extracranial metastases at time of BCBM diagnosis were categorized. Overall survival (OS) from time of BCBM diagnosis was calculated using the Kaplan-Meier method. Progression interval and receptor subtype switching from primary diagnosis to brain metastasis were computed and compared using Wilcoxon rank sum test and Fisher's exact test, respectively. **Results:** Eighty-six patients were included in this study (median age at time of BCBM diagnosis 54.3 [range 28.3-84.0] years, median follow up 26.0 months). These included 47 HR+, 15 HER2+, 20 triple negative (TN), 4 unknown subtype breast samples, and 42 HR+, 18 HER2+, 17 TN and 9 unknown subtype brain samples. OS was significantly shorter in patients with TN compared to HR+ or HER2+ subtype, whether the TN status was in the primary breast tumor (median 20.5 vs 34.0 months, p = 0.04, thresholded at year 2) or in the brain metastasis (median 16.0 vs 34.0 months, p = 0.02, thresholded at year 2). No significant difference in OS was observed between HR+ and HER2+ groups. There was no significant difference in the progression interval from primary diagnosis to brain metastasis among receptor subtypes. From primary tumor to brain metastasis, receptor subtype switching occurred in 10 out of 73 patients (13.7%) for estrogen, 20 out of 70 (28.6%) for progesterone (PR), and 6 out of 72 (8.3%) for HER2. Receptor subtype switching did not significantly correlate with OS. Presence of extracranial metastases at time of BCBM diagnosis corresponded to significantly lower OS compared to no extracranial metastasis (16.5 vs 36.0 months, p = 0.01). No significant difference in OS was observed between patients with cerebral vs cerebellar brain metastases. **Conclusions:** These data indicate that patients with TN BCBM disease have the worst overall survival among all receptor subtypes. Metastases in extracranial sites at time of BCBM diagnosis significantly decreased survival. Location of the brain metastasis and receptor subtype switching from primary diagnosis to BCBM, which was relatively infrequent outside of the PR group, did not significantly correlate with OS in this limited data set. Research Sponsor: Washington University School of Medicine, Men's Group Against Cancer.

1090 **Poster Session**

Clinical outcomes in patients (pts) with a history of central nervous system (CNS) metastases receiving talazoparib (TALA) or physician's choice of chemotherapy (PCT) in the phase 3 EMBRACA trial. *First Author: Jennifer Keating Litton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In the EMBRACA trial (NCT01945775) of pts with germline *BRCA1/2*-mutated HER2-negative locally advanced/metastatic breast cancer (ABC), the poly(ADP-ribose) polymerase (PARP) inhibitor TALA significantly improved progression-free survival (PFS) vs PCT (8.6 vs 5.6 mo; HR [95% CI] 0.54 [0.41-0.71]; $P < 0.0001$). Patient-reported outcomes favored TALA, and most common adverse events included anemia, fatigue, and nausea. Previous subgroup analyses found that pts with a history of CNS metastases had improved PFS for TALA vs PCT (HR [95% CI] 0.32 [0.15-0.68]; $P = 0.0016$) and improved objective response rate (ORR) 63.2% vs 15.8%, respectively (odds ratio [95% CI] 8.95 [1.86-52.26]; $P = 0.0013$). This retrospective subgroup analysis further explored the clinical characteristics and outcomes in pts with a history of CNS metastases in EMBRACA. **Methods:** Pts were randomized 2:1 to TALA or PCT. Pts with adequately treated and stable CNS metastases not requiring corticosteroids were included. This analysis assessed intracranial ORR and best overall response (BOR) based on investigator assessment per RECIST 1.1 in pts with intracranial disease at baseline (data cutoff 15-Sep-17), and overall survival (OS; data cutoff 30-Sep-19). **Results:** In the intent-to-treat (ITT) population, 63 pts (43/287 [15.0%] TALA and 20/144 [13.9%] PCT) had a history of CNS metastases, of which 33 (11.5%) pts (TALA) and 15 (10.4%) pts (PCT) had intracranial disease at baseline. Additional baseline characteristics are shown in the table. Intracranial ORR in pts with intracranial disease at baseline and unconfirmed complete or partial response was 18.2% (TALA) vs 20.0% (PCT) (odds ratio [95% CI] 0.78 [0.13-5.80]; $P = 0.765$). In pts with intracranial disease at baseline, an intracranial BOR of stable disease was 69.7% for TALA vs 33.3% for PCT. Median OS in pts with a history of CNS metastases was 12.9 mo (95% CI 9.4-15.6) for TALA and 13.4 mo (95% CI 8.8-17.6) for PCT (HR [95% CI] 0.67 [0.37-1.2]; $P = 0.1936$ [stratified log-rank test]). In the safety population ([n = 43, TALA]; [n = 19, PCT]), median treatment duration (range) with TALA was 5.0 (0.1-36.0) mo compared with 2.1 (0.4-6.9) mo for PCT. **Conclusions:** In this subgroup analysis, baseline characteristics between pts with a history of CNS metastases treated with TALA or PCT were comparable. More pts with intracranial disease at baseline treated with TALA vs PCT experienced stable disease. Intracranial ORR in pts with intracranial disease was 18.2% for TALA vs 20.0% for PCT. Treatment options for pts with a history of CNS metastases are limited and further investigation in larger data sets is warranted. Clinical trial information: NCT01945775. Research Sponsor: Pfizer.

	TALA (N = 43)	PCT (N = 20)
Median age, y	40.0	50.5
No. (%)		
TNBC	31 (72.1)	13 (65.0)
HR+	12 (27.9)	7 (35.0)
***BRCA1* status**	26 (60.5)	12 (60.0)
***BRCA2* status**	13 (30.2)	8 (40.0)
≥1 prior CT for ABC	29 (67.5)	16 (80.0)

1091 **Poster Session**

Genomic evaluation of tumor mutational burden-high (TMB-H) versus TMB-low (TMB-L) metastatic breast cancer to reveal unique mutational features. *First Author: Sarah Sammons, Duke University Medical Center, Duke Cancer Institute, Durham, NC*

Background: Tumor mutational burden (TMB) has emerged as an imperfect biomarker of immune checkpoint inhibition (ICI) outcomes in solid tumors. Despite the approval for pembrolizumab in all TMB-high (TMB-H) solid tumors, the optimal clinical approach to TMB-H or hypermutated advanced/metastatic breast cancer (MBC) is unknown with sparse prospective data. We hypothesize that TMB-H MBC will have unique genomic alterations compared to TMB-low (TMB-L) breast cancer that could inform novel therapeutic approaches. **Methods:** Tumor samples (N = 5621) obtained from patients with MBC were analyzed by next-generation sequencing (NGS) of DNA (592-gene panel or whole exome sequencing) and RNA (whole transcriptome sequencing) at Caris Life Sciences (Phoenix, AZ). TMB was calculated based on recommendations from the Friends of Cancer Research TMB Harmonization Project (Merino et al., 2020), with the TMB-H threshold set to ≥ 10 muts/Mb. IHC was performed for PD-L1 (Ventana SP142 ≥1% immune cells). Deficient mismatch repair (dMMR)/high microsatellite instability (MSI-H) was tested by IHC and NGS, respectively. **Results:** TMB-H was identified in 8.2% (n = 461) of MBC samples, with similar frequencies observed across molecular subtypes (7.8-8.6%, p = 0.85): HR+/HER2- (n = 3087) 7.8%, HR+/HER2+ (n = 266) 8.3%, HR-/HER2+ (n = 179) 7.8%, TNBC (n = 1476) 8.6%. The frequency of TMB-H was significantly increased in lobular (16%) versus ductal (5%) MBC ($p < 0.01$). TMB-H samples were enriched in genitourinary (42%), soft tissue (20%), and gastrointestinal non-liver (16%) biopsy specimens. Compared to TMB-L tumors, TMB-H tumors exhibited significantly higher mutation rates for TP53 (60 v 52%), PIK3CA (55 vs 31%), ARID1A (34 vs 11%), CDH1 (27 vs 11%), NF1 (22 vs 9%), RB1 (14 vs 5%), KMT2C (12 vs 7%), PTEN (12 vs 7%), ERBB2 (7 vs 2.9%), and PALB2 (3.3 vs 1%) genes ($p < 0.05$ each). Copy number alteration and fusion rates did not differ between TMB-H and TMB-L breast cancers. PI3K/AKT/MTOR, TP53, Histone/Chromatin remodeling, DNA damage repair (DDR), RAS, and cell cycle pathway alterations were detected in > 25% TMB-H MBCs ($p < 0.05$ each). dMMR/MSI-High (7.2 vs 0.3%, $p < 0.01$) and PD-L1 positivity (36 vs 28%, $p < 0.05$) frequencies were significantly increased in TMB-H tumors. DNA signature analyses including APOBEC and homologous recombination repair deficiency, as well as gene expression profiling to assess immune-related signatures and tumor microenvironment are underway. **Conclusions:** TMB-H breast cancers contain a unique genomic profile enriched with targetable mutations such as PIK3CA, ARID1A, NF1, PTEN, ERBB2, and PALB2. Concurrent predictive biomarkers of response to immune checkpoint inhibition such as MSI-H and PDL-1 positivity are also more prevalent in TMB-H MBC. These findings suggest novel combination strategies within TMB-H MBC could be explored. Research Sponsor: None.

1092 **Poster Session**

Decreased enrollment of patients with advanced lobular breast cancer compared to ductal breast cancer in interventional clinical trials. *First Author: Mary Kathryn Abel, University of California, San Francisco School of Medicine and Department of Surgery, San Francisco, CA*

Background: Response Evaluation Criteria in Solid Tumors (RECIST) criteria are often used to measure tumor response in cancer trials, especially in the stage IV setting. However, RECIST requires measurable disease, which is less common in invasive lobular breast carcinoma (ILC) of the breast, a diffusely growing tumor type, compared to invasive ductal carcinoma (IDC). We examined the prevalence of RECIST in breast cancer clinical trials, and whether there are differential trial enrollment rates by histology and stage. **Methods:** We analyzed the *clinicaltrials.gov* database to evaluate the proportion of interventional, stage IV clinical trials that require measurable disease as inclusion criteria or outcome measures. We then performed an institutional cohort study comparing the proportion of patients in the University of California, San Francisco (UCSF) OnCore clinical trials management system (CTMS) to the UCSF Cancer Registry between 2000-2018, stratified by histology and stage. We hypothesized that the proportion of patients with ILC in the CTMS would be significantly lower than in the cancer registry. **Results:** There were 146 actively-recruiting, interventional clinical trials for stage IV breast cancer that were identified in our search on *clinicaltrials.gov*. Overall, 108 (74%) required measurable disease for study participation. The UCSF Cancer Registry included 8,679 patients, while the UCSF OnCore CTMS included 1,511 patients (Table). In those with early stage disease, where RECIST is not typically used, there was no difference in the proportion of ILC patients enrolled in clinical trials versus in the cancer registry. However, among those with stage IV disease, there was a significantly lower proportion of patients with ILC in the CTMS than in the cancer registry (9.2% versus 17.9%, p = 0.005). In contrast, patients with stage IV IDC were overrepresented in the clinical trials database compared to the cancer registry. **Conclusions:** Patients with metastatic ILC were significantly less likely to be enrolled in clinical trials than those with metastatic IDC. This decreased enrollment may be due to the widespread use of RECIST, and further investigation is needed to ensure equity in access to clinical trials. Research Sponsor: None.

Two-sample tests of proportion evaluating patients enrolled in the UCSF Cancer Registry compared to the OnCore clinical trial management system (CTMS) by histology and stage.

	UCSF Cancer Registry	OnCore CTMS	P-Value Using Two-Sample Test of Proportions
Study Population	8,697	1,511	0.0486
IDC (n, %)	7320 (84.3%)	1304 (86.3%)	
ILC (n, %)	1359 (15.7%)	207 (13.7%)	
Early Stage (Stage I-III)	8,187	1,337	0.063
IDC (n, %)	6,916 (84.4%)	1,146 (85.7%)	
ILC (n, %)	1271 (15.5%)	191 (14.3%)	
Metastatic (Stage IV)	492	174	0.005
IDC (n, %)	404 (82.1%)	158 (90.8%)	
ILC (n, %)	88 (17.9%)	16 (9.2%)	

1093 **Poster Session**

Systemic chemotherapy in patients with brain only metastatic breast cancer: A retrospective analysis. *First Author: Akshjot Puri, Houston Methodist Cancer Center, Houston, TX*

Background: The treatment of patients with brain only metastatic breast cancer (BO-MBC) remains very challenging. There is also very limited literature informing on appropriate treatment or natural history of this entity. Systemic chemotherapy in addition to targeted therapy and/or anti-estrogen treatment is often used, but little is known if it adds to the overall or disease free survival. In this retrospective study, we examine this, as well as other factors which may be associated with increased risk of CNS or systemic recurrence in these patients. **Methods:** A database search at a single institution identified 178 patients with brain metastases (BM) from breast cancer out of which 45 patients had BO-MBC between 2007-2020. We collected demographic, clinical, radiographic and other treatment data. Leptomeningeal disease (LMD) was diagnosed by cerebrospinal fluid (CSF) cytology, neuroimaging, or both. We used the Brookmeyer and Crowley method. **Results:** The patients were followed for a median of 17.9 months; 36 out of 45 patients (80%) received local treatment for BM (surgery/radiation/both) and HER2 directed antibodies or tyrosine kinase inhibitors and/or anti-estrogen treatment, whereas 9 out of 45 patients (20%) received systemic chemotherapy in addition. There were 22 out of 45 (49%) HER2 +, 5 out of 45 (11%) HR + and 18 out of 45 (40%) triple negative breast cancer (TNBC) patients. There were 17 out of 45 patients (38%) who were deemed to have low burden of BM (defined as one to three BM and largest being ≤3 cm) whereas there were 24 out of 45 patients (53%) who had high burden of BM (defined as four or more BM or largest being > 3 cm). **Conclusions:** Patients with BO-MBC represent a distinct entity. Despite having better survival than patients with BM and extra CNS disease these patients have a high risk of developing LMD, CNS and systemic recurrences. The addition of chemotherapy to targeted therapy and/or anti-estrogens does not decrease the rates of systemic or CNS recurrence. The ER+ subset have a lower rate of development of systemic disease, as expected due to their relatively indolent biology. The CNS and systemic recurrence seem to be higher in patients with HER2+ cancers and counterintuitively even in those with low burden of BM; albeit these were statistically insignificant. Research Sponsor: None.

One year estimated time to recurrence	Chemotherapy	No chemotherapy		
Extra CNS	87.5% (95% CI: 38.7%, 98.1%)	81.8% (95% CI: 63.8%, 91.4%)	p=0.64	
CNS	71.4% (95% CI: 25.8%, 92%)	64.7% (95% CI: 46.2%, 78.2%)	p=0.78	
LMD	88.9% (95% CI: 43.3%, 98.4%)	71.1% (95% CI: 52.8%, 83.3%)	P=0.34	
	HER2+	TNBC	HR+	
Extra CNS	95.2% (95% CI: 70.7%, 99.3%)	76.3% (95% CI: 48.3%, 90.4%)	37.5% (95% CI: 1.1%, 80.8%)	p=0.47
CNS	69.1% (95% CI: 43.3%, 84.9%)	61.1% (95% CI: 35.3%, 79.2%)	66.7% (95%CI: 5.4% ,94.5%)	P=0.61
	Low BM burden	High BM burden		
Extra CNS	87.5% (95% CI: 58.6%, 96.7%)	75% (95% CI: 49.2%, 89%)	P=0.33	
CNS	75% (95% CI:46.3%, 89.8%)	57.8% (95% CI: 33.8%, 75.7%)	P=0.67	

1094 **Poster Session**

Metastasectomy versus radiation of secondary sites in stage IV breast cancer. *First Author: Nadeem Bilani, Cleveland Clinic Florida, Weston, FL*

Background: Prospective trials have yielded mixed results on the utility of surgery in metastatic breast cancer (mBC). Thus far, however, studies have focused primarily on the impact of lumpectomy or mastectomy. We previously showed that a combined approach involving resection of primary *and* secondary sites (i.e. 'metastasectomy') in patients with limited mBC was associated with improved overall survival (OS). We sought to evaluate the effect on OS of two approaches to loco-regional therapy (LRT) at secondary sites: metastasectomy versus radiation therapy. **Methods:** This is a retrospective analysis of patients diagnosed with mBC from 2010-2017 using the National Cancer Database. We identified 5 cohorts of patients by site of metastasis: mBC involving only 1) bone, 2) brain, 3) liver, or 4) lung; and 5) patients with metastasis involving >1 site. For each cohort, we used Kaplan-Meier (KM) models with log-rank testing to evaluate differences in OS, by the LRT approach at secondary sites (radiation versus metastasectomy). Prior to KM modeling, chi-squared statistics were used in each cohort to assess whether age, race, Charlson/Deyo score (CDS) for comorbidity, and receptor subtype were potential confounders of survival. The KM models were adjusted accordingly, as per the table below. **Results:** 53.4%) were between 50-70 years old, White (n=53,409, 78.9%), and had hormone receptor (HR)-positive/HER2 receptor-negative breast cancer. N=12,362 patients received radiation therapy at either the bone, brain, liver, or lung; while n=2674 underwent surgical resection of a metastatic site. Of patients with metastasis to 1 site (n=44,451), n=30,341(68.3%) involved the bone, n=1,119 (2.5%) involved the brain, n=5,227 (11.8%) involved the liver, and n=7,764 (17.5%) involved the lung. N=24,017 patients had metastatic disease involving > 1 site. KM modeling revealed superior OS of patients undergoing metastasectomy versus radiation of secondary sites in all 5 cohorts ($p<0.05$). The difference in median OS (ΔmOS) by LRT approach was more pronounced when metastasis involved only the liver (41.6 months) or lung (48.6 months), versus only the brain (9.7 months) or bone (8.7 months). **Conclusions:** Metastasectomy appears to confer a superior benefit for OS compared to radiation of secondary sites, particularly in patients with secondary site involvement limited to the liver or lung. More research is needed from prospective trials investigating surgical resection of metastatic sites. Research Sponsor: None.

		KM Median OS (months)			Log-rank
		Radiation	Metastasectomy	ΔmOS (months)	p-value
1 site of metastasis	Bone only*	39.2	47.9	8.7	0.012
	Brain only	11.9	21.6	9.7	0.006
	Liver only	39.2	80.8	41.6	<0.001
	Lung only	18.2	66.8	48.6	<0.001
>1 site of metastasis**		21.5	31.4	9.9	<0.001

*KM adjusted for age (50-70). **KM adjusted for age (50-70), receptor status (HR+/HER2-), and CDS (0-1).

1095 **Poster Session**

Survival among patients with untreated metastatic breast cancer. *First Author: Jennifer Kay Plichta, Department of Surgery, Duke University Medical Center, Durham, NC*

Background: Treatments for metastatic breast cancer (MBC) have significantly improved survival for patients who receive treatment, yet data describing the prognosis for untreated patients is lacking. Therefore, we sought to assess the survival outcomes of patients with de novo MBC who did not receive treatment. **Methods:** Adults with MBC at diagnosis (clinical M1 or pathologic M1) were selected from the NCDB (2010-2016) and stratified based on receipt of treatment (treated = received at least one treatment; untreated = received no treatments). Differences between patient groups were tested using Chi-square tests for categorical variables and t-tests for continuous variables. Overall survival (OS) was estimated using the Kaplan-Meier method for the overall cohort and stratified by select patient and/or disease characteristics, and groups were compared with log-rank tests. Cox Proportional Hazards models were used to identify factors associated with OS in the untreated MBC subgroup. **Results:** Of the 53,240 patients with de novo MBC, the median age was 61y (IQR 52-71), and the majority had a comorbidity score of 0 (81.2%). Within this cohort, 49,040 (92.1%) received at least one treatment (treated) and 4,200 (7.9%) had no documented treatments (untreated). Untreated patients were more likely to be older (median 68y vs 61y, $p < 0.001$) and have higher comorbidity scores ($p < 0.001$). Patients with untreated MBC were more likely to have triple negative disease (17.8% vs 12.6%), and a higher disease burden (≥2 metastatic sites: 38.2% untreated vs 29.2% treated, $p < 0.001$). The median unadjusted OS in the untreated subgroup was 2.5mo vs 36.4mo in the treated subgroup ($p < 0.001$). For those who survived at least 1mo post-diagnosis, the median unadjusted OS in the untreated subgroup was 6.9mo vs 37.3mo in the treated subgroup ($p < 0.001$), which increased to 18.6mo and 40.3mo for those who survived at least 3mo post-diagnosis ($p < 0.001$). In the untreated population, unadjusted OS varied by breast cancer subtype (median 3.8mo for HR+/HER2-, vs 2.6mo for HER2+, vs 2.1mo for triple negative, $p < 0.001$) and number of metastatic sites (4.1mo for 1 site, vs 1.8mo for 2 sites, vs 1.1mo for 3 sites, vs 1.2mo for ≥4 sites, $p < 0.001$). After adjustment, variables associated with a worse OS in the untreated cohort included older age, higher comorbidity scores, higher tumor grade, and triple negative (vs HR+/HER2-) tumor subtype (all $p < 0.05$), while the number of metastatic sites was not associated with survival; these same findings were also noted when the analysis was limited to those who survived at least 1mo post-diagnosis. **Conclusions:** Patients with de novo MBC who do not receive treatment are more likely to be older, present with comorbid conditions, and have clinically aggressive disease. Similar to those who do receive treatment, survival in an untreated population is associated with select patient and disease characteristics. However, the prognosis for untreated MBC is dismal. Research Sponsor: None.

TPS1096 **Poster Session**

Trastuzumab deruxtecan (T-DXd) combinations in patients with HER2-positive advanced or metastatic breast cancer: A phase 1b/2, open-label, multicenter, dose-finding and dose-expansion study (DESTINY-Breast07). *First Author: Fabrice Andre, Gustave Roussy, Université Paris-Sud, Villejuif, France*

Background: HER2-targeted therapies have improved survival in patients (pts) with HER2+ advanced/metastatic breast cancer (mBC) but challenges remain, including resistance to current HER2-targeted therapies. Also, additional treatment options are needed in pts with brain metastases (BM). In the phase 2 DESTINY-Breast01 trial, T-DXd demonstrated efficacy, with an objective response rate (ORR) of 61.4% and median progression-free survival (mPFS) of 19.4 mo in pts with previously treated HER2+ advanced/mBC (Modi SABCS 2020); data from an earlier cutoff of this trial supported approval of T-DXd in the US, Europe, and Japan. In a subgroup analysis of 24 pts with stable BM, T-DXd showed preliminary efficacy, with mPFS of 18.1 mo (Jerusalem ESMO Breast Cancer 2020). Here, we describe a phase 1b/2 trial evaluating the safety and preliminary antitumor activity of T-DXd monotherapy and combinations in pts with HER2+ advanced/mBC, including pts with stable and active BM. **Methods:** DESTINY-Breast07 (NCT04538742) is a global, multicenter, open-label, phase 1b/2 trial designed to evaluate the safety, tolerability, and preliminary antitumor activity of T-DXd monotherapy and combinations in pts with HER2+ advanced/mBC. This study consists of a T-DXd monotherapy module (module 0) and 5 combination modules of T-DXd plus (1) durvalumab, (2) pertuzumab, (3) paclitaxel, (4) durvalumab + paclitaxel, or (5) tucatinib, all in pts with no or stable BM. Two additional modules consisting of (6) T-DXd + tucatinib and (7) T-DXd monotherapy will include pts with untreated BM not requiring local therapy or previously treated BM that have progressed since local therapy (active BM). The need for chronic steroids or local therapy to manage BM symptoms is exclusionary. Modules 2 to 5 will each consist of 2 parts: dose finding (part 1) and dose expansion (part 2). Modules 0, 1, 6, and 7 will include part 2 only. Part 1 of individual modules will enroll pts who have had disease progression while receiving ≥1 prior line of therapy in the metastatic setting. In part 2, pts who have received no prior therapy (modules 0 to 5) or ≤1 prior therapy (modules 6 to 7) for metastatic disease will be randomized to receive a T-DXd combination regimen or monotherapy. The primary endpoints are determination of the recommended phase 2 doses (part 1 only) and safety and tolerability of T-DXd and combinations (parts 1 and 2). Secondary endpoints include ORR, PFS, PFS2, duration of response (DoR), and overall survival (all assessed in part 2 only) and pharmacokinetics and immunogenicity (parts 1 and 2). To assess central nervous system (CNS) activity, exploratory endpoints were added, including CNS-ORR, CNS-DoR, and CNS-PFS (by RECIST version 1.1 and RANO-BM criteria) as well as cognitive and symptom assessment using CANTAB, MDASI-BT, and NANO. Clinical trial information: NCT04538742. Research Sponsor: AstraZeneca.

TPS1097 **Poster Session**

HER2CLIMB-04: Phase 2 open label trial of tucatinib plus trastuzumab deruxtecan in patients with HER2+ unresectable locally advanced or metastatic breast cancer with and without brain metastases (trial in progress). *First Author: Ian E. Krop, Dana-Farber Cancer Institute, Boston, MA*

Background: Tucatinib (TUC) is an oral, reversible, small molecule tyrosine kinase inhibitor highly selective for human epidermal growth factor receptor 2 (HER2) with minimal inhibition of human epidermal growth factor receptor (EGFR). In the pivotal, randomized HER2CLIMB trial (NCT02614794), the combination of TUC + trastuzumab (T) + capecitabine (C) demonstrated statistically significant and clinically meaningful improvements in progression free survival (PFS), overall survival (OS), and PFS in patients (pts) with brain metastases (BM), compared to T + C alone. These data supported regulatory approvals in the US and internationally for TUC in combination with T + C in pts with HER2+ metastatic breast cancer (MBC). Trastuzumab deruxtecan (T-DXd) is an antibody-drug conjugate of trastuzumab and a topoisomerase I inhibitor payload approved in the US for treatment of HER2+ MBC in pts who have received 2 or more prior anti-HER2 regimens in the metastatic setting. Approval was based on data from the single arm Destiny-Breast01 trial (NCT03248492) where treatment with T-DXd resulted in a confirmed objective response rate (cORR) of 61.4% (95% CI: 54.0, 68.5) in pts with HER2+ MBC who had prior ado-trastuzumab emtansine treatment. Despite these advances, HER2+ MBC remains incurable, and pts will eventually progress on currently available therapies. Combining TUC and T-DXd may result in further improvement on the efficacy seen with either agent alone. **Methods:** HER2CLIMB-04 (NCT04539938) is a single arm, open-label phase 2 trial evaluating safety and antitumor activity of TUC + T-DXd in pts with HER2+ unresectable locally-advanced or MBC who have received 2 or more prior HER2-based regimens in the metastatic setting. Pts with BM, including active BM, may be enrolled. Ten pts will be enrolled in the safety lead-in portion of the trial and followed for at least 1 cycle. If safety of the combination is acceptable, the trial will continue until approximately 60 response-evaluable pts have been enrolled, approximately evenly distributed between pts with and without BM. The primary endpoint is cORR by investigator (INV) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Secondary endpoints are PFS, duration of response (DOR), and disease control rate (DCR) by INV per RECIST v1.1, OS, and safety. Exploratory endpoints will include cORR, PFS, DOR, DCR by independent central review per RECIST v1.1, pharmacokinetic analyses, biomarker analyses, and changes in patient-reported outcomes using the European Quality of Life 5-Dimension 5-Level instrument. Enrollment began in late 2020 in the United States. Clinical trial information: NCT04539938. Research Sponsor: Seagen Inc.

TPS1098 **Poster Session**

Trial in progress: A phase 1b/2 study of the PARP inhibitor niraparib in combination with trastuzumab in patients with metastatic HER2+ breast cancer (TBCRC 050). *First Author: Erica Michelle Stringer-Reasor, University of Alabama at Birmingham, Birmingham, AL*

Background: Approximately 20% of breast cancers (BC) express the human epidermal growth factor receptor 2 (HER2). Although HER2-directed therapies result in improved patient outcome, resistance ultimately occurs. Poly (ADP-Ribose) polymerase (PARP) inhibitors are currently indicated in cancers that express germline mutations in the DNA repair proteins BRCA1/2 due to their synthetic lethality against the homologous recombination repair (HR) pathway. In addition to its role in DNA damage repair, PARP1 has also been implicated in other cellular functions, including co-activation of genes such as NF-κB, which regulate tumor proliferation and HER2 drug resistance. Our group identified that HER2+ BC overexpress the PARP1 and phospho-p65 protein. In HER2+ BC cells and animal models, PARP inhibitors initiated apoptosis independent of a DNA repair deficiency, via inhibition of NF-kB signaling. Key proteins (p65, IKK-α) of the NF-κB-mediated growth pathways were reduced and IκBα was increased in the presence of PARPi, implicating another oncologic pathway in which HER2+ BC cells may be dependent. **Methods**: The study is a phase 1b/2, multicenter, single arm clinical trial evaluating the safety and efficacy of niraparib 200 mg orally days 1-21 with trastuzumab 6 mg/kg (cycle 1 loading dose of 8 mg/kg) intravenously on day 1 of a 21-day cycle for patients with unresectable or metastatic HER2+ BC. Eligible patients include metastatic HER2+ BC, progression on at least 1 prior HER2-targeted therapy, measurable disease, ECOG PS 0-1, and LVEF $\geq$ 50%. Stable/treated CNS disease allowed. Prior PARPi and known germline BRCA 1/2 excluded. Forty patients will be enrolled at 7 US sites within the Translational Breast Cancer Research Consortium. The primary objectives are determining the dose-limiting toxicity (DLT) of the combination and assessing the objective response rate. The phase 1b cohort has been completed (N=6). Enrollment in phase 2 began February 2021 with a total accrual goal of 40. Gehan's two-stage design will be used assuming the response rate is at least 24% and the response rate will be estimated with Clopper-Pearson exact method. Correlative aims include assessing blood and tissue biomarkers (e.g. PARP1, p65, phosphor-p65, let-7a miRNA, NF-kB, ctDNA, etc.) for association with clinical benefit and to predict response to therapy. Clinical trial information: NCT03368729. Research Sponsor: TESARO/GSK, Other Foundation.

TPS1099 **Poster Session**

Trial in progress: Phase I/II study of radiation therapy followed by intrathecal trastuzumab/pertuzumab in the management of HER2$^+$ breast leptomeningeal disease. *First Author: Kamran A. Ahmed, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: HER2$^+$ breast cancer patients with leptomeningeal disease (LMD) represent a poor prognosis population with a high unmet clinical need. Although a multitude of treatment options are available for the management of systemic disease, once metastases travel to the leptomeninges, patients have a lack of treatment options aside from traditional local approaches. Data from a phase I/II study reveals intrathecal (IT) trastuzumab to be well tolerated with improved overall survival (OS) compared to historical controls in HER2$^+$ breast LMD. Radiotherapy can improve the flow of IT therapy through the cerebrospinal fluid (CSF) and provide symptomatic relief. The monoclonal antibody pertuzumab is used in conjunction with trastuzumab in the management of metastatic and localized HER2$^+$ breast cancer. Given the role of radiotherapy in the management of LMD along with the role of pertuzumab in the management of HER2$^+$ breast cancer, there is a strong clinical rationale to combine radiotherapy with IT trastuzumab/pertuzumab in the management of HER2$^+$ breast LMD. **Methods:** The study is designed as a prospective, single-arm, nonrandomized, open-label, phase I/II trial of radiation therapy followed by IT trastuzumab/pertuzumab in the management of HER2$^+$ breast LMD. HER2$^+$ LMD patients identified by magnetic resonance imaging (MRI) and/or CSF cytology, $\geq$ 18, with a life expectancy $>$ 8 weeks are eligible. Treatment is initiated with radiotherapy, whole brain radiotherapy and/or focal brain/spine radiation followed by IT trastuzumab/pertuzumab. Safety and feasibility will be monitored by a modified toxicity probability interval-2 (mTPI-2) design. Dose reductions of IT trastuzumab will not be allowed. Once the maximum tolerated dose of IT pertuzumab is determined, the phase II portion of the study will commence to determine OS. Secondary objectives involve defining the CSF pharmacokinetics of IT trastuzumab/pertuzumab, evaluating the response rate (leptomeningeal and parenchymal), and progression free survival (leptomeningeal and parenchymal) following IT trastuzumab/pertuzumab. In the phase 2 portion, a single-arm two-stage trial is designed using the Restricted-Kwak-and-Jung's Method. The primary endpoint is one-year OS. An interim analysis will be performed after 20 patients are enrolled. This study is open with 1 patient enrolled at the time of submission. Clinical trial information: NCT04588545. Research Sponsor: Genentech.

TPS1100 **Poster Session**

acelERA Breast Cancer (BC): Phase II study evaluating efficacy and safety of giredestrant (GDC-9545) versus physician's choice of endocrine monotherapy in patients (pts) with estrogen receptor-positive, HER2-negative (ER+/HER2-) locally advanced or metastatic breast cancer (LA/mBC). *First Author: Miguel Martin, Hospital General Universitario Gregorio Marañón, Madrid, Spain*

Background: The standard-of-care therapy for ER+ BC typically involves modulation of estrogen synthesis and/or ER activity. Despite disease progression with standard treatments, growth and survival of the majority of tumors are thought to remain dependent on ER signaling; therefore, pts with ER+ BC can still respond to second- or third-line endocrine treatment (ET) after progression on prior therapy (Di Leo 2010; Baselga 2012). *ESR1* mutations may drive estrogen-independent transcription and proliferation leading to resistance. The highly potent, nonsteroidal oral selective ER degrader, giredestrant, achieves robust ER occupancy and is active regardless of *ESR1* mutation status. Phase I data have shown that giredestrant is well tolerated and active both as a single agent and in combination with the cyclin-dependent kinase 4/6 inhibitor (CDK4/6i), palbociclib (Lim 2020). Single-agent giredestrant has also shown encouraging antitumor activity in pts previously treated with fulvestrant and/or a CDK4/6i. **Methods:** acelERA BC (NCT04576455) is a randomized, open-label, multicenter phase II study evaluating the efficacy and safety of giredestrant vs. physician's choice of ET (fulvestrant or aromatase inhibitor) in males, or postmenopausal or pre/perimenopausal females with ER+/HER2– LA/mBC who have received 1–2 prior lines of systemic therapy in the LA or mBC settings, at least one of which must be ET. Randomization: 1:1 to receive giredestrant (30 mg PO QD on Days 1–28 of each 28-day cycle) or physician's choice of ET per local guidelines. Men and pre-/perimenopausal women will receive a luteinizing hormone-releasing hormone agonist. Eligibility: $\geq$18 years, ECOG PS 0–1, histologically or cytologically confirmed diagnosis of LA (recurrent or progressed) or metastatic adenocarcinoma of the breast, measurable disease (per modified RECIST v1.1) or evaluable bone lesions, and ER+/HER2– tumors (locally assessed). Primary endpoint: progression-free survival (PFS; investigator-assessed per RECIST v1.1). Secondary endpoints: overall survival, objective response rate, duration of response, clinical benefit rate, PFS in pts with baseline *ESR1* mutations, and quality of life. Safety, pharmacokinetics, biomarkers, and health status utility will also be assessed. Stratification: site of disease (visceral vs. nonvisceral), prior treatment with CDK4/6i (yes vs. no), and prior treatment with fulvestrant (yes vs. no). PFS will be compared using a stratified log-rank test; median PFS, using Kaplan–Meier analyses. Recruitment for the global enrollment phase is ongoing, the first patient was enrolled November 27, 2020. Clinical trial information: NCT04576455. Research Sponsor: F. Hoffmann-La Roche Ltd.

TPS1101 **Poster Session**

SERENA-4: A phase 3 comparison of AZD9833 (camizestrant) plus palbociclib, versus anastrozole plus palbociclib, for patients with ER-positive, HER2-negative advanced breast cancer who have not previously received systemic treatment for advanced disease. *First Author: Seock-Ah Im, Seoul National University Hospital, Seoul, South Korea*

Background: More than two thirds of patients with advanced breast cancer (ABC) have estrogen receptor-positive (ER+), human epidermal growth factor receptor 2-negative (HER2−) tumors. Current standard-of-care first-line treatments include an aromatase inhibitor (AI) or fulvestrant, a selective ER degrader (SERD), combined with cyclin-dependent kinase 4/6 (CDK4/6) inhibitors. Concurrent use of luteinizing hormone-releasing hormone (LHRH) agonists is recommended for men and premenopausal women with ABC. Nevertheless, almost all ABCs eventually become resistant to endocrine therapy (ET) and the disease is incurable. New therapies are needed to combat ET resistance, maintain patient quality of life (QoL), and delay the need for chemotherapy. AZD9833 (camizestrant) is an orally bioavailable, highly potent, next-generation SERD that demonstrated anti-cancer properties across a range of preclinical models, including those with ER-activating mutations (Scott *et al*, 2020). A phase I study (SERENA-1) has demonstrated that AZD9833 is well tolerated and has a promising antitumor profile when administered alone or in combination with palbociclib, a CDK4/6 inhibitor (Baird *et al*, *SABCS* 2020). SERENA-4 (NCT04711252) is a randomized, multicenter, double-blind, phase III trial to evaluate the safety and efficacy of AZD9833 in combination with palbociclib for patients with ER+ HER2− ABC who have not received any systemic treatment in the advanced disease setting. **Methods:** SERENA-4 will enroll 1,342 patients with *de novo* or recurrent ER+ HER2– ABC who have not previously received systemic treatment for their locoregionally recurrent or metastatic disease. Patients with recurrent disease must have received adjuvant AI or tamoxifen therapy for at least 24 months without relapse. Patients will be randomized 1:1 to receive orally either (a) AZD9833 (75 mg, once daily), palbociclib (125 mg, once daily for 21 days followed by 7 days off treatment) and anastrozole-matching placebo (once daily) or (b) anastrozole (1 mg, once daily), palbociclib (same as active arm), and AZD9833-matching placebo (once daily). Premenopausal women and men will also receive LHRH agonists. The primary endpoint will be progression-free survival (PFS; up to 5 years). Secondary endpoints will include overall survival (up to 8 years), length of second PFS period, objective response, time to chemotherapy, and changes in QoL measures. Enrollment began in January 2021. Acknowledgments: We thank Rose Goodchild, PhD, of Oxford PharmaGenesis, UK, for providing medical writing assistance. Funding: The SERENA-4 trial is funded and overseen by AstraZeneca. Clinical trial information: NCT04711252. Research Sponsor: AstraZeneca.

TPS1102 **Poster Session**

Saci-IO HR+: Randomized phase II trial of sacituzumab govitecan (SG) +/- pembrolizumab in PD-L1+ hormone receptor-positive (HR+) / HER2- metastatic breast cancer (MBC). *First Author: Ana Christina Garrido-Castro, Dana-Farber Cancer Institute, Boston, MA*

Background: Immune checkpoint inhibitors (ICIs) have not yet benefited most patients with MBC. In HR+ MBC, the first randomized trial combining an ICI with chemotherapy demonstrated no clinical benefit with the addition of pembrolizumab to eribulin.[1] The optimal ICI combination agent to overcome primary resistance in HR+ MBC is unknown. One promising agent is the anti-Trop-2-SN-38 antibody drug conjugate (ADC) SG, which led to median progression-free survival (PFS) of 5.5 months in HR+ MBC refractory to endocrine therapy.[2] This ADC may boost anticancer immunity by binding immune cell receptors to promote antibody-dependent cellular cytotoxicity.[3] In addition, the SN-38 payload of SG is the active metabolite of irinotecan, which depletes regulatory T cells, upregulates MHC class I and PD-L1 expression, and augments the antitumor activity of anti-PD-1/L1 antibodies in murine tumor models.[4] The irinotecan analogue camptothecin also enhances CD8+ cytotoxic T cell effector functions and antitumor immune responses by inhibiting NR4A transcription factors,[5] which have recently been shown to play a central role in inducing the T cell dysfunction associated with chronic antigen stimulation in solid tumors. **Methods**: This is a multi-center 1:1 randomized phase II trial to investigate whether the addition of pembrolizumab (200 mg IV every 3 weeks) to SG (10 mg/kg IV days 1+8 every 21 days) improves PFS compared to SG alone in HR+ HER2- MBC that is PD-L1+ by central assessment with 22C3 combined positive score (CPS) $\geq$ 1 (NCT04448886). Key eligibility criteria include at least 1 prior hormonal therapy and no more than 1 prior chemotherapy for HR+ MBC. Eligible patients must have evaluable disease, and previously treated brain metastases are permitted. Exclusion criteria include prior treatment with SG, irinotecan, and PD-1/L1 inhibitors. Based on a sample size of 110 patients, the trial has 80% power to detect a 3-month difference in median PFS from 5.5 months in the SG-alone cohort to 8.5 months in the SG + pembrolizumab cohort with a one-sided alpha of 0.1. Participants undergo mandatory baseline and on-treatment research biopsies if their disease is safely accessible. Tumor biopsies will be evaluated for Trop-2, immune cells, inhibitory checkpoints, transcriptomic signatures, and genomic alterations. Stool specimens will be submitted for microbiome analyses, and health-related quality of life will be assessed. The trial is currently open and enrolling patients. References: 1) Tolaney SM et al. *JAMA Oncol* 6, 1598-1605 (2020). 2) Kalinksy K et al. *Ann Oncol* 12, 1709-1718 (2020). 3) Cardillo TM et al. *Bioconjug Chem* 26, 919-931 (2015). 4) Iwai T et al. *Oncotarget* 9, 31411-31421 (2018). 5) Hibino S et al. *Cancer Res* 78, 3027-3040 (2018). Clinical trial information: NCT04448886. Research Sponsor: Merck and Immunomedics, Other Foundation.

TPS1103 **Poster Session**

persevERA Breast Cancer (BC): Phase III study evaluating the efficacy and safety of giredestrant (GDC-9545) + palbociclib versus letrozole + palbociclib in patients (pts) with estrogen-receptor-positive, HER2-negative locally advanced or metastatic BC (ER+/HER2– LA/mBC). *First Author: Nicholas C. Turner, Royal Marsden Hospital, London, United Kingdom*

Background: Modulating estrogen synthesis and/or ER activity is the mainstay of treatment for pts with ER+ BC. Despite substantial progress, many pts experience relapse during/after adjuvant endocrine therapy. However, even though resistant to aromatase inhibitors (AIs) or tamoxifen, growth and survival of the majority of tumors are thought to remain dependent on ER signaling. Therefore, pts with ER+ BC can still respond to second- or third-line endocrine treatment after progression on prior therapy (Di Leo 2010; Baselga 2012). Therapeutic resistance can arise from mutations in *ESR1*, which can drive estrogen-independent transcription and proliferation. The highly potent, non-steroidal oral selective ER degrader giredestrant achieves robust ER occupancy and is active regardless of *ESR1* mutation status. Phase I data indicate that giredestrant is well tolerated, with encouraging activity as a single agent and in combination with the CDK4/6 inhibitor palbociclib (Lim 2020). Single-agent activity was observed after prior treatment with fulvestrant and/or a CDK4/6 inhibitor (Jhaveri 2019). **Methods:** persevERA BC (NCT04546009) is a double-blind, placebo-controlled, randomized, multicenter phase III study designed to evaluate the efficacy and safety of first-line giredestrant + palbociclib in pts with ER+/HER2– LA/mBC. Randomization: 1:1 to either giredestrant (30 mg PO) plus letrozole placebo QD or letrozole (2.5 mg PO) plus giredestrant placebo QD on Days 1–28 of each 28-day cycle, with palbociclib (125 mg PO QD) on Days 1–21 of each 28-day cycle. Men and premenopausal women will receive an LHRH agonist. Eligibility: females or males $\geq$18 years old with measurable disease or evaluable bone disease and no prior treatment for advanced disease. Pts who received prior fulvestrant or who have relapsed within 12 months of completion of (neo)adjuvant therapy with an AI and/or prior therapy with CDK4/6 inhibitor are not eligible; relapse during tamoxifen therapy but $>$ 24 months after the start of tamoxifen therapy is allowed. Stratification: site of disease, disease-free interval since the end of (neo)adjuvant therapy, menopausal status, and geographic region. Primary efficacy endpoint: progression-free survival (determined locally by the investigator per RECIST v1.1). Secondary endpoints include overall survival, objective response rate, duration of response, clinical benefit rate, QoL, and safety. Enrollment is open (first patient in: Oct 9, 2020); target recruitment is 978 pts across all sites in a global enrollment phase. After completion of the global enrollment, additional pts may be enrolled in China. Clinical trial information: NCT04546009. Research Sponsor: F. Hoffmann-La Roche Ltd, Basel, Switzerland.

TPS1104 **Poster Session**

AMEERA-5: A randomized, double-blind phase III study of amcenestrant (SAR439859) + palbociclib versus letrozole + palbociclib for previously untreated ER+/HER2- advanced breast cancer. *First Author: Aditya Bardia, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Selective estrogen receptor degraders (SERDs) block estrogen receptor (ER) associated signaling and have created interest for treating patients (pts) with advanced ER+ breast cancer (BC). Fulvestrant is currently the only SERD available for advanced BC but requires intramuscular administration, limiting the applied dose, exposure and receptor engagement. Amcenestrant (SAR439859) is an oral SERD that binds with high affinity to both wild-type and mutant ER, blocking estradiol binding and promoting up to 98% ER degradation in preclinical studies. In the phase I AMEERA-1 study of pretreated pts with ER+/HER2- advanced BC, amcenestrant 150–600 mg once daily (QD) showed a mean ER occupancy of 94% with plasma concentrations $>$ 100 ng/mL and a favorable safety profile (Bardia, 2019; data on file). Combination therapy with amcenestrant + palbociclib (palbo) was also evaluated as part of this ongoing phase I study. CDK 4/6 inhibitors (CDK4/6i) combined with an aromatase inhibitor (AI), the gold standard for first line treatment for advanced breast cancer, prolong progression free survival (PFS) in pts with no prior treatment for ER+/HER2- advanced BC, but OS benefit has not been shown yet in postmenopausal pts. There remains a clinical need for more effective treatments in this setting. **Methods:** AMEERA-5 (NCT04478266) is an ongoing, prospective, randomized, double-blind phase III study comparing the efficacy and safety of amcenestrant + palbo with that of letrozole + palbo in pts with advanced, locoregional recurrent or metastatic ER+/HER2- BC who have not received prior systemic therapy for advanced disease. The study includes men, pre/peri-menopausal (with goserelin) and post-menopausal women. Pts with progression during or within 12 months of (neo)adjuvant endocrine therapy using any of the following agents are excluded: AI, selective estrogen receptor modulators, CDK4/6i. Pts are randomized 1:1 to either continuous amcenestrant 200 mg or letrozole 2.5 mg QD orally with matching placebos; both combined with palbo 125 mg QD orally (d1–21 every 28-d cycle). Randomization is stratified according to disease type (de novo metastatic vs recurrent disease), the presence of visceral metastasis, and menopausal status. The primary endpoint is investigator assessed progression free survival (PFS) (RECIST v1.1). Secondary endpoints are overall survival, PFS2, objective response rate, duration of response, clinical benefit rate, pharmacokinetics of amcenestrant and palbo, health-related quality of life, time to chemotherapy, and safety. Biomarkers will be measured in paired tumor biopsies and cell free deoxyribonucleic acid (cfDNA) over time. Target enrolment = 1066 pts; enrolment as of 1/2021 = 33 pts. Bardia A, et al., *J Clin Oncol*. 2019; 37 (15 suppl):1054 Clinical trial information: NCT04478266. Research Sponsor: Sanofi.

TPS1105 **Poster Session**

BEGONIA: Phase 1b/2, open-label, platform study of the safety and efficacy of durvalumab (D) ± paclitaxel (P) with novel oncology therapies for first-line metastatic triple-negative breast cancer (mTNBC): Addition of arm 7, D + datopotamab deruxtecan (Dato-DXd; DS-1062). *First Author: Peter Schmid, Barts Cancer Institute, Queen Mary University of London, London, United Kingdom*

Background: Patients (pts) with mTNBC have limited treatment options and poor prognosis. The combination of immune checkpoint inhibitors with chemotherapy shows promise, but only a subset of pts with mTNBC derive benefit, highlighting the need for new combinations. BEGONIA is an ongoing Simon 2-stage, multicenter, multi-arm platform study evaluating the safety and efficacy of D, an anti–PD-L1 monoclonal antibody, with or without P, in combination with novel oncology therapies as first-line treatment for mTNBC (NCT03742102). Dato-DXd is an antibody-drug conjugate (ADC) consisting of a humanized anti-trophoblast cell surface antigen 2 (TROP2) IgG1 monoclonal antibody, a stable tetrapeptide-based cleavable linker, and a topoisomerase I inhibitor payload. Dato-DXd displayed encouraging clinical activity with a manageable safety profile in heavily pretreated pts with metastatic NSCLC in the phase 1 TROPION-PanTumor01 (NCT03401385) study. TROP2 is highly expressed on breast and other epithelial tumors, and a TROP2 ADC showed activity in heavily pretreated pts with mTNBC (Bardia, *NEJM* 2019). **Methods:** Eligible female pts are aged ≥18 years with untreated unresectable, locally advanced or mTNBC, ≥12 months since prior taxane therapy, ECOG PS 0/1, adequate organ function, and ≥1 nonirradiated measurable lesion. For Arm 7, pts are excluded if they have clinically significant corneal disease, history of interstitial lung disease/pneumonitis, underlying pulmonary disorder, or prior treatment with an ADC containing a topoisomerase I inhibitor. Arm 7 will evaluate D (1120 mg) + Dato-DXd (6 mg/kg) given intravenously every 3 weeks until disease progression or unacceptable toxicity. Part 1 of each arm includes a total of 30 pts with a safety run-in (n=6) to observe dose-limiting toxicities, identify the recommended phase 2 dose (RP2D), and detect an efficacy signal for part 1 expansion. The primary endpoint of part 1 is safety and tolerability. Secondary endpoints include investigator-assessed objective response rate (ORR), duration of response, progression-free survival (PFS), and overall survival (OS). Once the RP2D has been established for part 1, a futility analysis will be performed with an option to expand the cohort to an additional 27 pts if expansion criteria are met. The primary endpoint for part 1 is ORR. Tumors will be assessed every 6 weeks per RECIST v1.1. Kaplan-Meier analysis will be used for PFS and OS. PD-L1 and TROP2 expression will be assessed by immunohistochemistry. Enrollment is ongoing. Clinical trial information: NCT03742102. Research Sponsor: AstraZeneca, Pharmaceutical/Biotech Company.

TPS1106 **Poster Session**

Saci-IO TNBC: Randomized phase II trial of sacituzumab govitecan (SG) +/- pembrolizumab in PD-L1– metastatic triple-negative breast cancer (mTNBC). *First Author: Ana Christina Garrido-Castro, Dana-Farber Cancer Institute, Boston, MA*

Background: Immune checkpoint inhibitors (ICIs) have not yet benefited most patients with breast cancer. In mTNBC, ICIs combined with chemotherapy have improved survival only in PD-L1+ mTNBC. The optimal ICI combination agent to overcome primary resistance in PD-L1– mTNBC is unknown. One promising agent is the anti-Trop-2-SN-38 antibody drug conjugate (ADC) SG, which led to median progression-free survival (PFS) of 5.6 months in mTNBC with ≥2 prior lines of chemotherapy.[1] This ADC may boost anticancer immunity by binding immune cell receptors to promote antibody-dependent cellular cytotoxicity.[2] In addition, the SN-38 payload of SG is the active metabolite of irinotecan, which depletes regulatory T cells, upregulates MHC class I and PD-L1 expression, and augments the antitumor activity of anti-PD-1/L1 antibodies in murine tumor models.[3] The irinotecan analogue camptothecin also enhances CD8+ cytotoxic T cell effector functions and antitumor immune responses by inhibiting NR4A transcription factors,[4] which have recently been shown to play a central role in inducing the T cell dysfunction associated with chronic antigen stimulation in solid tumors. **Methods**: This is a multi-center 1:1 randomized phase II trial to investigate whether the addition of pembrolizumab (200 mg IV every 3 weeks) to SG (10 mg/kg IV days 1+8 every 21 days) improves PFS compared to SG alone in mTNBC that is PD-L1– by standard of care testing with 22C3 CPS < 10 or SP142 immune cells $< 1\%$ (NCT04468061). Key eligibility criteria include no prior systemic therapy for mTNBC and evaluable disease. Previously treated brain metastases are permitted. Exclusion criteria include prior treatment with SG, irinotecan, and PD-1/L1 inhibitors. Based on a sample size of 110 patients per arm, the trial has 80% power to detect a 3-month difference in median PFS from 5.5 months in the SG-alone cohort to 8.5 months in the SG + pembrolizumab cohort with a one-sided alpha of 0.1. Participants undergo mandatory baseline and on-treatment research biopsies if their disease is safely accessible. Tumor biopsies will be evaluated for Trop-2, immune cells, inhibitory checkpoints, transcriptomic signatures, and genomic alterations. Stool specimens will be submitted for microbiome analyses, and health-related quality of life will be assessed. The trial is currently open and enrolling patients. References: 1) Bardia A et al. *Ann Oncol* 31, S1142-S1215 (2020). 2) Cardillo TM et al. *Bioconjug Chem* 26, 919-931 (2015). 3) Iwai T et al. *Oncotarget* 9, 31411-31421 (2018). 4) Hibino S et al. *Cancer Res* 78, 3027-3040 (2018). Clinical trial information: NCT04468061. Research Sponsor: Merck and Immunomedics, Other Foundation.

TPS1107 **Poster Session**

Trial in progress: A phase 3, randomized, double-blind trial of trilaciclib versus placebo in patients receiving first- or second-line gemcitabine and carboplatin for locally advanced unresectable or metastatic triple-negative breast cancer (PRESERVE 2). *First Author: Shom Goel, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Trilaciclib is an intravenous (IV), highly potent and selective, reversible cyclin-dependent kinase (CDK) 4/6 inhibitor that protects hematopoietic stem and progenitor cells during chemotherapy (myeloprotection) and may directly enhance antitumor immunity (anticancer efficacy). In a randomized phase 2 trial of trilaciclib administered prior to gemcitabine and carboplatin (GC) versus GC alone in advanced/metastatic triple-negative breast cancer (mTNBC), although the primary endpoint of myeloprotection was not met, the addition of trilaciclib resulted in a substantial improvement in median overall survival (OS; 19.8 months with trilaciclib vs 12.6 months with placebo, hazard ratio [95% CI] = 0.37 [0.21–0.63]; O'Shaughnessy et al. SABCS 2020 [PD1-06]). Clinically meaningful improvements in OS and progression-free survival (PFS) were also observed in both programmed death ligand-1 (PD-L1)–positive and –negative subsets. **Methods:** The PRESERVE 2 trial (EudraCT: 2020-004930-39) is a randomized, double-blind, placebo-controlled, international phase 3 trial evaluating the efficacy of trilaciclib administered prior to GC in patients with mTNBC. Two mTNBC patient populations will be studied and analyzed separately: cohort 1 (N = 170) will evaluate first-line, PD-1/PD-L1 inhibitor–naïve patients with ≥6 months between completion of last curative treatment and first recurrence; cohort 2 (N = 80) will evaluate second-line PD-L1–positive patients following ≥4 months of PD-1/PD-L1 inhibitor therapy in the advanced setting. Key eligibility criteria for both cohorts include age ≥18 years, Eastern Cooperative Oncology Group performance status of 0/1, and available tumor tissue. Patients will be randomized (1:1) to trilaciclib 240 mg/m^2 or placebo prior to gemcitabine 1000 mg/m^2 and carboplatin area under the curve 2 IV on days 1 and 8, every 21 days. Stratification factors (cohort 1 only) include tumor PD-L1 status by Ventana SP-142 IVD assay, disease-free interval, and country. Study treatment will continue until progressive disease per RECIST v1.1, unacceptable toxicity, or investigator/patient decision, after which, patients will be followed every 3 months for survival. Up to 80 patients will be consented for optional paired baseline and on-treatment biopsies. Archival tissue and serial peripheral blood will be collected from all patients. The primary endpoint is OS, and the key secondary endpoint is time to confirmed deterioration in fatigue. Other secondary endpoints include PFS, myeloprotection, and safety/tolerability. Exploratory endpoints will assess pharmacodynamic parameters, including those related to immune-based mechanisms, and efficacy by CDK4/6-dependence signatures. Study enrollment is open. Clinical trial information: 2020-004930-39. Research Sponsor: G1 Therapeutics, Inc.

TPS1108 **Poster Session**

NBE-002: A novel anthracycline-based antibody-drug conjugate (ADC) targeting ROR1 for the treatment of advanced solid tumors—A phase 1/2 clinical trial. *First Author: Anthony W. Tolcher, NEXT Oncology, San Antonio, TX*

Background: The receptor tyrosine kinase-like orphan receptor 1 (ROR1) is highly expressed during embryonic development, but is minimally present or absent on postpartum healthy tissues. ROR1 is expressed in a variety of hematological and solid tumors and is associated with aggressive cancer phenotype and poor clinical outcomes. NBE-002 is an ADC targeting ROR1, obtained by site-specific, enzymatic conjugation of the anthracycline-derivative PNU-159682, modified with a non-cleavable linker to a humanized recombinant IgG1 monoclonal antibody, based on a novel anti-human ROR1 monoclonal antibody XBR1-402 (Peng et al. (2017) J. Mol. Biol. 429: 2954-73). Direct anti-tumor activity of NBE-002 was evaluated in immunodeficient, ROR1 expression-low/-intermediate/-high PDX models of several carcinoma and sarcoma subtypes. The most pronounced anti-tumor effect was achieved in triple-negative breast cancer (TNBC), at doses as low as 0.033 mg/kg, suggesting a best-in-class therapeutic index in light of the high tolerability in preclinical toxicology models. Administration in a fully immune competent setting (EMT6/ROR1 orthotopic breast cancer model) led to a strong anti-tumor response and a long-lasting anti-tumor immune protection dependent on CD8 T cells. **Methods:** NBE-002-01 (NCT04441099) is a first-in-human, open-label, multi-center, phase (Ph) 1/2 study of NBE-002 in adult patients with advanced solid tumors. Ph 1 of the study consists of a Dose Escalation Cohort (DEC), utilizing an accelerated titration design, followed by a traditional 3+3 design, and an optional Safety Expansion Cohort (SEC). Ph 2 will include two parallel Expansion Cohorts (EC), enrolling patients with advanced TNBC (EC1) or other solid tumors (EC2), with Simon's two-stage design. Key eligibility criteria include Eastern Cooperative Oncology Group performance status of 0-2 (Ph 1) or 0-1 (Ph 2), adequate organ function defined as: hemoglobin ≥9.0 g/dL, neutrophils ≥1500 /μL, platelets ≥100000/μL, aspartate and alanine aminotransferases ≤2.5x the upper limit of normal (ULN), total bilirubin ≤1.5x ULN, creatinine ≤1.5x ULN, left ventricular ejection fraction ≥50%. The primary objectives are to assess safety and tolerability and to establish the recommended dose for further development (Ph 1), and to evaluate anti-tumor activity of (Ph 2). Secondary and exploratory objectives include characterization of immunogenicity as well as pharmacokinetic and pharmacodynamic profiles. NBE-002 is given intravenously once every three weeks until disease progression, unacceptable toxicity, withdrawal of consent, or other protocol-specific criteria are met. Ph 1 dose escalation was initiated on 17 JULY 2020 and is still recruiting in the US. Ph 2 is planned to be initiated in 2022. Clinical trial information: NCT04441099. Research Sponsor: NBE-Therapeutics.

TPS1109 **Poster Session**

A phase II clinical trial of talazoparib monotherapy for PALB2 mutation-associated advanced breast cancer. *First Author: Joshua James Gruber, Stanford University, Palo Alto, CA*

Background: PALB2 (Partner and Localizer of BRCA2) plays a critical role in the maintenance of genomic integrity through its role in the Fanconi anemia and homologous recombination DNA repair pathways. Our recently reported phase II clinical trial (Gruber, et al. JCO 2019) showed that talazoparib monotherapy was associated with single agent activity in germline PALB2 (gPALB2) mutation-associated advanced breast cancers. Of 5 patients with a germline PALB2 mutation, all 5 had reduction in target lesions $>$ 20% with 3 of 5 achieving a RECIST 1.1 response. All patients had visceral metastases and were heavily pretreated; one response occurred in a patient with 8 prior lines of therapy for metastatic breast cancer. Clinical activity of the PARP inhibitor olaparib was also demonstrated in breast cancer patients with gPALB2 mutations in the Olaparib Expanded trial (TBCRC 048). Thus, we believe there is significant value in generating additional PARP inhibitor monotherapy data in subjects with advanced PALB2 mutation-associated breast cancer. We propose this phase II trial to better estimate the rate of RECIST 1.1 objective response in this patient population. **Methods**: This is a single-arm, two-stage, non-randomized study to assess the objective response rate (ORR) of talazoparib monotherapy in patients with PALB2 mutation-associated advanced breast cancer. Eligible subjects will be adults with inoperable locally advanced or metastatic breast cancer with a germline or somatic PALB2 mutation with 0-3 prior therapies for advanced disease. Eligible patients must have a deleterious or suspected deleterious mutation in PALB2 on a CLIA approved commercial germline or next generation sequencing tumor assay. Study treatment is talazoparib 1 mg PO daily. In stage 1, ORR will be assessed after 15 patients; if at least 2 responses are observed then an additional 15 patients will be enrolled; if less than 2 responses are observed the study will be terminated. The primary objective is to evaluate whether talazoparib monotherapy can induce a 30% ORR in subjects with advanced breast cancer associated with a PALB2 mutation. Response will be assessed by RECIST 1.1. Secondary objectives include safety, PFS, clinical benefit rate, and patient-reported quality-of-life. Exploratory endpoints will assess for the presence of PALB2 loss-of-heterozygosity, biallelic mutations, correlation of ctDNA profile with treatment response and the correlation of germline versus somatic mutations with response rate. This trial is currently activated and enrolling at Stanford Cancer Center and it is expected that 4 additional sites will be added. **Conclusion**: This trial will evaluate gPALB2 as a biomarker for PARP inhibitor monotherapy in advanced or metastatic HER2- breast cancer. Clinical trial information: pending. Research Sponsor: Pfizer.

TPS1110 **Poster Session**

Phase II multicenter study of talazoparib for somatic *BRCA1/2* mutant metastatic breast cancer. *First Author: Neelima Vidula, Massachusetts General Hospital, Boston, MA*

Background: PARP inhibitors are approved for the treatment of HER2 negative metastatic breast cancer (MBC) with germline *BRCA1/2* mutations, based on phase III studies demonstrating an improvement in progression-free survival (PFS) compared to chemotherapy in this population and better patient reported outcomes (Robson, NEJM, 2017; Litton, NEJM, 2018). However, germline *BRCA1/2* mutations account for only 5-10% of breast cancer, limiting the current clinical applicability of PARP inhibitors. Somatic *BRCA1/2* mutations are detectable in circulating cell-free DNA (cfDNA) in ~13.5% of patients with MBC; in pre-clinical models, pathogenic somatic *BRCA1/2* mutations have been shown to respond to PARP inhibition (Vidula, CCR, 2020). The purpose of this study is to evaluate the efficacy of talazoparib, a PARP inhibitor, in patients with MBC who have somatic *BRCA1/2* mutations detectable in cfDNA, in the absence of a germline *BRCA1/2* mutation, which we hypothesize will be effective in this setting. This study may help expand the population of patients with MBC who benefit from PARP inhibitors. **Methods:** This is an investigator initiated multicenter, single arm, phase II clinical trial studying the efficacy of talazoparib in 30 patients with MBC who have pathogenic somatic *BRCA1/2* mutations detected in cfDNA. Patients with MBC who are found to have pathogenic somatic *BRCA1/2* mutations detected in cfDNA in the absence of a germline *BRCA1/2* mutation are eligible. Patients may have triple negative (with $\geq$ 1 prior chemotherapy), or hormone receptor positive/HER2 negative breast cancer (with $\geq$ 1 prior hormone therapy). Patients may have received any number of prior lines of chemotherapy, including a prior platinum (in the absence of progression). They must have adequate organ function and ECOG performance status $\leq$2, and should not have previously received a PARP inhibitor. Patients are treated with talazoparib 1 mg daily until disease progression or intolerability, with serial imaging using CT chest/abdomen/pelvis and bone scan performed at baseline and every 12 weeks, and cfDNA collection every 4 weeks. Primary endpoint is PFS by RECIST 1.1. Patients are being enrolled in a two-stage design with 80% power to demonstrate that the treatment is associated with "success" (PFS $>$ 12 weeks) in $\geq$53% patients (4% alpha). Secondary endpoints include objective response rate and safety (NCI CTCAE v 5.0). Exploratory analyses include studying serial changes in cfDNA *BRCA1/2* mutant allelic frequency and comparing pre-and post-treatment cfDNA for the emergence of *BRCA1/2* reversion and resistance mutations. This study is activated and open at Massachusetts General Hospital, where 2 patients are completing screening. It is also opening soon at 6 other academic centers (NCT03990896). Grant support includes a Pfizer ASPIRE award and 2020 Conquer Cancer Foundation of ASCO – Breast Cancer Research Foundation – Career Development Award. Clinical trial information: NCT03990896. Research Sponsor: Pfizer Aspire Award and Conquer Cancer Foundation of ASCO CDA.

TPS1111 **Poster Session**

Multi-center randomized study of pembrolizumab/carboplatin versus carboplatin alone in patients with chest wall disease from breast cancer: TBCRC 044. *First Author: Neelima Vidula, Massachusetts General Hospital, Boston, MA*

Background: Chest wall recurrence is a subtype of breast cancer that is challenging to treat, and associated with a short duration of response to treatment and an increased risk of development of distant metastases. Given the inflammatory nature of this disease and the association of chest wall disease with lymphovascular invasion, which is correlated with higher programmed cell death 1 (PD-1) expression, we hypothesized that immunotherapy may be beneficial as treatment. Combinations of immunotherapy and chemotherapy have a synergistic effect and demonstrated efficacy in the treatment of metastatic triple negative breast cancer (TNBC). This study is evaluating the efficacy of pembrolizumab, an anti-PD-1 antibody, in combination with carboplatin, in patients with chest wall infiltration from breast cancer. This drug combination has shown efficacy in advanced lung cancer. **Methods:** This is a multicenter, 2:1 randomized phase II study of pembrolizumab/carboplatin (Arm A, 56 patients) vs. carboplatin (Arm B, 28 patients) in 84 patients with chest wall disease from breast cancer, with or without distant metastases. Patients may have TNBC, hormone receptor positive/HER2 negative (following receipt of 2 prior hormone therapies), or HER2 positive breast cancer (with option to continue trastuzumab on study). Pembrolizumab is administered as 200 mg IV every 3 weeks, and carboplatin as AUC 5 IV every 3 weeks. Patients on Arm A may continue pembrolizumab +/- carboplatin (Arm Ax) after completion of 6 cycles of treatment, while patients in Arm B can cross-over to pembrolizumab (+/- carboplatin) on progression (Arm Bx). Patients must have adequate organ function, performance status $\leq$ 2, and may have received any number of lines of prior chemotherapy. Patients undergo serial chest wall photography and imaging (CT chest, abdomen, and pelvis, and bone scan) at baseline and every 6 weeks, as well as blood collection for correlative studies and chest wall biopsies at baseline and after 2 cycles of treatment. The primary endpoint is disease control rate (RECIST 1.1) at 18 weeks of treatment, and the study is powered to determine a 20% difference in disease control rates between arms (HR 0.52, a = 0.10, ß = 0.20). An interim analysis will occur for Arm B after 18 patients are enrolled, with a stopping rule for futility. Secondary endpoints include progression-free survival, toxicity (NCI CTCAE), and response based on irRECIST and tumor programmed death ligand 1 (PD-L1) expression. Exploratory objectives include evaluating changes in soluble PD-L1, tumor and peripheral blood immune composition, circulating tumor cells and cell-free DNA, and MYC oncogene expression. This study (NCT03095352) is open at 7 sites in the Translational Breast Cancer Research Consortium (TBCRC). 52 patients are enrolled. Grant funding is provided by Merck and UCSF. Clinical trial information: NCT03095352. Research Sponsor: Merck and UCSF Breast Oncology Program Development Grant.

1500 **Oral Abstract Session**

Outcomes of COVID-19 in cancer patients: Report from the National COVID Cohort Collaborative (N3C). *First Author: Noha Sharafeldin, Department of Hematology & Oncology, School of Medicine, University of Alabama at Birmingham, Birmingham, AL*

Background: The impact of COVID-19 has disproportionately affected every aspect of cancer care and research—from introducing new risks for patients to disrupting the delivery of treatment and continuity of research. Variation in risk of adverse clinical outcomes in COVID-19 patients by cancer type has been reported from relatively small cohorts. Gaps in understanding effects of COVID-19 on cancer patients can be addressed through the study of a well-constructed representative cohort. The NCATS' National COVID Cohort Collaborative (N3C) is a centralized data resource representing the largest multi-center cohort of COVID-19 cases and controls nationwide. We aimed to construct and characterize the cohort of cancer patients within N3C and identify risk factors for all-cause mortality from COVID-19. **Methods:** From the harmonized N3C clinical dataset, we used 3,295,963 patients from 39 medical US centers to construct a cancer patient cohort. We restricted analyses to adults ≥18 yo with a COVID-19 positive PCR or antigen test or ICD-10-CM diagnostic code for COVID-19 between 1/1/2020 and 2/14/2021. We followed N3C definitions where each lab-confirmed positive patient has one single index encounter. A modified WHO Clinical Progression Scale was used to determine clinical severity. All analyses were performed in the N3C Data Enclave on the Palantir platform. **Results:** A total of 372,883 adult patients with cancer were identified from the N3C cohort; 54,642 (14.7%) were COVID-19 positive. Most common represented cancers were skin (11.5%), breast (10.2%), prostate (8%), and lung cancer (5.6%). Mean age of COVID-19 positive patients was 61.6 years (SD 16.7), 47.3% over 65yo, 53.7% females, 67.2% non-Hispanic White, 21.0% Black, and 7.7% Hispanic or Latino. A total of 14.6% were current or former smokers, 22.3% had a Charlson Comorbidity Index (CCI) score of 0, 4.6% score of 1 and 28.1% score of 2. Among hospitalized COVID-19 positive patients, average length of stay in the hospital was 6 days (SD 23.1 days), 7.0% patients had died while in their initial COVID-19 hospitalization, 4.5% required invasive ventilation, and 0.1% extracorporeal membrane oxygenation. Survival probability was 86.4% at 10 days and 63.6% at 30 days. Older age over 65yo (Hazard ratio (HR) = 6.1, 95%CI: 4.3, 8.7), male gender (HR = 1.2, 95%CI: 1.1, 1.2), a CCI score of 2 or more (HR = 1.15, 95%CI: 1.1, 1.2), and acute kidney injury during hospitalization (HR = 1.3, 95%CI: 1.2, 1.4) were associated with increased risk of all-cause mortality. **Conclusions:** Using the N3C cohort we assembled the largest nationally representative cohort on patients with cancer and COVID-19 to date. We identified demographic and clinical factors associated with increased all-cause mortality in cancer patients. Full characterization of the cohort will provide further insights on the effects of COVID-19 on cancer outcomes and the ability to continue specific cancer treatments. Research Sponsor: None.

1501 **Oral Abstract Session**

The association of the affordable care's Medicaid expansion on survival in gynecologic cancer: A National Cancer Database study. *First Author: Anna Jo Smith, Johns Hopkins Department of Gynecology and Obstetrics, Baltimore, MD*

Background: Under the Affordable Care Act's 2014 Medicaid expansion, more than 12 million Americans gained health insurance. Whether such gains in insurance improve survival in gynecologic cancer is unknown. This study aims to determine whether Medicaid expansion is associated with improved survival among women with gynecologic cancers. **Methods:** We conducted a retrospective cohort study using a difference-in-differences study design comparing insurance status, stage at diagnosis, delays in treatment, and one-year survival before and after the ACA's Medicaid expansion in Medicaid expansion states (intervention group) compared to women in non-expansion states (control group). Using hospital-reported data from the 2010-2016 National Cancer Database, we compared outcomes overall for women ages 40-64 years old with endometrial, cervical, ovarian, or vulva/vaginal cancer and then stratified by cancer type, stage, race, and rural/urban status. We adjusted for patient (area-level income, area-level education, distance traveled for care, comorbidities), clinical (co-morbidities, grade) and hospital (academic facility) characteristics. **Results:** Our sample included 241,713 women with gynecologic cancer, 119,392 in expansion states and 122,321 in non-expansion states. Post-Medicaid expansion, there was a statistically significant 0.8 % increase in 1-year survival among patients in expansion states compared to non-expansion states (95% CI 0.1-1.5). There was also a significant reduction in uninsurance (-1.1%, 95%CI, –1.5, -0.7) and delays of 30+ days from diagnosis to treatment (-2.4%, 95%CI -3.4, -1.2). There was no significant change in early-stage diagnosis (0%; 95%CI -0.7-0.7). Improvements in one-year survival after Medicaid expansion were driven by ovarian cancer (difference-in-differences 2.2%, 95%CI 0.6-3.8) and in white women (difference-in-differences 0.8%, 95%CI 0.1-1.5), while there was no significant difference in one-year survival for non-white or rural women. **Conclusions:** The Affordable Care Act's Medicaid expansion was significantly associated with 1-year survival and insurance access among patients with gynecologic cancer. Insurance expansion efforts in non-Medicaid expansion states may improve survival for women with gynecologic cancer. Research Sponsor: Kelly Society Grant, Johns Hopkins Department of Gynecology and Obstetrics.

1502 **Oral Abstract Session**

Association between Medicaid expansion under the Affordable Care Act and survival among newly diagnosed cancer patients. *First Author: Xuesong Han, American Cancer Society, Atlanta, GA*

Background: Medicaid expansion under the Affordable Care Act (ACA) is associated with increased insurance coverage and early stage at diagnosis among patients with cancer. Whether these gains translate to improved survival is largely unknown, however. This study examines changes in one-year survival rates among persons newly diagnosed with cancer following the ACA Medicaid expansion. **Methods:** Patients aged 18-62 years from 41 population-based state cancer registries diagnosed pre-(2010-2012) and post-(2014-2016) ACA Medicaid expansion were followed through October 1, 2013 and December 31, 2016, respectively. Difference-in-differences (DD) analysis was conducted to estimate changes in one-year overall and cause-specific survival rates associated with Medicaid expansion, adjusting for age group, sex, race/ethnicity, area-level poverty, urban/rural status and region. Stratified analysis was conducted by cancer type, sex and area-level poverty. **Results:** A total of 2,537,818 patients diagnosed with cancer were included from Medicaid expansion (N = 1,492,729) and non-expansion (N = 1,045,089) states. During follow-up, 291,854 patients died including 246,660 deaths from cancer. The one-year overall survival rate (%) increased from 88.1 pre-ACA to 89.1 post-ACA in Medicaid expansion states and from 85.6 to 86.4 in non-expansion states for both sexes combined, resulting in a net increase of 0.4 (95%CI = 0.3-0.6) in expansion states after adjusting for sociodemographic factors. By cancer site and for both sexes combined, the increase in adjusted one-year overall survival in expansion states versus non-expansion states was greater for cancers of lung (DD = 1.6; 95%CI = 0.8-2.5), pancreas (DD = 2.2; 95%CI = 0.5-3.9) and liver (DD = 3.4; 95%CI = 1.7-5.1); as were the increases for cervix (DD = 1.3; 95%CI = 0.1-2.5), melanoma (DD = 0.4;95%CI = 0.04-0.9), non-Hodgkin lymphoma (DD = 1.2; 95%CI = 0.1-2.2) and esophagus (DD = 7.1; 95%CI = 0.5-13.7) among women. The improvement in one-year overall survival was larger among patients residing in the poorest areas (DD = 0.7; 95%CI = 0.3-1.1) compared to those in the richest areas (DD = 0.2; 95%CI = -0.2 to 0.5), leading to a narrowing survival disparity by area-level poverty. Patterns in one-year cause-specific survival were similar. **Conclusions:** Medicaid expansion was associated with greater increase in one-year overall survival rates, largely driven by the improvements in survival for cancer types with poor prognosis, suggesting improved access to timely and effective treatments. Furthermore, the increase was largest in poorest areas, highlighting the promising role of Medicaid expansion in reducing health disparities. Future studies should monitor changes in longer-term health outcomes following the ACA. Research Sponsor: None.

1503 **Oral Abstract Session**

Association of use of remote patient monitoring (RPM) with reduced hospitalizations in cancer patients with COVID-19. *First Author: Joshua Pritchett, Mayo Clinic Rochester, Rochester, MN*

Background: Patients with cancer and COVID-19 are at risk for poor clinical outcomes. An established multi-site remote patient monitoring (RPM) service was rapidly adapted to support a novel, interdisciplinary COVID-19 program for outpatient management of patients at high-risk for severe illness. The goal of this study was to assess the impact of the RPM program on clinical outcomes and acute care utilization in cancer patients diagnosed with COVID-19. **Methods:** This is a cross-sectional analysis following a multi-site prospective observational study performed at Mayo Clinic Cancer Center (MCCC). All adult patients with active cancer – defined as currently receiving cancer-directed therapy or in recent remission on active surveillance – and PCR-confirmed SARS-CoV-2 infection between March 18 and July 31, 2020 were included. RPM was comprised of in-home technology to assess symptoms and physiologic data with centralized nurse and physician oversight. **Results:** During the study timeframe 224 cancer patients were diagnosed with COVID-19 at MCCC. Initial management included urgent hospitalization (within 48 hours of diagnosis) in 34 patients (15%). Of the remaining 190 patients (85%) initially managed in the outpatient setting, those who did not receive RPM were significantly more likely to experience hospitalization than those receiving RPM (OR 3.6, 95% CI 1.036 to 12.01, P = 0.044). Following balancing of patient characteristics by inverse propensity weighting, rates of hospital admission for RPM and non-RPM patients were 3.1% and 11% respectively, implying that RPM was associated with an 8% reduction in hospital admission rate (-0.077; 95% CI: -0.315 to -0.019, P = 0.009). Use of RPM was also associated with lower rates of prolonged hospitalization, ICU admission, and mortality, though these trends did not reach statistical significance. **Conclusions:** In the midst of a global pandemic associated with inpatient bed, ventilator, and PPE shortages, the RPM program provided an effective strategy for outpatient clinical management and was associated with decreased rates of hospitalization, ICU admission, and mortality in cancer patients with COVID-19. This care model enabled simultaneous opportunity to mitigate the increased risks of exposure, transmission, and resource utilization associated with conventional care. Research Sponsor: None.

1504 **Oral Abstract Session**

Oncology patients' perspectives on remote patient monitoring for COVID-19. *First Author: Robert Michael Daly, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Oncology patients are particularly vulnerable to adverse outcomes from COVID-19 and require careful monitoring to identify early deterioration and render higher level care when indicated. Several institutions launched remote patient monitoring programs (RPMPs) to care for patients with COVID-19. We describe patients' perspectives on a COVID-19 RPMP at a National Comprehensive Cancer Center. **Methods:** Adult patients who had either tested positive for COVID-19 on an outpatient microbiology test or were discharged after hospitalization for the virus were eligible. Patients enrolled in the RPMP received a daily 10-question electronic patient-reported outcome assessment of COVID-19 symptoms and their responses generated alerts to a centralized monitoring team for new or worsening symptoms. A subset of high-risk patients also received a pulse oximeter which alerted when blood oxygen levels dropped below 93%. RPM was discontinued 14 days after a patient's positive test result and following 3 days without worsening symptoms or fever. Patients who exited the program and had completed at least one assessment were sent a patient engagement survey. The objective of the survey was to evaluate the patient's experience with digital monitoring and symptom management for COVID-19. The assessment was structured with objective response questions, including a net promoter score, and free text questions to elicit patient perspectives on RPM value. Free text responses were analyzed using grounded theory to identify primary themes regarding perceived value. **Results:** The survey was distributed to 452 patients; 241 responded as of June 10, 2020 (53% completion rate). The net promoter score was 91%. The table provides responses to objective questions. Qualitative analysis of free text responses identified the primary themes regarding patient perceived value which included: 1) Security: patients appreciated that the RPMP provided a clinical safety net; 2) Connection: patients appreciated the link to their clinical team during a period of isolation; 3) Empowerment: patients appreciated that the RPMP provided education on the virus and symptom management. **Conclusions:** RPMPs are perceived to be of value to oncology patients with COVID-19. A key barrier to maintaining these programs is cost. Policymakers should consider how these programs can be reimbursed in the future so that they can continue to provide care to vulnerable patients and keep them at home out of the acute care setting. Research Sponsor: None.

N=241	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
The time and effort it took to report symptoms was worth it	67%	25%	7%	0%	1%
By participating in the RPMP, I felt better able to manage my COVID-19 symptoms	48%	31%	18%	2%	1%
The RPMP helped me cope with my COVID-19 diagnosis	45%	30%	22%	2%	1%
Taking part in the RPMP made me feel more connected to my clinical team	55%	34%	8%	2%	1%
The RPMP helped prevent visits to the emergency room	38%	24%	30%	5%	3%

1505 **Oral Abstract Session**

CORONET; COVID-19 in Oncology evaluatiON Tool: Use of machine learning to inform management of COVID-19 in patients with cancer. *First Author: Rebecca Lee, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Patients (pts) with cancer are at increased risk of severe COVID-19 infection and death. Due to COVID-19 outcome heterogeneity, accurate assessment of pts is crucial. Early identification of pts who are likely to deteriorate allows timely discussions regarding escalation of care. Likewise, safe home management will reduce risk of nosocomial infection. To aid clinical decision-making, we developed a model to help determine which pts should be admitted vs. managed as an outpatient and which pts are likely to have severe COVID-19. **Methods:** Pts with active solid or haematological cancer presenting with symptoms/asymptomatic and testing positive for SARS-CoV-2 in Europe and USA were identified following institutional board approval. Clinical and laboratory data were extracted from pt records. Clinical outcome measures were discharge within 24 hours, requirement for oxygen at any stage during admission and death. Random Forest (RF) algorithm was used for model derivation as it compared favourably vs. lasso regression. Relevant clinical features were identified using recursive feature elimination based on SHAP. Internal validation (bootstrapping) with multiple imputations for missing data (maximum $\leq$2) were used for performance evaluation. Cost function determined cut-offs were defined for admission/death. The final CORONET model was trained on the entire cohort. **Results:** Model derivation set comprised 672 pts (393 male, 279 female, median age 71). 83% had solid cancers, 17% haematological. Predictive features were selected based on clinical relevance and data availability, supported by recursive feature elimination based on SHAP. RF model using haematological cancer, solid cancer stage, no of comorbidities, National Early Warning Score 2 (NEWS2), neutrophil:lymphocyte ratio, platelets, CRP and albumin achieved AUROC for admission 0.79 (+/-0.03) and death 0.75 (+/-0.02). RF explanation using SHAP revealed NEWS2 and C-reactive protein as the most important features predicting COVID-19 severity. In the entire cohort, CORONET recommended admission of 96% of patients requiring oxygen and 99% of patients who died. We then built a decision support tool using the model, which aids clinical decisions by presenting model predictions and explaining key contributing features. **Conclusions:** We have developed a model and tool available athttps://coronet.manchester.ac.uk/ to predict which pts with cancer and COVID-19 require hospital admission and are likely to have a severe disease course. CORONET is being continuously refined and validated over time. Research Sponsor: The Christie Charitable Foundation.

1506 **Oral Abstract Session**

The future of tele-oncology: Trends and disparities in telehealth and secure message utilization in the COVID-19 era. *First Author: Elad Neeman, San Francisco Medical Center, Kaiser Permanente Northern California, San Francisco, CA*

Background: The COVID-19 pandemic created an imperative to re-examine the role of telehealth in oncology. Herein we report trends and demographic disparities in utilization of telehealth and secure messaging (SM; i.e., email via portal/app), before and during the pandemic, at a large integrated healthcare system. **Methods:** This population-based retrospective cohort study examines utilization of various patient-provider visit types (office, video, telephone) and SM from 1/1/2019-9/30/2020 at 22 Kaiser Permanente Northern California Hematology and Oncology practices. We explored changes associated with the pandemic (i.e., since 03/2020, when stay home orders were introduced) as well as demographic differences, using Chi-square for categorical and the Mann-Whitney U Test for non-parametric comparisons. **Results:** During the study period, there were 334,666 visits and 1,161,239 SM sent between patients and providers. Since the pandemic, total monthly average of visits declined only slightly by 4.1%, but monthly average office visits decreased by 80% from 11,001 to 2,170, monthly average video visits increased from 40 to 4,666, and monthly average telephone visits increased by 69% from 5,114 to 8,663. The monthly average SM increased by 26% from 50,788 to 64,315. The trend of increasing telehealth utilization was sustained and stabilized between 07-09/2020. New consultations initially decreased from a mean of 1,995 per month (12.4% of all visits) in 2019, to a minimum of 1,179 (8.6%) by 05/2020, returning to 1,619 (11.7%) by 09/2020. Pandemic era video visits were a significantly higher fraction of all visits ($p < 0.01$) in: (1) younger patients (Gen Z 48%, Gen Y/Millennials 46%; Gen X 40%; Baby Boomers 34.4%; Pre-Boomers 24.5%); (2) patients with commercial insurance (39%) compared to those with Medicaid (32.7%) or Medicare (28.1%); (3) Primary English speakers (33.7%) compared to those who require an interpreter (24.5%);(4) Asians (35%) and non-Hispanic Whites (33.7%) compared to Blacks (30.1%) and Hispanic Whites (27.5%); (5) married/ domestic partner patients (35%) compared to single/divorced/widowed patients (29.9%); (6) patients with a Charlson comorbidity index $\leq$3 (36.2%) compared to $>$ 3 (31.3%); and (7) males (34.6%) compared to females (32.3%). Similar statistically significant SM utilization patterns were also seen. **Conclusions:** In the pandemic era, utilization of telehealth and SM rapidly increased in all demographic categories, shifting the landscape and resource allocation of hematology/oncology practices in a manner that is feasible and sustained. New consultations decreased early in pandemic with return to pre-pandemic levels by 09/2020. Utilization of video visits and SM significantly differ between various demographic populations with disparities seen by age, insurance plan, English proficiency, race/ethnicity, marital status, comorbidities, and gender. Research Sponsor: None.

1507 **Oral Abstract Session**

Documentation of goals of care (GOC) by medical oncologists is associated with improved oncology patient end-of-life (EOL) care outcomes. *First Author: Han Xiao, Memorial Sloan Kettering Cancer Center, Basking Ridge, NJ*

Background: Documenting GOC is integral to patient care and quality performance but has been underutilized by oncologists due to many barriers. As oncologists play a key role in initiating GOC discussions, we implemented a clinical initiative to improve their GOC documentation and evaluated the impact of such documentation on patient care during the EOL (last 30 days of life). **Methods:** We launched the initiative among 270 medical oncologists in an academic cancer center in 4/2020. A newly formulated GOC note to ease documentation was embedded in oncology outpatient and inpatient notes. Oncologists completed components in the GOC note that applied to their communication about GOC with the patient: 1) cancer natural history, 2) patient goals, and 3) EOL discussion: patient resuscitation preferences and, when pertinent, receptivity to hospice referral. GOC notes were pulled to a centralized location in the electronic health record (EHR) that displays documents relevant to patients' values, goals and preferences. A dashboard allowed continual monitoring of documentation performance. We evaluated the association between GOC notes and outcomes of patient care at EOL. We further analyzed the impact of EOL discussion on EOL care. **Results:** The GOC note completion rate steadily rose after implementation. GOC notes were present in EHR for 46% of 10,006 patients who were either seen in outpatient clinic or discharged from hospital during the 1st week of January 2021. Among 1790 patients who died between 7/1/20 and 12/31/20 and had either at least an outpatient visit or hospitalization during EOL, the median days from first GOC note and first EOL discussion to the patient's death were 71 days and 24 days, respectively. Linear regression analysis demonstrated that patients who had GOC note 60 days before death spent less time as inpatient during EOL (0.4 day less/patient, from 8.1 to 7.7, $P = 0.01$). When EOL discussion was documented 30 days before death, patients also spent less time in the hospital (1.2 days less/patient, from 9.7 to 8.5, $P < 0.001$) and in the ICU (0.3 days less/patient, from 1.7 to 1.4 ICU days, $P = 0.04$), and were 4% less likely to receive chemotherapy (from 38% to 34%, $P = 0.004$) at EOL. During the same period, among 1,009 patients with hospital admission in the last 30 days of life, those with a prior documented EOL discussion had shorter inpatient stay (7.7 vs 13.1 days, $P < 0.001$) and were more likely to be discharged to hospice (34% vs 22%, $P = 0.003$). **Conclusions:** During the COVID-19 pandemic, we successfully implemented GOC documentation by medical oncologists that is easily visible by the full care team. Documentation of GOC including EOL discussion was associated with fewer days in the hospital and ICU, increased hospice referral, and lower likelihood of receiving chemotherapy during patients' last 30 days of life. Research Sponsor: None.

1508 **Oral Abstract Session**

The effect of a lay health worker intervention on acute care use, patient experiences and end-of-life care: Results from a randomized clinical trial. *First Author: Manali I. Patel, Division of Oncology; Clinical Excellence Research Center; Stanford University School of Medicine, Stanford, CA*

Background: Previously, among Veterans with cancer, lay health workers (LHWs) trained to discuss patients' goals of care reduced acute care use, improved patient experiences and reduced total costs of care at the end-of-life. Among Medicare-Advantage beneficiaries with cancer, LHWs trained to proactively assess patient symptoms reduced symptom burden, acute care use and total costs of care. It is unknown whether LHWs can assist with both goals of care and symptom assessments in community settings. The objective of this randomized clinical trial was to determine the effect of a LHW-led goals of care and symptom assessment intervention on acute care use and secondarily goals of care documentation, satisfaction and end-of-life healthcare use among patients with advanced cancer in a community practice. **Methods:** Newly diagnosed patients with advanced stages of solid and hematologic malignancies who planned to receive care at the oncology practice were randomized from 8/11/2016 through 2/5/2020 into intervention and control groups. Patients completed validated satisfaction surveys at randomization and 9 months follow-up and were followed for 12 months. We compared risk of death using Cox Models, healthcare use and satisfaction using generalized regression models adjusted for length of follow-up. **Results:** 128 patients were randomized; 64 in the intervention and 64 in the control. The mean age was 67 years; 22% identified as Hispanic/Latino; 57% White, 30% Asian Pacific Islander, 8% Black or African American, 1% Native Hawaiian, 1% American Indian/Alaskan Native, 3% multiple races/ethnicities. There were no survival differences. Intervention patients were less likely to utilize the emergency department (OR: 0.35; 95% CI 0.17-0.72) and hospital (OR: 0.48; 95% CI 0.23-0.98) and had lower mean emergency department visits (1.05 +/- 1.74 versus 1.84 +/- 2.55, p = 0.04) and hospitalizations per year (0.63 +/- 1.28 versus 1.26 +/- 2.23, p = 0.04) as compared to control patients. More intervention patients had their goals of care documented (94% versus 52% $p < 0.001$) and used hospice (35% versus 14% p = 0.004) as compared to control patients. There were no differences in palliative care use (89% versus 77% p = 0.09). At 9 months follow-up as compared to baseline, intervention patients experienced greater improvements in satisfaction with care (difference-in-difference: 0.41, 95% CI 0.22-0.60, $p < 0.001$). Among 30 patients who died (n = 16 intervention; n = 16 control), more patients in the intervention used hospice (81% versus 43%) and fewer used acute care in the last month (37% versus 81%, p = 0.012) than in the control. **Conclusions:** An LHW intervention reduced acute care use among patients with cancer, improved patient experiences and end-of-life care. This intervention may be a scalable approach to improve care delivery and experiences for patients after a diagnosis of cancer. Clinical trial information: NCT03154190. Research Sponsor: U.S. National Institutes of Health.

1509 **Poster Discussion Session**

Impact of machine learning-directed on-treatment evaluations on cost of acute care visits: Economic analysis of SHIELD-RT. *First Author: Divya Natesan, Duke University Medical Center, Department of Radiation Oncology, Durham, NC*

Background: SHIELD-RT was a randomized controlled quality improvement study (NCT03775265) that implemented electronic health record-based machine learning (ML) to direct supplemental visits for high risk (HR) patients undergoing radiotherapy (RT). Acute care visits (ER visits or hospitalizations) were reduced from 22% to 12%. We evaluated the costs associated with acute visits in this study. **Methods:** Patients who initiated RT between 1/7/19 and 6/30/19 at a single institution were evaluated by a ML algorithm to identify HR courses (>10% risk of acute visit during RT). HR patients were randomized to standard weekly (S)*or* intervention of twice weekly (TW) evaluation during RT. Cost data associated with acute visits were obtained and compared between patients who underwent S or TW evaluations. Missing cost data were imputed using disease related groups (DRGs). Mean costs (standard deviation) were compared between arms with non-parametric Wilcoxon Rank Sum tests. **Results:** 311 HR courses were identified and randomized to either S (n=157) or TW (n=154) evaluations during RT. 85 patients (S: 51; TW: 34) had 121 distinct acute care visits (S: 74; TW: 47). Patients in the TW evaluation arm had fewer hospitalizations (29 vs 41) and ER visits (18 vs 33) than those in the S arm. There were fewer acute visits per patient in the TW arm (0.34) compared to S arm (0.49). Actual cost data was available for 102 visits at our institution, and imputed for 19 outside hospital visits. Mean cost associated with acute visits was lower in the TW arm ($1939, SD $5912) compared with the S arm ($4002, SD $11568; p=0.03). Differences in mean cost between arms are presented in the table. **Conclusions:** ML-directed evaluations for HR patients undergoing RT resulted in decreased costs of ER visits and hospitalizations. Costs were decreased across revenue centers, with the largest difference related to inpatient room costs. Future analyses will incorporate intervention costs, which are currently bundled with RT reimbursement. Research Sponsor: Duke Radiation Oncology Residency, Adam Olson Fund.

Cost of acute care during RT or within 15 days of RT completion.

	Standard (N=157)	Twice Weekly (N=154)	Difference in Means (95% CI)	*P-value*
Patients with Acute Care Visit(s) – N (%)	51 (32.5%)	34 (22.1%)		0.04
Overall ($)	4002 (11568)	1939 (5912)	2063 (7, 4119)	0.03
Inpatient ($)	3525 (10956)	1710 (5561)	1815 (-129, 3760)	0.05
Room ($)	2185 (7189)	967 (3362)	1218 (-38, 2474)	0.05
ICU ($)	769 (4199)	147 (1627)	622 (-91, 1335)	0.13
Non-ICU ($)	1416 (3664)	820 (2915)	597 (-143, 1336)	0.04
Ancillary/Patient Services ($)	1340 (4094)	743 (2280)	597 (-144, 1338)	0.06
Labs/Radiology/Diagnostics ($)	536 (1415)	313 (858)	223 (-39, 485)	0.05
Pharmacy ($)	397 (1599)	245 (1102)	152 (-155, 459)	0.05
Surgery, Anesthesia, Cardiology, Respiratory, Rehabilitation, Speech ($)	407 (1931)	185 (891)	222 (-115, 559)	0.03
Emergency Services ($)	477 (1653)	229 (568)	248 (-29, 525)	0.08

1510 **Poster Discussion Session**

Augmenting machine learning algorithms to predict mortality using patient-reported outcomes in oncology. *First Author: Ravi Bharat Parikh, University of Pennsylvania, Philadelphia, PA*

Background: Machine learning (ML) algorithms based on electronic health record (EHR) data have been shown to accurately predict mortality risk among patients with cancer, with areas under the curve (AUC) generally greater than 0.80. While patient-reported outcomes (PROs) may also predict mortality among patients with cancer, it is unclear whether routinely-collected PROs improve the predictive performance of EHR-based ML algorithms. **Methods:** This cohort study included 8600 patients with cancer who had an outpatient encounter at one of 18 medical oncology practices in a large academic health system between July 1st, 2019 and January 1st, 2020. 4692 (54.9%) patients completed assessments of symptoms, performance status, and quality of life from the PRO version of the Common Terminology Criteria for Adverse Events and the Patient-Reported Outcomes Measurement Information System Global v.1.2 scales. We hypothesized that ML models predicting 180-day all-cause mortality based on EHR + PRO data would improve AUC compared to ML models based on EHR data alone. We assessed univariate and adjusted associations between each PRO and 180-day mortality. To train the EHR-only model, we fit a Least Absolute Shrinkage and Selection Operator (LASSO) regression using 192 EHR demographic, comorbidity, and laboratory variables. To train the EHR + PRO model, we used a two-phase approach to fit a model using EHR data for all patients and PRO data for those who completed assessments. To test our hypothesis, we compared the bootstrapped AUC, area under the precision-recall curve (AUPRC), and sensitivity at a 20% risk threshold for both models. **Results:** 464 (5.4%) patients died within 180 days of the encounter. Decreased quality of life, functional status, and appetite were associated with greater 180-day mortality (Table). Compared to the EHR-only model, the EHR + PRO model significantly improved AUC (0.86 [95% CI 0.85-0.86] vs. 0.80 [95% CI 0.80-0.81]), AUPRC (0.40 [95% CI 0.37-0.42] vs. 0.30 [95% CI 0.28-0.32]), and sensitivity (0.45 [95% CI 0.42-0.48] vs. 0.33 [95% CI 0.30-0.35]). **Conclusions:** Routinely collected PROs augment EHR-based ML mortality risk algorithms. ML algorithms based on EHR and PRO data may facilitate earlier supportive care for patients with cancer. Association of PROs with 180-day mortality. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

PRO	Univariable, Odds ratio [95% CI]	Adjusted for ML mortality risk, Odds ratio [95% CI]
Functional status	2.13 [1.90, 2.39]	1.52 [1.33, 1.73]
Anxiety	1.31 [1.15, 1.48]	1.21 [1.05, 1.39]
Constipation	1.43 [1.26, 1.63]	1.17 [1.01, 1.35]
Decreased appetite	1.89 [1.69. 2.12]	1.33 [1.17, 1.52]
Diarrhea	1.13 [1.00, 1.27]	0.97 [0.85, 1.11]
Fatigue	1.79 [1.61, 2.00]	1.38 [1.22, 1.56]
Nausea	1.56 [1.39, 1.75]	1.23 [1.07, 1.39]
Sadness	1.38 [1.21, 1.57]	1.23 [1.06, 1.42]
Dyspnea	1.59 [1.42, 1.77]	1.26 [1.11, 1.43]
Quality of life	1.97 [1.74, 2.24]	1.44 [1.25, 1.65]

1511 **Poster Discussion Session**

Identification of patients at high risk for preventable emergency department visits and inpatient admissions after starting chemotherapy: Machine learning applied to comprehensive electronic health record data. *First Author: Dylan J. Peterson, Stanford University School of Medicine, Stanford, CA*

Background: Acute care use is one of the largest drivers of cancer care costs. OP-35: Admissions and Emergency Department Visits for Patients Receiving Outpatient Chemotherapy is a CMS quality measure that will affect reimbursement based on unplanned inpatient admissions (IP) and emergency department (ED) visits. Targeted measures can reduce preventable acute care use but identifying which patients might benefit remains challenging. Prior predictive models have made use of a limited subset of the data available in the Electronic Health Record (EHR). We hypothesized dense, structured EHR data could be used to train machine learning algorithms to predict risk of preventable ED and IP visits. **Methods:** Patients treated at Stanford Health Care and affiliated community care sites between 2013 and 2015 who met inclusion criteria for OP-35 were selected from our EHR. Preventable ED or IP visits were identified using OP-35 criteria. Demographic, diagnosis, procedure, medication, laboratory, vital sign, and healthcare utilization data generated prior to chemotherapy treatment were obtained. A random split of 80% of the cohort was used to train a logistic regression with least absolute shrinkage and selection operator regularization (LASSO) model to predict risk for acute care events within the first 180 days of chemotherapy. The remaining 20% were used to measure model performance by the Area Under the Receiver Operator Curve (AUROC). **Results:** 8,439 patients were included, of whom 35% had one or more preventable event within 180 days of starting chemotherapy. Our LASSO model classified patients at risk for preventable ED or IP visits with an AUROC of 0.783 (95% CI: 0.761-0.806). Model performance was better for identifying risk for IP visits than ED visits. LASSO selected 125 of 760 possible features to use when classifying patients. These included prior acute care visits, cancer stage, race, laboratory values, and a diagnosis of depression. Key features for the model are shown in the table. **Conclusions:** Machine learning models trained on a large number of routinely collected clinical variables can identify patients at risk for acute care events with promising accuracy. These models have the potential to improve cancer care outcomes, patient experience, and costs by allowing for targeted preventative interventions. Future work will include prospective and external validation in other healthcare systems. Research Sponsor: None.

Variable	ß-coefficient	Odds ratio [95% CI]	p-value
Prior Hospitalization	0.30	1.35 [1.20-1.51]	<0.001
Prior ED Visit	0.10	1.11 [1.00-1.23]	0.06
Low WBC Count	0.26	1.29 [1.11-1.49]	0.001
Elevated AlkPhos	0.19	1.20 [1.09-1.34]	<0.001
Elevated Pulse	0.09	1.09 [1.02-1.17]	0.01
Stage 4 Disease	0.17	1.19 [1.06-1.33]	0.003
Depression	0.29	1.33 [1.13-1.56]	<0.001
White Race	-0.12	0.89 [0.82-0.97]	0.005

1512 **Poster Discussion Session**

Evaluating a high-dimensional machine-learning model to predict hospital mortality among elderly cancer patients. *First Author: Edmund M. Qiao, Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA*

Background: Elderly hospitalized cancer patients face high risks of inpatient hospital mortality. Identifying patients at high risk of hospital mortality could help with risk stratification, and potentially help inform future interventions aimed at improving outcomes. We evaluated the predictive capacity of a high-dimensional machine-learning prediction tool to predict inpatient mortality, and compared the performance of this new tool to existing prediction indices. **Methods:** We identified cancer patients 75 and over who presented to an emergency department (ED) and were subsequently hospitalized from the National Emergency Department Sample (NEDS) between 2016 and 2018. We used an extreme gradient boosting approach to predict the risk of death during hospitalization. Model covariates included patient demographics, hospital characteristics, and International Classification of Diseases, version 10 (ICD-10) diagnosis codes recorded during the ED visit. The data were split 75%/25% into training/testing datasets. We constructed the model with training data and evaluated performance within the test data using area under the curve (AUC), with an AUC of 1.0 indicating perfect prediction. We compared the performance of this risk prediction model to standard prediction indices including the Hospital Frailty Risk Score, modified 5-item frailty index, and Charlson comorbidity index. **Results:** We identified 1,892,690 weighted-hospitalizations among elderly cancer patients, of which 133,379 (7.0%) who died in the inpatient setting. Our final predictive model included 238 features, which contained 5 demographic variables, 3 hospital characteristics, and 230 ICD-10 diagnosis codes. The predictive model achieved an AUC of 0.92. Our comparator models including the Hospital Frailty Risk Score, modified 5-item frailty index, and Charlson comorbidity index achieved AUCs of 0.67, 0.56, and 0.60, respectively. **Conclusions:** Using a high-dimensional machine-learning model enabled a high level of precision in predicting hospital mortality among elderly cancer patients, substantially out-performing existing prediction indices. High-dimensional prediction models show promise in helping to identify patients at risk of severe adverse outcomes, though additional validation is needed as well as research studying how to implement these tools into practice. Research Sponsor: U.S. National Institutes of Health.

1513 **Poster Discussion Session**

Risk for SARS-CoV-2 infection in patients with breast cancer treated with chemotherapy, biologic therapy or active surveillance: Patient outcomes from multicenter institution in New York. *First Author: Nibash Budhathoki, Perlmutter Cancer Center at NYU Langone Hospital-Long Island, Mineola, NY*

Background: In high-risk estrogen-receptor positive, HER2 positive, or triple negative breast cancer (BC), chemotherapy can increase cure rates in early-stage disease and prolong survival in setting of advanced disease. Real world data specific to BC is needed to counsel patients (pts) with BC on their risk for SARS-CoV-2 infection and mortality in the context of the SARS-CoV-2 pandemic. **Methods:** In this retrospective study, we abstracted clinical data including demographics, tumor histology, cancer treatment, and COVID-19 testing results status from the electronic medical record of 3778 BC patients who received cancer care from 02/01/2020 – 05/01/2020 in New York City at our cancer center. The primary endpoint of the study was incidence of SARS-CoV-2 infection by treatment type (cytotoxic chemotherapy (CT) vs non-cytotoxic therapies (endocrine and/or HER2 directed therapy (E/H)) diagnosed by either serology, RT-PCR, or documented clinical diagnosis. Probability of Treatment Weighting (IPTW) and Mann-Whitney Test were used to assess risk of SARS-CoV-2 infection by treatment and assess outcomes based on oncologic and non-oncologic risk factors respectively. **Results:** 3062 patients met inclusion criteria with 379 pts in CT, 2343 pts in E/H and 340 in NT groups. During study period 641 patients (20.9%) were tested by either PCR or serology with 64 patients (2.1%) diagnosed with COVID-19. All pts who tested positive by PCR and subsequently had serology testing were positive for IgG. The weighted risk of SARS-COV-2 infection was 3.5% in CT vs. 2.7% in E/H (p=0.523). 27 patients (0.9%) expired over follow up, with 10 deaths attributed to SARS-CoV-2 infection. The weighted risk for death was 0.7% with CT vs. 0.1% with E/H, p=0.24 (Table A). Age, BMI,CCI and advanced cancer stage were associated with increased mortality following SARS-CoV-2 infection (Table). **Conclusions:** CT was not associated with increased risk of infection with SARS-CoV-2 infection or death following infection. BC cancer treatment, including CT, can be safely administered with enhanced infectious precautions and should not be withheld particularly when given for curative intent. Research Sponsor: Departmental Funds.

(A) COVID-19 Infection and mortality by treatment group, (B) Outcomes by Demography,

A

SARS-CoV-2 Infection	Rate	Weighted Rates	Risk Difference% (95% CI)	p value
CT(N=18)	4.70%	3.50%	0.8(-1.7- 3.4)	0.52
E/H(N=43)	1.80%	2.70%		
COVID-19 Specific Mortality				
CT(N=4)	1.10%	0.70%	0.6 (-0.4 - 1.6)	0.24
E/H(N=2)	0.10%	0.10%		

B

	Alive N=54/(mean (SD))	Dead N=10/(mean (SD))	p value
Early vs Advanced BC	50 (93%) vs 6(60%)	4(7%) vs 4(40%)	0.02
Age	58.29 (13.56)	73.16(8.33)	0.001
BMI	29.16 (5.81)	33.45(8.53)	0.05
CCI	3.37(3.13)	6.1(3.14)	0.01

1514 **Poster Discussion Session**

Association of the COVID-19 pandemic with patterns of cancer services. *First Author: K Robin Yabroff, American Cancer Society, Atlanta, GA*

Background: The COVID-19 pandemic led to delays in medical care in the United States. We examined changes in patterns of cancer diagnosis and surgical treatment in 2020 using real-time electronic pathology report data from population-based SEER cancer registries in Georgia and Louisiana. **Methods:** Bi-weekly numbers, distributions, and patterns of pathology reports were compared between January 1st and December 31st in 2020 and the same period in 2019 by age group and cancer site. **Results:** During 2020, there were 29,905 fewer pathology reports than in 2019, representing a 10.2% decline. Absolute declines were greatest among adults aged ≥50 years (N=23,065); percentage declines were greatest among children and young adults ≤18 years (38.3%). By cancer site, percentage declines were greatest for lung cancer (17.4%), followed by colorectal (12.0%), breast (9.0%) and prostate (5.8%) cancers. Biweekly reports were statistically significantly lower in 2020 than in 2019 from late March through the end of December in most biweekly periods. The nadir was the month of April 2020 – the number of reports was at least 40% lower than in April 2019. The number of reports in 2020 compared with 2019 also declined sharply in early November (26.8%) and late December (32.0%). Numbers of reports in 2020 never consistently exceeded those in 2019 after the first decline. Patterns were similar by cancer site, with variation in magnitude and duration of declines. **Conclusions:** Significant declines in cancer pathology reports from population-based registries during 2020 suggest substantial delays in screening, evaluation of signs and symptoms, diagnosis, and treatment services for cancers with effective screening tests as well as in cancer sites and age groups without effective screening tests as an indirect result of the COVID-19 pandemic. Ongoing evaluation will be critical for informing public health efforts to minimize any lasting adverse effects of the pandemic on cancer screening, diagnosis, treatment, and survival. Research Sponsor: None.

Cancer Pathology Reports from SEER registries in Georgia and Louisiana during January-December 2019 and 2020.

		2019		2020		Decline in 2020	
	Total	Number	%	Number	%	Number	% (95% CI)
State	Georgia	294,113	100	264,208	100	29,905	10.2 (10.2 - 10.2)
	Louisiana	198,081	67.3	177,180	67.1	20,901	10.6 (10.5 - 10.6)
		96,032	32.7	87,028	32.9	9,004	9.4 (9.4 - 9.4)
Cancer site	Breast	65,714	22.3	59,767	22.6	5,947	9.0 (9.0 - 9.1)
	Prostate	15,597	5.3	14,700	5.6	897	5.8 (5.7 - 5.9)
	Colorectal	22,515	7.7	19,822	7.5	2,693	12.0 (11.9 – 12.0)
	Lung	33,530	11.4	27,686	10.5	5,844	17.4 (17.4 - 17.5)
	Other sites	156,757	53.3	142,233	53.8	14,524	9.3 (9.3 - 9.3)

1515 **Poster Discussion Session**

Growth in eligibility criteria content and failure to accrue among National Cancer Institute (NCI)-affiliated clinical trials. *First Author: John Stuart Peterson, University of Utah School of Medicine, Salt Lake City, UT*

Background: Cancer clinical trial accrual across diverse socioeconomic and demographic groups is a national priority, yet up to 20% of trials fail due to poor accrual. Eligibility criteria content may contribute to poor accrual, but effects are challenging to measure. We sought to evaluate growth of eligibility criteria within NCI-affiliated cancer trials and the impact on trial accrual over the past decade. **Methods:** We conducted a retrospective study with the Aggregate Analysis of ClinicalTrials.gov (AACT) (abstracted: 02/02/2021). We included NCI-affiliated, interventional Phase II or III trials that initiated between 01/01/2008 and 12/13/2018. We excluded active and recruiting trials that lacked accrual data on the Cancer Trials Support Unit website. Trials whose status was "Withdrawn", "Terminated", or "Suspended" due to low accrual, or had less than 50% target accrual after two years active were deemed accrual failures. Eligibility criteria were extracted from inclusion and exclusion criteria and complexity was estimated by the number of unique content words, calculated by removing duplicates and stop words from the word count. Association of unique word count with accrual failure was evaluated by univariable and multivariable logistic regressions, adjusting for other predictors of low accrual identified in earlier research. **Results:** Of 1197 trials included, 231 (19.3%) failed due to low accrual. Eligibility criteria increased in length from a median of 214 (IQR [23, 282]) unique content words in 2008 to 417 (IQR [289, 514]) in 2018. The rate of trial accrual failure increased with unique word count decile from 11.8% in the first decile (12 to 112 words) to 29.4% in the tenth decile (445 to 750 words) (P = 0.004). On multivariable analysis, unique word count remained independently associated with low accrual (OR: 1.07 per decile, 95%CI [1.01-1.13], P = 0.02), as did Phase III and metastatic disease settings (Table). **Conclusions:** Eligibility criteria content has increased dramatically in the last decade in NCI-affiliated trials. Increasing eligibility criteria content associates strongly with accrual failure, even after adjusting for multiple known predictors of accrual. These findings underscore the need for efforts to simplify eligibility criteria to improve trial accrual. Further investigation is ongoing to determine specific criteria qualities that portend accrual failure. Research Sponsor: None.

Multivariable Logistic Regression for Accrual Failure	OR (95% CI)
Number of unique content words (per decile)	1.07 (1.01, 1.13)
Common solid cancer	1.01 (0.69, 1.45)
Common liquid cancer	1.40 (0.93, 2.10)
NCI-approved targeted therapy as intervention	1.31 (0.90, 1.93)
Metastatic disease	1.53 (1.09, 2.16)
Tissue sample required	1.01 (0.74, 1.37)
Radiation therapy as intervention	0.85 (0.24, 2.35)
Phase III	1.78 (1.15, 2.70)

1516 **Poster Discussion Session**

The validity of progression-free survival (PFS) 2 as a surrogate endpoint for overall survival (OS) in randomized controlled trials (RCTs) of advanced solid tumors. *First Author: Rachel Woodford, St George Hospital, Lisarow, Australia*

Background: OS is the gold-standard endpoint for treatment efficacy in oncology RCTs. However, prolonged follow-up is required to obtain mature data, which impedes regulatory approval of potentially beneficial therapies. Furthermore, increasing therapeutic options including cross over to investigational agents at disease progression often confound OS findings. PFS-2, defined as time from randomization to progression on second-line therapy, has been proposed as a potential surrogate endpoint for OS. Using a meta-analytic approach, we aimed to assess the association between OS and PFS-2, and its validity compared with other surrogate endpoints. **Methods:** We performed an electronic literature search to identify RCTs of systemic therapies that reported PFS-2 as a pre-specified endpoint with defined follow up protocols. Articles were screened for eligibility and outcome data were extracted. Correlations in the relative treatment difference between treatment arms for OS vs PFS-2, PFS-1, and objective response rate (ORR) were assessed as the comparison of hazard ratios (HR) and odds ratio (OR) respectively. **Results:** 38 eligible RCTs comprising of 44 analysis units, with 19,031 patients across 8 unique tumor types were identified. The majority received targeted therapies (72.2%), followed by immunotherapy (IO; 26.3%). The correlations of HR-OS/HR-PFS-2, HR-OS/HR-PFS-1 and HR-OS/OR-ORR were $r = 0.67$ (95% CI 0.08-0.69), $r = 0.12$ (95% CI 0.00-0.13) and $r = 0.21$ (95% CI 0.00-0.33) respectively. Correlations between OS with surrogates was assessed in different subgroups according to post-progression survival times (SPP), types of treatment agents and rate of subsequent therapy after progression (table). **Conclusions:** Across diverse tumors and therapies, treatment effect on PFS-2 has modest to strong correlation with OS, but poor correlations were observed between OS-PFS-1 and OS-ORR respectively. Across all subgroups, PFS-2 performs consistently better than traditional surrogates of PFS-1 and ORR, validating and providing support for use in future RCTs. Research Sponsor: None.

		Correlation coefficient (*r*)		
Subgroups	**Analysis units (N)**	**HR-PFS-2/HR-OS**	**HR-PFS-1/HR-OS**	**OR-ORR/HR-OS**
SPP median≤10 months	16	0.88 (95% CI 0.40-0.90)	0.46 (95% CI 0.0-0.38)	0.25 (95% CI 0.0-0.38)
SPP median > 10 months	20	0.80 (95% CI 0.04-0.85)	0.22 (95% CI 0.0-0.36)	0.15 (95% CI 0.0-0.04)
IO agent	14	0.67 (95% CI 0.0-0.59)	0.62 (95% CI 0.09-0.87)	0.41 (95% CI 0.0-0.57)
Non-IO agent	30	0.67 (95% CI 0.03-0.73)	0.29 (95% CI 0.0-0.58)	0.12 (95% CI 0.0-0.1)
Subsequent therapy ≤50%	17	0.63 (95% CI 0.03-0.86)	0.64 (95% CI 0.16-0.68)	0.28 (95% CI 0.0-0.76)
Subsequent therapy > 50%	18	0.70 (95% CI 0.04-0.70)	0.58 (95% CI 0.02-0.88)	0.17 (95% CI 0.0-0.04)

1517 **Poster Discussion Session**

Impact of the Oncology Care Model on use of bone supportive medications, antiemetics, and growth factors. *First Author: Gabriel A. Brooks, Dana-Farber Cancer Institute, Boston, MA*

Background: The Oncology Care Model (OCM) is a voluntary, episode-based alternative payment model for cancer care launched by the Centers for Medicare & Medicaid Services in July 2016. OCM incentivizes participating practices to reduce spending during chemotherapy treatment while maintaining quality of care. We evaluated the impact of OCM on the use of costly supportive care medications. **Methods:** Using 100% Medicare claims (2013-2019), we evaluated use of outpatient supportive care medications during chemotherapy episodes assigned to OCM practices (n = 186) or propensity-matched comparison practices (n = 534). For bone supportive medications, we evaluated use of bisphosphonates and/or denosumab in beneficiaries with bone metastases from breast, lung, or prostate cancer. For anti-emetic drugs, we evaluated prophylactic use of neurokinin-1 (NK1) antagonists and long-acting (LA) serotonin antagonists. For white blood cell growth factors (GCSFs), we evaluated prophylactic use in beneficiaries starting chemotherapy for breast, lung, or colorectal cancer; we separately evaluated use of biosimilar (vs originator) filgrastim. Analyses employed the difference-in-differences (DID) approach, excepting the filgrastim biosimilar analysis where we assessed the adoption trend. **Results:** There was no OCM impact on receipt of any bone supportive medication (denosumab or bisphosphonate) among beneficiaries with bone metastases; however, OCM led to a relative decrease in use of denosumab for breast cancer (DID = -5.0 percentage points [90% CI -7.1, -2.8]), prostate cancer (-4.0 percentage points [90% CI -5.9, -2.2]), and lung cancer (-4.1 percentage points [90% CI -7.4, -0.9]). In beneficiaries starting chemotherapy regimens with high or moderate emetic risk, OCM led to reductions in prophylactic use of NK1 antagonists and LA serotonin antagonists (e.g. 6.0 percentage point reduction in use of NK1 antagonists during high emetic risk chemotherapy [90% CI -9.0, -3.1]); there was no impact on antiemetic use during low emetic risk chemotherapy. There was no OCM impact on use of prophylactic WBC growth factors among beneficiaries receiving chemotherapy with high risk for febrile neutropenia (FN). Among beneficiaries receiving chemotherapy with intermediate risk for FN, OCM led to a 7.6 percentage point reduction in prophylactic GCSF use for patients with breast cancer (90% CI -12.6, -2.7); however, there was no OCM impact on prophylactic GCSF use in patients with lung or colorectal cancer. Among beneficiaries receiving filgrastim, OCM led to faster adoption of biosimilar vs. originator filgrastim (differential trend estimate 2.6%, 90% CI 1.0, 4.4). **Conclusions:** OCM led to reduced use of some high cost supportive care medications, with patterns suggesting more value-conscious care. Alternative payment models have potential to drive value-based changes in medication use during cancer care. Research Sponsor: Centers for Medicare and Medicaid Services.

1518 **Poster Discussion Session**

Baseline and short-term financial burden (FB) in colorectal cancer (CRC) treated with curative intent: Early results of ECOG-ACRIN EAQ162CD. *First Author: Sheetal Mehta Kircher, Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL*

Background: Cancer therapy costs continue to rise, resulting in FB. FB in CRC treated with curative intent remains unexplored, particularly in the community oncology setting. We assess baseline FB and 3-month change, including predictors. **Methods:** Patients with newly diagnosed CRC treated with curative intent were enrolled through NCI Community Oncology Research Program (NCORP) Community Sites in a longitudinal study and completed the validated FACIT Comprehensive Score for Financial Toxicity (COST) instrument at baseline and 3 months. Higher COST score (range 0-44) indicates greater financial well-being. Pearson correlation compared baseline and 3-month measurements. Effects of patient demographics, clinical, self-efficacy variables (Table) and practice safety net affiliation were assessed using linear regression for baseline COST and COST difference at 3 months. F-tests identified covariates significantly predicting FB. **Results:** 450 and 296 participants completed the baseline and 3-month survey with a mean COST score 23.5 ± 11.9 and 24.6 ± 12.4, respectively ($r=0.80$, $p<0.001$), considered grade 1 or mild. Financial resource indicators such as income, insurance type, high-deductible insurance and savings, along with self-efficacy strongly predicted baseline FB (Table). No assessed covariates predicted COST difference. Safety-net affiliation (54/450, 12%) did not predict COST outcomes. **Conclusions:** Among those with CRC treated with curative intent in community settings, FB at treatment initiation and 3-month follow-up are highly correlated. Financial resources predict FB at treatment initiation. Self-efficacy to manage finances predicted FB, suggesting interventions such as financial counseling and navigation delivered early in the treatment course may minimize downstream FB. Clinical trial information: NCT03516942. Research Sponsor: U.S. National Institutes of Health.

Demographics and predictors of FB at baseline (n=450).

	n (%)	**Baseline COST covariates (p≤0.05)***
Age mean (SD, range)	61.0 (12.0, 65)	
Gender, Female	210 (46.7)	
Cancer stage		
I	68 (15.1)	
II	140 (31.1)	
III	242 (53.8)	
Race		-6.22 (-10.31- -2.13)
Black	33 (7.3)	REF
White	379 (84.2)	
Other	38 (8.4)	
Primary health insurance		
Medicaid, single service, none	30 (6.7)	
Medicare, Indian, Military	197 (43.8)	
Private	223 (49.6)	3.45 (0.68-6.23)
		REF
Annual household income		REF
Up to 29,999	111 (24.7)	
$30,000-59,000	136 (30.2)	
$60,000 and greater	192 (42.7)	6.49 (3.33-9.65)
Not answered	11 (2.4)	
Savings account		REF
Yes	198 (44)	-8.86 (-11.06- -6.66)
No	228 (50.7)	
Not answered	24 (5.3)	
High deductible plan		REF
Yes	147 (32.7)	5.04 (2.92-7.15)
No	275 (61.1)	
Not answered	28 (6.2)	
Self-efficacy mean (SD, range)	6.8 (2.4, 9.0)	1.6 (1.19-2.04)

*In addition to the above, the linear regression included cancer type, chemo planned, marital status, education level, number of comorbidities, safety net affiliation.

1519 **Poster Discussion Session**

Patient factors associated with time to medication receipt of oral anti-cancer drugs. *First Author: Morgan Rachel Lieberman Lichtenstein, Massachusetts General Hospital, Boston, MA*

Background: The past decade has seen a dramatic increase in the number of Food and Drug Administration approvals of oral anti-cancer drugs (OACDs). Most OACD prescriptions require coordination between providers, payers, specialty pharmacists, and financial assistance organizations, which can delay drug receipt. We evaluated median time to OACD receipt (TTR) from initial OACD prescription submission and assessed clinical and process-related factors associated with TTR. **Methods:** We prospectively collected data on all new OACD prescriptions for adult oncology patients at a large, urban outpatient cancer center from 1/1/2018 to 12/31/2019. We collected patient demographic, medical, and insurance data; prescription submission and delivery dates; and interactions with payers and financial assistance groups. TTR was defined as the number of days from OACD initial prescription to patient receipt of the drug. We estimated the median TTR across all patients and used multivariable logistic regression to identify factors associated with TTR above the median. **Results:** The cohort included 1080 patients who were prescribed 1269 new OACDs. Of these prescriptions, 84% (N=1069) were received, and 71% (N=896) required prior authorization. The median patient age was 66, 44% identified as Non-Hispanic White (White), 25% of patients had commercial insurance, 16% had Medicaid alone, and 58% had Medicare alone or in combination with another plan. The median TTR per patient was 7 days (IQR 0 – 142; 25% ≥ 14 days and 5% ≥ 30 days). In unadjusted analyses, insurance and race/ethnicity were associated with TTR. Compared with patients covered by Medicaid, those with Medicare and supplemental insurance (a partial, not free-standing plan) had nearly 2.5 times the odds of TTR >7 days controlling for other factors. Race/ethnicity showed a trend toward longer TTR with Non-Hispanic Black (Black) patients having a longer TTR compared to White patients, controlling for other factors. We did not observe statistically significant effects of either comorbidity or prior authorization requirement on TTR. **Conclusions:** Though the majority of oncology patients prescribed OACDs receive the drug, 71% of prescriptions required prior authorization and a quarter of patients waited at least two weeks. Disparities in TTR are primarily driven by financial factors, specifically insurance type. Research Sponsor: NCI.

Multivariable analysis: Factors associated with TTR > 7 days.

	N (%)	***OR (95% CI)***	***p-value***
Insurance Coverage			
Commercial	222 (25.0)	1.28 (0.81 – 2.02)	0.29
Medicaid	140 (15.8)	(Ref)	(Ref)
Medicare	149 (16.8)	1.25 (0.78 – 2.02)	0.35
Medicare + Medicaid	142 (16.0)	1.01 (0.62 – 1.63)	0.98
Medicare + Commercial	73 (8.2)	0.75 (0.40 – 1.38)	0.35
Medicare + Supplemental	146 (16.5)	2.45 (1.45 – 4.17)	0.001
Race/ethnicity			
White	391 (44.0)	(Ref)	(Ref)
Black	128 (14.4)	1.53 (1.00 – 2.37)	0.05
Hispanic	258 (29.1)	0.86 (0.59 – 1.24)	0.41

1520 **Poster Discussion Session**

Insurance coverage and care affordability in cancer survivors in 2016-2019. *First Author: Justin Michael Barnes, Saint Louis University School of Medicine, St. Louis, MO*

Background: The Affordable Care Act (ACA) led to improvements in insurance coverage and care affordability in cancer patients. However, the uninsured rate for the general US reached its nadir in 2016 and has been increasing since. We aimed to quantify the changes in insurance coverage and rate of care unaffordability in cancer survivors from 2016 to 2019. **Methods:** We queried data from the Behavioral Risk Factor Surveillance System (2016-2019) for cancer survivors ages 18-64 years. Outcomes of interest were the percentage of cancer survivors reporting insurance coverage and the percentage reporting cost-driven lack of care in the previous 12 months. Survey-weighted linear probability models adjusted for covariates (age, sex, race/ethnicity, income, education, marital status, and state Medicaid expansion status) were utilized to estimate the average yearly change (AYC) in the outcomes across 2016-2019. Mediation analyses evaluated the mediating effect of insurance coverage changes on changes in cost-driven lack of care. **Results:** A total of 178,931 cancer survivors were identified among the survey respondents. The percentage of insured cancer survivors between 2016 and 2019 decreased from 92.4% to 90.4% (AYC: -0.54, 95% CI = -1.03 to -0.06, P = .026). This translates to an estimated 164,638 cancer survivors in the United States who lost insurance coverage in the study period. There were decreases in private insurance coverage (AYC: -1.66, 95% CI = -3.1 to -0.22, P = .024) but increases in Medicaid coverage (AYC: 1.14, 95% CI = 0.03 to 2.25, P = .043). The decreases in any coverage were largest in individuals with income $<$ 138% federal poverty level (FPL) (AYC: -1.14, 95% CI = -2.32 to 0.04, P = .059; compared to $>$ 250% FPL, $P_{interaction}$= .03). Cost-driven lack of care in the preceding 12 months among cancer survivors increased from 17.9% in 2016 to 20% in 2019 (AYC: 0.67, 95% CI = 0.06 to 1.27, P = .03), which translates to an estimated 167,184 survivors in the US who skipped care due to costs. Changes in insurance coverage mediated 27.5% of the observed change in care unaffordability overall (p = .028) and 65.7% in individuals with income $<$ 138% FPL relative to $>$ 250% FPL (p = .045). **Conclusions:** Between 2016 and 2019, about 165,000 cancer survivors in the United States lost their insurance coverage and a similar number may have skipped needed care due to cost. Loss of insurance coverage was mostly among individuals with low socioeconomic status. Interventions to improve health insurance coverage among cancer survivors, such as the recent executive order to strengthen the ACA and further efforts promoting Medicaid expansion in additional states, may be important factors to mitigate these trends. Research Sponsor: None.

1521 **Poster Session**

Comparing FOLFOX delivery in trial and real-world populations using longitudinal cumulative dose. *First Author: Michael Webster-Clark, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Patterns of chemotherapy delivery are likely to differ between trial and real-world populations. Typical measures used to compare these patterns are calculated at treatment completion, potentially missing key differences in the timing and trajectory of delays and dose reductions. We used a new measure, longitudinal cumulative dose (LCD), to compare treatment delivery over time in trial and real-world populations. **Methods:** We compared chemotherapy delivery in patients with stage II-III colon cancer enrolled in the MOSAIC trial of 5-fluorouracil (5FU) vs oxaliplatin + 5FU (FOLFOX4) to patients treated from 2008-2019 in the US Oncology Network with FOLFOX4, FOLFOX6, or mFOLFOX6. For each patient, we computed oxaliplatin LCD as the cumulative oxaliplatin dose received at a given timepoint (t) divided by the final standard oxaliplatin dose. We then estimated the median and 25th and 75th percentiles for oxaliplatin LCD within each regimen at day 68 (before the standard timing of the 7th dose), 168 (two weeks after the standard end of treatment), and 250. **Results:** The table shows the number of patients receiving each treatment regimen and the median and interquartile range for oxaliplatin LCD at each time. Higher LCDs in the trial show delivery closer to standard treatment, meaning fewer delays, dose reductions, and discontinuations. Differences between the medians, 25th percentiles, and 75th percentiles of LCD in each regimen were small at day 68 but grew considerably by days 168 and 250. **Conclusions:** Divergence from the standard dosing schedule was larger in real-world versus trial settings and varied by oxaliplatin regimen. LCD, as a longitudinal measure, showed that differences in delivery between trial and real-world populations grew substantially over time (even after 168 days and the standard end of treatment) possibly as real-world patients experienced more side effects and barriers to treatment than trial participants. These discrepancies in LCD may cause poorer outcomes in real-world settings than expected based on randomized trials. Research Sponsor: Patient Centered Outcomes Research Institute.

Regimen	Number receiving regimen	Median (IQR) oxaliplatin LCD, day 68 (ideal = 50%)	Median (IQR) oxaliplatin LCD, day 168 (ideal = 100%)	Median (IQR) oxaliplatin LCD, day 250 (ideal = 100%)
MOSAIC				
FOLFOX4	1110	40% (32% - 41%)	77% (58% - 88%)	85% (59% - 95%)
US Oncology				
FOLFOX4	48	36% (32% - 41%)	73% (54%, - 85%)	77% (54% - 89%)
FOLFOX6	152	34% (28% - 37%)	66% (50% - 79%)	68% (52% - 84%)
mFOLFOX6	2937	34% (28% - 35%)	60% (43% - 73%)	62% (43% - 76%)

1522 **Poster Session**

Impact of a regimen-level prior authorization tool on provider adherence to clinical guidelines' and cost savings in a Medicare advantage population. *First Author: Heeseon Yeon, CVS Health, Wellesley, MA*

Background: In 2019, a large national health system developed a comprehensive approach to improve the quality and cost of cancer care; this solution included a Web-based clinical decision support prior authorization (PA) tool, Novologix (NLX), which approves at the regimen rather than drug level to reduce administrative burden and elevate the quality of care. Evidence-based guidelines in NLX are updated in real-time via a partnership with the National Comprehensive Cancer Network (NCCN). The purpose of this study is to evaluate the NCCNconcordance of PAs submitted via NLX and total cost of care for Medicare Advantage (MA) patients with non-small cell lung cancer (NSCLC) who received NCCNconcordant versus non-concordant therapies. **Methods:** Eligible patients included MA patients diagnosed with NSCLC; our initial analysis included only the NSCLC subset of patients. NCCN regimen concordance was identified from pharmacy and medical claims and defined as concordant if the entire prescribed treatment regimen matched an NCCNregimen; patients not receiving an NCCN recommended regimen were deemed to be non-concordant. Total cost of care for MA patients with NSCLC were calculated. **Results:** From April-December 2020, 279 PAs were submitted via NLX and 83% were automatically approved in real-time. PAs not automatically approved were deemed concordant after peer-to-peer consultations that led to NCCN concordance; no PA denials were made. In the first half of 2020, 2,690 MA patients with NSCLC were identified; 2,166 (81%) patients were defined as NCCN concordant. Beginning with and including the first treatment and for 30-days thereafter, total cost of care for concordant patients averaged $19,321 while non-concordant patients averaged $26,405, a statistically significant savings of $7,084 (p $<$ 0.001). **Conclusions:** Preliminary findings with a MA NSCLC population suggest engaging oncology practices through an enhanced payer-provider collaboration and implementing an automated regimen-level precertification process with real-time NCCNupdates can facilitate lower cost, and more efficient oncology care. Financial savings by encouraging providers to follow NCCN guidelines may lead to a 27% reduction in total cost of care with further proper adjustment on population bias; this may lead to similar findings in other cancer types. Future studies are needed to measure the long-term impact of this program on total cost of care for other care models and cancer types. Research Sponsor: None.

1523 **Poster Session**

Germline testing in community oncology patients with somatic BRCA1/2 mutations. *First Author: Kate Principe, Texas Oncology, Houston, TX*

Background: The primary purpose of tumor mutation profiling (TMP) is to molecularly characterize tumors to identify targeted treatments and improve outcomes, but it may also uncover germline mutations with implications for patients and families. In September 2016, the National Comprehensive Cancer Network (NCCN) added "BRCA1/2 mutation detected by TMP" as a criterion for germline BRCA1/2 testing. This study aims to assess rates of germline testing, with and without genetic consultations, for individuals with a somatic BRCA1/2 finding in community oncology centers. **Methods:** Retrospective data was abstracted from an internal database of results from four TMP laboratories. Individuals with a somatic BRCA1/2 pathogenic/likely pathogenic (P/LP) variant reported from January 1, 2017 to December 31, 2019 were included. Clinical data was obtained from electronic medical records. The project was approved by the Texas Oncology Privacy Board. **Results:** 221 patients had a P/LP somatic BRCA1/2 result on TMP, 138 of which were BRCA1/2 spectrum tumors (breast, ovary, pancreas, prostate). 144/221 patients (65.2%) had BRCA1/2 germline testing. 133/221 (60.2%) met NCCN guidelines for germline BRCA1/2 testing independent of their somatic results; they were statistically more likely to undergo germline testing than patients who did not otherwise meet germline BRCA1/2 testing criteria (p=2.3e-16) (Table). 70/144 (48.6%) had a germline P/LP BRCA1/2 mutation identified. At locations with genetic providers versus those without, there was a significant difference in rates of genetic consultation (p=0.02) but not in the rate of germline testing (p=0.3). This indicates patients were more likely to receive pre- and post-test counseling at clinics offering in-house genetic consultations. **Conclusions:** Most individuals who had a P/LP somatic *BRCA1/2* mutation identified on TMP underwent germline genetic testing. As 60.2% of our cohort qualified independently for germline testing, somatic*BRCA1/2*results may not have been the driving force behind germline testing. However, individuals who had a non-*BRCA1/2*-spectrum tumor were significantly less likely to have the recommended confirmatory germline testing. Quality improvement initiatives can focus on improving rates of counseling and germline testing for patients with somatic*BRCA1/2* mutations, regardless of tumor type. Research Sponsor: None.

Rate of germline testing, genetic consultation, and pathogenic germline *BRCA1/2* mutations.

	Met NCCN criteria independent of somatic result (n= 133)	Did not meet NCCN criteria independent of somatic result (n= 88)	*BRCA1/2* spectrum tumor (n=138)	Non-*BRCA1/2* spectrum tumor (n=83)
Had germline genetic testing	116 (87.2%)	28 (31.8%)	118 (85.5%)	26 (31.3%)
Had genetic consultation	74 (55.6%)	21 (23.9%)	73 (52.9%)	22 (26.5%)
Germline P/LP*BRCA1/2* mutation identified	63 (54.3%)	7 (8.0%)	63 (45.7%)	7 (8.4%)

1524 **Poster Session**

Patient navigation plus hospital at home to improve COVID-19 outcomes for cancer patients. *First Author: Brittany K. Ragon, Levine Cancer Institute, Charlotte, NC*

Background: Reports suggested cancer patients were at greater risk for increased morbidity and mortality from COVID-19. A process to mitigate these risks was established at Levine Cancer Institute (LCI) in partnership with Atrium Health's (AH) Hospital at Home (HAH) initiative. This virtual health navigation process employed expertise from the departments of Hematologic Oncology and Blood Disorders, Oncology, and Supportive Oncology, including a specialized nurse navigation team, to rapidly identify COVID-19 positive LCI patients, monitor them under physician supervision, and escalate care as needed with AH HAH program. **Methods:** AH Information Services created an automated list of LCI COVID-19 positive patients with a daily database. Each patient was reviewed by a nurse navigator. Review included hematologic or oncologic diagnosis, outpatient or inpatient status, and any COVID-19 symptoms. Once a malignant diagnosis was confirmed, a diagnosis-specific navigator contacted and screened the patient with a COVID assessment tool. Documentation was forwarded to the primary oncologist/hematologist. The tool scored patients for surveillance and treatment needs. A score of 0-2 prompted phone assessment every 48-72 hours, and score of 3-5 required every 24-48 hour calls with physician involvement when appropriate. If score of ≥6, care was escalated to LCI nurse/physician for admission to AH acute care HAH or conventional inpatient admission. **Results:** From inception on 3/20/2020 to data review date of 12/2/2020, 974 LCI patients were identified as COVID-19 positive and reviewed for nurse navigation (Table). Of the 974, 488 were navigated. Given limited resources, patients with benign conditions were not assigned a navigator, though a similar process was created for sickle cell disease. Of the 974, 75 are now deceased. Only 25 are deceased among the 488 navigated. **Conclusions:** The COVID-19 pandemic presented unprecedented circumstances to our patients and their clinicians. LCI expeditiously put policies and procedures in place to mitigate the intersection of COVID-19 and cancer. The multidisciplinary response strategy liaising between AH HAH and LCI followed, assessed, and assisted LCI COVID-19 positive patients. With our embedded nurse navigation team's specialized attention along with enhanced physician oversight and close collaboration with AH HAH, opportunities for care escalation or adjustments in cancer-focused care were promptly identified. Analysis is ongoing to elucidate the lower mortality rate observed among navigated patients. Research Sponsor: None.

COVID-19 positive patients defined by LCI criteria from 3/20/20-12/2/20, N=974.

Characteristic	N (%)
Diagnosis	
Hematologic Malignancy	143 (15)
Solid Malignancy	561 (57)
Hematologic and Solid Malignancy	6 (1)
No Malignancy Identified	264 (27)
Navigated Patients	488 (50)
Deceased Patients	
Navigated	25 (3)
Not Navigated	50 (5)

1525 **Poster Session**

The influence of race on financial toxicity among cancer patients. *First Author: John Panzone, SUNY Upstate Medical University, Syracuse, NY*

Background: Studies show that cancer patients and survivors are likely to endure financial toxicity long after being diagnosed. **Methods:** To examine the influence of race on financial toxicity among individuals with a history of cancer, a US based cross sectional study was conducted using data on 1,328 cancer patients collected from the Health Information National Trends Survey. Multivariable logistic regression analyses were used to analyze the relationship between race and financial toxicity, adjusting for known confounders. **Results:** Blacks, Hispanics and other races were shown to have a lower rate of insurance compared to Whites. Whites were also more likely to receive cancer treatment than other races (6.1% received no treatment vs 15.0% of Blacks, 17.8% of Hispanics, and 9.7% of other races, $p<0.001$). Considerably more Whites underwent surgical treatment of their cancer (77%) vs. 60% of Blacks, 55% of Hispanics and 74.2% of other races, $p<0.001$. Blacks were found to be over 5 times more likely to be denied insurance (OR 5.003, 95% CI 2.451-10.213, $p<0.001$) and more than twice as likely to be hurt financially than Whites (OR 2.448, 95% CI 1.520-3.941, $p<0.001$). Other racial minorities were also more than twice as likely to be hurt financially than Whites (OR 2.421, 95% CI 1.248-4.698, p=0.009) (Table). **Conclusions:** These data suggest that race is significantly associated with increased rates of being hurt financially and being denied insurance due to cancer. Awareness of race inequality should be raised so that equal cancer treatment can be provided, irrespective of race, gender or socioeconomic status. Research Sponsor: None.

	Patient denied health insurance coverage			Patient hurt financially		
	Odds Ratio	95% CI	p-value	Odds ratio	95% CI	p-value
Race (White reference)	-	-	-	-	-	-
Hispanic	2.188	0.945-5.067	0.068	1.494	0.915-2.438	0.109
Black	5.003	2.451-	<0.001	2.448	1.520-3.941	<0.001
Other	1.486	10.213	0.536	2.421	1.248-4.698	0.009
Types of cancer treatments (none	-	0.423-5.213	-	-	-	-
reference)	1.410	0.569-3.495	0.458	1.401	0.902-2.176	0.133
Surgery only	0.292	0.033-2.615	0.271	2.067	1.023-4.176	0.043
Radiotherapy only	2.827	0.719-	0.137	5.985	2.556-	<0.001
Chemotherapy only	1.784	11.107	0.318	2.685	14.017	0.001
Surgery + radio	2.436	0.572-5.561	0.136	5.132	1.536-4.695	<0.001
Surgery +chemo	1.659	0.756-7.849	0.567	3.361	2.680-9.826	0.016
Radio +chemo	2.312	0.293-9.404	0.125	7.556	1.249-9.041	<0.001
Surgery + radio +chemo		0.792-6.749			4.067-14.041	
Annual Income (0$-49,999$ reference)	-	- -	-	-	-	-
50,000$-99,999$	1.093	0.580-2.060	0.783	0.801	0.565-1.137	0.214
>, = 100,000$	0.115	0.025-0.52	0.005	0.493	0.315-0.772	0.002

Additional variables included in the analyses but not shown were US Census region, age of diagnosis, survey year, gender, education, rural vs. metro residence, marital status, and health insurance.

1526 **Poster Session**

Successful implementation of an ePRO remote monitoring system in patients receiving chemotherapy in a community oncology practice. *First Author: Michael A. Kolodziej, ADVI, Washington, DC*

Background: Remote symptom monitoring of patients receiving cancer treatment has been shown to improve patient outcomes in the research setting. However, there is little evidence that this technology can be implemented and scaled in the real world with the same benefits. **Methods**: Highlands Oncology Group (HOG) is a 19 physician medical oncology group in Northwest Arkansas. Beginning in June 2020, HOG offered patients receiving parenteral cancer therapy enrollment onto Expain: an EMR-integrated, electronic patient-reported outcomes (ePRO) system which enables remote symptom monitoring during systemic cancer therapy. Patients reported distress and symptoms using the NCCN Distress Thermometer and Problem List instrument. The practice prospectively defined patient reporting intervals based on disease and treatment protocol, as well as thresholds for each symptom that would trigger a nursing notification. Following clinical review, nurses initiated interventions including a telephone call, urgent office visit, or referral to an emergency room when necessary. **Results**: From June 2020 – January 2021, HOG treated 1261 patients with IV chemotherapy. 769 patients were offered enrollment and 569 (73.9%) were successfully enrolled onto the ePRO system. At the time of enrollment 419 (73.6%) of enrolled patients were in an Oncology Care Model (OCM) episode. Common reasons for declined enrollment were: low symptom burden, non-English speaker, and approaching the end of treatment. Of enrolled patients, the most common tumor types were: gastrointestinal (21.8%), breast (17.5%), and thoracic (16.1%). Patients reported using Expain's mobile app (89.1%) or Interactive Voice Response interface (IVR, 10.1%) with the following frequency: once a month (12%), twice a month (30%), 3 reports a month (35%), and 4 reports or more (23%); Of patients successfully enrolled 52.72% were still reporting after 3 months. The most common reasons specified for opting-out were: death, hospice admission, and completion of the treatment course. 50% of reports exceeded the practice-defined threshold for a nursing notification. The nurses initiated a follow-up call in response to 78.8% of notifications, and of these calls, 21.2% resulted in an urgent office evaluation. The most common problems triggering an office evaluation were: high NCCN Distress Thermometer score (17.1%), fatigue (16.1%), pain (11.5%), nausea (9.4%), and dyspnea (4.5%). **Conclusions**: ePRO-based remote monitoring of patients receiving parenteral cancer therapy in routine clinical care is feasible. Patient enrollment and retention are high across all tumor types. Symptoms reported by patients were concordant with previous publications, and a small percent (7% of reports) required an acute office visit. It is expected that office intervention will reduce the use of ER and inpatient services. Research Sponsor: None.

1527 **Poster Session**

The role of experience and clinical decision support in clinical trial accrual within oncology. *First Author: Waqas Haque, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Patient accrual for cancer clinical trials is suboptimal. The complexity of applying eligibility criteria and enrolling patients may deter oncologists from recommending patients for a trial. As such, there is a need to understand how experience, training, and clinical decision support impact physician practices and intentions related to trial accrual. **Methods:** From May to September 2017, we conducted a survey on clinical trial accrual in a national sample of medical, surgical, and radiation oncologists. The 20-minute survey assessed barriers and facilitators to clinical trial accrual, including experience (e.g., "In the past 5 years, have you been a study or site PI of a trial?"), training (e.g., "Did you receive training about trial design and recruitment as part of medical school, residency, or fellowship? After fellowship?"), and clinical decision support (e.g., "What kind of clinical decision support has your practice implemented?). We used logistic regression to identify factors associated with frequency of discussing trials (with ≥25% of patients) and likelihood of recommending a trial to a patient (likely or very likely) in the future. **Results:** Survey respondents (n = 1,030) were mostly medical oncologists (59%), age 35-54 years (67%), male (74%), and not in academic practice (58%). About 18% of respondents (n = 183) reported discussing trials with ≥25% of their patients, and 80% reported being likely or very likely to recommend a trial to a patient in the future. Prior experience as principal investigator of a trial was associated with both frequency of discussing trials (OR 3.27, 95% CI 2.25, 4.75) and likelihood of recommending a trial in the future (OR 5.22, 95% CI 3.71, 7.34), as was receiving additional training in clinical trials after fellowship (discussion with patients: OR 2.48, 95% CI 1.80, 3.42; recommend in future: OR 1.92, 95% CI 1.37, 2.69). Implementing clinical decision support was not associated with discussing trials with ≥25% of patients (OR 1.12, 95% CI 0.76, 1.67), but was associated with being likely to recommend a trial in the future (OR 1.73, 95% CI 1.11, 2.71). **Conclusions:** In a national survey of oncologists, we observed differences in physician practices and intention related to clinical trial accrual. Whereas the vast majority (80%) reported being likely or very likely to recommend trials in the future, far fewer (20%) reported discussing trials with their patients within the past 5 years. Implementation of clinical decision support – electronic tools intended to optimize patient care and identification of patient eligibility – was not associated with frequency of past discussion of clinical trials but was associated with recommending a trial in the future. Given the stronger association between experience as a site Principal Investigator and recommending a trial, future research should explore how improving opportunities to lead a clinical trial impact trial accrual. Research Sponsor: None.

1528 **Poster Session**

Impact of COVID-19 pandemic on time to treatment initiation for patients with advanced cancer. *First Author: Samuel U Takvorian, University of Pennsylvania, Philadelphia, PA*

Background: The COVID-19 pandemic has disrupted US healthcare delivery and led to delays in life-prolonging therapy for some conditions. Its impact on diagnosis and timely care delivery for patients (pts) with cancer is unknown. We assessed the pandemic's impact on time from advanced diagnosis to systemic treatment initiation (TTI) for pts with newly diagnosed advanced solid cancers. **Methods:** We performed a controlled interrupted time series analysis using the nationwide Flatiron Health electronic health record-derived de-identified database, which originated from ~280 US cancer clinics. The study sample included pts ≥ 18 years diagnosed with advanced solid cancers from Jan 1-Jul 31 in 2019 or in 2020, excluding a 30-day period (Mar 8-Apr 7) encompassing the start of most state stay-at-home orders. We used Cox proportional hazards models to estimate standardized predicted probabilities of TTI within 30 days of advanced diagnosis before (Jan-Mar) and during (Apr-Jul) the pandemic in 2020, compared to historical controls in 2019, adjusted for age, sex, race, insurance, performance status, and cancer type. Interactions by cancer type and race examined heterogeneity of effects. **Results:** The study included 12,977 pts (median age 69 yrs [IQR 61-77]; 47.4% female; 59.4% non-Hispanic white). At the time of analysis, fewer advanced cancer diagnoses were recorded in 2020 (Jan-Mar 2,409; Apr-Jul 3,027) than in 2019 (Jan-Mar 2,910; Apr-Jul 4,631). Compared to Apr-Jul 2019, pts diagnosed with advanced cancer during the COVID-19 period were more likely to have de novo (vs recurrent) disease (67.3% vs 56.8%). In adjusted models, the COVID-19 period was associated with an increased probability of treatment within 30 days (adjusted difference-in-differences +5.2 percentage points [ppts]). TTI improvements were not observed for pts with advanced breast cancer or Black pts, but effect differences across subgroups were not statistically significant (Table). **Conclusions:** Among pts diagnosed with advanced cancer, the COVID-19 pandemic was associated with shorter time to systemic therapy initiation. These treatment patterns may reflect the fewer advanced cancer diagnoses and higher proportion of de novo cancers observed during this period. Longer follow-up and data maturity are needed to understand the impact of the pandemic on clinical outcomes. Research Sponsor: None.

Adjusted probability of treatment within 30 days of advanced diagnosis (%).

	Jan-Mar 2019	Apr-Jul 2019	Jan-Mar 2020	Apr-Jul 2020	Adjusted difference-in-differences, ppts
Overall	43.2	41.1	46.4	49.5	5.2*
Breast (n=1,498)	58.2	56.1	66.6	61.1	-3.4
Urothelial (n=738)	36.4	36.9	39.4	46.9	7.0
Renal (n=687)	35.2	35.0	40.2	48.9	9.0
Prostate (n=961)	38.0	35.1	38.2	61.5	26.2
Pancreas (n=1,192)	52.6	53.3	57.1	59.6	1.7
NSCLC (n=5,476)	40.8	37.5	42.4	44.2	5.2
Colorectal (n=2,425)	41.2	39.5	45.0	45.6	2.2
White (n=7,709)	43.5	41.5	46.7	49.5	4.8
Black (n=1,188)	40.5	37.1	47.2	44.0	0.1

*p=0.043.

1529 **Poster Session**

Socio-economic disparities and accessibility to age-appropriate screening tools. *First Author: Noha Soror, Western Reserve Health Education, Warren, OH*

Background: Pervasive racial and ethnic health disparities continue to be reported throughout the U.S. population. An increasing number of studies have discussed racial disparities in cancer statistics as well as socio-economic differences. The purpose of this study is to investigate sociodemographic health care disparities and the prevalence of cancer diagnosis in the context of challenges in medical services accessibility due to financial burden. **Methods:** Analysis of pooled cross-sectional data using 2017 Behavioral Risk Factor Surveillance System (BRFSS). Differences between our comparison groups were computed using chi square test for categorical values and t-test for continuous variables. Demographic factors were analyzed through weighted regression for accessibility to cancer treatment and prior cancer screening. **Results:** We report data from a total of 436,198 respondents to the 2017 BRFSS survey, with cancer prevalence 9.8% and higher prevalence of cancer among females and elderly population (70 years and older). Racial disparities differed significantly between respondents with and without history of cancer, with higher prevalence in Hispanic and multiracial minorities, 19% and 14%, respectively. We also report, differences in annual income are significantly associated with increased cancer prevalence in lower socioeconomic populations. Nineteen percent of participants who had annual income less than 25k were diagnosed with cancer. Additionally, analyzing the association between delayed medical care due to financial burden and its correlation with accessibility to age-appropriate cancer screening tools. We report significant differences in receipt of cancer screening among respondents, with consistently lower probabilities of receiving age-appropriate screening tools among participants who experienced delays in medical care due to cost, that applies to all screening tools. Among respondents who did not receive screening mammograms, 17% reported delays in medical care due to medical cost. Twelve percent of participants who did not receive screening colonoscopy suffered delays in medical care due to cost. Also, among participants who did not receive screening for prostate cancer with PSA testing, 11% reported delays in medical care due to cost. **Conclusions:** Health care disparities in cancer screening continue to persist including differences in socioeconomic classes and access to medical services. In this study, we report that patients with delayed access to medical services due to cost are not adequately receiving age-appropriate screening for cancer. Given the deleterious effects of delayed diagnosis and treatment of cancer, it is important that public health and clinical professionals utilize tools to improve cancer screening accessibility to minorities with socio-economic disparities. Research Sponsor: None.

1530 **Poster Session**

Comparison of clinician and model estimates of risk for hospitalization during systemic therapy for advanced cancer. *First Author: Lukas P Emery, Dartmouth-Hitchcock Medical Center, Lebanon, NH*

Background: Patients receiving treatment for advanced cancer are at substantial risk for unplanned hospitalization. A validated two-variable risk model can identify patients at increased risk for hospitalization. However, little is known about how model-based estimates of hospitalization risk compare with assessments of treating clinicians. **Methods:** We identified patients initiating a new line of systemic therapy for advanced non-hematologic cancer. For each patient, we assigned three categorical estimates of 30-day hospitalization risk. The first risk estimate was generated by a validated two-variable risk prediction model with inputs of pretreatment plasma sodium and albumin (PMID: 30995122); continuous risk scores were converted to risk tertiles. We solicited a second risk estimate by real-time survey of a treating oncology clinician; clinicians were instructed to estimate hospitalization risk as low, intermediate, or high, as compared with other patients. A third hybrid risk estimate retained the highest risk category from either the clinician or model risk assessment. We describe the agreement of clinician and model-based estimates of 30-day hospitalization risk, and we compare the sensitivity and specificity of clinician, model, and hybrid high-risk assessments, using McNemar's test. We compared discrimination of the three risk estimates via the area under the ROC curve (AUC). **Results:** We identified 104 patients with valid clinician and model hospitalization risk estimates and complete 30-day follow-up. The most common cancer type was lung cancer (27%), the median age was 68 years, and 62% of patients were male. 30-day hospitalization occurred in 21 patients (20.2%). There was moderate to poor agreement between clinician and model categorical estimates of hospitalization risk (weighted kappa = 0.245). The proportion of patients identified as high-risk by the clinician, model, and hybrid assessments was 15.4%, 26.0%, and 33.7%. Sensitivity and specificity of the high-risk categorization for 30-day hospitalization were 38% and 90% for the clinician assessment, 57% and 82% for the model assessment (NSS for comparison with clinician assessment), and 76% and 77% for the hybrid assessment (greater sensitivity [p = 0.008] and lesser specificity [p = 0.001] than clinician assessment). The AUC values for the clinician, model, and hybrid assessments were 0.674, 0.757, and 0.764, respectively. **Conclusions:** Compared with the estimate of a treating clinician, a two-variable risk model exhibited similar sensitivity and specificity for 30-day hospitalization risk. A hybrid risk assessment incorporating information from the risk model significantly improved on the sensitivity of the clinician risk assessment. Future research should test strategies to prevent hospitalizations by targeting interventions to high-risk patients. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

1531 **Poster Session**

People with cancer are likely to accept the COVID-19 vaccine, but politics tracks with attitudes: An inspire and COSMO survey. *First Author: Don S. Dizon, Lifespan Cancer Institute and Brown University, Providence, RI*

Background: Vaccines are a major step towards control of the COVID-19 pandemic. Estimates from multiple surveys of the general public indicate that 40 to 60% plan to be vaccinated, with some data suggesting that uptake differs by political leanings. The views of people with cancer on COVID-19 vaccination have not been reported. We report survey results of people with cancer, evaluating intent and attitudes toward COVID-19 vaccinations. **Methods:** An online survey included self-identified patients with cancer, ≥18 years old, in the Inspire Online Community (www.inspire.com). Invitation was restricted to only members of Inspire's cancer support groups who agreed to be contacted for research. Quantitative data were summarized with descriptive statistics. Data were analyzed by chi-square, ANOVA, and post hoc Tamhane' T2 testing. **Results:** 750 responded with the most common cancers represented being prostate (30%), thyroid (24%) ovarian (20%), bladder (8%) and breast (4%). 44% were between 46 and 65 years old and 48% were over 65. Of these, 38% reported being on active treatment. The majority were white (91%), female (56%) and had a bachelor's degree or higher (72%). Respondents represented the South (38%), West (28%), Midwest (20%), and Northeast (18%). Nearly half of respondents lived in a suburb near a large city. Almost 40% reported an annual income of > $100,000 and 13% reported income < $50,000/year. The proportion that would "definitely" or "most probably" get the COVID-19 vaccine was 80%, with significantly greater interest in people with prostate (85%), bladder (82%) and ovarian cancer (81%). Those with breast cancer reported the highest levels of being uncertain (23%) and 30% of those with thyroid cancer reported they would "probably" or "definitely" not get vaccinated. Older age, male sex, and college graduates were significantly more likely to get vaccinated. Concerns about side effects were reported by 54%, with younger patients significantly more concerned than those 66 years and older. Of 158 participants who listed other reasons they would not get vaccinated, 23% were concerned that the research and development was rushed and 11% worried about how it might interact with a compromised immune system. Using the 2020 Electoral College map to indicate political leaning at the state level, there was no significant difference in vaccine uptake, although significantly more people from blue states agreed that vaccination was the best defense against COVID-19 compared to those from red states (67 vs 33%, p < .05). **Conclusions:** People with cancer are much more interested in COVID-19 vaccination compared to the general public. Despite this, a large percentage of people with cancer reported distrust in either the government and/or the healthcare industry. Although vaccine attitudes tracked with political leanings at the state level, intention to get vaccinated did not. Research Sponsor: None.

1532 **Poster Session**

Choosing unwisely: Low-value care in older adults with a diagnosis of myelodysplastic syndrome. *First Author: Sudipto Mukherjee, Leukemia Program, Department of Hematology and Medical Oncology, Taussig Cancer Institute, Cleveland Clinic, Cleveland, OH*

Background: In tandem with the Choosing Wisely initiative, ASCO's Cost of Care Task Force has proposed a list of low-value (LV) procedures and therapies that may be of limited benefit to patients. Myelodysplastic syndrome (MDS) is the most common myeloid malignancy in the US. A complete diagnostic evaluation (CDE) of MDS requires a bone marrow biopsy, fluorescence in situ hybridization and chromosomal analysis. As a potential LV procedure, we evaluated receipt of CDE in MDS patients with isolated or no cytopenias and no transfusion dependence. **Methods:** Using national 2011-2014 Medicare data, we identified fee-for-service Medicare patients 66 years of age or older with an MDS diagnosis, one or no cytopenias, and no blood transfusions in the 16 weeks before or after an MDS diagnosis (n = 16,779). We examined the following variables that may have provided a clinical context to (or not to) pursue CDE – demographics (age, race, sex); number of Elixhauser comorbid conditions (< 5 vs >5); nursing home status, prior history of lymphoma, myeloma, MGUS and other cancers; chronic kidney disease (CKD); colonoscopy; and therapies received including erythropoiesis stimulating agents (ESAs), hypomethylating agents (HMAs) or lenalidomide. We conducted Classification and Regression Tree (CART) analysis, a machine learning approach to identify combinations of factors in patients with little clinical justification for CDE, and Cox proportional hazards regression analysis to compare survival outcomes between those with or without CDE. **Results:** Over half of our study population (51%) received CDE. Of those, 46.6% were 80 years of age or older, 4.8% were nursing home residents; and 33.6% had 5 or more chronic conditions. Results from CART analysis showed that among patients with an isolated cytopenia (e.g., isolated anemia), 46.0% of patients >80 years (n = 860), and 57.7% (n = 1,156) of those in the 66-79 age group underwent CDE in the absence of CKD, colonoscopy, HMA, or ESA. Among those with no cytopenia (n = 3890), 866 patients received CDE in the absence of HMA, ESA, or history of lymphoma or progression to leukemia. In adjusted analyses, no survival benefit was associated with receipt of CDE (p = 0.24). **Conclusions:** A substantial number of patients with an MDS diagnosis, isolated or no cytopenias, and no transfusion dependence received a CDE in the absence of other diagnoses, procedures, or therapies that may have explained the clinical decision to perform CDE. These procedures entail costs, pain and anxiety, but do not appear to yield useful information to guide clinical management, as evidenced by the comparable survival outcomes between patients who did and did not undergo CDE. To promote patient-centered care, careful patient selection that reduces unnecessary CDE in MDS patients should be a priority in clinical decision-making. Research Sponsor: Celgene (now Bristol Myers Squibb).

1533 **Poster Session**

The impact of COVID-19 on clinical cancer care: An individual-patient level analysis. *First Author: Lynsey M Drewett, Department of Oncology, University of Cambridge and Cambridge Breast Cancer Research Unit, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

Background: At the outset of the COVID-19 pandemic, concerns for the safety of patients receiving anti-cancer treatment coupled with pressures on healthcare services prompted review of standard clinical care pathways in the UK. Revised consensus treatment guidelines were generated. Individual patient-level data regarding actual treatment modifications implemented in clinical practice are lacking. **Methods:** All anti-cancer treatment plans of patients with breast, lung, renal, hepatopancreatobiliary, CNS cancers and melanoma attending a single academic cancer centre in the UK between 16 March and 31 May 2020 were reviewed and any modifications to standard practice were documented. The effect of patient (age, ECOG performance status [PS], sex) and cancer (site, stage, treatment intent) characteristics on likelihood of treatment modifications were analysed using univariable and multivariable models. **Results:** Treatment plans for 925 patients were reviewed: median patient age was 63 (range 19-97); 66% were female; 73% were PS 0-1; 45% were on a curative pathway. Overall, 47% of all patients had one or more modifications made to their treatment plans: 53% of surgeries (primarily being delayed); 41% of radiotherapy (primarily reduced fractions delivered); 39% of systemic therapy prescriptions. 96-100% of all systemic therapy modifications resulted in treatment de-escalation, excluding endocrine therapy used as a bridge to defer primary breast cancer surgery. Biological therapy was predominantly interrupted (49%), immunotherapy was mostly omitted entirely (36%), and chemotherapy varied between interruptions (39%) or omissions (31%). Relative to the likelihood of modification to chemotherapy, surgery was significantly more likely to be modified (OR 1.69 95%CI 1.20-2.38). Chemotherapy, radiotherapy, biological therapy and immunotherapy were all modified to a similar degree. Multivariate analysis identified PS ≥ 2 (OR 1.79, 95% CI 1.18–2.75), but not patient age, as a predictor of treatment modification. Some tumour types were less likely to undergo any modification: stage 1-3 lung (OR 0.13, 95%CI 0.04-0.37), stage 4 lung (OR 0.26 95%CI 0.24–0.60) and stage 4 renal cancer (OR 0.22 95%CI 0.09-0.52). **Conclusions:** This single centre analysis demonstrated almost half of cancer patients had their treatment modified, the overwhelming majority resulting in treatment de-escalation. The impact of the treatment modifications on overall cancer patient outcomes remains to be determined. Research Sponsor: None.

1534 **Poster Session**

Are National Cancer Institute Cancer Centers (NCI-CC) providing adolescents and young adults (AYA) with cancer focused clinical services? A national survey. *First Author: Katherine Daunov, Case Western Reserve University, Cleveland, OH*

Background: AYA patients with cancer have inferior outcomes compared to their pediatric and adult counterparts. The NCI recommends they be treated by AYA focused healthcare professionals within an AYA oncology program. This survey captures the current landscape of AYA oncology care in the United States. **Methods:** An online survey was sent to 272 cancer centers in September 2020, in coordination with Teen Cancer America and included all clinically designated NCI-CC. The survey asked about the presence of an AYA program, types of patients, dedicated resources, clinical space, type of providers, associated support services, educational efforts, importance of AYA oncology care, and how well these services are provided. **Results:** In total, we received 93 responses, a 34% response rate, including 50 NCI centers, a 72% response rate. Only half (49%) of NCI-CC reported having an AYA program, and 70% were started in the past 5 years. One-third (32%) of centers reported plans to start an AYA program. Most programs included patient ages from $\geq$15 (56%) to $\leq$39 (63%) with a variety of cancers – most commonly hematologic (49%) and sarcoma (49%) and least commonly lung (36%), breast (38%), and head and neck cancer (38%). AYA programs are generally embedded in both adult and pediatric oncology services (63%). On average, cancer centers reported seeing 25-50 new AYA patients/month and 100-200 follow-up visits/month. Few programs reported a dedicated inpatient space (4%) or outpatient space (9%). Most NCI-CC have supportive services available for all oncology patients, but fewer of these services were dedicated specifically to AYA patients: navigators (92% vs. 71%), social work (98% vs. 57%), psycho-oncology (96% vs. 54%), dietician (98% vs. 24%), physical therapy (98% vs. 18%), chaplaincy (98% vs. 18%), and child life (83% vs. 26%). Other services available to the AYA population included sexual health (62%), academic support (62%), and career resources (36%). A minority of centers (30%) provided AYA training to their staff. A majority of NCI-CC felt AYA programs were important-very important (60%). They reported providing good-excellent overall AYA care (59%), but this dropped to 22% for sexual health and education of staff, which was relatively consistent across centers (Table). **Conclusions:** This survey is the first ever national survey to assess AYA oncology programs. Despite greater emphasis on the AYA cancer population, only half of NCI-CC report having a dedicated program, and areas of improvement include education of staff and sexual health services for patients. Self-report of providing good to excellent AYA care in specific areas. Research Sponsor: None.

	Overall	Fertility	Psycho-Oncology	Survivorship	Symptoms	End of Life	Research	Education	Sexual Health
NCI-CC	58%	65%	65%	65%	57%	49%	37%	22%	22%
Academic	67%	71%	83%	61%	67%	67%	44%	22%	39%
Community	59%	53%	47%	53%	53%	68%	42%	21%	21%

1535 **Poster Session**

Patterns in cancer management changes for patients with COVID-19 in northern California. *First Author: Michael Glover, Stanford University Medical Center, Stanford, CA*

Background: The COVID-19 pandemic affected oncology practice in ways that are still evolving. In particular, COVID-19 has led to changes in cancer treatment for patients (pts) infected with COVID, which may have long-term implications for both COVID and cancer-related outcomes. In this retrospective analysis, we describe changes in cancer management over time for cancer pts diagnosed with COVID-19 at two academic institutions in Northern California. **Methods:** Adult and pediatric pts diagnosed with COVID-19 receiving active cancer management, defined as therapy/surgery/diagnostics within 3 weeks of COVID diagnosis, were identified through the EMR. Patients whose care was affected by COVID-19 were identified and analyzed for significant intra-group differences with regards to management type, treatment intent, and the time of COVID-19 diagnosis ("early" was defined as March to June 2020 and "late" as July 2020 to January 2021). The duration and characteristics of such changes were compared across subgroups. Chi-squared test was used to compare the incidence of delays between subgroups. **Results:** Among 134 COVID-positive pts on active cancer management, 83 (62%) had significant changes in management that consisted primarily of treatment delays. More delays were identified in patients treated with curative intent earlier in the course of the pandemic compared to later (OR 4.1, p=0.022). This difference was not seen among pts treated with palliative intent. In addition, pts on oral (PO) therapy were significantly less likely to have treatment changes than those on IV/IM therapy (OR 0.32, p=0.005). This difference was driven by a decrease in management changes for those on PO therapy in the later time period (OR 0.27, p=0.026). Pts diagnosed later were more likely to have delays due to clinical reasons rather than institutional policy (OR 6.2, P<.005). The median delay in both time frames was 21 days. Comparison of subgroups is shown in the table. **Conclusions:** We found significant changes in management of cancer pts with COVID-19 that evolved over time. Oncologists have become increasingly willing to continue therapy for cancer pts treated with curative intent and pts on oral therapy. Changes in cancer therapy have become more frequently related to patient clinical status, and less so due to institutional policies. It will be important to analyze how these changes in management are ultimately reflected in cancer outcomes in order to equip patients and oncologists to react to the next pandemic. Research Sponsor: Stanford Cancer Center.

Characteristic	Active cancer management (N=134)	Incidence of delay in management (N=83)	P Value for delays (N=83)
Date			
March-June	55 (41%)	38 (46%)	0.21
July-January	80 (60 %)	45 (54%)	
Management			
IV/IM Therapy	56 (42%)	40 (48%)	.04*
PO therapy	58 (43%)	26 (31%)	
Other	20 (15%)	17 (20%)	
Intent			
Curative	51 (38%)	27 (33%)	0.09
Palliative	83 (62%)	56 (67%)	
Reason			
Clinical		41 (49%)	
Non-clinical		42 (51%)	

*(IV/IM vs PO).

1536 **Poster Session**

Feasibility of fully remote administration of problem-solving skills training (PSST) to adult cancer survivors in community settings. *First Author: Katia Noyes, University of Rochester Medical Center, Rochester, NY*

Background: Cancer survivors experience significant stress throughout cancer treatment and especially during transition back to normal life. These stressors are particularly severe for rural or socially disadvantaged patients with limited access to care. Improving their problem-solving skills is known to help patients make reasoned and timely decisions about survivorship care that reduce stress and enhance quality of life, physical and social functioning, and overall cancer prognosis. This pilot implementation study examined barriers to and facilitators of providing Problem-Solving Skills Training (PSST) to adult cancer survivors and their caregivers in community settings. **Methods:** Patients (n = 50) who completed their definitive cancer treatment and cancer survivorship visit within the previous 6 months were recruited from two regional cancer centers and affiliated community cancer clinics. Patients with NCCN distress level >2 were randomly assigned to either care as usual (CAU) or 8 weekly PSST sessions using the Bright IDEAS system of teaching problem solving. Training was offered by a trained therapist in person at the patient's preferred location or remotely. Patients were invited but not required to include a supportive other (SO). Patient outcomes were assessed at baseline (T1), the end of the intervention/3 months (T2), and 3 months post intervention/6 months (T3). We examined patient and caregiver preferences for mode of communication and therapy, barriers to PSST participation, and adherence rates. An independent consultant interviewed patients and caregivers about factors that promote or inhibit intervention sustainability and its wider adaptation and usefulness. **Results:** Average age of the participants was 63 years (45-87) with gender, racial and ethnic distributions representative of the local population (64% women, 88% white). Women were 80% less likely to include a SO than men. Among the third of the patients recruited fully remotely, 50% preferred receiving consent materials via regular mail and 18% preferred electronic communication. Among the two patients lost to follow-up before PSST completion and one patient who withdrew despite reporting significant distress, none had a SO in the study. Seventy-six percent of the PSST patients completed the training (defined as > 6 sessions). After study completion, all patients and caregivers reported high satisfaction with Bright IDEAS and high probability of continuing to use the skills learned. **Conclusions:** Despite significant distress and numerous reported social challenges, patients and caregivers in the PSST arm demonstrated high adherence, skill retention and overall satisfaction. Future research should be tailored to accommodate the preferred type of communication and recruitment approaches of the targeted population and emphasize the positive role of informal caregivers. Clinical trial information: NCT03567850. Research Sponsor: U.S. National Institutes of Health.

1537 **Poster Session**

The HOLA COVID-19 study: Evaluating the impact of caring for patients with COVID-19 on cancer care delivery in Latin America. *First Author: Carolina Bernabe Ramirez, Essen Medical Group, Bronx, NY*

Background: The severe acute respiratory syndrome 2 (SARS-cov-2) virus causing COVID-19 has brought great challenges to global health services affecting cancer care delivery, outcomes, and increasing the burden in oncology providers (OP). Our study aimed to describe the challenges that OP faced while delivering cancer care in Latin America. **Methods:** We conducted an international cross-sectional study using an anonymous online survey in Spanish, Portuguese, and English. The questionnaire included 43 multiple choice questions. The sample was stratified by OP who have treated patients with COVID-19 versus those who have not treated patients with COVID-19. Data was analyzed with descriptive statistics and Chi-square tests. **Results:** A total of 704 OP from 20 Latin American countries completed the survey (77% of 913 who started the survey). Oncologists represented 46% of respondents, followed by 25% surgical-oncologists. Of the respondents, 56% treated patients with COVID-19. A significant proportion of OP reported newly adopting telemedicine during COVID-19 (14% vs 72%, p=0.001). More than half (58%) of OP reported making changes to the treatments they offered to patients with cancer. As shown in the table, caring for patients with COVID-19 significantly influenced practice patterns of OP. Access to specialty services and procedures was significantly reduced: 40% noted significantly decreased or no access to imaging, 20% significantly decreased or no access to biopsies, 65% reported delays in surgical oncology referrals, and 49% in radiation oncology referrals. A vast majority (82%) reported oncologic surgeries were delayed or cancelled, which was heightened among those treating patients with COVID-19 (87% vs 77%, p=0.001). **Conclusions:** The COVID-19 pandemic has significantly affected the way cancer care is delivered in globally. Although changes to healthcare delivery are necessary as a response to this global crisis, our study highlights the significant disruption and possible undertreatment of patients with cancer in Latin America that results from COVID-19. Research Sponsor: None.

	Cared for patients with COVID-19 (%)	Did not care for patients with COVID-19 (%)	P-value
Changed to a less effective CT regimen with less side effects	53	39	0.006
Stopped CT in patients previously on treatment	29	18	0.001
Delayed CT start	45	28	0.001
Cancelled or stopped adjuvant CT	25	18	0.026
Discontinued palliative CT	40	28	0.001
Cancelled adjuvant RT	22	19	0.265
Used less multi-drug CT regimens	41	32	0.013
Increased use of oral CT	53	41	0.002
Cancelled or delayed concurrent chemoradiation	35	25	0.004

Abbreviations: CT = chemotherapy; RT = radiation therapy.

1538 **Poster Session**

Bridging the gaps between tertiary and community care networks: Results from a southern California survey research analysis. *First Author: Alex Chehrazi-Raffle, City of Hope National Medical Center, Duarte, CA*

Background: Although many tertiary cancer centers offer access to myriad research protocols, the majority of patients nevertheless receive treatment at community practices. We sought to examine the barriers that hamper clinical collaboration between tertiary and community practice environments in Southern California. **Methods:** A 31-item survey was distributed to community and tertiary oncologists using REDCap, a browser-based electronic data capture system. Survey questions assessed the following attributes: demographics and features of clinical practice, referral patterns, availability and knowledge pertaining to clinical trials, strategies for knowledge acquisition, and integration of community and tertiary practices. **Results:** The survey was distributed to 98 oncologists, 85 (87%) of whom completed it in full. The most common institutional affiliations were City of Hope Comprehensive Cancer Center (58%), University of California, Los Angeles (10%), and Cedars Sinai Medical Center (8%). In total, 52 (61%) respondents were community practitioners and 33 (38%) were tertiary oncologists. A majority (56%) of community oncologists defined themselves as general oncologists whereas almost all (97%) tertiary oncologists reported a subspecialty. Clinical trial availability was the most common reason for pt referrals to tertiary centers (73%). The most frequent barrier to tertiary referral was financial considerations (59%). Clinical trials were offered by 97% of tertiary practitioners as compared to 67% of community oncologists (p = 0.001). Of note, while a majority of tertiary center providers (52%) described the primary value of community practices to be a source of referrals for clinical trials, most community oncologists (82%) reported only a minimal-to-moderate understanding of clinical trials available at regional tertiary centers. **Conclusions:** Community oncologists refer patients to tertiary centers primarily with the intent of clinical trial enrollment; however, significant gaps exist in their knowledge of trial availability. Our results identify the need for enhanced communication and collaboration between community and tertiary providers to expand patients' access to clinical trials. Research Sponsor: None.

1539 **Poster Session**

An automated EHR-based tool to facilitate patient identification for biomarker-driven trials. *First Author: Shailendra Lakhanpal, Birmingham Hem Onc, Mountain Brk, AL*

Background: Clinical trial eligibility increasingly requires information found in NGS tests; lack of structured NGS results hinders the automation of trial matching for this criterion, which may be a deterrent to open biomarker-driven trials in certain sites. We developed a machine learning tool that infers the presence of NGS results in the EHR, facilitating clinical trial matching. **Methods:** The Flatiron Health EHR-derived database contains patient-level pathology and genetic counseling reports from community oncology practices. An internal team of clinical experts reviewed a random sample of patients across this network to generate labels of whether each patient had been NGS tested. A supervised ML model was trained by scanning documents in the EHR and extracting n-gram features from text snippets surrounding relevant keywords (i.e. 'Lung biomarker', 'Biomarker negative'). Through k-fold cross-validation and l2-regularization, we found that a logistic regression was able to classify patients' NGS testing status. The model's offline performance on a 20% hold-out test set was measured with standard classification metrics: sensitivity, specificity, positive predictive value (PPV) and NPV. In an online setting, we integrated the tool into Flatiron's clinical trial matching software OncoTrials by including in each patient's profile an indicator of "likely NGS tested" or "unlikely NGS tested" based on the classifier's prediction. For patients inferred as tested, the model linked users to a test report view in the EHR. In this online setting, we measured sensitivity and specificity of the model after user review in two community oncology practices. **Results:** This NGS testing status inference model was characterized using a test sample of 15,175 patients. The model sensitivity and specificity (95%CI) were 91.3% (90.2, 92.3) and 96.2% (95.8, 96.5), respectively; PPV was 84.5% (83.2, 85.8) and NPV was 98.0% (97.7, 98.2). In the validation sample (N = 200 originated from 2 distinct care sites), users identified NGS testing status with a sensitivity of 95.2% (88.3%, 98.7%). **Conclusions:** This machine learning model facilitates the screening for potential patient enrollment in biomarker-driven trials by automatically surfacing patients with NGS test results at high sensitivity and specificity into a trial matching application to identify candidates. This tool could mitigate a key barrier for participation in biomarker-driven trials for community clinics. Research Sponsor: This study was sponsored by Flatiron Health, which is an independent subsidiary of the Roche Group.

1540 **Poster Session**

Transitioning ifosfamide based chemotherapy to the outpatient setting: A model of implementation of transitioning chemotherapy outpatient in a safety net hospital. *First Author: Cindy Banh, University of Arizona College of Pharmacy, Tucson, AZ*

Background: Ifosfamide displays clinical activity against germ cell tumors as well as soft-tissue and bone sarcomas. It is used in different oncology regimens and commonly administered inpatient due to patient monitoring and side effect management. Transitioning certain chemotherapy regimens to the outpatient setting provides a novel approach to treating patients while maximizing patient satisfaction and decreasing total patient care costs[1]. There is limited data and protocol development to transition ifosfamide regimens to the ambulatory setting. This study's purpose is to characterize a pharmacy managed ambulatory oncology workflow for transitioning ifosfamide based-regimens to the outpatient setting. **Methods:** A retrospective cohort chart review was conducted at a single center and included patients 18 years and older receiving at least one cycle of ifosfamide therapy between September 1, 2013 and July 31, 2019. The primary outcome was to evaluate the side effect profile and cost of treatment of ifosfamide. The secondary endpoint included number of hospitalizations. The adverse event grading system was defined using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. The highest grade observed for adverse effects was documented for every cycle of each patient. The cost was evaluated by labs ordered, drug used, length of stay in the hospital for chemotherapy or adverse reactions. **Results:** Ifosfamide therapy of 86 patients (57 OP, 29 IP) was reviewed. The predominant OP regimens were adriamycin-ifosfamide-mesna (AIM) with 43.9% and ifosfamide-etoposide (IE) with 29.8%. Grade 4 anemia, thrombocytopenia, and neutropenia were most frequent in IP vs OP therapies (22.9% IP vs 4.3% OP, 21.6% IP vs 9.2% OP, and 22.8% IP vs 19.6% OP respectively). Neutropenic fever (NF) occurred in 20 OP patients which were predominantly treated with AIM or IE, and led to average hospital stay of 6 days. Neurotoxicity, treated with methylene blue (MB), occurred in 4 OP patients. OP therapy saved a total of 783 hospital days, leading to a cost savings of $2,103,921. **Conclusions:** Transitioning to outpatient therapy is feasible for academic and community infusion centers. Administration of chemotherapy in the outpatient setting has shown to be safe, well-tolerated, and associated with decreased total cost of care, thereby lowering costs under the oncology care model when compared with inpatient chemotherapy costs. Research Sponsor: None.

1542 **Poster Session**

Trends of cancer associated with modifiable behavior in the U.S.: Is there a difference based on age, gender, or race? *First Author: Cheng-I Liao, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan*

Background: To examine trends in modifiable behaviorally related cancers among men and women in the United States. **Methods:** Data were obtained from the United States Cancer Statistics (USCS) database for all cancers diagnosed between 2001 and 2017. Alcohol-associated cancers, HPV-associated, obesity-associated, physical inactivity-associated, and tobacco-associated were defined using ICD-O-3 site codes. SEER*Stat 8.3.8 and Joinpoint regression program 4.8.0.1 were used to calculate the trends of associated cancers expressed per 100,000. **Results:** In 2017 the incidence of cancers in women associated with alcohol, smoking and obesity were 168/100,000, 134/100,000 and 121/100,000 respectively. Based on analysis of trends of women from 2001 to 2017, alcohol, smoking and physical inactivity related cancers decreased with an annual percent change (APC -0.51%, -0.96%, -0.92% respectively, $p < 0.001$). However, there was no significant change in obesity, HPV, or post menopausal female breast cancer related cancers (APC: 0.07%, 0.09%, -0.08% respectively, $p = 0.303$, 0.181, 0.569). Based on age, in women less than 65, rates of obesity related cancers are increasing. Based on racial groups, all rates of cancer associated with modifiable factors are decreasing, however Hispanic women have an increasing rate of obesity related cancers (APC 0.46%, $p < 0.001$). When examining differences in region, all rates of cancer are decreasing or unchanged except the south has an increasing rate of obesity related cancer (APC 0.28%, $p < 0.001$). Using a projection model, obesity will become the highest incidence cancer in Hispanic women by 2035, surpassing alcohol and tobacco. In 2017 the incidence of cancers in men associated with tobacco, obesity, and alcohol were 209/100,000, 111/100,000 and 81/100,000 respectively. Based on analysis of trends in men alcohol, smoking, physical inactivity and obesity related cancers decreased (APC -1.42%, -1.59%, -3.15%, -0.41% respectively, $p < 0.001$). HPV related cancers have increased (APC 2.36%, $p < 0.001$). In men less than 60 years old, the rates of obesity related cancers are increasing. Using a prediction model, obesity is predicted to surpass tobacco as the most common social cause of cancer in 2020 for men 35-39, 2024 in men 40-44 and in 2030 in men 45-49. **Conclusions:** In women, most modifiable factors associated with cancer are decreasing except in obesity and HPV related cancers. In men, these rates of cancer are decreasing except HPV related cancers. However, rates of obesity related cancers are on the rise in Hispanic women and younger men. Obesity is set to become the major modifiable factor for many associated cancers. Research Sponsor: Fisher Foundation and Denise Cobb Hale.

1543 **Poster Session**

Dedicated clinical trial tissue tracking database to improve turn-around time at high-volume center. *First Author: Peter Blankenship, Sarah Cannon Research Institute, Nashville, TN*

Background: Tissue requirements in oncology clinical trials are increasingly complex due to prescreening protocols for patient selection and serial biopsies to understand molecular-level treatment effects. Novel solutions for tissue processing are necessary for timely tissue procurement. Based on these needs, we developed a Tissue Tracker (TT), a comprehensive database for study-related tissue tasks at our high-volume clinical trial center. **Methods:** In this Microsoft Access database, patients are assigned an ID within the TT that is associated with their name, medical record number, and study that follows their request to external users: pathology departments, clinical trial coordinators and data team members. To complete tasks in the TT, relevant information is required to update the status. Due to the high number of archival tissue requests from unique pathology labs, the TT has a "Follow-Up Dashboard" that organizes information needed to conduct follow-up on all archival samples with the status "Requested". This results in an autogenerated email and pdf report sent to necessary teams. The TT also includes a kit inventory system and a real-time read only version formatted for interdepartmental communication, metric reporting, and other data-driven efforts. The primary outcome in this study was to evaluate our average turnaround time (ATAT: average time from request to shipment) for archival and fresh tissue samples before and after TT development. **Results:** Before implementing the TT, between March 2016 and March 2018, we processed 2676 archival requests from 235 unique source labs resulting in 2040 shipments with an ATAT of 19.29 days. We also processed 1099 fresh biopsies resulting in 944 shipments with an ATAT of 7.72 days. After TT implementation, between April 2018 and April 2020, we processed 2664 archival requests from 204 unique source labs resulting in 2506 shipments (+28.0%) with an ATAT of 14.78 days (-23.4%). During that same period, we processed 1795 fresh biopsies (+63.3%) resulting in 2006 shipments (+112.5%) with an ATAT of 6.85 days (-11.3%). **Conclusions:** Oncology clinical trials continue to evolve toward more extensive tissue requirements for prescreening and scientific exploration of on-treatment molecular profiling. Timely results are required to optimize patient trial participation. During the intervention period, our tissue sample volume and shipments increased, but the development and implementation of an automated tracking system allowed improvement in ATAT of both archival and fresh tissue. This automation not only improves end-user expectations and experiences for patients and trial sponsors but this allows our team to adapt to the increasing interest in tissue exploration. Research Sponsor: None.

1544 **Poster Session**

Oncology patient and provider preferences regarding rapid radiology result release to online portals. *First Author: Jonathan Bleeker, Sanford Health, Sioux Falls, SD*

Background: Spurred by changes in legislation and technology, rapid patient access to medical results has never been higher. Many health systems now release results of radiology tests within 24 hours of completion, meaning patients may see results before being able to discuss them with the ordering provider. Generally, surveys have demonstrated that patients are in favor of rapid result availability, but research on rapid result release to oncology patients with distinct concerns is scant. **Methods:** Starting in February 2020, oncology providers throughout Sanford Health, a multi-site primarily rural integrated practice in the upper Midwest were invited to complete an online survey regarding their opinions on rapid result release. Starting in February 2020, oncology patients were invited to complete a similar survey. This survey was open until August 2020, when 100 patients had completed the survey; both surveys contained both categorical and narrative results. **Results:** Oncology providers had a generally more negative opinion of rapid radiology result release to online portals compared to patients. 65% of patients believed radiology results should be released within 24 hours of resulting; only 12% of providers shared this view. 66% of providers shared that they did not feel comfortable with patients' ability to interpret radiology results and only 13% felt that "normal" results should be released immediately to an online portal; this number decreased to 3% when results were "abnormal". Patient opinions on appropriate result release were impacted by test results as well. For "normal" radiology results, 50% of patients favored initial communication be via online portal without discussion with a provider; for "abnormal" results, this number decreased to 28%. 43% of patients had learned of an "abnormal" result via online portal before discussion with a provider; 66% of these patients felt that this was a positive which allowed them to process information prior to the visit; 33% felt that it created undue anxiety. 94% of providers reported having a patient contact them regarding a test result prior to a planned visit, with 60% providers sharing this happens at least once weekly. When asked what improvements could be made to the system currently in place at Sanford, 80% of providers suggested holding radiology results until direct communication with the provider can occur; only 8% of patients suggested the same intervention. **Conclusions:** Rapid result release is generally a patient satisfier, although oncology patients do distinguish abnormal from normal results in terms of rapid release. It is a dissatisfier for providers both due to concerns regarding patients' ability to interpret results and due to excess work created by rapid release. Ongoing work should focus on ways to allow patients to access resources to make medical results more interpretable if reviewed prior to provider visits. Research Sponsor: None.

1545 **Poster Session**

Veterans on anticancer medications in rural and community environment support (VA CARES) program: A pharmacist-led telemedicine medication management program for veterans receiving oral antineoplastic therapies through the MISSION Act. *First Author: Regan Healy, George E. Wahlen Department of Veterans Affairs Medical Center, Salt Lake City, UT*

Background: Cancer therapies are leveraging oral targeted treatments over traditional cytotoxic chemotherapy (CT) at an increasing rate. Compared to CT, use of oral antineoplastic treatments (OATs) shift some of the burden of medication management onto patients. To address these challenges, several health systems have developed multidisciplinary OAT management teams or 'clinics' whereby an Oncology Clinical Pharmacist (OCP) collaborates with oncology teams to ensure optimal use of these agents. Through the VA MISSION Act of 2018, Veterans can be prescribed treatments in the community which are dispensed by VA. These Veterans often live in rural areas and may lack access to comprehensive medication management resources. **Methods:** The VA CARES Program is a telemedicine medication management 'clinic' and care delivery model for patients receiving OATs leveraging custom designed health information technology (HIT) tools to remotely coordinate OAT related care. Veterans are automatically enrolled in the program if they have OATs prescribed by community providers which are to be dispensed by VA . An OCP provides telemedicine medication management services. The OCP performs a screening assessment, ensures appropriate indication and dosing, reviews baseline laboratory results, and performs a thorough drug-drug interaction analysis. The OCP then provides OAT education. Throughout the duration of therapy the OCP ensures necessary therapeutic monitoring, and regularly follows up with the Veterans. Subsequent encounters are to assess knowledge, adherence, toxicities, new drug-drug interactions, and need for OAT refills. The outcome measures for the VA CARES Program include safety (number and type of pharmacist interventions), economic benefits (cost savings or cost avoidance), and patient satisfaction. **Results:** In the initial 13 months, the VA CARES Program screened N = 78 and enrolled N = 64 (82%) Veterans from three VA medical facilities in VISN-19 from January 2020 to January 2021. The CPS performed n = 342 telemedicine visits and n = 80 interventions leading to improved safety, effectiveness, and/or an economical benefit. The most common interventions included detection and/or prevention of drug-drug interactions (n = 45) and adverse events (n = 18), drug not indicated (n = 13), alternative therapy suggested (n = 7), and limited-quantity dispensed (n = 7). The CPS interventions saved an estimated $210,864 in medication-related costs or avoidance. The Veterans surveyed were highly satisfied with the program services. **Conclusions:** Telemedicine delivery of oncology medication management by an OCP across systems is feasible, and provides clinical and economic benefits. Research Sponsor: U.S. Dept. of Veterans Affairs, Health Services Research and Development Service (RVR 19-483).

1546 **Poster Session**

Utilization of preoperative breast MRI among women with newly diagnosed breast cancer. *First Author: I-Wen Pan, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The use of preoperative (pre-op) breast MRI remains controversial. Current practice may rely on patient characteristics and providers' clinical judgment. This national study examined factors associated with pre-op breast MRI among women with newly diagnosed breast cancer (BC) and explored sources of variations. **Methods:** We applied the Nattinger algorithm to identify women with incident BC diagnosed between Mar 2008 and Dec 2018 from OPTUM Clinformatics database. Patients who had 26 months of full enrollment, 14 months before and 12 months after the first (index) BC surgery, and no pre-op radiotherapy were included. We defined pre-op MRI as patients who had an MRI between the date of BC diagnosis and date of index surgery. We conducted multivariable logistic regression models to examine factors associated with pre-op MRI and performed separate analyses for elderly (age > = 65) and non-elderly (age < 65) women. **Results:** 61,865 women (non-elderly: 27,309, elderly: 34,556) were included in the analysis. The crude rate of pre-op MRI increased from 7.4% in 2008 to 14.6% in 2018 (p-value < .001). For the non-elderly, women who were older (adjusted rates: 60-64, 10% vs 20-49, 12.1%), had no distant metastasis (10.6% vs. 12.3% with metastasis), no neoadjuvant chemotherapy (9.9% vs 15.0% with neoadjuvant), and 2 or more comorbidities (9.0% vs. 11.1% with zero comorbidity) were less likely to undergo pre-op MRI (all p-value < .001). Compared to white women (adjusted rate 10.6%), African Americans were more likely to have pre-op MRI (12.7%, p < .001) and Hispanics were less likely (8.14%, P < .001). There was no association between Health Management Organization (HMO) status and receipt of pre-op MRI among non-elderly. For elderly women, older age, more comorbidities, no distant metastasis, and no neoadjuvant chemotherapy were similarly associated with less pre-op MRI use. There was no significant association between race and receipt of pre-op MRI. Moreover, elderly women with HMO insurance were less likely to receive pre-op MRI. In both age groups, we observed wide geographic variations, with significant interaction between census division and HMO enrollment among elderly group only (Table). **Conclusions:** The use of pre-op MRI nearly doubled from 2008 and 2018. In addition to demographic and clinical characteristics, regional practice pattern variations and insurance type played a key role in the receipt of pre-op MRI among newly diagnosed breast cancer patients. Future study to understand this phenomenon is warranted. Research Sponsor: Alliance.

Census division	Age < 65 (%)	Non HMO, Age > = 65 (%)	HMO, Age > = 65 (%)
New England	5.13	11.04	7.52
Mid Atlanta	9.91	13.06	7.58
East North Central	11.46	20.41	16.92
West North Central	18.33	16.61	15.13
South Atlanta	11.36	14.04	11.76
East South Central	9.39	17.99	10.00
West South Central	10.05	10.47	0.40
Mountain	9.37	15.68	1.17
Pacific	4.03	8.60	0.68

1547 **Poster Session**

Combining hematoxylin and eosin (H&E) stained images and RNA sequencing (RNA-Seq) data to predict overall survival (OS) in patients with non-small cell lung cancer (NSCLC). *First Author: Teresa M Karrer, Roche, Basel, Switzerland*

Background: IMpower150 was a phase 3 clinical trial that evaluated the efficacy of atezolizumab in patients with metastatic nonsquamous NSCLC; it demonstrated no significant OS benefit in the ACP (atezolizumab+carboplatin+paclitaxel) arm vs the BCP (bevacizumab+carboplatin+paclitaxel) control arm (hazard ratio [HR]=0.85; 95%CI, 0.71-1.03). The objective of this analysis was to identify a subpopulation of patients that benefits from ACP using H&E stained images and RNA-Seq data. **Methods:** Spatial statistics algorithms were applied to the coordinates of tumor cells and lymphocytes of the H&E stained images to capture spatial heterogeneity of the tumor microenvironment. The normalized and log-transformed RNA-Seq data underwent a nested feature selection procedure using a Cox proportional hazard model with L1 regularization and stability selection. Cutoffs for gene selection were determined using a permutation strategy with a false discovery rate <0.001. To investigate the association between the 41 derived spatial features, significant genes and OS, a Cox proportional hazard model with L2 regularization was fitted only for the ACP group. Survival groups were further identified using nested Monte Carlo Cross Validation to prevent over-fitting. **Results:** A total of 236 ACP and 235 BCP patients who had both H&E stained images and RNA-Seq data were analyzed. In the predicted long survival group, ACP patients had significantly longer median OS vs BCP patients based on H&E stained images (HR=0.61; 95%CI, 0.41-0.90;*P*=0.013) and RNA-Seq data (HR=0.64; 95%CI, 0.41-0.99;*P*=0.042). The combination of both modalities further improved the OS benefit between the arms (HR=0.44; 95%CI, 0.27-0.73;*P*=0.001). Data-driven selection of genes relevant for the prediction of OS included-*MAML3*,*AC024475.4*,*RGPD1*,*LCE3D* and*AC004156.1*. **Conclusions:** Our approach was able to stratify a subpopulation of patients that significantly benefited from ACP compared with BCP treatment, particularly when integrating both H&E stained images and RNA-Seq data, which demonstrated the complementary value of both modalities. Our results could inform the development of a companion diagnostic that predicts individualized treatment response. Clinical trial information: NCT02366143. Research Sponsor: Roche.

1548 **Poster Session**

Use of deep learning frameworks to detect super-responder and super-survivor stage IV squamous non-small-cell lung cancer (NSCLC) patients treated with a gemcitabine and cisplatin combination. *First Author: Carlos Maria Maria Galmarini, Topazium Artificial Intelligence, Madrid, Spain*

Background: Synthetic fingerprints integrate clinical data within computational models allowing the identification of particular clinical subpopulations at a given moment. We here describe a deep learning strategy to detect super-responder and super-survivor patients with squamous NSCLC by setting up synthetic fingerprints and using unsupervised deep learning frameworks (UDLF). **Methods:** Through www.projectdatasphere.org, we accessed the control arm clinical data (N = 548) of the randomised phase III SQUIRE trial (NCT00981058). This trial included patients with stage IV squamous NSCLC who had not received previous chemotherapy. These patients were treated with gemcitabine 1,250 mg/m^2 (IV, 30-min infusion, d1/d8) and cisplatin 75 mg/m^2 (IV, 120 min infusion, d1) on a 3-week cycle for a maximum of six cycles. Synthetic fingerprints resulted of the integration of 180 features collected during the first 3 cycles including demographics, medical history, physical exam, concomitant medication, histopathology, PK parameters, adverse events and common labs. These fingerprints were used as input for the UDLF. The resultant clusters were correlated with overall-response rate (ORR) and overall survival (OS). **Results:** After missing data removal and feature standardization, 192 patients were eligible for the study. The UDLF was able to generate two different clusters: P0 (n = 107) and P1 (n = 84). ORR was higher in the P1 than in the P0 cluster (mean 41.6% [95% CI 31.7-52.3] vs. 28.0% [95% CI 20.4-37.2]; p = 0.04). OS was significantly longer in the P1 than in the P0 cluster (median 13.2 months vs. 9.7 months; hazard ratio 1.56 [95% CI 1.12-2.17; p = 0.008]). Feature contribution analysis showed that P1 had more patients and more events of grade III/IV neutropenia. In contrast, P0 had more patients and more events of grade III/IV nausea and vomiting. Other major differences were observed on vital signs (SBP, DBP, HR, RR, Temp), concomitant medication (osmotically-active laxatives, dexamethasone, furosemide, granisetron and ondansetron) and in hematological (RBC, HGB, HCT, MCV, WBC, neutrophils, monocytes, lymphocytes) and biochemistry (albumin, globulins, ALP, LDH, creatinine, BUN, urea, sodium, magnesium and phosphate) tests. **Conclusions**: Our findings show that synthetic fingerprints and subsequent deep learning analysis can be of use to identify patients with clinical characteristics associated with high-response rate and long-term survival. Research Sponsor: None.

1549 **Poster Session**

Predicting disease progression and mortality in metastatic colorectal cancer patients (mCRC) through an artificial intelligence-based analytical tool. *First Author: Carlos Maria Maria Galmarini, Topazium Artificial Intelligence, Madrid, Spain*

Background: Predicting the clinical course of metastatic disease remains a key challenge in CRC. Estimating prognosis of these late-stage patients can avoid undertreatment or overtreatment and also guide the follow-up intensity. This study has investigated the ability of an artificial intelligence-based analytical tool to identify those mCRC patients with high risk of disease progression and mortality based on their clinical parameters. **Methods:** Throughwww.projectdatasphere.org we accessed datasets of two randomised phase III trials including chemo-naïve (NCT00364013, n = 1183 patients) and chemo-refractory (NCT00113763, N = 483) mCRC patients. We generated synthetic fingerprints (SF) for each patient through the integration of 44 clinical features (demographics, anthropometrics, medical history, blood tests and treatment characteristics) collected, respectively, during the screening phase and the first month of inclusion in each trial. These SF were then input into a deep learning framework (DLF) to identify subgroup of patients based on their similarities. The resultant clusters were correlated with progression-free survival (PFS) and overall survival (OS). **Results:** After discarding missing data, 861 chemo-naïve and 341 chemo-resistant mCRC patients were eligible for the study. In the chemo-naïve cohort, the SF/DLF system was able to detect two different clusters: C0 (n = 31) and C1 (n = 830). Patients in C0 had a higher risk of progression (median PFS 6.2 months vs. 9.1 months; hazard ratio 1.83, 95% CI 1.16-2.88; p = 0.008) and death (median OS 13.2 months vs. 20.1 months; hazard ratio 2.84, 95% CI 1.68-4.80; p < 0.001) compared to patients in C1. When applied to the chemo-resistant cohort, the SF/DLF system was again able to identify two different clusters: P0 (n = 159) and P1 (n = 182). Patients in P0 had a higher risk of progression (median PFS 1.7 months vs. 1.8 months; hazard ratio 1.32, 95% CI 1.05-1.67; p < 0.001) and death (median OS 6.1 months vs. 6.8 months; hazard ratio 1.34, 95% CI 1.07-1.68; p = 0.01) compared to patients in P1. In both cases, feature contribution analysis showed that major differences between clusters were related to clinical status, anthropometrics and haematological and biochemistry tests. **Conclusions:** Our SF/DLF system can identify mCRC subtypes based on distinct clinical features that correlate with higher risk of progression and death. Further work is required to validate this approach as a novel prognostic biomarker tool for monitoring mCRC patients. Research Sponsor: None.

1550 **Poster Session**

Impact of a deep learning model to reduce variation and costs of federally mandated breast density legislation. *First Author: Katherine Cavallo Hom, Massachussetts General Hospital, Boston, MA*

Background: Dense breast tissue is an independent risk factor for malignancy and can mask cancers on mammography. Yet, radiologist-assessed mammographic breast density is subjective and varies widely between and within radiologists. Our deep learning (DL) model was implemented into routine clinical practice at an academic breast imaging center and was externally validated at a separate community practice, with both sites demonstrating high clinical acceptance of the model's density predictions. The aim of this study is to demonstrate the influence our DL model has on prospective radiologist density assessments in routine clinical practice. **Methods:** This IRB-approved, HIPAA-compliant retrospective study identified consecutive screening mammograms without exclusion performed across three clinical sites, over two time periods: pre-DL model implementation (January 1, 2017 through September 30, 2017) and post-DL model implementation (January 1, 2019 through September 30, 2019). Clinical sites were as follows: Site A (the academic practice where the DL model was developed and was implemented in late 2017); Site B (an affiliated community practice which implemented the DL model in late 2017 and was used for external validation); and Site C (an affiliated community practice which was never exposed to the DL model). Patient demographics and radiologist-assessed mammographic breast densities were compared over time and across sites. Patient characteristics were evaluated using Wilcoxon test and Pearson's chi-squared test. Multivariable logistic regression models evaluated the odds of a dense breast classification as a function of time period (pre-DL vs post-DL), race (White vs non-White) and site. **Results:** A total of 85,865 consecutive screening mammograms across the three clinical sites were identified. After controlling for age and race, adjusted odds ratios (aOR) of a mammogram being classified as dense at Site C compared to Site B before the DL model was implemented was 2.01 (95% CI 1.873, 2.157,p<0.001). This increased to 2.827 (95% CI 2.636, 3.032,p< 0.001) after DL implementation. The aOR of a mammogram being classified as dense at Site A after implementation compared to before implementation was 0.924 (95% CI 0.885, 0.964,p<0.001). **Conclusions:** Our findings suggest implementation of the DL model influences radiologist's prospective density assessments in routine clinical practice by reducing the odds of a screening exam being categorized as dense. As a result, clinical use of our model could reduce downstream costs of supplemental screening tests and limit unnecessary high-risk clinic evaluations. Research Sponsor: Massachusetts General Hospital.

Site:	Percent Mammograms classified as dense in 2017	Percent Mammograms classified as Dense in 2019	Post-DL:Pre-DL aOR of a Dense Mammogram classification (95%CI)
A	42.9%	40.6%	0.924 (0.885,0.964)
B	47.0%	41.2%	0.808 (0.739,0.883)
C	65.5%	67.7%	1.132 (1.084, 1.182)

1551 **Poster Session**

Automated identification of immune related adverse events in oncology patients using machine learning. *First Author: Wenxin Xu, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Immune related adverse events (irAEs) are a major cause of morbidity among cancer patients treated with immune checkpoint inhibitors (ICIs). irAEs are difficult to identify systematically, which represents a major barrier to the conduct and reproducibility of irAE research. Automated approaches would facilitate cohort identification and understanding of risk factors for irAEs following ICI therapy. **Methods:** Patients treated with one or more ICIs at a single tertiary cancer center were identified. Patients who received ICIs outside the clinical trial context were used as a development cohort. For each date containing clinical documentation, proxy outcomes expected to correlate with grade 2+ irAEs including irAE related diagnosis codes, key laboratory values, prescriptions for topical and systemic steroids, and irAE keywords were extracted. Intermediate machine learning models were trained to predict the presence of each proxy outcome using structured and unstructured patient data. We used clinical trial irAEs extracted from adverse event tables found in the electronic health record as the "gold standard" outcome for a final training and evaluation cohort. A logistic regression model was used to combine predictions from each intermediate model and generate an overall probability score for each irAE type on a given encounter date. Ten-fold cross-validation was used to evaluate the final machine learning model on a held-out sample of clinical trial patients. Encounter level models were evaluated for predicting the onset of a given irAE on a given date, and patient level models for predicting irAE onset within 6 months of ICI initiation. **Results:** We identified 3,765 patients treated with ICIs off-trial and 1106 patients treated on ICI clinical trials. Among trial patients, overall incidence of any grade 2+ irAE was 21%. The combined irAE models were able to predict prospective gold standard irAE labels with accurate discrimination at both the encounter and patient level (Table). **Conclusions:** Machine learning models can identify irAEs among cancer patients in an automated manner, which may facilitate research to mitigate toxicities and optimize clinical outcomes. Validation of these methods in an external institutional cohort is underway. Research Sponsor: None.

	Encounter level (n=1106 pts; 23688 encounters)				Patient level (n=1076 pts with 6 months followup after ICI)			
Gr 2+ irAE	Incidence	AUROC	AUPRC	Best F1	Incidence	AUROC	AUPRC	Best F1
Colitis	0.003	0.81	0.21	0.33	0.035	0.82	0.42	0.52
Pneumonitis	0.003	0.83	0.34	0.45	0.020	0.86	0.38	0.45
Hepatitis	0.004	0.94	0.38	0.50	0.032	0.92	0.42	0.52
Thyroiditis	0.008	0.92	0.35	0.47	0.062	0.93	0.65	0.69
Dermatitis	0.004	0.82	0.11	0.23	0.043	0.81	0.38	0.48

AUROC = area under receiver operating characteristic curve; AUPRC = area under precision-recall curve.

1552 **Poster Session**

Automated imaging-based stratification of early-stage lung cancer patients prior to receiving surgical resection using deep learning applied to CTs. *First Author: Felipe Soares Torres, University of Toronto, Toronto, ON, Canada*

Background: Computed tomography (CT) imaging is an important tool to guide further investigation and treatment in patients with lung cancer. For patients with early stage lung cancer, surgery remains an optimal treatment option. Artificial intelligence applied to pretreatment CTs may have the ability to quantify mortality risk and stratify patients for more individualized diagnostic, treatment and monitoring decisions. **Methods:** A fully automated, end-to-end model was designed to localize the 36cm x 36cm x 36cm space centered on the lungs and learn deep prognostic features using a 3-dimensional convolutional neural network (3DCNN) to predict 5-year mortality risk. The 3DCNN was trained and validated in a 5-fold cross-validation using 2,924 CTs of 1,689 lung cancer patients from 6 public datasets made available in The Cancer Imaging Archive. We evaluated 3DCNN's ability to stratify stage I & II patients who received surgery into mortality risk quintiles using the Cox proportional hazards model. **Results:** 260 of the 1,689 lung cancer patients in the withheld validation dataset were diagnosed as stage I or II, received a surgical resection within 6 months of their pretreatment CT and had known 5-year disease and survival outcomes. Based on the 3DCNN's predicted mortality risk, patients in the highest risk quintile had a 14.2-fold (95% CI 4.3-46.8,p < 0.001) increase in 5-year mortality hazard compared to patients in the lowest risk quintile. **Conclusions:** Deep learning applied to pretreatment CTs provides personalised prognostic insights for early stage lung cancer patients who received surgery and has the potential to inform treatment and monitoring decisions. Research Sponsor: None.

3DCNN Predicted Mortality Risk Quintiles	Number at Risk						HR	p
	0 years	1 year	2 years	3 years	4 years	5 years		
1 (lowest risk)	52	52	51	51	50	49	–	–
2	52	51	48	45	43	41	3.99	0.034
3	52	52	50	47	41	41	3.94	0.035
4	52	49	45	43	39	36	6.18	0.004
5 (highest risk)	52	43	33	28	25	24	14.21	< 0.001

1553 **Poster Session**

Trajectories of machine learning-predicted mortality risk among patients with cancer and associated end-of-life utilization. *First Author: Manqing Liu, University of Pennsylvania, Philadelphia, PA*

Background: Machine learning (ML) algorithms outperform traditional tools used for prognostication and may facilitate earlier discussions between oncologists and patients (pts) about hospice enrollment and treatment modification. Identifying longitudinal trajectories of mortality risk may help clinicians and health systems understand which populations such algorithms are likely to benefit. **Methods:** We identified trajectories of mortality risk and their association with existing metrics of end-of-life care quality, using electronic health and registry data from a prospective cohort of 3,280 pts with cancer who were seen in 18 tertiary or community medical oncology practices within a large academic health system between January 2018 and May 2020 and died prior to November 2020. A validated ML algorithm (c-statistic 0.89; Parikh et al, JAMA Oncol, 2020) prospectively generated mortality risk predictions prior to all encounters. Functional principal component analysis (FPCA) identified modes of variation for all patient-level mortality risk predictions associated with encounters prior to death. Adjusted logistic regression analyses tested associations between mortality risk trajectory and metrics of high-quality end-of-life care. **Results:** FPCA revealed 2 trajectories that represented 36% and 64% of all pts in the cohort. The first cluster ("unpredictable") consisted of pts whose ML-predicted mortality risk rose sharply within 30 days of death. The second cluster ("predictable") consisted of pts whose ML-predicted mortality risk was higher at baseline and rose gradually until death. Individuals with predictable mortality risk trajectories were more likely to have worse performance status, high comorbidity burden, and gastrointestinal (GI) malignancies (Table). Predictable trajectories were associated with higher hospice enrollment (adjusted odds ratio [aOR] 1.87, 95% CI 1.48-2.37), less inpatient death (aOR 0.72, 95% CI 0.56-0.92), less end-of-life intensive care unit admissions in the last 30 days of life (aOR 0.74, 95% CI 0.57-0.95), and less chemotherapy in the last 14 days of life (aOR 0.77, 95% CI 0.55-1.08). **Conclusions:** Over one-third of deaths among pts with cancer follow an unpredictable trajectory. For pts with unpredictable trajectories, overreliance on ML predictions could perpetuate aggressive end-of-life care. Research Sponsor: National Palliative Care Research Center, U.S. National Institutes of Health.

Characteristics of mortality trajectories.

Characteristics	OR†	P value
Age		
< 75 (Ref)		
≥ 75	0.73	<0.01
Comorbidity number		
0-1 (Ref)		
2	1.51	<0.01
3+	3.70	<0.01
ECOG performance status		
0-1 (Ref)		
2+	1.29	0.03
Cancer stage		
Stage I-III (Ref)		
IV	2.02	<0.01
Cancer type		
Breast (Ref)		
GI	1.56	0.03
Genitourinary	1.18	0.49
Gynecology	1.37	0.43
Leukemia	1.11	0.71
Lymphoma	0.63	0.06
Melanoma	0.73	0.25
Myeloma	0.54	0.01
Neuro	0.28	<0.01
Thoracic	0.87	0.50

†Odds of belonging to predictable trajectory, relative to unpredictable trajectory.

1554 **Poster Session**

Use of remote patient monitoring in the care of COVID-positive patients in oncology. *First Author: Laura Pugliese, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cancer patients face an increased risk of developing acute complications from COVID-19. Remote monitoring can help with the critical need for early detection of symptoms among those diagnosed with COVID-19, enabling timely symptom management that can mitigate clinical deterioration. In response to this need, Memorial Sloan Kettering Cancer Center fast-tracked a program to monitor patients with COVID-19 from home, using an electronic symptom-tracking questionnaire and digital pulse oximeter to track patients' status and alert care teams to intervene if symptoms worsened. A multi-disciplinary group composed of Oncology providers, advanced practice providers, nursing, nursing informatics and biomedical informatics formed to manage the program. **Methods:** Memorial Sloan Kettering launched a remote monitoring program for patients diagnosed with COVID-19 on March 25, 2020. All patients testing positive for COVID-19 were enrolled in the program and asked to complete a daily symptom tracking questionnaire accessed through their patient portal or administered verbally over the phone. A subset of high risk patients were also provided with a digital pulse oximeter linked to their patient portal and capable of transmitting readings directly to the care team. Clinicians received alerts for patients reporting symptoms or an oxygen saturation below 92%. Alerts resulted in an immediate response from the care team to determine if the patient needed additional care. We retrospectively evaluated the program usage, outcomes and learnings from March 25, 2020 to December 22, 2020. **Results:** In total, 1,721 patients were enrolled in the program from March 25, 2020 to December 22, 2020. Among these, 210 were deemed high risk patients who received a pulse oximeter in addition the daily symptom questionnaire. Over this period, 27% of patients triggered an alert from an electronic symptom questionnaire, and 63% of patients with a pulse oximeter triggered an alert from their device. Among patients who triggered an alert of any kind, 3% were triaged to a higher level of care. Patients reported that the program was highly valued and alleviated anxiety about their care. Iterative improvements were made to the program over time in response to the evolving knowledge about care for patients with COVID-19. **Conclusions:** Memorial Sloan Kettering was able to quickly implement a program to detect and triage symptoms among patients with COVID-19 and cancer. Refinements were made over time to many aspects of the program in response to learnings about care related to COVID-19, including to clinical eligibility, alert criteria, monitoring duration and workflows. The program also demonstrated value for patients who felt more comfortable with their care while being monitored remotely. This program established a successful model for remote monitoring of patients with COVID-19 with the potential to be scaled to other institutions or clinical areas. Research Sponsor: None.

1555 **Poster Session**

A natural language processing tool for automatic identification of new disease and disease progression: Parsing text in multi-institutional radiology reports to facilitate clinical trial eligibility screening. *First Author: Eric J. Clayton, Oncology Hematology Care, Cincinnati, OH*

Background: Screening every patient for clinical trials is time-consuming, costly and inefficient. Developing an automated method for identifying patients who have potential disease progression, at the point where the practice first receives their radiology reports, but prior to the patient's office visit, would greatly increase the efficiency of clinical trial operations and likely result in more patients being offered trial opportunities. **Methods:** Using Natural Language Processing (NLP) methodology, we developed a text parsing algorithm to automatically extract information about potential new disease or disease progression from multi-institutional, free-text radiology reports (CT, PET, bone scan, MRI or x-ray). We combined semantic dictionary mapping and machine learning techniques to normalize the linguistic and formatting variations in the text, training the XGBoost model particularly to achieve a high precision and accuracy to satisfy clinical trial screening requirements. In order to be comprehensive, we enhanced the model vocabulary using a multi-institutional dataset which includes reports from two academic institutions. **Results:** A dataset of 732 de-identified radiology reports were curated (two MDs agreed on potential new disease/dz progression vs stable) and the model was repeatedly re-trained for each fold where the folds were randomly selected. The final model achieved consistent precision (>0.87 precision) and accuracy (>0.87 accuracy). See the table for a summary of the results, by radiology report type. We are continuing work on the model to validate accuracy and precision using a new and unique set of reports. **Conclusions:** NLP systems can be used to identify patients who potentially have suffered new disease or disease progression and reduce the human effort in screening or clinical trials. Efforts are ongoing to integrate the NLP process into existing EHR reporting. New imaging reports sent via interface to the EHR will be extracted daily using a database query and will be provided via secure electronic transport to the NLP system. Patients with higher likelihood of disease progression will be automatically identified, and their reports routed to the clinical trials office for clinical trial screening parallel to physician EHR mailbox reporting. The over-arching goal of the project is to increase clinical trial enrollment. 5-fold cross-validation performance of the NLP model in terms of accuracy, precision and recall averaged across all the folds. Research Sponsor: US Oncology Research.

Type	Accuracy	Precision	Recall	Support
CT	85%	85%	85%	453
MRI	88%	87%	88%	88
PET	92%	93%	92%	117
Bone	85%	88%	85%	34
XR	90%	88%	90%	40
Overall	87%	87%	87%	732

1556 **Poster Session**

Extracting non-small cell lung cancer (NSCLC) diagnosis and diagnosis dates from electronic health record (EHR) text using a deep learning algorithm. *First Author: Alexander S. Rich, Flatiron Health, New York, NY*

Background: Identifying patients with a particular cancer and determining the date of that diagnosis from EHR data is important for selecting real world research cohorts and conducting downstream analyses. However, cancer diagnoses and their dates are often not accurately recorded in the EHR in a structured form. We developed a unified deep learning model for identifying patients with NSCLC and their initial and advanced diagnosis date(s). **Methods:** The study used a cohort of 52,834 patients with lung cancer ICD codes from the nationwide deidentified Flatiron Health EHR-derived database. For all patients in the cohort, abstractors used an in-house technology-enabled platform to identify an NSCLC diagnosis, advanced disease, and relevant diagnosis date(s) via chart review. Advanced NSCLC was defined as stage IIIB or IV disease at diagnosis or early stage disease that recurred or progressed. The deep learning model was trained on 38,517 patients, with a separate 14,317 patient test cohort. The model input was a set of sentences containing keywords related to (a)NSCLC, extracted from a patient's EHR documents. Each sentence was associated with a date, using the document timestamp or, if present, a date mentioned explicitly in the sentence. The sentences were processed by a GRU network, followed by an attentional network that integrated across sentences, outputting a prediction of whether the patient had been diagnosed with (a)NSCLC and the diagnosis date(s) if so. We measured sensitivity and positive predictive value (PPV) of extracting the presence of initial and advanced diagnoses in the test cohort. Among patients with both model-extracted and abstracted diagnosis dates, we also measured 30-day accuracy, defined as the proportion of patients where the dates match to within 30 days. Real world overall survival (rwOS) for patients abstracted vs. model-extracted as advanced was calculated using Kaplan-Meier methods (index date: abstracted vs. model-extracted advanced diagnosis date). **Results:** Results in the Table show the sensitivity, PPV, and accuracy of the model extracted diagnoses and dates. RwOS was similar using model extracted aNSCLC diagnosis dates (median = 13.7) versus abstracted diagnosis dates (median = 13.3), with a difference of 0.4 months (95% CI = [0.0, 0.8]). **Conclusions:** Initial and advanced diagnosis of NSCLC and dates of diagnosis can be accurately extracted from unstructured clinical text using a deep learning algorithm. This can further enable the use of EHR data for research on real-world treatment patterns and outcomes analysis, and other applications such as clinical trials matching. Future work should aim to understand the impact of model errors on downstream analyses. Research Sponsor: This study was sponsored by Flatiron Health, which is an independent subsidiary of the Roche Group.

Metric	Initial	Advanced
Diagnosis Sensitivity	.98	.95
Diagnosis PPV	.95	.85
Date of diagnosis 30-Day Accuracy	.90	.84

1557 **Poster Session**

Clinical accuracy of information extracted from prostate needle biopsy pathology reports using natural language processing. *First Author: Risa Liang Wong, University of Washington, Seattle, WA*

Background: Patients with prostate cancer are diagnosed through a prostate needle biopsy (PNB). Information contained in PNB pathology reports is critical for informing clinical risk stratification and treatment; however, patient comprehension of PNB pathology reports is low, and formats vary widely by institution. Natural language processing (NLP) models trained to automatically extract key information from unstructured PNB pathology reports could be used to generate personalized educational materials for patients in a scalable fashion and expedite the process of collecting registry data or screening patients for clinical trials. As proof of concept, we trained and tested four NLP models for accuracy of information extraction. **Methods:** Using 403 positive PNB pathology reports from over 80 institutions, we converted portable document formats (PDFs) into text using the Tesseract optical character recognition (OCR) engine, removed protected health information using the Philter open-source tool, cleaned the text with rule-based methods, and annotated clinically relevant attributes as well as structural attributes relevant to information extraction using the Brat Rapid Annotation Tool. Text pre-processing for classification and extraction was done using Scispacy and rule-based methods. Using a 75:25 train:test split (N = 302, 101), we tested conditional random field (CRF), support vector machine (SVM), bidirectional long-short term memory network (Bi-LSTM), and Bi-LSTM-CRF models, reserving 46 training reports as a validation subset for the latter two models. Model-extracted variables were compared with values manually obtained from the unprocessed PDF reports for clinical accuracy. **Results:** Clinical accuracy of model-extracted variables is reported in the Table. CRF was the highest performing model, with accuracies of 97% for Gleason grade, 82% for percentage of positive cores ($<$ 50% vs. $\geq$50%), 90% for perineural or lymphovascular invasion, and 100% for presence of non-acinar carcinoma histology. On manual review of inaccurate results, model performance was limited by PDF image quality, errors in OCR processing of tables or columns, and practice variability in reporting number of biopsy cores. **Conclusions:** Our results demonstrate successful proof of concept for the use of NLP models in accurately extracting information from PNB pathology reports, though further optimization is needed before use in clinical practice. Research Sponsor: American Cancer Society, Fred Hutchinson Cancer Research Center, University of Washington.

Model	Primary Gleason Pattern	Secondary Gleason Pattern	Total Gleason Score	Number of Positive Cores (N = 98)	% Positive Cores (< 50% vs. ≥50%) (N = 98)	Perineural or Lymphovascular Invasion (N = 40)	Non-Acinar Histology (N = 6)
CRF	0.90	0.90	0.97	0.48	0.82	0.90	1.00
SVM	0.89	0.89	0.95	0.40	0.85	0.57	0.50
Bi-LSTM	0.89	0.89	0.94	0.50	0.81	0.80	0.17
Bi-LSTM-CRF	0.88	0.87	0.95	0.55	0.79	0.95	0.83

1558 **Poster Session**

Machine learning prediction of COVID-19 mortality in cancer patients. *First Author: Rodrigo Dienstmann, Oncoclínicas, São Paulo, Brazil*

Background: COVID-19 is a challenge for clinical decision-making in cancer patients and the allocation of healthcare resources. An accurate prognosis prediction to effectively triage patients is needed, especially in the community oncology practice. **Methods:**Nationwide cohort from Oncoclínicas Brazil was used to validate previously developed multivariable logistic regression (mLR) model (Ferrari et al, JCO GO 2021) and to construct a machine learning Random Forest (RF) algorithm as predictor of 30-day mortality after SARS-CoV-2 detection by RT-PCR in cancer patients diagnosed in an outpatient setting. To find the most important baseline clinical determinants of early COVID-19-related death via Gini index, a RF with 100,000 trees was trained in 75% of the dataset, and the performance was assessed in the remaining 25%. We then compared the accuracy of different models in terms of sensitivity, specificity and area under the receiver operating characteristics curves (AUC). **Results:**From March to December 2020, 533 patients with COVID-19 were prospectively registered in the database. Median age was 60 years (19-93) and 67% were female. Most frequent cancers were breast in 34%, hematological in 16%, and gastrointestinal in 15%. Comorbidities were common (52%), as was current/former smoking history (17%). Most patients were on active systemic therapy or radiotherapy (84%) in the advanced or metastatic disease setting (55%). The overall mortality rate was 15% (CI95% 12%-18%). We validated the original mLR model trained in the first 198 patients: management in a non-curative setting (odds ratio [OR] 3.7), age $\geq$ 60 years (OR 2.3), and current/former smoking (OR 1.9) were significant predictors of death in the expanded cohort. Presence of comorbidities (OR 1.9) also defined poor outcome in the updated mLR model, which yielded low sensitivity (74%), specificity (68%) and AUC (0.78). With RF modeling, the most significant predictors of 30-day death after COVID-19 (in decreasing order) were older age, treatment of advanced or metastatic disease, tumor type (respiratory tract, brain and unknown primary cancers had higher mortality), COVID-related symptom burden at baseline evaluation and treatment regimen (immunotherapy combinations had higher mortality). The RF model demonstrated high sensitivity (89%), specificity (88%) and AUC (0.96). **Conclusions:**The results highlight the possibility that machine learning algorithms are able to predict early mortality after COVID-19 in cancer patients with high accuracy. The proposed prediction model may be helpful in the prompt identification of high-risk patients based on clinical features alone, without having to wait for the results of additional tests such as laboratory or radiologic studies. It can also help prioritize medical resources and redefine vaccination strategies. A web-based mortality risk calculator will be created for clinical decision support. Research Sponsor: None.

1559 **Poster Session**

Improving tumor mutational burden calibration in non-European patients. *First Author: Elio Adib, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: Tumor mutational burden (TMB), has been recently granted FDA approval as a biomarker for ICI treatment in tumors with a high mutation load ($\geq$ 10/MB). To leverage this biomarker in the clinical setting, it is necessary to evaluate its application in diverse patient populations. In particular, tumor-only sequencing may overestimate TMB in non-EUR populations for which reference panels are small or unavailable, and thus have poorer predictive performance. Herein, we investigate the effect of TMB overestimation in non-EURs on patient diagnosis and clinical outcomes in a real world patient cohort. **Methods:** TMB was computed using a tumor-only NGS platform (Oncopanel) for 8349 cancer patients (pts) of 7 cancer types (Table). Genetic ancestry was inferred directly from tumor sequencing data and confirmed for a subset of pts using germline SNP arrays. TMB was compared using Wilcoxon rank-sum test between European (EUR) and non-EUR pts. TMB percentile rank by ancestral group (East Asian, African, European) and tumor histology was computed. In non-EUR pts, TMB was calibrated by reassigning its value to the corresponding percentile rank in EUR pts having the same cancer (AH-TMB). Tumors with raw TMB $\geq$ 10/MB were assigned as TMB-high (TMBH; with the rest referred to as TMBL for TMB-low) and those with calibrated AH-TMB $\geq$ 10/MB as AH-TMBH. A subset of pts treated with ICIs at DFCI and of EUR ancestry were analyzed. TMB was intentionally mis-calibrated in EURs (MC-TMB), to mimic the TMB overestimation observed in non-EURs. Associations between TMBH status and overall survival (OS) was assessed using Cox regression. **Results:** Uncalibrated TMB was significantly higher in tumors from non-EUR pts overall (p $<$0.0001, Table) as anticipated, whereas this difference was not observed in tumors with matched germline filtering. We reassigned non-EUR pts into low/high groups using calibrated AH-TMB, which changed the assignment of 67/670 non-EURs, most of which (65/67) were downgraded from TMBH to AH-TMBL. In the ICI-treated cohort, there was a strong association between TMBH status and OS (p = 2e-11, HR = 0.6) whereas MC-TMBH (mimicking the miscalibration in non-EUR samples) had a weaker association with OS (p = 0.0013, HR = 0.8). Importantly, pts assigned to TMB-H due to miscalibration (90 TMB-L/MC-TMBH pts) had shorter OS compared to the true TMBH group (p = 3e-6, HR = 1.9). **Conclusions:** In this analysis, we showed that tumor-only sequencing platforms can overestimate TMB in non-EUR pts, impacting treatment decisions and outcomes. Replacing raw TMB counts with an ancestry-adjusted measure could optimize TMB application in the clinical setting when germline sequencing is not available. Accurate ancestry inference can be performed using tumor-only sequencing. Research Sponsor: None.

Cancer Type	p (EUR vs. non-EUR)
Non-small cell lung	0.0005
Melanoma	0.16
Colorectal	6e-7
Esophagogastric	0.01
Head and neck	0.02
Renal cell carcinoma	0.13
Urothelial carcinoma	0.3
Overall	1e-7

1560 **Poster Session**

A machine learning tool to predict mortality risk among patients with metastatic cancer in outpatient oncology care. *First Author: Brandon Butler, McKesson Corporation, The Woodlands, TX*

Background: End-of-life management is a well-known challenging aspect of cancer care. In particular, timely hospice enrollment is a leading quality metric in the Oncology Care Model that has substantial room for improvement. An automated algorithmic tool that can incorporate the wealth of available EHR data and rapidly identify patients with a high risk of imminent mortality could be a valuable asset to supplement important clinical decisions and improve timely hospice care. **Methods:** A retrospective study cohort was formed using patients with metastatic cancer from US Oncology Network (USON) practices participating in the Oncology Care Model (OCM) between January 1, 2017 and June 30, 2019. Patients were required to have at least one record for lab values and vital signs in the EHR database. Patients were excluded from the study cohort if they were not enrolled in the OCM program or did not have a diagnosis for metastatic cancer. The patients satisfying the selection criterion were used to train and optimize the model. The training dataset was also used for internal validation and hyperparameter tuning until the final model was produced. As external validation, the final model was independently tested on 3 separate holdout datasets including OCM patients between July 1, 2019 and March 31, 2020. To avoid bias, all holdout datasets used for validation were excluded from the model. **Results:** A multivariable model to predict 90-day mortality was developed using a retrospective dataset derived from EHR data and Medicare claims data. A logistic regression algorithm using L1 (lasso) regularization yielded the best performance compared to other model candidates. The performance on the training cohort was given by a cross-validated AUC score of 0.85 (95% CI, 0.84 to 0.86). Further, external validation conducted using 3 independent holdout datasets demonstrated impressive generalizability marked by stable performance scores across multiple time periods (AUC between 0.84 and 0.85). **Conclusions:** This study builds upon previous work and further establishes the utility of machine learning to predict risk of imminent mortality for advanced cancer patients using available EHR data. A data-driven tool that estimates the probability of 90-day mortality could be leveraged as a powerful supplementary aid to clinicians managing end-of-life care at oncology practices. Research Sponsor: McKesson / US Oncology Network (USON).

1561 **Poster Session**

The surgical oncology clinical trial landscape: A cross-sectional analysis of ClinicalTrials.gov from 2008-2020. *First Author: Nirosha D. Perera, School of Medicine, Stanford University, Stanford, CA, and Department of Internal Medicine, Mayo Clinic, Rochester, MN*

Background: Surgical interventions are studied less often than medical or radiation interventions in oncology clinical trials. We characterized surgical oncology trials registered on ClinicalTrials.gov, analyzed funding sources and identified features associated with early discontinuation and results reporting. **Methods:** We employed a cross-sectional study design with descriptive, logistic regression, cox regression, time series and survival analyses. We downloaded all 270,172 studies registered on the Aggregate Analysis of the ClinicalTrials.gov database from October 1, 2008 to March 9, 2020. After excluding non-interventional trials, applying cancer/oncology specific Medical Subject Heading terms to the remaining trials and excluding phase 1 trials, 27,915 trials were identified for manual review. Primary exposure variables were trial focus: neoplasia site and treatment modality (surgical interventions included investigations of outcomes from surgical resection or intra-operative/peri-operative changes), and funding: industry, U.S. government, academic. **Results:** 26,815 trials were found to have true oncology content; 1,661 (6.2%) involved surgical oncology, representing 311,789 patients. Funding sources were: 82.7% by academic institutions, 10.9% by industry, and 6.2% by U.S. government. The most studied neoplasia sites were colorectal (17.4% of trials), breast (10.7%), gastric (10.5%), hepatic (8.6%), lung (7.5%), brain/CNS (6.7%) and cervical (6.6%). U.S. government funded surgical oncology trials had the lowest risk of early discontinuation (adjusted HR 0.65, 95% CI: 0.58-0.73, p<0.001) and the highest odds of results reporting (adjusted OR 1.35, 95% CI: 1.08-1.68, p=0.008) (Table). **Conclusions:** There is a paucity of surgical oncology clinical trials compared to other treatment modalities, especially in context of surgery's role in overall cancer care. From 2008-2020 only 6.2% of trials focused on surgical oncology, and U.S. government funded trials displayed the lowest hazard of early discontinuation and highest odds of results reporting. Stakeholders should look to government funded trials as models of improvement, but must increase representation and results dissemination of surgical oncology trials to guide treatment recommendations. Surgical oncology trial features and associated early discontinuation/results reporting. Research Sponsor: Stanford Medical Students Association - funding for the abstract submission fee only.

	Early discontinuation HR (95% CI, p value)	Results Reporting OR(95% CI, p value)
Industry	1	1
Academic	0.71 (0.65-0.78,**0.0001**)	0.35 (0.28-0.43,**0.0001**)
U.S. Government	0.65 (0.58-0.73,**0.0001**)	1.35 (1.08-1.68,**0.008**)
Colorectal	1.1 (0.95-1.28, 0.193)	0.61 (0.42-0.87,**0.006**)
Breast	1.13 (1.00-1.28, 0.058)	0.77 (0.57-1.02, 0.072)
Gastric	0.88 (0.69-1.11, 0.277)	0.50 (0.28-0.91,**0.023**)
Hepatic	1.19 (1.02-1.39,**0.030**)	0.73 (0.47-1.12, 0.15)
Lung	1.15 (1.01-1.30,**0.035**)	1.14 (0.85-1.53, 0.37)

1562 **Poster Session**

NCI's national treatment trial networks: Experience and adaptations during COVID-19. *First Author: Margaret M. Mooney, National Cancer Institute, Rockville, MD*

Background: The National Cancer Institute supports several national trial networks which responded rapidly to the COVID-19 pandemic to overcome operational barriers to clinical cancer research. The National Clinical Trials Network (NCTN) focuses on late phase treatment trials, while the Experimental Therapeutics Clinical Trials Network (ETCTN) conducts early phase treatment trials. We report findings on the experience and adaptations of these networks during COVID-19. **Methods:** Using 2019 and 2020 accrual data, we analyzed changes in accrual levels and demographics. We also evaluated changes in trial activation numbers and timelines. In July 2020, we surveyed 255 investigators from academic and community sites to assess changes in research practices and get feedback on modified processes implemented by NCI to address trial conduct during the pandemic. **Results:** Accrual across the NCTN and ETCTN fell significantly in mid-March 2020, dropping from a weekly average of 307 patients in February to 169 the week of March 23-29. Accrual began to recover in June and July but did not return to pre-pandemic levels until September. Accrual in November and December 2020 followed the patterns seen in 2019, with short-term drops around major holidays. Non-White participants were enrolled to NCTN and ETCTN trials at similar monthly rates throughout 2019 and 2020, with slightly higher overall enrollment in 2020 (23.7% vs. 22.7%). New trials continued to be developed and activated throughout 2020. Between 2017 and 2019, an average of 71 trials were activated per year (NCTN = 46, ETCTN = 25), compared to 84 activated in 2020 (NCTN = 58, ETCTN = 26). The average time to trial activation was similar or slightly longer in 2020 compared to 2019. The investigator survey yielded 111 responses (43.5% response rate). 43% of respondents' sites paused enrollment to phase 1 trials during the pandemic, compared to 18% for phase 3 trials. Many sites temporarily stopped opening new trials and processing specimens. Sites were more likely to keep enrolling to trials offering clear potential benefit and pause complex trials that required more patient contact. Respondents attributed some of the decline in accrual to a reduction in overall patient volume, increased patient concerns, and reduced research staff on site. Respondents were asked to rate the usefulness of modified trial processes NCI put in place during the pandemic. Telehealth was rated most useful (avg. 4.6/5), followed by shipping oral IND agents to enrolled patients (4.5/5), remote informed consent (4.2/5), coordinating care with local providers (3.9/5), and remote auditing (3.7/5). **Conclusions:** The cancer trials community has an opportunity to learn from working through the challenges of COVID-19. NCI will seek to continue and expand on modifications to clinical trial processes that have the potential to improve operational efficiency, reduce cost, and help bring trials to more patients. Research Sponsor: None.

1563 **Poster Session**

The TIME Trial Network to facilitate rapid clinical trial activation, patient screening, and enrollment in molecularly targeted trials. *First Author: Stephanie OLeary, Tempus Labs, Chicago, IL*

Background: Clinical trials that require patients to have specific actionable mutations based on next generation sequencing (NGS) present unique problems, such as recruiting patients with rare mutations, low enrollment rates, and distance between patients and trial sites. Such barriers can slow the pace of trial enrollment and delay the development of new therapeutic options. **Methods:** Tempus Labs has partnered with experienced research sites and pharmaceutical companies with molecularly targeted clinical trials to create the TIME Trial Network. The study portfolio includes pharmaceutical sponsored phase I-III clinical trials across solid tumors and hematological malignancies, targeting actionable mutations. This network was established to ensure rapid just-in-time (JIT) activation of trials by streamlining start-up activities (i.e., execution of CTAs and study budgets/financial exhibits, regulatory paperwork, SIV planning and conduct, drug and study supply shipments, submission to the central IRB, and sponsor-specific requirements). Rapid activation begins upon receipt of an activation form from a site partner. "Site Activated" describes a site that has fulfilled all regulatory, documentation, contracting requirements, and has sponsor approval to screen and enroll patients. **Results:** In Q4 2020, JIT activations were completed for 6 unique interventional clinical trials across 10 sites in 8 US states in the TIME Trial Network. On average, sites were activated in 9.4 business days. Patients enrolled had rare NGS mutations and were from geographically diverse locations. In one urgent case, trial activation, patient consent, screening, and treatment were achieved in 5 business days. In total, 91.7% of patients consented to trial. The average timeline from activation to consent was 4.5 days (range 0 - 24 days), with half of patients consenting within 1 business day. 45.5% of patients who consented to trial received the study drug within 1 day of consent; 2 patients dosed on day of consent. **Conclusions:** Over a 3-month period, on average, TIME Trial sites were activated in 9.4 days (compared to the 20+ week industry-wide average), and patient consent was completed in 4.5 days. Rapid JIT activations through the TIME program provide significant improvements in trial enrollment timelines and increase access to therapies nationwide. JIT activations may be especially useful for rural, underserved communities, as sites can enroll diverse patient populations and help address the equity gap in clinical trials across ethnic groups. Research Sponsor: Tempus Labs.

TIMELINE	MINIMUM**	MAXIMUM**	AVERAGE**
IRB Submission to Approval	1	9	2.5
Activation Initiated to Fully Executed Contract	3	9	5.8
Activation Initiated to Activation Completed	4	15	9.4
Site Activated to Patient Consented*	Same Day	24	4.5

*1 patient consented Q1 2021; related data are excluded **Business Days.

1564 **Poster Session**

Nodule net: A prospective safety net program to reduce loss to follow-up and increase early detection of lung cancer. *First Author: Harpreet Singh, Froedtert and Medical College of Wisconsin, Milwaukee, WI*

Background: Inadequate follow-up of suspicious lung nodules can result in a delay in diagnosis and potential progression to advanced staged lung cancer. A multidisciplinary lung nodule program entitled "Nodule Net" was implemented in 2017 to provide a safety net, increase the rate of follow-up, streamline management. The program consisted of a multidisciplinary team with EMR notification by the radiologist to a centralized nurse navigator for inclusion in a follow-up database, outreach with reminders to the primary care provider if follow-up was not completed, and referral for management where appropriate. In this study, we sought to evaluate program effectiveness in tracking and rate of follow-up imaging of suspicious pulmonary nodules. **Methods:** 2,398 chest CT scans were reviewed between January and May 2018 for the presence of a lung nodule that required follow-up. Nodules known to be inflammatory or associated with a metastatic malignancy were excluded. Baseline demographics, medical history, primary care affiliation, type of imaging scan, nodule characteristics, and presence and specifics of follow-up recommendations were collected. For reports that did not include a follow-up recommendation, Fleischner's recommendations were applied or an independent pulmonologist's review was completed. The rate of follow-up imaging was recorded and compared with historical rates prior to Nodule Net implementation. Prevalence ratios were generated for each comparison. **Results:** 1,367 (57%) reported lung nodules. Recommendations for follow-up imaging were recorded in 632 (46.2%), and 523 (82.8%) of these were reported to the program navigator. The rate of follow-up completion of those referred to the program was significantly higher [408 (78%)] than standard of care prior to program implementation [442/1202 (36.8%), (2.90, 95% CI: 2.65-3.18)]. Out of 408 patients who completed follow-up, nodule net outreach was required in 116 (28.4%). Of these 116, malignancy was identified in 4/116 (3.4%). Increased nodule size requiring referral was identified in 17 (14.7%). Out of 109 who were not transmitted to the program navigator and not present in the database, 57 (52.3%) had completed the recommended follow-up compared with 78% among those referred (1.49, 95% CI:1.23-1.79). **Conclusions:** Management of lung nodules is a complex process with poor follow-up completion reported in prior studies (29%-33%). Implementation of a multidisciplinary lung nodule care program for tracking lung nodules led to a significant increase in completion of recommended follow-up imaging. Developing a comprehensive lung nodule management program using software and navigation may further enhance detection, reduce human errors, augment the necessary follow-up for suspicious lung nodules, and ultimately the prevalence of advanced stage lung cancer. Research Sponsor: None.

1565 **Poster Session**

Oncology trial enrollment trends following the first wave of the COVID-19 pandemic. *First Author: Elizabeth W. Lamont, Acorn AI at Medidata, a Dassault Systèmes Company, Boston, MA*

Background: The first wave of the COVID-19 pandemic was associated with a negative effect on global oncology clinical research and development including documented decreases in new trial launches and patients enrolling on existing trials. We sought to evaluate secular trends in patient enrollment on global oncology trials of drugs and/or biological agents coincident with trends in the pandemic through 10/31/2020. **Methods:** This time-series study of global oncology clinical trial patient enrollment relied on data from the Medidata Enterprise Data Store, which comprises studies using the RAVE electronic data capture platform, and eCDC. We quantified the number of patients enrolling on oncology trials according to contiguous pandemic waves between 01/05/2020 and fixed right censoring at 10/31/2020. For this study, we defined pandemic waves empirically through review of peaks and nadirs of global case counts/week from eCDC data: wave 1 (01/05/2020-05/02/2020), wave 2 (05/03/2020-08/22/2020), wave 3 (08/23/2020-10/31/2020). We used negative binomial regressions to evaluate associations between time periods (i.e., waves) and counts of new trial enrollees and time periods and counts of new COVID-19 patients. **Results:** A total of 54,752 patients enrolled in 1,176 oncology trials world-wide during the observation period: 14,888 patients during wave 1, 19,631 patients during wave 2, and 20,233 patients during wave 3 of the pandemic. Compared to wave 1, the incidence of new trial enrollees increased by 10% in wave 2 (incidence rate ratio [IRR] 1.10, 95% confidence interval [CI] 0.95-1.26) and by 29% in wave 3 (IRR 1.29, 95% CI: 1.10-1.52). Over the same period, 47,336,995 people were diagnosed with COVID-19 infection: 3,481,165 patients during wave 1, 20,205,244 patients during wave 2, and 23,650,586 patients during wave 3. Compared to wave 1, the incidence of new COVID-19 patients increased by 617% in wave 2 (IRR 6.17, 95% CI: 2.76-13.77) and by 1,155% (IRR 11.55, 95% CI: 4.61-28.95) in wave 3. **Conclusions:** Despite substantial increases in the incidence of COVID-19 following the first wave of the pandemic, the number of patients enrolled in oncology clinical trials increased notably during the same period. Future research seeks to understand the mechanism through which the oncology research and development enterprise adapted to the shock of the COVID-19 pandemic. eCDC Source: European Centre for Disease Prevention and Control. Data provided subject to license available at:https://www.ecdc.europa.eu/en/copyright Research Sponsor: Acorn AI at Medidata, a Dassault Systemes company.

1566 **Poster Session**

Efficacy analysis of a remote symptom management platform. *First Author: Paris A. Kosmidis, Care Across, London, United Kingdom*

Background: Quality of life of cancer patients is a critical part of cancer care. Symptom management is evolving as a multidisciplinary approach, and is increasingly delivered through a combination of physical and remote interactions. CareAcross is an online platform offering personalized, guidelines-based support to cancer patients, that complements physicians' support and enables remote monitoring. This analysis investigated the improvement in the quality of life of cancer patients delivered through such remote support. **Methods:** Patients engage with an online interactive platform to receive personalized support based on a variety of parameters, through algorithms incorporating their exact diagnoses, treatments and comorbidities, and more. For symptom management, patients report the presence of specific side-effects via brief questionnaires; for each side-effect reported, they receive tailored support (text and multimedia) to help overcome it. These online questionnaires are repeated periodically to capture the outcome of the supportive process, and provide additional support as necessary. A retrospective analysis evaluated the efficacy of the personalized support: each patient's reported side-effects were compared before versus after receiving the support, hence calculating the reduced incidence. **Results:** 2203 patients from 8 countries, with breast, lung, prostate or colorectal cancer (1563, 404, 159 and 77, respectively) reported side-effects, received support, and updated their reports at least once. The median follow-up period was 4.9 months. The patient-reported outcomes on their quality of life revealed substantial improvement, regardless of cancer type (lowest recorded improvement = 25.7%). Commonly reported side-effects included sleep problems, dry mouth, constipation, changes in food taste, and more (see Table). Side-effects reported in specific cancer types also showed substantial improvement, including hot flushes (breast; 32.0% improvement), dyspnea (lung; 38.1%), bowel dysfunction (prostate; 80%) and others. The efficacy of the support to breast, prostate or colorectal cancer patients was similar; support to lung cancer patients exhibited the lowest efficacy ($p < 0.05$). Fatigue was the most common side-effect. It was also the most resistant to improvement compared to all others ($p < 0.05$). **Conclusions:** Digital remote support of cancer patients is a realistic option to improve quality of life. Randomized controlled trials can help quantify its impact on health economics, hospital admissions, resource utilization, and other aspects. Research Sponsor: None.

Side-effect & Improvement rates per cancer type	Breast	Lung	Prostate	Colorectal
Fatigue	37.1%	25.7%	44.7%	38.5%
Sleep problems	41.9%	55.8%	49.2%	33.3%
Dry mouth	62.0%	51.7%	65.9%	52.0%
Constipation	56.3%	52.0%	73.5%	81.0%
Food taste	72.4%	58.2%	91.7%	80.0%
Diarrhea	71.6%	63.4%	84.0%	77.3%
Reduced appetite	75.4%	62.6%	78.6%	53.8%
Mouth sores	83.6%	71.1%	75.0%	78.6%

1567 **Poster Session**

Risk factors associated with skeletal-related events following denosumab cessation among patients with bone metastases from solid tumors: A real-world machine learning approach. *First Author: Alison Stopeck, Stony Brook Cancer Center, Stony Brook University, Stony Brook, NY*

Background: The anti-RANKL monoclonal antibody denosumab has been shown to be superior to the bisphosphonate zoledronate for the prevention of skeletal-related events (SREs) in patients with incident bone metastases (BM) from solid tumors (ST). Clinical guidelines recommend the use of a bone-targeting agent for SRE prevention for ≥ 2 years. However, real-world treatment patterns in the U.S. suggest that the denosumab treatment duration is often < 1 year. Applying a machine learning approach, we sought to identify risk factors associated with SRE incidence following cessation of denosumab to help inform optimal clinical SRE prevention strategies. **Methods:** Using the Optum PanTher Electronic Health Record repository, patients diagnosed with incident BM from a primary ST between 1 Jan 2007 and 1 Sep 2019 were evaluated for inclusion in the study. Eligible patients had to receive ≥ 2 consecutive 120 mg denosumab doses on an every 4-week (± 14 days) schedule and have a minimum follow-up ≥ 1 year after the last denosumab dose or an SRE occurring between days 84 and 365 after denosumab cessation. Extreme gradient boosting was used to develop an SRE risk prediction model evaluated on a test dataset. Impact and relative importance of available medical, clinical, and treatment factors on SRE risk following denosumab cessation were extracted from the model using Shapley additive explanations (SHAP). Univariate analyses on risk factors with the highest importance from pooled and tumor-specific models were also conducted. **Results:** A total of 1,414 patients (breast, n = 563 [40%]; prostate, 421 [30%]; lung, 180 [13%]; other cancers, 250 [17%]) met inclusion criteria, with a median of 253 (min, 88; max, 2726) days of denosumab treatment; 490 (35%) experienced ≥ 1 SRE following denosumab cessation. With a meaningful model performance based on an area under the receiver operating characteristic (AUROC) score of 77%, SHAP identified several significant factors that predicted an increased SRE risk following denosumab cessation, including prior SREs, shorter denosumab treatment duration, and a higher number of clinic visits as the top-ranked factors (Table). **Conclusions:** A machine learning approach to SRE risk factor identification may help clinicians better assess the individualized patient's need for denosumab treatment persistence and improve patient outcomes. Results from tumor-specific groups will be presented at the meeting. Research Sponsor: Amgen Inc.

SHAP risk factors that increase risk of SRE 3 to 12 months after denosumab cessation in ST with BM (declining importance).

- **Prior SREs (e.g., cumulative number, timing)**
- **Denosumab treatment duration (≤ 10 months)**
- **≥ 4 average monthly clinic visits**
- **Age < 56 years**
- **Initiation of denosumab (≤ 3 months after BM diagnosis)**
- **≥ 3 unique, anti-cancer drugs prescribed to patient**
- **Prostate cancer**
- **Hypertension**
- **Hospitalization**

1568 **Poster Session**

AI-based imaging biomarker in mammography for prediction of tumor invasiveness. *First Author: Hyeonseob Nam, Lunit Inc., Seoul, South Korea*

Background: The preoperative diagnosis of ductal carcinoma in situ (DCIS) by core needle biopsy (CNB) can be upstaged in the final pathology, and this possibility is linked to the controversy over whether axillary staging is necessary in primary operation. In this study, we developed an artificial intelligence (AI)-powered Imaging Biomarker in Mammography (IBM) that can predict tumor invasiveness in preoperative mammography and evaluated its performance in an external validation cohort. **Methods:** A total of 151,764 exams of 4-view mammograms were collected from five institutions of three countries to develop the AI algorithm for breast cancer detection, where 31,776 were cancer exams. In previous studies, the performance of this breast cancer detection algorithm has already been evaluated, and in this study, we further developed the AI-powered IBM for predicting tumor invasiveness on top of the AI algorithm for breast cancer detection. To develop the AI-powered IBM for predicting invasiveness, final diagnosis information was collected for 8,251 cancer exams (472 DCIS, 388 ductal carcinoma in situ (DCIS-MI), and 7,391 invasive ductal carcinoma (IDC)), and 886 cancer exams (44 DCIS, 51 DCIS-MI, 791 IDC) were additionally collected for internal validation. The AI-powered IBM was developed via two stages of training – 1) training with diagnosis labels (cancer vs non-cancer), followed by 2) fine-tuning with invasiveness labels (DCIS, DCIS-MI, IDC). The AI-powered IBM also tested in an external validation cohort of 699 cancer exams (68 DCIS, 19 DCIS-MI, 612 IDC) and all the exams were confirmed by surgical biopsy. **Results:** The AI-powered IBM showed an area under the curve (AUC) values of 0.968 for breast cancer detection and it successfully distinguished IDC from DCIS and DCIS-MI with AUC values of 0.898 and 0.851, respectively (Table). In addition, the AUC value in terms of discriminating between DCIS and DCIS-MI was 0.752. When the AI-powered IBM was tested in the external cohort, it could detect breast cancer with the AUC of 0.952 and, its performance in terms of invasiveness prediction was similar that of the internal validation (IDC vs DCIS, 0.810; IDC vs DCIS-MI, 0.846), which supports the AI-powered IBM is applicable to the unseen mammography exam. **Conclusions:** The AI-powered IBM can distinguish IDC from DCIS and DCIS-MI in mammography. The results support that the AI-powered IBM can be used as a biomarker to help determine the surgical plan that includes whether or not to perform the axillary dissection. Research Sponsor: Lunit Inc.

The performance of AI-powered IBM for differentiating cancer subtype.

		DCIS vs DCIS-MI + IDC	DCIS + DCIS-MI vs IDC	DCIS vs IDC	DCIS vs DCIS-MI	DCIS-MI vs IDC
Internal validation	breast-level	0.904	0.882	0.911	0.774	0.856
	case-level	0.890	0.873	0.898	0.752	0.851
External validation	breast-level	0.748	0.833	0.819	0.636	0.882
	case-level	0.747	0.817	0.810	0.633	0.846

1569 **Poster Session**

Continuous unobtrusive assessment of meaningful change in older adults with cancer: The Pacific Aging & Cancer Study Collaborative—PACS collaborative. *First Author: Chao-Yi Wu, Oregon Center for Aging & Technology (ORCATECH), Oregon Health & Science University, Portland, OR*

Background: Knowledge of changes in health that precede a cancer diagnosis is challenging because of a lack of longitudinal, objective measurement techniques. Current approaches rely on periodic assessment via self-report which may miss when and how health changes, particularly when changes may appear subtly over time. Remote-monitoring technologies provide a mechanism to continuously, passively, and unobtrusively monitor changes in health so that trajectories of change in relation to a life event (i.e., cancer diagnosis, treatment) can be detected and described. We examined the changes in*digital* indicators of health and life events 1 year before and after a self-reported cancer diagnosis in community-dwelling adults aged 65 and older. **Methods:** This is a secondary, retrospective data analysis of older adults who self-reported a new cancer diagnosis in the Oregon Center for Aging & Technology (ORCATECH) cohort. Ten older adults (age = 71.8±4.9 years, 30% women) were included with various cancer types (esophageal, prostate, uterine, pancreatic, b-cell follicular lymphoma, multiple myeloma, basal cell melanoma, basal and/or squamous cell carcinoma). Daily physical activity was measured using step counts derived from an actigraph watch. Weekly health and life events (pain severity, loneliness, hospitalization/emergency room (ER) visits, days away from home overnight) were self-reported from weekly online surveys. **Results:** A total of 3,624 days of actigraphy data (210 ± 88 days pre-cancer; 153 ± 81 days post-cancer) and 750 weeks of self-reported online survey data (36 ± 12 weeks pre-cancer; 39 ± 14 weeks post-cancer) were collected. Longitudinal linear mixed-effects models revealed that the trajectory of step counts was different pre- and post-cancer (β = -1.52, $p < .001$), with a gradual decrease in step counts before a cancer diagnosis. The trajectory of pain severity was different pre- and post-cancer (β = 0.01, $p < .001$), with a gradual increase in pain severity before a cancer diagnosis. There was a gradual increase in the occurrence of hospitalization/ER visits (OR = 1.07, p = 0.02) and days away from home overnight (OR = 1.04, p = 0.01) before a cancer diagnosis. Feelings of loneliness increased over time, regardless of pre- or post-cancer (OR = 1.04, $p < .001$). **Conclusions:** Changes in health and life events 1-year before a cancer diagnosis in older adults with varying cancer types and severity were unobtrusively observed. This study suggests that a remote-monitoring technology platform deployed in homes can detect meaningful intra-individual changes before and after a cancer diagnosis. Future studies can employ this technology as a pathway for improving the timeliness of detection and more effective therapeutic follow-up for older adults. Research Sponsor: U.S. National Institutes of Health.

1570 **Poster Session**

Feasibility of integrating the Outcomes4Me smartphone navigation application into the care of breast cancer patients (FIONA). *First Author: Steven J. Isakoff, Massachusetts General Hospital, Boston, MA*

Background: Patients diagnosed with breast cancer (BC) face complex decisions about their care and many studies have shown that improved patient engagement results in increased satisfaction and better outcomes. Patient engagement includes education, treatment option selection, symptom tracking and reporting, and clinical trial opportunities. We conducted a pilot study to determine the feasibility of introducing the Outcomes4Me patient engagement app into the standard of care experience of BC patients. **Methods:** This was a pilot study (NCT04262518) conducted at an academic medical center. Eligible patients had any subtype of stage 1-4 BC and were on any type of chemo-, hormonal-, targeted-, or radiation-therapy for BC during the study period. Participants downloaded the app on their smartphone and their app usage was evaluated. Surveys were administered at baseline and end of study. Clinicians caring for patients using the app were surveyed at the end of the study. The primary endpoint was feasibility, defined as at least 40% of patients engaging with the app at least 3 times over the 12-week study period. Additional endpoints included usability, satisfaction, correlation of patient reported data with the EHR, clinical trial matching, and patient experience. **Results:** Between June 2020 and December 2020, 107 patients enrolled; results are reported for 90 patients with complete data as of 1/24/21. Baseline demographics: median age 53 (range: 27-77); 90% White, 4% Black, 3% Asian; 66% had hormone positive/HER2-, 20% HER2+, and 13% triple negative BC; 31% had stage 4 disease. At study entry, 93% had never used an app to help with their disease or treatment options. Over the 12 week study period, 58% of patients engaged with the app at least 3 times, meeting the primary feasibility endpoint. Patients engaged with the app on average 5.5 days (range: 0-40) with 20% engaging on more than 10 days during the study. The mean System Usability Score was 71 (median = 76) and was similar across age groups. The 5 app features deemed most ('somewhat' or 'very') helpful were: background about their BC (76%), information about treatment options (74%), newsfeed about their BC (70%), symptom tracking (65%), and clinical trial information (65%). 53% said that the app helped them keep track of symptoms and 33% said they are more likely to explore or enroll in a clinical trial after using the app. **Conclusions:** Integration of the Outcomes4Me app into the care management of BC patients is feasible with acceptable usability. Our results suggest that use of a patient smartphone app may be helpful for many aspects of patient education and engagement for patients with BC. The results also suggest that this type of intervention can help patients better track their symptoms and make them aware of clinical trials, potentially facilitating the management of side effects and accelerating clinical trials recruitment. Clinical trial information: NCT04262518. Research Sponsor: Outcomes4Me.

1571 **Poster Session**

Daily step counts to predict hospitalizations during chemoradiotherapy for head and neck cancer. *First Author: Elena S. Izmailova, Koneksa Health, NY, NY*

Background: Wearable activity trackers could provide useful data for managing cancer patients with respect to treatment selection, toxicity monitoring, and implementation of supportive care measures. Here, we seek to evaluate the association between daily step counts and hospitalizations in a cohort of patients with head and neck cancer (HNC). **Methods:** This analysis consists of patients enrolled in one of three prospective trials involving activity monitoring (NCT02649569, NCT03115398, NCT03102229) during chemoradiation. Study subjects were asked to wear a commercial fitness tracker continuously during the therapy. ECOG performance status (PS) was assessed at baseline, and quality of life (QoL) EORTC QLQ-C30 questionnaires were completed weekly. Multivariable Cox regression models with time-dependent covariates (average step count over the past 3 days, most recent QoL score) and time-fixed covariates (age, sex, baseline PS, study number, baseline tumor volume, and treatment setting [definitive versus postoperative]) were used to identify predictors of first hospital admission during the chemoradiotherapy course. In addition to the Cox regression models, linear mixed models were fitted with daily step count as the dependent variable to examine its relationship with certain independent variables including age, sex, weekend status, days after treatment initiation, and study number. **Results:** Sixty-six HNC patients who received chemoradiotherapy between 2015 and 2019 were included in the analysis. Median age was 60 (range: 27-88). 47% of patients had ECOG PS score 0, 47% ECOG score 1, and 6% ECOG score 2. 29% of patients had HPV-positive oropharyngeal tumors, and the most common other tumor subsites were larynx (27%), and nasopharynx (12%). The Cox regression survival model demonstrated a 26% reduction in the short-term hospitalization risk for every 1000 daily steps (averaged over the past 3 days, hazard ratio 0.74; 95% confidence interval (CI) 0.55-0.98, p = 0.0367). Hospitalizations were not significantly associated with most recent QoL or baseline ECOG PS. Additionally, according to the linear mixed model results, daily step count was not associated with age (p = 0.8048). Study subjects moved less on weekends (on average 245 fewer steps on weekends than weekdays, 95% CI 134-357, $p < 0.0001$). Also, an increase in most recently measured ECOG PS was associated with a decrease in daily step count (167 fewer steps for every increase in ECOG PS, 95% CI -289 to -45, $p < 0.0072$). **Conclusions:** Daily step counts are a dynamic predictor of hospitalizations in patients undergoing chemoradiotherapy for head and neck cancer. Interventional studies are needed to demonstrate feasibility of leveraging physical activity data to optimize supportive care during cancer therapy and enhance cancer care quality. Clinical trial information: NCT02649569, NCT03115398, NCT03102229. Research Sponsor: None.

1572 **Poster Session**

Towards reducing cancer burden within the Medicaid program: Impact of Medicaid expansion on cancer stage at diagnosis. *First Author: Siran M. Koroukian, Case Western Reserve University, Cleveland, OH*

Background: Studies to date have shown post-Medicaid expansion (M-exp) decreases in the percentage of cancer patients who are uninsured and improvements in cancer stage at diagnosis in states that expanded Medicaid as part of the Affordable Care Act. However, most studies have examined impact of M-exp on stage outcomes at the population level, or among Medicaid and uninsured, rather than solely in the Medicaid population. Using cancer registry data from a non M-exp state (Georgia (GA)) and two M-exp states (Ohio (OH) and New Jersey (NJ)), we compared changes in cancer stage in patients on Medicaid, accounting for individual- and contextual-level characteristics at the Zip Code Tabulation Area (ZCTA) level. **Methods:** We used GA, OH, and NJ cancer registry data for individuals 20-64 years of age and diagnosed with incident invasive female breast (BC), cervical (CC), and colorectal cancer (CRC). Data spanned from 2010-2017 for GA and OH, and from 2011-2016 for NJ (for BC and CRC only), with 2014 marking the year in which Medicaid was expanded in OH and NJ. We retrieved demographic data (age, race/ethnicity, sex for CRC, insurance status, and cancer stage from the cancer registries), and obtained ZCTA-level data from the American Community Survey (e.g., income, education, and female-headed households). We defined late-stage diagnosis as regional- or distant- stage. We conducted multivariable logistic regression models by state and cancer site to examine changes in late-stage cancer diagnosis pre- and post-M-exp, accounting for individual- and ZCTA-level covariates. **Results:** The number of patients with incident cancer who were on Medicaid increased by 41.7% (n = 1757 to 2490), 59.6% (327 to 522), and 76.4% (953 to 1681) for BC, CC, and CRC cancers, respectively, in Ohio; by 92.4% (433 to 833) for BC and by over 100% for CRC (232 to 496) in NJ; but by 12.7% (662 to 746) among CRC patients in GA, where the number of BC and CC patients on Medicaid remained relatively stable. Adjusting for individual and contextual-level factors, the adjusted risk ratio (ARR and (95% Confidence Interval)) for late-stage disease was lowest for BC patients in OH (0.93 (0.87, 0.99)) and for CRC patients in GA (0.94 (0.89, 0.99)). The ARR for BC and CRC in NJ were not statistically significant, though they trended towards improvement. Similarly, changes in late-stage for CC were not statistically significant in OH or in GA. **Conclusions:** The increased number of cancer patients in Medicaid and the reductions in late-stage diagnosis observed may potentially translate into reduced, or at least stabilized, cancer-related morbidity and mortality burden among Medicaid beneficiaries over time. However, reductions in late-stage diagnosis were not consistent across cancer sites or states, possibly due to differences in population demographics, health behaviors, healthcare seeking patterns, and state-level cancer prevention efforts. Research Sponsor: American Cancer Society.

1573 **Poster Session**

Disparities in government and nonprofit organization funding may hinder clinical trial development for underfunded cancers. *First Author: Suneel Deepak Kamath, Cleveland Clinic, Taussig Cancer Institute, Cleveland, OH*

Background: National Cancer Institute (NCI) and nonprofit organization (NPO) funding is critical for research and advocacy, but may not be equitable across cancers. This could negatively impact clinical trial development for underfunded cancers. **Methods:** This study evaluated funding from the NCI and NPOs with > $5 million in annual revenue supporting leukemia, lymphoma, melanoma, lung, breast, colorectal, pancreatic, hepatobiliary, prostate, ovarian, cervical and endometrial cancers from 2015-2018 based on publically available reports and tax records. The primary objectives were to assess for disparities in NCI and NPO funding across different cancers compared to their median incidence and mortality from 2015-2018, and to determine if underfunding correlates with fewer clinical trials found in clinicaltrials.gov. Correlations between combined NCI and NPO funding for each cancer and its incidence, mortality and number of clinical trials were evaluated using descriptive statistics and Pearson correlation coefficients. **Results:** Diseases with the largest combined NCI+NPO funding were breast ($3.75 billion), leukemia ($1.99 billion) and lung cancer ($1.56 billion). Those with the least funding were endometrial ($94 million), cervical ($292 million), and hepatobiliary cancers ($348 million). These data are summarized in the Table. Disease-specific NCI+NPO funding correlated well with incidence, but less so with mortality (Pearson correlation coefficients: 0.74 and 0.63, respectively). Disease-specific NPO funding correlated moderately well with incidence, but was poorly correlated with mortality (Pearson correlation coefficients: 0.54 and 0.39, respectively). Breast cancer, leukemia and lymphoma were consistently well-funded compared to their incidence and mortality, while colorectal, lung, hepatobiliary and uterine cancers were consistently underfunded. The amount of NCI funding, NPO funding and combined NCI+NPO funding for a particular cancer each correlated strongly with the number of clinical trials for that disease (Pearson correlation coefficients: 0.88, 0.87 and 0.91, respectively). **Conclusions:** Many cancers with high incidence and mortality are underfunded. Cancers with higher mortality rates receive less funding, particularly from NPOs. Underfunding strongly correlates with fewer clinical trials, which could impede future advances in underfunded cancers. Research Sponsor: None.

	Leukemia	Lymphoma	Breast	Lung	Colon	Pancreas	Liver	Melanoma	Uterine	Cervix	Ovary	Prostate
NCI+NPO Funding (millions)	$1,997	$1,299	$3,746	$1,595	$971	$942	$348	$660	$94	$292	$505	$1,215
Funding/Incidence	$33,162	$16,041	$14,852	$7,140	$7,191	$17,645	$6,757	$8,072	$1,555	$22,529	$22,669	$7,030
Funding/Deaths	$81,762	$61,616	$91,411	$10,165	$19,418	$22,191	$10,948	$67,089	$8,825	$70,359	$35,713	$44,765

1574 **Poster Session**

Determinants of enhanced vulnerability to Covid-19 in U.K. cancer patients: Results from the OnCovid study. *First Author: David James Pinato, Department of Surgery and Cancer, Imperial College, London, United Kingdom*

Background: Despite high contagiousness and rapid spread, SARS-Cov-2 has led to heterogeneous outcomes across affected nations. Within Europe, the United Kingdom is the most severely affected country, with a death toll in excess of 100.000 as of February 2021. We aimed to compare the national impact of Covid-19 on the risk of death in UK cancer patients versus those in continental Europe (EU). **Methods:** We performed a retrospective analysis of the OnCovid study database, a European registry of cancer patients consecutively diagnosed with Covid-19 in 27 centres from February 27 to September 10, 2020. We analysed case fatality rates and risk of death at 30 days and 6 months stratified by region of origin (UK versus EU). We compared patient characteristics at baseline, oncological and Covid-19 specific therapy across cohorts and tested these in multivariable Cox regression models to identify predictors of adverse outcome in UK versus EU patients. **Results:** Compared to EU patients (n = 924), UK patients (n = 468) were characterised by higher case fatality rates (40.38% versus 26.5%, $p < 0.0001$), higher risk of death at 30 days (hazard ratio, HR 1.64 [95%CI 1.36-1.99]) and 6 months after Covid-19 diagnosis (47.64% versus 33.33%, $p < 0.0001$, HR 1.59 [95%CI 1.33-1.88]). UK patients were more often males, of older age and more co-morbid than EU counterparts ($p < 0.01$). Receipt of anti-cancer therapy was lower in UK versus EU patients ($p < 0.001$). Despite equal proportions of complicated Covid-19, rates of intensive care admission and use of mechanical ventilation, UK cancer patients were less likely to receive anti-Covid-19 therapies including corticosteroids, anti-virals and interleukin-6 antagonists ($p < 0.0001$). Multivariable analyses adjusted for imbalanced prognostic factors confirmed the UK cohort to be characterised by worse risk of death at 30 days and 6 months, independent of patient's age, gender, tumour stage and status, number of comorbidities, Covid-19 severity, receipt of anti-cancer and anti-Covid-19 therapy. Rates of permanent cessation of anti-cancer therapy post Covid-19 were similar in UK versus EU. **Conclusions:** UK cancer patients have been more severely impacted by the unfolding of the Covid-19 pandemic despite societal risk mitigation factors and rapid deferral of anti-cancer therapy. The increased frailty of UK cancer patients highlights high-risk groups that should be prioritised for anti-SARS-Cov-2 vaccination. Continued evaluation of long-term outcomes is warranted. Research Sponsor: None.

1575 **Poster Session**

Time intervals between U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) new cancer therapy approvals. *First Author: Mark Lythgoe, Imperial College London, London, United Kingdom*

Background: Novel therapies are transforming cancer care. Regulatory review and approval are essential to deliver safe and efficacious innovations to patients. Studies prior to 2010 describe quicker approval decisions for new oncology drug registrations with the FDA compared to the EMA (median delay 238 days). Both regulatory agencies have subsequently improved procedures to expedite approval times. We compared regulatory market authorisation dates at the FDA and EMA for new oncology therapies from 2010-2020. **Methods:** New oncology therapeutic approvals between 2010-2020 were identified from the FDA and EMA regulatory databases. We analysed only initial approvals (not supplementary licenses) for active anti-cancer therapies (excluding biosimilars and supportive drugs). The delay in regulatory approval between the FDA and EMA was calculated in calendar days. We further analysed therapies by therapeutic class, evaluating for significant differences. **Results:** We identified 108 new therapy registrations during the study period. 104 (96.3%) therapies were approved by the FDA and 90 (83.3%) had EMA market authorisation. 4 (3.7%) drugs were not FDA registered, including 3 unsuccessful applications and 1 which sought licensing in a different indication. 18 (16.5%) drugs were not EMA registered, including 9 (8.8%) which did not pursue EMA licensing, 3 (2.9%) withdrawn licensing applications, 3 (2.9%) sought licensing in different tumour group/indication, 1 (0.9%) rejected application and 2 (1.9%) with applications under review at submission date. Of the 86 drugs approved by both agencies, 80 were approved first by the FDA and 6 by the EMA. The median delay in approval between the FDA and EMA was 227 days (IQR:124-354 days). Table shows approvals by therapeutic class. The shortest median time difference for approval was for monoclonal antibodies (171 days) with the longest for kinase inhibitors (281 days). **Conclusions:** This study shows more new oncology therapies are approved by the FDA than the EMA. Patients in the US typically have access to approved therapies earlier than in Europe. From 2010 to 2020 the median delay between FDA and EMA approval was 227 days, falling by 11 days compared to 2003-10, [non-statistically significant]. Such lengthy delays could exceed the life expectancy of many patients with advanced cancer. Innovations for accelerated approval at both the FDA (e.g. Project Orbis) and EMA (e.g., PRIME) have potential to lead to faster approval. Research Sponsor: None.

Therapeutic Class	Approved First by FDA	Approved First by EMA	Median Time difference between approvals in days (IQR)
Kinase Inhibitor	37	0	281 (137-367)
Monoclonal Antibody	18	2	171 (100-265)
Antibody Drug Conjugate	4	1	266 (220-395)
Cytotoxic Chemotherapy	5	1	245 (145-336)
Other*	16	2	242 (179-328)
Total	80	6	227 (124-357)

*Includes PARP inhibitors, radionuclides, oncolytic viruses, vaccines, cell-based and novel small molecules.

1576 **Poster Session**

Implementation of insurance marketplaces and changes in diagnosis stage in low-income cancer patients. *First Author: Uriel Kim, Case Western Reserve University, Cleveland, OH*

Background: Millions of low-income Americans gained insurance coverage through Medicaid expansion and the "Marketplaces" of the Affordable Care Act (ACA). How Marketplaces have specifically improved cancer outcomes among these individuals is unclear. Thus, we examined changes in insurance status and diagnosis stage following the ACA among low-income (139-250% of the Federal Poverty Level [FPL]), non-elderly patients (ages 30-64). **Methods:** In Ohio's cancer registry, we identified patients diagnosed with one of the top 16 cancers before (2011-2013, "Pre-ACA") and after (Q3 of 2014-2016, "Post-ACA") the implementation of the ACA's insurance Marketplaces and either had private insurance or no insurance. Low-income patients were isolated using a novel, geographically-driven approach called probability weighting. **Results:** The uninsured percentage dropped from 12.9% to 4.9% between the Pre- and Post-ACA periods in the study sample (N = 10,747). An estimated 11.1% of individuals had Marketplace insurance Post-ACA. A significant but modest Post-ACA (versus Pre-ACA) shift toward non-metastatic disease was identified (Adjusted Odds Ratio [AOR]: 0.95, 95%CI: 0.90-0.99). The largest site-specific shifts were observed for thyroid (AOR: 0.50, 95%CI: 0.30-0.83) and ovarian (AOR: 0.74, 95%CI: 0.58-0.93) cancers. In a control analysis of wealthier (400%+ FPL), privately insured individuals, no significant shifts were identified (AOR: 0.97, 95%CI: 0.92-1.02). **Conclusions:** This is the first study to show an effect in cancer stage at diagnosis from the Affordable Care Act's Insurance Marketplaces. We found that the Marketplaces greatly reduced the number of low-income, uninsured cancer patients, translating to significant improvements in cancer stage at diagnosis. As policy makers contemplate modifications to the ACA, they should carefully consider the impact of those changes on the highly vulnerable population of low-income cancer patients. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

1577 **Poster Session**

Pre-screening as a tool for increasing oncology trial enrollment. *First Author: Jennifer J. Wu, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY*

Background: Recruiting underserved patients onto therapeutic oncology trials is imperative in light of cancer disparities. Many institutions have increased enrollment with data mining tools that match patients to clinical trials, but such expensive tools are unavailable in a public safety net healthcare system. **Methods:** The NYU Perlmutter Cancer Center Clinical Trials Office implemented a quality improvement program aimed to increase therapeutic trial enrollment at Bellevue Cancer Center (BCC), an affiliated public hospital. The initiative utilized one employee to manually pre-screen patients via the EMR, cancer registries, and conferences. The program aimed to identify eligible patients for therapeutic trials and those subsequently enrolled. **Results:** During the two years preceding the pre-screening program, 31 patients were enrolled onto therapeutic clinical trials at BCC. For a period of two years (7/2017-7/2019) following the initiation of this program, 255 patients were identified, of which 143 (56.1%) enrolled onto trials. Of those enrolled, 55 were referred to NYU for trials not open at BCC. Among the 143 enrolled patients, 64% were female, 56% were non-white, and 57% did not speak English (spanning 16 languages). The median age was 55, and the top three disease groups were breast, GI, and thoracic. 83% of our patients reside in low-income areas, with 62% in both low income and Health Professional Shortage Areas (HPSA). **Conclusions:** Dedicating one employee to screening led to a 4.6 fold increase in accruals, successfully augmenting therapeutic trial enrollment in a healthcare setting with scarce resources, providing broader access to clinical trials for underserved populations. Research Sponsor: None.

Demographics of enrolled patients.

Category		Count	Percent of Total
Gender	Female / Male	91 / 52	63.64 / 36.36
Age	<60 / >60	92 / 51	64.34 / 35.66
Race	Asian Indian	46	32.17
	Black or African American	26	18.18
	Other / Unknown	13	9.09
	White	58	40.56
Ethnicity	Hispanic or Latino	49	34.27
	Not Hispanic or Latino	89	62.24
	Unknown	5	3.50

1578 **Poster Session**

Improvement in incident resolution time with implementation of an electronic patient management solution at a community oncology practice. *First Author: Lalan S. Wilfong, Texas Oncology/The US Oncology Network, Dallas, TX*

Background: Value-based care models such as the Oncology Care Model incentivize practices to reduce hospitalizations and emergency department (ED) visits. Texas Oncology found that most ED visits occurred during regular business hours. Prolonged patient call back times were consistently rated poorly on satisfaction surveys and often led to ED visits for symptoms that could be managed in our offices. We partnered with Navigating Cancer (NC) to implement an electronic patient management technology solution. **Methods:** For each of our 200 locations, call volume was estimated based on clinic volume. We then reallocated or hired dedicated triage nurses and operators. Incoming calls were entered into the NC dashboard by operators as incidents which were routed based on symptom priority following system generated prompts. Incident volumes and resolution times were tracked. We instituted PDSA cycles at all locations with a goal of less than 90-minute resolution of symptom-related incidents Utilizing the electronic dashboard allowed us to continue this initiative during the COVID-19 public health emergency as our staff could work remotely. Nurses were able to document if a potential ED visit was avoided. These data points allowed our practice to establish comprehensive and strategic actions plans for quality improvement. **Results:** We finalized implementation of the system in February of 2020. Total incidents for 2020 were over 1 million, averaging over 5000 per location. Resolution time for all incidents started at 3.2 hours pre-implementation and improved to 2.2 hours in December of 2020. Resolution times for symptom-related incidents started at 2.3 hours pre-implementation and ended at 1.5 hours in December of 2020 with over 60% resolved under one hour. 8% of symptom-related incidents resulted in definite or probable ED avoidances by nursing assessment. Shortness of breath, vomiting, chills, and weakness were the top symptom types addressed for ED avoidances. **Conclusions:** An electronic patient management solution with PDSA cycles of quality improvement can markedly reduce call back times, especially for symptom related calls. We believe managing symptoms in a timely fashion will lower ED visits and hospitalizations as well as improve patient satisfaction. We will report on these outcomes once available. Research Sponsor: None.

Triage incident resolutions.

Time Period	Implementation Period	Post-Implementation Period
Category	Q3 2019	ALL 2020
Patients	16,848	412,760
Triage Incidents	31,567	1,150,990
Resolution Time, mean (hours)		
All Incidents	3.16	2.22
Symptom Incidents	2.34	1.49
Symptom Incident Resolution Time, categorical, n (%)		
< 1 hour	2,717 (55.2)	66,151 (61.6)
> 1 hour	2,205 (44.8)	41,251 (38.4)
Symptom Incident ED Avoidances, n (%)		
Definitely	321 (1.0)	1,508 (1.4)
Probably	844 (2.7)	6,979 (6.5)
No	21,704 (68.8)	66,769 (62.1)
Unknown	8,689 (27.5)	32,300 (30.0)

1579 **Poster Session**

Cancer patient satisfaction with telehealth: Survey results from a large NCI-designated cancer institute. *First Author: Divya Natesan, Duke University Medical Center, Department of Radiation Oncology, Durham, NC*

Background: Telehealth (TH) utilization for patients at our cancer institute increased in 2020 in response to the COVID-19 pandemic, however oncology-specific TH patient satisfaction is unknown. **Methods:** Monthly TH utilization at a single large NCI-designated institute from 3/1/2020-11/30/2020 was reviewed. Utilization was calculated as chargeable TH visits (new video, established video, phone) as a proportion of all consult/follow up visits. Patient satisfaction surveys for oncology TH visits for MD/PA/NP providers were reviewed from 4/1/2020-11/30/2020. Surveys were sent after every TH visit, unless the patient had a prior visit in the past 3 months. Percent (%) top box score (TBS) was defined as proportion of responses in the highest possible response category (i.e. very good). % TBS was reported for 14 survey items in 4 domains: technology, access, care provider (CP), and overall assessment. Satisfaction was assessed over time and according to patient factors: generation, gender, insurance type, employment status, and clinic site. The Cochrane-Armitage trend test was used to compare proportions of TBS responses across monthly time points. **Results:** TH comprised 21% (22,055/103,461) of all encounters in the study period. TH use increased from 9% in 3/2020 to a peak of 47% in 4/2020. In 11/2020, TH use was 18%. 28.0% (2,286/8,173) of TH patient surveys were returned. Multiple patient satisfaction metrics were improved over time (Table). Patients had higher satisfaction with phone compared to video visits with regards to technology (86% vs 76%) and access (80% vs 72%). Millennials (born 1981-1995) had higher satisfaction with access to TH (87%) compared to Gen X (1965-1980) (77%), Baby Boomer (1946-1964) (74%), and Silent Generation (1928-1945) (72%), however all generations had similar levels of satisfaction with technology (range 77-80%). Disabled patients had higher overall satisfaction of TH (82%) versus those working full time or retired (71%). Patients with commercial insurance had worse overall satisfaction of TH compared to other insurance types (65% vs 72%). Patients with encounters in genitourinary, thoracic, and endocrine oncology clinics had the highest levels of overall satisfaction (75%) compared to other clinics (69%). There were no observed differences in TH satisfaction according to gender. **Conclusions:** TH cancer patient satisfaction is high and has improved over time, however satisfaction differs by patient demographics. Further data are needed to best select patients appropriate for TH. Research Sponsor: None.

Patient satisfaction (% TBS) over time.

	4/2020	11/2020	P-Value
CP Discussed Treatments	86%	93%	0.01
CP Included You in Decisions	87%	93%	0.01
Ease of Talking with CP	80%	87%	0.004
Video Connect	76%	85%	<0.001
Audio Connect	77%	86%	0.002
TH Visit Compared to In-Person Visit	52%	65%	<0.001
Likelihood of Recommending Practice	67%	82%	<0.001
Overall Satisfaction	65%	80%	<0.001

1580 **Poster Session**

Patterns of telehealth utilization during the COVID-19 pandemic and preferences for post-pandemic telehealth use: A national survey of oncology clinicians. *First Author: Christopher Manz, University of Pennsylvania, Philadelphia, PA*

Background: Rarely used in routine practice pre-pandemic, telehealth utilization for cancer care rose significantly during the COVID-19 pandemic. Increased familiarity with telehealth has led to calls to continue its use after the pandemic ends. Yet national patterns of oncology telehealth utilization by visit type, preferences for telehealth use post-pandemic and barriers to telehealth for patients with cancer have not been described. **Methods:** 9,336 survey invitations were emailed to US-based ASCO members who have agreed to receive communications. Survey distribution was equally divided over five US regions, and practice type (e.g., academic, community) was reflective of ASCO membership proportions. The survey was open and data collected from January 4-28, 2021. Non-respondents received two reminder emails at week intervals. Analysis is descriptive. **Results:** 200 respondents completed the survey (2%). Respondents were 72% medical oncologists, 66% urban, 64% academic-affiliated, and from 42 states. 99% currently offered telehealth. 63% used telehealth for <=30% of all patient visits in the last 30 days; 18% used telehealth for more than half of visits. Telehealth utilization varied by visit type (table). 64% reported that the care delivered in telehealth visits was similar quality to in-person visits (29% worse). Assuming no regulatory or financial barriers to telehealth use after the pandemic, 92% would like to use telehealth for at least some visit types; only 8% prefer not to use telehealth. 20% would like to use telehealth for all visits types, and 64%, 54%, 33% and 17% would like to use telehealth for survivorship, symptom management, evaluation of patients receiving treatment and new patient visits, respectively (multiple selections allowed). Major barriers to telehealth were lack of patient access to technology (reported by 81%), limited patient technological proficiency (80%), language barriers (45%), uncertainty about future reimbursement (41%) and lack of administrative resources to support clinicians (33%). 68% agreed that the barriers increase cancer care disparities. **Conclusions:** Telehealth utilization was widespread during the COVID pandemic and varied by visit type. Most respondents plan to use telehealth in the future, but report barriers to continued use that worsen disparities. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Telehealth visits in last 30 days by type.

% reporting for each visit type	No telehealth visits	< half	≥ half
New patient	28	50	22
Consent	33	52	16
Evaluation for patients receiving systemic therapy	23	53	24
Post surgery/radiation	35	44	21
Survivorship	9	40	51
Symptom management	7	55	37
Discussion of important results	10	54	36
Discussion of goals of care	26	55	19

*Each cell is the percent of respondents who reported none, < half, or ≥ half of visits of the visit type in the last 30 days occurred as telehealth. Rows may not sum to 100 due to rounding.

1581 **Poster Session**

Improving cancer patient care with a digital telemonitoring platform: The ConnectPatienToDoctor study. *First Author: Carole Helissey, Clinical Research Unit, Military Hospital Begin, Saint-Mandé, France*

Background: During COVID19 pandemic, clinicians have had to face two challenges in an unprecedented context: ensuring continuity of patient care for a disease that involves a life-threatening prognosis while reducing patients' vulnerability to this virus. The ConnectPatientToDoctor study aimed to evaluate a connected telemonitoring platform,*Cureety*, in cancer patient care. **Patients and Methods:** This prospective study was conducted at the Military Hospital Bégin. Each cancer patient was allowed to respond to a personalized symptomatology questionnaire based on CTCAE v.5.0, and personalized to their pathology and treatment. An algorithm evaluated the health status of the patient based on the reported adverse events and provided adapted recommendations. The calculated score allows to classify the patient into four different levels: (1) Correct State (green) (2) Compromised State (yellow) (3) State to be monitored (orange) (4) Critical State (red) In the case of orange or red classification, the patient was invited to call the hospital. In case of green or yellow classification, the patient received therapeutic advice set by the doctor, for each of the adverse events reported. The primary endpoint was to assess the feasibility of monitoring cancer patient with the connected platform. The secondary endpoint was to assess patient and caregivers' satisfaction. **Results:** There were 108 patients included in the program between July 1st, 2020 and January 31st, 2021. The median age was 70 and 77% presented a metastatic stage. The most represented cancer was prostate (50%), followed by lung (24%) and breast (15%). Overall, 1864 questionnaires were completed by the patients, resulting in 543 yellow alerts and 133 orange or red alerts. More than 60% of the alerts was managed through outpatient care or with a rapid intervention to resolve the adverse events. On a satisfaction scale from 1 to 10, where 10 was the highest, 72% of the patients responded with a 9 or 10. And all caregivers were satisfied because they could offer a better care, prioritize care, and save time. **Conclusions:** Participants in ConnectPatientToDoctor study reported that they had a clear benefit from using a connected platform to monitor their treatment. Patients felt less isolated and felt that they benefited from personalized care. This solution makes it possible to streamline the patient care process. Research Sponsor: None.

Patients' characteristics.

Variables	N (%)
Number of patients	108
Median age (range)	70 years (55-100)
Gender	
Female	31 (28.7%)
Male	56 (51.9%)
Not collected	21 (19.4%)
Location	
Prostate	54 (50.0%)
Lung	26 (24.1%)
Breast	17 (15.7%)
Other	11 (10.2%)
Stage	
Localized	16 (14.8%)
Metastatic	83 (76.9%)
Other	9 (8.3%)
Systemic Treatment	
Chemotherapy	23 (21.3%)
Hormonotherapy	44 (40.7%)
Immunotherapy	33 (30.6%)
Targeted therapy	8 (7.4%)
Patient included in a trial study	25 (23.1%)

1582 **Poster Session**

Telehealth: Reducing or increasing cancer care disparities? *First Author: Patricia Jewett, University of Minnesota, Minneapolis, MN*

Background: During the COVID-19 pandemic, most cancer care in the United States transitioned to telehealth (phone or video visits) to reduce infection risks for patients and providers. Telehealth may simplify care logistics (e.g. reduce travel and waiting times), but it may also unintentionally exacerbate existing disparities in healthcare utilization by race/ethnicity, age, or rural/urban status. As telehealth will likely continue long-term, we examined telehealth use at a comprehensive cancer center during the COVID-19 pandemic across patient populations with established disparities in cancer treatment and outcomes. **Methods:** We retrospectively reviewed telehealth visits from March until December 2020 among individuals diagnosed with cancer at the University of Minnesota Masonic Cancer Center (MCC). We used Chi-squared tests and GEE logistic regression to compare video vs. phone visits by age, urban/rural status, and race/ethnicity (American Indian / American Native [AIAN], Asian, Non-Hispanic Black/African American [NH Black/AA], Hispanic, Multiple, Native Hawaiian / Pacific Islander [NHPI], NH White). **Results:** Over the study period, 42,171 telehealth visits were performed with 11,097 patients at the MCC. Patients had a mean age of 62.7±13.9 years; 59.2% were female; 88.7% lived in urban areas; 90.0% of patients were NH White, 4.4% NH Black/AA, 3.0% Asian, 1.5% Hispanic, 0.8% AIAN, 0.3% of multiple races, and 0.1% NHPI. The most common cancer sites were breast (24.1%), hematological (21.0%), gynecologic (10.0%), and lung (8.4%). NH White individuals were more likely (53.9%) to use video than AIAN (39.7%), Black/AA (37.8%), or NHPI individuals (34.9%). Video use was less common among rural (45.3%) than urban (53.7%; $p<.0001$) residents, and among individuals aged 65 or older (45.2%) vs. younger than 65 (59.5%; $p<.0001$). In a logistic regression, adjusted for continuous age and urban/rural status, all race/ethnic groups except Multiple were less likely to use video than NH White individuals (vs. phone; Table). **Conclusions:** Our findings underscore disparities in telehealth use for cancer care across historically underserved populations. Future research should evaluate potential underlying contributors to these disparities such as technology access, internet capability, and fear of discrimination. Additional research is also needed to determine whether video vs. phone visits affect cancer outcomes, therefore indicating true disparity. Research Sponsor: None.

Logistic regression, adjusted for age and urban/rural status: use of video vs. phone, University of Minnesota Masonic Cancer Center, March-December 2020.

Race / Ethnicity	Odds Ratio	95% Confidence Interval	P
American Indian / Alaskan Native	0.53	0.35-0.79	.002
Asian	0.68	0.56-0.83	.0002
Non-Hispanic Black	0.43	0.36-0.51	<.0001
Hispanic	0.64	0.49-0.84	0.002
Native Hawaiian / Pacific Islander	0.47	0.24-0.93	.03
Non-Hispanic Multiple	0.71	0.41-1.24	.23
Non-Hispanic White	1 (Ref.)		

1583 **Poster Session**

Can COV Direct: Effectiveness of a tele-medicine self- care interventions for cancer survivors during COVID 19 pandemic. *First Author: Narayanankutty Edavalath Warrier, Malabar Institute of Medical Sciences, Calicut, India*

Background: Good mental health improves the overall quality of life. Anxiety and depression in post-treatment cancer survivors is common and can affect adversely on the individual. CanCovDirect is a novel, tele-medicine self-care intervention for cancer survivors. We practiced a randomized controlled superiority trial to compare CanCovDirect with usual standard care (SC) in this population.**Methods:** Individuals completing cancer treatment within the past 3 years who had symptoms with or without anxiety or depression were recruited from clinical and community settings in Northern Kerala. We allocated the participants using block randomization (CanCovDirect plus SC or to SC alone). Assessments of anxiety and depression severity (Centre for Epidemiological Studies-Depression scale [CES-D]; primary outcome) and secondary outcomes anxiety symptoms (Hospital Anxiety and Depression Scale) health-related quality of life (Short Form Survey-12 mental and physical component summaries), were conducted at baseline, as well as 3 and 6 months (primary time point). Analyses of outcomes were adjusted for covariates using linear regression. **Results:** Participants recruited between June 2020 and November 2020 were randomly assigned to CanCovDirect (n = 152) or SC (n = 152). Among 350 participants randomly assigned, 304 (86.85%) completed the primary outcome at 6 months. CanCovDirect participants reported less severe anxiety and depressive symptoms on the CES-D than SC participants at 6 months, adjusted effect size (ES) 1.68 (95% CI, 1.28 to 2.05). CanCovDirect participants also had significantly greater quality of life compared with SC. Exploratory analysis suggested that types of cancer was a modifier of the primary outcome (interaction term P value = .04); the intervention was effective in women (ES, 0.62; 95% CI, −0.45 to 0.89). **Conclusions:** CanCovDirect is an essential method of managing mild-moderate depression and anxiety symptoms in cancer survivors. Research Sponsor: None.

1584 **Poster Session**

mPalliative Care Link: Examination of a mobile solution to palliative care coordination among Tanzanian cancer patients. *First Author: Mamsau Ngoma, Ocean Road Cancer Institute Cancer Institute, Dar Es Salaam, Tanzania, United Republic of*

Background: Cancer is a growing public health concern in Tanzania (and throughout sub-Saharan Africa), with a majority of cases presenting in late stage with associated distress, ie, pain. Access to specialty palliative care (PC) is a national priority in Tanzania; however, there are limited numbers of PC specialists (hereafter, specialists). Mobile health promises to extend the reach of a limited pool of specialists through inter-professional, community-based care coordination. This work assessed the effectiveness of a smartphone-/web-based application, mobile Palliative Care Link (mPCL), to extend specialist access via shared data and communication with local health workers (LHWs). Central to mPCL is the African Palliative care Outcome Scale (POS), adapted for automated, scheduled mobile symptom assessment and response. **Methods:** Following consent, incurable adult cancer patients were randomized at hospital discharge from a large urban, government-supported Tanzanian cancer institute to one of two study arms—mPCL or phone-contact POS collection. Baseline sociodemographic, clinical and POS data were recorded. Twice-weekly POS responses were collected and managed via mPCL or by phone-contact with clinician study personnel for up to 4-months depending on respective study arm. Patient end-of-study care satisfaction was assessed via phone-survey. **Results:** Forty-nine patients per arm participated. Comparison of baseline characteristics showed a trend toward more women (p= 0.07) and higher discharge morphine use (p= 0.09) in the mPCL versus phone-contact groups, respectively, and significant between-group differences in cancer types (p= 0.003). Proportion of deaths were near-equal comparing groups [26% (n= 13) mPCL versus 28% (n= 14) phone-contact]. Overall symptom severity was lower in the phone-contact group (p <0.0001) and symptom severity decreased over time in both groups (p= 0.0001); however, between-group change in overall symptoms over time did not vary (p= 0.34). Care satisfaction was high overall in both groups with few between-groups differences, ie, greater provider response to questions and concerns in the phone-contact arm and greater provision of spiritual support in the mPCL arm. **Conclusions:** Higher symptom severity scores in the mPCL arm likely reflecting between-group sociodemographic/clinical differences and clinical support of phone-contact arm participants. Similar rates of care satisfaction in both groups suggest that, compared to phone-based support, mPCL may facilitate effective symptom-focused care in a more efficient and scalable manner. Study limitations include a small sample of patients from a single urban hospital and lack of a true usual care arm. Broader study of mPCL's cost-efficiency and utility in Tanzania is needed. This work promises to close a large PC gap in under-resourced settings throughout Tanzania and other LMICs. Research Sponsor: U.S. National Institutes of Health.

1585 **Poster Session**

Implementing virtual mind-body programming to support cancer patients during COVID-19. *First Author: Jun J. Mao, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Despite growing evidence of mind-body therapies for physical and psychological health among patients with cancer, their access remains limited. The COVID-19 pandemic has further disrupted the delivery of necessary cancer and supportive care; thus, the need to support patients with cancer is unprecedented. To expand the reach and access of mind-body therapies, we developed, implemented, and evaluated a novel virtual mind-body program for patients with cancer. **Methods:** We rapidly developed a 7-day a week virtual mind-body program, Integrative Medicine at Home (IM@Home), for patients with cancer (ages ≥18 years) and deployed it on April 1st, 2020. IM@Home included mind-body group therapy classes in fitness, meditation, yoga, dance, tai chi, and music delivered using Zoom video conferencing. Classes ranged from 30-45 minutes and were led by an integrative medicine clinician. Patients had the option to register for a 1-month, 3-month, or 6-month membership to gain unlimited access to all virtual mind-body classes. Multimethod evaluation was conducted using the RE-AIM conceptual framework to guide surveys and qualitative interviews. Surveys were analyzed using descriptive statistics and interviews were analyzed using grounded theory. **Results:** Between April 2020 and January 2021, IM@Home registered over 32,000 class participants, with a weekly average attendance of 700-800 participants. In a 4-month post-deployment survey (n = 131), nearly all participants were satisfied with IM@Home (93.9%) and would recommend the program to friends and family (95.4%). A majority of participants also found IM@Home to be simple to use (87.0%) and said the program had a variety of classes that interested them (93.1%). Three-quarters of participants (74.8%) were taking 3 to 7 classes a week (range: 1 to 15 classes), among which the most popular classes were fitness (88.7%), chair yoga (37.1%), and tai chi (33.1%). Most participants preferred a 3-month membership (51.6%), followed by a 6-month membership (19.5%). In qualitative interviews (n = 30), participants reported IM@Home helped them to: 1) maintain structured routines and stay motivated to exercise; 2) cope with COVID-19-related and cancer-related stressors; and 3) connect with their fellow cancer patient community and foster social relationships during a time of isolation. **Conclusions:** Virtual mind-body programming, through IM@Home, reached many patients with cancer to address their physical and psychological challenges during COVID-19. As patients with cancer experience high physical and psychological symptom burden following diagnosis, future clinical trials are needed to evaluate the specific effects of IM@Home when integrated into active treatment and survivorship care. Research Sponsor: Translational and Integrative Medicine Research Fund at Memorial Sloan Kettering Cancer Center, U.S. National Institutes of Health.

TPS1586 **Poster Session**

Exploring the role of digital health coaching for men with prostate cancer. *First Author: Nathan Handley, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA*

TPS1586Background: Toxicity leading to impaired quality of life is common among men receiving treatment for Prostate Cancer (PCa). Digital interventions may be beneficial in enhancing health self-efficacy in managing symptom burden. This study evaluates the feasibility and preliminary outcomes of digital health coaching intervention on men with PCa. **Methods:** This pilot study aims to recruit up to 100 adult, English-speaking men with PCa who in the last 2 years have required active treatment, defined as cancer management via active surveillance, surgery, radiation, androgen deprivation, chemotherapy, hormonal therapy, immunotherapy or a combination of these modalities. Men will be enrolled across the catchment area of Jefferson Health using social media and a variety of other outreach tools approved by the Institutional Review Board. Consented patients are enrolled in a 3-month digital health coaching program which combines weekly calls with up to 4 nudges of evidence-based content delivered via text or email weekly. The program focuses on a weekly health topic, such as physical, mental, social, or financial health, and managing symptoms, and empowers participants to set health goals of importance to them. Primary endpoints include feasibility, defined as 60% of participants completing the 3-month program. The main secondary endpoints measured are health self-efficacy as measured by the Cancer Behavior Inventory-Brief (CBI-B), quality of life, as measured by the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP), financial toxicity as measured by the Comprehensive Score of Financial Toxicity (COST) and physical and mental health as measured by the Patient Reported Outcomes Measurement Information System-Global Health 10 (PROMIS-10). Outcomes are captured on enrollment and monthly through program completion for a total of 4 data points. Summary statistics will be used to describe patient demographic and clinical characteristics of the study population. Summary statistics will also be used to describe CBI, EPIC-CP, PROMIS and COST by assessment time. The change in CBI-B scores from baseline to 3 months will be calculated along with 95% confidence intervals. Additional LMMs will be created to assess the relationship between self-efficacy (CBI) and quality of life (EPIC-CP), financial toxicity (COST) and global health (PROMIS- SF10). Research Sponsor: Philadelphia Prostate Cancer Biome Project.

TPS1587 **Poster Session**

Primary care oncology model (PCOM): Implementation of a model integrating primary and oncology care for patients taking oral anticancer agents. *First Author: Emily R. Mackler, University of Michigan Health System, Ann Arbor, MI*

TPS1587Background: Non-adherence to oral anticancer agents (OAA) has been reported among 30% of individuals. Often, individuals with cancer are not just managing their new OAA but also medications to treat multiple chronic conditions (MCC). Multiple factors contribute to the extent patients on OAAs and MCC medications adhere to therapy. The objective of this study is to improve medication, symptom, and disease management of patients with hematological malignancies and MCC through care coordination between pharmacists. **Methods:** Design. This is a multi-center prospective single arm pilot study at two academic medical centers in Michigan and Tennessee. Subjects. Ninety participants will be recruited, 60 from site 1 and 30 from site 2. Inclusion criteria are: adults > 18 years, diagnosed with and initiating oral treatment for chronic myeloid leukemia, chronic lymphocytic leukemia, or multiple myeloma, diagnoses of at least 2 chronic conditions, where one is type 2 diabetes, hypertension, congestive heart failure, depression/anxiety, gastroesophageal reflux disease, hyperlipidemia, or chronic obstructive pulmonary disease, taking at least two chronic medications, and able to provide electronic consent. Exclusion criteria are: inability to speak English, and diagnosis of type 1 diabetes or HIV. Intervention. Participants will complete two Patient Reported Outcome Measures (PROMs) for their OAA that will be reviewed by the oncology pharmacist, with follow-up to the care team if needed. Participants will be scheduled for a Comprehensive Medication Review with a primary care pharmacist for up to two visits for their chronic medications. The intervention over 2 months, and the oncology and primary care pharmacists communicate via electronic health record about medications, symptoms, and disease control. Outcomes. The primary endpoints are (a) dose-adjusted adherence by proportion days covered (PDC) for the OAA and (b) PDC for chronic condition medications, assessed using 6 months of prescription claims. Data will be collected from patients using REDCap surveys and abstracted data will be entered into REDCap. Implementation by pharmacists and patient acceptability will be examined. Analysis. The association of OAA and chronic medication adherence (PDC) will be examined via correlation. Participant demographics ,clinical characteristics, and the symptom experience from the PROM will be described. Using CMR results, medication problems, recommendations, and changes will be provided. Program implementation will be assessed and patient perceptions obtained from post-CMR interviews. A joint display for the quantitative and qualitative data for feasibility, appropriateness, and acceptability from pharmacists will be completed. Results: Screening and recruitment has begun. Clinical trial information: NCT04595851 and NCT04663100. Research Sponsor: AstraZeneca.

TPS1588 **Poster Session**

A study evaluating targeted therapies in participants who have advanced solid tumors with genomic alterations or protein expression patterns predictive of response (MyTACTIC). *First Author: Axel Grothey, West Cancer Center and Research Institute, OneOncology Research Network, Germantown, TN*

TPS1588Background: Cancer treatment is evolving toward a more personalized approach in which the intersection of genomics, pathology and imaging methods leads to individualized care. Furthermore, identification of novel genomic alterations and other biomarkers has the potential to lead to customized, targeted treatments. Matching specific therapies to tumor biomarkers has the potential to yield valuable clinical information. Here we present a multiarm basket trial that matches patients with a broad array of metastatic solid cancers to investigational therapies alone or in combination based on specific, targetable genomic alterations or protein expression patterns that are potentially predictive of response (MyTACTIC). Historically, such trials have been conducted at large academic medical centers rather than community centers, where most US patients with cancer receive treatment. Prioritizing community centers for this study presents an exciting opportunity to generate data from a more representative patient population. **Methods:** This phase II, multicenter, nonrandomized, open-label study is enrolling approximately 200 participants with advanced solid tumors that harbor alterations including mutations, fusions, amplifications and protein loss in specific biomarkers that include human epidermal growth factor receptor 2 (HER2), phosphoinositide 3-kinase (PI3K), anaplastic lymphoma kinase (ALK), proto-oncogene tyrosine-protein kinase (ROS1), protein kinase B (AKT), phosphatase and tensin homolog (PTEN), high tumor mutational burden (TMB), high microsatellite instability (MSI) and deficient mismatch repair (dMMR). Patients aged ≥18 years with positive local biomarker results from tissue or blood samples will be enrolled from community oncology centers and practices. Eligibility criteria have been broadened to allow enrollment of a diverse population of patients, including those with nonmeasurable disease, HIV or viral hepatitis infections, and to allow for previous treatment with anticancer agents in the same class. Once general and arm-specific criteria are met, patients will be assigned to 1 of 10 treatment arms to receive mono- or combination therapy with targeted agents, immunotherapy and/or chemotherapy (≤25 patients per arm). The primary objective is to evaluate confirmed objective response rate, as assessed by the investigator according to RECIST version 1.1 or RANO criteria for primary central nervous system tumors. Progression-free survival, duration of response, overall survival and safety will also be assessed. Special attention has been paid to the study design and implementation to ensure equitable access, along with flexibility to add additional baskets. Enrollment is ongoing. Clinical trial information: NCT04632992. Research Sponsor: Genentech, Inc.

TPS1589 **Poster Session**

Comprehensive ambulatory monitoring during immunotherapy in patients with advanced melanoma: A prospective trial (CAMP-IT). *First Author: Milan Kos, Amsterdam UMC, University of Amsterdam, Department of Medical Oncology, Cancer Center Amsterdam, Amsterdam, Netherlands*

TPS1589Background: The emergence of immune checkpoint inhibitors has improved survival outcomes for patients with advanced melanoma. However, these treatment modalities are also associated with specific immune-related toxicities. These are often reversible after prompt recognition and initiation of appropriate management, but can result in severe morbidity and hamper health-related quality of life (HRQoL) if left undetected. Hence, accurate and regular monitoring of these patients is critical. Recent advances in*mHealth* technologies and the rapidly expanding armamentarium of wearable devices allow for real-time objective (vital signs and physical activity) data and patient-reported outcome measurement (PROMs) collection and, hence, serve this purpose. We hypothesize that collection of real-time objective data adds to the early detection of disease- and treatment-related adverse events. The primary objective of this study is to determine the feasibility of collecting real-time PROMs, vital signs, and physical activity data in advanced melanoma patients receiving immunotherapy using a comprehensive ambulatory monitoring platform (CAMP) that consists of a smartphone app, activity monitor, digital thermometer, and online dashboard for physicians. **Methods:** In this prospective multi-center trial, patients (n = 50) with advanced melanoma, scheduled to receive immunotherapy with immune checkpoint inhibitors, and with access to a smartphone are eligible for inclusion. Consenting patients will be asked to wear a FitBit Versa 2.0 during waking hours, collect daily temperature measurements using a Withings Smart Temporal thermometer, and answer weekly toxicity questionnaires (NCI PRO-CTCAE) using the smartphone app for the duration of the study (12 weeks). Primary outcome is feasibility in terms of (i) participation rates, (ii) wear-time, (iii) compliance rates with in-app questionnaires and temperature measurements, and (iv) satisfaction with the platform. Secondary exploratory outcomes include associations between CAMP-derived parameters and clinical outcomes: performance status (PS), HR-QoL scores (EORTC QLQ-C30 questionnaire), unplanned hospitalizations, physician-assessed adverse events, and 1-year survival outcomes. PS and HR-QoL will be rated at baseline, mid-study, and end-of-study. The occurrence of adverse events will be documented up to 12 months from baseline. Survival outcomes will be compared to a propensity score matched group from the Netherlands Cancer Registry. Accrual has started in February 2021. Clinical trial information: NL8827. Research Sponsor: BMS.

2000 **Oral Abstract Session**

Alliance A071601: Phase II trial of BRAF/MEK inhibition in newly diagnosed papillary craniopharyngiomas. *First Author: Priscilla Kaliopi Brastianos, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: Craniopharyngiomas, a rare brain tumor along the pituitary-hypothalamic axis, can cause significant clinical sequelae. Surgery and radiation, the only effective treatments, can cause significant morbidity. Genetic analysis of craniopharyngiomas revealed that 95% of papillary craniopharyngiomas (PCP) have BRAF *V600E* mutations (Brastianos et al. Nature Genetics 2014). We evaluated the efficacy of BRAF/MEK inhibition in patients (pts) with previously untreated PCP. **Methods:** Eligible pts without prior radiation whose PCP screened positively for BRAF mutations were treated with oral vemurafenib/cobimetinib in 28-day cycles. The primary endpoint of response rate (RR) based on centrally determined volumetric data was evaluated in 16 pts, where a partial response was defined as >20% decrease in volume. This single arm, Simon two-stage phase 2 trial had 89% power to detect a true RR of at least 30% (vs. the null RR 5%; alpha=0.04). In this design, 3 or more observed volumetric responses in 16 evaluable pts would be considered promising activity. **Results:** In the 16 pts evaluated, 56% were female, and the median age was 49.5 years. Median follow-up was 22 months (95% CI: 16-26.5) and median number of treatment cycles was 8. Three patients progressed after therapy was discontinued and none have died. Based on volumetric response criteria, 14 of 15 pts with volumetric data available for central review had response to therapy (93%; 95% CI: 68% to 99.8%). Of 16 patients evaluable based on local review, 15 had response to therapy (93.75%; 95% CI: 70% to 99.8%). The median tumor reduction was -83% (range: -52% to -99%). The one nonresponder received 2 days of treatment before coming off therapy due to toxicity. Median progression-free survival was not reached. Grade 3 toxicities at least possibly related to treatment occurred in 12 pts (rash in 6 pts). Grade 4 toxicities were observed in two pts: hyperglycemia (n=1) and increased CPK (n=1). Three pts discontinued treatment for adverse events. **Conclusions:** Vemurafenib/cobimetinib resulted in an objective response in all pts who received 1 or more cycles of therapy. Our study indicates that BRAF/MEK inhibitors could be a powerful tool in the treatment of previously untreated PCP and warrants further evaluation in larger studies. A second arm of this study is enrolling pts with progressive PCP after prior radiotherapy. Support: U10CA180821, U10CA180882; U24CA196171, U10CA180868 (NRG); Genentech; https://acknowledgments.alliancefound.org. Clinical trial information: NCT03224767. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

2001 **Oral Abstract Session**

ALK inhibitors for treatment of adult-onset neuroblastoma. *First Author: Jessica Stiefel, MSKCC, New York, NY*

Background: Neuroblastoma (NB), a rare malignancy of the sympathetic nervous system, is a tumor of early childhood with > 90% of cases diagnosed before 5 years of age. Adult-onset NB (AON) is extremely rare and differs significantly from childhood disease. AON, while more indolent, is usually metastatic at diagnosis, generally chemotherapy-resistant, and almost invariably lethal. Additionally, standard therapies for NB such as dose-intensive chemotherapy and anti-GD2 antibody are poorly tolerated by adults. Prior studies have shown AON is enriched for genomic aberrations especially *ALK* (Suzuki *et al* 2018). Although *ALK* inhibitors (ALKi) are effective for therapy of lymphoma and non-small cell lung cancer, their use in AON has not previously been reported. **Methods:** Retrospective review of patients > 18 years old at diagnosis seen at Memorial Sloan Kettering Cancer Center (MSKCC) was performed after IRB approval. Response to ALKi was evaluated using International Neuroblastoma Response Criteria; objective responses were also noted. Progression-free (PFS) and overall survival (OS) was calculated using Kaplan-Meier methods. **Results:** Since 1979, 52 patients with AON were seen at MSKCC. Of 23 patients evaluated, 14 (61%), harbored somatic *ALK* mutations. Seven were treated with FDA-approved ALKi. One patient initially diagnosed at 12 years of age was treated with ALKi following a relapse 15 years later. Overall, all ALKi were well-tolerated; reported adverse events included grade 1-2 nausea and vomiting (n = 6), and neurologic symptoms including hallucinations, drowsiness, and dizziness (n = 1 patient each) which resolved after stopping ALKi. Four patients received > 1 ALKi either due to progressive disease or intolerance. Most patients responded to the first ALKi with objective though partial response (n = 5) while one had progressive disease (PD). Median time to progression for initial ALKi was 15.5 months (10-45). One patient with no evaluable disease after four prior relapses was treated with alectinib for 36 months without PD. Of the patients treated with a second ALKi (n = 4), 1 had CR and 2 had PR after not having progressed previously, while the other had stable disease. Median OS from beginning treatment with first ALKi was 46.5 (17-74) months. **Conclusions:** AON is a rare disease which is a therapeutic challenge. Enrichment of *ALK* mutations permits consideration of targeted therapy. ALKi were well tolerated, often associated with significant responses, and treatment with serial ALKi led to ongoing benefit. Given this, ALKi should be considered for treatment in future AON cases. Research Sponsor: None.

2002 **Oral Abstract Session**

Efficacy and safety of larotrectinib in adult and pediatric patients with tropomyosin receptor kinase (TRK) fusion-positive primary central nervous system tumors. *First Author: Sébastien Perreault, Department of Neurosciences, CHU Hopital Sainte-Justine, Montréal, QC, Canada*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in various tumor types, including central nervous system (CNS) tumors. Larotrectinib is a first-in-class, highly selective TRK inhibitor approved for the treatment of adult and pediatric patients with TRK fusion cancer, with an objective response rate (ORR) of 78% across 175 adult and pediatric patients with various non-CNS cancers (McDermott et al, ESMO 2020). We report data on patients with TRK fusion-positive primary CNS tumors. **Methods:** Patients with primary CNS tumors harboring an *NTRK* gene fusion enrolled in two clinical trials (NCT02637687, NCT02576431) were identified. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. Response was investigator assessed. **Results:** As of July 2020, 33 patients with TRK fusion-positive CNS tumors were identified: 19 high-grade gliomas (HGG), 8 low-grade gliomas (LGG), 2 glioneuronal tumors, 2 neuroepithelial tumors, 1 CNS neuroblastoma, and 1 small round blue cell tumor. The patients had gene fusions involving *NTRK2* (n = 24; 73%), *NTRK1* (n = 5; 15%), and *NTRK3* (n = 4; 12%). Median age was 8.9 years (range 1.3–79.0); 26 patients were pediatric (< 18 years). Patients were heavily pre-treated with 45% having 2 or more prior lines of systemic therapy. The ORR in all patients was 30% (95% CI 16–49): 3 complete responses (all in pediatric patients), 7 partial responses (2 pending confirmation), 20 stable disease (including 15 pts > 6 months), and 3 progressive disease. The ORR in patients with HGG and LGG were 26% (95% CI 9–51) and 38% (95% CI 9–76), respectively. In all patients, the 24-week disease control rate was 73% (95% CI 54–87). Twenty-three of 28 patients (82%) with measurable disease had tumor shrinkage. The median time to response was 1.9 months. Median duration of response (DoR) was not reached (95% CI 3.8–not estimable [NE]) at a median follow-up of 12.0 months. The 12-month DoR rate was 75% (95% CI 45–100). Median PFS was 18.3 months (95% CI 6.7–NE) at a median follow-up of 16.5 months. Median overall survival (OS) was not reached (95% CI 16.9–NE) at a median follow-up of 16.5 months, with a 12-month OS rate of 85% (95% CI 71–99). Duration of treatment ranged from 1.2 to 31.3+ months. Treatment-related adverse events (TRAE) were reported by 20 patients and were Grade 3–4 in 3 patients (9%). There were no treatment discontinuations due to TRAEs. **Conclusions:** In patients with TRK fusion-positive CNS tumors, larotrectinib demonstrated rapid and durable responses, high disease control rate, and a favorable safety profile. These results support testing for *NTRK* gene fusions in patients of all ages with CNS tumors. Clinical trial information: NCT02637687, NCT02576431. Research Sponsor: Bayer Pharmaceuticals and Loxo Oncology, a subsidiary of Lilly.

2003 **Oral Abstract Session**

The 1994 National Cancer Institute's strategy to fund multi-institutional, multidisciplinary consortia to design and conduct early phase clinical trials in patients with high grade gliomas. *First Author: Stuart A. Grossman, Johns Hopkins Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: : In the early 1990's, the NCI suspended activities of the Brain Tumor Study Group seeking to shift clinical brain tumor research from phase III trials to innovative and correlative rich phase I/II studies. In 1994, NCI funded three early phase brain tumor consortia, later reduced to two consortia in 1999 and one in 2009. In 2020, the NCI announced it would discontinue funding the brain tumor consortium and emphasize pre-clinical glioblastoma drug development (RFA-CA-20-047). **Methods:** The activities of the New Approaches to Brain Tumor Therapy (NABTT: 1994-2009) and Adult Brain Tumor Consortium (ABTC: 2009-2021) were summarized using data from the Central Operations Office that served the consortia for 27 years. **Results:** From 1994-2020, 48 consortium meetings were held to discuss, develop, conduct, and evaluate early phase clinical trials. These involved multidisciplinary brain tumor experts (neuro-oncologists, neurosurgeons, radiation oncologists, neuropathologists, statisticians, pharmacologists, imaging experts, immunologists, etc) from 27 US academic centers and hospitals. 85 clinical trials were written, approved by NCI and the Brain Malignancy Steering Committee, and conducted. Most trials evaluated NCI-provided therapeutic agents. 34 trials were conducted in collaboration with 27 pharmaceutical companies eager to develop malignant brain tumor therapeutics; for 9 of these the consortia held the IND. 4870 patients were accrued: 3375 to therapeutic and 1495 to non-therapeutic studies. 49 grant proposals were submitted to fund consortium activities with a 46% approval rate. 91 peer reviewed manuscripts were published, with 174 presentations and abstracts. 18 pharmaceutical symposia were conducted to attract new agents toward early phase brain tumor research. Consortia sponsored 34 Guest Lectureships and multidisciplinary symposia to focus on relevant critical research areas. Additionally, the consortia provided unique opportunities for young faculty to lead multicenter NABTT/ABTC trials with appropriate support and mentorship. **Conclusions:** Therapeutic progress for high grade gliomas has been slow for many reasons (95% of systemically administered agents do not penetrate the blood-brain barrier, inherent treatment resistance, immunologically "cold" phenotype, etc). NABTT/ABTC focused multidisciplinary, multi-institutional experts on major challenges unique to brain tumor research. The consortia developed innovative early phase clinical studies rich in correlative endpoints, fostered research grants, hosted relevant topical symposia, and provided leadership roles for young investigators while bringing together the NCI, industry, and committed multidisciplinary academicians to explore novel therapeutic options for patients with primary brain tumors. Research Sponsor: NCI.

2004 **Oral Abstract Session**

EORTC 1709/CCTG CE.8: A phase III trial of marizomib in combination with temozolomide-based radiochemotherapy versus temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma. *First Author: Patrick Roth, Department of Neurology, University Hospital Zürich, Zürich, Switzerland*

Background: Patients with newly diagnosed glioblastoma receive postoperative standard therapy with radiotherapy (RT), and concomitant and up to six cycles of maintenance temozolomide (TMZ) chemotherapy (TMZ/RT→TMZ). Marizomib is a novel, irreversible and brain-penetrant pan-proteasome inhibitor with encouraging findings in preclinical models and early-stage clinical trials for patients with newly diagnosed and recurrent glioblastoma. Therefore, a phase 3 trial was designed to explore the activity of marizomib in addition to TMZ/RT→TMZ. ClinicalTrials.gov Identifier: NCT03345095 **Methods:** EORTC 1709/CCTG CE.8 is a multicenter, randomized, controlled, open label phase 3 superiority trial. Eligibility criteria included histologically confirmed newly diagnosed glioblastoma and a Karnofsky performance status (KPS) > 70. Eligible patients were stratified for institution, age, KPS as well as extent of surgery, and centrally randomized in a 1:1 ratio. The primary objective of this study is to compare overall survival (OS) in patients receiving marizomib in addition to standard treatment with patients receiving standard treatment only. Secondary endpoints include progression-free survival (PFS), safety, neurocognitive function, and quality of life. **Results:** The study was opened at 49 EORTC sites in Europe, 23 CCTG sites in Canada, and 8 sites in the US. Patient enrolment started in June 2018 and was close to completion at the time of a planned interim analysis in September 2020. A total of 749 patients (of the planned 750) were randomized when the IDMC recommended to discontinue enrollment. Age, KPS and extent of resection were well balanced between the 2 study arms. No difference in median OS was observed between the standard arm (15.9 months) and the marizomib arm (15.7 months; HR = 0.99). Median PFS was 6.1 vs. 6.2 months (HR = 1.02). Patients in the marizomib group had more often grade 3/4 treatment-emergent adverse events (TEAE) compared to the standard therapy group (42.6% vs. 20.5%), including ataxia, hallucinations and headache. **Conclusions:** The addition of marizomib to standard radiochemotherapy did not improve OS or PFS in patients with newly diagnosed glioblastoma. Final survival analyses including determination of MGMT promoter methylation status and analyses of other secondary endpoints are ongoing. Clinical trial information: NCT03345095. Research Sponsor: Celgene / BMS.

2005 **Oral Abstract Session**

A Phase 0 'trigger' trial of CDK4/6 plus ERK1/2 inhibitors in recurrent glioblastoma. *First Author: Nader Sanai, Ivy Brain Tumor Center, Barrow Neurological Institute, Phoenix, AZ*

Background: The RB-CDK4/6 and MAPK signaling pathways are dysregulated in glioblastoma (GBM). Our recent phase 0 study of ribociclib in recurrent GBM patients suggested that CDK4/6 inhibitor monotherapy is not durable. In this ongoing, dual-drug phase 0 study (NCT04391595), we evaluate the tumor pharmacokinetics (PK) and tumor pharmacodynamics (PD) of abemaciclib, a selective CDK4/6-inhibitor, plus LY3214996, a selective ERK1/2 inhibitor, in recurrent GBM patients. **Methods:** Adult patients eligible for this open-label, multicenter phase 0 protocol had recurrent GBM with (1) intact RB expression, (2) >30% pERK expression, and (3) CDKN2A/B deletion or CDK4/6 amplification. Prior to a planned resection, patients received six days of abemaciclib (150mg BID) plus LY3214996 (200mg QD). In a Time-Escalation Arm, ten patients were assigned to 3-5 hour or 7-9 hour intervals from final drug dose to tumor removal. Tumor tissue (gadolinium [Gd]-enhancing and nonenhancing regions), cerebrospinal fluid (CSF), and plasma were collected. Total and unbound drug concentrations were measured using validated LC-MS/MS methods. Tumor PD effects, including RB and RSK phosphorylation, were compared to matched archival or pre-treatment biopsied tissue. A PK 'trigger' (*i.e.,* unbound concentration > 5x biochemical IC_{50}) was set for each drug. Gd-nonenhancing tumor tissue exhibiting abemaciclib and LY3214996 concentrations in excess of their trigger threshold qualified patients for postoperative dual-drug therapy. **Results:** In this interim analysis, no dose-limiting toxicities were observed. In Gd-nonenhancing tumor regions, median unbound concentrations of abemaciclib (including its equipotent M2 and M20 metabolites) were 31.2 nM (3-5 hour cohort) and 25.1 nM (7-9 hour cohort). In the same tissue, median unbound concentrations of LY3214996 were 52.0 nM (3-5 hour cohort) and 10.2 nM (7-9 hour cohort). Tumor RB and RSK phosphorylation decreased in 6/10 and 2/10 patients, respectively. Gd-enhancing tumor proliferation (MIB-1) was decreased in 8/10 patients. 5/10 patients exceeded PK thresholds for both abemaciclib (12 nM) and LY3214996 (25 nM), thereby entering the study's therapeutic expansion phase. **Conclusion:** Abemaciclib and LY3214996 achieve pharmacologically-relevant concentrations in Gd-non-enhancing GBM tissue and are associated with suppression of the RB pathway and tumor proliferation. Following 6 days of presurgical drug exposure, the Optimal Time Interval (OTI) for tissue sampling was 3-5 hours after the final drug dose. Based on this interim analysis, the trial will accrue an additional 25 patients at this OTI. Clinical trial information: NCT04391595. Research Sponsor: The Ben and Catherine Ivy Foundation, Other Foundation.

2006 **Oral Abstract Session**

Evaluating the benefit of adaptive randomization in the CC-115 arm of the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A phase II randomized Bayesian adaptive platform trial in newly diagnosed MGMT unmethylated glioblastoma. *First Author: Rifaquat Rahman, Dana-Farber/Brigham and Women's Cancer Center, Boston, MA*

Background: Adaptive randomization adjusts enrollment rates based upon early trial results, which can allow for decreased enrollment for therapies less likely to meet the primary endpoint of a trial. CC-115, a CNS-penetrant, oral inhibitor of mammalian target of rapamycin kinase (mTOR) and deoxyribonucleic acid-dependent protein kinase (DNA-PK), was evaluated in the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) trial. As CC-115 was discontinued due to concerns about toxicity and unfavorable risk-to-benefit ratio, we sought to investigate the impact of adaptive randomization in its testing. **Methods:** In INSIGhT, adults with newly diagnosed MGMT-unmethylated glioblastoma and available genomic data are adaptively randomized to an experimental arm or the control arm of standard radiotherapy with concurrent and adjuvant temozolomide. Patients randomized to CC-115 received it (10mg po BID) with radiotherapy and as adjuvant monotherapy, and a safety lead-in 3+3 design was used for this arm. By simulating the INSIGhT trial with standard uniform randomization, we estimated the reduction of enrollment rate and sample size of the CC-115 arm that was attributable to adaptive randomization. **Results:** Twelve patients were randomized to CC-115; 58% (n = 7) patients had possible treatment-related CTCAE grade > 3 toxicity. Compared to the control arm, there was no significant difference in progression-free survival (PFS, HR 0.66, 95% CI 0.32-1.36, p = 0.3) or overall survival (OS, HR 0.93, 95% CI 0.43-2.03, p = 0.8). Based on early PFS results, randomization probability to CC-115 decreased from 25% to 16%. At the time of the CC-115 arm closure, 14% of enrolled INSIGhT patients had been randomized to this arm. Compared to average expected enrollment by standard randomization, the use of adaptive randomization decreased the number of patients randomized to CC-115 by 50% (12 patients vs. 18 patients [95% CI 11-25 patients]). **Conclusions:** The INSIGhT trial, designed with adaptive randomization, facilitated more efficient testing of CC-115 and decreased the number of patients allocated to the CC-115 arm relative to a standard randomization design. Clinical trial information: NCT02977780. Research Sponsor: Puma Biotechnology, Inc.; Celgene Corp.; Eli Lilly and Company; Accelerated Brain Cancer Cure, Burroughs Wellcome Fund.

2007 **Oral Abstract Session**

Olaparib in recurrent IDH-mutant high-grade glioma (OLAGLI). *First Author: Francois Ducray, Service de Neuro-oncologie, Hôpital Neurologique, Hospices Civils de Lyon, Lyon, France*

Background: There is a need to develop new treatments in IDH-mutant high-grade gliomas recurring after radiotherapy and chemotherapy. Based on preclinical studies showing that IDH-mutant tumors could be vulnerable to PARP inhibition we launched a phase II study to test the efficacy of olaparib (Lynparza) monotherapy in this population. **Methods:** Adults with recurrent high-grade IDH-mutant gliomas after radiotherapy and at least one line of alkylating chemotherapy (PCV or TMZ), KPS > 60, normal organ function were enrolled. The primary endpoint was 6 months PFS according to RANO criteria. Patients were treated with olaparib 300 mg twice daily. We used a single-stage Fleming design with p0 = 30%, p1 = 50%, a type I unilateral error rate of 5% and a power of 80%. **Results:** 35 patients with recurrent IDH-mutant gliomas (IDH1R132H-mutant n = 32, other IDH mutation n = 3, 1p/19 codeleted n = 16, 1p/19q non-codeleted n = 14) were enrolled (malignantly transformed low-grade gliomas n = 21, anaplastic gliomas n = 8, glioblastomas n = 6). Median time since diagnosis was 7.4 years (1-22 years), median time since radiotherapy was 2.8 years (0.6-18 years), median number of previous chemotherapy lines was 2 (1-5). With a median follow-up of 11 months, 30 patients had stopped treatment due to tumor progression and 2 patients were still on treatment 16 to 18 months after treatment start. At 6 months, 11/35 patients were progression-free (31 %). According to RANO criteria, based on local investigator analysis, 2 patients (5%) had a partial response and 14 patients a stable disease (37%) with a median duration of response of 9 months (4-18 months+). Median PFS and OS were 2.3 and 15.9 months and were similar in 1p/19q codeleted and non-codeleted patients. A grade 3 olaparib-related adverse event was observed in 5 patients (14%, lymphopenia n = 3, fatigue n = 2, diarrhea n = 1) and a grade 2 in 15 patients (43%), most frequently consisting in fatigue (23%), gastrointestinal disorders (20%) and lymphopenia (20%). No patient definitively stopped olaparib due to side effects. **Conclusions:** In this heavily pre-treated population of recurrent IDH-mutant gliomas, olaparib monotherapy was well tolerated and resulted in some activity supporting its evaluation in association with alkylating chemotherapy in recurrent IDH-mutant gliomas in future studies. Clinical trial information: NCT03561870. Research Sponsor: French Ministry of Health, Other Foundation, Pharmaceutical/Biotech Company.

2008 **Oral Abstract Session**

Impact of mutant IDH (mIDH) inhibition on DNA hydroxymethylation, tumor cell function, and tumor immune microenvironment (TIME) in resected m*IDH1* lower-grade glioma (LGG). *First Author: Min Lu, Agios Pharmaceuticals, Inc., Cambridge, MA*

Background: Somatic mutations in *IDH1* and *IDH2* occur in ~80% and ~4% of LGGs, respectively, promoting tumorigenesis via increased levels of the oncometabolite D-2-hydroxyglutarate (2-HG). Vorasidenib (VOR; AG-881) is an oral, brain-penetrant, dual inhibitor of mIDH1/2; ivosidenib (IVO; AG-120) is a first-in-class oral inhibitor of mIDH1. In this ongoing perioperative study, treatment with IVO/VOR reduced 2-HG levels in resected tumors vs untreated control tumors in patients (pts) with LGG (NCT03343197; Mellinghoff SNO 2019). We assessed the biological impact of 2-HG suppression on tumors and TIME. **Methods:** Pts (n = 49) with recurrent, non-enhancing, mIDH1-R132H LGG eligible for resection were randomized to IVO (500 mg QD/250 mg BID), VOR (10/50 mg QD), or no treatment, for 4 weeks preoperatively. Tumor tissue samples collected at surgery were assessed in genomic (n = 42), transcriptomic (n = 42), and immunohistochemistry (IHC; n = 43) analyses. Unpaired t-test was used for statistical comparisons. **Results:** Optimal 2-HG suppression (post-treatment 2-HG below the upper limit of 2-HG levels in a reference set of 15 wild-type [wt] IDH samples) was observed in 23 of 40 pts, including 9 (90%) pts receiving VOR 50 mg QD and 6 (50%) receiving IVO 500 mg QD. Of samples with valid biomarker data, those with optimal 2-HG suppression (n = 21) showed upregulation of neural differentiation-related gene expression, but downregulation of stemness-related gene expression, vs those with suboptimal 2-HG suppression (post-treatment 2-HG above upper limit of wt IDH 2-HG levels; n = 17; $p < 0.01$). IHC analysis of the proliferation marker Ki-67 showed a ~2-fold decrease in Ki-67–positive cells in samples with optimal 2-HG suppression (mean 2.7%; n = 22) vs those with suboptimal suppression (5.8%; n = 16; $p < 0.05$). Epigenetic analysis revealed a ~2-fold increase in mean 5-hydroxymethylcytosine (5hmC) levels in samples with optimal (0.36%; n = 17) vs suboptimal 2-HG suppression (0.2%; n = 15; $p < 0.05$), suggesting reversal of TET2 inhibition. IHC analysis of TIME revealed increases in mean CD3+ and CD8+ tumor-infiltrating lymphocyte levels in samples with optimal (1.05% [CD3]/0.22% [CD8]; n = 22) vs suboptimal 2-HG suppression (0.44% [CD3]/0.07% [CD8]; n = 16; $p < 0.05$). Optimal 2-HG suppression was associated with upregulation of gene expression related to type I interferon signaling and antigen presentation ($p < 0.01$). **Conclusions:** These data suggest that both tumor-intrinsic and -extrinsic mechanisms underlie 2-HG suppression by VOR and IVO. VOR, and IVO to a lesser extent, increased 5hmC, promoted cellular differentiation, and inhibited tumor cell proliferation; both also increased T-cell infiltration, activated interferon signaling, and increased antigen presentation capability. These data support development of VOR in combination with immunotherapy. Clinical trial information: NCT03343197. Research Sponsor: Agios Pharmaceuticals, Inc.

2009 **Clinical Science Symposium**

First-in-human CAN-3110 (ICP-34.5 expressing HSV-1 oncolytic virus) in patients with recurrent high-grade glioma. *First Author: E. Antonio Chiocca, Brigham and Women's Hospital, Boston, MA*

Background: Recurrent glioma patients have few therapeutic options and an expected survival of only 7 to 10 months. New treatments to improve the prognosis of this patient population are a dire medical need. Oncolytic viruses (OVs) are emerging as important new agents for cancer treatment. The first FDA approved OV was talimogene laherparepvec (Imlygic, T-Vec) for treatment of melanoma. T-Vec, as most other clinical HSV-1 based OVs, is deleted in the ICP34.5 gene, which is responsible for HSV-1 neurovirulence. However, deletion of ICP34.5 also impedes efficient viral replication. CAN-3110 (rQNestin34.5v2) maintains a copy of the HSV1 ICP34.5 gene under transcriptional control of the tumor-specific promoter for nestin to drive robust tumor-selective replication. CAN-3110 replicates in malignant glioma cells far above levels seen with ICP34.5 deleted viruses. This potency also created the hypothetical risk for increased neurovirulence, thus the regulatory advice to conduct a cautious nine-dose-level Phase-1 dose escalation study in patients with recurrent high-grade glioma (HGG). **Methods:** From September 2017 to February 2020, thirty patients with biopsy-confirmed recurrent high-grade glioma were treated in an open label clinical trial. Patients with multifocal, multicentric, tumors larger than 5 cm, and tumors that had recurred multiple times were eligible. All patients received best standard of care treatments as indicated by their physician. CAN-3110 was injected intratumorally starting at $1x10^6$ plaque forming units (pfu) and dose-escalating (3+3 design) by half log increments up to $1x10^{10}$ pfu. Tissue (when possible) and blood samples were obtained before and during treatment for experimental medicine analyses. **Results:** CAN-3110 was well tolerated with no dose limiting toxicity observed. The initial tissue diagnosis of the recurrent tumor for the 30 subjects was 26 glioblastoma, 3 anaplastic oligodendroglioma, and 1 anaplastic astrocytoma. The median overall survival (mOS) of the entire study group is 13.25 months. Post-treatment tissue is available for 18/30 subjects and revealed persistence of HSV antigen and CD8+ T cell infiltrates. Additional response, immunologic (including T cell receptor repertoire), transcriptomic and single cell RNA sequencing analyses are ongoing. **Conclusions:** Administration of CAN-3110 into recurrent glioma was well tolerated without evidence of ICP34.5-induced encephalitis/meningitis. Histological and molecular analyses showed evidence of biological activity and that CAN-3110 injection was associated with immune activation and viral antigen persistence. Although definitive clinical efficacy cannot be determined in this small phase 1 study, OS of CAN-3110 treated subjects compares favorably to historical reports and warrants further clinical studies. Clinical trial information: NCT03152318. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

2010 **Clinical Science Symposium**

Phase 1 dose-escalation trial using convection-enhanced delivery of radiolabeled monoclonal antibody for diffuse intrinsic pontine glioma following external radiation therapy. *First Author: Mark M. Souweidane, Weill Cornell Medical College, New York, NY*

Background: The prognosis of diffuse intrinsic pontine glioma (DIPG) is dire with a median overall survival less than one-year. ^{124}I-omburtamab is a radiolabeled monoclonal antibody that targets B7-H3 epitope. We evaluated the safety of administering escalating doses and volumes of ^{124}I-omburtamab via convection-enhanced delivery (CED) in children with DIPG. **Methods:** MSKCC 11-011 trial is a standard 3+3 phase 1, open-label, dose escalation study in patients with non-progressive DIPG. CED of ^{124}I-omburtamab was performed between 4-14 weeks post-external radiation therapy. Nine dose levels of a single injection of ^{124}I-omburtamab (Y-mAbs Therapeutics, USA) (range 0.25 to 8.0 mCi; and volume of infusion (V_i) from 250 to 8,000 µl) have been evaluated so far. Patients were assessed weekly for 30 days. **Results:** 46 children were evaluable for primary and secondary endpoints. The median age at enrolment was 6.5 years (range 2-17). Two patients have experienced AEs CTCAE grade 3 that were categorized as dose limiting toxicities (DLTs), which led to inclusion of three more patients at both the 4 and 6 mCi dose levels. Eight patients have reported transient AEs of grade 3 considered related to ^{124}I-omburtamab. The acute grade 3 AEs were generally indicative of nervous system effects due to volume intolerance or radiation injury, and included hemiparesis (n = 3), dysarthria (n = 3), ataxia (n = 3), dysphagia (n = 2), muscular weakness (n = 2) and gait disturbance (n = 1). There were no related AEs CTCAE grade 4 or 5. Estimations of distribution volumes based on T2-weighted imaging were linearly related to volume with a mean volume of distribution/volume of infusion ratio (V_d/V_i) between 3 and 3.5. The mean ratio of lesion-to-whole body absorbed dose was ~1000. Median overall survival from diagnosis across all cohorts was 14.8 months (n = 46, 95% CI 11.5, 16.8) and the survival rate estimates (with 95% confidence intervals) at 1, 2, 3 and 5 years were 0.63 (0.46;0.76); 0.13 (0.05;0.26); 0.08 (0.02;0.19); and 0.04 (0.00;0.16), respectively. Four patients have survived > 3 years; two remain alive at 46 and 96 months and two have died at 43 and 53 months, both with CNS disease outside of the treatment field and one with extra-CNS metastases. **Conclusions:** ^{124}I-omburtamab via CED into the brain stem of children with DIPG and previously irradiated provides a possibility for improved treatment of DIPG. A dose of 8mCi and an infusion volume of 8,000 µl is considered safe and may provide a distribution volume large enough to cover tumor volumes up to 20 cm^3. The median overall survival of all patients included in the trial appears to be increased with 3-4 months compared to historical control data from consortia trials. A phase 2 trial aiming at investigating the efficacy of radiolabeled omburtamab administered via CED is being planned. Clinical trial information: NCT01502917. Research Sponsor: YmAbs Therapeutics.

2011 **Clinical Science Symposium**

Cerebrospinal fluid circulating tumor cells as a predictive biomarker for proton craniospinal irradiation for leptomeningeal metastases. *First Author: N. Ari Wijetunga, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Leptomeningeal metastasis (LM) involves seeding of tumor cells to the cerebrospinal fluid (CSF) and the leptomeninges. Proton craniospinal irradiation (pCSI) has been shown to be potentially effective for patients with solid tumor LM. We evaluated whether CSF circulating tumor cells (CSF-CTC) and neuroimaging correlate with outcomes in patients with LM treated with pCSI. **Methods:** We reviewed a single-institution retrospective database of patients treated with pCSI for LM between 2018-2020 who had ≥ 3 months (mos.) follow-up and identified 58 patients. Pre-pCSI CSF-CTC using CellSearch and magnetic resonance imaging (MRI) data, and post-pCSI CSF-CTC nadir before initiation of new cancer-directed therapy were assessed. The optimal cutoff for pre-pCSI CSF-CTC was determined using maximally selected rank statistics. Kaplan Meier analysis was used to identify univariate correlates with CNS progression free survival (CNS PFS) and overall survival (OS), calculated from start of pCSI. Multivariate Cox proportional hazards modeling was used to test independence of univariate associations. **Results:** The median follow-up for patients who were censored (n = 15, 26%) was 15 mos. (interquartile range (IQR): 9 -21). Most patients were diagnosed with lung (n = 27, 47%) or breast cancer (n = 22, 38%). The median CNS PFS and OS were 6 mos. (IQR: 3 – 9) and 8 mos. (IQR: 5 – 18), respectively. Of the 49 patients with pre-pCSI CSF-CTCs analyzed, CSF-CTCs were identified in 43 (88%). Pre-pCSI CSF-CTC< 53/3mL was associated with improved CNS PFS (11.8 vs 6.0 mos., p = 0.01), and a trend toward improved OS (16.7 vs 7.7 mos., p = 0.08). On pre-pCSI MRI, patients with parenchymal brain metastases (n = 33, 57%) had worse OS (6.7 vs 12.7 mos., p = 0.01) but not CNS PFS. Patients with both brain and spine LM (n = 42, 72%) compared to those only one site or no visible disease (n = 16, 28%) showed worse CNS PFS (5.8 vs 7.5 mos., p = 0.03) and OS (7.7 vs 16.7 mos., p = 0.05). In a multivariate model, pre-pCSI CSF-CTC was significantly associated with CNS PFS (p = 0.03) while brain and spine LM on MRI was not (p = 0.20) No patient had an increase in CSF-CTC immediately post-pCSI, and in those with both detectable pre-pCSI CSF-CTCsand a post-pCSI. measurement(n = 29, 50%), the median decrease at nadir was 37/3mL (range: 0-200) occurring at a median of 1.6 mos. (range: 0.5 -5.2). A decrease in CSF-CTC > 37/3mL was associated with improved CNS PFS (7.1 vs 4.4 mos., p = 0.04) but not OS (12.5 vs.7.7 mos., p = 0.2). **Conclusions:** Proton CSI is an effective treatment for patients with solid tumor LM and can result in prolonged disease control in some patients. Lower CSF-CTC count prior to pCSI and larger changes after pCSI are predictive of survival outcomes, arguing for early pCSI intervention for solid tumor LMD. Early treatment escalation after pCSI can be considered for patients with high pre-pCSI CSF-CTC and a smaller nadir post-pCSI. Research Sponsor: U.S. National Institutes of Health.

2012 **Clinical Science Symposium**

Serial plasma and CSF cell-free tumor DNA (cf-tDNA) tracking in diffuse midline glioma patients undergoing treatment with ONC201. *First Author: Evan Cantor, University of Michigan, Ann Arbor, MI*

Background: Diffuse midline glioma (DMG) with the H3K27M mutation is a lethal childhood brain cancer, with patients rarely surviving 2 years from diagnosis. There are few available means of monitoring the disease beyond serial MRI scans, making clinical decision making slow, difficult, and often reactive. **Methods:** We conducted a multi-site phase 1 trial of the imipridone ONC201 for children with H3K27M-mutant glioma (NCT03416530). Patients enrolled on Arm D of the trial (n=24) underwent serial lumbar puncture (baseline, 2 and 6 months) for cell-free tumor DNA (cf-tDNA) analysis at time of MRI. Additionally, patients on all arms of the trial at the University of Michigan underwent serial plasma collection. CSF collection was feasible in this cohort, with no procedural complications. We collected a total of 96 plasma samples and 53 CSF samples from 29 patients, including those with H3F3A (H3.3) (n=13), HIST13HB (H3.1) (n= 4), and unknown H3 status/not biopsied (n=12) [range of 0-8 CSF samples and 0-10 plasma samples]. We performed digital droplet polymerase chain reaction (ddPCR) analysis and/or amplicon-based electronic sequencing (Oxford Nanopore) of cf-tDNA samples and compared variant allele fraction (VAF) to radiographic change (maximal 2D tumor area on MRI). **Results:** Preliminary analysis of samples (n=58) demonstrates a correlation between changes in tumor size and H3K27M cf-tDNA VAF, when removing samples with concurrent bevacizumab. Analysis of remaining CSF and plasma samples is ongoing, including analysis of novel biomarkers of response. In multiple cases, early reduction in CSF cf-tDNA predicts long-term clinical response ($>$1 year) to ONC201 and does not increase in cases of later-defined pseudo-progression (radiation necrosis). For example, a now 9-year old patient with thalamic H3K27M-mutant DMG underwent treatment with ONC201 after initial radiation and developed an increase in tumor size at 4 months post-radiation (124% baseline) of unclear etiology at the time. Meanwhile, her ddPCR declined from baseline 6.76% VAF to $<$1%, which has persisted, with now near complete response (85% tumor reduction) at 30 months on treatment from diagnosis. **Conclusions:** In summary, we present the feasibility and utility of serial CSF/plasma monitoring of a promising experimental therapy for DMG. Research Sponsor: Defeat DIPG.

2013 **Poster Discussion Session**

Long-term results of the GEINO 1401 TRIAL: Randomizing patients to stop or to continue temozolomide until 12 cycles. *First Author: Marta Domenech, Institut Catala d'Oncologia Badalona. Applied Research Group in Oncology (B- ARGO Group), Institut Investigació Germans Trias i Pujol (IGTP), Badalona, Spain*

Background: We previously presented our results of the GEINO 1401 trial that randomized patients diagnosed with glioblastoma and treated with chemoradiotherapy and adjuvant temozolomide (TMZ) followed by six cycles of TMZ, to receive an extended use of TMZ up to 12 cycles or to control. We found no differences in 6-months neither progression free survival (PFS) nor overall survival (OS). In this report we actualize our results and analyse long-term survivor patients (LTSP). **Methods:** The trial NCT02209948 randomized (ratio 1:1) 159 patients diagnosed with glioblastoma who had been treated with standard therapy to stop treatment or to continue up to 12 cycles of TMZ. Patients were stratified based on their O6-methylguanine-DNA-methyltransferasa (MGMT) methylation status and presence or absence of measurable disease at inclusion. We update here OS outcomes and analyse the data of LTSP defined as an OS over 30 months from diagnosis. **Results:** At a median follow-up of 20 months, 82.4% of the patients had died and 89.9% had progressed. The median OS from randomization was 22.0 months for the control arm and 18.2 for the experimental arm: HR 0.957 (95%CI 0.806-1.136, p = 0.615). At 2 years from randomization there were a 61% of survivors in the TMZ group and 62% in the control group. There were a 49.7% of LTSP showing no differences between TMZ and control group. We found a higher prevalence of methylated MGMT in LTSP, but no differences were shown in patients with or without measurable disease at inclusion, status of IDH and the use of bevacizumab after progression. **Conclusions:** Adding 6 cycles of TMZ after the first 6 adjuvant cycles confers no additional benefit in OS. Nearly 50% of the patients included in GEINO 1401 who had been previously treated with TMZ 6 cycles without progressing were LTSP. Clinical trial information: NCT02209948. Research Sponsor: Spanish Institute Carlos III.

2014 **Poster Discussion Session**

Preliminary results of the abemaciclib arm in the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT): A phase II platform trial using Bayesian adaptive randomization. *First Author: Eudocia Quant Lee, Dana-Farber Cancer Institute, Boston, MA*

Background: The cyclin D-CDK4/6-Rb pathway is activated in most glioblastomas. Abemaciclib is a potent CDK4/6 inhibitor with good brain penetration approved for HR+/HER2- breast cancer. In order to efficiently evaluate the potential impact of abemaciclib on overall survival (OS) in newly diagnosed glioblastoma and to simultaneously develop information regarding potential genomic biomarker associations, abemaciclib was included as an arm on the Individualized Screening Trial of Innovative Glioblastoma Therapy (INSIGhT) trial. INSIGhT is a phase II platform trial using response adaptive randomization and deep genomic profiling to more efficiently test experimental agents in MGMT unmethylated glioblastoma and potentially accelerate identification of novel therapies for phase III testing. Initial randomization was equal between abemaciclib, control, and two other experimental arms but subsequent randomization was adapted based on efficacy as determined by progression-free survival (PFS). Ineffective arms were discontinued and new arms added by protocol amendment. We report preliminary results for the abemaciclib arm which has completed accrual. **Methods:** Patients with newly diagnosed MGMT-unmethylated glioblastoma were randomized to receive either radiotherapy with concomitant and adjuvant temozolomide at standard doses or standard radiochemotherapy followed by adjuvant abemaciclib (150-200 mg orally BID). Treatment continued until progression or development of unacceptable toxicities. The primary endpoint was OS which was assessed using the log-rank test estimated via the Kaplan Meier method using a type I error of 5%. The hazard ratio (HR) was estimated using a cox proportional hazards model. Association between abemaciclib efficacy and cyclin D-CDK4/6-Rb pathway genomic alterations was also investigated. **Results:** There were 142 patients (69 control; 73 treated with abemaciclib). Abemaciclib was generally well-tolerated with no new toxicity signals identified. PFS was significantly longer (HR 0.67; p = 0.03, logrank test) with abemaciclib (median 6.54 months) compared to the control arm (median 5.88 months). For patients with activation of the CDK4 pathway the PFS HR was 0.64 (p-value = 0.04). However, there was no significant improvement in overall survival (HR 0.9; p-value $>$ 0.05) between abemaciclib (median 15.5) compared to the control arm (median 15.5). **Conclusions:** Abemaciclib was well-tolerated and prolonged PFS but there is no evidence of an overall survival improvement compared to standard radiochemotherapy. Clinical trial information: NCT02977780. Research Sponsor: Dana-Farber Cancer Institute.

2015 **Poster Discussion Session**

Randomized phase 2 study of nivolumab (nivo) plus either standard or reduced dose bevacizumab (bev) in recurrent glioblastoma (rGBM). *First Author: Manmeet Singh Ahluwalia, Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Neurological Institute, Taussig Cancer Institute and Cleveland Clinic, Cleveland, OH*

Background: Trials with anti-PD1 in rGBM have shown limited efficacy. VEGF is highly up regulated proangiogenic growth factor in GBM contributing to tumor-associated immunosuppression. Preclinical data suggests a potential dose effect of anti-VEGF therapy on immunomodulation. Hence, a combination of anti-PD1 and anti-VEGF may be a promising approach in rGBM. **Methods:** 90 patients with first-recurrent GBM were randomized (1:1) to nivolumab (240 mg IV Q2 weeks) with bevacizumab at standard (10 mg/kg; Arm A) or at low dose (3 mg/kg; Arm B) IV Q2 weeks. Stratification included extent of resection, age, performance status and MGMT methylation status. Single cell RNA sequencing with CITE-seq was used to analyze blood samples from pre- and 8 weeks post-treatment among 8 responders and 8 non-responders. Progression-free survival (PFS) and overall survival (OS) were compared between two arms. **Results:** 90 patients (Median age 60.6 years ranged 27.4-86.4, 67.8% male, median KPS 80) were enrolled between May 2018 and Jan 2020. Patients were followed in median 7.7 months (Range 0.7, 28.2). 35 of 88 patients were MGMT methylated (2 indeterminate). Overall OS was not significantly different between arm A and arm B (1 year: 41.1 vs 37.7%, p = 0.14), while OS was better for arm A in age $>$ 60 (At 1-year: 46.2% vs 23.8%; Median: 10.6 vs 5.9 months; P = 0.046). OS was no different in the two arms for age $\leq$ 60 years (At 1-year: 35.6% vs 56.4; Median 8.0 vs 12.4 months; P = 0.90). Single cell RNA sequencing with CITE-seq was used to analyze blood samples from 16 patients, baseline and 8 weeks post treatment. Standard dose bevacizumab treated patients had decreased myeloid derived suppressor cells and an inflammatory response gene signature at 8 weeks. Most frequent toxicities ($>$ 20%) included fatigue (45.6%), proteinuria (34.4 %), diarrhea (28.9%), hypertension (23.3%) and lipase increase (21.1%). Toxicities in grade 3-4 were hypertension (7.8%), fatigue (5.6) and other non-neurological toxicities including DVT, PE, infection, and abnormal liver function. **Conclusions:** Overall PFS and OS rates appear similar for nivolumab with either standard or low-dose bevacizumab compared to historical benchmarks of bevacizumab monotherapy. Nivolumab with standard bevacizumab may benefit older but not younger patients. Ongoing response evaluation and immunocorrelative data will be presented. Clinical trial information: NCT03452579. Research Sponsor: Bristol Myers Squibb.

2016 **Poster Discussion Session**

Digital measurement of functional status of patients with glioblastoma. *First Author: Yasaman Demastani, Karyopharm Therapeutics Inc., Newton, MA*

Background: Among the primary aims of new therapies for glioblastoma (GBM) are the reduction of morbidity and restoration or preservation of quality of life (QoL). Selinexor (SEL) is a first-in class, oral, selective inhibitor of nuclear export which blocks exportin 1 (XPO1), forcing the nuclear retention and reactivation of tumor suppressor proteins, ultimately causing cell death in cancer cells. SEL is approved for the treatment of previously treated multiple myeloma and DLBCL. XPORT-GBM-029 (NCT04421378) is a phase 1 dose finding study followed by an open-label randomized phase 2, 3-arm trial to evaluate SEL in combination with standard therapies for newly diagnosed and recurrent GBM: Arm A (ndGBM, uMGMT) – radiation +/- SEL; Arm B (ndGBM, mMGMT) – radiation and temozolomide +/- SEL; Arm C (rGBM) – lomustine +/- SEL at first relapse. We look to identify sensitive, reliable, and clinically meaningful digital assessments of the functional status of ndGBM and rGBM patients via a patient-centric approach. **Methods:** XPORT-GBM-029 incorporates standard clinical and imaging evaluations of GBM progression with novel digital tools that objectively measure motor and cognitive function. The study is conducted at 50 sites globally with the aim of enrolling 350 patients with newly diagnosed and recurrent GBM. Following discussions with KOLs and patient advocacy partners at EndbrainCancer, we surveyed GBM patients and their caregivers to identify disease manifestations critical to patients' QoL. The survey revealed four key areas impacting patients' QoL that can be affected by GBM therapies and can be objectively monitored: cognitive function, lateralization, fatigue, and sleep. In this trial we use objective measurements to evaluate SEL's effects on GBM patients' QoL. Patients wear inertial sensors to measure their activity and sleep and complete a cognitive battery at baseline and before each MRI. **Results:** Associations between objective digital measures of activity, gait, fatigue, sleep, and cognition will be examined with respect to clinical assessments including physical examinations, modified Response Assessment in Neuro-Oncology (mRANO), Neurologic Assessment in Neuro-Oncology (NANO), Karnofsky Performance Score (KPS) and Patient Reported Outcome (PRO) QoL questionnaires. Descriptive summary statistics and plots are employed in exploratory data analysis, and other advanced data mining methods may also be considered. **Conclusions:** XPORT-GBM-029 trial is probably the first large, prospective, longitudinal study in GBM patients employing digital markers and may provide useful information regarding the utility of wearable and mobile devices for measuring functional outcomes in clinical trials. Clinical trial information: NCT04421378. Research Sponsor: Karyopharm Therapeutics Inc.

2017 **Poster Discussion Session**

Superior overall survival (OS) and disease-free survival (DFS) predictions for patients with glioblastoma multiforme (GBM) using Cellworks Singula: myCare-022-03. *First Author: Patrick Y. Wen, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

Background: The Cellworks Singula Therapeutic Response Index (TRI) has been developed to assist clinicians and GBM patients in choosing between competing therapeutic options. In contrast to approaches that consider single aberrations, which often yield limited benefit, Cellworks utilizes an individual patient's next generation sequencing results and a mechanistic multi-omics biology model, the Cellworks Omics Biology Model (CBM), to biosimulate downstream molecular effects of cell signaling, drugs, and radiation on patient-specific in silico diseased cells. For any individual patient and alternative therapy, Cellworks integrates this biologically modeled multi-omics information into a continuous Singula TRI Score, scaled from 0 (low therapeutic benefit) to 100 (high therapeutic benefit). We demonstrate that Singula is strongly associated with OS and DFS beyond standard clinical factors, including patient age, patient gender, and physician prescribed treatments (PPT). **Methods:** In this study, Singula's ability to predict response was evaluated in a retrospective cohort of 100 GBM patients with OS and DFS data from The Cancer Genome Atlas (TCGA) project, treated with PPT. As a primary analysis of the CBM and TRI Score, Cox Proportional Hazards (PH) regression and likelihood ratio (LR) tests were used to assess the hypothesis that Singula is predictive of OS and DFS above and beyond patient age, patient gender, and PPT. A p-value < 0.05 for the corresponding likelihood ratio statistic was required to be considered significant. **Results:** Multivariate analyses were performed to assess the performance of the Singula Therapy Response Index after adjusting for the contribution of standard clinical factors. The same Singula TRI algorithm and clinical cutoffs were used for all clinical outcome measures. These analyses, shown in the table, suggests that the proposed Singula TRI provides predictive value of OS and DFS above and beyond patient age, patient gender, and PPT. **Conclusions:** The Singula TRI Score provides a continuous measure scaled from 0 (low benefit) to 100 (high benefit) for alternative GBM therapeutic options. In this retrospective cohort, Singula was strongly predictive of OS and DFS and provided predictive value beyond PPT, patient age and gender. These results will be further validated in larger scale, prospectively designed clinical studies. Research Sponsor: None.

LR analysis for TRI.

	OS	OS	OS	DFS	DFS	DFS
Test	df	χ^2	p-value	df	χ^2	p-value
Likelihood Ratio	1	6.2326	0.0125	1	4.9160	0.0266

2018 **Poster Discussion Session**

A multisite clinical trial of spectroscopic MRI-guided radiation dose escalation for newly-diagnosed glioblastomas. *First Author: Hui-Kuo George Shu, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Glioblastoma (GBM) is the most common adult primary malignant brain tumor. These pts have poor outcomes [median overall survival (OS) ~ 16 months] despite radiation therapy (RT) to 60 Gy and temozolomide (TMZ). Magnetic resonance spectroscopy (MRS) measures levels of specific metabolites in the brain including choline (Cho) and N-acetyl aspartate (NAA). Previously, we found that high Cho/NAA ratios can aid in localizing regions of brain at high risk for GBM recurrence that may not be appreciated on standard contrast-enhanced (CE) MRI. Based on this finding, we conducted a clinical trial to assess the feasibility and safety of using an advanced volumetric MRS technique termed spectroscopic MRI (sMRI) to guide RT dose escalation for newly-diagnosed GBMs. **Methods:** Our clinical trial (NCT03137888) funded by the NCI (RO1CA214557) enrolled pts at 3 institutions (Emory U, U Miami, Johns Hopkins U) from 5/2017 to 4/2019. This study was approved by the IRB at each respective institution. Eligibility criteria included newly-diagnosed GBM pts $\geq$ 18 years of age with a tumor site that could be adequately imaged by sMRI. Cho/NAA ratio was normalized to the contralateral normal appearing white matter (NAWM). For RT planning, standard gross tumor volumes (GTV1 & 2) were defined based on T2-FLAIR and T1 CE MRIs and 5 mm margins were added to generate clinical tumor volumes (CTV1 & 2). GTV3 (= CTV3, sMRI-defined) was generated by the union of residual CE tumor and Cho/NAA $\geq$ 2x NAWM. To remain eligible, CTV3 was required to be $\leq$ 65 cc. Planning target volumes (PTVs) were generated by applying a 3 mm margin around CTVs. 50.1, 60 and 75 Gy in 30 fractions were prescribed to PTV1, PTV2 and PTV3, respectively. All pts received standard concurrent/adjuvant TMZ. Survival curves were generated by the Kaplan-Meier method. Toxicities were assessed according to CTCAE v4.0. **Results:** 30 pts met eligibility and were treated on study. Mean/median ages were 56.4/58.9 years. 9 pts (30%) were MGMT methylated; 2 pts (6.7%) harbored an IDH1 mutation. With median followup of 21.4 months in censored pts, median OS was 23.0 months. 11 of 30 pts were documented to have experienced grade 3 or greater toxicities that were at least possibly due to their treatment. Of the 7 pts who experienced these by 9 months post-RT, most were attributable to TMZ (thrombocytopenia x 4, thrombocytopenia/neutropenia x 1, transaminitis x 1) and only one case (headaches/fatigue x 1) could potentially be ascribed to RT. Increased risk of pseudoprogression or radiation necrosis, especially beyond 3 months post-RT, was noted but these were clinically manageable and did not result in toxicity $\geq$ grade 3. **Conclusions:** Dose-escalated RT to 75 Gy guided by sMRI appears feasible and safe for pts with newly-diagnosed GBMs. OS outcome is also quite promising and warrants additional testing. Based on these results, a phase II randomized trial is planned at ECOG-ACRIN (EAF211). Clinical trial information: NCT03137888. Research Sponsor: U.S. National Institutes of Health.

2019 **Poster Discussion Session**

Gene expression signature to predict radiation response in lower-grade gliomas. *First Author: David C Qian, Department of Radiation Oncology, Winship Cancer Institute of Emory University, Atlanta, GA*

Background: Standard of care for lower-grade glioma (LGG) is maximal safe resection and risk-adaptive adjuvant therapy. While patients who benefit the most from adjuvant chemotherapy have been elucidated in prospective randomized studies, comparable insights for adjuvant radiotherapy (RT) are lacking. We sought to identify and validate patterns of gene expression that are associated with differential outcomes among LGG patients treated by RT from two large genomics databases. **Methods:** Patients from The Cancer Genome Atlas (TCGA) with LGG (WHO grade II–III gliomas) treated by surgery and adjuvant RT were randomized 1:1 to a training set or an internal validation set. Using patients in the training set, association between gene expression from resected tumor and progression-free survival (PFS) as well as overall survival (OS) was evaluated with adjustment for clinicopathologic covariates. A genomic risk score (GRS) was then constructed from the expression levels of top genes also screened for involvement in glioma carcinogenesis. The prognostic value of GRS was subsequently validated in the internal validation set of TCGA and a second distinct database, compiled by the Chinese Glioma Genome Association (CGGA). **Results:** From TCGA, 289 patients with LGG received adjuvant RT alone (38 grade II, 30 grade III) or chemoradiotherapy (CRT) (51 grade II, 170 grade III) between 2009 and 2015. From CGGA, 178 patients with LGG received adjuvant RT alone (40 grade II, 13 grade III) or CRT (41 grade II, 84 grade III) between 2004 and 2016. The genes comprising GRS are *MAP3K15*, *MAPK10*, *CCL3*, *CCL4*, and *ADAMTS1*, involved in MAP kinase activity, T cell chemotaxis, and cell cycle transition. High GRS, defined as having a GRS in the top third, was significantly associated with worse outcomes independent of age, sex, glioma histology, WHO grade, *IDH* mutation, 1p/19q co-deletion, and chemotherapy status in the training set (OS HR 2.74, $P < 0.001$; PFS HR 1.61, $P = 0.014$). These findings were further validated in the internal validation set (OS HR 1.84, $P = 0.015$; PFS HR 1.58, $P = 0.027$) and again in the CGGA external validation set (OS HR 1.72, $P = 0.001$). Association between GRS and outcomes was observed only among patients who received RT (RT alone or CRT), in both TCGA and CGGA. **Conclusions:** This study successfully identified an expression signature of five genes that stratified outcomes among LGG patients who received adjuvant RT, with two rounds of validation leveraging independent genomics databases. Expression levels of the highlighted genes were associated with survival only among patients whose treatments included RT, but not among those with omission of RT, suggesting that expression of these genes may be predictive of radiation treatment response. While additional prospective studies are warranted, interrogation of these genes to determine high/low GRS may be considered in the multidisciplinary management of LGGs. Research Sponsor: U.S. National Institutes of Health.

2020 **Poster Discussion Session**

Comparison of immune microenvironment between primary lung tumors and paired brain metastatic tumors. *First Author: Likun Chen, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: Lung cancer is one of the most common causes of brain metastases (BMs) and is always associated with poor prognosis. To evaluate the characteristics of the tumor immune microenvironment in brain metastases of non-small-cell lung cancer (NSCLC), we investigated the immunophenotype of primary NSCLC and paired brain metastases. **Methods:** Forty-three Chinese patients with NSCLC who had BMs at presentation or during the course of their disease were admitted to the Sun Yat-Sen University Cancer Center (Guangzhou, China) from 2000 to 2019. RNA sequencing (RNA-seq) of eighty-six formalin-fixed, paraffin embedded (FFPE) samples from primary lung tumors and paired brain metastases of 43 patients was conducted to comprehensively analyze the tumor immune microenvironment. **Results:** Our data revealed that brain metastases compared with primary lung tumors exhibited reduced tumor infiltrating lymphocytes (TILs) (all 28 immune cell subtypes $P < 0.05$), lower fraction of activated CD8 T cell and effector memory CD8 T cell in total TILs ($P = 0.028$, $P < 0.001$, respectively); higher fraction of macrophage and neutrophil in total TILs ($P < 0.001$, $P < 0.01$, respectively). Comparing with the primary lung tumors, the scores of some immune related signatures, including MHC non-class signature, IFN gamma signature and T-cell-inflamed gene-expression profile (GEP) signature, were significantly lower in brain metastases ($P = 0.004$, $P = 0.009$, $P = 0.004$, respectively), while the score of MHC class-II signature was higher in brain metastases ($P = 0.045$). We found the distributions of tumor microenvironment immune types (TMIT) in brain metastases and primary lung tumors were different. Brain metastases contained significantly lower proportion of TMIT I (high PD-L1/ high CD8A) (23%) than primary lung tumors (47%) ($P < 0.05$). Besides, we found three immune inhibitory checkpoint molecules, namely C10orf54 (VISTA), CTLA4 and CD274 (PD-L1) were downregulated in brain metastases than in primary lung tumors ($P < 0.001$, $P < 0.001$, $P = 0.034$, respectively). Moreover, there was poor correlation of PD-L1 expression between paired brain metastases and primary lung tumors ($R = 0.28$, $P = 0.068$). Unsupervised hierarchic cluster analysis revealed the primary lung tumors had two distinct patterns of immune gene signatures, namely Cluster A and Cluster B, and the tumors in Cluster B were immune rich, but associated with poor prognosis (log-rank $P = 0.021$). **Conclusions:** Our work illustrates the immune landscape of brain metastases from NSCLC, and suggests that the tumor immune microenvironment in brain metastases compared with primary lung tumors is further immunosuppressed, that may help guide immunotherapeutic strategies for NSCLC brain metastases. Research Sponsor: National Natural Science Foundation of China (81572270).

2021 **Poster Discussion Session**

Profiling of immune checkpoint biomarkers by multiplex immunofluorescence in breast cancer brain metastases. *First Author: Gaia Griguolo, Department of Surgery, Oncology and Gastroenterology, University of Padua, and Division of Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padova, Italy*

Background: Despite potential clinical implications, the complexity of immune microenvironment in breast cancer (BC) brain metastases (BM) is still poorly understood. Multiplex immunofluorescence (mIF) allows simultaneous visualization of several IF labeled proteins while maintaining spatial information. This novel technique can be used to comprehensively describe BCBM immune microenvironment, potentially providing useful information to guide novel therapeutic approaches. **Methods:** Clinical data and archival BM samples from 60 BC patients undergoing neurosurgery (2003-2018) at three institutions were collected. BCBMs were characterized using a custom mIF panel, including immune checkpoint and co-inhibitory molecules (CD3, PD1, PD-L1, TIM3, LAG3, CD163) and localization (keratin for tumor recognition) markers. Mean marker density was determined by digital image analysis (positive cells/mm2) and classified in tumor and stroma areas. Associations between immune marker densities, BC subtype and overall survival from BM diagnosis (OS) were studied. **Results:** Sixty BCBM samples were analyzed; 32% HR+/HER2-, 38% HER2+, 30% HR-/HER2-. At a median follow-up of 43 months, the only clinical variable associated with OS was BC subtype (shortest for HR-/HER2- and longest for HER2+, p=0.02). In the total sample area and tumor area, no significant difference in marker density was observed according to BC subtype. In the stroma area, a significant difference in TIM3+ cell density was observed according to BC subtype (highest density in HR+/HER2- and lowest density in HER2+ tumors, Kruskal-Wallis p=0.017). Higher CD163 density (a marker of M2 macrophage polarization), both in the tumor and in the stroma area, was significantly associated with worse OS, even after correction by BC subtype. In the subgroup of patients with HR+/HER2- BCBM, high TIM3+ cell density in the stroma area was significantly associated with longer OS (median OS 54.1 versus 23 months respectively for TIM3+ density above and below median value; p=0.01). **Conclusions:** In BCBM, stromal TIM3+ immune infiltrate differs according to BC subtype. M2 macrophage polarization is consistently associated with worse OS across all BC subtypes and might represent a potential therapeutic target for these patients. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	Univariate Cox Model for OS		Multivariable Cox Model for OS (correction by BC subtype)	
	Hazard Ratio (95% CI)	p-value	Hazard Ratio (95% CI)	p-value
CD163+ tumor area (positive cells/mm^2)	1.004 (1.000-1.007)	0.034	1.005 (1.001-1.009)	0.016
CD163+ stroma area (positive cells/mm^2)	1.001 (1.000-1.002)	0.021	1.001 (1.000-1.002)	0.024
CD163+ total area (positive cells/mm^2)	1.003 (1.002-1.005)	<0.001	1.004 (1.002-1.007)	<0.001

2022 **Poster Discussion Session**

Phase 1, 2 trial of concurrent anti-PD1 and stereotactic radiosurgery for melanoma and non-small cell lung cancer brain metastases (NCT02858869). *First Author: Mohammad Khurram Khan, Emory University, Atlanta, GA*

Background: The safety and efficacy of concurrent pembrolizumab (anti-PD1) and stereotactic radiosurgery (SRS) for brain metastases (BM) is unknown. **Methods:** Patients with melanoma or NSCLC, 1-10 brain metastases, ≥ 1 extra-cranial lesion, age ≥ 18, and ECOG 0-1 were treated with anti-PD1 every 3 weeks. SRS was administered 1-2 days after starting anti-PD1. SRS used three different radiation arms: Arm A used 6 Gray (Gy) in 5 fractions (fx), Arm B used 9 Gy in 3 fx, and Arm C used 18-21 Gy in single fx. Primary endpoint was grade 3 CNS toxicity at 3 months (CTCAE v 4.0). Secondary endpoints were overall survival (OS), local control (LC) within the SRS field, intracranial progression free survival (IC-PFS), extra-cranial progression free survival (EC-PFS), rate of extra-cranial clinical benefit, and immunological changes. OS, LC, IC-PFS, and EC-PFS were estimated using the Kaplan-Meier method, and covariates were compared using log-rank tests. 95% confidence intervals for 6-month and 12-month were estimated using Greenwood's formula. **Results:** 25 patients were treated from 2016 until 2020. The mean age was 61. The mean number of CNS lesions was 2.7. The mean number of extra-cranial lesions was 2.5. Six were enrolled on Arm A, 12 on Arm B, and 7 on Arm C. 21 had melanoma. 4 had NSCLC. Of the melanoma, 8 were BRAF-, 10 were BRAF+, and 3 had unknown mutation status. 12 patients (48%) had progressed on prior immunotherapy and/or other oncological therapies. The trial met its primary endpoint, with no grade 3 CNS toxicity at 3 months. Two patients (8%) experienced ≥ Grade 3 anti-PD1 related toxicity, and no grade 5 toxicity was noted. The median OS was 32.8 months. The 6 and 12 month OS were 79.1% (56.5-90.8%) and 67.8% (43.3-83.5%), respectively. The 1 year OS was similar between previously treated and treatment naïve patients (71.8% vs. 65.6%), suggesting some role for SRS in overcoming therapy resistance. However, with longer follow-up, the OS trended worse (p=0.07) for previously treated patients. LC was 95.7% (72.9-99.4%) at 6 and 12 months. IC-PFS at 6 months was 69.1% (45.8-83.9%), and at 12 months was 57.5% (33.7-75.5%). The EC-PFS at 6 and 12 month was 54.5% (32.1-72.4%) and 43.6% (22.3-63.2%), respectively. Clinical benefit, which was defined as a best overall response of stable disease or better according to RECIST 1.1, occurred in 12 patients (48%). No outcome differences were noted amongst the three different SRS arms. 70% of the patients demonstrating early activation (within 3 weeks of starting SRS/anti-PD1) of CD8+PD1+Ki67+ T cells demonstrated a clinical benefit. 100% of patients that failed to show early activation of CD8+PD1+Ki67+ T cells progressed. **Conclusions:** Concurrent pembrolizumab (Anti-PD-1) and SRS is safe and effective. Early activation of CD8+PD1+Ki67+ T cells correlates with improved outcome. Further trials testing pembrolizumab and SRS are justified. Clinical trial information: NCT02858869. Research Sponsor: Merck Pharmaceuticals.

2023 **Poster Discussion Session**

A phase II trial combining nivolumab and stereotactic brain radiosurgery for treatment of brain metastases in patients with NSCLC. *First Author: Philip Wong, Department of Radiation Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Previous studies suggested activity of anti-PD-1 in brain metastases from non-small cell lung cancer (NSCLC) and renal cell cancer (RCC). This investigator initiated phase 2 trial examined the safety and efficacy of combining nivolumab with radiosurgery (SRS) in the treatment of patients with brain metastases from NSCLC and RCC. **Methods:** This is a multicentre open-label trial (NCT02978404) in which patients diagnosed with NSCLC or RCC, having ≤ 10 cc of un-irradiated brain metastases, no whole brain radiotherapy and no prior immunotherapy were eligible. Study treatment commenced with a dose of nivolumab (240mg or 480mg IV), which was continued for up to 2 years at bi-weekly or monthly intervals until progression. SRS (15-21Gy) to all visible un-irradiated brain lesions was administered within 14 days after the first dose of nivolumab (cycle 1). Patients were followed by brain MRI, CT scan of the chest, abdomen and pelvis, neurocognitive and quality of life questionnaires (FACT-Br) every 3 months. The primary endpoint was intracranial progression free survival (icPFS), with death and disease progression within the brain as events. Results from NSCLC patients are presented here. **Results:** Of the 26 study patients, 22 NSCLC patients were enrolled between Aug 2017 and January 2020. Patients had a median of 2 (1-9) brain metastases. The median diagnosis-specific graded prognostic score was 2 (1-3). Median treatment and follow-up durations were 4.3 months (0-24.8 months) and 11 months (0-24.8 months), respectively. Forty-two percent of the patients had received prior cytotoxic chemotherapy, and 1 patient had received prior brain SRS. PD-L1 status was known for 21 of the 22 NSCLC (12 with ≥50% PD-L1 expression (DAKO 22C3). Median icPFS was 5.0 months (3 intracranial progression and 8 deaths without progression in the brain). Accounting for death as a competing risk, the 1-year cumulative incidence of intracranial relapse was 17.4%. Median extracranial PFS and overall survival were 2.9 months and 14 months, respectively. Four grade 3 adverse events in 2 patients were related to nivolumab or SRS. The rate of survival free of neurocognitive decline (Hopkins Verbal Learning Test total recall) was estimated to be 89% by 4 months. Mean FACT-Br total scores were 89.4 at baseline and improved ($p = 0.01$) to 139.3 within 2-4 months. **Conclusions:** Neurocognitive and quality of life assessments suggest that upfront SRS during nivolumab is well tolerated. High intracranial control was observed, but deaths from extracranial disease progression resulted in short icPFS. Studies evaluating the strategic addition of SRS combined with more efficacious systemic treatments are needed. Clinical trial information: 02978404. Research Sponsor: Bristol Myers Squib.

2024 **Poster Discussion Session**

Multi-center, single arm phase II study of the dual mTORC1/mTORC2 inhibitor vistusertib for patients with recurrent or progressive grade II-III meningiomas. *First Author: Scott Randall Plotkin, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Grade II/III meningiomas represent about 20% of tumors and have increased rates of recurrence with no approved medical therapies. Historically, the progression-free survival at 6 months (PFS-6) for these tumors is 25%. The Response Assessment in Neuro-Oncology (RANO) group identified a PFS-6 rate of > 35% to be of interest for trials of grade II/III meningioma. **Methods**: *NF2* gene inactivation occurs in the majority of meningiomas and is associated with mTORC1 activation. Human studies of everolimus for neurofibromatosis 2 patients documented growth arrest in only a minority of tumors. Based on our studies showing mTORC2/SGK1 pathway activation in *NF2*-deficient meningiomas and the known paradoxical activation of the mTORC2/AKT pathway in meningiomas, we hypothesized that dual inhibition of mTORC1/2 would be superior in meningiomas. Treatment of primary meningioma cells with vistusertib led to decreased cell proliferation and showed greater efficacy than rapamycin, regardless of *NF2* expression. We studied the effect of vistusertib in patients with progressive or recurrent grade II/III meningiomas (NCT03071874). Vistusertib was administered orally at 125mg twice daily on two consecutive days each week. MRIs were obtained every 2 cycles (1 cycle = 28 days). Tumor size was defined as the largest cross-sectional area. Progression was defined as ≥25% increase in the sum of products of all measurable lesions over smallest sum observed. The primary endpoint was PFS-6. Secondary endpoints included toxicity, radiographic response, and correlative studies including immunohistochemistry for mTORC1/2 pathway activation and genetic biomarkers. **Results**: Twenty-eight patients (13 female), with a median age of 58 years (range, 32 to 77 years), were enrolled in this multicenter study. The median Karnofsky performance status was 80. Twenty-five patients have been followed to six months or to tumor progression. The median duration of treatment was 6.5 month (range, 1-18 months). Four patients chose to discontinue treatment, 1 withdrew to intercurrent illness, and 1 was withdrawn due to non-compliance. PFS-6 is 51.5% (CI, 29.3% - 70.0%). Adverse events at least possibly related to vistusertib with frequency > 10% include nausea (54%); fatigue (36%); hypophosphatemia (29%); diarrhea, anorexia, dry mouth, and hypertriglyceridemia (all 14%); hypertension, vomiting, increased ALT, constipation, and weight loss (all 11%). **Conclusions**: Vistusertib treatment was associated with a PFS-6 rate that exceeds the RANO target of 35% for recurrent high-grade meningioma. The follow-up data continue to mature. Adverse events were tolerable in this patient population. Correlative studies to identify biological factors that correlate with response are under way. These data support the initiation of larger randomized studies of vistusertib in this setting. Clinical trial information: NCT03071874. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

2025 **Poster Session**

Radiosurgery dose reduction for brain metastases on immunotherapy (RADREMI): Early results from a multicenter phase I trial. *First Author: Shearwood McClelland, Indiana University School of Medicine, Indianapolis, IN*

Background: The rate of symptomatic radiation necrosis in patients treated with immune checkpoint inhibitor (ICI) therapy and concomitant single-fraction stereotactic radiosurgery (SRS) is as high as 20% (Martin et al., JAMA Oncology 2018). Here, we present the first results from the Radiosurgery Dose Reduction for Brain Metastases on Immunotherapy (RADREMI) trial, aimed to identify reduced-dose SRS that is safe and efficacious for this patient population. **Methods:** RADREMI is a prospective multicenter, single arm phase I pilot study. Patients age > 18 receiving ICI with SRS for 1-10 brain metastases on MRI from biopsy-confirmed primary malignancy with estimated median survival of at least 6 months (by disease-specific graded prognostic assessment) and no history of whole brain radiation therapy were eligible. The primary endpoint was six-month symptomatic radiation necrosis (defined as a six-month rate of clinical symptomatology requiring steroid administration and/or operative intervention concomitant with imaging findings consistent with radiation necrosis), based on a historical six-month symptomatic radiation necrosis rate of 16% and an expected rate of 5%. Secondary endpoints included six-month local control and six-month radiographic radiation necrosis. Local control was defined according to Response Assessment in Neuro-Oncology (RANO) criteria, and was compared to historical controls of 87-91% six-month local control with RTOG 90-05 SRS dosing. The Fisher's exact test was used for statistical analysis. This trial is registered at clinicaltrials.gov, NCT04047602. **Results:** Between December 18, 2019 and January 21, 2021, 39 lesions were treated in 17 patients receiving ICI delivered within 30 days before SRS from whom we recruited and obtained consent. All patients were treated with RADREMI dosing, which involved SRS doses of 18 Gy for lesions 0-2 cm, 14 Gy for lesions 2.1-3 cm, and 12 Gy for lesions 3.1-4 cm. The most common ICI used was single-agent pembrolizumab (49% of lesions, 59% of patients), followed by single-agent nivolumab (31% of lesions, 12% of patients). For the 11 lesions (six patients) meeting the primary endpoint (median follow-up = 259 days), the six-month symptomatic radiation necrosis rate was 0% per treated lesion, and 0% per treated patient, which was not significantly different from historical controls ($p = 0.478$). The six-month local control rate was 100% per treated lesion, and 100% per treated patient, comparable to historical controls ($p = 0.476$). **Conclusions:** In the first prospective trial to investigate dose-reduced SRS with concomitant ICI in treating metastatic brain disease, early results support the safety and efficacy of RADREMI dosing in this patient population. These findings warrant further multi-institutional collaborative trials of RADREMI dosing for this population. Clinical trial information: NCT04047602. Research Sponsor: Indiana University Simon Comprehensive Cancer Center Clinical Trials Office.

2026 **Poster Session**

Changes in the blood-brain barrier properties in vitro after treatment with sera from breast cancer patients with primary cancer and visceral, bone or cerebral metastases. *First Author: Carolin Julia Curtaz, University of Würzburg, Department of Gynecology and Obstetrics, Würzburg, Germany*

Background: The progression of brain metastases during breast cancer correlates with poor overall survival, but also with a reduced quality of life. During the metastatic progression of breast cancer, the key event for entry into the brain is the migration of cancer cells across the blood-brain barrier (BBB). To date, it is still controversial which serum factors play a role in cerebral expansion and what effects they have on the BBB. We hypothesize that sera from breast cancer patients with cerebral metastases contain unique factors that can affect BBB integrity. **Methods:** We used the $CD34^+$ cells-derived human in vitro BBB model (brain-like endothelial cells, BLECs) in co-culture with brain pericytes, which was validated in our previous studies, to analyse the BBB properties after patient sera treatment. We used paracellular permeability measurements for fluorescein (400 Da), immunofluorescence staining, Western blot and mRNA analysis to examine the effects of patient sera on the properties of BBB in vitro. We collected serum samples from five patient cohorts (30 patient per group planned/150 in total/ current recruited patients 130): 1) healthy donors (current recruited patients- 23), 2) breast cancer patients with primary cancer (recruited patients- 30), 3) breast cancer patients with bone metastases (recruited patients- 29), 4) visceral metastases (recruited patients- 30), or 5) cerebral metastases (current recruited patients-18). We then used 2% patient sera in cell culture medium to treat the cells for 24 hours. **Results**: Sera from breast cancer patients with cerebral and bone metastases led to a significant increase in the paracellular permeability for fluorescein. This could also be visualized by immunostaining cells with anti-claudin-5 antibody. Tight junction protein claudin-5 and occludin mRNA was reduced in BLECs, while mRNA of efflux pumps Breast cancer resistance protein (BCRP) and P-glycoprotein (P-GP) was induced in BLECs treated with serum from breast cancer patients with primary cancer, cerebral and visceral metastases. At the protein level, efflux pumps BCRP and P-GP were induced in cells treated with sera from breast cancer patients with cerebral metastases, while they were reduced in cells treated with sera from breast cancer patients with bone metastases. **Conclusions:** Sera from breast cancer patients with primary cancer and breast cancer metastases have an effect on the integrity of BBB in vitro. Reduced barrier properties of brain endothelial cells can contribute to the formation of cerebral metastases in advanced stages of breast cancer. Keywords: metastatic breast cancer, blood-brain barrier, in vitro models Research Sponsor: UniBund Wuerzburg, VogelStiftung Würzburg Germany.

2027 **Poster Session**

Real-world outcomes of breast cancer patients with brain metastases treated with radiotherapy in Ontario: A population-based study. *First Author: Katarzyna Joanna Jerzak, University of Toronto, Toronto, ON, Canada*

Background: Brain Metastases (BrM) are a major cause of morbidity and mortality in patients with metastatic breast cancer (MBC). Real-word data regarding time to development of breast cancer BrM and survival outcomes is lacking. **Methods:** We conducted a retrospective, observational population-based cohort study to assess treatment patterns and outcomes of patients with de-novo MBC who received radiotherapy for intracranial metastatic disease between January 2009 and December 2018. We used population health administrative databases in Ontario held at ICES, an independent, non-profit research institute. Primary endpoints were i) cumulative incidence of radiotherapy for BrM accounting for the competing risk of death, and ii) time from MBC diagnosis to brain radiotherapy. Secondary endpoints included overall survival (OS) and radiation therapy toxicity. Data were censored if patients were alive on the same therapy at last available follow-up with the last cut-off date being March 31, 2019. Kaplan-Meier analyses were performed for the time to event endpoints and compared using the log-rank test. Cumulative incidence of radiotherapy for BrM from the diagnosis of MBC was calculated using the Cumulative Incidence Function (CIF), accounting for the competing risk of death using a competing risk analysis. Multivariable regression models were used to account for confounding variables. **Results:** 3,916 patients with de-novo MBC were identified, among whom 549 (14%) developed BrM requiring radiotherapy; cumulative incidence of BrM at 7-year follow-up was highest among patients with HER2+/HR- (34.7%) and HER2+/HR+ (28.1%) disease, followed by triple negative MBC (21.9%) and HR+/HER2- (12.1%) subtypes. The median time from diagnosis of MBC to first radiotherapy treatment for BrM was 7.5 months, 15.0 months, 16.8 months and 19.8 months, in TNBC, HER2+/HR-, HR+/HER2- and HER2+/HR+ subtypes, respectively. The median OS from radiotherapy among patients with breast cancer BrM was 5.1 months in the overall cohort. When analyzed by subtype, the median OS was 2.6 months, 4.8 months, 8.7 months, and 9.4 months in TNBC, HR+/HER2, HER2+/HR+ and HER2+/HR- subtypes, respectively. In a multivariable Cox regression model, a triple negative or HR+/HER2- breast cancer subtype, treatment with WBRT, age > 60 and a high-income quintile (4 or 5) were independently prognostic for shorter OS after adjustment for the index year at diagnosis. Patients treated with stereotactic radiosurgery (SRS) had lower 30-day mortality (6.4% vs. 18.9%, $p = 0.003$) and lower likelihood of hospitalization within 30 days of therapy (9.6% vs. 20.2%, $p = 0.015$) compared to patients treated with WBRT. **Conclusions:** Approximately 1 in 7 patients with MBC will require radiotherapy for BrM. Our data support the use of SRS when clinically indicated and provide insights regarding the time to development of BrM by breast cancer subtype. Research Sponsor: Eli Lilly.

2028 **Poster Session**

The efficacy and clinical survival outcome of different first-line treatments in EGFR-mutant non-small cell lung cancer with brain metastases. *First Author: Huijuan Wang, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer Hospital, Zhengzhou, China*

Background: Brain metastasis is one of the most important factors for poor prognosis of lung cancer, and the incidence of brain metastasis in EGFR-mutant(m+) advanced NSCLC is more common. The first-generation EGFR TKI is a standard first-line treatment. The purpose of this study is to explore the best method for EGFRm+ NSCLC with brain lesions, and to find out correlative factors influencing survival outcome. **Methods:** The clinical data of NSCLC with brain metastases was retrospectively analyzed. All patients had received 1st generation EGFR TKI, and patients were divided into 4 group, group A : EGFR TKI monotherapy, group B: EGFR TKI plus chemotheapy(CT),Group C:EGFR TKI plus bevacizumab, group D :EGFR TKI plus CT plus bevacizumab.The efficacy of intracranial and extracranial lesions and survival outcome were analyzed. **Results:** A total of 584 EGFRm+ advanced NSCLC patients from December 2017 to May 2020 were screened,and 228(39%) had brain metastasis at baseline in the treatment-naive. Among them, 194pts had complete medical record and follow-up data. At the follow-up date (January 1, 2021), 147pts had disease progressed and 78pts had died. Intracranial PFS of group A,B,C,D were 11.1m(n = 97), 11.3m(n = 59) , 21.2m(n = 19), and 18.9m(n = 19), respectively. No difference was found between A and B group (P = 0.745), so as C and D group (P = 0.684).But, the intracranial PFS of group C+D(with bevacizumab) was significantly longer than group A+B(11.3m (95%CI 12.2-14.8) vs 21.0m (95%CI 15.2-22.7), P = 0.007).The extracranial PFS of groups A, B, C, and D were 11.0m, 14.3m, 21.7m, and 18.9m, respectively,and the P value were 0.006, 0.002, and 0.011, respectively when compared with group A. The mOS of groups A ,B were 27.8m and 24.2m,respectively, but group C and D had not yet reached. The intracranial ORR of group A, B, C, and D were 17.9% (14/78), 37.3% (19/51), 60.0% (9/15), and 66.7% (10/15), respectively. The extracranial ORR were 48.5% (47/97), 81.1% (43/53), 73.7% (14/19), and 73.7% (14/19),respectively. **Conclusions:** For EGFR-mutant NSCLC with brain metastases, the first-generation EGFR-TKI plus bevacizumab can significantly improve the efficacy of intracranial lesions, delay the progression of intracranial lesions, and prolong suvival time, Although the first-generation EGFR-TKI plus CT could improve extracranial ORR when compared with ERGF-TKI monotherapy, it has limited efficacy on intracranial lesions and could not increase survival time. Research Sponsor: None.

2029 **Poster Session**

Heterogeneity of HER2 expression in circulating tumor cells of patients with breast cancer brain metastases and impact on brain disease control. *First Author: Douglas Guedes Castro, A.C. Camargo Cancer Center, São Paulo, Brazil*

Background: The HER2 expression switching in circulating tumor cells (CTC) of breast cancer is dynamic and may have prognostic and predictive clinical implications. This study aims to analyse the association between expression of HER2 in CTC of patients with breast cancer brain metastases (BCBM) and brain disease control. **Methods:** Exploratory analysis of a prospective assessment (NCT02941536) of CTC before (CTC1) and 4–5 weeks after (CTC2) stereotactic radiotherapy/radiosurgery (SRT). CTC were isolated and quantified by a method of isolation by size of tumors and analyzed by immunocytochemistry to evaluate the expression of HER2. Distant brain failure-free survival (DBFFS), the primary endpoint, and overall survival (OS) were estimated by Kaplan-Meier estimator. Log-rank tests were applied in order to compare the survival curves. For multivariate analysis of prognostic factors that affected DBFFS and OS, the Cox proportional model was adjusted. **Results:** The median age at SRT was 54 (34-70), the diagnosis-specific graded prognostic assessment (DS-GPA) was 1–2 in 17.5% and 2.5–4 in 82.5% and the primary immunophenotype (PIP) was HER2-enriched in 51%, luminal B (LB) in 31% and triple negative (TN) in 18% of the total of 39 patients. CTC were detected in all 39 patients before SRT and the median CTC1 was 2 CTC/mL. After SRT, CTC were detected in 34 of 35 patients (4 deaths between CTC1 and CTC2) and the median CTC2 was 2.33 CTC/mL. HER2 was expressed in CTC1 and/or CTC2 in 9 patients, of which only 2 patients had PIP HER2-enriched. After a median follow-up of 16.6 months, there were 15 patients with distant brain failure and 16 deaths. The median DBFFS and OS were 15.3 and 19.5 months, respectively. Median DBFFS was 7 months in patients with PIP TN and was not reached in PIP LB and HER2-enriched (p = 0.036); 14 months in patients with DS-GPA 1-2 and 7 months with DS-GPA 2.5-4 (p = 0.017); 10 months in patients without HER2 expressed in CTC and not reached in patients with HER2 expressed in CTC (p = 0.012). Median OS was 4.8 months in patients with PIP TN and was not reached in PIP LB and HER2-enriched (p = 0.0026); 19.54 months in patients with DS-GPA 1-2 and 7.6 months with DS-GPA 2.5-4 (p = 0.00088); 17 months in patients without HER2 expressed in CTC and not reached in patients with HER2 expressed in CTC (p = 0.104). On multivariate analysis, DBFFS was superior in patients with PIP HER2-enriched (HR 0.128, 95% CI 0.025–0.534; p = 0.013) and OS was superior in patients with PIP HER2-enriched (HR 0.073, 95% CI 0.018-0.288; p < 0.0001) and LB (HR 0.224, 95% CI 0.062–0.816; p = 0.023). The status of expression of HER2 in CTC was not included in Cox model for DBFFS due to lack of events in patients with HER2 expressed in CTC. **Conclusions:** The expression of HER2 in CTC was associated with a longer DBFFS and the switching of HER2 expression between PIP and CTC may have impact on prognosis and treatment selection of BCBM. Research Sponsor: International Atomic Energy Agency.

2030 **Poster Session**

Outcomes of immunotherapy (ICI) alone vs tyrosine kinase inhibitors (TKI) alone versus ICI and TKI combined in renal cell carcinoma brain metastasis. *First Author: Patrick Joseph O'Shea, Cleveland Clinic, Cleveland, OH*

Background: Renal cancer is the fourth most common cause of metastatic tumors to the brain. Tyrosine kinase inhibitors (TKIs) targeting VEGFR and other receptors, such as sunitinib, pazopanib, etc., have been used as first line for renal cell carcinoma brain metastasis (RCCBM). Immune Checkpoint Inhibitors (ICIs) targeting PD-L1 and CTLA-4 interactions, such as nivolumab and ipilimumab respectively, have also been used as first line treatment for RCCBM. However, the efficacy of TKIs alone, ICIs alone, or TKIs and ICIs combined as first line treatment has emerged as a topic of interest. **Methods:** Patients with RCCBM treated with either TKIs, ICIs, or both at our tertiary care center from 2010-2019 were evaluated. Overall Survival (OS) was measured from initiation of either TKI or ICI therapy to date of death or last follow up. The Cox proportional hazard model was used to determine differences in OS. **Results:** 218 patients with RCCBM were included. Of these, 32 were treated with ICIs alone, 112 were treated with TKIs alone, and 76 were treated with a combination of ICIs and TKIs. For ICI treatment alone the median age at diagnosis was 61 years (Interquartile range (IQR) 38-82), 72% of the patients were male, and 97% were white. For TKI treatment alone the median age at diagnosis was 58 years (IQR 37-82), 70% of the patients were male, and 92% were white. For the combination cohort the median age at diagnosis was 63 years (IQR 45-79), 69% of the patients were male, and 97% were white. OS for patients receiving ICI, TKI, and combination treatment had a median of 69.1, 42.7, and 126.0 months and a 2-year rate of 77%, 69%, and 93%, respectively. With ICI treatment as a reference, TKI treated patients had an OS hazard ratio of 1.32 (95% CI = 0.78 - 2.21, p = 0.30) and ICI/TKI combination had an OS hazard ratio of 0.52 (95% CI = 0.30 - 0.92, p = 0.024). **Conclusions:** A combination treatment of ICIs and TKIs was associated with an increase in OS when compared to treatment with either TKIs or ICIs alone in patients with RCCBM. These results should be interpreted cautiously due to treatment selection bias. Further studies need to be done to control for other patient variables such as performance status, number of intracranial lesions, and extra-cranial metastasis. Research Sponsor: None.

Overall survival outcomes for RCCBM patients.

Outcome	Treatment	No Obs	Estimated Median (months)	2-year rate	Hazard Ratio (95%CI)	P
OS	ICI	30	69.1	77% (57%, 88 %)	Ref	
	Both ICI and TKI	76	126.0	93% (85 %, 97 %)	0.52 (0.30, 0.92)	0.024
	TKI	112	42.7	69% (60 %, 77 %)	1.32 (0.78, 2.21)	0.30

2031 **Poster Session**

Outcomes of first-generation versus third-generation epidermal growth factor receptor (EGFR) inhibitors in non-small cell lung cancer with brain metastases (NSCLCBM). *First Author: Vineeth Tatineni, Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH*

Background: Non-small cell lung cancer (NSCLC) is the most common cause of brain metastases, with 10-30% of patients developing brain metastases. EGFR is a transmembrane glycoprotein that is mutated in up to 50% of NSCLCs. First-generation EGFR tyrosine kinase inhibitors (TKI), such as erlotinib and gefitinib, are limited by blood-brain barrier (BBB) penetration and exon 20 (T790M) tumor mutations. Third-generation EGFR TKIs, such as osimertinib, have shown better BBB penetration and efficacy against T790M mutations. In this retrospective study, we evaluated the overall survival (OS) and progression-free survival (PFS) in NSCLCBM patients treated with first and third-generation EGFR TKIs. **Methods:** NSCLCBM patients diagnosed between 2010 and 2019 at our tertiary care center were investigated. Information regarding molecular marker status, systemic therapies, and date of progression were collected. OS was defined as the start date of systemic therapy to the date of last follow-up or death. OS and PFS were estimated by the Cox proportional model. **Results:** A total of 193 NSCLCBM patients with an EGFR mutation were identified. 33 EGFR mutant patients received first-generation EGFR TKIs, of which 56.7% were females, 82.1% were white, and had a median age of 63.2 years. 22 patients received third-generation EGFR TKIs, 64.1% being female, 76.9% being white, and with a median age of 71.5 years. The median OS (mOS) in patients who received first and third-generation EGFR TKIs was 59.8 months and 65.9 months respectively (p-value (p) = 0.06). The median PFS (mPFS) between the first and third-generation EGFR TKI cohorts was 44.3 months and 66.9 months respectively (p= 0.048, hazard ratio (HR) = 0.50 (95% confidence interval (CI) = 0.25, 0.99). **Conclusions:** Newer generation of targeted therapies in NSCLCBM have focused on overcoming previous efficacy hurdles, including BBB penetration and resistant mutations. We determined that there was a significant mPFS benefit in osimertinib compared to erlotinib or gefitinib, and a trend towards significant mOS benefit in osimertinib compared to erlotinib or gefitinib in patients with NSCLCBM. However, these results should be interpreted cautiously due to treatment selection bias, and further studies need to be conducted on brain metastases lesion size and response rates. Research Sponsor: None.

Outcomes of first-generation and third-generation EGFR TKIs.

Systemic Therapy	Patients (N)	mOS (months)	Hazard Ratio (95% CI)	P-value	mPFS (months)	Hazard Ratio (95% CI)	P-value
Erlotinib or Gefitinib	33	59.8	Reference	Reference	44.3	Reference	Reference
Osimertinib	22	65.9	0.51 (0.26, 1.03)	0.06	66.9	0.50 (0.25, 0.99)	0.048

2032 **Poster Session**

Clinical and genomic predictors of brain metastases (BM) in non-small cell lung cancer (NSCLC): An AACR Project GENIE analysis. *First Author: Protiva Rahman, Vanderbilt University Medical Center, Nashville, TN*

Background: 30-50% of patients with non-early NSCLC will eventually develop BM, with a median survival of less than one year from BM diagnosis. There are no widely accepted clinical risk models for development of BM in patients without them at baseline. We predicted the binary risk of BM using clinical and genetic factors from a large multi-institutional cohort. **Methods:** Stage II-IV NSCLC patients from the AACR Project GENIE Biopharma Consortium dataset were eligible. This consisted of 4 academic institutions who curated clinical data of patients who had somatic next-generation tumor sequencing (NGS) between 2015-2017. We excluded patients who had BM at baseline, died within 30 days of NSCLC diagnosis, or did not undergo brain imaging. Covariates included demographics, anticancer therapies (received up to 90 days prior to BM development and within 5 years from NSCLC diagnosis), and NGS data; radiotherapy (RT) data were not available. NGS features included mutations and copy number alterations. These features were restricted to those classified as oncogenic by OncoKB. Univariate feature selection with Fisher's test ($p<.1$) was performed on medication and genetic features. We compared 5 different machine learning models for prediction: random forest (RF), support vector machine (SVM), lasso regression, ridge regression, and an ensemble classifier. We split our data into training and test sets. 10-fold cross-validation was done on the training set for parameter tuning. The area under the receiver-operating curve (AUC) is reported on the test set. **Results:** 956 patients were included, 192 (20%) in the test set. Univariate features associated with BM were treatment with etoposide, Asian race, presence of bone metastases at NSCLC diagnosis, mutations in *TP53* and *EGFR,* amplifications of *ERBB2* and *EGFR,* and deletions of *RB1, CDKN2A* and *CDKN2B.* Univariate features inversely associated with BM were older age, treatment with nivolumab, vinorelbine, alectinib, pembrolizumab, atezolizumab, and gemcitabine, as well as mutations in *NOTCH1* and *KRAS.* Ridge regression had the best AUC, 0.73 (Table). **Conclusions:** We achieved reasonable prediction performance using commonly obtained clinical and genomic information in non-early NSCLC. The biologic role of the associated alterations deserves further scrutiny; this study replicates similar findings for *EGFR* and *KRAS* in a much smaller cohort. Certain subsets of NSCLC patients may benefit from increased surveillance for BM and transition to drug therapies known to effectively cross the blood-brain barrier, e.g., nivolumab and alectinib. Inclusion of additional covariates, e.g., brain RT, may further improve model performance. Research Sponsor: American Association for Cancer Research GENIE BioPharma Collaborative.

	Lasso	Ridge	SVM	RF	Ensemble
Demographics (D)	0.68	0.70	0.62	0.72	0.70
D + Meds	0.69	0.69	0.68	0.70	0.69
D + Genes	0.68	0.73	0.70	0.72	0.72
D + Meds + Genes	0.70	0.71	0.68	0.72	0.70

2033 **Poster Session**

Presentation and management of patients with brain metastases of primary melanoma, non-small cell lung cancer, and breast cancer origin. *First Author: Yuki Kawahara, University of South Florida Morsani College of Medicine, Tampa, FL*

Background: As systemic therapy improves; the prevalence of brain metastases is increasing. Screening brain MRIs are currently recommended for all stage ≥ II non-small cell lung cancer (NSCLC) and stage IIIB–IV melanoma patients, but only when neurologic symptoms arise in stage IV or recurrent breast cancer (BC) patients. This study assessed the presentation and institutional outcomes treating brain metastases (BM) of BC, NSCLC, and melanoma origin. **Methods:** Patients with BM treated between 2014 and 2019 with primary melanoma, NSCLC, and BC were identified. Characteristics of initial BM diagnoses were retrieved from clinical chart review. Kruskal-Wallis and Pearson's chi-square tests were used to test differences between groups. Overall survival (OS) was calculated from dates of initial BM diagnosis using the Kaplan–Meier method. **Results:** A total of 959 patients were identified (BC 18%, NSCLC 51%, melanoma 31%). BC patients were younger at initial presentation (BC median age: 57, NSCLC 65, melanoma 62, $p< 0.0001$). At BM diagnosis, BC patients were more likely to have concurrent systemic metastasis (BC 77%, NSCLC 42%, melanoma 69%, $p< 0.0001$), at least 5 BM (BC 27%, NSCLC 14%, melanoma 13%, $p= 0.0004$), and leptomeningeal disease (BC 23%, NSCLC 6%, melanoma 6%, $p< 0.0001$). Patients with BC were significantly more likely to receive whole brain radiation therapy (WBRT) (BC 58%, NSCLC 37%, melanoma 22%, $p< 0.0001$) and less likely to receive stereotactic radiation (BC 26%, NSCLC 48%, melanoma 58%, $p< 0.0001$) following initial BM diagnosis. There were no significant differences in surgical resection between cancer types (BC 24%, NSCLC 24%, melanoma 29%, $p =0.166$). Median OS was shorter for BC (BC 9.9 months, NSCLC 10.3 months, melanoma 13.7 months, $p= 0.0006$) following BM diagnosis. **Conclusions:** Our institutional analysis found BC patients were more likely to be younger, present with more advanced brain disease, require WBRT, and have poorer OS than NSCLC and melanoma patients following initial brain metastasis diagnosis. This may be due in part to a lack of brain MRI screening recommendations in BC. Further investigation is needed to determine which BC patients are at sufficient risk to warrant brain MRI screening. Research Sponsor: None.

2034 **Poster Session**

Outcomes of first, second, and third-generation anaplastic lymphoma kinase (ALK) inhibitors in non-small cell lung cancer brain metastases (NSCLCBM). *First Author: Vineeth Tatineni, Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, OH*

Background: Non-small cell lung cancer (NSCLC) is the most common cause of brain metastases. ALK, which codes for tyrosine kinase receptors, is rearranged in 4-7% of NSCLC. First-generation ALK inhibitors have restricted efficacy due to poor blood-brain barrier (BBB) penetration and ALK-resistant tumor mutations. Second-generation ALK inhibitors have shown better BBB penetration, while third-generation ALK inhibitors were efficacious even against ALK-resistant mutations. In this retrospective study, we investigated the overall survival (OS) and progression-free survival (PFS) in NSCLCBM patients treated with first, second, and third-generation ALK inhibitors. **Methods:** NSCLCBM patients between 2010 and 2019 were evaluated. We analyzed data regarding molecular marker status, systemic therapies, and date of progression. OS was defined as the start date of systemic therapy to the date of last follow-up or death. The Cox proportional model was used to estimate OS and PFS. **Results:** A total of 90 patients had ALK gene rearrangement. 16 ALK positive patients received first-generation ALK inhibitor (crizotinib), with a median age of 59.2 years, 50% of the cohort being female and 83.3% being white. Another 17 patients received second-generation (alectinib, ceritinib, brigatinib) and third-generation ALK inhibitors (lorlatinib), with a combined median age of 52.2 years and a cohort of 52.6% females and 72.2% white patients. The 5-year OS rate was 49% (95% confidence interval (CI) = 24%, 71%) for first-generation ALK inhibitors and 76% (95% CI = 40%, 92%) for second and third-generation ALK inhibitors (p-value (p) = 0.019). The median PFS (mPFS) for patients who received first-generation ALK inhibitors was 45.3 months and for those who received second or third-generation ALK inhibitors was 180.1 months. The respective 5-year PFS rate was 43% (95% CI = 19%, 65%) and 72% (95% CI = 42%, 89%). **Conclusions:** Newer generations of targeted therapies in NSCLCBM have improved BBB penetration and effectiveness against resistant mutations. We determined that there was a significant 5-year OS benefit in patients who received second and third-generation ALK inhibitors compared to first-generation ALK inhibitors, and a respective trend towards significant PFS benefit in newer-generation ALK inhibitors when compared to first-generation. These results are encouraging, but the effect on intracranial lesion size and response rates should be examined in the future. Research Sponsor: None.

Outcomes of first-generation vs. second and third-generation ALK inhibitors.

Systemic Therapy	Patients (N)	mOS (months)	5-Year OS Rate (95% CI)	P-value	mPFS (months)	5-Year PFS Rate (95% CI)	P-value
Crizotinib	16	51.6	49% (24%, 71%)	Reference	45.3	43% (19%, 65%)	Reference
Alectinib, Ceritinib, Brigatinib, or Lorlatinib	17	NA	76% (40%, 92%)	0.019	180.1	72% (42%, 89%)	0.061

2035 **Poster Session**

An investigation into the impact of next generation sequencing on the use of targeted treatments in glioblastoma. *First Author: Jordan John, Northwestern Feinberg School of Medicine, Chicago, IL*

Background: Next-generation sequencing (NGS) provides clinicians immense amounts of information about a patient's cancer. NGS allows the detection of a wide range of gene alterations undetectable by older techniques. This has the promise to help guide clinicians in their decision-making as genetic alterations can be both prognostic and predictive. NGS may reveal new treatment options for patients with glioblastoma. The goal of this project was to evaluate how often NGS results influence the use of targeted treatment agents in glioblastoma. This study did not investigate the impact of NGS on reclassification of cancers, prognosis, or treatment decisions outside of the use of targeted therapy. **Methods:** We conducted a retrospective chart review to see if adult glioblastoma patients received treatments for potentially actionable gene alterations and for fusion variants because of NGS. Here we looked at alterations labeled as actionable from the Tempus company's NGS results. We collected diagnosis and treatment information from the Electronic Medical Record and from the Electronic Data Warehouse. We examined if patients after receiving NGS would receive targeted treatment, as that likely indicated these treatments were given due to NGS indication. We excluded cytotoxic chemotherapy agents and bevacizumab as these therapies are utilized regardless of a targeted gene indication. This analysis excluded treatments received in clinical trials in which enrollment was independent of NGS. This analysis looked at the proportion of patients with actionable alterations that were treated with targeted agents. **Results:** 261 glioblastoma patients were found on NGS to have mutations which were potentially actionable. Thirty-three of these patients (12.6%) received a respective targeted therapy, and the other 228 patients (87.4%) did not receive an NGS guided targeted therapy. 97 patients had EGFR copy number gains or EGFR gain of function mutations of which 21 were treated with depatuxizumab mafodotin, and one additional patient who was treated with ABBV 321. Of the NGS treatment guided therapies, depatuxizumab mafodotin was the most used targeted agent in our sample set. Additionally, there were 30 patients with fusion variants and 11 of them were FGFR3-TACC3 fusions. Of these 11, 4 received targeted regimens (36.4%) with either TAS-120, pemigatinib, erdafitinib, or erdafitinib with ponatinib. The other fusion variants were not acted upon. **Conclusions:** These preliminary results suggest that NGS data currently does not frequently impact treatment decisions for glioblastoma . Although this study is limited by being a single institution study, future efforts include expanding this analysis to multiple institutions. With improvements in therapeutics as well as with wider availability of NGS testing, sequencing data may impact a larger percentage of glioblastoma patients. Research Sponsor: None.

2036 **Poster Session**

Palliative care service utilization and advance care planning issues for adult glioblastoma patients: A systematic review. *First Author: Adela Wu, Stanford University Medical Center, Stanford, CA*

Background: Glioblastoma (GBM) is a devastating disease with a median survival under 2 years and a 10-year survival rate of 0.71%. As patients with GBM suffer simultaneously from both a terminal cancer and a neurodegenerative disease, proactive provision of advance care planning (ACP) and palliative care (PC) seem appropriate. We conducted a systematic review exploring the published literature on the prevalence of ACP, healthcare services utilization at the end of life (EOL, including PC services), and location of death among adults with GBM, and the experiences of their caregivers. **Methods:** We systematically searched PubMed, Embase, Scopus, and Cochrane Library from database inception until 12/20/2020, using search terms including 'glioblastoma', 'end of life', 'advance care planning', and 'advance directive'. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines were followed. Inclusion criteria were quantitative and qualitative studies written in English of adults with GBM and their caregivers, with at least 20 subjects. Included studies were assessed for quality using the Newcastle-Ottawa Scale. **Results:** We screened 344 article abstracts and 39 full text articles to yield a final cohort of 16 articles that fit inclusion criteria. These studies reported the experiences of 10,706 GBM patients and 123 caregivers. All were nonrandomized studies conducted in six countries with all but two published in 2014 or later. Across studies, ACP documentation varied from 4-55%, PC referral was pursued in 39-40% of cases, and hospice referrals were made for 66-76% of adult GBM patients. Hospitalizations frequently occurred at the EOL, 20-56% of patients spent over 25% of their overall survival time hospitalized, and 39-64 % of deaths occurred in the home setting. Caregivers commonly reported restrictions on their ability to work (60%), financial barriers to care (29%), and feeling unprepared (29%). **Conclusions:** Despite having both a terminal disease and neurocognitive decline, a majority of adults with GBM do not pursue ACP or have access to PC. There is a dearth of focused and high-quality studies on ACP, PC, and hospice use among adults with GBM. Prospective studies that address these and additional aspects related to end-of-life care in this population, such as healthcare costs and inpatient supportive care needs, are needed. Research Sponsor: None.

2037 **Poster Session**

Phase 1 dose-escalation study of ACT001 in patients with recurrent glioblastoma and other advanced solid tumors. *First Author: Jason D. Lickliter, Nucleus Network Limited, Melbourne, Australia*

Background: ACT001, an orally-available parthenolide derivative targeting NF-κB and STAT3 signaling pathways, has immunomodulatory effects and showed promising activity in preclinical models of glioblastoma (GBM). The updated data in this report summarizes clinical findings from this first-in-human clinical trial of ACT001 in patients with advanced solid tumors, including GBM. **Methods:** Eligible patients were adults with ECOG PS 0-1 and satisfactory hematologic, renal and hepatic function. Additionally, GBM patients had progressive disease despite initial radiation and temozolomide, measurable tumor and no radiation treatment within 3 months prior to enrollment. ACT001 was given orally BID until intolerance or disease progression. Dose escalation followed a standard 3+3 design. Gliomas were imaged with MRI every 8 weeks and responses assessed using RANO criteria. **Results:** A total of 24 patients were enrolled as of this report: 14 with primary GBM, 2 with secondary GBM, 2 with anaplastic astrocytoma, 2 with colorectal cancer and 1 with each of anaplastic oligioastrocytoma, diffuse intrinsic pontine glioma, non-small cell lung cancer and pleural epithelioid mesothelioma. Median age was 49 years old (range 32-72). ACT001 dose levels were 100 mg BID, 200 mg BID, 400 mg BID, 600 mg BID, 900 mg BID and 1200 mg BID. Study drug treatment was well tolerated with no dose-limiting toxicity or ACT001-related SAE observed. The originally-planned maximum dose of 600 mg BID and the 1200 mg BID dose were expanded to 7 and 5 patients, respectively. The plasma half life of ACT001 was approximately 3-4 hours and no accumulation was observed after multiple dosing. Cmax and $AUC_{0\text{-last}}$ were approximately dose linear across the evaluated dose range. Of the 19 patients with recurrent malignant gliomas, a complete remission was observed in 1 patient with GBM (ongoing 27 months from starting ACT001) and stable disease lasting $\geq$ 6 months was seen in 3 patients. Preliminary biomarker analysis of PBMC samples revealed a post-treatment reduction in CD4+ Treg cells at some dose levels. **Conclusions:** In this first-in-human phase 1 study, ACT001 was well tolerated and showed satisfactory bioavailability and preliminary evidence of anti-tumor activity in malignant glioma patients dosed at 400 mg BID or lower. A phase 1b trial in recurrent GBM patients of ACT001 at 200-400 mg BID in combination with anti-PD-1 therapy is planned. Clinical trial information: ACTRN12616000228482. Research Sponsor: Accendatech AU Pty Ltd.

2038 **Poster Session**

Efficacy finding cohort of a cancer peptide vaccine, TAS0313, in treating recurrent glioblastoma. *First Author: Yoshiki Arakawa, Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan*

Background: TAS0313 is a cancer vaccine cocktail comprising three long peptides with a total of 12 cytotoxic T lymphocyte (CTL) epitope peptides. These peptides were derived from eight cancer-associated antigens (EGFR, KUA, LCK, MRP3, PTHRP, SART2, SART3, and WHSC2) that are overexpressed in various cancer types including glioblastoma (GBM). We performed a single-arm, multicenter efficacy confirmatory cohort study as part of the TAS0313 Phase I/II study in patients with recurrent GBM. **Methods:** The enrolled patients with histologically or cytologically confirmed grade IV GBM (including gliosarcoma, giant cell glioblastoma, and epithelioid glioblastoma) had at least one of the following HLA types: HLA-A*02:01, -A*02:06, -A*02:07, -A*11:01, -A*24:02, -A*31:01, or -A*33:03. Eligible patients were those who received standard radiotherapy and temozolomide, had a confirmed first or second recurrence, or progression with measurable disease outcomes with good performance status (Karnofsky Performance Status score $>$ 70). TAS0313 (27mg) was subcutaneously administered on days 1, 8, and 15 of cycles 1 and 2 and day 1 of cycle 3 or later in 21-day cycles until disease progression or unacceptable toxicity occurred. Tumor response was evaluated using The Response Assessment in Neuro-Oncology criteria. The antigen-specific CTL and immunoglobulin G (IgG) were analyzed by ELISPOT assay and Luminex assay, respectively, before and after treatment. The primary objective was to evaluate the efficacy of TAS0313. Secondary and exploratory methods were used to evaluate the safety and immune response of TAS0313. **Results:** As of 10th September 2020, 10 patients have been treated with TAS0313 (eight with GBM and two with gliosarcoma). The median age of participants was 56.5 [range, 33–69 years], and methylation status of the MGMT promoter was methylated in four patients, unmethylated in four, and unknown in two. The best overall response was partial response 1/10 (10.0%) and stable disease 4/10 (40.0%). One case showed 69.1% tumor shrinkage. The treatment of two patients was ongoing for over 7 months. The 6-month progression-free survival (PFS) rate was 25.0%, and the median PFS was 2.3 months. The most common adverse drug reactions (ADRs) were grade 1–2 injection site reactions and pyrexia. There were no grade 4 or 5 ADRs. In some patients, TAS0313 treatment was confirmed to increase CTL and IgG levels compared with pre-treatment samples. **Conclusions:** TAS0313 showed promising efficacy with expected immune responses and favorable safety and tolerability in patients with recurrent GBM. Further investigation of TAS0313 is warranted to validate our findings. Clinical trial information: JapicCTI-183824. Research Sponsor: TAIHO PHARMACEUTICAL Co., Ltd.

2039 **Poster Session**

A phase II study of anlotinib combined with STUPP regimen in the treatment of patients with newly diagnosed glioblastoma (GBM). *First Author: Peijing Li, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital), Hangzhou, China*

Background: STUPP regimen is now the standard treatment for newly diagnosed GBM, while the effectiveness is limited. This study assessed the efficacy and safety of anlotinib, a multitarget tyrosine kinase inhibitor, combined with the STUPP regimen in treating these patients. **Methods:** This is a phase II, multicenter, open-label, single-arm trial (NCT04119674). Thirty-three patients (17 males and 16 females) were enrolled from 8 hospitals in China between January 2019 and February 2021. Inclusion criterion included 1) newly diagnosed histologically confirmed glioblastoma (WHO grade IV), 2) 2-6 weeks (wks) after surgery with healed incision, 3) 18-70 years old, 4) KPS$\geq$60, 5) at least one measurable lesion according to RANO criteria, 6) radiotherapy (RT), chemotherapy, immunotherapy or biotherapy naïve. All patients received 54-60 Gy radiation (1.8-2.0 Gy per fraction, five days per week) concurrently with temozolomide (TMZ, 75mg/m^2, orally, QD) and anlotinib (8mg, orally, QD, d1-14/3wks). Adjuvant therapy started four weeks after RT completion, including six cycles of TMZ (150-200mg/m^2, orally, d1-5/4wks) and eight cycles of anlotinib (8mg, orally, QD, d1-14/3wks). Patients who completed adjuvant therapy were administrated anlotinib continuously until disease progression or unacceptable toxicity. The primary endpoint was progression-free survival (PFS). Safety assessment was done in patients who received at least one dose of study agent. **Results:** The median age is 52 (range 32-69) years. Analyses included data collected through February 6, 2021. The median treatment duration was 6.5 months. The median PFS was not reached, and the median overall survival (OS) was 17.4 months [95%CI 11.6-23.2]. The 1-year PFS and OS rate was 84.0% and 100.0%, respectively. Tumor response occurred in 21 patients, 63.6% (21/33) objective response (CR/PR), and 24.2% (8/33) patients had stable disease (SD).The clinical benefit rate (CBR), defined as the proportion of patients who achieved durable disease control (CR/PR/SD) more than six months, was 57.6% (19/33). Hypertension (6.1%) was the most common $\geq$grade 3 adverse event. No treatment related death occurred in this study through the last follow-up. Overall, toxicities are mild and manageable. **Conclusions:** Anlotinib combined with the STUPP regimen is efficacious and well-tolerated in newly diagnosed GBM patients. Clinical trial information: NCT04119674. Research Sponsor: None.

2040 **Poster Session**

A phase I/II study to evaluate the safety and efficacy of a novel long-acting interleukin-7, NT-I7, for patients with newly diagnosed high-grade gliomas after chemoradiotherapy: The interim result of the phase I data. *First Author: Jian Li Campian, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: High-grade gliomas (HGG) patients can develop prolonged lymphopenia after standard radiation therapy (RT) and temozolomide (TMZ), which has been shown to correlate with worse survival. Interleukin-7 (IL-7) level, a cytokine that stimulates T-cell homeostasis and proliferation, is disproportionally low in HGG patients with lymphopenia. NT-I7 (efineptakin alfa) is the first-in-class long-acting recombinant human IL-7 that supports proliferation and survival of CD4+ and CD8+ T-cells in humans and mice. Our previous study demonstrated that NT-I7 could correct lymphopenia and improve the survival of orthotopic murine glioma models. The current study aims to examine the safety of administering NT-17 after chemoradiotherapy to HGG patients and its effect on systemic absolute lymphocyte count (ALC). **Methods:** All patients with newly diagnosed HGG who have completed concurrent RT/TMZ were considered eligible, regardless of ALC. NT-I7 was initially administered intramuscularly within 1 week after completion of RT/TMZ and then every 12 weeks for up to 4 doses. Patients also received adjuvant TMZ 4 weeks after RT/TMZ. The phase I study tested 6 dose levels of NT-I7, including 60, 120, 240, 540, 720, and 960 mcg/kg, adopting an accelerated phase for the first two doses followed by the standard 3+3 design. The primary endpoint was the safety of NT-I7 in HGG. The Phase II study is a double-blinded randomized study with 10 patients per arm to evaluate the effect of NT-I7 on ALC compared to placebo controls. Blood samples at baseline and during the NT-I7 administrations will be collected for immune profiling by CyTOF, single-cell RNA-sequencing, and cytokine analysis. **Results:** Phase I was completed with 19 patients (2 anaplastic oligodendrogliomas and 17 glioblastomas), with a median age of 58 years (range: 25-78). Median baseline ALC was 1000 cells/mm3 before NT-I7 administration, and the median baseline dexamethasone use was 0 mg/day (range 0-12). The median number of NT-I7 doses given was 2 (range: 2-4). Treatment-related adverse events (TRAEs) were dose-dependent. The most common TRAEs were grade 1/2 injection site reactions (50%), flu-like symptoms (26%), rash (21%), and fatigue (21%). Two patients had dose-limiting toxicities at 960 mcg/kg (a grade 3 elevated alanine aminotransferase and a grade 3 muscle pain). ALC was increased in a dose-dependent manner with a range of 1.3 – 4.1 fold at week 4 after NT-I7 injection and lasted up to 12 weeks. Thus, 720 mcg/kg was identified as the recommended phase II dose (RP2D). **Conclusions:** NT-I7 is well tolerated for HGG patients after chemoradiotherapy and has a RP2D of 720 mcg/kg. Immune profiling and cytokine analysis are ongoing and will be updated. The Phase II randomized study to evaluate the effect of NT-I7 vs placebo on ALC and survival is ongoing. Clinical trial information: NCT03687957. Research Sponsor: NeoImmuneTech, Other Foundation.

2041 **Poster Session**

PD-L1-R: A MR based surrogate for PD-L1 expression in Glioblastoma multiforme. *First Author: Francesco Sforazzini, CCU Translational Radiation Oncology, German Cancer Research Center (DKFZ), Medical Faculty, Heidelberg (HD) University Hospital (UKHD), National Center for Tumor Diseases, UKHD, HD Ion-Beam Therapy Center (HIT), German Cancer Consortium (DKTK) center HD, Heidelberg, Germany*

Background: Efficacy of PD-L1 immune checkpoint inhibitor therapy in Glioblastoma multiforme (GBM) is limited and the prognostic value of PD-L1 in GBM is an active field of research. We therefore sought to identify a MR based surrogate for PD-L1 expression in GBM. **Methods:** T1 post contrast images (T1ce) acquired immediately before surgery of 121 subjects with primary GBM (RTK I, II and mesenchymal subtype, as determined from Illumina Human Methylation array data) were analyzed. Following standard pre-processing (bias filed correction, brain extraction), 1150 radiomics features were calculated from gross tumor volumes (GTV). The cohort was then divided into training/validation (70%/30%). Cross-validation and model-selection were applied to identify features associated with PD-L1-M expression (estimated from methylation data and highly correlated with PD-L1 RNA-sequencing based measure, as recently reported). Features were used to identify two groups of tumors differing in PD-L1-M expression (PD-L1-R high and low), for which a logistic regression model was trained. Overall survival was assessed between PD-L1-R high/low. **Results:** PD-L1-R high and low groups showed significant differences in PD-L1-M values (training: p=0.002, validation: p=0.04, full cohort: $p<0.001$). The same model was used to split tumors into 2 groups, using features from non-T1ce sequences. All of the tested MR modalities showed at least a trend in PD-L1-M values in the two groups (T2w: p=0.037, T1w: p=0.089, FLAIR: p=0.091). Further investigations on the whole cohort (121 subjects) showed that PD-L1-R low group was enriched for RTK II sub-type (48%), while PD-L1-R high for mesenchymal sub-type (48%). Refer to Table 1 for more information. In addition, evaluation of survival data showed a difference in overall survival (likelihood ratio test p value 0.048, OR 0.52, 95% CI [0.27; 0.98]), with the PD-L1-R high group having a better prognosis. **Conclusions:** We presented a radiomics model PD-L1-R which allowed to identify GBM with low and high PD-L1-M expression from T1 post contrast agent images. Future work should validate these findings in independent cohorts. Research Sponsor: Marie SkÅ‚odowska-Curie grant agreement No. 766276.

GBM tumor sub-types in the two groups identified using the proposed radiomics signature.

	# Subjects	Mean PD-L1-M	# RTK I	# RTK II	# Mesenchymal
PD-L1-R High	60	-3.08	8	23	29
PD-L1-R Low	61	-5.35	17	29	15

The p value between the tumor sub-types in the two groups was 0.015 (calculated using Fisher's test). The results refer to the whole cohort, using features extracted from T1ce images.

2042 **Poster Session**

Gene fusions in glioblastoma: Results of Gliocat project. *First Author: Ainhoa Hernandez Gonzalez, Institut Catala d'Oncologia Badalona. Applied Research Group in Oncology (B- ARGO Group), Institut Investigació Germans Trias i Pujol (IGTP), Badalona Barcelona, Spain*

Background: Malignant gliomas are heterogeneous diseases in genetic basis. The development of sequencing techniques, such as RNA-Sequencing, has identified many gene rearrangements encoding novel oncogenic fusions. Gene fusion discovery can potentially lead to the development of novel treatments, however studies of gene fusions in glioma remain limited. **Methods:** The GLIOCAT project studied 139 patient samples of newly diagnosed glioblastoma who had received the standard first-line treatment from 2004 to 2015, to identify gene fusion events from glioblastoma transcriptome data (RNA-Seq). The molecular subtype could be studied in 124 cases. RNA-Seq reads were mapped against the reference human genome with STAR-fusion version 0.7.0, specifically, with FusionInspector validate (http://star-fusion.github.io). Two other platforms, FusionHub (https://fusionhub.persistent.co.in) and Oncofuse (www.unav.es/genetica/oncofuse.html), were applied to eliminate false positives or previously described in healthy tissue and to predict of the oncogenic potential each fusion. **Results:** A total of61 patients showed 103 different fusions, a median of two fusions by sample. The majority of gene fusions were intrachromosomal and most frequently implied chromosome was 12 followed by 7. In addition, fusions were more common in patients with MGMT promoter methylation, TCGA classical subtype and 18 IGS subtype. There were no differences in age, sex, type of surgery or long survivors ($>$ 30 months). Ten fusions were already described in cancer, including three in gliomas (FRS2-KIF5A, EGFR-SEPT14 and FGFR3-TACC3). From the detected fusions, 22 of them included an oncogene or protooncogene. **Conclusions:** In our study, we report the landscape of gene fusions from a large data set of glioblastomas analyzed by RNA-seq. The majority of the fusions were private fusions. A minority of these recur in a low frequency but as many as a quarter of them included an oncogene or protooncogene. RNA-seq of GBM patient samples it is an important tool for the identification of patient-specific fusions that could drive personalized therapy. Furtherless, we will plan to validate this gene fusions. Research Sponsor: Carlos III Health Institute, La Fundació La Marató.

2043 **Poster Session**

Improved risk stratification via integration of radiomics and dosiomics features in patients with recurrent high-grade glioma undergoing carbon ion radiotherapy (CIRT). *First Author: Patrick Salome, CCU Translational Radiation Oncology, German Cancer Research Center (DKFZ), Medical Faculty, Heidelberg (HD) University Hospital (UKHD), National Center for Tumor Diseases, UKHD, HD Ion-Beam Therapy Center (HIT), German Cancer Consortium (DKTK) center HD, Heidelberg, Germany*

Background: Unique radiobiological and physical properties of carbon ion radiotherapy (CIRT) may be favorably utilized to improve outcome in recurrent High-Grade Glioma (rHGG). There are currently no standardized criteria for stratification of rHGG patients for re-irradiation (re-RT). This study evaluated the impact of morphological data (radiomics) and physical information (dosiomics) in stratifying rHGG patients for CIRT. **Methods:** Quantitative radiomics and dosiomics features were extracted from CIRT planning CTs with dose distribution (DD) and multiparametric MRIs (mpMRI, pre re-RT) of 141 patients (recurrent grade III: n=56 40%, grade IV: n=85 60%) treated with a median dose of 42 Gy (RBE) and a median fraction of 13. The MR sequences considered are T1 weighted pre-and post-contrast agent, fluid-attenuated inversion recovery (FLAIR) and apparent diffusion coefficient (ADC). Benefit of a re-RT risk score (RRRS), comprising the initial tumour grade, age and the Karnofsky Performance Score was shown to correlate with superior outcome in CIRT and conventional re-RT and was also studied here in parallel. Feature sets - a) RRRS, b) radiomics, c) dosiomics features - were evaluated both separately and combined. Multiple feature selection methods were used independently on the CT, DD and the MR sequences, followed by a stepwise Cox's Proportional Hazard model selection per modality or combination thereof. Multivariable models were ranked by 10-fold cross-validated concordance index (C-I). **Results:** Compared to the RRRS model (OS/PFS, C-I: 0.68/0.61), the multimodality model considering radiomics and dosiomics features (RD) allowed improved prognostic separation (OS/PFS, C-I: 0.77/0.70). The RD signature consisted of 12 and 10 textural features for the OS and PFS models. Combining the RD model with RRRS yielded the best performance (OS/PFS, C-I: 0.78/0.73). No significant correlation between the textural features and the prescribed dose, tumor grade and volume was found, with the Spearman's correlation coefficient ranging between -0.06 to 0.17. **Conclusions:** Integrating multimodal information outperforms unimodal prognostic separation of rHGG following CIRT, highlighting the importance to consider biological, physical and morphological data for patient stratification. Prospective validation studies of this multimodal stratifier is warranted. Research Sponsor: Funding by the H2020 MSCA-ITN PREDICT project.

Mean C-I with 95% confidence intervals for the considered models.

	RRRS		DD		CT- mpMRI		RD		RD-RRRS	
	C-I	95% CI	C-I	95% CI	C-I	95% CI	C-I	95% CI	C-I	95% CI
OS	0.68	[0.66 0.69]	0.71	[0.70 0.72]	0.76	[0.74 0.76]	0.77	[0.75 0.77]	0.78	[0.77 0.79]
PFS	0.61	[0.60 0.62]	0.69	[0.68 0.70]	0.68	[0.67 0.68]	0.70	[0.68 0.71]	0.73	[0.72 0.74]

Radiomics features extracted from the mpMRI and the RT CT.
Dosiomics features extracted from the DD. DD: dose distribution, RD: radiomics and dosiomics.

2044 **Poster Session**

A phase I dose-escalation study to evaluate pharmacokinetics, safety and tolerability of ACT001 in patients with advanced glioma. *First Author: Yehui Shi, Tianjin Medical University Cancer Hospital, Tianjin, China*

Background: Management of advanced gliomas including glioblastoma multiforme (GBM) remains as an unmet medical need. Here we report our clinical experience with ACT001, or dimethylamino micheliolide, a synthesized derivative from parthenolide (a natural product of sesquiterpene lactone class), in Han Chinese patients with advanced glioma. **Methods:** Adult patients were enrolled in a 3+3 dose escalation phase 1 study with the following pre-defined ACT001 cohorts: 100mg, 200mg, 400mg, 600mg and 900mg, twice a day (BID). Pharmacokinetics and adverse events were evaluated during the study. Imaging studies were performed using RANO criteria to assess the therapeutic afficacy. **Results:** 16 patients with advanced glioma were enrolled in this single agent dose escalation study including 8 primary GBM, 4 astrocytoma (grade 2-3) and 4 other advanced glioma. The median age was 49 years (range: 31-70). Safety evaluation was performed in five cohorts and 13 of the 16 subjecst were evaluable for drug tolerability analysis. ACT001 was tolerated very well and no DLT or MTD was identified. Other than grade 1 adverse reactions (AE) in most cases and grade 2 AEs in other clinical findings, no drug-related grade 3 AE was noted. Pharmacokinetic analysis indicates that there was approximately linear correlate between the drug exposure (C_{max}, $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$) and study drug dosages evaluated. $T_{1/2}$ is 4 hours with mean Cmax increased from approximate 300ng/ml to 5000ng/ml in a dose dependent manner with no significant dose accumulation during repeated dosing challenge. Post baseline MRI scans were performed in 11 out of 16 subjects. Among these 11 subjects, 1 GBM patient had a partial response (PR) at end of cycle 2 but had disease progressed at end of cycle 4; two non-GBM patients had a stable disease (SD) lasting for 5 or 6 cycles respectively before being taken off study due to disease pregression (PD) and other 8 patients had a PD. Of note, 9 out of these 11 subjects had stable or even improved clinical performance by the time they were taken off study due to PD. Five other subjects withdrew their consents or were taken off study due to clinical disease progression. Of note, subject S12 with diffusive astrocytoma was taken off study due to PD while still with a stable clinilcal performance and stereotactic biopsies targeting the progressed lesion didn't reveal viable tumor tissues other than presence of macrophage/microglia. This subject was still alive 666 days after being taken off study. The mode of ACT001 actions is proposed to be at least partially related to its effects on tumor immune microenvironment. **Conclusions:** ACT001 was safe and tolerated well in patients. Clinical response was observed including a pathologic response in a subset of patients dosed at lower dose cohorts. iRANO criteria will be used in future studies based on its impacts on tumor immune microenvitonment. Clinical trial information: ChiCTR-OIC-17013604. Research Sponsor: Accendatech Co., Ltd.

2045 **Poster Session**

Pilot trial treating recurrent GBM patients with precision medicine regimens. *First Author: Jennifer Leigh Clarke, University of California, San Francisco, San Francisco, CA*

Background: Recurrence of GBM after initial treatment with surgery, radiation, and chemotherapy is nearly universal. Salvage therapies have limited efficacy with median overall survival (OS) of approximately 9 months and 6-month-progression-free survival (PFS-6) of 10-25% for both targeted and traditional therapies. Given GBM's molecular heterogeneity, targeting a single molecular abnormality in isolation has consistently failed as a strategy, and precision combination approaches are needed. **Methods:** The primary objective was to demonstrate the feasibility of implementing a personalized drug regimen for patients (pts) with surgically resectable recurrent GBM within 35 days of surgery. Secondary objectives included safety and efficacy. Eligible pts signed consent before surgery, and tumor tissue was analyzed using the CLIA-approved "UCSF500" next-generation sequencing panel with paired tumor/germline sequencing. A specialized genomic tumor board made individualized treatment recommendations incorporating sequencing results of the recurrent tumor and clinical history for each pt, using up to 4 FDA-approved drugs in combination (all drugs provided by study). Correlative studies will be reported separately. **Results:** 19 pts signed consent and 16 pts had surgery on trial, 1 with pathology showing treatment effect only. The remaining 15 pts were all genetically profiled and successfully started their individualized treatment within 35 days of surgery, meeting the primary feasibility endpoint. **Conclusions:** Implementation of an individualized treatment regimen was feasible in a timely fashion in surgically resectable recurrent GBM pts, with encouraging preliminary efficacy results. Further investigation is warranted, both to validate efficacy and to streamline this approach in larger pt populations. Clinical trial information: NCT03681028. Research Sponsor: Glioma Precision Medicine Program.

Drug Used	(Epi)Genetic alteration	# of pts treated
Afatinib	EGFR amplification +/- mutation or rearrangement	10
Abemaciclib	CDKN2A/B deletion or CDK4 amplification	8
Olaparib	ATRX loss or MGMT hypermethylation	5
Everolimus	PTEN loss +/- PIK3CA mutation	5
Trametinib	NF1 loss	2
Propranolol	TP53 mutation	1

2046 **Poster Session**

$ATRX^{Loss}$ to impair glioma stem cell viability and self-renewal via proton radiotherapy induced necrosis. *First Author: Angel Garces, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Glioblastoma Multiforme (GBM-Grade IV) is the most aggressive form of glioma in the USA carrying only a 15 month median survival time. Although $IDH1^{R132H}$ is traditionally associated with improved glioma patient survival and clinical response to chemotherapy, astrocytoma (LGG) patients also harbor $ATRX^{Loss}$, an inactivation of the ATRX chromatin remodeling protein shown to impair DNA damage repair via non-homologous end joining. The recent discovery of glioma stem cells (GSCs), a subpopulation of chemoradioresistant, self-renewable, tumor initiating cells known to promote tumor recurrence, presents a new target for therapeutic intervention. However, the mechanisms by which $ATRX^{Loss}$ contributes to GSC proton radiotherapy (PRT) sensitivity, a more tumor specific and cytotoxic form of radiation therapy than conventional X-rays (XRT), are not well understood. *We hypothesize that $ATRX^{Loss}$ impairs GSC post-radiation viability and self-renewal capacity by promoting necrosis to a higher extent after PRT than XRT.* **Methods:** Isogenic TS543-$ATRX^{WT}$ and TS543-$ATRX^{Loss}$ patient derived glioma cells were cultured as neurospheres and treated with 2-8 Gy XRT or PRT. GSC viability was quantified using the CellTiterGlo 3D assay 12 days after irradiation. The Annexin V apoptosis and necrosis assay was conducted every 8 hours up to 72 hours after irradiation. GSC self-renewal, based on neurosphere formation frequency, was quantified using extreme limiting dilution analysis (ELDA). **Results:** $ATRX^{Loss}$ significantly decreased TS543 GSC viability after 2-8 Gy radiation therapy compared to $ATRX^{WT}$ (Unpaired t-test with Welsh's correction and Holm-Sidak's Multiple Comparisons Test $p<0.0001$). TS543-$ATRX^{Loss}$ also significantly inhibited GSC self-renewal over TS543-$ATRX^{WT}$ when subject to either 6 Gy PRT or XRT (Pairwise $Pr(>\chi^2)<0.01$). Interestingly, PRT significantly reduced GSC viability to a higher extent than XRT in both TS543-$ATRX^{WT}$ and TS543-$ATRX^{Loss}$, which demonstrates the effectiveness of PRT to treat $ATRX^{Loss}$ gliomas. Follow up studies confirmed that $ATRX^{Loss}$ sensitizes TS543 GSCs more extensively to the cytotoxic effects of PRT compared to XRT via the upregulation of necrosis at 72 hours post-irradiation (Two-way ANOVA with Tukey's post-hoc Multiple Comparisons Test $p<0.0001$). **Conclusions:** We conclude that $ATRX^{Loss}$ substantially contributes to PRT sensitivity in GSCs, thereby supporting the benefits of PRT for astrocytoma patients. Our future experiments will further elucidate the biological mechanisms by which $ATRX^{Loss}$ confers PRT sensitivity, especially via dsDNA damage. Research Sponsor: U.S. National Institutes of Health.

2047 **Poster Session**

Evaluation of GM-CSF and $AS01_B$ adjuvants in a phase I/IIa trial of a therapeutic CMV vaccine (VBI-1901) against recurrent glioblastoma (GBM). *First Author: Patrick Y. Wen, Dana-Farber Cancer Institute, Boston, MA*

Background: Cytomegalovirus (CMV) antigens have been reported in over 90% of GBMs. $CD4^+$ and $CD8^+$ T cells are most frequently directed against the gB and pp65 antigens, respectively, and are immunogenic targets in a CMV-based GBM vaccine. **Methods:** We enrolled a total of 20 patients with KPS at least 70 and first recurrence of GBM into 2 arms of the Phase IIa extension of gB/pp65 enveloped virus-like particles (eVLPs) adjuvanted with either GM-CSF given intradermally or with $AS01_B$ given intramuscularly (NCT03382977). Patients were vaccinated with VBI-1901 every 4 weeks, with serologic immune-monitoring 2 weeks after each vaccination and surveillance brain MRI scans every 6 weeks. **Results:** 10 patients (6 women, 4 men) with a median age of 58 (33-67 yrs) were enrolled into the GM-CSF arm and 10 patients (3 women, 7 men) with a median age of 65 (40-67) enrolled into the $AS01_B$ arm. Disease control rates of 40% and 50% were observed in the GM-CSF and $AS01_B$ arms, respectively, with 2 sustained PRs in the GM-CSF arm. The 6-month OS rate for the GM-CSF arm is 80% and is estimated to be comparable for the $AS01_B$ arm. CMV-specific CD4+ effector memory T cells may correlate with tumor responses in both arms of the study, with $AS01_B$ boosting higher frequencies of these cells regardless of baseline CD4/CD8 ratio. **Conclusions:** These encouraging results from both arms of the trial justify further clinical evaluation in a randomized, controlled trial expected to begin later in 2021. Clinical trial information: NCT03382977. Research Sponsor: VBI Vaccines Inc, Pharmaceutical/Biotech Company, U.S. National Institutes of Health, William Rhodes and Louise Tilzer-Rhodes Center for Glioblastoma at NewYork-Presbyterian Hospital.

2048 **Poster Session**

Targeted agents recommended by the CNS TAP tool compared to those selected by a tumor board in a molecularly-driven clinical trial in children and young adults with DIPG. *First Author: Holly Roberts, University of Michigan Medical School, Ann Arbor, MI*

Background: Genetic sequencing of diffuse intrinsic pontine glioma (DIPG) and diffuse midline glioma (DMG) biopsy specimens has revealed genomic heterogeneity, fueling an interest in individualized, targeted treatment options. The Pacific Pediatric Neuro-Oncology Consortium recently completed a feasibility study PNOC003: Molecular Profiling for Individualized Treatment Plan for DIPG (NCT02274987), in which a multidisciplinary tumor board recommended targeted agents based on the molecular and genetic profiling of each patient's tumor. Separately, our group developed a numeric scoring tool of targeted anticancer agents, the Central Nervous System Targeted Agent Prediction (CNS TAP) tool, which combines pre-clinical, clinical, and CNS penetration data with patient-specific genomic information to generate a numeric score for each agent to objectively evaluate these targeted therapies for use in patients with CNS tumors. We hypothesized that highly-scored agents within the CNS-TAP tool would overlap, at least in part, with the agents recommended by the molecular tumor board in PNOC003. **Methods:** For each study participant (n=28), a retrospective analysis was completed, utilizing the genomic report to identify actionable genetic alterations and to input patient-specific data into CNS TAP to identify the highest scoring agents. We compared high-scoring agents within the CNS TAP tool with recommendations from the PNOC003 tumor board for each of the enrolled 28 patients. **Results:** Overall, 93% (26/28) of patients had at least one agent recommended by both the tumor board and CNS TAP. Additionally, 39% (37/95) of all agents recommended by the tumor board were also selected by CNS TAP, with additional analysis ongoing. **Conclusions:** There was significant overlap between the highest-scoring and selected agents via CNS TAP compared with those chose by the molecular tumor board. Through this work, we also identified factors that likely contributed to the discordance in choice of targeted therapies. Without clinician input, the CNS TAP tool is unable to account for drug-drug interactions, includes only designated anticancer agents, and cannot easily be updated in real time, requiring extensive manual literature review for each included agent. However, CNS TAP provides an objective evaluation of targeted therapies, in contrast to inherently subjective recommendations of a tumor board. Given the discordance identified between these methods and the strengths of each, a prospective study incorporating both CNS TAP and a molecular tumor board for targeted therapy selection in patients with high grade glioma is warranted. Research Sponsor: None.

2049 **Poster Session**

A phase I/IIa study to evaluate the safety and efficacy of blood-brain barrier (BBB) opening with the SonoCloud-9 implantable ultrasound device in recurrent glioblastoma patients receiving IV carboplatin. *First Author: Ahmed Idbaih, Inserm U 1127, Cnrs Umr 7225, Sorbonne Universités, UPMC Univ Paris 06 Umr S 1127, Institut Du Cerveau Et De La Moelle Épinière, ICM, Paris, France*

Background: Low intensity pulsed ultrasound (LIPU) in conjunction with intravenous microbubbles can transiently and reversibly disrupt the blood-brain barrier (BBB), allowing for an increase in the tissue concentration of chemotherapy agents in the brain. Mass spectrometry data from preclinical models (mouse, swine) showed a $>$ 5x enhancement in carboplatin brain concentrations, which correlated well with the spatial distribution of a Gadolinium (Gd) contrast agent used for magnetic resonance imaging (MRI). **Methods:** The primary objective of this phase I/IIa study (NCT03744026) was to demonstrate the safety of BBB disruption using LIPU in patients with recurrent glioblastoma. This study was a 3+3 design using escalating numbers (3, 6, 9) of activated 1 MHz ultrasound emitters. Nine patients were treated in the escalation phase and another 12 patients were treated with 9 emitters in the expansion phase. Eligibility included recurrent GBM (any recurrence) with a maximum tumor size of $<$ 70 mm. The SonoCloud-9 device (CarThera, Paris, France) was implanted during tumor debulking/resection surgery and replaced the bone flap, with the device targeting the tumor and surrounding peritumoral brain. The device was activated every four weeks for a duration of 270 seconds, concomitantly with IV DEFINITY microbubbles (10 ml/kg), to disrupt the BBB prior to administration of carboplatin (AUC 4-6). MRI was performed to verify safety and evaluate efficacy of BBB disruption with Gd enhancement. **Results:** No DLTs were observed. The overall tolerance of the SonoCloud-9 implant was good, with two transient, manageable grade 3 wound infections and one grade 1 acquired meningocele event considered as probably related to the overall procedure. The most frequent neurologic adverse events were grade 1 blurred vision (5%) and dizziness (5%). **Conclusions:** Significant Gd enhancement was observed after more than 90% of sonication sessions, suggesting effective BBB disruption and carboplatin enhancement. Clinical trial information: NCT03744026. Research Sponsor: CarThera.

2051 **Poster Session**

Malignant glioma subset from Actuate 1801: A phase 1/2 study of 9-ING-41, a glycogen synthase kinase 3 beta (GSK-3β) inhibitor, as a single agent and combined with chemotherapy, in patients with refractory hematologic malignancies or solid tumors. *First Author: Yazmin Odia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: GSK-3β, a serine/threonine kinase, is a key regulator of metabolism and glycogen biosynthesis. GSK-3β aberrant overexpression promotes tumor progression and chemotherapy resistance through NF-κB and p53-mediated apoptotic pathways. GSK-3β inhibition impacts immunomodulation through downregulation of checkpoints, such as PD-L1 and LAG-3, and increasing NK and T-cell mediated killing of tumor cells. 9-ING-41 is a small-molecule potent selective GSK-3β inhibitor with preclinical antitumor activity against several tumor types. In chemoresistant PDX models of glioblastoma (GBM), 9-ING-41 enhanced the antitumor effect of CCNU and CPT-11. **Methods:** In the first-in-human study (NCT03678883), patients (pts) with refractory malignancies received 9-ING-41 monotherapy (n = 65) or in combination with one of 8 cytotoxic regimens after prior treatment with the same chemotherapy (n = 162). We report the subset of pts with recurrent gliomas treated with 9-ING-41 monotherapy IV twice a week in 21-day cycles at different dose levels (3.3, 5, 9.3, 15mg/kg), or in combination with lomustine 30 mg/m^2 orally once weekly in 84-day cycles. Primary objective was safety and tolerability. **Results:** An RP2D of 15mg/kg IV was confirmed across all 9 regimens, no accentuation of chemotherapy-related toxicity noted. Of 18 glioma patients enrolled, 13 were GBM, 2 anaplastic astrocytomas, 1 diffuse astrocytoma, and 1 anaplastic oligodendroglioma. Four patients received single agent 9-ING-41, 14 treated concurrently with lomustine. Demographics: 6 female, 12 male; median age 52 (30-69) years; median ECOG was 1 (0-2). All received first-line radiation and temozolomide (18/18), prior therapies for recurrences included nitrosoureas (15/18), bevacizumab (8/18), TTFields (6/18), immune checkpoint inhibitor (4/18). Median recurrences 3 (1-6). Genomic alterations from available NGS reports included: IDH WT (11), IDH mutation (3), MGMT promoter unmethylated (11), MGMT promoter methylated (1), 1p19q co-deletion (10), EGFR amplification (6), EGFR v3 mutation (3), TERT promoter mutation (6), PTEN loss (3), NF1 rearrangement (2), ATRX loss (2), TP53 mutated (4), CDKN2A deletion (2), RB1 loss (1), PALB-2 mutation (10). No SAEs or grade 3/4 AEs attributed to 9-ING-41 were noted; AEs included G1/2 transient vision changes (9/18, 50%), infusion reactions (4/18, 22%). Side effects from lomustine included: G3/4 thrombocytopenia (3/14, 21%), and G1/2 fatigue (4/14, 28%). Best overall response: 1 minimal response (-43%) after 2 cycles of 9-ING-41 and lomustine. Median days on therapy was 55 (4-305), 4/18 (22%) were stable for 20 weeks or longer. **Conclusions:** These results show 9-ING-41 alone or in combination is safe and warrants further study in glioma patients. Clinical trial information: NCT03678883. Research Sponsor: Actuate Therapeutics.

2053 **Poster Session**

The clinical significance of telomerase reverse transcriptase (*TERT*) promoter mutations, telomere length and O6-methylguanine DNA methyltransferase (*MGMT*) promoter methylation status in newly diagnosed and recurrent *IDH*-wildtype glioblastoma (GBM) patients (PTS): A large mono-institutional study. *First Author: Giuseppe Lombardi, Department of Oncology, Oncology 1, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy*

Background: the clinical significance of *TERT* promoter mutations, telomere length and their interactions with *MGMT* promoter methylation status in patients with *IDH*-wildtype GBM patients remain unclear. We performed a large mono-institutional study to better investigate their impact and their interaction on clinical outcomes **Methods:** *TERT* promoter mutations (C228T and C250T), relative telomere length (RTL) and *MGMT* methylation status were assessed in 278 newly diagnosed and in 65 recurrent *IDH*-wildtype GBM PTS which were treated at Veneto Institute of Oncology (Padua, Italy) from Dec 2016 to Jan 2020. We have retrospectively explored association between gene characteristics and neuroradiological response (RANO criteria), progression-free survival (PFS), overall survival (OS). Telomere length was measured by monochrome multiplex PCR and RTL values were calculated as a telomere/single-copy gene ratio **Results:** characteristics of newly diagnosed GBM PTS were: median age 63 ys, ECOG PS 0-1 in 71% of PTS, radical surgery in 38%, 78% received radiation therapy plus TMZ, *MGMT* was methylated in 53%, *TERT* promoter was mutated in 80% (75% C228T, 25% C250T), median RTL was 1.57 (range 0.4-11.37). Objective response rate was reported in 15% of PTS, median OS was 15ms (95% CI 13-18ms), median PFS was 8ms (95% CI 7-9ms). At multivariable analysis, *TERT* promoter mutations and RTL were not associated with clinical outcomes; about OS, *TERT* promoter mutations and RTL reported a HR of 1.05 (95% CI 0.64-1.64) and 0.99 (95% CI 0.89-1.10), respectively; *MGMT* methylated tumors showed significant improved PFS and OS with a HR of 0.54 (95% CI 0.40-0.71) and 0.47 (95% CI 0.34-0.64), respectively. All interactions among *MGMT* status, *TERT* mutation status and RTL were not statistically significant. Characteristics of recurrent GBM PTS were: median age 55 ys, ECOG PS 0-1 in 60% of PTS, *MGMT*met in 37%, TERT promoter mutations in 75% (75% C228T, 25% C250T), RTL was 1.67 (range 0.68-8.87). At multivariable analysis, only *MGMT* methylated tumors resulted significantly associated to prolonged OS (HR 0.16; 95% CI 0.07-0.40). No gene interaction was significant. **Conclusions:** for the first time worldwide, we analyzed the impact of *TERT* promoter mutations, RTL and *MGMT* methylation status in both newly diagnosed and recurrent *IDH*-wildtype GBM PTS. *TERT* promoter status and RTL were not associated with clinical outcomes at both diagnosis and relapse. *MGMT* promoter methylation status was the only prognostic factor in both cases. No significant interaction was demonstrated between *TERT* promoter mutations, RTL and *MGMT* methylation status. Research Sponsor: None.

2054 **Poster Session**

Resection and surgically targeted radiation therapy for locally recurrent GBM. *First Author: David Brachman, GT Medical Technologies, Tempe, AZ*

Background: Recurrent GBM (rGBM) is a diffuse disease, and resection (R) alone does not provide durable local control (LC) or prolong overall survival (OS). Hypothesizing R plus immediate radiation (RT) may achieve durable LC and secondarily improve OS by permitting time for subsequent potentially effective but biologically slower treatments to have an impact, we prospectively evaluated R combined with a novel surgically targeted radiation therapy (STaRT) device utilizing Cs-131 embedded in bioresorbable collagen tiles. **Methods:** From 2/13-2/18 patients (pts) with locally recurrent GBM were treated on a prospective single arm trial (ClinicalTrials.gov, NCT#03088579) of maximum safe resection and immediate RT (GammaTile, GT Medical Technologies, Tempe AZ). Upon resection the at-risk areas of the surgical bed were lined with the GammaTile (GT) device, delivering 60-80 Gy at 5 mm. Follow up treatments were not specified but captured; no pt. underwent additional local therapy without progression, and no pt. was lost to follow up. We present study specified endpoints of local control (LC), overall survival (OS), and adverse events (AE), and a post hoc, hypothesis-generating analysis of outcomes by receipt of systemic (Sys) therapy. **Results:** 28 locally recurrent GBM were treated, 20 at first progression (range 1-3). Median age was 58 years (yrs.) (range 21-80), KPS 80 (60-100), female: male ratio 10:18 (36/64%). MGMT was methylated in 11%, unmethylated in 18%, and unknown in 71%. For all pts., median OS was 10.7 months (mo.) (range .1-42.3), and radiographic LC was 8.8 mo. (range .01-34.5). LC (defined as $<$ 15 mm from surgical bed) was maintained in 50% of pts., and no first failure was local. 12 mo. OS was 75% for pts. $<$ 50 yrs. vs. 43% for $>$ 50 yrs. (HR .46, p = .009). MGMT, KPS, and sex were non-predictive. After R+GT, 17 pts. received $>$ 1 cycle of systemic therapy (Sys), either as adjuvant or salvage, alone or in combination. Sys was bevacizumab (BEV) in 15 pts., temozolomide (TMZ) in 12, and lomustine (CCNU) in 8 (N $>$ 17 as some pts. received $>$ 1 Sys). Post hoc analysis disclosed a 15.1 mo. OS for pts. receiving $>$ 1 cycle of Sys (Sys+, N = 17) vs. 6.5 mo. for no Sys (Sys-, N = 11) (hazard ratio (HR) .38, p = .017)). LC was 11.4 mo. for Sys+ and 2.1 mo. for Sys- (HR .44; p = .16)). Median OS (mo.) for BEV+ vs. BEV- was 16.7/4.5 (HR .38, p = .017), for TMZ+ vs. TMZ- 17.5/6.7 (HR .40, p = .025) and for CCNU+ vs. CCNU- 17.5/7.9 (HR .61, p = .25), respectively. Three attributed AE occurred, 1 dehiscence requiring surgery and 2 radiation brain effects, medically treated. 4 unrelated deaths occurred $<$ 60 days post-op, all in the Sys- cohort, impacting their opportunity for subsequent treatment. **Conclusions:** In this study local treatment alone was insufficient to achieve prolonged OS. Post hoc analysis suggests R+GT coupled with Sys may have potential to impact OS in rGBM patients. GT was FDA cleared in 2020 for use in newly diagnosed malignant and all recurrent intracranial neoplasms. Clinical trial information: NCT#03088579. Research Sponsor: Foundation For Cancer Research and Education, Other Government Agency.

2055 **Poster Session**

Health-related quality of life for glioblastoma short and long-term survivors receiving treatment with TTfields. *First Author: Joshua David Palmer, The James Cancer Hospital at The Ohio State University, Columbus, OH*

Background: The aim of this study was to administer the first large-scale, international survey eliciting real-world patient-reported quality-of-life (QoL) for patients with newly diagnosed and long-term glioblastoma (GBM) currently receiving treatment with TTFields. **Methods:** A survey was designed and mailed to 2,815 patients actively using TTFields for treatment of GBM in the United States (US, n = 2,182) and Europe (EU, n = 633). The survey included 1) demographic information, 2) patient-reported clinical information and 3) EuroQol's EQ-5D-5L and EQ visual analogue scale (EQ-VAS) surveys. Univariate and multivariate analyses were performed on five dimensions (mobility, self-care, usual activity, pain/discomfort, anxiety/depression) of the EQ-5D-5L and EQ-VAS to understand the impact of patient demographics and clinical characteristics on QOL. **Results:** A total of 1,106 patients were included (39.3% response rate) with 782 and 324 responses in the US and EU, respectively. The median time from diagnosis was 14 mos (range, 0-301 mos) and ≥24 mos in 28.4% of patients. Patients were mostly male (62.3%) with a mean age of 58.5 (SD = 12.5) and 69.3% had stable disease. Mean EQ-VAS was 68.2 for all patients and was significantly higher for those with $>$ 15 months since diagnosis compared to $<$ 15 months since diagnosis (p = 0.008). There were significantly fewer problems reported on self-care (p = 0.04) and usual activity (p = 0.007) in patients with a longer time since diagnosis in the univariate analysis. In the multivariate analysis, patients with a longer time since diagnosis reported significantly better EQ-VAS (p = 0.04). The effect size in the multivariate analysis for time since diagnosis on EQ-VAS was higher in the progressed subgroup (p = 0.17) compared to the broader sample (0.08). The EQ-VAS and all five dimensions including mobility, self-care, usual activity, pain/discomfort, and anxiety/depression were improved for stable patients compared to progressed patients in the univariate and multivariate analyses. However, when stratified by progression status, progressed patients with longer time from diagnosis had significantly fewer reported problems with mobility (p = 0.04), self-care (p = 0.004) and usual activity (p = 0.008), and significantly better self-rated health status (p = 0.02). **Conclusions:** GBM survivors receiving TTFields reported significantly improved health status over time since diagnosis. Long-term survival with TTFields does not have a detriment in patient reported quality of life, in fact with longer time from diagnosis QOL significantly improves. This is true for patients with stable and progressed disease. Future prospective clinical trials are needed to further study the impact of our treatment and tumor progression on patient QOL. Research Sponsor: Novocure Inc.

2056 **Poster Session**

Scalp-sparing radiation with concurrent temozolomide and tumor treating fields (SPARE) for patients with newly diagnosed glioblastoma. *First Author: Ryan C Miller, Sidney Kimmel Medical College at Thomas Jefferson University, Philadelphia, PA*

Background: Standard of care for patients with newly diagnosed glioblastoma includes concurrent chemoradiation and maintenance temozolomide with Tumor Treating Fields (TTFields). Preclinical studies suggest TTFields and radiation treatment have synergistic effects. We report our clinical trial evaluating safety and tolerability of scalp-sparing radiation with concurrent temozolomide and TTFields. **Methods:** This is a single arm pilot study. Adult patients (age ≥ 18 years) with newly diagnosed glioblastoma and a KPS of ≥ 60 were eligible. All patients received concurrent scalp-sparing radiation (60 Gy in 30 fractions) with temozolomide (75 mg/m2 daily) and TTFields (200 kHz). Maintenance therapy included temozolomide and continuation of TTFields. Radiation treatment was delivered through TTFields arrays. The primary endpoint was safety and toxicity of TTFields concurrent with chemoradiation in patients with newly diagnosed glioblastoma. **Results:** A total of 30 patients were enrolled in the trial. Twenty were male and ten were female, with a median age of 58 years (range 19 to 77 years). Median KPS was 90 (range 70 to 100). Median follow-up was 8.9 months (range 1.6 to 21.4 months). Twenty (66.7%) patients had unmethylated MGMT promotor status and ten (33.3%) patients had methylated promoter status. Median time from surgery to radiation was 34 days (26 to 49 days). Scalp dose constraints were achieved for all patients, with the mean dose having a median value of 8.3 Gy (range 4.3 to 14.8 Gy), the D20cc median was 26.1 Gy (range 17.7 to 42.8 Gy), and the D30cc median was 23.5 Gy (range 14.8 to 35.4 Gy). Skin adverse events (AEs; erythema, dermatitis, irritation, folliculitis) were noted in 83.3% of patients, however, these were limited to Grade 1 or 2 events, which resolved spontaneously or with topical medications. No patient had radiation treatment interruption due to skin AEs. Other Grade 1 events included pruritus (33.3%), fatigue (30%), nausea (13.3%), headache (10%), dizziness (6.7%), and cognitive impairment (3.3%). Other Grade 2 events included headache (3.3%). Nineteen patients (63.3%) had progression, with a median PFS of 7.6 months (range 1.6 to 12.7 months). Overall survival was not reached. **Conclusions:** Concurrent TTFields (200 kHz) with scalp-sparing chemoradiation is a safe and feasible treatment option with limited toxicity. Future randomized prospective trials are warranted to define therapeutic advantages of concurrent TTFields with chemoradiation. Clinical trial information: NCT03477110. Research Sponsor: None.

2057 **Poster Session**

Phase 1 trial of drug resistant immunotherapy: A first-in-class combination of MGMT-modified $\gamma\delta$ t cells and temozolomide chemotherapy in newly diagnosed glioblastoma. *First Author: Louis B. Nabors, University of Alabama at Birmingham, Birmingham, AL*

Background: Temozolomide (TMZ) transiently upregulates NKG2D ligands targeted by innate immune effector cells. Lymphodepletion impairs this immune response, however, genetic modification of *ex vivo* expanded $\gamma\delta$ T cells with an MGMT-expressing lentivector confers resistance to TMZ, allowing concurrent chemotherapy and $\gamma\delta$ T cell infusion, thereby targeting the tumor when NKG2DL are maximally expressed. This Drug Resistant Immunotherapy (DRI) is currently being evaluated in a Phase 1 first in human study (NCT04165941) and interim safety and biologic correlative analysis are detailed here for the first dosing cohort. **Methods:** Adults with newly diagnosed, untreated glioblastoma (GBM), adequate organ function, and a KPS≥70% will be enrolled. Subjects undergo subtotal resection and placement of a Rickham reservoir followed 3-4 weeks by apheresis from which $\gamma\delta$ T cells are expanded, transduced with an MGMT-expressing lentivector, harvested, and cryopreserved. Standard of care induction TMZ/radiation therapy is initiated followed by 6 cycles of maintenance TMZ. Intravenous TMZ (150mg/m^2) and intracranial dosing of 1 x 10^7 $\gamma\delta$ T cells occur on day 1 of each maintenance cycle. Daily oral TMZ 150mg/m^2 follows for Days 2-5. Dose level 1 (DL1) subjects receive 1 fixed dose of $\gamma\delta$ T cells and DL2 receive 3 doses administered on Day 1 of each of first 3 cycles of TMZ dependent on absence of dose limiting toxicity. Primary endpoint is safety; secondary endpoints include progression free and overall survival. Immunologic and genomic correlative analyses are being conducted at specific time points from peripheral blood and cerebral spinal fluid collected from the Rickham. **Results:** Six subjects (4 females, 2 males) have been enrolled in DL1. All subjects were IDH1-WT with 5 subjects MGMT unmethylated and 1 methylated. Of these, 1 generated inadequate gd T cells and 2 withdrew consent prior to DRI treatment. For the 3 that received DRI, treatment-related adverse events with maximum CTCAE Grade 3 occurred in 1 subject; UTI, dehydration, and thrombocytopenia. The most common Grade 1/2 events included: fever, leukopenia, nausea, and vomiting which were attributable to TMZ or radiotherapy. Circulating T cells remained below normal range throughout maintenance phase in 2/3 subjects. NK and gd T cell numbers remained within low normal range for 3/3 and 2/3 subjects, respectively. Serum Th1 (IFNg, IL-2, TNFa) and Th2 (IL4, IL5, IL-10) cytokines were within clinical range although TNFa remained elevated from the gdT cell infusion through day +30 in 2 subjects. **Conclusions:** Administration of MGMT-gene modified gdT cells and TMZ as DRI is feasible in lymphodepleted subjects during TMZ maintenance phase and sufficiently safe to warrant further investigation at additional doses. Clinical trial information: NCT04165941. Research Sponsor: In8-bio Inc.

2058 **Poster Session**

Cost-effectiveness of concomitant and adjuvant temozolomide for glioblastoma patients with unmethylated O^6-methylguanine-DNA methyltransferase promoter regions in the United States. *First Author: Manav Dev Midha, Department of Economics, Case Western Reserve University, Cleveland, OH*

Background: Promoter region methylation of the O^6-methylguanine-DNA methyltransferase (MGMT) gene has emerged as a predictive factor for longer overall (OS) and progression-free (PFS) survival response to concomitant and adjuvant temozolomide (TMZ) chemotherapy in glioblastoma. Recently, several investigators have suggested the small survival benefit of TMZ for unmethylated patients is insufficient to warrant the increased risk of adverse events and that these patients should instead be enrolled in clinical trials. This study informs the debate by estimating the incremental costs and benefits associated with TMZ use in methylated and unmethylated patients based on available published evidence. **Methods:** Published OS and PFS Kaplan-Meier curves were digitized, parameterized, and extrapolated to ten years. Partitioned Survival Analysis trees were constructed in TreeAge Pro 2020. Costs of TMZ, RT, and inpatient hospitalization were included, among others. It was assumed that all patients receive surgery prior to beginning radiation, and that RT and TMZ (six adjuvant cycles) dosing was standard. Published utilities associated with the progression-free and post-progression health states, subject to each treatment, were used. A 3% annual discount rate and a willingness-to-pay of $150,000/quality-adjusted life year (QALY) were assumed. Probabilistic sensitivity analysis (PSA) was conducted. **Results:** In methylated patients, RT + TMZ versus RT is associated with $67,622 in additional costs and 10.91 additional quality-adjusted life months (QALMs). In unmethylated patients, RT + TMZ versus RT is associated with $9,203 in additional costs and 2.24 additional QALMs. The implied incremental cost effectiveness ratios (ICERs) support TMZ use in both populations and suggest it is more favorable for unmethylated patients ($74,378/QALY and $49,302/QALY for methylated and unmethylated patients, respectively). However, the incremental net monetary benefit (INMB) associated with TMZ use is substantially smaller for unmethylated patients ($18,797 versus $68,753) due to the smaller survival gains for this population. PSA results indicate that TMZ is more likely to be cost-effective for methylated (89.3%) than unmethylated (77.4%) patients. **Conclusions:** Post-radiation clinical trial enrollment should be considered instead of TMZ for unmethylated glioblastoma patients. While the estimated ICER justifies the use of TMZ for unmethylated patients – in fact, does so more strongly than for methylated patients – the relatively small incremental health benefit is plausibly outweighed by the opportunity cost of not enrolling these patients in clinical trials that offer the possibility of more substantive gains to current and future glioblastoma patients. Research Sponsor: None.

2059 **Poster Session**

Comprehensive molecular pharmacodynamic assessment identifies response markers of intermediary metabolism associated with BPM 31510-IV treatment in advanced glioblastoma multiforme patients. *First Author: Seema Nagpal, Stanford University, Stanford, CA*

Background: BPM 31510-IV is a drug-lipid conjugate nanodispersion containing oxidized Coenzyme Q10 (CoQ10) in clinical development for glioblastoma multiforme (GBM). In a recently concluded Phase 1 study of BPM 31510-IV (NCT03020602), in addition to safety and tolerability, longitudinal pharmacodynamic samples (20 samples/cycle of 28 days) were collected at various times in patient's refractory to radiation, temozolomide, and bevacizumab. **Methods:** Comprehensive multi-omic (proteomic, lipidomic, metabolomic) profiles were generated from buffy coat (proteomics only), plasma, and urine matrices. These data were further analyzed using bAIcis, a Bayesian statistics based artificial intelligence (AI) software, creating causal networks linking clinical information and endpoints to molecular composition of diverse biomatrices of patients prior to, as well as during, treatment with BPM 31510-IV. Twelve subjects comprised the intent to treat population (ITT) which were stratified across days of treatment (DR1; $\leq$28 days; DLT period; n=6) and (DR2, OS; $>$28 days; n=6). Bayesian networks and regression analysis were performed on the outputs of the analysis. Molecular analyte panels (combination of proteins, lipids, and metabolites) descriptive of progression free survival (PFS), adverse events (possibly/probably related to BPM 31510-IV), and of overall survival (OS) were generated. **Results:** Significant alteration ($p<0.05$) of metabolically associated protein and critical metabolite drivers of intermediary metabolism were identified as causally related to PFS. Significant quantitative changes in levels of several proteins (buffy coat) and metabolites (urine) were identified with probable or possible associations to adverse events in BPM 31510-IV treated subjects. **Conclusions:** Overall, alterations in proteins and metabolites influencing mitochondrial function and intermediary metabolism that differentiated responders versus non-responders and identified potential markers of adverse events associated with BPM 31510-IV exposure were identified and will be further explored for complementary diagnostic utility. Research Sponsor: BERG LLC.

2060 **Poster Session**

Phase I study of ruxolitinib with radiation and temozolomide in patients with newly diagnosed grade III gliomas and glioblastoma. *First Author: Yasmeen Rauf, Cleveland Clinic, Cleveland, OH*

Background: Ruxolitinib is a novel, potent, and selective inhibitor of JAK1 (Janus kinase 1) and JAK2 with modest to marked selectivity against TYK2 (tyrosine kinase 2) and JAK3, respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function. JAK signaling involves recruitment of signal transducers and activators of transcription (STATs) to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK/STAT pathway has been associated with several types of cancer and increased proliferation and survival of malignant cells. **Methods:** Newly diagnosed patients with unmethylated MGMT Glioblastoma or grade III glioma were recruited to Arm 1. Every patient received ruxolitinib and 60 Gy radiation for 6 weeks over 6 weeks (2Gy x 30). The dose of Ruxolitinib was administered given the 3+3 design. Level 1 or starting dose was 10 mg twice daily, level 2 was 15 mg twice daily, level 3 was 20 mg twice daily and level -1 was 5 mg twice daily. Arm 2 was started once safe dose was established for Arm 1 for each dose level. Patients with methylated MGMT glioblastoma or grade III glioma were eligible for Arm 2. Every patient received ruxolitinib + radiation x 60 Gy + daily temozolomide at 75 mg/m2 for 6 weeks over 6 weeks. Overall survival (OS) and progression-free survival (PFS) were estimate by Kaplan-Meier method and compared using log rank test. **Results:** 45 patients had survival data, 25 patients were Arm I and 20 arm II. The median OS and PFS were 18.2 (95% CI: 3.6-NA) months for Arm 1 and were not reached for Arm 2. OS and PFS Rate at 1 year was 61% (95% CI: 43-85%) and 51% (35-76%) for Arm 1, and 95% (85-100%) for Arm 2 ($p = 0.01$ and $p = 0.002$), respectively. **Conclusions:** Patients that received ruxolitinib + radiation x 60 Gy + daily temozolomide at 75 mg/m2 for 6 weeks over 6 weeks (Arm 2) had significantly better PFS and OS than those that received ruxolitinib + radiation x 60 Gy alone. Clinical trial information: NCT03514069. Research Sponsor: Case Comprehensive Cancer Center.

2061 **Poster Session**

Safety and feasibility of rhenium-186 nanoliposome (^{186}RNL) in recurrent glioma: The ReSPECT phase 1 trial. *First Author: Andrew J. Brenner, University of Texas Health San Antonio Cancer Center, San Antonio, TX*

Background: While external beam radiation therapy (EBRT) remains a central component of the management of primary brain tumors, it is limited by tolerance of the surrounding normal brain tissue. Rhenium-186 NanoLiposome (^{186}RNL) permits the delivery of beta-emitting radiation of high specific activity with excellent retention in the tumor. We report the results of the phase 1 study in recurrent glioma. **Methods:** A Phase 1 dose-escalation study of ^{186}RNL in recurrent glioma utilizing a standard 3+3 design was undertaken to determine the maximum tolerated dose of ^{186}RNL. ^{186}RNL is administered by convection enhanced delivery (CED). Infusion is followed under whole body planar imaging and SPECT/CT. Repeat SPECT/CT imaging is performed immediately following, and at 1, 3, 5, and 8 days after ^{186}RNL infusion to obtain dosimetry and distribution. Subjects were followed until disease progression by RANO criteria. **Results:** Eighteen subjects were treated across 6 cohorts. The mean tumor volume was 9.4 mL (range 1.1 – 23.4). The infused dose ranged from 1.0 mCi to 22.3 mCi and the volume of infusate ranged from 0.66 mL to 8.80 mL. From 1 – 4 CED catheters were used. The maximum catheter flow rate was 15 μl/min. The mean absorbed dose to the tumor volume was 239 Gy (CI 141 – 337; range 9 - 593), to normal brain was 0.72 Gy (CI 0.34 – 1.09; range 0.005 – 2.73), and to total body was 0.07 Gy (CI 0.04 – 0.10; range 0.001 – 0.23). The mean absorbed dose to the tumor volume when the percent tumor volume in the treatment volume was 75% or greater (n = 10) was 392 Gy (CI 306 – 478; range 143 – 593). Scalp discomfort and tenderness related to the surgical procedure did occur in 3 subjects. The therapy has been well tolerated, no dose-limiting toxicity has been observed, and no treatment-related serious adverse events have occurred despite markedly higher absorbed doses typically delivered by EBRT in patients with prior treatment. Responses have been observed supporting the clinical activity. Final results from the dose escalation will be presented. **Conclusions:** ^{186}RNL administered by CED to patients with recurrent glioma results in a much higher absorbed dose of radiation to the tumor compared to EBRT without significant toxicity. The recommended Phase 2 dose is 22.3 mCi in 8.8 mL of infusate. Clinical trial information: NCT01906385. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Cohort	Activity (mCi)	Infusate Volume(mL)	Concentration (mCi/mL)	Subjects
1	1.0	0.66	1.5	3
2	2.0	1.32	1.5	3
3	4.0	2.64	1.5	3
4	8.0	5.28	1.5	3
5	13.4	5.28	2.5	3
6	22.3	8.80	2.5	3

2062 **Poster Session**

Autologous stem cell transplantation (ASCT) versus whole brain radiation (WBRT) as a consolidation therapy in primary CNS lymphoma (PCNSL): A nationwide analysis. *First Author: Yazan Samhouri, Division of Medical Oncology, Allegheny Health Network, Pittsburgh, PA*

Background: High dose methotrexate-based regimens remain the most effective treatment against PCNSL but optimal consolidative strategy has yet to be determined. There is lack of high scale clinical trials comparing WBRT versus ASCT as consolidation therapy. Only two phase II randomized clinical trials (PRECIS and IELSG 32) have addressed this question. In this comprehensive national cancer database (NCDB) analysis, we examine the effect of WBRT versus ASCT on survival in PCNSL, we also sought to investigate clinical and socioeconomic predictors of treatment selection **Methods:** We conducted a retrospective cohort analysis using de-identified data accessed from the NCDB. The NCDB provided records of 16579 patients diagnosed with PCNSL between 2004 and 2016. We excluded patients who tested positive for HIV, and those who started chemotherapy > 120 days or started radiation > 365 days since diagnosis, to account for immortal time bias. Patients were divided into two treatment groups based on consolidation therapy: ASCT and WBRT. Multivariable regression models were used to analyze predictors of treatment selection. To account for variable baseline characteristics, we used propensity score weighting methodology. Survival estimates were calculated using the Kaplan-Meier and Cox proportional hazard regression methods **Results:** We identified 1620 patients with PCNSL who fulfilled the inclusion criteria. ASCT and WBRT were received by 197 patients and 1423 patients, respectively (Table). On multivariable analysis, increased age decreased the odds of receiving ASCT (OR 0.997, CI: 0.996-0.999, P <.001). Patients live in rural areas (OR 1.174, CI: 1.051-1.312, P= .005), those with higher education (OR 1.089, CI: 1.020-1.163, P=.01), and those who live further from the treating facility (OR 1.001, CI: 1.001-1.001, P<.001) received more ASCT. With a median follow up duration of 27.8 months, adjusted-median OS was 91.4 months and not reached for WBRT and ASCT groups, respectively (log-rank P<.001). Adjusted 3-year OS was 82% and 67% in ASCT and WBRT, respectively (HR: 0.43, CI: 0.29-0.64, P<.001) **Conclusions:** Consolidation with ASCT had improved OS compared with WBRT. There is a trend toward increased ASCT use and decreased WBRT use over the study period. We found clinical and socioeconomic factors that affected treatment selection. Research Sponsor: None.

	ASCT n(%)	WBRT n(%)	P-value
Age, mean(SD)	54.7 (12.5)	54.5 (13.5)	0.70
Sex (Female)	91 (46)	113 (45)	0.72
Race			0.998
Whites	170 (86)	217 (86)	
Blacks	4 (2)	5 (2)	
Hispanics	15 (8)	20 (8)	
Facility			0.995
Community Cancer Program	4 (2)	5 (2)	
Comprehensive Community Cancer Program	32 (16)	43 (17)	
Academic/Research Center	155 (79)	197 (78)	

2063 **Poster Session**

Predictive value of lymphocyte immunophenotyping (LIP) in primary central nervous system lymphoma (PCNSL). *First Author: Axel Berthelot, APHM, Marseille, France*

Background: Immunity plays an important role in PCNSL development. PCNSL predictive factors need to be improved. Objective: to evaluate the characteristics and predictive value of blood LIP in PCNSL patients. **Methods:** we prospectively analyzed blood LIP in all newly PCNSL referred to our institution between December 2013 and January 2020. LIP analysis was performed before rituximab and chemotherapy administration. The clinical, radiological, histological, biological and treatment data were retrospectively collected. **Results:** fifty-three patients were included with a median age of 69.7 (range 21.7-87.5). Median KPS was 60 (range 30-100). All patients presented with cerebral involvement, 13 (25%) with cerebrospinal fluid extension and 8 (15%) with ocular extension. Thirty-four patients (62%) benefited of steroid treatment at the time of LIP. Patients characteristics did not differ depending on steroid intake. Forty-eight patients (95%) benefited of polychemotherapy with high-dose methotrexate as first line treatment. We observed three (6%) lymphoproliferative syndromes on the LIP and 33 patients (64%) presented with one or several lymphopenias: 21 (40%), 24 (46%) and 9 (17%) NK, T and B lymphopenias respectively. Only 11 patients (21%) had normal LIP. Median CD4/CD8 ratio was 2.11 (range 0.54-9.11). This ratio was normal, low or high in 27%, 28% and 44% of patients respectively. The presence of steroids did not impact LIP results, including CD4 (p = 0.475) or CD8 (p = 0.726) rates and CD4/CD8 ratio (p = 0.727). Complete or partial responses, stable and progressive disease (PD) were observed in 24 (50%), 10 (21%), 4 (8%), and 10 (21%) patients respectively. CD4/CD8 ratio tended to be different between refractory (PD patients) and non-refractory patients (p = 0.077). A ROC curve analysis was performed with an AUC of 0.684 allowing the selection of a CD4/CD8 ratio cutoff of 1.97 with a sensibility, specificity, positive predictive value, and negative predictive value to identify refractory patients of 90%, 55%, 35% and 95% respectively. Median progression-free survival (PFS) and overall survival (OS) were 14.7 (95%CI: 6.5-22.9) and 43.2 (95%CI: 21.6-64.9) months, respectively. In multivariate analyses, adjusted by KPS, a CD4/CD8 ratio > 1.97 was associated with poor PFS (p = 0.043, HR = 3.32 [1.02-4.88]) and tended to be associated with worse OS (p = 0.064). **Conclusions:** LIP at baseline may predict refractory disease and exhibits a prognostic value in PCNSL patients. Research Sponsor: None.

2064 **Poster Session**

A phase II, open-label, single-arm trial of pembrolizumab for refractory atypical and anaplastic meningioma and hemangiopericytoma. *First Author: Shlomit Yust-Katz, Davidoff Cancer Center, Rabin Medical Center, Petah Tikva, Israel*

Background: Grade II and III meningiomas are invasive tumors which tend to recur following initial treatment and are associated with shorter survival (relative to grade I). Hemangiopericytoma (HPC) is a dural based tumor that originates in the pericytes in the walls of capillaries. Treatment options for these tumors include surgical resection and radiation. There are no defined standard treatments after failure of these modalities, and efficient systemic treatments are lacking. This trial concept was formed following previous reports of high PD-L1 levels in anaplastic meningioma. We currently report our initial experience with pembrolizumab for refractory atypical/anaplastic meningioma (RAM) and HPC patients. **Methods:** This is a single arm, single institute, phase 2 trial. Inclusion criteria included patients with RAM or HPC whose all previous lines of treatment were exhausted. All patients were treated with pembrolizumab (200mg every 3 weeks) until disease progression. Primary endpoint was 6- and 12-months progression free survival (PFS). The study was planned for 25 patients and we report here preliminary results. **Results:** Through February 2021, 12 patients were enrolled to this study (two with HPC, 10 with RAM). After a median follow up of 18.5 months, the 6 and 12 months PFS were 25% and 16.7% respectively, with a median PFS of 2.75 months. Two patients had a partial response while all others progressed, making the overall response rate 16.7%. One of the responders had HPC and has been stable for 30 months, while the second had atypical meningioma and was stable for 13 months. Median survival has not been yet reached; 1 year survival rate was 82.5%. Grade 3 toxicities included hyperglycemia, elevated liver enzymes and fatigue (that did not cause treatment discontinuation), with no grade 4 or 5 toxicities. PD-L1, mutation burden, MSI and other genomic analyses are still pending. **Conclusions:** Pembrolizumab induced a low response rate for RAM and HPC. However, a subset of patients might benefit from this treatment with a prolonged response period. To define this subpopulation further molecular studies are needed. Clinical trial information: NCT03016091. Research Sponsor: MSD.

TPS2065 **Poster Session**

LUMINOS-101: Phase 2 study of PVSRIPO with pembrolizumab in recurrent glioblastoma. *First Author: Andrew E. Sloan, University Hospitals Cleveland Medical Center & Seidman Cancer Center, Cleveland, OH*

Background: The prognosis for patients (pts) with recurrent (r) glioblastoma (GBM) is poor, with no highly effective approved therapies. Treatment failure may result from poor penetration of drugs through the blood-brain barrier and the immunosuppressive nature of the tumor microenvironment (TME). PVSRIPO, a recombinant poliovirus (PV):rhinovirus chimera, is a novel, non-neurovirulent, intratumoral immunotherapy. Trial results in rGBM pts show greater long-term survival with PVSRIPO monotherapy (21%, 36-60 months [mos]) vs criteria-matched external controls (4%, 36 mos; 2%, 60 mos; Desjardins 2018 *NEJM*). PVSRIPO targets CD155 (PV receptor), expressed on solid tumors and on APC. PVSRIPO infection results in inflammatory-mediated destruction of tumor cells but non-lethal lingering infection in TME APC. This leads to type I/III interferon-dominant inflammation and, ultimately, tumor antigen-specific T cell activation and recruitment (Brown 2017 *Sci Transl Med*), which is potentiated by immunologic recall to intratumoral replicating virus via prior vaccination. Induction of type 1 IFN dominant inflammation and compensatory activation of the PD-1:PD-L1 immune checkpoint (IC) pathway support investigation of PVSRIPO in combination with PD-1/L1 IC inhibitors. Immunologically cold mouse glioma models show PVSRIPO+anti-PD-1 therapy resulted in greater anti-tumor response than either agent. **Methods:** LUMINOS-101 is a phase 2, multicenter, open-label, single-arm study of intratumoral infusion of PVSRIPO (Day 1: $5x10^7$ $TCID_{50}$) followed by the anti-PD-1 monoclonal antibody pembrolizumab (200mg IV q3w) in adult pts with rGBM. The trial objective is to evaluate anti-tumor activity and safety and tolerability of the combination. Eligibility criteria include pts ≥18 years who had prior PV and boost IPOL® immunizations, histologically confirmed supratentorial rGBM, infusible 1 to ≤5.5cm enhancing disease, confirmed disease progression following prior therapies, and KPS ≥70. Key exclusion criteria include multifocal disease; discontinuation of prior anti-PD-1/L1 agent for toxicity; prior intratumoral therapy, immunotherapy, or radiotherapy within 12 weeks; high-dose systemic corticosteroids; chemotherapy, anti-VEGF, or TTF therapy ≤1-6 weeks depending on the therapy; serious cerebral herniation syndrome; extensive leptomeningeal, subependymal, or ≥1cm enhancing disease crossing the midline; and severe active comorbidities. Primary endpoints are objective response rate, duration of response, and safety. Secondary endpoints include overall and progression-free survival and disease control rate and duration. Exploratory endpoints include assessment of tumor and blood for biomarkers of response. The initially planned safety lead-in period is now fully enrolled. Recruitment is ongoing in the US, and results will inform the design of a randomized phase 3 trial. Clinical trial information: NCT04479241. Research Sponsor: Istari Oncology.

TPS2066 **Poster Session**

BrainStorm: A brain metastases research platform to tackle the challenge of central nervous system (CNS) metastases in solid tumors (Oncodistinct 006). *First Author: Nuria Kotecki, Institut Jules Bordet, Bruxelles, Belgium*

Background: Better knowledge on the evolving epidemiology and biology of CNS metastases are key elements for the development of new treatment strategies and identification of promising therapeutic targets. A multidisciplinary Brain Metastases Clinical Research Platform called BrainStorm was launched by the Jules Bordet Institute and the Oncodistinct network. The BrainStorm program includes mainly patients with non-CNS metastatic solid tumors with high risk of developing CNS metastases allowing to build a large database focusing on three time periods: before the diagnosis of CNS metastases (Part A), at diagnosis (Part B) and after the diagnosis of CNS metastases (Part C). **Methods:** Subjects with newly diagnosed non-CNS metastases or up to 24 months from diagnosis of non-CNS metastases from triple-negative and HER2-positive breast cancer, lung cancer and melanoma are eligible for part A of the program. Subjects presenting with a 1st CNS event and not yet enrolled (previously mentioned cohorts and a cohort of other tumor types) can enter directly in parts B and subsequently part C of the study. Eligible subjects are followed for 48 months for relevant clinical data, neurological examinations, quality of life, survival status, and undergo examinations and samplings (Table 1). A total of 280 subjects (40 per cohort) with a 1st CNS event will be enrolled. The main objectives of the program are to collect clinical and biological data with the aim to identify risk factors for CNS metastases development (Part A) and to better understand the biology of CNS metastases (brain and leptomeningeal –Parts B and C) aiming to discover new targets for therapy and intensify the multidisciplinary approach for the management of CNS metastases from solid tumors. The translational part of the program will evaluate among others the use of cerebrospinal fluid circulating tumor DNA (CSF-ctDNA) as a surrogate for CNS metastases in order to characterize its molecular landscape. Currently, the study is recruiting in several sites within the Oncodistinct network. The data collected will help to develop innovative multidisciplinary research projects that could be implemented in all parts of the BrainStorm program. Clinical trial information: NCT04109131. Research Sponsor: Fondation Cancer Luxembourg, Other Foundation, Les amis de l'Institut Bordet.

Main study procedures in the BrainStorm program.

		Part A Pre-diagnosis of CNS metastases		Part B At CNS metastases diagnosis	Part C Post-diagnosis of CNS metastases
Main Study Assessments	**SCREENING**	**At inclusion**	**Part A visits**	**As close as possible to the diagnosis of CNS metastases and no later than 6 weeks after diagnosis**	**Follow-up**
Medical consultation *(with neurological examination)*	X		X	X	X
Brain magnetic resonance imaging		X	X	X	X
Quality of Life Questionnaires				X	X
Archival tumor tissue collection (primary or non CNS-metastatic)	X				
Plasma sample		X	X	X	X
Whole blood sample		X		X	
Cerebrospinal fluid sample				X	X (if clinically indicated)

TPS2067 **Poster Session**

A phase III multicenter randomized controlled trial of postsurgical stereotactic radiotherapy versus surgically targeted radiation therapy (STaRT) for the treatment of large (>2.5cm) newly diagnosed brain metastases: Trial in progress. *First Author: Jeffrey S. Weinberg, MD Anderson Cancer Center, Houston, TX*

Background: Resection (R) followed by single or multi-fraction stereotactic radiosurgery (SRT) of brain metastases lowers resection bed recurrence compared to R alone. Nevertheless, for larger (>2.5cm) brain metastasis, 12-month recurrence rates after R+SRT can exceed 20–30%. Aiming to improve outcomes, a permanently implanted collagen tile brachytherapy device (GammaTile or GT, GT Medical Technologies, Tempe, AZ) utilizing Cs-131 seeds embedded within a bioresorbable collagen tile was developed and is described as Surgically Targeted Radiation Therapy (STaRT) to distinguish it from external beam radiation therapy. It is hypothesized that immediate adjuvant radiotherapy (RT) and/or RT dose intensification could improve outcomes. The device is FDA-cleared for this indication and early commercial use is demonstrating favorable safety and efficacy outcomes. STaRT allows rapid dose delivery of radiation therapy directly to the tumor bed with predictable dosimetry immediately at the time of resection, and an intense but localized radiation treatment, which may confer a reduced risk for radiation necrosis compared to other therapies. The device is easily placed with minimal additional operative time and limited staff radiation exposure. It is hypothesized that R+ STaRT will increase the surgical bed recurrence-free survival, while reducing the impact on functional and neurocognitive status compared to R+SRT. **Methods:** Multicenter, randomized, comparison trial of patients with resectable, previously untreated "index" brain metastases measuring ≥2.5–5 cm, and 0–3 other tumors, will be preoperatively randomized 1:1 to undergo either R+ SRT or R+STaRT to the index lesion; unresected tumors in both groups will receive SRT. Planned sample size is 180 from 13 sites . Enrollment will open in Q1. Primary endpoint is surgical bed-recurrence free survival. Secondary endpoints include overall survival, quality of life (Functional Assessment of Cancer Therapy-Brain, Linear Analog Self-Assessment), neurocognition (Hopkins Verbal Learning Test, Trail Making Tests, Controlled Oral Word Association), functional status (Karnofsky Performance Scale, Barthel-ADL), and adverse events. Follow-up will be at 1,3,6,9, and 12 months, then every 6 months through 24 months. This will be the first randomized trial comparing R+SRT versus R+STaRT delivered by Cs-131 sources in permanently implanted resorbable collagen tile carriers. Primary and secondary outcome measures will be captured to elucidate the potential risks and benefits of these two differing post-operative RT delivery methods in the setting of newly diagnosed metastatic brain tumors. Clinical trial information: NCT04365374. Research Sponsor: GT Medical Technologies.

TPS2068 **Poster Session**

The potential utility of end-binding protein 1 (EB1) as response-predictive biomarker for lisavanbulin: A phase 2 study of lisavanbulin (BAL101553) in adult patients with recurrent glioblastoma. *First Author: Crescens Tiu, The Royal Marsden NHS Foundation Trust, Sutton, United Kingdom*

Background: Lisavanbulin (BAL101553, prodrug of BAL27862) is a novel tumor checkpoint controller that promotes tumor cell death by modulating the spindle assembly checkpoint. BAL27862 is a lipophilic, small molecule (MW 387) shown in rodents to penetrate the brain (1:1 plasma ratio) with promising antitumor activity in orthotopic models of glioblastoma (GB) as monotherapy or in combination with radiotherapy (RT) ± chemotherapy. In a completed phase 1 study (Lopez et al. ESMO 2020, NCT02490800) with daily oral lisavanbulin in patients with recurrent GB or high-grade glioma, the RP2D was determined at 25 mg/day. In this phase 1 study, two patients (out of 20 patients) with GB show a long-lasting (> 2 years) clinical benefit with improvement in clinical symptoms and in target and/or non-target GB lesions as per RANO criteria. Both patients show strong end-binding protein 1 (EB1) expression in their GB tissues as assessed by immunohistochemistry staining. EB1, a protein located on the plus-ends of microtubules, is involved in microtubule (MT) function and has been associated with stemness of glioma cells and a more aggressive disease. Data from GB mouse models suggest that EB1 is a predictive marker for response to lisavanbulin. The prevalence of EB1-positivity in GB is estimated at ~5%. This ongoing phase 2 study is an extension of the completed Phase 1 study and is conducted to confirm prospectively whether EB1 is a response-predictive biomarker for lisavanbulin in GB. **Methods:** This is an ongoing multicenter, open-label, phase 2 study using a Simon Two-Stage design to assess the efficacy of lisavanbulin in patients with recurrent GB. The study is being performed in the UK, Switzerland and Germany. Patients with histologically-confirmed GB and recurrent disease after prior RT with alkylating chemotherapy (de-novo/primary GB) or after prior chemotherapy or RT (secondary GB), are eligible for enrollment if their GB archival tumor tissue is EB1-positive. EB1-positivity is defined as moderate to strong EB1-staining in at least 70% of GB tumor cells using a CE-marked immunohistochemistry Clinical Trial Assay (Targos Molecular Pathology GmbH). The primary study objective is the overall response rate by RANO, with MRI scans being performed every 8 weeks. Secondary endpoints include progression-free survival and overall survival. Adverse events are assessed using CTCAEv5. To develop a potential RNA-based response signature, molecular profiling of tumor tissue is performed using whole transcriptome sequencing (RNAseq) in each patient enrolled in the study to define the genomic expression profiles in patients with EB1-positive GB. Nine evaluable patients are to be enrolled in Stage 1, and an additional 10 patients will be enrolled in stage 2 if at least 2 objective responses per RANO criteria are observed in stage 1. Clinical trial information: 02490800. Research Sponsor: Basilea Pharmaceutica International Ltd.

TPS2069 **Poster Session**

Phase 2 trial of newly diagnosed high-grade glioma treated with concurrent radiation therapy, temozolomide, and BMX-001. *First Author: Katherine B. Peters, Duke University, Durham, NC*

Background: High-grade gliomas (WHO grade III-IV) patients experience marked morbidity and mortality. While the standard of care for newly diagnosed high-grade glioma patients is surgery followed by concurrent chemotherapy and radiation therapy (RT), the outcomes remain poor. BMX-001 ($MnTnBuOE\text{-}2\text{-}PyP^{5+}$) is a metalloporphyrin with differential action in response to radiation therapy and chemotherapy-induced oxidative stress. As shown in preclinical evaluations, BMX-001, when used with radiation, can protect normal, healthy tissues and augment cell kill in malignant cancer cells, notably, human glioblastoma xenografts. We evaluated the safety of BMX-001 in combination with concurrent RT and temozolomide (TMZ) in a phase 1 study of newly diagnosed high-grade glioma patients and we found that BMX-001 is safe and well-tolerated in this population. The maximum tolerated dose of BMX-001 during concurrent RT and TMZ was determined to be 28 mg delivered subcutaneously (SC) followed by 16 biweekly SC doses at 14 mg (Peters et al., Neuro-Oncology 2018). **Methods:** For this multi-site, open-label, phase 2 study (NCT02655601), we will randomize approximately 160 patients 1:1 to concurrent RT and TMZ with BMX-001 versus concurrent RT and TMZ alone. Key eligibility criteria include newly diagnosed histologically confirmed high-grade glioma (WHO III-IV), 18 ≥ years, and Karnofsky performance status ≥ 70%. The primary endpoint is overall survival. Secondary endpoints are objective cognitive performance, bone marrow protection, safety and tolerability, progression-free survival, overall tumor response rate, and plasma pharmacokinetics. Exploratory endpoints are patient-reported outcomes of health-related quality of life (as assessed by Functional Assessment of Cancer Therapy–Brain, Functional Assessment of Cancer Therapy-Cognition, and Functional Assessment of Chronic Illness Therapy-Fatigue), qualitative hair loss, and white matter integrity (as measured by MRI diffusion tensor/susceptibility imaging). Since November 2018, this phase 2 study has enrolled 147 of 160 high-grade glioma patients at nine sites in US. Clinical trial information: NCT02655601. Research Sponsor: BMX through an STTR grant, as above.

TPS2070 **Poster Session**

Safety and efficacy study of retifanlimab and epacadostat in combination with radiation and bevacizumab in patients with recurrent glioblastoma. *First Author: Jian Li Campian, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Recurrent glioblastoma (rGBM) after chemoradiotherapy has a dismal outcome with very limited treatment options. Addition of reirradiation to bevacizumab appears to improve progression-free survival (PFS) but does not improve overall survival (OS). Immune checkpoint inhibitors of programmed cell death-1 (PD-1) pathway appear to have limited single-agent activity for rGBM due to its immunesuppressive microenvironment. Indoleamine 2,3 dioxygenase 1 (IDO1) is an inducible and rate-limiting enzyme that catabolizes tryptophan (Trp) into kynurenine (Kyn). IDO1 is over-expressed in 50~90% of GBM patients, and high IDO1 levels correlate with reduced OS. Epacadostat is a highly potent and selective oral inhibitor of IDO1 and may increase tumor sensitivity to anti-PD-1 blockade. Retifanlimab is a humanized anti-PD-1 monoclonal antibody directed against PD-1. The purpose of this study is to evaluate the safety and efficacy of combining retifanlimab plus or minus epacadostat with reirradiation and bevacizumab for rGBM patients. **Methods:** This is an open-label nonrandomized phase II study of two sequential cohorts for bevacizumab-naïve adults with rGBM: retifanlimab + bevacizumab+ radiation (cohort A), and retifanlimab + epacadostat + bevacizumab + radiation (cohort B). Each cohort will enroll 24 evaluable patients. Key eligibility criteria include candidates for reirradiation and bevacizumab, age $\geq$ 18 years, Karnofsky performance status $\geq$ 60%, and dexamethasone dose $\leq$ 4 mg/day. The primary endpoint is OS. Secondary endpoints include PFS, neurologic functions, and toxicity. The correlative endpoints include studies assess the anti-glioma immune response, serum Kyn/Trp ratio, and RNA expression of IDO1 and PD-L1 from available tissue. The trial is actively enrolling. At the time of abstract submission, 16 of the planned 24 patients in Cohort A have been enrolled. Clinical trial information: NCT03532295. Research Sponsor: Incyte Corporation.

Treatment regimen.

	Dose			
Treatment	**Retifanlimab**	**Epacadostat**	**Bevacizumab**	**Radiation**
Cohort A	500 mg IV Q4W	–	10 mg/kg IV Q2W	3.5 Gy x 10 QD
Cohort B	500 mg IV Q4W	600 mg PO Twice daily	10 mg/kg IV Q2W	3.5 Gy x 10 QD

TPS2071 **Poster Session**

A phase 1/2 study of selinexor in combination with standard of care therapy for newly diagnosed or recurrent glioblastoma. *First Author: Yazmin Odia, Miami Cancer Institute, Baptist Health South Florida, Miami, FL*

Background: Glioblastoma multiforme (GBM) is the most common and aggressive primary brain tumor with a median overall survival (OS) of 15 months for patients with newly diagnosed GBM (ndGBM) and 5-7 months for patients with recurrent GBM (rGBM). To improve the prognosis of patients with GBM, novel therapies are urgently needed. Selinexor is a first-in class, oral, selective inhibitor of nuclear export that blocks exportin 1 (XPO1), forcing the nuclear retention and reactivation of tumor suppressor proteins, ultimately causing death of cancer cells. Selinexor is an FDA-approved treatment for patients with heavily pretreated multiple myeloma, for patients who received at least one prior therapy, and for patients with relapsed/refractory diffuse large B-cell lymphoma. Increased XPO1 expression in gliomas was associated with higher pathological stage and poorer prognosis. In a phase 2 study in rGBM (NCT01986348), selinexor demonstrated encouraging intratumoral penetration and single-agent efficacy at 80 mg once weekly with durable response and disease stabilization in heavily pretreated patients. In preclinical studies, selinexor showed synergy with radiation, temozolomide, or lomustine. The current trial tests the hypothesis that the addition of selinexor to standard therapy will improve clinical outcomes for patient with ndGBM or rGBM. **Methods:** This phase 1 dose finding study is followed by a 1:1 randomized phase 2 (n= 350) efficacy exploration trial to independently evaluate 3 regimens: Arm A – radiation +/- selinexor in unmethylated O^6-methylguanine-DNA-methyltransferase (uMGMT) ndGBM; Arm B – radiation and temozolomide +/- selinexor in mMGMT ndGBM; Arm C – lomustine +/- selinexor in first relapsed rGBM following frontline radiation and temozolomide. The phase 1 primary endpoint is maximum tolerated dose/recommended phase 2 dose, with secondary endpoints of overall response rate (ORR) per modified Response Assessment in Neuro-Oncology (mRANO), duration of response (DOR), progression free survival (PFS), and OS. The phase 2 primary endpoint for Arms A and B in ndGBM is PFS, with key secondary endpoints being OS, PFS at 6 months, ORR, and DOR. For Arm C, the phase 2 primary endpoint is OS, while key secondary endpoints are PFS, PFS at 6 months, ORR, and DOR. The study has 70% power to detect a hazard ratio of 0.67 between selinexor and control for primary efficacy in Arms A and B, and 80% power to detect a hazard ratio of 0.70 for Arm C. We are currently enrolling patients nationwide. Clinical trial information: NCT04421378. Research Sponsor: Karyopharm Therapeutics Inc.

TPS2072 **Poster Session**

First-in-human dose escalation and food effect study of oral ONC206 in adults with recurrent primary CNS neoplasms. *First Author: Brett Theeler, Neuro-Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: The majority of recurrent CNS tumors lack effective systemic therapy options following surgical resection and adjuvant radiotherapy. ONC201, the founding member of the imipridone class of small molecules, has induced durable tumor regressions in patients with diffuse midline glioma, H3 K27M-mutant (DMG H3K27M). ONC206, the second imipridone to enter clinical development, is a DRD2 antagonist and ClpP agonist that exhibits differentiated receptor pharmacology and gene expression profiles in tumors relative to ONC201. The compound is orally bioavailable, penetrates the blood-brain barrier, and exhibits anti-cancer efficacy without toxicity in several preclinical cancer models with pronounced efficacy in myc-overexpressing CNS tumors. **Methods:** A first-in-human, open label, dose escalation, and food effect Phase I study of oral ONC206 (NCT04541082) is currently enrolling. Patients must be 18 years or older and diagnosed with a recurrent, primary CNS neoplasm. Eligible diseases include recurrent glioblastoma, WHO Grade 2 and 3 infiltrating glial neoplasms, DMG H3K27M, ependymoma, medulloblastoma, malignant meningiomas, and other rare primary CNS neoplasms. Dose escalation, initially with weekly dosing, will follow a standard 3+3 design. After the MTD is established, a food effect cohort will enroll with a balanced, single-dose, two-arm, two-period, crossover design. The primary endpoint is to determine DLT during the first 28-day cycle. Secondary endpoints will include objective response rate by RANO criteria, overall and progression-free survival, and disease control rate. Exploratory biomarker analyses based on preclinical correlations with efficacy will include DRD2, DRD2 dimer, ClpP, DRD5, c-myc, and n-myc expression. Clinical trial information: NCT04541082. Research Sponsor: U.S. National Institutes of Health.

TPS2073 **Poster Session**

A multicenter observational study of cs-131 seeds embedded in a collagen carrier tile in intracranial brain neoplasms: Trial in progress. *First Author: K. Stuart Lee, Vidant Health, Greenville, NC*

Background: Brachytherapy is an efficacious means for radiation delivery in the treatment of a spectrum of central nervous system tumors. Traditional brachytherapy methods have been limited by uneven dose distribution, complicated workflow, extended procedural times, the cost of dedicated equipment, and frequent adverse events. To address these issues, a permanently implanted device with Cs-131 radiation seeds embedded in a bioresorbable collagen carrier tile (GammaTile [GT], GT Medical Technologies, Tempe, AZ USA) was developed. Described as surgically targeted radiation therapy (STaRT) to distinguish it from external beam radiation therapy, the device is FDA-cleared for use in newly diagnosed malignant intracranial neoplasms and recurrent intracranial tumors, and has demonstrated excellent safety and local control outcomes in early commercial use. **Methods:** The overarching primary objectives of this multicenter, prospective, observational (phase IV) registry study are to evaluate "real-world" clinical outcomes and patient reported outcomes that measure the safety and efficacy of STaRT using the GT device. The registry is planned for 600 prospectively enrolled subjects at up to 50 enrolling sites. All adult patients undergoing surgical resection of brain tumors of any pathology with intra-operative GT placement are eligible for enrollment, upon consent. Information on patient demographics, tumor pathology, overall survival, adverse events related to radiation or surgery, and quality of life (FACT-Br and LASA) will be collected. Serial MRIs will be collected, and timing of surgical bed recurrence and/or distant recurrence will be collected. Data will be collected at 1-, 3-, 6-, 9-, 12-, 18-, and 24-months, then every 6 months through 5 years. Results will be used to benchmark clinical outcomes of GT therapy, allow for comparisons to other existing treatments, and facilitate the design of future clinical trials. Enrollment opened on November 15, 2020, and seven subjects have been enrolled to date at three centers. This study will be the first observational study of resection plus STaRT, delivered by Cs-131 sources in permanently implanted bioresorbable collagen tile carriers, and will allow for evaluation of this treatment approach in a real world setting, as well as provide an information platform for cross-comparison of results obtained from ongoing GT clinical trials. Clinical trial information: NCT04427384. Research Sponsor: GT Medical Technologies.

TPS2074 **Poster Session**

GBM AGILE: A global, phase 2/3 adaptive platform trial to evaluate multiple regimens in newly diagnosed and recurrent glioblastoma. *First Author: Patrick Y. Wen, Dana-Farber/Brigham and Women's Cancer Center, Harvard Medical School, Boston, MA*

Background: GBM AGILE, Glioblastoma Adaptive, Global, Innovative Learning Environment, is an international, multi-arm, seamless phase 2/3 response adaptive randomization platform trial designed to evaluate multiple therapies in newly diagnosed (ND) and recurrent glioblastoma (GBM) with the goal of identifying effective therapies matching them accurately to different patient subtypes in an accelerated manner. It is a collaboration between academic investigators, patient organizations and industry to support new drug applications for newly diagnosed and recurrent GBM. **Methods:** The primary objective of GBM AGILE is to identify therapies that effectively improve overall survival in patients with ND or recurrent GBM. Bayesian response adaptive randomization is used within subtypes of the disease to assign participants to investigational arms based on their performance. Operating under a Master Protocol, GBM AGILE allows multiple drugs from different pharmaceutical companies to be evaluated simultaneously and/or over time against a common standard of care control. Based on performance, a drug may graduate and move to a rapid stage 2 (phase 3) within the trial, and the totality of the data can be used for a new drug application. An active pipeline is critical to the ongoing success of GBM AGILE. With the leadership of the trial's Arm Selection Committee, uniform processes for including new drugs have been established to ensure a consistent review of drugs/drug combinations over the course of the trial. Factors considered include relevant pre-clinical data, preliminary evidence for antitumor activity. pharmacokinetic data to support proposed drug dosing and administration, and potential biomarkers helpful for the development of a drug. GBM AGILE provides an efficient mechanism to screen and develop robust information regarding the efficacy of proposed novel therapeutics and associated biomarkers for GBM and to quickly move therapies and biomarkers into clinic. GBM AGILE received IND approval from the FDA in April 2019, screening its first patient in June 2019. Site activation is ongoing in the US, with over 35 active sites and over 425 patients screened (as of February 2021). Expansion to Canada, Europe and China are under progress. Clinical trial information: NCT03970447. Research Sponsor: Bayer, Kazia Therapeutics Limited, Kintara Therapeutics Inc, Other Foundation.

2500 **Oral Abstract Session**

Clinical activity of systemic VSV-IFNβ-NIS oncolytic virotherapy in patients with relapsed refractory T-cell lymphoma. *First Author: Joselle Cook, Mayo Clinic, Rochester, MN*

Background: Oncolytic virotherapy is a novel immunomodulatory therapeutic approach for relapsed refractory hematologic malignancies. The Indiana strain of Vesicular Stomatitis Virus was engineered to encode interferon beta (IFNβ) and sodium iodine symporter (NIS) to produce VSV-IFNβ-NIS. Virally encoded IFNβ serves as an index of viral proliferation and enhances host anti-tumor immunity. NIS was inserted to noninvasively assess viral biodistribution using SPECT/PET imaging. We present the results of the phase 1 clinical trial NCT03017820 of systemic administration of VSV-IFNβ-NIS among patients (pts) with relapsed refractory Multiple Myeloma (MM), T cell Lymphoma (TCL) and Acute myeloid Leukemia (AML). **Methods:** VSV-IFNβ-NIS was administered at $5x10^9$ $TCID_{50}$ (50% tissue culture infectious dose) dose level 1 to dose level 4, $1.7x10^{11}$ $TCID_{50}$. The primary objective was to determine the maximum tolerated dose of VSV-IFNβ-NIS as a single agent. Secondary objectives were determination of safety profile and preliminary efficacy of VSV-IFNβ-NIS. Correlative objectives included monitoring viremia and virus shedding. Adverse events (AEs) are reported based on CTCAE V4; cytokine release syndrome (CRS) grading was based on Lee (Blood 2014) criteria. **Results:** 15 pts received VSV-IFNβ-NIS: MM (7), TCL(7) and AML(1); 3 pts were treated at each dose level (DL) 1 through 3 (respectively 0.05, 0.17, and 0.5×10^{11} $TCID_{50}$), & 6 pts were treated at dose level 4 ($1.7x10^{11}$ $TCID_{50}$). There were no dose limiting toxicities. The most frequent grades 3 & 4 AEs were hematologic: lymphopenia (46.6 & 26.6%), neutropenia (13.3% & 6.7%). CRS grades 1 (6.7%) and 2 (46.6%) were the non-hematologic AEs of note; mostly at DL 4. Only 1 pt required transient pressor support. Responses were seen in pts with T cell lymphoma. At DL2, there was a partial response (PR) lasting 3 months in a pt, post 12 prior lines of therapy. At DL4 there was a 6 month PR in a pt with PTCL and another pt with cutaneous relapse of PTCL who enjoys an ongoing CR, more than 1 year post VSV infusion; both pts received 5 prior lines of therapy. Viremia was detected in all pts at the end of infusion only up to 72 hrs post infusion; no infectious virus was recovered in buccal swabs or urine. Neutralizing anti-VSV antibodies were present by day 29. IFN levels were detectable within 30 mins of infusion, peaking between 4 & 48 hrs. TCL pts mounted higher hIFNβ levels within 48 hrs; the pt with CR mounted peak hIFNβ response of 18213.3pg/ml at 48 hrs post infusion, 15-fold higher than any other pt. **Conclusions:** VSV-IFNβ-NIS can be safely administered by IV infusion among heavily pretreated pts with hematologic malignancies. VSV-IFNβ-NIS as a single agent appears to be most effective at DL4 among patients with TCL, with an ongoing CR in a patient at DL4 more than 1 year post administration. Future trials of combination strategies with immunemodulatory drugs are currently being planned. Clinical trial information: NCT03017820. Research Sponsor: Mayo Myeloma SPORE.

2501 **Oral Abstract Session**

Phase II evaluation of the triple combination of PDS0101, M9241, and bintrafusp alfa in patients with HPV 16 positive malignancies. *First Author: Julius Strauss, Laboratory of Tumor Immunology and Biology, NCI, NIH, Bethesda, MD*

Background: There are more than 630,000 cases of HPV associated malignancies including cervical, oropharyngeal and anal cancer worldwide annually. HPV 16 is responsible for the majority of these cases. About 15-20% of HPV associated malignancies respond to PD-(L)1 inhibitors, but for the overwhelming majority of patients who progress on these immunotherapies there is no effective standard of care therapy. Preclinical studies have shown that the triple combination of PDS0101 (Versamune-HPV), a liposomal multipeptide therapeutic vaccine targeting HPV 16 E6/E7, M9241, a tumor-targeting immunocytokine composed of IL-12 heterodimers fused to a monoclonal antibody targeting free DNA in necrotic tumor regions, and bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, resulted in maximum HPV-specific T cell responses, T cell tumor infiltration and tumor reduction as compared to any one or two of these agents alone. **Methods:** Fourteen pts with HPV 16+ relapsed or refractory advanced cancer were enrolled to the triple combination of PDS0101, M9241 and bintrafusp alfa (NCT04287868). Pts received bintrafusp alfa at 1200 mg flat dose i.v. every 2 weeks, M9241 at 16.8 mcg/kg s.c. every 4 weeks and PDS0101 given as two separate 0.5 ml s.c. injections every 4 weeks. Dose reductions of M9241 to 8 mcg/kg were allowed as well as skipped doses of any agent for ongoing toxicities. **Results:** Fourteen pts with advanced HPV 16+ cancers (5 cervical, 2 vaginal/vulvar, 4 anal, 3 oropharyngeal) were treated. 4/14 (28.6%) pts had a grade 3 treatment related toxicity including grade 3 hematuria in 2 pts with cervical ca and prior pelvic radiation and grade 3 AST/ALT elevation in 2 pts, one with anal ca and one with vaginal ca. For one patient with grade 3 AST/ALT elevation dose reduction of M9241 from 16.8 to 8 mcg/kg allowed for continued treatment with AST/ALT remaining at grade 1 or less. One additional patient had transient asymptomatic grade 4 neutropenia. No other treatment related grade 3 or greater toxicities were noted. 10/14 (71%) pts have had objective responses: 1 CR (anal ca) and 9 PRs (3 cervical, 2 vulvar/vaginal, 2 anal, 2 oropharyngeal) with 9/10 of these responses ongoing after a median 5 month of follow up. Of the 14 pts, 6 pts have checkpoint naïve disease and 8 pts have checkpoint refractory disease. 5/6 (83%) pts with checkpoint naïve disease and 5/8 (63%) pts with checkpoint refractory disease have had objective responses. Analyses of immune responses and other immune correlates are ongoing. **Conclusions:** Triple combination of PDS0101, M9241 and bintrafusp alfa appears to have a manageable safety profile along with early evidence of notable clinical activity for pts with both checkpoint naïve as well as checkpoint refractory HPV 16+ advanced malignancies. Clinical trial information: NCT04287868. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

2502 **Oral Abstract Session**

First report of the safety/tolerability and preliminary antitumor activity of HB-201 and HB-202, an arenavirus-based cancer immunotherapy, in patients with HPV16+ cancers. *First Author: Alan Loh Ho, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Human papillomavirus 16 (HPV16) is linked to several cancer types. Treatment options are limited for patients with HPV16 positive (HPV16+) recurrent or metastatic cancers. Generation and maintenance of HPV16+ malignant state require stable expression of HPV16-specific E7 and E6 oncoproteins, also a source of immunogenic neoantigens. HB-201 and HB-202 are replicating live-attenuated vectors based on lymphocytic choriomeningitis virus and Pichinde virus, respectively, which express the same non-oncogenic HPV16 E7E6 fusion protein to induce tumor-specific T-cell responses. This is a first-in-human phase 1/2 study of HB-201 monotherapy and HB-201 & HB-202 alternating 2-vector therapy. Dose escalation is ongoing with a 3+3 design. **Methods:** Phase 1 is assessing different regimens and dose levels of HB-201 monotherapy and HB-201 & HB-202 alternating 2-vector therapy given intravenously (IV) with or without an initial intratumoral administration. The patient population includes HPV16+ head and neck squamous cell carcinoma (HNSCC) and other HPV16+ cancers. Safety, tolerability, and preliminary antitumor activity by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 or immune RECIST are assessed. **Results:** As of Jan 2021, 25 patients with a median of 3 prior anticancer treatments have been enrolled. All had HPV16+ confirmed genotype; the most common primary site was oropharynx (72%). No dose-limiting toxicities were reported. Treatment-emergent adverse events (TEAEs) occurred in 21 patients (84%), were generally mild or moderate, with events related to study drug reported in 14 patients (56%). TEAEs reported in >10% of patients regardless of causality included fatigue, pyrexia, nausea, decreased appetite, anemia, arthralgia, chills, constipation, diarrhea, hypertension, influenza-like illness, pneumonia, and vomiting. Serious TEAEs developed in 6 patients (24%), including 1 with grade 5 hemorrhagic shock deemed unrelated to study drug. Grade 3 fatigue was the only serious or grade ≥3 TEAE assessed as related to study drug. TEAEs caused no treatment discontinuation. There were 18 patients evaluable for efficacy. For the 16 patients on HB-201 monotherapy, assessment of target lesions showed 2 partial responses (including 1 patient with an unconfirmed immune CR) and 6 patients had stable disease (SD). For the 2 patients on HB-201 & HB-202 alternating therapy, both had SD. So far, the longest duration of response was 4.8 months (144 days) and the maximum decrease in tumor diameter was 60%, both seen in HNSCC patients receiving HB-201 IV. **Conclusions:** HB-201 monotherapy and HB-201 & HB-202 2-vector alternating therapy were generally well-tolerated and showed preliminary antitumor activity as monotherapy in heavily pre-treated patients with HPV16+ HNSCC and other solid tumors. Clinical trial information: NCT04180215. Research Sponsor: Hookipa Biotech Gmbh.

2503 **Oral Abstract Session**

Phase 1 study of SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with advanced solid tumors. *First Author: Dan Liu, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Early Drug Development Center, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Dual inhibition of PD-1/PD-L1 and TGF-β pathways is a promising therapeutic strategy for multiple tumor types. SHR-1701 is a novel bifunctional anti-PD-L1/TGF-βRII agent. This dose escalation and expansion phase 1 study aimed to evaluated the safety and preliminary anti-tumor acitivity of SHR-1701 in refractory solid tumors. **Methods:** The dose escalation period was initiated by accelerated titration (1 mg/kg Q3W) and then switched to 3+3 scheme (3, 10, 20, and 30 mg/kg Q3W and 30 mg/kg Q2W). The dose expanded at doses of 10, 20, and 30 mg/kg Q3W and 30 mg/kg Q2W. The primary objectives were to determine the safety profile, MTD, and RP2D of SHR-1701. **Results:** 17 pts (1 mg/kg Q3W [n = 1]; 3, 10, 20 and 30 mg/kg Q3W [n = 3 each]; 30 mg/kg Q2W [n = 4]) were enrolled in dose escalation part. No DLT was observed and MTD was not reached. Another 32 pts (10 mg/kg Q3W [n = 8]; 20 and 30 mg/kg Q3W [n = 9 each]; 30 mg/kg Q2W [n = 6]) were enrolled in dose expansion part. Of 49 enrolled pts, 33 pts (67.3%) had received ≥2 lines of prior systemic therapy. As of data cutoff on Oct 30, 2020, the median duration of SHR-1701 exposure was 6.0 weeks (range, 2.0-78.6). The most common reported TRAEs were increased ALT/AST, anemia, hypothyroidism, and increased bilirubin/conjugated bilirubin, with incidence > 15%. The incidence of irAEs reported by the investigator was 46.9% and 4 pts received systemic corticosteroids. Hypothyroidism and rash were the most common irAEs with incidence > 10%. The incidence of Grade ≥3 TRAEs was 18.4%. The incidence of Grade ≥3 irAEs was 10.2%. 1 pt suffered early death for liver failure more likely caused by tumor progression. PK analysis showed a linear dose-exposure relationship with SHR-1701 dosing from 1 to 30 mg/kg. The peripheral PD-L1 target occupancy rate exceeded 90%, and nearly complete TGF-β1 trapping was detected in all dose groups. Of 49 enrolled pts, 45 pts completed at least once efficacy evaluation. The ORR was 17.8% (95% CI, 8.0%-32.1%), with 8 pts achieving PR (2 lung adenocarcinoma, 1 HCC, 1 ESCC, 1 dMMR-CRC, 1 renal cancer, 1 epiglottis cancer, and 1 pancreatic acinar cell carcinoma). The DCR was 40.0% (18/45; 95% CI, 25.7%-55.7%). Majority of responses (7/8) were still ongoing, and the median DoR had not been reached yet. Based on data of saftety, PK, PD, and efficacy, we recommended 30 mg/kg Q3W as the RP2D. **Conclusions:** SHR-1701 showed acceptable safety profile and encouraging antitumor activity in refractory solid tumors, establishing the foundation for further exploration. Clinical trial information: NCT03710265. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

2504 **Oral Abstract Session**

COM701 with or without nivolumab: Results of an ongoing phase 1 study of safety, tolerability and preliminary antitumor activity in patients with advanced solid malignancies (NCT03667716). *First Author: Daniel A. Vaena, West Cancer Center and Research Institute., Memphis, TN*

Background: COM701 is a novel first in class humanized IgG4 monoclonal antibody that binds with high affinity to poliovirus receptor related immunoglobulin domain containing (PVRIG), blocking its interaction with its ligand, PVRL2. Blocking of PVRIG leads to enhanced activation of T/NK cells and in mouse models inhibits tumor growth. We report new and updated results on safety/tolerability/pharmacokinetics and antitumor activity from this ongoing study including final results in dose escalation combination cohort, monotherapy expansion cohort (MEC). **Methods:** We enrolled a total of 51 DLT-evaluable pts: Arm A (COM701 mono dose escalation), 16 pts in 8 cohorts (0.01 – 20 mg/kg IV Q3/4 wks); Arm B (COM701 0.3 – 20 mg/kg + nivolumab (NIVO) 360 mg/480 mg IV Q3/Q4 wks), 15 pts in 5 cohorts; 20 pts in MEC (NSCLC, OVCA, breast, endometrial and CRC) at the recommended dose for expansion(RDFE), 20 mg/kg IV Q4 wks. Key inclusion criteria: Age ≥18 yrs, histologically confirmed metastatic solid malignancy, has exhausted available standard tx, ECOG 0-1, prior ICI permissible (except prior tx with a PVRIG inhibitor). Key exclusion criteria: active autoimmune disease requiring systemic tx, hx inflammatory lung disease. Primary objectives – safety/tolerability of COM701 ± NIVO (AEs, CTCAE v4.03), PK, RDFE. Key secondary/exploratory objectives - antitumor activity of COM701 ± NIVO (RECIST v1.1), evaluation of PVRL2 expression in tumor biopsy, blood cytokines and immunophenotyping. **Results:** No DLTs were reported in Arms A or B. COM701 PK profile similar in Arm A, 20 mg/kg IV Q4 wks (cohort 8) and Arm B cohort 5 (COM701 20 mg/kg + NIVO 480 mg; all IV Q4 wks). Frequency of TEAEs in safety population (N=54 pts): pts on COM701 mono (N=38)- No AE (4), Grade≤2 (21), G3 (11), G4 (1), G5 (1, PD), pts on combo (N=16) - Grade≤2 (8), G3 (7), G5 (1, PD). Serious TEAE: pts on COM701 mono 11/38, pts on combo 6/16. Most frequent AEs in Arm A: Grade ≤2 fatigue 12/38 pts (31%), nausea 9/38 (23%); Arm B: fatigue 7/16 pts (44%) and AST increased 4/16 pts (25%). Antitumor activity - in Arm A (cohort 8), a pt with platinum resistant primary peritoneal cancer had confirmed PR ongoing 14 months. In Arm B (COM701 10 mg/kg + NIVO 480 mg, all IV Q4 wks), a pt with anal SCCA; confirmed CR, ongoing 18 months, last tx with prior PD on NIVO. In addition, a pt with renal cell CA had confirmed SD [ongoing 13 months, COM701 0.3 mg/kg + NIVO 360mg; IV Q3 wks],] In MEC, 30% (6/20 pts) had best response of SD [1-endometrial, 3 NSCLC, 2 OVCA], 2 pts [NSCLC, OVCA] ongoing at 6/4 months. Overall 16pts had prior tx-refractory disease, 9(56%) had best response of ≥SD. Of 18 pts with prior tx with ICI, 13 (72%) had best response of ≥SD. Datacut 14Dec2020. **Conclusions:** COM701 ± NIVO well tolerated with no new safety signals. Encouraging signal of antitumor activity including in pts with prior tx with ICI or prior tx-refractory disease. Clinical trial information: NCT03667716.. Research Sponsor: Compugen Ltd.

2505 **Oral Abstract Session**

Preliminary clinical and biologic results of GB1275, a first-in-class oral CD11b modulator, alone and with pembrolizumab, in advanced solid tumors (KEYNOTE A36). *First Author: Haeseong Park, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: GB1275 is a first-in-class, oral CD11b modulator that reduced myeloid-derived suppressor cells (MDSCs) and tumor associated macrophages (TAMs), repolarized M2 immunosuppressive TAMs to an M1 phenotype, resulting in increased tumor infiltration of activated CD8+ T cells and antitumor efficacy in preclinical models. Here, we report preliminary results from an ongoing, first-in-human dose-escalation study in specific advanced tumors using GB1275 alone or with pembrolizumab. (NCT04060342) **Methods:** Phase 1 comprises dose escalation and expansion. During dose escalation, cohorts of 3 to 6 subjects were sequentially assigned to ascending dose levels of GB1275 from 100 mg to 1200 mg BID in one of two dosing regimens: Regimen A [GB1275 monotherapy orally (PO) twice a day (BID)] and Regimen B [GB1275 PO BID plus pembrolizumab 200 mg IV every 3 weeks (q3wks)]. Dose escalation was based on safety including dose-limiting toxicities (DLTs). Following dose escalation, up to 40 subjects with specific tumor types are to be treated in expansion with the selected GB1275 dose plus pembrolizumab to assess safety, pharmacokinetics, and preliminary clinical and biomarker activity. **Results:** As of January 8, 2021**,** 45 subjects were treated [44 in dose escalation: 23, Regimen A; 21, Regimen B. 1 in expansion, Regimen B], with median (range) GB1275 exposure of 42.0 days (4-263). No DLTs were reported. GB1275-related adverse events occurred in 24/45 (53.3%) subjects; photosensitivity reaction (20.0%), dysesthesia (13.3%) and pruritus (13.3%) were most frequent (≥10%). Stable disease was reported in 6/19 (31.6%) response-evaluable subjects in Regimen A and 9/16 (56.3%) in Regimen B. In Regimen B (800 mg), one partial response was reported in a subject with MSS-CRC treated for 263 days, and one prolonged stable disease (227 days) was reported in a gastric cancer (GC) subject previously treated with pembrolizumab plus bavituximab for less than 3 months due to progression; both subjects are continuing study treatment. A dose-dependent increase in GB1275 systemic exposure was observed up to 800 mg BID. Down-regulation of peripheral MDSCs was seen with both regimens. Regimen-dependent gene clusters in whole blood were noted. An increase in tumor infiltrating lymphocyte (TIL) counts was noted in both Regimens A and B. **Conclusions:** Dose escalation of GB1275, up to 1200 mg in Regimens A and B, demonstrated tolerability as monotherapy and combined with pembrolizumab in subjects with advanced cancers. Encouraging antitumor activity in Regimen B (800 mg) was observed in subjects with MSS-CRC and GC. Biological activity reflected by MDSC modulations in blood and TIL Increases in tumor biopsies with GB1275 alone and with pembrolizumab supports the mechanism of GB1275. GB1275 800 mg BID plus pembrolizumab 200 mg IV q3wks was selected for evaluation in the expansion phase. Clinical trial information: NCT04060342. Research Sponsor: Gossamer Bio, Inc.

2506 **Oral Abstract Session**

Preliminary results of a phase II study of alrizomadlin (APG-115), a novel, small-molecule MDM2 inhibitor, in combination with pembrolizumab in patients (pts) with unresectable or metastatic melanoma or advanced solid tumors that have failed immuno-oncologic (I-O) drugs. *First Author: Anthony W. Tolcher, Texas Oncology-San Antonio Babcock, San Antonio, TX*

Background: Alrizomadlin (APG-115) restores *TP53* function, activating p53-mediated apoptosis in tumor cells with wild-type *TP53* and/or MDM2 amplification. Alrizomadlin also functions as a host immunomodulator and hence may restore antitumor activity in pts with cancers failing PD-1/PD-L1 blockade. **Methods:** This US multicenter trial assessed alrizomadlin combined with pembrolizumab in pts with unresectable/metastatic melanoma or advanced solid tumors that had failed I-O drugs; or pts with malignant peripheral nerve sheath tumor (MPNST), liposarcoma, or ATM mutant solid tumors that had failed any standard therapy. Eligible pts had ECOG performance status of 0-2 and no CNS metastases. The phase II study cohorts included pts with melanoma, NSCLC, solid tumor with ATM mutation, well-differentiated/dedifferentiated liposarcoma, urothelial carcinoma, and MPNST. Alrizomadlin was administered orally at 150 mg once every other day for 2 consecutive weeks with 1 week off and pembrolizumab at 200 mg via IV infusion for 30 minutes on Day 1 of a 21-day cycle. **Results:** As of December 25, 2020, 84 pts had been treated in 6 cohorts: melanoma (n = 26), NSCLC (n = 23), ATM mutation (n = 9), liposarcoma (n = 14), urothelial (n = 9), and MPNST (n = 3). In the PD-1/PD-L1 inhibitor-failed melanoma cohort, there was 1 confirmed partial response (PR) out of 5 pts with uveal melanoma, 2 PR (1 confirmed and 1 unconfirmed) of 5 pts with mucosal melanoma, and 1 confirmed PR of 11 pts with cutaneous melanoma. ORR in the melanoma cohort was 17.4% (4/23 evaluable pts), and the disease control rate was 60.9% (14/23). In the MPNST cohort, 1 of 3 pts had an unconfirmed ongoing PR. In I-O drug-failed NSCLC (n = 14 evaluable) and urothelial (n = 5 evaluable) cohorts, each reported 1 confirmed PR. Common treatment (alrizomadlin or pembrolizumab)-related adverse events (TRAEs) (≥ 10%) were nausea (63.1%), thrombocytopenia (36.9%), vomiting (33.3%), fatigue (31.0%), decreased appetite (27.4%), diarrhea (21.4%), neutropenia (15.4%), and anemia (11.9%). Grade ≥ 3 TRAEs (≥ 5%) included thrombocytopenia (20.2%), neutropenia (14.2%), and anemia (8.3%). Eleven pts discontinued treatment due to AEs: 5 were treatment related, including 2 grade 4 thrombocytopenia, and 1 each of grade 2 vomiting, grade 2 fatigue, and grade 2 posterior reversible encephalopathy syndrome (PRES). Three treatment-related SAEs were PRES, pyrexia, and asthenia. **Conclusions:** Alrizomadlin combined with pembrolizumab is well tolerated and may restore antitumor effects in pts with cancer resistant to or intolerant of I-O drugs, as suggested by preliminary antitumor activities in multiple tumor types. Internal study identifiers: APG-115-US-002; Keynote MK-3475-B66. Clinical trial information: NCT03611868. Research Sponsor: Ascentage Pharma Group Corp Ltd (Hong Kong).

2507 **Oral Abstract Session**

Safety and efficacy of a novel anti-CD20/CD19 bi-specific CAR T-cell therapy (C-CAR039) in relapsed or refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL). *First Author: Aibin Liang, Tongji Hospital of Tongji University, Shanghai, China*

Background: C-CAR039 has been developed as a novel 2nd generation 4-1BB bi-specific CAR-T targeting both CD19 and CD20 antigens with an optimized bi-specific antigen binding domain. C-CAR039 can eradicate CD19/CD20 single or double positive tumor cells *in vitro* and *invivo*. The tissue cross reactivity and whole genome membrane proteome array studies further confirmed the specificity of C-CAR039. **Methods:** GMP manufacturing of C-CAR039 was carried out in a serum free and fully closed semi-automatic system. Dose escalation and expansion studies were conducted to evaluate the safety and efficacy of C-CAR039 in r/r B-NHL patients. C-CAR039 was administered as a single intravenous dose after a 3-day cyclophosphamide plus fludarabine conditioning regimen. **Results:** As of 1/31/2021, 28 patients were infused and 25 (DLBCL, n = 22; PMBCL, n = 1; tFL, n = 1; FL, n = 1) were evaluable for safety and efficacy at dose ranges of 1.0×10^6 to 5.0×10^6 CAR-T cells/kg. The median age was 54 (range, 28-71) years, median number of prior lines of therapy was 3 (range, 1–5), 76% (19/25) of patients were in Ann Arbor Stage III/IV, and 80% (20/25) were refractory to their last treatment. 5 patients (20%) received bridging therapy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT 2019 criteria. Of the 25 patients, 24 (96%) experienced CRS, 23 (92%) were grade 1 or 2, 1 patient was grade 3. Median time to onset of CRS was 3 days (range, 0-10), with median duration of 4 days (range, 1-25). 2 patients had a grade 1 ICANS. Grade≥3 neutropenia, anemia, thrombocytopenia and infection were reported in 88%, 40%, 16% and 0% of patients, respectively. The best overall response rate was 92%, complete response (CR) rate was 84% and median time to response was 1.0 month (range, 0.9-1.2). With a median follow-up of 5.3 months, 76% remained in CR. Kaplan Meyer estimation of PFS at 6 months was 87.3% (95% CI, 71.2 to 100.0). Median duration of response has not been reached. Furthermore, C-CAR039 showed an encouraging cellular kinetic profile. In 25 evaluable patients, the median T_{max} was 11 day, the median C_{max} was 139,497 copies/mg gDNA, and the median $AUC_{0-28DAY}$ of 1,673,844 day*copies/μg gDNA. **Conclusions:** C-CAR039 demonstrated a favorable safety profile and promising efficacy in this early clinical trial in patients with r/r B-NHL that might allow it to differentiate from existing therapies. The early clinical efficacy signal is encouraging and compares favorably to anti-CD19 CAR-T and peer therapies. These findings will be evaluated in more patients with longer follow-up to confirm safety, efficacy and duration of response. Clinical trial information: NCT04317885, NCT04655677, NCT04696432, NCT04693676. Research Sponsor: Cellular Biomedicine Group Inc.

2508 **Oral Abstract Session**

Safety and efficacy of a novel anti-CD20 chimeric antigen receptor (CAR)-T cell therapy in relapsed/refractory (r/r) B-cell non-Hodgkin lymphoma (B-NHL) patients after failing CD19 CAR-T therapy. *First Author: Aibin Liang, Tongji Hospital of Tongji University, Shanghai, China*

Background: Relapse due to loss of the CD19 targeted epitope presents a therapeutic challenge of CD19 CAR-T therapy. These patients universally have a poor outcome and the unmet medical need is high. CD20 is a proven therapeutic target for B-NHL, supported by approved and widely used monoclonal antibody therapy. C-CAR066 is a novel 2nd generation chimeric antigen receptor T (CAR-T) therapy targeting CD20 antigen. Preclinical studies suggest that C-CAR066 has superior anti-tumor activity compared to CAR-Ts derived from scFVs of Leu16, Rituximab and Obinutuzumab and anti-CD19 BBZ CAR with FMC63. **Methods:** A phase I clinical trial (NCT04036019) was conducted to evaluate the safety and efficacy of C-CAR066 in subjects with r/r B-NHL who were previously treated with anti-CD19 CAR-T therapy. Patients ($\geq$ 18 years) with r/r DLBCL, r/r FL or r/r MCL, ECOG $<$ 2 were eligible. GMP manufacture of C-CAR066 was in a serum free and fully closed semi-automatic system. A 3-day cyclophosphamide plus fludarabine regimen was followed by a single infusion of C-CAR066. Bridging therapy was allowed. **Results:** As of Jan 31, 2021, 7 patients (6 DLBCL, 1 tFL) were enrolled and infused with C-CAR066 at dose ranges of 2.0 x 10^6 to 4.8x10^6 CAR-T cells/kg. The manufacturing success rate was 100%. The median age was 51 (range, 41-62) years, and 42.9% (3/7) patients were male. The median number of prior lines of therapy was 5 (range, 2-6). One patient (14.3%) underwent autologous stem cell transplant (ASCT) and one patient received bridging therapy. Cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded according to ASTCT 2019 criteria. All 7 patients experienced CRS and most (85.7%) were grade 1 or 2. One patient had grade 4 CRS and recovered after treatment with tocilizumab and corticosteroids. Median time to onset of CRS was 5 days (range, 1-9), with median duration of 4 days (range, 2-17). There were no episodes of ICANS. Grade $\geq$3 neutropenia, anemia, thrombocytopenia, and infections were reported in 57.1%, 42.9%, 28.6%, and 14.3% of patients, respectively. At a median follow-up of 7.8 months, the best overall response rate was 100%, with 71.4% (5/7) achieving complete response (CR). Median time to response was 1.0 month (range, 0.9-2.7). Median time to CR was 2.7 months (range, 0.9-2.8). By the cutoff date, 3 patients (2 PR, 1 CR) had disease progression. Median duration of response was not reached. **Conclusions:** C-CAR066 has shown a favorable safety profile and promising efficacy in patients with r/r B-NHL following failure of CD19 CAR-T therapy. These results show that C-CAR066 has a different mechanism of action compared to anti-CD-19 CAR-T therapy and could provide a solution to address the unmet medical need in B-NHL patients that have failed anti-CD19 CAR-T therapy. Clinical trial information: NCT04036019. Research Sponsor: Cellular Biomedicine Group Inc.

2509 **Poster Discussion Session**

Phase Ib study of the anti-TGF-β monoclonal antibody (mAb) NIS793 combined with spartalizumab (PDR001), a PD-1 inhibitor, in patients (pts) with advanced solid tumors. *First Author: Todd Michael Bauer, Sarah Cannon Research Institute, Tennessee Oncology, PLLC, Nashville, TN*

Background: TGF-β plays a key role in regulating the tumor microenvironment. Emerging evidence suggests TGF-β is a key activator of cancer-associated fibroblasts, leading to fibrotic network development and immune exclusion. Preclinical data in murine models showed that TGF-β blockade alleviates intratumoral fibrosis, augmenting the efficacy of PD-1 immunotherapy. NIS793 is a human IgG2 mAb that binds to TGF-β. This study investigates NIS793 + spartalizumab in pts with advanced solid tumors. **Methods:** Pts initially received NIS793 (0.3–1 mg/kg Q3W) monotherapy; following evaluation of two dose levels, dose escalation continued with NIS793 + spartalizumab (NIS793 0.3–30 mg/kg Q3W + spartalizumab 300 mg Q3W; or NIS793 20–30 mg/kg Q2W + spartalizumab 400 mg Q4W) in pts with/without prior anti-PD-(L)1 therapy. In dose expansion, pts with non-small cell lung cancer (NSCLC) resistant to prior anti-PD-(L)1 or pts with microsatellite stable colorectal cancer (MSS-CRC) were treated at the recommended dose for expansion (RDE). Paired tumor biopsies were required from all pts. The primary objectives were to characterize safety and tolerability of the combination and determine the RDE. **Results:** By December 1, 2020, 60 pts were treated in the dose-escalation phase, mainly with NIS793 + spartalizumab (n = 49), and 60 pts were treated in dose expansion (MSS-CRC: n = 40; NSCLC: n = 20). Two pts were still receiving treatment. No dose-limiting toxicities were observed, and the RDE was established as 30 mg/kg (2100 mg) NIS793 + 300 mg spartalizumab Q3W. Overall 50% pts experienced $\geq$1 treatment-related AE (TRAE). The most common were rash (n = 15/120), pruritus (n = 10/120), fatigue (n = 9/120), and nausea (n = 8/120). Grade 3/4 TRAEs occurred in 11% pts, with rash (3%) being the most common. Treatment-related serious AEs were reported in 8 pts; 6 were grade 3/4 in severity. No deaths occurred due to AEs; 3 (2.5%) pts discontinued due to AEs. PK for NIS793 was linearly dose proportional with no obvious correlation between exposure and response. Two pts achieved a partial response (PR; one confirmed in clear cell renal cell carcinoma and one unconfirmed in NSCLC) during dose escalation of the combination. Two confirmed PRs were achieved in the MSS-CRC dose-expansion group. Biomarker data showed evidence of target engagement through increased TGF-β/NIS793 complexes and depleted active TGF-β in peripheral blood. Gene expression and protein analyses in tumor biopsies displayed decreased TGF-β target genes, decreased TGF-β signatures and increased immune signatures suggesting modulation of the TGF-β pathway and preliminary evidence of biological activity. **Conclusions:** Data showing target engagement and TGF-β pathway inhibition supported the proof of mechanism of NIS793. The RDE of the combination was established and well tolerated in pts with advanced solid tumors. Clinical trial information: NCT02947165. Research Sponsor: Novartis.

2510 **Poster Discussion Session**

Safety, pharmacokinetic and pharmacodynamic results from dose escalation of SAR439459, a TGFβ inhibitor, as monotherapy or in combination with cemiplimab in a phase 1/1b study. *First Author: Stephen K. Williamson, University of Kansas Medical Center, Westwood, KS*

Background: SAR439459 is a human anti-TGFβ monoclonal antibody that neutralizes all isoforms of TGFβ. In preclinical models, combining SAR439459 with an anti-PD-1 showed improved anti-tumor activity compared to single agent. Here we report preliminary results of SAR439459 ± cemiplimab in a first in human study. **Methods:** This is an open-label study (dose escalation and expansion) of SAR439459 ± cemiplimab administered intravenously in adult patients with advanced solid tumors to determine safety and tolerability, the maximum tolerated dose (MTD) and/or maximum administered dose (MAD) of SAR439459 ± cemiplimab, pharmacokinetics (PK); pharmacodynamic (PD) and preliminary clinical benefit. In Part 1A, SAR439459 (0.05-15 mg/kg) was administered as monotherapy Q2W in an adaptive Bayesian design with overdose control. In Part 1B, SAR439459 doses cleared from monotherapy were administered in combination with fixed dose of cemiplimab (3 mg/kg Q2W or 350 mg Q3W) in a 3+3 design. **Results:** As of 31 January 2020, 28 (1A) and 24 (1B) patients with ECOG performance status of 0-1 with a median age of 60.5 and 63 years respectively were enrolled. In Part 1A, 25 patients (89.3%) had at least one treatment emergent adverse event (TEAE) and 15 (53.5%) experienced grade (G)$\geq$ 3 events. In Part 1B, 22 patients (91.7%) had at least one TEAE and 14 (58.3%) experienced G $\geq$ 3 events. Dose-limiting toxicities (DLTs) were evaluable in 24 and 21 patients respectively. In 1A, 2 DLTs were reported in 2 of 8 evaluable patients in dose level (DL) 4: G5 brain stem hemorrhage in a patient on concomitant low molecular weight heparin treatment and G3 myocardial infarction in a patient with diabetes, chronic kidney disease, chronic obstructive pulmonary disease, and hypertension. In 1B, 1 of 6 evaluable patients in DL5 had DLTs (G3 ALT and AST increase). MTD was not reached in either part. Ten patients had best overall response of stable disease: 6 in 1A and 4 in 1B. The PK of SAR439459 was dose proportional over the dose range tested with no evidence of cemiplimab effect on SAR439459 PK, when given in combination. Treatment with SAR439459 ± cemiplimab led to rapid reduction in total plasma TGFβ level in all dose levels tested and induced CD8 & NK cells expansion and Th1 cytokines production, suggesting peripheral T cell activation. Preliminary results from paired tumor biopsies collected from patients treated with SAR439459 ± cemiplimab in expansion showed trend of TGFβ signaling pathway inhibition and conversion from excluded to inflamed tumor-immune phenotype. **Conclusions:** SAR439459 ± cemiplimab showed an acceptable tolerability profile overall. MTD was not reached. Peripheral and tumor target engagement and modulation of key immune cells was observed in treated patients. Dose expansion cohorts are currently enrolling selected solid tumor patients. Funding: Sanofi. Clinical trial information: NCT03192345. Research Sponsor: Sanofi.

2511 **Poster Discussion Session**

Preliminary safety, pharmacokinetics (PK), pharmacodynamics (PD) and clinical efficacy of ulildlimab (TJ004309), a differentiated CD73 antibody, in combination with atezolizumab in patients with advanced cancer. *First Author: Francisco Robert, University of Alabama at Birmingham Comprehensive Cancer Center, Birmingham, AL*

Background: CD73 is implicated in tumor resistance to checkpoint immunotherapy (CPI) and plays a critical role in adenosine-mediated immune suppression. Ulildlimab, a differentiated CD73 antibody, inhibits the adenosine pathway in a non-competitive and unique intra-dimer binding mode. Ulildlimab suppresses tumor growth when combined with a PD-(L)1 inhibitor in multiple pre-clinical models. **Methods:** This 3+3 dose-escalation phase 1 study (NCT03835949) evaluated safety, tolerability, PK, PD and preliminary efficacy in cancer patients. Ulildlimab was administered intravenously at doses of 5, 10 or 15 mg/kg weekly (QW) or 15 or 20 mg/kg every 3 weeks (Q3W) alone in the first cycle and in combination with atezolizumab (1,200 mg Q3W) starting on week 4. Soluble CD73 in serum and CD73 receptor occupancy (RO) in circulating $CD19^+$ B cells were measured. Expression of PD-L1, CD73 and A2A receptor was analyzed in baseline tumor specimens (n = 14). Tumor responses were assessed by RECIST/iRECIST. **Results:** As of 17 January 2021, 20 patients with advanced solid tumors were enrolled (M:F 8:12; mean age = 64; median prior regimens = 3 (range 1-9)). Ulildlimab was well-tolerated with no dose limiting toxicity. The most common treatment-related adverse events were first dose infusion related reactions (65%, n = 13) most commonly comprising chills/rigors, nausea, and vomiting (Grade 1 or 2) that resolved in subsequent infusions. PK appears linear at doses $\geq$ 10 mg/kg and modelling indicated a mean derived effective half-life of ~19 days. Soluble CD73 was undetectable and complete RO was achieved in all patients after the first dose at $\geq$ 10 mg/kg. Anti-drug antibody was detected in 3/20 patients (15%). Among 13 efficacy-evaluable patients dosed at $\geq$ 10 mg/kg, complete response (CR = 1) and partial response (PR = 2) were observed in 3 patients (ORR = 23%) together with 3 stable disease (SD) patients (DCR = 46%). One PD-(L)1 inhibitor naïve patient with clear cell ovarian cancer achieved CR at 10 mg/kg QW and remains on study after 12 months. Two patients with NSCLC dosed at 15 mg/kg QW and 20 mg/kg Q3W, respectively, achieved PR. One patient failed nivolumab and the other received no prior PD-(L)1 inhibitor treatment. CD73 was expressed on 78% (mean) of malignant cells from archival tumor specimens in responders compared to 23% in non-responders. **Conclusions:** Ulildlimab is safe and well tolerated up to 20 mg/kg Q3W and 15 mg/kg QW. Full saturation of circulating and cell-bound CD73 was achieved at doses $\geq$ 10 mg/kg. Ulildlimab exhibited evidence of clinical activity in both PD-(L)1 treatment naïve and refractory cancer patients with high archival tumor expression of CD73. The results of this phase 1 study encourage further clinical investigation to evaluate the efficacy of ulildlimab in the treatment of solid tumors. Clinical trial information: NCT03835949. Research Sponsor: TRACON Pharmaceuticals Inc.

2512 **Poster Discussion Session**

BDB001, an intravenously administered toll-like receptor 7 and 8 (TLR7/8) agonist, in combination with pembrolizumab in advanced solid tumors: Phase 1 safety and efficacy results.

First Author: Manish R. Patel, Florida Cancer Specialists and Sarah Cannon Research Institute, Sarasota, FL

Background: BDB001 is an intravenously administered TLR 7/8 dual agonist immune modulator capable of reprogramming dendritic cells to produce antitumor activities. BDB001 monotherapy has demonstrated favorable tolerability and robust systemic immune activation leading to durable clinical responses in a phase I dose escalation trial. Here, we report on the safety and efficacy of BDB001 in combination with pembrolizumab in a phase I dose escalation trial in advanced solid tumors (NCT03486301). **Methods:** BDB001-101 is a phase 1, open label, dose escalation/expansion trial of BDB001 (IV, Q1W) in combination with pembrolizumab (IV, Q3W) in patients with advanced solid tumors. The primary endpoint was safety and tolerability. Secondary endpoints included efficacy, pharmacokinetics and pharmacodynamic profiling of immune activation. **Results:** Twenty-three subjects with 13 different tumor types were enrolled across 4 dose levels. Sixty one percent were female, median age was 63 years (range, 33-86), median number of prior therapies was 3 (range, 1-8), and 48% of tumors had progressed on prior anti-PD-(L)1 therapy. Overall, BDB001 in combination with pembrolizumab was well tolerated and dose-limiting toxicities were not observed. The most common treatment related adverse events (TRAEs) were fever (39.1%), fatigue (39.1%), chills/rigor (34.8%), pruritus/rash (21.7%), and nausea (13.0%). Most of these TRAEs were grade 1 or 2 and transient. Only 3 (13.0%) subjects experienced grade 3 TRAEs of fatigue, rash, stomatitis, and alkaline phosphatase elevation. There were no grade 4 or 5 TRAEs. Pharmacodynamic evaluation of plasma cytokine levels showed robust increases in interferon gamma and interferon inducible protein-10 (IP-10) at BDB001 Dose Level 3 and 4. Preliminary efficacy evaluation of the 14 subjects treated at Dose Level 3 and 4 showed durable and deep clinical responses in 4 (29%) subjects with anti-PD-(L)1 mAb refractory melanoma, hepatocellular carcinoma, cholangiocarcinoma, and platinum-resistant ovarian carcinoma. The responses were observed by the initial efficacy assessment at 9-weeks, with some seen as early as 4-weeks. In addition, 4 (29%) subjects had stable disease for a disease control rate of 57%. To date, median time on treatment is 14.4 weeks (range, 6.0 – 42.1+) with 3 subjects still active on treatment. **Conclusions:** Intravenously administered BDB001 in combination with pembrolizumab is well tolerated. Rapid and deep clinical responses were observed, supported by robust systemic immune activation. BDB001 in combination with pembrolizumab is a promising novel therapeutic option for patients with advanced solid tumors and is being evaluated in an ongoing dose expansion trial. Clinical trial information: NCT03486301. Research Sponsor: Seven and Eight Biopharmaceuticals Inc.

2513 **Poster Discussion Session**

ARTISTRY-1: Nemvaleukin alfa monotherapy and in combination with pembrolizumab in patients (pts) with advanced solid tumors.

First Author: Valentina Boni, START Madrid CIOCC Madrid, Madrid, Spain

Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel, engineered cytokine that selectively binds the intermediate-affinity interleukin-2 (IL-2) receptor complex to preferentially activate $CD8^+$ T cells and natural killer cells with minimal expansion of regulatory T cells, designed to leverage antitumor effects of the IL-2 pathwaywhile mitigating potential toxicity that would limit use. **Methods:** ARTISTRY-1 (NCT02799095) is a phase 1/2 study. Parts A (dose escalation 0.1-10 μg/kg) and B (6 μg/kg [recommended phase 2 dose]) are monotherapy; pts receive intravenous nemvaleukin for 5 days every 14 or 21 days. In Part C, pts receive nemvaleukin (3 or 6 μg/kg) every 21 days in combination with pembrolizumab (200 mg on day 1). We present safety and antitumor activity (RECIST v1.1, iRECIST) data as of 12/02/2020. **Results:** In Part A, 39 pts received nemvaleukin. No dose-limiting toxicities were observed; maximum tolerated dose was not reached. Part B enrolled immune checkpoint inhibitor–pretreated pts into melanoma or renal cell carcinoma (RCC) cohorts. 18 pts with melanoma enrolled; 10 were evaluable, 2 (both with metastatic mucosal melanoma) achieved a partial response (PR; 1 unconfirmed). 24 pts with RCC enrolled; 1 of 16 evaluable pts achieved a PR (awaiting confirmation). 12 pts in each cohort continue on study. In Parts A and B, treatment-related adverse events in ≥40% included chills (74.4% and 52.4%, respectively) and pyrexia (74.4% and 47.6%, respectively). In Part C (83 evaluable pts), 12 objective responses (OR) were observed; an additional 5 pts had stable disease (SD) >6 months (1 pt with breast cancer, 2 with ovarian cancer, and 2 with non-small-cell lung cancer). Nemvaleukin did not demonstrate any additive toxicity to that already established with pembrolizumab alone. OR data are summarized in the table. **Conclusions:** Nemvaleukin was generally well tolerated and demonstrated antitumor activity as monotherapy and in combination with pembrolizumab. Pharmacodynamic studies to identify biomarkers are ongoing. Future research of monotherapy and combination therapy with nemvaleukin is warranted. Clinical trial information: NCT02799095. Research Sponsor: Alkermes, Inc.

Study Part	Monotherapy		Combination Therapy[a]							
Tumor Type	Melanoma (n=10)	Renal Cell Carcinoma (n=16)	Ovarian Cancer (n=15)	Cervical Cancer (n=5)	Breast Cancer[b] (n=4)	Pancreatic Cancer (n=2)	Esophageal Cancer (n=5)	Melanoma (n=1)	Bladder Cancer (n=4)	Hodgkin's Lymphoma (n=1)
Pts with OR (n)	2	1	3	1	2	1	2	1	1	1
Pts on therapy ≥6 months (n)[c]	1	0	5	0	2	0	2	0	0	0
Best response for each pt[d]	PR, uPR	PR (awaiting confirmation)	CR, PR, uPR	PR	iPR, uPR	PR	PR, PR	CR	PR	PR (awaiting confirmation)
Weeks on study for each pt with OR[c]	15, 57+	16+	34, 43+, 99+	17+	88, 16	17	35+, 40+	16+	8+	15+

[a]CPI pretreated or naïve pts.
[b]TNBC, ER+Her2-.
[c]Investigator assessed.
[d]Additional pts experienced SD >6 months.
CR, complete response; iPR, immune partial response; PR, partial response; uPR, unconfirmed PR.

2514 **Poster Discussion Session**

Preliminary results of a phase 1b study of fruquintinib plus sintilimab in advanced colorectal cancer.

First Author: Ye Guo, Shanghai East Hospital, Shanghai, China

Background: To explore the safety and synergistic anti-tumor effect of fruquintinib (a VEGFR inhibitor) in combination with sintilimab (an anti-PD-1 Ab) in patients (pts) with advanced colorectal cancer (CRC) and other solid tumors. **Methods:** This is an ongoing phase Ib/II, multicenter, two-stage study. Pts with variety cancer types, including CRC, were enrolled and is continuously enrolling in the study. For this interim analysis, all pts were analyzed for safety whereas only CRC pts were analyzed for efficacy. MMR status were analyzed for all enrolled CRC pts. Stage 1 was classical "3+3" dose escalation with pts assigned to one of the following 4 cohorts, fruquintinib taken orally at 3mg (Cohort A, 3 weeks on/ 1 week off), 4mg (Cohort B, 3 weeks on/ 1 week off), 5mg-intermittent (Cohort C, 2 weeks on/ 1 week off) or 3mg-continuous (Cohort E, once daily), while sintilimab was given at 200mg intravenously with Q4W in Cohort A and Cohort B whereas Q3W in Cohort C and Cohort E. DLT was observed for 28 days. Stage 2 was dose expansion with pts receiving 5mg-intermittent or 3mg-continuous fruquintinib plus sintilimab (200mg, Q3W). The primary endpoints were safety and tolerability and secondary endpoint was objective response rate (ORR). **Results:** As of Jan 5, 2021, 44 CRC pts which failed to at least 2 previous lines of therapy containing fluoropyrimidine, oxaliplatin or irinotecan were enrolled. They received either 5mg-intermittent or 3mg-continous dosage (n = 22, each), the ORR was 22.7% (10/44, 95% CI: 11.5-37.8%) with 27.3% (6/22, 95% CI: 10.7-50.2%) in 5mg-intermittent group and 18.2% (4/22, 95% CI: 5.2-40.3%) in 3mg-continuous group. With a median follow-up time of 8.3 (range: 0-9.6) months, the K-M estimated median PFS was 6.8 (95% CI:5.6-NA) months and 4.3 (95% CI:3.5-NA) months for 5mg-intermittent group and 3mg-continuous group, respectively. Overall, 60 pts were enrolled for safety analysis, including 23 in stage1 and 37 (only CRC) in stage 2. In stage 1, all pts experienced TEAEs, 52.2% of which were ≥ grade 3. The most frequently reported TEAEs were TSH increasing (73.9%), fecal occult blood positive (56.5%), and Palmar-plantar erythrodysaesthesia syndrome (PPES) (56.5%). SAEs occurred in 8 (34.8%) pts and no treatment-related death was reported. One patient in Cohort B reported manageable DLT. In stage 2, all pts experienced TEAEs, 18 (48.6%) pts experienced ≥ grade 3 TEAEs with 6 (31.6%) in 5mg-intermittent group and 12 (66.7%) in 3mg-continuous group. The most common TEAEs were proteinuria (45.9%) and TSH increasing (37.8%). TEAEs leading to either fruquintinib or sintilimab discontinuation occurred in 3 (5%) pts each. **Conclusions:** Fruquintinib plus sintilimab showed promising efficacy and favorable safety profile in advanced CRC. Clinical trial information: NCT03903705. Research Sponsor: Hutchison MediPharma Limited, Pharmaceutical/Biotech Company.

2515 **Poster Discussion Session**

Safety and efficacy of AK112, an anti-PD-1/VEGF-A bispecific antibody, in patients with advanced solid tumors in a phase I dose escalation study.

First Author: Jermaine Coward, ICON Cancer Care, South Brisbane, QLD, Australia

Background: AK112 is a tetrameric bispecific antibody targeting PD-1 and VEGF-A. Published data suggests that the combination of anti-VEGF-A with immune checkpoint inhibitor (ICI) therapy produces complementary and synergistic antitumor effects. Given the strong correlation between VEGF-A and PD-1 expression in the tumor microenvironment, it is postulated that the simultaneous blockade of these 2 targets by AK112 as a single agent might achieve higher target binding specificity and produce enhanced antitumor activity, with an improved safety profile, compared to the co-administration of anti-PD-(L)1 and anti-VEGF therapies. Here, we present preliminary safety and efficacy data from a dose escalation study of AK112. **Methods:** A multicenter, phase I, open-label dose escalation and expansion study in advanced solid tumors that are resistant/refractory to standard therapies, began in December 2019 to determine the safety and efficacy of AK112 (0.3 mg/kg to 30 mg/kg) administered IV every 2 weeks (Q2W) using an accelerated titration followed by 3+3+3 dose escalation design. Selected dose escalation cohorts were expanded to a maximum of 18 subjects with selected solid tumor types for further evaluation of safety, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and anti-tumor activity. Pts with prior exposure to ICI were eligible. PD studies examined serum VEGF levels and PD-1 receptor occupancy (RO) on circulating T-cells as an indication of target engagement. **Results:** As of 13 Jan 2021, 29 pts, median age 60 years [30-76], have received AK112 at doses of 0.3 mg/kg (n = 1), 1.0 mg/kg (n = 3), 3.0 mg/kg (n = 3), 10.0 mg/kg (n = 13), 20.0 mg/kg (n = 8), and 30.0 mg/kg (n = 1) Q2W. Treatment-related adverse events (TRAEs) occurred in 55.2% of pts. G3 TRAEs occurred in 10.3% [3/29] and treatment-related SAEs occurred in 3.4% [1/29] of pts. There was no G4 TRAE. No DLT occurred. TRAEs leading to treatment discontinuation occurred in 6.9% of pts [2/29]. Most frequent TRAEs were arthralgia (17%), diarrhea (14%), rash (10%), and fatigue (10.3%). Of the 17 evaluable pts treated at doses ≥ 3 mg/kg Q2W, the ORR was 23.5% (4/17) and disease control rate (DCR) was 64.7% (11/17). Among the 4 responders, a responder (endometrial ca) had not received prior ICI or bevacizumab, 2 responders (ovarian ca, mesothelioma) had received prior ICI therapy; and a responder (microsatellite stable colorectal ca) was previously treated with bevacizumab. **Conclusions:** AK112, up to 20 mg/kg Q2W (inclusive), can be given safely to pts and demonstrated encouraging anti-tumor activity with an ORR of 23.5% when dosed ≥ 3 mg/kg Q2W in a pt population with various solid tumors resistant/relapsed to standard therapies. Enrolment is currently ongoing at 30.0 mg/kg Q2W and in dose escalation cohorts selected for expansion. Updated data, including PK, serum VEGF, and RO will be presented. Clinical trial information: NCT04047290. Research Sponsor: Akeso Biopharma, Inc.

2516 **Poster Discussion Session**

A first-in-human study of AO-176, a highly differentiated anti-CD47 antibody, in patients with advanced solid tumors. *First Author: Howard A. Burris III, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: AO-176 is a humanized IgG2 antibody that specifically targets CD47. Expressed by multiple tumor types, CD47 binds to signal regulatory protein a (SIRPa) on phagocytes, including macrophages and dendritic cells. The CD47-SIRPa complex results in a "don't eat me" signal that allows the tumor to escape removal by the innate immune system, disabling the generation of an adaptive immune response. The differentiated mechanisms of action of AO-176 include promotion of phagocytosis, direct tumor cell killing through programmed cell death type III and induction of damage associated molecular patterns/immunogenic cell death, preferentially binding to tumor cells vs. normal cells, and enhanced binding at an acidic pH as found in tumor microenvironments. AO-176 has negligible binding to RBCs. **Methods:** In a phase 1/2 first-in-human study (NCT03834948) of AO-176, pts with advanced solid tumors associated with high CD47 expression and an ECOG PS of 0-1 were enrolled into escalating dose cohorts of AO-176 given IV every 7 days. Objectives included evaluation of safety, dose-limiting toxicity (DLT) and recommended phase 2 dose (RP2D), antitumor activity, pharmacokinetic (PK) parameters and exploratory biomarkers. **Results:** As of 4 Jan 2021, 27 pts were enrolled (median age 64 years; 67% female; 67% ECOG PS 1; median [range] of 4 [1-7] prior therapies for metastatic disease). Dose levels of 1, 3, 10, 20 and 20 (using step-up dosing) mg/kg were evaluated in >250 infusions. Most common (>10%) treatment-related adverse events (TRAEs) of any grade were thrombocytopenia and infusion-related reaction (IRR) (33% each), anemia (22%) with no evidence of hemolysis, nausea (19%), and fatigue (15%). The only G3+ TRAE occurring in >10% of pts was asymptomatic, brief thrombocytopenia (22%). No platelet transfusions were given. DLTs included IRRs in 2 pts dosed at 20 mg/kg, and asymptomatic thrombocytopenia and a cerebrovascular accident in 1 pt each in the 20 mg/kg step-up cohort. The RP2D was 10 mg/kg. Implementation of additional pre-medication and a 6-hr infusion duration in cycle 1 eliminated subsequent IRRs. Dexamethasone tapering and shortening of the infusion duration to 2 hrs was successful in all pts after cycle 1. Interim PK analysis of AO-176 demonstrated consistent exposure with linear PK. The $T_{1/2}$ was ~5 days. One pt with endometrial carcinoma who had not responded to any of 4 prior systemic regimens had a confirmed PR and remains on study for >1 year. 7 pts had SD as a best response, with 2 pts (endometrial carcinoma, gastric cancer) on study for >6 mos. **Conclusions:** AO-176 is a well-tolerated, differentiated anti-CD47 therapeutic. Durable anti-tumor activity was observed. Evaluations of AO-176 in combination with paclitaxel in pts with select solid tumors (NCT03834948) and as a single-agent in pts with multiple myeloma (NCT04445701) are ongoing. Clinical trial information: NCT03834948. Research Sponsor: Arch Oncology.

2517 **Poster Discussion Session**

First-in-human phase 1 dose escalation study of HX009, a novel recombinant humanized anti-PD-1 and CD47 bispecific antibody, in patients with advanced malignancies. *First Author: Aflah Roohullah, South Western Sydney LHD, Liverpool, Australia*

Background: HX009 is a novel humanized antibody fusion protein which binds to CD47 and PD-1 concurrently. HX009 significantly inhibited tumor growth in mouse xenograft models. In Cynomolgus monkeys, the highest non-severely toxic dose in repeat dose testing was 15mg/kg. HX009-I-01 (ClinicalTrials.gov: NCT04097769) is a first-in-human study evaluating the safety and efficacy of HX009 in subjects with advanced malignancies. Here we report the preliminary results from this study. **Methods:** The study is being conducted in Australia at 3 sites. The study design follows a 3+3 dose-escalation scheme, enrolling cohorts of at least 3 subjects (except the first dose level) sequentially until MTD or the maximum dose is reached. HX009 is administered as single agent every 2 weeks via intravenous infusion. The 7 dose levels planned are: 0.1mg/kg (1 subject), 0.3mg/kg, 1mg/kg, 2mg/kg, 3mg/kg, 5mg/kg, 7.5mg/kg. All AEs are graded using NCI CTCAE v5.0. Efficacy assessments are per RECIST 1.1. Blood samples are obtained for pharmacokinetics (PK) and for immunogenicity assessments by the development of Antidrug Antibodies. **Results:** As of the January 22 2021 cutoff date, 21 patients (12M/9F) with a median age of 69.0 years (range 38-86) have received dose levels of 0.1-7.5 mg/kg. Patients with the following tumor types have been enrolled: colorectal cancer (7), squamous cell carcinoma (3), endometrial cancer (2), breast cancer (3), malignant epithelioid mesothelioma (1), gallbladder cancer (1), pancreatic cancer (1), glioblastoma(1), ovarian cancer (1), gastro-esophageal junction adenocarcinoma (1). Patients had received a median of 3 (range 1-9) prior anti-cancer regimens. Treatment-related AEs have been reported in 10 (47.6%) patients to date. Most AEs are grade 1 or 2. The most frequent treatment-related AEs include nausea (n = 2, G1), rash (n = 2, G1), vomiting (n = 2, G1), and decreased appetite (n = 2, G1). Only 1 treatment-related SAE of pneumonitis. One treatment-related anemia (G2), and no thrombocytopenia. No DLT was observed in all 7 dose levels. Among 18 patients who have had at least one post-baseline tumor assessments, partial responses (PR) have been achieved in 3 patients with the following tumor types (dose level): gallbladder adenocarcinoma (1mg/kg), triple negative breast cancer (5mg/kg), metastatic squamous cell carcinoma of head and neck (5mg/kg). In addition, there are 6 patients with best overall response of stable disease. As of the data cutoff date, 6 patients are still receiving treatment. Updated clinical and PK results will be presented at the meeting. **Conclusions:** HX009, on an every 2 weeks dosing schedule, up to 7.5 mg/kg, is well-tolerated, without any DLT to date. Antitumor activity was seen at 1 mg/kg and 5 mg/kg cohorts with objective responses in multiple tumor types; Further investigation in phase Ib/II studies is warranted. Clinical trial information: NCT04097769. Research Sponsor: HanX Biopharmaceutical Inc, Hangzhou, China.

2518 **Poster Discussion Session**

Phase I INSIGHT platform trial: Advanced safety and efficacy data from stratum D evaluating feasibility and safety of eftilagimod alpha (soluble LAG-3 protein) combined with avelumab in advanced solid tumors. *First Author: Thorsten Oliver Goetze, Krankenhaus Nordwest, University Cancer Center Frankfurt and Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt Am Main, Germany*

Background: Stratum D of the INSIGHT platform trial evaluates s.c. eftilagimod alpha (efti, IMP321) combined with avelumab in advanced solid tumors. Efti is an MHC class II agonist which activates antigen-presenting cells followed by CD8 T-cell activation. Combination with PD-1/PD-L1 blockade aims at enhanced efficacy. **Methods:** This IIT platform trial consists of 5 strata: intratumoral (A) or intraperitoneal efti (B); s.c. efti with SOC (C) or with PD-L1 inhibition (D). Strat E is currently under development and starts soon with a new efti combination. This abstract focuses on preliminary data of Strat D. Patients (pts) received 800mg avelumab i.v. q2w along with s.c. efti: 6mg in cohort 1 (coh 1, 6 pts), 30mg in cohort 2 (coh 2, 6 pts). Primary endpoint: safety. **Results:** Recruitment has been completed with 12 pts (coh 1: gastric, gallbladder, colon cancer, pleural mesothelioma; coh 2: gastric, gastroesophageal, anal, rectum, cervix uteri). No dose limiting toxicities (DLTs) occurred. 10 serious adverse events (SAEs) were reported, none of them considered causally related (4 in 3 pts of coh 1 [1 acute renal insufficiency grade 5 in 1 pt, 2 preileus grade 3 in 1 pt, hearing impaired grade 4 in 1 pt] and 6 in 4 pts of coh 2 [1 anal hemorrhage and 1 gallbladder obstruction in 1 pt, 1 eye pain and 1 surgery to replace the feeding tube in 1 pt, each grade 3, 1 skin infection grade 2, 1 diffuse myocardial fibrosis grade 5]. 1 AE of special interest (AESI) possibly related with avelumab (sarcoidosis grade 1) occurred in coh 1. 2 pts completed max treatment duration with 24 cycles. In coh 1, 47 adverse events (AEs; grade 1-2, 29; grade 3, 14; grade 4, 3; grade 5, 1) occurred in 5 pts. Most common grade 1-2 AEs were nausea, pain in 33%, 33% of the pts. Most common grade 3 AEs were ileus, vomiting in 33%, 33% of the pts. 2 AEs grade 4 (hearing impaired, sepsis) and 1 AE grade 5 (acute renal insufficiency) were reported. All AEs grade 3-5 were considered causally unrelated. In coh 2, 51 adverse events (AEs; grade 1-2, 29; grade 3, 19; grade 4, 2; grade 5, 1) occurred in 5 pts. The most common grade 1-2 AE was hypothyroidism in 33% of the pts. 1 AE grade 5 (diffuse myocardial fibrosis) was reported. Only 1 AE grade 3-5 was considered causally related (urinary tract infection grade 3 related with avelumab). 5 pts showed partial response as best response (2 coh 1: colon, pleural mesothelioma; 3 coh 2: gastric, anal, cervical), 1 stable disease with clinical progression (coh 2) (all but one of these pts still alive), 5 disease progressions acc. to RECIST 1.1 (3 coh 1, 2 coh 2), 1 clinical progression (coh 1). Signals of activity were also observed in pre-treated *MSS/PD-L1$_{low}$* pts. **Conclusions:** Combined treatment with avelumab 800mg and efti 6mg (coh 1) or 30 mg efti (coh 2) seems feasible and safe. No unexpected AEs occurred. Signals of efficacy with CPI combination were seen (DCR 50%). Clinical trial information: NCT03252938. Research Sponsor: IMMUTEP.

2519 **Poster Discussion Session**

Pan cancer analysis of the intra-tumoral microbiome's correlation with racial disparities. *First Author: Wei Tse Li, University of California San Diego, San Diego, CA*

Background: Microbiome composition can influence cancer development and is moderated by diet, hygiene, sanitation, and other environmental variables. For example, a Mediterranean diet could increase breast *Lactobacillus* abundance, while the gut microbiome changes dramatically with fructose intake. Recent studies have revealed correlations between microbial abundance and racial disparities in cancer. Given these reports, it is critical to examine whether environmental influences on the microbiome contribute to racial disparities in cancer incidence and prognosis. **Methods:** We examined the intra-tumoral microbiome in the lungs, breasts, bladder, colon, rectum, cervix, head and neck, prostate, and pancreas (n = 4,169). Raw tumor RNA sequencing data were downloaded from The Cancer Genome Atlas (TCGA) and aligned to bacterial genomes. Microbial abundance was correlated to race, ethnicity, and prognostic variables (Kruskal-Wallis test or Cox regression, $p < 0.05$). **Results:** We identified several microbes correlated with racial disparities for breast and bladder cancer, two microbes for lung squamous cell carcinoma, and one microbe for colon cancer. For breast cancer, African Americans have the highest mortality rate, followed by white Americans and Asian Americans. We found that four microbes, all under the order Burkholderiales, were positively correlated with poor prognosis and were most abundant in African Americans and least abundant in Asian Americans. Therefore, increased abundance of these microbes may contribute to the observed mortality differences between races. For bladder cancer, Asian Americans have the lowest incidence and mortality rates. Seven microbes, including two *Geobacillus*, two *Pseudomonas*, and two Burkholderiales, positively correlate with good prognosis and are upregulated in Asian Americans. High *Pseudomonasfluorescens* abundance is positively correlated with decreased risk of death (HR: 0.57, 95% CI: 0.38-0.85). High abundance of the Burkholderiales *R. pickettii* (HR: 0.62, 95% CI: 0.42-0.92) and *V. paradoxus* (HR: 0.59, 95% CI: 0.36-0.98) also exhibit the same trend. *Geobacillus* and *Pseudomonas* are both present in food, while Burkholderiales can cause nosocomial infections and are altered by diet. **Conclusions:** Our study is the most comprehensive to date investigating racial differences in the intra-tumoral microbiome. Our data serve as a starting point for exploring whether environmental influence of microbial abundance contributes to racial disparities in cancer. Research Sponsor: None.

2520 **Poster Discussion Session**

Safety and efficacy of neoadjuvant pembrolizumab in mismatch repair deficient localized/locally advanced solid tumors. *First Author: Kaysia Ludford, The University of Texas MD Anderson, Houston, TX*

Background: Pembrolizumab (Pembro), anti-PD1 therapy, is FDA approved for refractory microsatellite instability high (MSI-H)/deficient mismatch repair (dMMR) advanced/metastatic solid tumors. The robust activity of anti-PD1 therapy in these tumors argues for a neoadjuvant organsparing approach. However, the role of anti-PD1 monotherapy in the neoadjuvant setting is unknown. **Methods:** This is a phase 2 open-label, single center trial (NCT04082572) of MSI-H/dMMR non-metastatic solid tumors with localized unresectable or high risk resectable (defined as ≥ 20% recurrence) with measurable disease per RECISTv1.1 and ECOG PS 0/1. Treatment is Pembro 200mg every 3 wks for 8 cycles (6 months) followed by surgical resection with option to continue therapy for 18 cycles (12 months) followed by observation. First restaging is at 6 wks and includes baseline and 3-week 70-gene ctDNA assessment. To continue on study, patients are required to have PR/CR, SD with tumor shrinkage or SD with decline in ctDNA [highest variant allele frequency (VAF) baseline mutation]. The co-primary endpoints are safety and pathological complete response (pCR). Key secondary endpoints are response rate and organsparing at one year for patients who declined surgery. **Results:** Between 12/2019 and 2/2021, 32 pts were enrolled and treated. Enrolment goal of 35 anticipated to be met by 4/2021. Baseline characteristics included 13 females, median age of 63 yrs (range 26 - 91), Lynch syndrome in 12 pts, BRAF V600E mutation in 11 pts. Tumor type included 24 CRC and 8 non-CRC (1 endometrial, 1 gastric, 1 meningeal, 2 duodenal, 1 ampullary, 2 pancreatic). At baseline disease was resectable in 23 (72%). Among 30 evaluable pts, best overall response rate was 77%: 30% CR (n = 9), 47% PR (n = 14), 20% SD (n = 6), 3% PD (n = 1). Only one pt progressed after initial SD of -18%. Median follow-up is 6.1 months (range 0.1 - 14). Among the 6 (20%) pts who underwent surgery, pCR was seen in 3 (50%). A non-operative approach (pembro for 12 months) has been chosen in 15 pts and 1-year organ-sparing was seen in 2/2 evaluable pts. Treatment-related grade 3/4 immune adverse events (TRAE) were seen in 3 (9%) pts: grade 3 immune hepatitis (2) and grade 3 type 1 diabetes (1). Baseline ctDNA was positive in 17 (53%) pts with a median of 4 mutations per pt (1 - 35) and median highest VAF of 0.9% (range 0.3% to 38.2%). Among 26 pts with successful tumor tissue testing, median tumor mutations were 10.5, range 1 to 21 (Oncomine 134 gene panel). ctDNA decline at 3 weeks was seen in 14/17 (82%) patients. Luminal disease was present in 24 pts with endoscopic response of: CR in 13 (54%), major response 1, pending follow-up evaluation 6, not evaluated 3, and no response in 1. **Conclusions:** Neoadjuvant pembrolizumab is safe with encouraging clinical activity and this data suggests that a non-operative management for dMMR/MSI-H localized solid tumors should receive further investigation. Clinical trial information: NCT04082572. Research Sponsor: Merck and Co.

2521 **Poster Session**

Early safety and efficacy from a phase I open-label clinical trial of CD137(4-1BB) agonistic antibody LVGN6051 as monotherapy and in combination with pembrolizumab. *First Author: Siqing Fu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: LVGN6051, a monoclonal antibody against CD137 (also known as 4-1BB or TNFRSF9) with an engineered Fc capable of selectively binding to the Fcγ receptor IIB, acts as a conditional CD137 agonist, resulting in immune activation optimally in tumor microenvironment (Qi, Nat. Commun. 2019). In preclinical models, LVGN6051 demonstrated robust anti--tumor efficacy and safety as a single agent and in combination with anti-PD-1 antibodies. Therefore, we have initiated this first-in-human study of LVGN6051 alone or in combination with pembrolizumab for the treatment of advanced or metastatic malignancy. **Methods:** This study includes accelerated dose escalation monotherapy up to 2 mg/kg of LVGN6051, and traditional 3 + 3 design for higher doses of LVGN6051 alone or in combination with pembrolizumab. Then, this study will enroll patients with specific types of malignancies following Simon's two-stage design. Both agents are administered once every 3 weeks. Primary objectives of this study were to define the safety profile and to establish the recommended phase 2 dose (RP2D) of LVGN6051 alone or in combination with pembrolizumab. Pharmacokinetics, immunogenicity, pharmacodynamics and clinical efficacy will be also evaluated. **Results:** At the cut-off date on January 18, 2021, 16 subjects have been enrolled into the monotherapy cohorts (n=12, no DLT observed up to 7 mg/kg), and the combination cohort (n=4, ongoing at LVGN6051 2 mg/kg and pembrolizumab 200 mg, one DLT observed). No treatment-related adverse event (TRAE) was observed in monotherapy. Treatment-emergent adverse events (TEAE) in combination included increased ALT/AST, thrombocytopenia, and fatigue. In the combination cohort, one patient with predominant hepatic metastases and history of intermittent grade 2 hepatic impairment experienced grade 3 increased ALT/AST (DLT) on cycle 1 day 15 that were resolved to her baseline without corticosteroids on cycle 1 day 18. TRAE included increased ALT/AST, thrombocytopenia, neutropenia, nausea and fatigue. Seven of 10 evaluable patients in the monotherapy cohorts demonstrated stable disease with the longest treatment being 8+ months. Tumor reductions by >10% were observed in melanoma and neuroendocrine tumor on monotherapy. One patient with metastatic head and neck squamous cell carcinoma who had progressed on an anti-PD-L1 based therapy showed an immune partial response (iPR) for 6+ months to the combination therapy. **Conclusions:** Preliminary evidence showed that LVGN6051 was well tolerated and tumor shrinkages were observed. While we continue assessing its safety profile, antitumor activity was observed in the LVGN6051 and pembrolizumab cohort. The favorable safety profile and preliminary antitumor activity warrant further evaluation in patients with advanced malignancies. Clinical trial information: NCT04130542. Research Sponsor: Lyvgen Biopharma Holdings Limited.

2522 **Poster Session**

Activity results of the GATTO study, a phase Ib study combining the anti-TA-MUC1 antibody gatipotuzumab with the anti-EGFR tomuzotuximab or panitumumab in patients with refractory solid tumors. *First Author: Elena Garralda, Early Drug Development Unit (UITM), Vall d'Hebron University Hospital and Institute of Oncology (VHIO) and Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain*

Background: The phase I GATTO study explored the feasibility, tolerability and preliminary activity of combining Gatipotuzumab (GAT), a novel humanized monoclonal antibody binding to the tumor-associated epitope of mucin-1 (TA-MUC1), and an anti-EGFR antibody. Preclinical evidence suggests a complex interaction between TA-MUC1 and EGFR on the cell surface of epithelial tumors and synergistic antibody dependent cell cytotoxicity activity with the double targeting. **Methods:** Initially 20 patients with refractory metastatic disease were treated with GAT administered at 1400 mg Q2W in combination with the glyco-optimized anti-EGFR antibody Tomuzotuximab (TOM) at 1200 mg Q2W. Due to the risk of infusion related reactions, three cycles of TOM were given before start of combined treatment with GAT. After this regimen was proven safe and no DLT was observed, 30 additional patients including colorectal cancer (CRC) already treated with anti-EGFR antibodies, non-small cell lung cancer (NSCLC), head and neck and breast cancers received TOM and GAT administered at the same doses, with GAT treatment starting already one week after the first dose of the anti-EGFR antibody. As allowed in the study expansion, Panitumumab (PAN) was used in place of TOM in 9 CRC patients at investigator's choice. **Results:** By the time of the final analysis in January 2021, 52 patients were enrolled, and 50 received at least one dose of both GAT and anti-EGFR antibodies. Safety was overall good and results are reported in a separate abstract. Because of the difference in treatment schedule, activity results of the two parts of the study are summarized separately. There were 2 and 4 RECIST partial responses in the first and second part of the study, all in CRC patients. In the expansion phase, the median Progression Free Survival (PFS) of CRC patients who received TOM (10) and PAN (9) was 1.9 and 5.5 months, respectively. There were 2 responses in each subgroup and the duration of response was 3.8 and 7.2 months in patients receiving TOM and PAN, respectively. The PFS for NSCLC was 5.3 months and 2 heavily pretreated patients achieved a prolonged control of disease of 10.6 and 9.4 months. The trial was accompanied by a comprehensive translational research program for identification of biomarkers, including soluble TA-MUC1 in serum. In the extension phase patients with baseline values above median appeared to have improved PFS and overall survival; this was not the case for patients of the first part of the study who received GAT only after 3 doses of TOM. **Conclusions:** Combination of TA-MUC1 and EGFR targeting antibody is safe and feasible. Interesting anti-tumor activity was observed in heavily pretreated CRC and NSCLC patients. Levels of soluble TA-MUC1 may have predictive value and potentially be a companion biomarker for further development of the combination Clinical trial information: NCT03360734. Research Sponsor: Glycotope GmbH.

2523 **Poster Session**

Phase I study of LBL-007, a novel anti-human lymphocyte activation gene 3 (LAG-3) antibody in patients with advanced solid tumors. *First Author: Yuankai Shi, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: LAG-3 is an immune checkpoint receptor expressed on activated T cells to negatively regulate these cells, resulted in tumor immune escape. LBL-007, a novel anti-LAG-3 antibody, was developed by screening of a human antibody phage display library and demonstrated specific binding to human LAG-3, stimulation of IL-2 release and blockage of LAG-3 binding to its ligands including MHC II. It has shown that LBL-007 significantly inhibited tumor growth in a mouse MC38 tumor model in hLAG-3 knock-in mice with more pronounced tumor inhibition when combined with an anti-PD-1 antibody. **Methods:** A phase I, multicenter, open-label and first-in-human study was conducted to evaluate the safety, tolerability, and PK in patients with advanced solid tumors. The dose escalation phase was designed with 6 dose cohorts of LBL-007 at 0.05, 0.25, 1, 3, 6 and 10 mg/kg (iv every 2 weeks), using a modified 3+3 design. Key inclusion criteria included: age≥18 years, histologically/cytologically confirmed advanced solid tumors, failed ≥2 lines of prior standard therapies, ECOG of 0-1, and adequate hematologic, renal, hepatic, and cardiac function. Patients who received anticancer or immunotherapy 4 weeks from first dose of LBL-007 were excluded. The primary endpoints were tolerability and safety. Adverse events (AEs) were graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Any potential efficacy was assessed by objective response rate (ORR) evaluated by CT/MRI per RECIST 1.1. **Results:** From March 12th, 2020 to Feb 9th, 2021, 17 patients were evaluated in this study. There were no dose limiting toxicities (DLTs) at any dose cohorts, and patients were tolerated very well. Overall, there were 129 adverse events (AEs), and 8 events were serious adverse event (SAE), of which 5 were defined as suspected unexpected serious adverse reaction (SUSAR), but most unlikely treatment related AEs (TRAEs). All AEs regardless of attribution included anemia, hypocalcemia, and flu related respiratory infection, etc. The most common AEs were anemia (14, 10.9%), hypocalcemia (6, 4.7%) and thrombocytopenia (4, 3.1%). Totally, there were 8 patients without disease progression, defined as SD at the first evaluation and sustained for 3.5-9 months. The target lesions in 2 of these 8 patients were reduced by 18.9% and 23.2% (both in esophagus cancer). The progression-free survival of these 2 patients was 4.4 and 9.0 months, respectively. Patients are also being enrolled into the indication exploratory phase (3 and 6 mg/kg), testing the combination therapy with an anti-PD-1 antibody in patients with melanoma and other solid tumors. **Conclusions:** The dose escalation part of the study revealed tolerability of LBL-007 with an impressive safety profile, and potentially some encouraging signs of anti-tumor activities. Clinical trial: Chinaclinicaltrials.org.cn (1900025904). Clinical trial information: CTR20210196. Research Sponsor: Leads Biolabs.

2524 **Poster Session**

Safety and tolerability results of the GATTO study, a phase Ib study combining the anti-TA-MUC1 antibody gatipotuzumab with the anti-EGFR tomuzotuximab or panitumumab in patients with refractory solid tumors. *First Author: Sebastian Ochsenreither, Charité Comprehensive Cancer Center, Berlin, Germany*

Background: The phase I GATTO study explored the feasibility, tolerability and preliminary activity of combining gatipotuzumab (GAT), a novel humanized monoclonal antibody binding to the tumor-associated epitope of mucin-1 (TA-MUC1) and an anti-EGFR antibody. Preclinical evidence suggests a complex interaction between TA-MUC1 and EGFR on the cell surface of epithelial tumors driving carcinogenesis processes and synergistic antibody dependent cell cytotoxicity activity with the dual targeting. **Methods:** Initially the study enrolled in a primary phase (PP) 20 patients with EGFR positive metastatic solid tumors, for whom no standard treatment was available. The first 6 patients were enrolled into a safety run-in phase and the number of dose-limiting toxicities (DLTs) was evaluated, in order to de-escalate the doses if needed. Patients received GAT administered at 1400 mg Q2W in combination with the glyco-optimized anti-EGFR antibody tomuzotuximab (TOM) at 1200 mg Q2W. Due to the risk of infusion related reactions (IRR), the first dose of TOM was reduced to 720 mg split over 2 consecutive days and three cycles of TOM monotherapy were given before start of treatment with GAT. As this regimen was proven safe, no DLT was observed and the initial dose remained unchanged, the study was amended to enroll in an expansion phase (EP) 30 additional patients with refractory colorectal cancer (CRC), non-small cell lung cancer (NSCLC), head and neck and breast cancers. TOM and GAT were given at the same doses and GAT treatment started already one week after the first dose of the anti-EGFR antibody. Additionally investigator had the choice to use a commercial anti-EGFR antibody in place of TOM. **Results:** By the time of the final analysis in January 2021, 52 refractory patients were enrolled and 50 received at least one dose of both GAT and anti-EGFR antibodies. Panitumumab (PAN) was used in 9 CRC patients. Because of the difference in treatment schedule, results are summarized separately for the 20 and 30 patients in PP and EP. Overall, the combined treatment was well tolerated and no DLT was observed in the whole study, nor related SAE or death. There were no treatment emergent adverse events (TEAEs) leading to dose interruptions or reductions in the PP and 2/30 (6.7%) patients in EP stopped both TOM and GAT. 16 IRRs were reported in 8/20 (40%) PP patients, and 40 IRRs in 10 (33.3%) EP patients. Only one event of chills was severe and only 6 events were related to GAT in the EP, all others to TOM. Other frequent TEAEs were those commonly observed with anti-EGFR treatment such as skin toxicity in 17 (85%) PP and 26 (86.7%) EP patients and hypomagnesemia in 10 (50%) PP and 7 (23.3%) EP patients. **Conclusions:** Combination of TA-MUC1 and EGFR targeting antibody is safe and feasible. Future studies should test this combination together with chemotherapy Clinical trial information: NCT03360734. Research Sponsor: Glycotope GmbH.

2525 **Poster Session**

Changes in T lymphocyte subsets in different tumors before and after radiotherapy: A meta-analysis. *First Author: Xiaoxia Zhu, Radiation Oncology Department, Zhujiang Hospital, Southern Medical University, Guangzhou, China*

Background: Radiation therapy (RT) induces an immune response, but the relationship of this response with tumor type is not fully understood. **Methods:** We searched English-language electronic databases including PubMed, EMBASE, and the Cochrane Library to collect studies about the changes in CD3+ T lymphocytes, CD4+ T lymphocytes, and CD8+ T lymphocytes before and after radiotherapy in tumor patients from January 2015 to December 2019. The quality of the included literature was evaluated using the NOS scale provided by the Cochrane Collaboration, and statistical software RevMan 5.4 was used to analyze the included literature. $p < 0.05$ was considered to indicate statistical significance. **Results:** A total of 17 studies in 15 articles involving 1735 tumor patients were included. All data were collected within 1 month before or after radiotherapy. Meta-analysis showed that numbers of $CD3^+$ T lymphocytes were significantly reduced after radiotherapy compared with before treatment (standard mean difference [SMD]: -0.76; 95% CI [-1.46, -0.06]; p = 0.03), as were those of $CD4^+$ T lymphocytes (SMD: -0.50; 95% CI: [-0.88, -0.12]; p = 0.01), but there was no statistically significant difference for CD8+ T lymphocytes (SMD: 0.19; 95% CI: [-0.23, 0.62]; p = 0.38). Subgroup analysis showed significant decreases in CD3+ T lymphocytes in liver cancer,esophageal cancer, head and neck cancer , pancreatic cancer and breast cancer after radiotherapy**.** Numbers of CD4+T lymphocytes increased after radiotherapy in breast cancer,and a decrease was observed in liver cancer, esophageal cancer, colorectal cancer , and head and neck cancer. CD8+ T lymphocyte numbers also increased compared with before radiotherapy in esophageal cancer, lung cancer , and colorectal cancer . But a decrease in liver cancer and head and neck cancer. **Conclusions:** Numbers of CD3+ and CD4+ T lymphocytes decreased after radiotherapy, whereas CD8+ T lymphocytes showed no significant change. Within 1 month of radiotherapy, the tumor microenvironment showed an immunosuppressive state. The degree of immune response induced by radiotherapy differed between tumor types. Research Sponsor: National Natural Science Foundation of China [No. 81972853, No.81572279], Clinical Research Startup Program (LC2019ZD009).

2526 **Poster Session**

A phase 1, open-label, dose escalation study of the safety and tolerability of T3011 in advanced cutaneous or subcutaneous malignancies. *First Author: Andrew Mark Haydon, Alfred Health, Melbourne, VIC, Australia*

Background: T3011 is a genetically modified, next-generation oncolytic HSV-1 with 2 exogenous genes encoding the active heterodimer human interleukin 12 (IL-12) and the Fab fragment of an anti-human PD-1 antibody. Locally produced IL-12 induces the synthesis of interferon-gamma (IFN-γ) production, enhancing cytolytic activity of natural killer cells and cytotoxic T lymphocytes. The anti PD-1 antibody blocks checkpoint inhibition of T effector cells. Extensive preclinical studies demonstrate that T3011 (and murine equivalent T3855) has potent antitumor activities. **Methods:** This phase 1 multicenter, open-label, dose escalation study evaluates the safety of intratumoral (IT) T3011 given once every other week (Q2W) in patients (pts) with advanced cutaneous or subcutaneous malignancies. The primary objective is to determine the Recommended Phase 2 Dose of T3011 based on the overall safety, pharmacokinetic and pharmacodynamic profile. Eligible pts are ≥ 18 years, have cutaneous or subcutaneous advanced cancer that has progressed on standard treatment and at least 1 measurable tumor lesion (≥ 10 mm) suitable for T3011 IT injection. Part 1 of the study uses a 3+3 design to evaluate the safety and tolerability of T3011 monotherapy in 4 escalating doses (1×10^6, 1×10^7, 5×10^7, and 1×10^8 PFU/mL). Up to 4 mL of T3011 may be injected based on tumor size. Total enrollment will be determined by toxicities observed. **Results:** As of Feb. 14, 8 pts have received IT T3011 (Q2W): 3 in Cohort 1 (1×10^6), 3 in Cohort 2 (1×10^7), and 2 in Cohort 3 (5.0×10^7 PFU/ml). Maximum doses per pt was 11. Enrollment continues in Cohort 3. T3011 was well tolerated with no ≥ Grade 3 treatment-related adverse events (AEs), no DLTs or treatment-related SAEs reported to date. Common AEs were pain at injection site, leukopenia, anemia, hypocalcemia, nausea, fever, headache, dermatitis, and diaphoresis. Viral shedding was analyzed in blood, urine and saliva at various times during the study. No Viral DNA was detected in blood or urine samples (first 3 pts analyzed) to date. Biopsy samples taken from injected tumors from 2 melanoma pts (Cohort 1) revealed significant reduction of viable tumor cells after 4 injections (Week 9) compared with baseline. In particular, one post-treatment biopsy contained 45% tumor necrosis area with dramatic increases of CD8 + and NKT cells. CD3+ and CD4+ cells as well as PD-1 expression were increased in post-treatment biopsies of both pts. **Conclusions:** T3011 IT injection was well tolerated at the first 2 dose levels. Post treatment biopsies from 2 pts (Cohort 1) demonstrated significantly reduced tumor cell viability as well as increased lymphocyte infiltration indicating on-target anti-tumor activities of T3011. To date, 5 out of 6 evaluable pts had SD as best response and 6 enrolled pts remain on study. Dose escalation is continuing. Clinical trial information: NCT04370587. Research Sponsor: None.

2527 **Poster Session**

Safety and PK/PD of ALLO-647, an anti-CD52 antibody, with fludarabine (Flu)/cyclophosphamide (Cy) for lymphodepletion in the setting of allogeneic CAR-T cell therapy. *First Author: Michael Timothy Tees, Moffitt Cancer Ctr and Rsrch Inst, Tampa, FL*

Background: Allogeneic chimeric antigen receptor (CAR) T cell therapy holds promise in addressing logistical/manufacturing challenges of autologous CAR T cell therapy. ALLO-501 (anti-CD19; uses Cellectis technologies) and ALLO-715 (anti-BCMA) are allogeneic CAR T cell products whose a) disrupted TCRα constant gene may reduce GvHD risk, and b) edited CD52 gene may permit use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells. **Methods:** The ongoing ALPHA (ALLO-501) and UNIVERSAL (ALLO-715) trials include patients (pts) with relapsed/refractory large B-cell or follicular lymphoma and multiple myeloma, respectively. The lymphodepletion regimen included ALLO-647 (39 mg [low dose, LD; n = 33], 60 mg [n = 12], or 90 mg [high dose, HD; n = 27]) with Flu 30 mg/m^2/d x 3d +/- Cy 300 mg/m^2/d x 3d (Flu+Cy, n = 66; Cy, n = 6) (ALLO-647/Flu +/- Cy) before CAR T infusion. A mixed-effects population pharmacokinetic (PK) model was fit to ALLO-647 concentration *vs.* time data. Pharmacodynamic (PD) effects on host T cells, IL15, and CAR T cell expansion were also studied. **Results:** As of the data cut, 72 pts were treated. Common Grade ≥3 AEs were neutropenia (71%), thrombocytopenia (42%), anemia (39%), and lymphopenia (28%). Neutrophil, hemoglobin, and platelet counts did not differ by ALLO-647 dose, suggesting these dim-$CD52^+$ cells were unaffected. Gr ≥3 infections were seen in 21% pts; 33 had infusion-related reactions (IRR; Gr 1: 13%; Gr 2: 32%; Gr 3: 1.4%). IRR incidence and severity were higher with HD ALLO-647. The optimal PK model included a saturable (concentration-dependent) elimination pathway; clearance varied as a function of baseline lymphocyte count (LC). Serum ALLO-647 levels increased with dose; median modelled Cmax was 4,224 and 14,139 ng/mL for LD and HD, respectively. With ALLO-647/Flu +/- Cy, all but 2 pts reached a LC nadir < 0.05×10^9 cells/L, typically by D-3. Duration of lymphodepletion was typically longer with HD ALLO-647. Median duration of T-cell suppression (< 10 cells/μl) was ~ 8.5 and 13.6 days from CAR T infusion, respectively, for LD and HD ALLO-647. With HD, T cell counts were < 10 through D+28 in 17 pts and > 10 in 2. In 68 evaluable pts, compared to LD, HD ALLO-647 was associated with higher D0 serum IL15 levels, which have been linked to improved clinical response (eg, Kochenderfer *JCO* 2017). Higher CAR T expansion was also observed post D+14 with HD ALLO-647 compared to LD, creating an opportunity for clinical response. **Conclusions:** ALLO-647/Flu +/- Cy had a tolerable safety profile and produced a deep and durable window of lymphocyte depletion. ALLO-647 exhibited target-mediated drug disposition; clearance increased with higher baseline LC. HD was associated with higher IL15 levels and better CAR T expansion, suggesting dose responses. Enrollment in both studies is ongoing; updated safety and PK/PD data will be presented. Clinical trial information: NCT04093596. Research Sponsor: Allogene Therapeutics.

2528 **Poster Session**

Novel CoupledCAR technology for treating colorectal cancer. *First Author: Lei Xiao, Innovative Cellular Therapeutics Co., Ltd, Shanghai, China*

Background: Chimeric antigen receptor (CAR) T cell therapy has made significant progress in the treatment of blood cancers such as leukemia, lymphoma, and myeloma. However, the therapy faces many challenges in treating solid tumors. These challenges include physical barriers, tumor microenvironment immunosuppression, tumor heterogeneity, target specificity, and limited expansion in vivo. **Methods:** We designed a CAR lentivirus vector that consisted of a humanized CD19-specific single-chain variable fragment (scFv), a 4-1BB costimulatory domain, and a CD3ζ signaling domain.The lentivirus was produced by transfecting HEK-293T cells with CAR lentiviral vectors and viral packaging plasmids. Patient's CD3 T cells was cultured in X-VIVO medium containing 125U/mL 1interleukin-2 (IL-2), and transduced with CAR lentivirus at certain MOI 24h after stimulated by anti-CD3/CD28 magnetic beads. Transduction efficiency was evaluated at 7 to 9 days after CAR lentivirus transduction, and quality controls for fungi, bacteria, mycoplasma, chlamydia, and endotoxin were performed. After infusion, serial peripheral blood samples were collected, and the expansion and the cytokine release of CART cells were detected by FACS and QPCR,respectively. The evaluation of response level for patients were performed at month 1,month 3,and month 6 by PET/CT. **Results:** We engineered CoupledCAR T cells with lentiviral vectors encoding an anti-GCC (guanylate cyclase 2C) CAR molecule. To verify the safety and efficacy of CoupledCAR-T cells for treating solid tumors, we conducted several clinical trials for different solid tumors, including seven patients with colorectal cancer. These seven patients failed multiple rounds of chemotherapy and radiotherapy. In the clinical trial, the metastatic colorectal cancer patients were infused with autologous anti-GCC CoupledCAR-T cells range from 4.9×10^5/kg to 2.9×10^6/kg. We observed that CoupledCAR-T cells expanded significantly in the patients and infiltrated tumor tissue sites, demonstrating enhanced anti-tumor activities. PET/CT showed significant tumor shrinkage and SUV max declined, and the ongoing responses were monitored. Patient 3 achieved complete response and the best overall response rate (ORR, include complete remission, complete metabolic response, and partial response.) was 57.1% (4/7), complete remission (CR) rate was 14.3% (1/7). **Conclusions:** In conclusion, the clinical data demonstrated that CoupledCAR-T cells effectively expanded, infiltrated tumor tissue sites, and kill tumor cells in patients with colorectal cancer. We used immunotherapy to achieve complete remission in patients with advanced colorectal cancer for the first time. We are recruiting more colorectal cancer patients to further test the safety and efficacy of anti-GCC CoupledCAR T cells. Since our CoupledCAR technology is a platform technology, we are expanding it to treat other solid tumors using different target tumor markers. Research Sponsor: N/A.

2529 **Poster Session**

First-in-human data of ALLO-501A, an allogeneic chimeric antigen receptor (CAR) T-cell therapy and ALLO-647 in relapsed/refractory large B-cell lymphoma (R/R LBCL): ALPHA2 study. *First Author: Frederick Lundry Locke, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Allogeneic CAR T cell therapy addresses logistical/manufacturing challenges inherent in autologous (auto) CAR T therapy. ALLO-501A, which uses Cellectis technologies, is an allogeneic anti-CD19 CAR T cell product whose a) disrupted TCRα gene may reduce GvHD risk, and b) edited CD52 gene may permit use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells. **Methods:** The ongoing ALPHA2 study is a single-arm, open-label, 2 phase study of ALLO-501A in non-HLA matched patients (pts) with R/R LBCL and ≥2 prior lines of therapy. Prior auto CD19 CAR T therapy is allowed if tumors remain $CD19^+$. Following lymphodepletion (LD) with ALLO-647 (60 mg or 90 mg), fludarabine 30 mg/m^2/d x 3d (Flu), and cyclophosphamide 300 mg/m^2/d x 3d (Cy), escalating doses of ALLO-501A (40 [DL1] or 120 [DL2] x 10^6 viable CAR T cells) were administered. Retreatment was allowed for PD or SD with suboptimal CAR T expansion. Pts who had ≥SD at D28 could receive a second dose in a consolidation cohort. Phase 1 assessed safety/tolerability and cell kinetics of escalating doses of ALLO-501A following LD. **Results:** By 1/15/21, 11/11 enrolled pts received ALLO-647 (60 mg: n=6; 90 mg: n=5). Mean duration from enrollment to start of therapy was 6 days. After LD, 1 and 9 pt(s) were treated with ALLO-501A at DL1 and DL2, respectively; 1 pt developed CNS lymphoma and was not treated. Of 10 pts treated, 1 pt received retreatment and 4 pts were enrolled in the consolidation cohort. Pts had a median age of 60 years; 8 were ≥ stage III at diagnosis, 5 had IPI scores ≥3, and 3 had baseline LDH > 2x ULN. Median number of prior therapies was 3 (range 2 – 7); 3 pts had received auto CD19 CAR T cell therapy. 4/8 evaluable pts had rapidly PD at study entry. Median FU was 1.7 months. No dose modifications were required and no pt experienced DLTs. The most common AEs were anemia, leukopenia, neutropenia and thrombocytopenia (73%); and lymphopenia (64%). No GvHD or ICANS were reported. CRS was seen in 2 (18%) pts, both Grade < 3. Infusion-related reactions, all grade <3, were observed in 4 (36%) pts. D28 response data are available for 8 pts: 1 died of PD before D28; 4 additional pts had PD, including 2 who progressed 2 and 3 mos. after auto CAR T; 1 had SD; and 2 (both DL2) had CR. Of those in CR, 1 had peak ALLO-501A expansion at D14, persistence until D42, and ongoing CR at 4 mo; 1, with a 4-mo response to prior auto CAR T, had peak expansion at D28 and remains in ongoing CR at D56 after ALLO-501A with pending persistence. **Conclusions:** This dose escalation cohort contained heavily pretreated, actively progressing pts, some of whom had failed auto CAR T. Preliminary data suggest an acceptable safety profile following ALLO-501A and ALLO-647 and early signs of efficacy in LBCL. Enrollment into the consolidation cohort is ongoing; updated clinical/biomarker data of resistance and clinical activity will be presented. Clinical trial information: NCT04416984. Research Sponsor: Allogene Therapeutics.

2530 **Poster Session**

CAR-T cells to deliver engineered peptide antigens and reprogram antigen specific T cell responses against solid tumors. *First Author: Daniel Y Lee, University of Pennsylvania, Philadelphia, PA*

Background: Neoantigen depleted malignancies such as colorectal cancer demonstrate primary resistance to immune checkpoint blockade, and solid tumors in general have shown resistance to chimeric antigen receptor (CAR) T cell therapy. However, CAR-T cells have been shown to be capable of delivering various therapeutic molecules in a targeted fashion to the tumor microenvironment, in some cases through extracellular vesicles (EVs). In vivo studies have shown that the presentation of foreign viral peptides by solid tumors can reprogram bystander virus-specific cytotoxic T cells (CTLs) against tumor cells. In this study, we demonstrate that CAR-T cells can deliver engineered peptide antigens to solid tumors, leading to presentation on tumor cells and anti-tumor response. **Methods:** Second generation CAR-T cells (41BB endodomain) targeting human CD19 (19BBz) or human mesothelin (M5BBz) were generated via retroviral and lentiviral transduction respectively. CAR-T cells were engineered to co-express peptides such as SIINFEKL of ovalbumin and NLVPMVATV of CMV pp65 among others. Peptides were isolated from EVs via ultracentrifugation. For in vivo studies, C57BL/6 or NSG mice were injected on the flank with relevant tumors and treated with peptide-CAR-T cells. In vitro studies utilized flow cytometry and xCELLigence killing assays. **Results:** Murine 19BBz CAR-T cells expressing the SIINFEKL peptide of ovalbumin (ova-19BBz) were found to transfer SIINFEKL peptide to tumor cells via EVs *in vitro* and *in vivo*, leading to peptide presentation on MHC-I of tumor cells. This resulted in significantly delayed tumor growth in tumor bearing mice transfused with OT-I T cells to mimic an existing antigen specific T cell pool. We expanded on these findings by isolating EVs from human M5BBz CAR-T cells expressing CMV viral peptides. Peptide-CAR-T EVs were co-cultured with human ovarian cancer cells to assess presentation to Jurkat T cells. Finally, we utilized primary human T cells from CMV+ healthy donors to assess the clinical feasibility of our peptide delivery approach. **Conclusions:** CAR-T cells can be engineered to deliver peptides to tumor cells for presentation and subsequent targeting by antigen specific CTLs. This represents a novel strategy for the treatment of non-immunogenic tumors. Research Sponsor: Mark Foundation for Cancer Research, Other Foundation, U.S. National Institutes of Health.

2531 **Poster Session**

A single-arm phase Ib study of autologous cytokine-induced killer (CIK) cell immunotherapy in combination with sintilimab plus chemotherapy in patients with advanced non-small cell lung cancer (NSCLC)-CCICC-002. *First Author: Xiubao Ren, Department of Biological Therapy, Tianjin Cancer Institute & Hospital, Tianjin, China*

Background: Immune checkpoint inhibitors plus chemotherapy had showed benefits for advanced non–small-cell lung cancer (NSCLC) patients without targetable mutations. Autologous cytokine-induced killer (CIK) cells can restore the antitumor immunity to improve patient outcome. Combining CIK cells with anti-PD-1 mAb plus chemotherapy may strengthen the results in patients with advanced NSCLC. **Methods:** This is a single-center, open-label, phase 1b trial of combination CIK cells with sintilimab (anti-PD-1 mAb) plus chemotherapy in stage IIIB-IV NSCLC patients. Systemic therapy naïve patients received platinum-based doublet chemotherapy, sintilimab, and CIK cells every 3 weeks for 4 cycles，then sintilimab, and CIK cells for maintenance therapy until disease progression or unacceptable toxicity. **Results:** From May 2019 to Jan 2021, 34 patients (19 squamous，15 non-squamous NCSLC)aged 46-73 years (median age 64 years) were enrolled. Among 32 evaluable patients, the ORR was 81.3% (73.7% in squamous and 92.3% in non-squamous NSCLC)and DCR was 100%. Among the 25 PR assessed by RECIST, CMR was demonstrated in 5 (23.1%) by PET-CT. Among 3 patients with brain metastases, 2 patients achieve intracranial CR, and 1 was PR. With a median follow-up of 7.5 months, the median DOR was not reached (range 0.5m-NA), and the median PFS and OS were not mature. Grade 3 or more TRAEs included pneumonia (n = 3); thrombocytopenia, leukopenia (n = 2 each); anemia, dysphagia, cardiomyopathy, rash (n = 1 each). Biomarkers and subgroups which correlated with efficacy and AEs are being analyzed included TMB, PDL1 expression, distribution of TILs, cytokines and so on. **Conclusions:** CIK cells therapy in combination with sintilimab plus chemotherapy were well tolerated and showed encouraging efficacy. Further studies are warranted to confirm these preliminary results. Research Sponsor: Tianjin Medical University Cancer Institute and Hospital. Clinical trial information: NCT03987867. Research Sponsor: National Key Technologies R&D Program of China grant Awards No. 2015BAI12B12 and 2018YFC1313400.

	All pts (n=32)	Squamous NCSLC (n=19)	Non-Squamous- NCSLC (n=13)
MCR, n (%)	5 (15.6%)	2 (10.5%)	3 (23.1%)
PR, n (%)	21 (65.6%)	12 (63.2%)	9 (69.2%)
SD, n (%)	6 (18.8%)	5 (26.3%)	1 (7.7%)
ORR：% (95%CI)	81.3% (67%-95.5%)	73.7% (51.9%-95.5%)	92.3% (75.5%-109.1%)
PFS at 6 month	84.4% (70.4%-98.6%)	81.2% (61.8%-100.6%)	90% (71.4%-108.6%)

2532 **Poster Session**

A phase I-IIa study of genetically modified Tie-2 expressing monocytes in patients with glioblastoma multiforme (TEM-GBM Study). *First Author: Gaetano Finocchiaro, Neuro-Oncology Unit-IRCCS San Raffaele Scientific Institute, Milan, Italy*

Background: Genetically modified cell-based therapies are relevant in immuno-oncology due to their potential for tumor specificity & potential durability. We developed a cell-based treatment, Temferon, relying on ex-vivo transduction of autologous HSPCs to express therapeutic payloads within the tumor microenvironment. Temferon targets IFNa to Tie-2 expressing macrophages (TEMs). **Methods:** TEM-GBM is an open-label, Phase I/IIa dose-escalation study evaluating safety & efficacy of Temferon in up to 21 newly diagnosed patients with glioblastoma & unmethylated MGMT promoter. Autologous HSPCs are transduced ex-vivo with a lentiviral vector encoding for IFNa. The transgene expression is confined to TEMs due to the Tie2 promoter & the post-transcriptional regulation by miRNA-126. **Results:** As of January 17 2021, 15 patients have been enrolled; 9 received Temferon (D+0) with follow-up of 61 – 559 days. There was rapid engraftment & hematological recovery after the conditioning regimen. Median neutrophil & platelet engraftment occurred at D+13 & D+12, respectively. Temferon-derived differentiated cells, as determined by the presence of vector genomes in the DNA of peripheral blood & bone marrow cells, were found within 14 days post treatment & persisted subsequently, albeit at lower levels (up to 18 months). We also detected very low concentrations of IFNa in the plasma (median 5pg/ml at D+30; baseline $<$ LLOQ) & in the cerebrospinal fluid, suggesting tight regulation of transgene expression. Three deaths occurred: two at D+343 & +402 after Temferon administration due to disease progression, & one at D+60 due to complications following the conditioning regimen. Seven patients had progressive disease (PD; range D+27-239) as expected for this tumor type. SAEs include infections, venous thromboembolism, brain abscess, hemiparesis, GGT elevation & poor performance status compatible with autologous stem cell transplantation, concomitant medications & PD. Four patients underwent second surgery. These recurrent tumors had gene-marked cells present & increased expression of IFN-responsive gene signatures compared to diagnosis, indicative of local IFNa release by TEMs. In one patient a stable lesion (as defined by MRI) had a higher proportion of T cells & TEMs within the myeloid infiltrate & an increased IFN-response signature than in a progressing lesion. The T-cell immune repertoire changed with evidence for expansion of tumor-associated clones. Tumor microenvironment characterization by scRNA & TCR sequencing is ongoing. **Conclusions:** Our interim results show that Temferon is well tolerated by patients, with no dose limiting toxicities identified to date. The results provide initial evidence of Temferon potential to modulate the TME of GBM patients, as predicted by preclinical studies. Clinical trial information: NCT03866109. Research Sponsor: Genenta Science.

2533 **Poster Session**

In-depth immune and molecular profiling of melanoma patients receiving adoptive T-cell therapy reveals biomarkers of efficacy in ATATIL study. *First Author: Angela Orcurto, Department of Oncology, Ludwig Institute for Cancer Research Lausanne, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland*

Background: Adoptive cell therapy (ACT) using tumor-infiltrating lymphocytes (TIL) has demonstrated a curative potential for patients with metastatic melanoma (MM). Nevertheless, activity remains unsatisfactory in many patients, requiring development of biomarkers that predict therapeutic efficacy. We report results of a single-center phase I study to assess feasibility, safety and efficacy of TIL-ACT in MM patients (NCT03475134). **Methods:** Patients with MM refractory to at least one prior line of therapy received TIL therapy with lymphodepleting chemotherapy before T-cell infusion, followed by high-dose interleukin-2. RDG- and FDG-PET imaging was performed before and after TIL infusion. Multispectral immuno-fluorescence (mIF) imaging and bulk-RNA sequencing (Seq) were performed on tumor samples pre-ACT and post-ACT (day+30 and upon progression). Single-cell RNA-Seq and TCR-Seq were performed on pre-ACT tumor and ACT product, as well as on tumor-reactive and neoantigen-specific TILs and on longitudinal blood samples. **Results:** As of 02/02/2021, thirteen patients (enrolled between March 2018 and December 2020) have successfully completed TIL-ACT therapy, with a median follow-up of 9.5 months (IQR 3.0 -24.6). Median age was 53 years (range 20-69) and all were previously treated with PD-1 based blockade. Median number of TILs infused was 55.0 x10^9 cells (range 12.8-84.7). The best overall response rate by RECIST 1.1 and disease control rate in evaluable patients was 41.7% (5/12) and 50% (6/12) respectively at 3 months. Two patients have an ongoing near-complete response at 3 years. Up to data cut-off, 10 patients have progressed by RECIST v1.1, with median PFS of 4.8 months (95% CI 1.5 - 9.6), while median OS is not reached. mIF revealed biomarkers of response, which may allow proper identification of patients in subsequent studies. In addition, deep sequencing of bulk and neoepitope-specific TIL clonotypes highlighted transcriptomic signatures revealing cell programs regulating *in vitro* expansion, *in vivo* blood persistence as well as tumor infiltration post-ACT. RGD-PET data will also be presented. **Conclusions:** We demonstrate reproducibility of TIL-ACT in our center, consistently with previous reports. Comprehensive translational studies reveal immune correlates of clinical responses that contribute to the understanding of mechanisms of TIL potency and will guide the development of next-generation cell products. Clinical trial information: NCT03475134. Research Sponsor: Ludwig Institute for Cancer Research, Canton de Vaud, and BMS.

2534 **Poster Session**

PSMA targeted armored chimeric antigen receptor (CAR) T-cells in patients with advanced mCRPC: A phase I experience. *First Author: Matthew H. Carabasi, Thomas Jefferson University, Philadelphia, PA*

Background: CART-PSMA-TGFβRDN cells are autologous T cells engineered via lentiviral transduction to express a dominant negative form of TGFβRII (TGFβRDN) and a chimeric antigen receptor (CAR) with specificity to prostate specific membrane antigen (PSMA). The TGFβRDN renders CAR T cells resistant to TGFβ-mediated immunosuppression. CART-PSMA-02 is a multi-center, open-label, Phase 1 study evaluating the safety and feasibility of dosing patients with metastatic castration resistant prostate cancer (mCRPC) with CART-PSMA-TGFβRDN (NCT04227275). **Methods:** This is a 3+3 dose escalation study to determine the recommended phase 2 dose and schedule of CART-PSMA-TGFβRDN cells following lymphodepleting chemotherapy with cyclophosphamide and fludarabine. Single and fractionated doses are being evaluated. A cohort expansion will enroll patients to further explore the safety of the selected dose and schedule. **Results:** As of January 2021, 6 patients (pts) have been treated. Two pts were treated in the first dose level (1-3 x10^7 transduced T cells (TDN)). Four pts were treated in the second dose level (1-3 x 10^8 TDN with fractionated dosing). AEs occurring in $\geq$50 % of pts included cytokine release syndrome (CRS), anemia, thrombocytopenia, increased creatinine, nausea, fatigue, pyrexia and dehydration. No DLTs occurred in the 1st dose level. Four pts in the 2nd dose level developed CRS (3 Gr 1 and 1 Gr 2). One pt developed rapid G2 CRS that progressed to Gr 5 encephalopathy and Gr 5 multi-organ failure. Ferritin levels peaked at 56,974 ng/ml (baseline 2,903 ng/mL) despite aggressive immunosuppressive therapy including tocilizumab, dexamtheasone and anakinra. The post infusion cytokine profile indicated elevations in IL-1RA, TNF-alpha, VEGF, IL-10, MIP-1b, IFN-gamma, GM-CSF and notably lower levels of IL6 compared to published reports of CD19 CART-mediated CRS. Autopsy findings were consistent with HLH/MAS, confirming overactivity of the monocyte/macrophage compartment. Based on these observations, a modified immune toxicity management strategy that includes prophylactic anakinra (an IL1R antagonist) was instituted. Preliminary evidence of clinical activity of CART-PSMA-TGFβRDN was noted in the 2nd dose level. Two of 3 pts with 1 month follow-up demonstrated PSA decreases from baseline (1 with $>$95% decrease, 1 with $>$50% decrease). Both pts had stable disease per RECIST v1.1. A third pt with only 1 week follow-up had a 40% PSA decrease. Additional data analyses from all infused patients are ongoing and data from pts managed with modified immune toxicity management will be presented. **Conclusions:** Initial data indicates a unique immune toxicity profile and the potential for anti-tumor activity in mCRPC pts treated with CART-PSMA-TGFβRDN. Modified immune toxicity management could lead to identification of a manageable safety profile and therapeutically active dose. Clinical trial information: NCT04227275. Research Sponsor: Tmunity Therapeutics, Inc.

2535 **Poster Session**

A single-arm phase Ib study of multiple target cytotoxic T-lymphocyte (MCTL) in combination with toripalimab as second-line therapy in advanced non-small cell lung cancer (NSCLC). *First Author: Xiubao Ren, Department of Biological Therapy, Tianjin Cancer Institute & Hospital, Tianjin, China*

Background: Anti-PD-1/ PD-L1 (programmed cell-death 1) mAb treatment has been approved in the US and in Europe as second-line treatment for advanced NSCLC because of the good tolerance and efficacy in comparison with docetaxel. Unfortunately, The objective response rate is only around 20%. Multiple Target Cytotoxic T-lymphocyte (MCTL) cells can restore the antitumor immunity to improve patient outcome. Combining MCTL cells with anti-PD-1 mAb may strengthen the results as second-line treatment in patients with advanced NSCLC. (NCT04193098). **Methods:** This is a single-center, open-label, phase 1b trial of combination MCTL cells with toripalimab (anti-PD-1 mAb)as second-line treatment for advanced NSCLC. Systemic therapy patients received toripalimab every 3 weeks for 12 cycles and received MCTL cells every 3 weeks for 9 cycles, then toripalimab and MCTL cells for maintenance therapy until disease progression or unacceptable toxicity. **Results:** From June 2019 to October 2020, 14 pts aged 43-70 years (median age 59 years) were enrolled. The squamous/non-squamous ratio was 50%/50%. 8 (57.1%) were men, 13(92.8%) were ECOG PS=0-1, 5 (35.7%) had pleural effusion, and 3 (21.4%) had bone metastases. Among 13 evaluable pts, the ORR and DCR were 38.4% and 71.4%, At the time of data cutoff, the median DOR was not reached (range 8.25m-NA), the median PFS was 399 days (range 192d-NA), and the median OS were not mature. Adverse events (AEs) occurred in 5 (38.4%), No grade$\geq$3 AEs events occurred. Immune-related AEs were thyroid hypofunction (3, 23%) and weak (2, 15.4%). Biomarkers which correlated with efficacy and AEs are being analyzed. **Conclusions:** Multiple Target Cytotoxic T-lymphocyte (MCTL) in combination with toripalimab as second-line treatment for advanced NSCLC because of the well tolerated and encouraging efficacy. Further studies are warranted to confirm these results. Research Sponsor: Tianjin Medical University Cancer Institute and Hospital. Clinical trial information: NCT04193098. Research Sponsor: National Natural Science Foundation of China grants Awards No. U20A20375.

2536 **Poster Session**

Initial results of a first-in-human, dose escalation study of a cell-based vaccine in HLA A*02+ patients (pts) with recurrent, locally advanced or metastatic HPV16+ solid tumors: SQZ-PBMC-HPV-101. *First Author: Antonio Jimeno, University of Colorado Comprehensive Cancer Center, Aurora, CO*

Background: Ineffective MHC-I presentation of tumor antigens to CD8+ T cells limits T cell activation and the efficacy of cancer vaccines. The Cell Squeeze technology drives peripheral blood mononuclear cells (PBMCs) through a microfluidic chip leading to temporary cell membrane disruption and delivery of HPV16 E6 and E7 antigens cytosolically. These antigen presenting cells (APC) were matured with CpG7909 and were not genetically modified. Preclinically, this approach showed improvement in MHC-I presentation for human and murine cells. In murine tumor studies, m-SQZ-PBMC-HPV elicited robust CD8+ T cell responses and improved anti-tumor effects when compared to other vaccine modalities. **Methods:** SQZ-PBMC-HPV-101 included pts with incurable HPV16+ cancers progressing after unlimited prior therapy, ECOG 0-1, adequate organ function and a biopsiable lesion. After leukapheresis at the study site, manufacturing of the cryopreserved product took $<$ 24 hours with a vein-to-vein time of approx. 1 week. Out-patient SQZ-PBMC-HPV was given IV q 3 weeks without a conditioning regimen. Double antigen priming (DP) was introduced with Cohort 3 and occurred on Cycle 1 Days 1 and 2. Maximum treatment duration for each patient was determined by the cell batch size. Response was assessed via RECIST 1.1 and iRECIST. Investigational biomarkers were measured pre- and post-treatment. **Results:** 12 pts [anal (7), head and neck (3), and cervical (2)] were dosed in 3 cohorts (3 pts in 0.5 x10e6/kg, 5 pts in 2.5 x10e6/kg, and 4 pts in 2.5x 10e6/kg [DP]). Median lines of prior Tx were 4 (range 1 - 7) and all but one pt were pretreated with checkpoint inhibitors (CPI); 10 pts had liver or lung metastases. All batches of SQZ-PBMC-HPV demonstrated CD8 activation in vitro after thawing, and batch size did not limit therapy duration at dose levels tested to date. Median number of doses were 3 (3 - 10), 3 (2 - 4), and 3 (3 – 4) in the 3 cohorts, respectively. One pt (10 doses) remained on study for 42 weeks. Tx was well-tolerated and there were no DLTs, Grade (G) $>$3 related SAEs or related G $>$3 AEs. One pt in cohort 1 experienced both a G2 infusion-related reaction and cytokine release syndrome. One pt in cohort 2 was not evaluable for DLT. Four out of 10 evaluable pts had stable disease per RECIST 1.1 as the best response. Preliminary tumor analyses pre- and post-therapy indicated increased immune activity in some patients after SQZ infusion. **Conclusions:** SQZ-PBMC-HPV-101 demonstrated clinical feasibility of the Cell Squeeze technology and favorable tolerability of engineered APCs. The study allows for the characterization of the immunogenicity of engineered APCs in humans. Preliminary results warrant the testing in combination with CPI. Efficacy, safety, and correlative biomarker data will be presented, from pre- and post-therapy biopsies and blood samples. Clinical trial information: NCT04084951. Research Sponsor: SQZ Biotechnologies.

2537 **Poster Session**

Anakinra (AKR) prophylaxis (ppx) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) receiving orvacabtagene autoleucel (orva-cel). *First Author: Luciano J. Costa, University of Alabama at Birmingham, Birmingham, AL*

Background: Orva-cel is a B-cell maturation antigen–targeted chimeric antigen receptor (CAR) T cell therapy being evaluated in the phase 1/2 EVOLVE study (NCT03430011) in pts with RRMM who had at least 3 prior lines of therapy (Tx). We previously reported safety and efficacy in the phase 1 study and established the recommended dose (RD) of orva-cel as 600 $\times$ 10^6 CAR^+ T cells (Mailankody et al, ASCO 2020). Cytokine release syndrome (CRS), a dominant toxicity of CAR T cell therapy, is mediated in part by IL-1. We explore the role of ppx with AKR, an IL-1 signaling inhibitor, on reducing the incidence of grade (G) $\geq$2 CRS after orva-cel treatment at the RD. **Methods:** Fourteen pts were enrolled sequentially for AKR ppx and treated with orva-cel at the RD. The non-AKR ppx control group comprised the remainder of the phase 1 pts receiving orva-cel at the RD (n = 19). The median follow-up (range) was 3.0 mo (1.8–6.2) for the AKR ppx group and 8.8 mo (5.3–12.2) for the non-AKR ppx group. AKR was administered as 100 mg SC the night before orva-cel infusion, 3 h before the infusion (Day 1), and q24 h on Days 2–5. Dosing was increased to q12 h if CRS developed. CRS was graded by Lee (2014) criteria. Tocilizumab (T) and steroids (S) were used per protocol-specified treatment management guidelines. **Results:** Disease characteristics and outcomes are shown in the table. In AKR ppx and non-AKR ppx groups, median number of prior regimens was 6 and 5, and bridging Tx was used in 57% and 68% of pts, respectively. The total frequency of CRS was similar in the 2 groups, but with less G 2 in the AKR ppx pts; relative risk (95% CI) = 0.54 (0.21, 1.38). No G $\geq$3 CRS was seen in either group. The incidence of neurological events (NE), G $\geq$3 infection, and macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH) was similar. T and S use was numerically lower with AKR ppx. Orva-cel expansion kinetics were similar in the 2 groups. All pts had a 2-month efficacy assessment, with ORR in 100% of AKR ppx and 95% of non–AKR ppx pts. **Conclusions:** In this nonrandomized evaluation of AKR ppx with orva-cel treatment, the incidence of G $\geq$2 CRS was lower in pts receiving AKR ppx. The use of AKR ppx produced no adverse effect on the incidence of NE, infection, or MAS/HLH, nor on orva-cel expansion or disease response. These results warrant further study of AKR ppx in CAR T cell therapy. Clinical trial information: NCT03430011. Research Sponsor: Bristol-Myers Squibb Company.

Disease characteristics and safety outcomes in the phase 1 EVOLVE study.

	AKR ppx, n = 14	Non–AKR ppx, n = 19
International staging system, stage I / II / III, %	43 / 36 / 21	47 / 37 / 16
Measurable serum and/or urine M-protein, n (%)	13 (93)	14 (74)
LDH >ULN, n (%)	3 (21)	0 (0)
CRS, G 1 / G 2 / G $\geq$3, %	64 / 29 / 0	37 / 53 / 0
CRS time to onset / duration, median (range), days	2 (1–11) / 3 (2–8)	2 (1–2) / 3 (1–7)
NE, G 1 / G 2 / G $\geq$3, %	7 / 7 / 7	5 / 5 / 0
Infection, G 1 / G 2 / G $\geq$3, %	0 / 0 / 14	16 / 11 / 11
MAS/HLH, G 1 / G 2 / G $\geq$3, %	0 / 7 / 0	5 / 0 / 5
Any T / multiple T / any S / T + S, %	79 / 29 / 43 / 43	90 / 37 / 63 / 63

2538 **Poster Session**

Preliminary analysis of a phase 1/2 study of NEXI-001 donor-derived multi-antigen-specific $CD8^+$ T-cells for the treatment of relapsed acute myeloid leukemia (AML) after allogeneic hematopoietic cell transplantation (HCT). *First Author: Monzr Al Malki, City of Hope Medical Center, Duarte, CA*

Background: Allogeneic HCT is a potentially curative therapy for many patients with AML that relies on a graft-versus-leukemia (GvL) effect. Patients who relapse after allogeneic HCT have a poor prognosis and few treatment options. Donor lymphocyte infusion (DLI) can achieve a GvL effect in some patients, however, efficacy is frequently associated with the development graft-versus-host disease (GVHD). There is a substantial need for treatment approaches that enhance the benefit of GVL while decoupling toxicities associated with GVHD. **Methods:** We report ongoing results from a first-in-human study (NCT04284228) of a non-genetically engineered, donor-derived adoptive cellular therapy product, NEXI-001, which contains multiple populations of $CD8^+$ T cells that recognize different HLA 02.01-restricted peptides from the WT1, PRAME, and Cyclin A1 antigens. NEXI-001 contains T cell memory subtypes that combine anti-tumor potency with long-term persistence. **Results:** At the time of this analysis, 7 patients with relapsed AML after allogeneic HCT were enrolled. Five Patients were treated with single infusions of NEXI-001 at three different dose levels: 50, 100 and 200 million. Currently, the median follow-up is 5 months. Significantly, GVHD, cytokine release syndrome, neurotoxicity, or NEXI-001-related adverse events were not observed. NEXI-001 treatment resulted in reductions in red blood cell and platelet transfusions and increased donor chimerism. Decreases in myeloblasts in bone marrow and peripheral blood and reduction in the size of an extramedullary myeloid sarcoma were suggestive of an anti-leukemia effect (Table). Correlative studies indicate that NEXI-001 $CD8^+$ cells undergo a rapid proliferation after infusion and are also associated with a robust hostlymphocyte recovery that occurs as quickly Day 3 after infusion. NEXI-001 infused $CD8^+$T cells are detectable by multimer staining in peripheral blood of patients and proliferate over time. TCR sequencing analyses determined that infused NEXI-001 cells contain T cell clones that were undetectable in the peripheral blood of patients at baseline but were detected in blood and bone marrow and persist over time. **Conclusions:** NEXI-001 has the potential to enhance GvL effect without the associated toxicities of GVHD, cytokine release syndrome, and neurotoxicity. Due to these encouraging results, the trial will proceed with an evaluation of repeated NEXI-001 dosing Clinical trial information: NCT04284228. Research Sponsor: NexImmune Inc.

Pt	NEXI-001 Dose	SAE	Initial Clinical Response
1	50m	No	Stable BM blasts Decreased need for transfusions Increased ANC Improved donor chimerism
2	100m	No	Stable BM blasts 18% reduction in size of myeloid sarcoma
3	100m	No	No response
4	100m	No	Stable BM blasts Decrease in PB blasts Decreased need for transfusions Increased ANC
5	200m	No	Stable BM blasts

2539 **Poster Session**

Progression prediction model for solid tumors with clinical and immunological parameters. *First Author: Aleksei Viktorovich Novik, N.N. Petrov National Medical Research Center of Oncology, Saint-Petersburg, Russian Federation*

Background: The immune system has well-known relation to tumor progression. Numerous immune-related parameters exist, but only a minor part could be used as biomarkers, especially dynamic ones. We trained a progression prediction model based on clinical features and peripheral immune system assessments. **Methods:** Patients with immunogenic (melanoma, 295, kidney cancer, 81), non-immunogenic (soft tissue sarcoma, 47, colorectal cancer, 26) and multiple primary tumors (29) with immunologic assessments before treatment (23.5%), on therapy (58.3), and in follow-up after the treatment (18.2%) were randomly divided in 7:3 ratio to the training and test groups. Counts of lymphocytes, T-, B, NK cells, cytotoxic lymphocytes, T-helpers were used as immunologic parameters. Age, sex, disease, stage, therapy, mutational status, last response on treatment, disease and therapy duration, previous treatments were used as clinical ones. The model was trained to predict disease progression in the next three months using "Catboost" gradient boosting. We used ROC AUC to test model performance and Yoden's index for optimal cutoff calculation. We also studied the influence of model prediction on overall survival (OS) and time to progression (TTP) on the test dataset using the Kaplan-Meyer method and Cox regression. **Results:** We used 1682 assessments of immune parameters (immune status, IS) done in 354 patients (average 5 per patient) to train the model and 616 IS in 124 patients for validation. All IS of one patient were in the same group. The ROC AUC value of the model was 0.801. The model prediction of progression increased the probability of progressive disease from 37.5 to 62% and decreased the response rate from 37,5% to 8.4% (p = 0.016). The model prediction did not add information over known prognostic factors for OS in the multifactorial model but was an independent prognostic factor for TTP (HR 2.204, p = 0.011). False-positive results separate the group of patients with poor prognosis (OS 16 months, TTP 6 months) among patients with clinical benefit from patients with favorable prognosis (OS 61 months, TTP 18 months, $p < 0.001$), who had a truly negative model prediction. The possibility of prognosis improvement with therapy change was an essential factor for OS and TTP prediction ($p < 0.001$). The model was useful in predicting higher OS in patients with disease progression (p = 0.033) and shorter response duration in patients with clinical benefit (p = 0.03). **Conclusions:** Our progression prediction model provides clinically useful information and can be used for decision making in several clinical situations. Its utility should be tested in a prospective trial. Research Sponsor: None.

2540 **Poster Session**

Concordance of blood and tissue TMB from NGS testing in real-world settings and their ability to predict response to immunotherapy. *First Author: Emma Sturgill, Sarah Cannon Research Institute, Nashville, TN*

Background: Tumor mutational burden (TMB) detected by tissue-based Next Generation Sequencing (NGS) is a biomarker for immunotherapy (IO) response. Plasma-based NGS vendors have developed methods for quantifying TMB from circulating tumor DNA; however, the concordance of blood-TMB (bTMB) and tissue-TMB (tTMB) in real-world settings has not been examined. In this study, we analyzed paired bTMB-tTMB values from cancer patients in community oncology clinics who underwent both plasma- and tissue-based NGS testing to determine whether bTMB predicts response to IO equal to tTMB. **Methods:** We analyzed 112 patient-matched bTMB-tTMB pairs from 102 unique patients in community oncology settings who received both plasma- and tissue-based NGS profiling at any point in care. NGS results were reported by Foundation Medicine (n = 28 plasma, n = 66 tissue), Guardant Health (n = 78 plasma), and Caris Life Sciences (n = 42 tissue). NGS results were linked with electronic medical records in Genospace, Sarah Cannon's precision medicine platform. Pearson's correlation (r) and Lin's concordance (ρ) coefficients were used for statistical analysis. **Results:** bTMB exceeded the patient-matched tTMB by an average 2.4-fold; therefore, while the two values showed a positive linear correlation (r^2= 0.62, p = 0.01e-27) their concordance was only moderate (ρ = 0.58, n = 112). Gastrointestinal cancers exhibited the lowest correlation (r^2= 0.01, p = 0.5) and concordance (ρ = 0.03, n = 35). The discordance between bTMB and tTMB was not an outcome of the specimens being collected on different dates, as the bTMB/tTMB ratio did not correlate with the time between plasma and tissue specimen collection (r^2= 0.003, p = 0.84, n = 112). While a majority of bTMB-tTMB pairs had agreement in high *vs.* low status (High ≥ 10 mut/Mb; Low < 10 mut/Mb), a considerable portion were bTMB-High/tTMB-Low (see table). Strikingly, the bTMB-High/tTMB-Low patients who received IO had an average time to treatment failure (TTF) that surpassed that of the bTMB-High/tTMB-High cohort (see table). Considering bTMB alone, patients with a high status outperformed those with a low status on IO (bTMB-High: TTF = 200 days, n = 21; bTMB-Low: TTF = 125 days, n = 12). **Conclusions:** In real-world settings where tissue- and plasma-based NGS panels are ordered as standard of care, bTMB values are consistently higher than tTMB values. This discrepancy leads to plasma-based tests resulting a TMB-High designation more frequently than tissue-based NGS tests. Patients who are TMB-High by plasma perform relatively well on IO, indicating that bTMB may be a particularly effective biomarker of IO sensitivity. Research Sponsor: None.

	tTMB-High	tTMB-Low
bTMB-High	n = 19 (17%) TTF = 183 days (n = 13)	n = 34 (30%) TTF = 227 days (n = 8)
bTMB-Low	n = 5 (5%) TTF = N/A	n = 54 (48%) TTF = 125 days (n = 12)

2541 **Poster Session**

Genomic immunotherapy (IO) biomarkers detected on comprehensive genomic profiling (CGP) of tissue and circulating tumor DNA (ctDNA). *First Author: Takayuki Yoshino, National Cancer Center Hospital East, Kashiwa, Japan*

Background: The dramatic impact of IO on treatment outcomes has heightened interest in predictive biomarkers, including genomic markers such as tumor mutational burden (TMB) and microsatellite instability (MSI). The recent FDA approval of pembrolizumab for previously treated advanced solid tumors with elevated TMB (≥10 mut/Mb on FoundationOne CDx, F1CDx) now requires a better understanding of the prevalence of this and other IO biomarkers detected on CGP, including differences between TMB detected in tissue and mutational burden detected in blood (bTMB). **Methods:** Tissue and plasma biopsies were profiled with two CGP panels of 324 genes with 0.8 Mb genome coverage (F1CDx and FoundationOne LiquidCDx). Mutational burden was calculated by counting somatic variants (single nucleotide and indels, including synonymous variants, excluding germline and driver mutations) with variant allele frequency (VAF) ≥5% in tissue (TMB) or ≥0.5% in ctDNA (bTMB). MSI score was assessed using 95 repetitive loci and principal component analysis (tissue) or >1,800 repetitive loci (plasma). ctDNA levels were estimated using composite tumor fraction (cTF), a metric based on aneuploidy and VAF. **Results:** Pan-cancer, TMB ≥10 was detected in 19% of tissue cases (29,238/156,294) and was common in melanoma (53%), small cell (41%), NSCLC (40%), bladder (39%), and endometrial (24%). bTMB ≥10 was detected in 13% of liquid biopsies (806/6,295); prevalence by cancer type was correlated with prevalence of elevated TMB (r = 0.81). Samples with bTMB ≥10 had an elevated cTF (median 13%, IQR 5 - 31%) as compared to samples with bTMB <10 (median 1.8%, IQR 0.6 - 7%, p < 0.001). Among 353 cases with both tissue and liquid CGP results (median 11 months apart), the relative prevalence of TMB ≥10 (12%) and bTMB ≥10 (13%) were similar, with concordant detection in 303 cases (86%). MSI-high (MSI-H) was seen in 2.2% of tissue CGP (3,461/156,294), most often in endometrial (19%), stomach (6.0%), and colorectal (5.3%) cancers, while MSI-H was detected in 0.68% of ctDNA specimens (43/6,295), which were also those with elevated cTF (median 11%, IQR 7 - 23%). Of 3,504 cases with MSI-H signature on tissue or liquid CGP, 1,619 (46%) had a pathogenic mutation detected in *MLH1/MSH2/MSH6/PMS2* (15% predicted germline). *CD274* amplification was detected in 1,207 cases (0.77%) of tissue CGP and 11 cases (0.17%) in ctDNA. **Conclusions:** Elevated bTMB is overall less prevalent than elevated tissue TMB, though these biomarkers are detected in similar cancer types. Detection of bTMB ≥10 and MSI-H in liquid biopsy was associated with elevated ctDNA levels, suggesting a limit of detection, and potentially indicating a more aggressive biology in samples positive for these biomarkers. Further investigation is needed to understand the utility of bTMB for identifying high TMB tumors that may benefit from IO. Research Sponsor: Foundation Medicine.

2542 **Poster Session**

Impact of circulating tumor DNA (ctDNA) detection on survival outcomes of patients (pts) treated with immune-checkpoint inhibitors (ICIs) in early clinical trials. *First Author: Vladimir Galvao, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: Detection of ctDNA is a promising tool for managing pts in oncology. Most methods require whole-genome sequencing of tumor samples followed by the design of personalized panels for tracking purposes. In this work, we evaluated the prognostic and predictive value of total ctDNA quantification, using shallow whole-genome sequencing (shWGS) exclusively from plasma samples, in a prospective cohort of pts treated with ICIs in early clinical trials. **Methods:** IchorCNA pipeline was used to quantify ctDNA of shWGS from plasma ctDNA samples of pts treated with ICIs in phase 1 trials, collected at baseline and prior to cycle 2 (prec2). We investigated the association and correlation of ctDNA levels with surrogate markers for tumor burden (LDH levels, summatory of target lesions (TL), liver metastasis) using Spearman and Kruskal-Wallis tests. Kaplan-Meier estimates of overall survival (OS) of pts with baseline detectable ctDNA levels versus undetectable ctDNA were calculated. A multivariate Cox proportional hazards model, including continuous classical prognostic factors (LDH, albumin, hemoglobin, derived Neutrophil-to-Lymphocyte ratio (dNLR), platelets, number of metastases sites, ECOG PS) and ctDNA was performed. An estimate of progression free survival (PFS) of pts with ctDNA increase levels in preC2 versus a non-increase group was evaluated. **Results:** Since January 2018, 113 pts with no standard-treatment options were included. Median (m) follow up was 14.8 months (mo). Baseline ctDNA levels correlated significantly with baseline TL (R = 0.4, p < 0.001) and LDH levels (R = 0.61, p < 0.001). Pts with liver metastasis had higher levels of ctDNA (11,68 ng/ml) versus pts with no liver disease (2,31 ng/ml) (p < 0,001). In the survival analysis pts with detectable baseline ctDNA (74 pts) had significantly shorter OS compared with pts with undetectable ctDNA (39 pts); median 9.6 m (8.4 – 16.4) and NA m (13.6-NA), respectively (HR = 2.25 [1.18-4.29] p < 0.01). In the multivariate analysis, only ctDNA and albumin levels maintained the impact in OS (HR = 1.03, p < 0.05 and HR = 0.22, p < 0.05, respectively). Pts with early increases in ctDNA had a shorter PFS compared with those with a stabilization or decrease, median 1.9 m (1.6 – 4.0) and 3.0 m (2.6 – 3.8), respectively (HR = 2.19 [1.31-3.67], p < 0.01). **Conclusions:** Quantification of baseline ctDNA using shWGS is a strong independent prognostic factor. Early dynamic changes of ctDNA could be a useful tool to predict PFS outcomes. Research Sponsor: Swiss Bridge Award and BBVA Foundation.

2543 **Poster Session**

Analysis of immune checkpoint blockade biomarkers in elderly patients using large-scale cancer genomics data. *First Author: Rossin Erbe, Johns Hopkins School of Medicine, Baltimore, MD*

Background: Immune checkpoint blockade (ICB) immunotherapy in some cases elicits striking patient responses, but its efficacy appears to be dependent on several incompletely understood factors. Most studies of ICB therapies in elderly patients have concluded that they received no reduced benefit or even increased benefit compared to the younger patients analyzed, despite the systemic age-related immune changes that might be expected to produce a less effective immune response, such as loss of the capacity to generate new naive T cells. To understand and apply these results, it is necessary to investigate the relationship of age and the immune tumor microenvironment. **Methods:** We apply bioinformatics methods to genomic, transcriptomic, and clinical data from 9,523 patients across 31 cancer types from TCGA, 15,557 patients with breast, colon, or head and neck cancers from Caris Life Sciences, and 37,961 patients across 8 cancer types collected by GENIE. From these data we apply multivariate linear models across and within individual tumor types to estimate age-related associations to tumor mutational burden (TMB), T cell receptor diversity (miTCR), differential gene expression (edgeR), pathway enrichment (mSigDB and fgsea), and immune cell type infiltration (Quantiseq and MIXTURE). **Results:** Our analysis of large-scale molecular and clinical databases associates patient age with changes in several major biomarkers of ICB response. Notably, a robust correlation between increased tumor mutational burden and age was found across three different large cohorts (TCGA, Caris Life Sciences, and GENIE) in most ICB-approved cancer types. In the TCGA data, TMB increased with age pan-cancer ($p < 1x10^{-16}$) and in 7 of 9 ICB-approved cancer types. These associations were validated in the larger cohort of patient samples in GENIE, which demonstrated correlations between increased TMB levels and patient age in all eight ICB-approved cancer types assayed (Table), as well as in the Caris colorectal (q < 0.001) and breast (q < 0.001) cancer cohorts. Significant associations of age to other biomarkers of ICB response (checkpoint gene expression, immune infiltration, and immune related pathway signaling) will be presented. **Conclusions:** These results provide context for the efficacy of ICB in elderly patients, highlight potential biomarkers for the treatment of elderly patients with immunotherapies, and strongly suggest the value of large-scale prospective study of elderly cancer patients treated with ICB. Research Sponsor: U.S. National Institutes of Health.

Cancer Type	Estimated change in logTMB per year of age	Adjusted p-value	n
Breast	0.00550	9.17×10^{-28}	9485
Melanoma	0.0152	4.16×10^{-26}	3120
Esophagogastric	0.0120	8.23×10^{-20}	2133
Renal Cell Carcinoma	0.00942	5.91×10^{-15}	1329
Head and Neck	0.0125	5.90×10^{-12}	1255
Bladder	0.0107	3.14×10^{-10}	1762
Non-Small Cell Lung	0.00260	6.13×10^{-4}	10620
Colorectal	0.00230	1.34×10^{-3}	8257

2544 **Poster Session**

SER-ONCOVID: Seroconversion in solid-tumor cancer patients after COVID-19 diagnosis.

First Author: Anna Pous, ICO Badalona, Barcelona, Spain

Background: Cancer patients (pts) represent a high-risk population for severe COVID-19. Cancer-associated immunosuppression may hinder in the development of anti-SARS-CoV-2 antibodies. **Methods:** Data regarding baseline characteristics, COVID-19 and anti-SARS-Cov2 IgG were collected from cancer pts (solid tumors) who tested positive for COVID-19 (PCR+) between March and April 2020 at Catalan Institute of Oncology. We prospectively assessed anti-SARS-Cov2 IgG seroprevalence at 3 and 9 months post infection and explored clinico-pathologic factors associated with IgG positivity. We explored the impact of potential factors influencing antibody production at >9 months. **Results:** Of 49 pts registered between 10th March-26th April 2020, 21 died <3 months after the infection and 5 pts refused to participate, leaving 23 eligible pts for IgG testing. With respect to those not tested, IgG tested cohort was younger (median age: 64.0 vs 72.9 years, p = 0.001) and presented oncologic remission in 68.2% of cases (vs 34.6%, p = 0.043) at COVID-19 diagnosis. Median time from PCR+ to first and second IgG determination was 3.2 months (Interquartile range [IQR]: 2.9-4.1) and 9.5 months (IQR: 8.8-9.8), respectively. Out of 23 pts, 15 had both determinations and 8 had only one (3 in the first time point, 5 in the second one). We identified 16/18 pts IgG+ (88.9%) at 3 months and 17/20 pts IgG+ (85%) at 9 months. One IgG+ pt became IgG- at the second determination, one was IgG- at both timepoints, and one had an inconclusive result at the first but negative at the second timepoint. Key characteristics of patients by IgG result 9 months after COVID-19 diagnosis are shown in the table. **Conclusions:** We describe a high seroprevalence of anti-SARS-CoV-2 IgG at 3 and 9 months after COVID-19 diagnosis in solid tumour patients, irrespective of anti-cancer therapy exposure. Pts who were IgG+ at 9 months were older, and more likely to have required oxygen during prior COVID-19 in comparison to IgG- pts suggesting that infection severity may promote durable immunity. Frequency of early stage cancers was higher among IgG+ pts, suggesting less cancer-related immunosupression. Older (>70 years) and advanced cancer pts were under-represented in this series, warranting confirmation of these preliminary results in a larger cohort. Research Sponsor: None.

Characteristics of patients by IgG result determined at 9 months after COVID-19 diagnosis.

Characteristics assessed at COVID infection	IgG- (n=3)	IgG+ (n=17)
Median Age (years)	49.0 [49.0; 50.0]	66.0 [62.0; 70.0]
Neoplasms Breast	1 (33%)	6 (35%)
Urogenital	1 (33%)	4 (24%)
Digestive	0 (0%)	3 (17%)
Others	1 (33%)	4 (24%)
Early stage/Metastatic cancer	1(33%)/2(67%)	13(77%)/4(24%)
Active Cancer Treatment*	3 (100%)	14 (82%)
O2 support during COVID-19	0 (0%)	12 (61%)
COVID treatment (Tocilizumab/Remdesivir)	0 (0%)	4 (24%)

*Chemotherapy, immunotherapy, hormonal therapy, targeted therapy.

2545 **Poster Session**

Using the tumor microenvironment to identify predictors of immunotoxicity to checkpoint inhibitors.

First Author: William Alexander, University at Buffalo, Buffalo, NY

Background: While Immune checkpoint inhibitors (ICI) have revolutionized the field of oncology, the benefits have come at the cost of serious side effects known as immune-related adverse events (irAEs). Approaches that can predict patients' susceptibility to irAEs are key to their early detection and management. In the present study, we investigate the association between irAEs reported during ICI therapy across multiple cancer types and markers of tumor immune response. Our primary objective is to explore potential biomarkers for assessing patients' risk of irAEs. **Methods:** 472 patients were evaluated who had tumor immune profiling performed paraffin embedded formalin fixed archival tumor biopsy samples using Omniseq Immune Report Card (IRC) and subsequently underwent ICI therapy. The IRC consisted of enumeration of tumor infiltrating lymphocytes (TILs) by immunohistochemistry (IHC) and TIL-associated genes by RNA-Seq, PD-L1 expression by IHC, and tumor mutational burden (TMB) by DNA-Seq. irAE type and grade were determined based on retrospective chart review. Fisher's exact test was used to determined statistically significant associations between immune markers and irAE development. **Results:** Patients with lung (55%), ovarian (9%), and melanoma (5%) cancers constituted the majority of the cases. The median age of patients was 61, with 56% being female and 44% male. Most patients underwent treatment with (94%). irAEs developed in 36% of patients, with 2% of patients developing high-grade irAEs (Grade 3 or 4). Skin (11%), thyroid (10%), and GI (9%), were the most commonly affected organ systems. Increased TILs were associated with increased risk for any irAE (p = 0.04). A stronger association was noted in patients who underwent anti-PD-1/L1 monotherapy (p = 0.01) and/or in cases of lung cancer (p = 0.01). Interestingly, subanalyses by gender showed a statistically significant correlation between increased TILs and risk for any irAE in males (p = 0.006) but not in females (p = 0.63). High PD-L1 (defined as > 70% by IHC) was also significantly associated with increased risk for any irAE (p = 0.03). Subanalyses by gender and age again showed a similar association in females (p = 0.0002) and/or patients < 65 years (p = 0.04). high TMB and any irAE in female patients (p = 0.01) and in breast cancer cases (p = 0.03). On multivariate analysis, TILs by IHC appeared to be the strongest predictor of irAEs (p = 0.03). **Conclusions:** The tumor immune microenvironment (TME) has been shown to influence response to ICI, yet its association with irAEs has not been well studied. Our analysis sheds light on potential TME predictors for irAE in patients receiving ICI therapy. Further studies are needed to deepen our understanding of immune toxicity and to develop tools for identifying patients who are at risk. Research Sponsor: U.S. National Institutes of Health.

2546 **Poster Session**

A 4-chemokine signature to predict intermediate immunogenicity in homologous recombination repair deficient tumors.

First Author: Joan Miguel Romero, Research Institute of the McGill University Health Centre, Montreal, QC, Canada

Background: Treatment responses to immune checkpoint blockade (ICB) associate with T cell tumor inflammation. Tumors with mismatch repair deficiency display an inflammatory tumor phenotype and respond to ICB. Similarly, tumors with homologous recombination repair deficiency (HR-d) may be primed for ICB treatment. We have previously shown that a panel of 4 chemokines identifies a subclass of pancreatic cancer with markers of T cell-inflammation. Here, we evaluated this 4-chemokine signature in cancer types with HR-d molecular subclasses. **Methods:** We combined paired transcriptomes and genomic data of breast (n = 699), ovarian (n = 174) and prostate (n = 457) cancers from the Cancer Genome Atlas and tumor-enriched pancreas cancers (n = 121) to evaluate the 4-chemokine signature in HR-d vs. HR-proficient tumors across these 4 cancers. Metrics of antitumor immunity were also compared. **Results:** Across tumor types, elevated expression of the 4-chemokine signature (chemokine-hi) associated with transcriptional hallmarks of a T cell-mediated antitumor response, including antigen presenting cell stimulation, antigen presentation, and T cell activity. In tumors with a predominant COSMIC signature 3, which associates with HR-d, the 4-chemokine signature predicted intermediate levels of T cell-inflammation. **Conclusions:** These data suggest that 1) the 4-chemokine signature may be a clinically relevant biomarker in identifying subclasses of tumours responsive to immunotherapies, and that 2) HR-d tumors harbor intermediate immunogenicity. Correlation of treatment responses to immunotherapies with the 4-chemokine signature is needed validate its predictive value as a biomarker for treatment stratification with immunotherapies. Research Sponsor: Quebec Cancer Consortium.

			HR-d (Signature 3*)		
	Lo+Med score	Hi score	score	Lo+Med vs Hi p-value	Lo+Med vs HR-d p-value
Pancreas		n = 84	n = 29	n = 8**	
APC costimulation	-0.095	0.46	0.20	< 0.01	0.23
Batf3DC score	0.087	0.59	0.36	< 0.01	0.21
MHC I presentation	-0.26	0.42	0.0086	< 0.001	0.50
Cytolytic activity score	-0.28	1.36	0.0078	< 0.001	0.172
T effector score	-0.30	1.34	0.60	< 0.001	< 0.05
Breast		n = 495	n = 164	n = 40	
APC costimulation	-0.28	0.95	0.24	< 0.001	< 0.01
Batf3DC score	-0.37	1.00	0.094	< 0.001	0.15
MHC I presentation	-0.32	1.06	0.28	< 0.001	< 0.05
Cytolytic activity score	-0.60	1.93	0.46	< 0.001	< 0.001
T effector score	-0.58	1.94	0.77	< 0.001	< 0.001
Ovarian		n = 93	n = 32	n = 49	
APC costimulation	-0.29	0.58	0.48	< 0.001	< 0.001
Batf3DC score	-0.33	0.84	0.16	< 0.001	< 0.001
MHC I presentation	-0.30	0.99	0.49	< 0.001	< 0.001
Cytolytic activity score	-0.57	1.72	0.68	< 0.001	< 0.001
T effector score	-0.68	1.31	0.68	< 0.001	< 0.001
Prostate		n = 327	n = 110	n = 20***	
APC costimulation	-0.32	0.71	0.31	< 0.001	< 0.001
Batf3DC score	-0.25	0.93	0.26	< 0.001	< 0.01
MHC I presentation	-0.211	0.73	0.12	< 0.001	< 0.01
Cytolytic activity score	-0.39	1.10	0.35	< 0.001	< 0.01
T effector score	-0.044	1.10	0.17	< 0.001	< 0.01

2547 **Poster Session**

First-in-human dose escalation of ALPN-202, a conditional CD28 costimulator and dual checkpoint inhibitor, in advanced malignancies.

First Author: Justin C Moser, HonorHealth Research and Innovation Institute, Scottsdale, AZ

Background: Strong preclinical rationale has emerged for combining checkpoint inhibition (CPI) with T cell costimulatory agonists, particularly CD28, a critical T cell costimulatory molecule recently recognized as a key target of checkpoint inhibition. ALPN-202 is a variant CD80 vIgD-Fc fusion that mediates PD-L1-dependent CD28 costimulation and inhibits the PD-L1 and CTLA-4 checkpoints. It has demonstrated superiority to CPI-only therapies intumor models, while demonstrating favorable safety in preclinical toxicology studies. **Methods:** This is a cohort-based, open-label dose escalation and expansion study of ALPN-202 in adults with advanced solid tumors or lymphoma (NCT04186637). Subjects with cancers refractory to standard therapies (including approved CPIs), or cancers without available standard or curative therapy are eligible. After two planned single-subject cohorts, a standard 3+3 dose escalation has been implemented with two dose schedules in parallel, Q1W and Q3W. Objectives include evaluation of safety and tolerability, PK, PD and preliminary anticancer activity of ALPN-202. Disease assessments are evaluated by RECIST v1.1 for solid tumors or by Lugano Classification for lymphoma. **Results:** As of January 2021, 20 subjects with advanced malignancies have received ALPN-202. Dose-dependent PK and target saturation have been preliminarily observed. So far, ALPN-202 has been well tolerated at dose levels ranging from 0.001 to 1 mg/kg weekly, with no DLTs. Low-grade skin toxicities (grade 1-2 rash) have been observed in 4 subjects (20%). Among 11 evaluable subjects, an unconfirmed partial response has been observed in one subject with colorectal carcinoma, while stable disease has been observed in 5 subjects with colorectal carcinoma, mesothelioma (2), cholangiocarcinoma, and renal cell carcinoma – for a preliminary clinical benefit (PR+SD) rate of 100% (4/4) at dose levels of 0.3 mg/kg and higher, or 54% (5/11) overall (table). The meeting presentation will update this data, which is expected to include the conclusion of Q1W dose escalation, as well as immune correlates. **Conclusions:** First-in-human dose escalation with ALPN-202 has been well tolerated at doses capable of engaging CD28 costimulation *in vivo* in association with dual PD-L1/CTLA-4 checkpoint inhibition, with early signs of anti-tumor activity. These findings suggest that CD28 agonism can be safely achieved in humans, and further suggest that dose expansion with ALPN-202 is warranted to assess the relevance of controlled CD28 costimulation as a novel approach to cancer immunotherapy. Clinical trial information: NCT04186637. Research Sponsor: Alpine Immune Sciences.

Regimen	Weekly					Every 3 Weeks			
Dose	**0.001 mg/kg**	**0.01 mg/kg**	**0.1 mg/kg**	**0.3 mg/kg**	**1 mg/kg**	**0.3 mg/kg**	**1 mg/kg**	**All Dose Regimens**	**Doses ≥ 0.3 mg/kg**
N Enrolled	1	2	4	6	3	3	1	20	13
N Evaluable	1	2	4	1	0	3	0	11	4
PD	-	2 (100%)	3 (75%)	-	-	-	-	5 (45%)	-
SD	-	-	1 (25%)	1 (100%)	-	3 (100%)	-	5 (45%)	4 (100%)
PR	1 (100%)	-	-		-	-	-	1 (9%)	-

2548 **Poster Session**

Phase 1A clinical trial of the first-in-class fascin inhibitor NP-G2-044 evaluating safety and anti-tumor activity in patients with advanced and metastatic solid tumors. *First Author: Vincent Chung, City of Hope, Duarte, CA*

Background: Fascin inhibitors block tumor metastasis and increase antigen uptake in intra-tumoral dendritic cells. Filopodia, finger-like protrusions on cell surfaces, are necessary for migration of metastatic tumor cells and intra-tumoral dendritic cells. Fascin is the primary actin cross-linker in filopodia and elevated levels correlate with increased risk of metastasis, disease progression and mortality. NP-G2-044 is a novel small molecule that inhibits function of fascin. Pre-clinical data demonstrate drug-associated reductions in tumor growth and metastasis, enhanced immune response and survival in treated animals, and drug-drug synergism when combined with anti-PD-1 antibodies. **Methods:** This multicenter phase 1A clinical trial was designed to evaluate safety and tolerability of NP-G2-044 and to identify the drug's recommended phase 2 dose (RP2D) using a 3+3 dose escalation design. NP-G2-044 was administered to patients (pts.) with treatment-refractory solid tumor malignancies as a single oral daily dose for 6-week cycles that included 4 weeks on (daily dosing) and 2 weeks off (rest). **Results:** A total of 23 pts. were enrolled in 7 dose cohorts ranging from 200-2100 mg. QD. Overall, NP-G2-044 appeared well-absorbed and distributed with Tmax of ~4 hrs and T1/2 of 20-24 hrs. Across all cohorts, no DLTs, drug-related SAEs or patient deaths were observed. Based on PK and safety findings, 1600 mg. daily was selected as the provisional RP2D. While no formal RECIST-based objective responses were observed, consistent with the drug's non-cytotoxic mechanism of action, preliminary signals of anti-tumor and anti-metastatic activity were observed. These include dose proportional increases in duration of treatment, progression-free-survival, and metastasis-free interval, in particular for 4/4 late-stage ovarian cancer patients (table). Comparison of time on treatment (TOT) for ovarian cancer patients. **Conclusions:** In this first-in-human clinical trial, the novel fascin inhibitor, NP-G2-044, appeared safe and well tolerated. Signals of single-drug anti-tumor and anti-metastatic activity were observed. A phase 2A clinical trial with a particular focus on Ovarian Cancer will seek to elucidate signals of RP2D activity in both monotherapy and the combination of NP-G2-044 with anti-PD-(L)1 immune checkpoint inhibitors. Clinical trial information: NCT03199586. Research Sponsor: Novita.

Patient	Cancer Type	Last Prior Therapy	Time on Last Prior Therapy	Time on NP-G2-044	TOT Improvement	Metastatic Sites Prior to NP-G2-044	New METS on NP-G2-044
023	Ovary	CSF1R Inhibitor	~60 days	170 days	~183%	Liver, Colon, Pancreas, Bladder	No
027	Ovary	Doxorubicin	~105 days	170 days	~62%	Lung, Lymph Node, Peritoneum	No
028	Fallopian Tube	Anti-LIF1	~90 days	158 days	~76%	Lung, Lymph Node	No
031	Ovary	Liposomal Doxorubicin	~90 days	251 days	~179%	Peritoneum, Liver, Abdominal wall, Ilium	No

2549 **Poster Session**

Preliminary results from a phase 1/2 study of BDC-1001, a novel HER2 targeting TLR7/8 immune-stimulating antibody conjugate (ISAC), in patients (pts) with advanced HER2-expressing solid tumors. *First Author: Manish Sharma, START-Midwest, Grand Rapids, MI*

Background: BDC-1001 is a novel ISAC consisting of an investigational trastuzumab biosimilar chemically conjugated to a TLR 7/8 agonist with a non-cleavable linker. BDC-1001 was designed to activate the innate immune system, eliciting antibody-mediated effector functions (eg, antibody-dependent cellular phagocytosis) and a durable adaptive immune response. In preclinical tumor models resistant to anti-HER2 treatments, BDC-1001 demonstrated potent and durable immune-mediated antitumor efficacy. **Methods:** A 4-part, phase 1/2 dose-escalation/expansion study was initiated to evaluate BDC-1001 ± PD1 inhibitor pembrolizumab in pts with HER2-expressing solid tumors who had progressive disease on standard of care (NCT04278144). Preliminary results of the monotherapy dose escalation (Part 1) are reported. Pts with advanced metastatic HER2-expressing (IHC2/3+) or amplified solid tumors received BDC-1001 IV q3w in a 3+3 design w/ 12 pts/cohort backfill allowed. Primary objectives were to evaluate safety, tolerability, dose-limiting toxicities (DLTs) and determine a phase 2 dose; secondary objectives were to assess pharmacokinetics (PK), pharmacodynamics and preliminary anti-tumor activity. **Results:** As of Jan 29, 2021, 20 pts w/ a median age of 65 (46-85) have enrolled in 4 dose levels (0.15mg/kg to 5 mg/kg). Cancer types include breast, biliary, cervical, colorectal (CRC), lung, gastroesophageal, salivary, urinary tract and endometrial. Pts had received a median of 4 (1-7) prior therapies; 65% received >1 prior anti-HER2 therapy. All pts completed the 21-day DLT period; no DLTs or drug-related serious adverse events (AEs) have been observed. AEs deemed related to BDC-1001 have been mild to moderate including infusion-related reactions. The MTD has not been reached (treatment duration 5-17+wk); enrollment is ongoing. PK evaluations showed Cmax levels consistent with predicted modeling based on non-human primates (NHP). One pt with microsatellite stable (MSS) HER2+ CRC with lung metastases had a confirmed partial response after 4 cycles and remains on study; 2 additional pts with metastatic MSS HER2+ CRC had stable disease (SD) and a pt with heavily pretreated MSS endometrial cancer with lung metastases had confirmed SD and remains on treatment 17+ wk; 3 of these pts had received 2 prior anti-HER2 therapies. **Conclusions:** In this first-in-human study, BDC-1001 appears to be well-tolerated up to the dose tested to date (5 mg/kg), with Cmax levels achieved as predicted by NHP modeling. Evidence of clinical activity have been observed, including in pts previously treated with anti-HER2 therapy. Dose escalation is ongoing and will be followed by combination dosing with CPI and the phase 2 component in selected tumors. Clinical trial information: NCT04278144. Research Sponsor: Bolt Biotherapeutics.

2550 **Poster Session**

Preliminary results of a first-in-human phase I dtudy of IMM01, SIRPα Fc protein in patients with relapsed or refractory lymphoma. *First Author: Mingyuan Sun, State Key Laboratory of Experimental Hematology, National Clinical Research Center for Hematological Disorders, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College., Tianjin, China*

Background: IMM01 is a recombinant human signal regulatory protein α (SIRPα) IgG 1 fusion protein that exerts dual-mechanism antitumor activity via engagement of activating tumor cell phagocytosis and stimulating T-cell anti-tumor responses by binding CD47 on tumor cell membrane. IMM01 displays promising preclinical characteristics regarding its receptor occupancy/tumor exposure/efficacy relationship. Unlike anti-CD47 monoclonal antibodies, IMM01 shows unique property of weak human erythrocyte conjugation so as avoiding severe hemolysis. **Methods:** Monotherapy of IMM01 was conducted in 14 enrolled subjects with relapsed or refractory lymphoma who had failed standard therapies. Dose escalation was performed in routine design of accelerated single-patient followed by standard 3+3 to establish the preliminary data of safety as well as determination of a recommended expansion dosage. Each cycle contains 4 dosing weekly followed by a week rest. The tumor responses were evaluated based on Lugano Classification 2014. IMM01 pharmacokinetics (PK) and pharmacodynamics (PD) analyses were performed. **Results:** As of February 08, 2021, a total of 14 patients (median age 49 y; median prior therapy 3) were enrolled in 6 escalated dose cohorts (0.003 mg/kg, 0.01 mg/kg, 0.05 mg/kg, 0.15 mg/kg, 0.5 mg/kg and 1.0 mg/kg). The common tumor types were follicular lymphoma, Hodgkin lymphoma, diffuse large B-cell lymphoma. No DLTs were observed up to 1.0 mg/kg. One SAE (grade 2 increased amylase and grade 3 increased lipase) was reported, which induced by disease progression on pancreas. The most common treatment related adverse events were thrombocytopenia (54%), neutrophil count decreased (36%), Pyrexia (36%) and Anaemia (27%). There were grade 1 or 2 except for one patient experienced a grade 3 platelet count decreased (lower baseline at 70×10^9/L). Transient platelet count decrease after 2 hours and return to baseline at 24 to 48 hours post first infusion. In 12 evaluated patients, one patient with FL had a CR and maintained a 26-week response at the dose of 0.01 mg/kg. One patient with HL who had failed PD-1 inhibitor was confirmed PR at 27 weeks and continues the therapy, and one patient with MZL maintained SD for 12 weeks at the dose of 0.15 mg/kg. One patient with HL failed PD-1 inhibitor and one patient with FL maintained a shrunk SD for 12 weeks at the dose of 0.5 mg/kg. One patient with AITL was evaluated as a shrunk SD after 5 doses treatment at the dose of 1.0 mg/kg. Terminal half-life of IMM01 range from 53.8 hours to 73.3 hours. The AUC and C_{max} of IMM01 show nonlinear increases in the dose range of 0.05 mg/kg to 0.5 mg/kg. **Conclusions:** Preliminary data from the present phase 1 study of IMM01, a SIRPα IgG 1 fusion protein, demonstrate that IMM01 has an excellent preliminary safety, tolerability and promising anti-tumor activity up to doses of 1.0 mg/kg. Clinical trial information: ChiCTR1900024904. Research Sponsor: ImmuneOnco Biopharmaceuticals (Shanghai) Co.,Ltd.

2551 **Poster Session**

Results of a phase 1 study of SRF388, a first-in-human, first-in-class, high-affinity anti-IL-27 antibody in advanced solid tumors. *First Author: Amita Patnaik, START, San Antonio, TX*

Background: IL-27 is an immunosuppressive cytokine, consisting of two subunits p28 and EBI3, that upregulates immune checkpoint receptors (eg, PD-L1, TIGIT) and downregulates proinflammatory cytokines such as IFNγ, TNFα, and IL-17. SRF388 is a first-in-class, fully human IgG1 antibody to IL-27 that blocks the interaction between IL-27 and its receptor, thereby promoting immune activation in the tumor microenvironment. The IL-27 pathway is activated in hepatocellular carcinoma (HCC) and renal cell carcinoma (RCC), and high circulating levels of EBI3 are associated with inferior outcomes in both. Circulating EBI3 levels may serve as a predictive biomarker of SRF388 activity. **Methods:** Patients with advanced solid tumors refractory to standard therapy were enrolled in a phase 1 dose-escalation study (accelerated single patient followed by standard 3+3) to establish the preliminary safety of SRF388 as a monotherapy and to identify a dose suitable for expansion (NCT04374877). SRF388 was administered intravenously every 4 weeks. Tumor response was assessed by RECIST v1.1. SRF388 pharmacokinetic (PK) and pharmacodynamic (PD) [phospho-STAT (pSTAT) inhibition] analyses were performed. **Results:** As of January 26, 2021, 12 patients have received SRF388 at doses ranging from 0.003 to 10 mg/kg with 2 patients undergoing intra-patient dose escalation. Median age was 68 years, 67% were female, and ECOG PS was 0/1 (42%/58%). Median number of prior therapies was 2 (range 1–9), and 75% were anti-PD-(L)1 experienced (n = 9). The only treatment-related adverse events observed across dose levels were low-grade fatigue (n = 1, 8%), nausea (n = 1, 8%) and excess salivation (n = 1, 8%). No dose-limiting toxicities (DLTs) or $\geq$ Grade 3 related toxicity have occurred. Mean time on study is 12.5 weeks (range 4–40). One patient with RCC who received prior anti-PD-1 has prolonged stable disease for $>$ 9 months. SRF388 PK are linear with estimated $T_{1/2}$ ranging from 6–19 days. There is evidence of accumulation and no anti-drug antibody development to date. Maximal inhibition of the IL-27 signaling pathway as measured by $>$ 90% pSTAT inhibition in whole blood was achieved starting at 0.3 mg/kg. Given combined evidence of near-complete pathway inhibition and preclinical human equivalent dose modeling projecting biologically active doses, additional slots were opened for RCC and HCC starting at 1 mg/kg. **Conclusions:** Preliminary results of IL-27 pathway blockade with a first-in-class therapeutic demonstrates that SRF388 is well tolerated at doses that achieve maximal inhibition of downstream pSTAT signaling through the dosing period. Expansions are planned in HCC and RCC. Updated data including the recommended phase 2 dose, clinical outcomes, PK/PD and correlative analyses will be presented. Clinical trial information: NCT04374877. Research Sponsor: Surface Oncology.

2552 **Poster Session**

Selection of the recommended phase 2 dose (RP2D) for subcutaneous nemvaleukin alfa: ARTISTRY-2. *First Author: Omid Hamid, The Angeles Clinic and Research Institute, Los Angeles, CA*

Background: Nemvaleukin alfa (nemvaleukin, ALKS 4230) is a novel engineered cytokine that selectively binds the intermediate-affinity interleukin-2 receptor to preferentially activate CD8$^+$ T and natural killer (NK) cells with minimal expansion of regulatory T cells (T_{regs}),designed for use as a cancer immunotherapy. ARTISTRY-2 (NCT03861793) is an ongoing phase 1/2 study evaluating the safety, efficacy, and pharmacokinetic and pharmacodynamic (PD) responses of subcutaneous (SC) nemvaleukin in combination with pembrolizumab in patients (pts) with advanced solid tumors. **Methods:** In phase 1, cohort-specific doses of SC nemvaleukin are administered on an every-7-day (q7d) or every-21-day (q21d) schedule during a 6-week monotherapy lead-in period, followed by combination with pembrolizumab 200 mg q21d. We present safety, PD effects, and preliminary clinical activity outcomes as of 12/02/2020. **Results:** 57 pts received nemvaleukin doses ranging from 0.3 mg to 6 mg q7d or 1 mg to 10 mg q21d. The most frequent tumor types (> 5 pts) were colorectal, pancreatic, ovarian, and lung; median number of prior therapies was 4. Treatment-related adverse events (TRAEs) in > 30% pts overall were pyrexia (43.9%), chills (38.6%), injection site erythema (33.3%), injection site reaction (33.3%), and fatigue (31.6%). 3 mg q7d (n = 7) had no drug-related dose reductions, discontinuations, or deaths during the monotherapy or combination periods. 6 mg was declared the maximum tolerated dose (MTD) for q7d dosing as 2 of 8 pts experienced dose-limiting toxicities (DLTs). For 6 mg q21d (n = 7), no drug-related dose reductions, discontinuations, or deaths have occurred during the monotherapy period; combination period data are not mature. 10 mg was declared the MTD for q21d dosing as 1 of 9 pts experienced DLTs and 3 had TRAEs leading to dose reductions. Systemic exposure to nemvaleukin increased with increasing dose. Increases in NK cells and CD8$^+$ T cells of approximately 16-fold and 3-fold, respectively, at 3 mg q7d, and approximately 8-fold and 3-fold, respectively, at 6 mg q21d were observed, with minimal change in T_{regs}. 46 pts had at least 1 on-treatment scan as of the data cutoff date, and 30 (65%) had stable disease (SD) on the first scan. Of the 30 pts with ≥2 scans, 13 (43%) had 2+ consecutive scans of SD. 16 of 57 pts remain on therapy. Antitumor activity data for more recent cohorts are still maturing. Based on the totality of the safety, PD effects, and antitumor activity data, 3 mg q7d was selected as the RP2D for SC nemvaleukin. **Conclusions:** SC nemvaleukin 3 mg q7d was generally well tolerated as monotherapy and in combination with pembrolizumab, and demonstrated robust PD effects on NK cells and CD8$^+$ T cells with minimal expansion of T_{regs}. These PD effects are similar to or greater than those observed with intravenous nemvaleukin. Thus, 3 mg q7d was selected as RP2D; phase 2 expansion cohorts for combination with pembrolizumab are enrolling. Clinical trial information: NCT03861793. Research Sponsor: Alkermes, Inc.

2553 **Poster Session**

Initial results from a phase 1b study of ORIC-101, a glucocorticoid receptor antagonist, in combination with nab-paclitaxel in patients with advanced solid tumors. *First Author: Raghad Karim, NEXT Oncology, San Antonio, TX*

Background: ORIC-101 is a potent and selective, orally bioavailable, small molecule antagonist of the glucocorticoid receptor (GR). Preclinical studies have demonstrated that activation of GR signaling leads to decreased responsiveness to chemotherapeutics (eg, taxanes) and antiandrogens across multiple tumor types. Mechanistically, ORIC-101 inhibits GR transcriptional activity and blocks the prosurvival signals mediated by the activated nuclear hormone receptor. **Methods:** A 3+3 dose escalation design was used to assess safety, pharmacokinetics (PK), pharmacodynamics (PD), and select the Recommended Phase 2 Dose (RP2D) of ORIC-101 in combination with nab-paclitaxel (nab-pac; NCT03928314). ORIC-101 doses ranging from 80 to 240 mg once daily, given either intermittently or in a continuous dosing regimen, were evaluated in combination with weekly nab-pac at 75 or 100 mg/m^2. Plasma PK and PD biomarkers were assessed on day 1 and after repeat dosing. PD modulation in blood-derived peripheral blood mononuclear cells (PBMCs) was assessed by RT-qPCR for GR target genes. Antitumor activity was assessed by RECIST v1.1. **Results:** 21 patients with 10 different solid tumors, with and without a prior taxane, were treated in 5 cohorts. ORIC-101 exposure increased with dose, with no evidence for drug-drug interaction with nab-pac. In the initial cohort at 240 mg ORIC-101 and 100 mg/m^2 nab-pac, 2 patients experienced dose limiting toxicities (DLTs) of Grade 3 fatigue and Grade 4 neutropenia/thrombocytopenia, respectively. No further DLTs were observed in subsequent cohorts and the RP2D was established as 160 mg ORIC-101 dosed once daily continuously for 21 days with nab-pac 75 mg/m^2 given on days 1, 8, and 15 of each 28-day cycle, without requirement for prophylactic granulocyte colony-stimulating factor (G-CSF). The most common (> 15%), all grade treatment-related adverse events (AEs) were nausea (38%), diarrhea (33%), fatigue (29%), leukopenia (29%), neutropenia (29%), anemia (24%), and 19% of patients had increased liver function tests and alopecia. Biomarker data demonstrated ORIC-101-induced reduction in GR target gene expression in PBMCs, indicating PD modulation at all dose levels of ORIC-101. Preliminary antitumor activity was observed in 3 taxane-refractory patients with breast, endometrial, and pancreatic cancers. **Conclusions:** The combination of ORIC-101 and nab-paclitaxel demonstrated an acceptable tolerability profile and does not require prophylactic G-CSF. PK and PD showed no evidence of drug-drug-interaction and demonstrated GR target inhibition. Preliminary antitumor activity was observed in patients with solid tumors that previously progressed on a taxane-containing regimen. Dose expansion is ongoing at the RP2D in dedicated pancreatic, ovarian, triple negative breast cancers, and tissue-agnostic cohorts. Clinical trial information: NCT03928314. Research Sponsor: ORIC Pharmaceuticals.

2555 **Poster Session**

Results of a phase 1 dose-escalation study of AMV564, a novel T-cell engager, alone and in combination with pembrolizumab in patients with relapsed/refractory solid tumors. *First Author: Niharika B. Mettu, Duke University Medical Center, Durham, NC*

Background: Myeloid-derived suppressor cells (MDSC) contribute to an immunosuppressive tumor environment and are a barrier to immune therapy. CD33 signaling in immature myeloid cells promotes expansion of MDSC and production of immunosuppressive factors. AMV564 is a potent T cell engager that selectively depletes MDSC while promoting T cell activation and proliferation, via preferential binding to areas of high CD33 density. **Methods:** In this 3+3 dose escalation study, patients with relapsed/refractory solid tumors for whom no recognized standard therapy exists received AMV564 once daily via subcutaneous (SC) injection on Days 1-5 and 8-12 of a 21-day cycle, either alone or in combination with pembrolizumab (200 mg IV q3w). Study endpoints included incidence and severity of adverse events (AEs), pharmacokinetics (PK), and preliminary anti-tumor activity (using RECISTv1.1 criteria). **Results:** As of January 29, 2021, 20 patients were dosed in 3 monotherapy dose cohorts (15, 50, and 75 mcg/day), and 10 patients were dosed in 3 combination therapy cohorts (5, 15, and 50 mcg/day). Enrolled patients were: median age 64 years, 47% female, had received median 3.5 prior lines of therapy; 7 patients (35%) had received prior checkpoint inhibitor therapy (6 monotherapy patients, 1 combination therapy patient). No dose-limiting toxicity was observed and a maximum-tolerated dose was not reached in either the monotherapy or combination therapy cohorts. The most common treatment-related AEs (occurring in > 10% of patients, in order of decreasing frequency) in the monotherapy cohort were pyrexia, injection site reactions, fatigue, anemia, hypotension, pruritis, chills, and nausea. There were 2 cases of grade 2 cytokine release syndrome (CRS) at 75 mcg/day, both of which resolved after anti-IL6 therapy and study treatment was resumed. The most common treatment-related AEs in the combination cohorts (> 10% frequency) were injection site reaction, pyrexia, fatigue, pruritis, and anemia. No cases of CRS were noted in the combination cohorts. In preliminary PK analysis, estimated median plasma half-life for AMV564 after SC injection was > 48 hours, with dose-related increases in peak plasma concentration. Clinical responses were seen with monotherapy and combination therapy, including a complete response (CR) in a monotherapy-treated patient with ovarian cancer refractory to all standard therapies and anti-PD-1 therapy. **Conclusions:** AMV564 was well tolerated across multiple dose levels as monotherapy and in combination with pembrolizumab. Subcutaneous injection resulted in clinically relevant plasma exposures. Single-agent and combination therapy anti-tumor activity was observed. Further exploration of AMV564 clinical efficacy in expansion cohorts is ongoing. Clinical trial information: NCT04128423. Research Sponsor: Amphivena Therapeutics.

2556 **Poster Session**

A phase 1b, open-label, dose-escalation study to evaluate camidanlumab tesirine (Cami) as monotherapy in patients (pts) with advanced solid tumors. *First Author: Igor Puzanov, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Depletion of tumor-infiltrating CD25+ regulatory T cells (T_{regs}), which inhibit tumor-specific immune responses, could contribute to tumor eradication. Cami (ADCT-301), an anti-CD25, pyrrolobenzodiazepine-based antibody-drug conjugate, targets CD25+ T_{regs}. A mouse surrogate has shown potent antitumor activity in solid tumor models. Here we report preliminary data from the monotherapy arm of a phase 1b trial of Cami in pts with selected advanced solid tumors. **Methods:** The monotherapy dose-escalation part of this open-label study enrolled pts (aged ≥18 years) with selected advanced solid tumors and no suitable existing therapy. The primary objective was to characterize safety and tolerability, and to identify the recommended phase 2 dose of Cami monotherapy. Secondary and exploratory objectives included evaluation of preliminary antitumor activity, pharmacokinetics (PK), pharmacodynamics (PD), and immunogenicity. Pts received Cami every 3 weeks (1 cycle) with dose escalation per a 3+3 design. Disease control rate (DCR) was assessed (complete and partial responses [CR, PR] and stable disease). **Results:** At data cut-off (Dec 17, 2020), 44 pts were enrolled, with primary tumor types (stage IVA/B: 27 pts; 61.4%) of colorectal (15 pts; 34.1%), pancreatic (14 pts; 31.8%), head and neck, ovarian/fallopian tube, and renal cell carcinoma (all 3 pts; 6.8%), non-small cell lung cancer (2 pts; 4.5%), gastric, esophageal/GEJ, melanoma, and triple-negative breast cancer (each 1 pt; 2.3%). Median (range) age was 60.5 (33–82) years; median (range) number of prior systemic therapies was 4 (1–9). Pts received a median (range) of 2 (1–6) Cami cycles at doses of 20–150 μg/kg. Median (range) treatment duration was 22 (1–178) days. No dose-limiting toxicities were reported. The maximum tolerated dose (MTD) was not reached. All-grade treatment-emergent adverse events (TEAEs) in ≥20% pts were nausea (18 pts; 40.9%), decreased appetite and fatigue (each 16 pts; 36.4%), constipation (13 pts; 29.5%), abdominal pain (11 pts; 25%), and rash (10 pts; 22.7%). The only Grade ≥3 TEAE in ≥10% pts was anemia (5 pts; 11.4%). Grade 3 autoimmune AEs (colitis, immune-mediated AE, systemic inflammatory response syndrome) and neurologic AEs (dysphagia and asthenia, but not GBS) were reported in 3 (6.8%) and 2 (4.5%) pts, respectively. 1 (2.3%) Cami-related TEAE led to treatment withdrawal; no Cami-related TEAEs were fatal. DCR was 25% (95% CI: 11.1, 34.7); 11/44 pts attained stable disease. No pts had CR or PR. **Conclusions:** Dose escalation of Cami monotherapy is complete. The safety profile is encouraging and MTD was not reached. PK/PD data will be presented. 150 μg/kg is the highest dose investigated for single-agent Cami and the highest to be investigated combined with pembrolizumab in selected advanced solid tumors in the current protocol. Funding: ADC Therapeutics SA NCT03621982. Clinical trial information: NCT03621982. Research Sponsor: ADC Therapeutics SA.

2557 **Poster Session**

ItRECIST adapted efficacy assessment in solid tumors treated with intratumoral immunotherapy. *First Author: Honey Kumar Oberoi, Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain*

Background: The development of human intratumoral therapy (HIT-IT) has surged as a promising strategy to overcome resistance to checkpoint inhibitors (CPI), promoting a stronger tumor-specific immune response while reducing systemic exposure. A broad variety of agents (i.e: oncolytic viruses, toll-like receptors agonists) administered both in superficial- and deep-seated lesions are being currently tested in clinical trials (CT). Due to the local intervention on tumors, radiological assessment by standard RECIST is challenging and new methods of response that capture and integrate the local and systemic response to HIT-IT are needed. We aimed to evaluate the feasibility and clinical utility of itRECIST (Goldmacher et al., 2020) in patients (pts) treated with HIT-IT in early phase CT. **Methods:** Retrospective analysis of a cohort of pts with different solid tumor types enrolled in CT including HIT-IT in our institution between August'18 and January'21. Clinical characteristics were collected. Efficacy in target-injected (T-I) and target-non-injected (T-NI) lesions was assessed by objective response rate (ORR) and disease control rate (DCR), as per itRECIST. Overall disease ORR and DCR were assessed per RECIST 1.1/ iRECIST. Treatment-related adverse events (TRAEs) were assessed with CTCAE v.5.0. ORR was calculated with Clopper-Pearson method. Survival analysis was made using Kaplan-Meier method. **Results:** A total of 37 pts were included. Median age was 66 years, 19 pts (51%) were male, all pts had ECOG 0-1. 24 pts (65%) were CPI-naïve. Median previous lines of therapy was 2 (range [r]: 0-11). All pts (100%) received minimum 1 dose of HIT-IT. 6 pts (16%) were treated with monotherapy and 31 pts (84%) in combination with CPI. Median HIT-IT and CPI doses administered were 4 (r: 1-9) and 2 (r: 1-13), respectively. Injected lesions: cutaneous (16.2%), subcutaneous (21.6%), lymph node (32.4%), liver (29.7%). Median size of T-I lesions was 40 mm (r: 19-260). At data cutoff, 32 pts were evaluable. Median follow-up was 14.4 weeks (r: 1.0-81.1). Per RECIST 1.1, overall ORR was 6% (95% CI, 5-7) and DCR was 38% (95% CI, 21-56). Per itRECIST, ORR was 19% (95% CI, 7-36) and DCR was 63% (95% CI, 44-79) in T-I lesions (n = 32), and 10% (95% CI, 22-27) and 48% (95% CI, 29-67) in T-NI lesions (n = 29). Mean decrease in responding T-I and T-NI lesions was -47% (r: -21 to -100) and -41% (r: -26 to -59), respectively. No non-target (NT) lesion was injected. Median progression-free survival was 7.4 weeks (95% CI, 6.6 – 8.2). Median overall survival was 10.0 months (95% CI, 2.3 – 17.7). Incidence of TRAE was 58% (grade 1-2 IT-related pyrexia 43%; grade 3-4, 5%). No treatment-related deaths were recorded. **Conclusions:** ItRECIST is feasible to implement and adds precision to the radiological assessment of local and distant anti-tumor activity of HIT-IT. No safety issues were detected in our cohort. Research Sponsor: BBVA Foundation.

2558 **Poster Session**

Targeting innate immunity with BXCL701 in combination with pembrolizumab in patients with advanced solid cancers: Phase 2 basket study. *First Author: Ozgur Karakuzu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BXCL701 is an oral competitive inhibitor of dipeptidyl peptidases (DPPs), primarily DPP8/9, which triggers the inflammasome to alert and prime immune cells, leading to induction of IL-18 and IL-1ß. BXCL701 therefore, can induce an innate immune reaction and tumor inflammation, bridging between innate and adaptive immunity, potentially leading to synergistic anticancer activity when combined with PD-1 antibody pembrolizumab. **Methods:** This is a phase 2, open-label, single-center study (NCT04171219) of oral BXCL701 0.3 mg BID on days 1-14 and intravenous pembrolizumab 200 mg on day 1 of a 21-day cycle with a safety lead-in to evaluate RECIST/iRECIST response rate in patients with advanced solid cancers. After confirming safety and dose limiting toxicities (DLT) in the first 6 patients, additional patients are being enrolled to an immune checkpoint inhibitors (iCPI) naïve cohort and iCPI pretreated cohort. Each cohort is planned to enroll 9 patients in the first stage, and if a partial (PR) or complete response (CR) is observed the cohort is expanded to a total of 17 patients in the second stage. The treatment is considered promising if at least 3 PRs or CRs are observed in a cohort of 17 patients. **Results:** As of February 11, 2021, 16 patients were treated; 5 patients (prostate cancer, endometrial cancer, liposarcoma, basal cell carcinoma, squamous cell carcinoma of unknown primary) were enrolled in the iCPI naïve cohort and 11 patients (leiomyosarcoma [2], squamous cell carcinoma of unknown primary, triple negative breast cancer, uveal melanoma, melanoma, uterine myxoid sarcoma, pleomorphic sarcoma, colorectal cancer, anaplastic astrocytoma, prostate cancer) were enrolled to iCPI pretreated cohort. Among all 16 patients, there was 1 episode of grade 4 hypotension (recovered) and 1 episode of grade 5 hypotension attributed to BXCL701, which resulted in implementation of risk-mitigation strategies such as gradual dose escalation and blood pressure monitoring. In the CPI naïve cohort, of 4 patients with available imaging, 1 had a PR (microsatellite stable endometrial cancer [-62%]) and 1 durable stable disease (SD -10%, basal cell carcinoma on therapy for 6+ months). In the CPI pretreated cohort, of 9 patients with available imaging, 1 had a PR (-31%, uveal melanoma) and 3 durable SD (-22%, pleomorphic sarcoma on therapy for 8+ months; +4%, squamous cell carcinoma of unknown primary on therapy for 6 months; +5%, uterine myxoid sarcoma on therapy for 6 months). **Conclusions:** BXCL701 in combination with pembrolizumab demonstrated encouraging signals of activity in selected difficult-to-treat cancers. Prespecified efficacy endpoints were met in the first stage and both cohorts will proceed to second-stage of the study Clinical trial information: NCT04171219. Research Sponsor: BioXcel Therapeutics.

2559 **Poster Session**

GS-3583, a novel FLT3 agonist Fc fusion protein, to expand conventional dendritic cells in healthy volunteers. *First Author: Nishanthan Rajakumaraswamy, Gilead Sciences, Inc., Foster City, CA*

Background: Conventional dendritic cells subtype 1 (cDC1) play a vital role in the priming and expansion of tumor specific CD8+ T cells and their recruitment to tumor microenvironment (TME). However, cDC1s are often underrepresented in the TME. Systemic administration of Fms-like tyrosine kinase 3 ligand (FLT3L), a hematopoietic growth factor that binds to FLT3 on myeloid and lymphoid progenitor cells, leads to expansion of cDC1s in the periphery which can then be recruited into the TME. We hypothesize that FLT3 pathway stimulation using GS-3583, a FLT3 agonist Fc fusion protein, has the potential to promote T cell mediated anti-tumor activity. **Methods:** This was a first-in-human placebo-controlled study of GS-3583 in healthy volunteers to evaluate the safety, PK, and PD of escalating single doses (ranging from 75μg to 2000μg) of GS-3583. The study was blinded to the subjects and the investigator. Each dose cohort enrolled 8-12 healthy subjects who received GS-3583 or placebo as single IV infusion at 3:1 ratio. Subjects were observed in the phase 1 unit for 15 days and then for 12 weeks as outpatients. As part of the PD evaluation, we investigated the changes in the number of cDC1s and cDC subtype 2 (cDC2) cells. **Results:** As of 8th Feb 2021, selected safety, PK and PD data from the first 3 cohorts were available. GS-3583 was well tolerated and all subjects had been discharged. To date, there have been no serious or grade 3 or higher adverse events. Preliminary PK analysis suggested dose-dependent increase in GS-3583 exposure (AUC and C_{max}). Preliminary PD analysis shows that administration of GS-3583 resulted in dose-dependent increases in cDC1/cDC2 cells that peaked at day 5 or day 8 and returned to baseline within three weeks of drug administration. **Conclusions:** GS-3583 was safe and well tolerated and induced dose dependent expansion of dendritic cells in the periphery. In patients with cancer, this increase in dendritic cells can be utilized to enhance anti-tumor responses to immuno-oncology therapies. Research Sponsor: Gilead Sciences, Inc.

Cohort	1	2	3	4
Subjects treated(A=active; P=placebo)	8(6A; 2P)	8(6A; 2P)	12(9A; 3P)	-
Age, yearsmedian (range)	32 (20, 38)	27 (23, 45)	22 (18, 45)	-
Male n (%)	5 (62.5%)	5 (62.5%)	8 (66.7%)	-
cDC1 peak cell count*median (Q1, Q3)	Day 5 69.6 (62.9, 89.2)	Day 5 169.0 (121.1, 215.1)	Day 8 76.2 (17.0, 97.1)	
cDC1, fold change from baseline*median (Q1, Q3)	Day 5 1.85 (1.38, 2.4)	Day 5 6.42 (5.62, 7.17)	Day 8 7.83 (3.83, 10.56)	-
cDC2 peak cell count*median (Q1, Q3)	Day 5 1346.0 (1124.8, 1395.1)	Day 5 2937.0 (1679.8, 3731.9)	Day 8 10637.4 (7496.6, 13602.8)	-
cDC2, fold change from baseline*median (Q1, Q3)	Day 5 1.20 (0.71, 1.85)	Day 5 7.61 (3.21, 8.03)	Day 8 15. 41 (7.76, 22.13)	-

* Data shown only from the subjects who received GS-3583; placebo data are excluded

2560 **Poster Session**

Safety and efficacy of murine PVSRIPO plus anti-PD-1 immune checkpoint inhibitor (ICI) in a melanoma tumor model. *First Author: Lauren Neighbours, Istari Oncology, Morrisville, NC*

Background: Most patients with advanced melanoma (mel) fail/acquire resistance to ICI, including anti-(α) PD-1. PVSRIPO is a novel intratumoral immunotherapy derived from the Sabin type 1 attenuated poliovirus (PV) that targets CD155, widely expressed on solid tumors and antigen-presenting cells (APCs) of the tumor microenvironment. Therapy leads to direct tumor cell death and type I/III interferon-dominant innate inflammation, mediating priming and recruitment of tumor antigen-specific T cells. Inflammation-mediated upregulation of the PD-1/L1 IC suggests greater anti-tumor response could be achieved with PVSRIPO + αPD-1. The aim of this preclinical study was to evaluate the efficacy and safety of murine PVSRIPO (mRIPO) + αPD-1 in an aggressive mel tumor model (B16-F10.9-OVA in human-CD155 transgenic mice [C56Bl/6]). **Methods:** Mice were randomized to 4 groups (G) of 12: (G1 [control]: vehicle [v] + IgG; G2: v + αPD-1; G3: mRIPO + IgG; G4: mRIPO + αPD-1). Tumor cells (5 x 10^5) were implanted into the right (R) and left (L) flanks. When tumor volume (vol) was ~25 mm^3, 15 μL v or 1 x 10^7 $TCID_{50}$ mRIPO was injected into R (Day 1) and L (Day 4) tumors; αPD-1 or IgG (250 μg, 100 μL ip) was given on Days 1 and 4 and q 3 days until termination (Day 13). Weight, hematology, chemistry, and inflammatory cytokines were assessed pre/post-tumor implantation. Tumor vol was assessed every other day, with gross/histologic exam at termination. **Results:** 47 mice without health issues were euthanized as planned; 1 G1 animal required early euthanasia for tumor ulceration. Microscopic findings: increased mononuclear cell tumor infiltrates (G2 and G4); less severe L tumor growth necrosis in G2, G3, and G4 vs G1. There were no specific treatment-related changes in serum cytokines in G4. See the table below for summary of total tumor vol changes vs control; the most significant reduction was observed in G4. No tumor cells were observed via histopathology at Day 13 in R flanks of 1 mouse in G2; 3 in G3; and 8 in G4; and only G3 (n=1) and G4 (n=5) mice had no evidence of L flank tumor cells, with regression evident before L tumor mRIPO injection (ie, abscopal response). **Conclusions:** mRIPO + αPD-1 had the greatest overall anti-tumor response, and the combination was well tolerated. These results suggest combination therapy is not associated with untoward immune-mediated toxicity and highlight the potential for enhanced efficacy in injected and uninjected tumors. A phase 2 clinical trial of PVSRIPO ± αPD-1 in unresectable αPD-1 refractory mel is enrolling (LUMINOS-102, NCT04577807). Research Sponsor: Istari Oncology.

Geometric mean ratio (95% CI; p-value) of total tumor vol (R+L) relative to group 1/control.

Group	Day 3	Day 5	Day 9	Day 13
2	0.9 (0.7, 1.1); 0.4	1.0 (0.7, 1.3); 0.8	0.9 (0.6, 1.2); 0.3	0.7 (0.5, 1.1); 0.1
3	0.9 (0.7, 1.1); 0.2	0.9 (0.7, 1.1); 0.2	0.7 (0.5, 1.0); 0.08	0.6 (0.4, 0.9); **0.01**
4	0.9 (0.7, 1.1); 0.3	0.6 (0.5, 0.8); **0.001**	0.5 (0.3, 0.7); **<0.001**)	0.3 (0.2, 0.5); **<0.001**

2561 **Poster Session**

Resetting the tumor microenvironment to favor anti-tumor immunity after local ablation. *First Author: Corrine Audrey Nief, Duke University, Department of Biomedical Engineering, Durham, NC*

Background: Percutaneous tumor ablation is a non-surgical method of tumor destruction that leaves necrotic tumor debris *in situ*. Tumor associated antigens released after ablation have the potential to initiate a systemic anti-tumor immune response, however the hostile tumor microenvironment hinders antigen presentation and T cell activity. We hypothesized that resetting the tumor microenvironment with oral sodium bicarbonate to decrease tumor acidity and low-dose cyclophosphamide to deplete pro-tumor immune cells would improve the ability of ablation to initiate anti-tumor immunity. **Methods:** Tumor growth, overall survival, and metastatic burden was assessed in orthotopic tumor models of triple-negative breast cancer (67NR, 4T1, and E0771). Tumor ablation was performed on palpable tumors using percutaneous ethanol injection (PEI) with 6% ethylcellulose to improve retention in the tumor. Surgical excision was used as a negative control to test the role of *in situ* tumor debris. Before ablation mice were placed on 200 mM of sodium bicarbonate (SB) in their drinking water and received a single intraperitoneal injection of 200 mg/kg of cyclophosphamide (CP). Mice surviving to 60 days after tumor implant without a primary tumor or signs of metastases were considered "cured" and re-challenged with 50e5 tumor cells in the contralateral mammary pad. T cell dependance was assessed with in vivo CD8 depletions. **Results:** The combination of PEI+SB+CP produced a potent anti-tumor response, curing a majority of mice (5/7 of E0771, 8/12 of 67NR, 7/12 of 4T1). No mice were cured using PEI alone, SB alone, CP alone, or any combination of two therapies (0/51 of E0771, 0/73 of 67NR, 0/75 of 4T1,). Re-challenge tumor growth was hindered in mice cured with PEI+SB+CP. Mice receiving PEI+SB+CP had significantly less metastases and lived longer than mice receiving surgical excision alone or surgical excision with SB+CP. Additionally the anti-metastatic response of PEI+SB+CP was undone when CD8+ T cells were depleted. **Conclusions:** Here the anti-tumor response of local ablation produced by PEI was enhanced by priming the tumor with low-dose CP and oral SB in metastatic breast cancer. These results suggest that tumor ablation with CP and SB can create a T cell dependent, personalized immune response to a tumor using only low-cost, easily accessible supplies, and the host's own tumor. Research Sponsor: National Institutes of Health.

2562 **Poster Session**

Phase 1 trial of the adenosine A_{2A} receptor antagonist inupadenant (EOS-850): Update on tolerability, and antitumor activity potentially associated with the expression of the A_{2A} receptor within the tumor. *First Author: Laurence Buisseret, Institut Jules Bordet, Brussels, Belgium*

Background: Tumors produce high levels of extracellular adenosine which suppress anti-tumor immune responses. Blocking A_{2A} receptors, predominantly expressed on tumor-infiltrating immune cells, can reverse the immunosuppressive effect of adenosine. Inupadenant is a non brain-penetrant, potent and highly selective small molecule antagonist of the A_{2A} receptor that remains active even at the high adenosine concentrations found in tumors. **Methods:** This is the phase I portion of an ongoing first-in-human, clinical trial (NCT02740985) to evaluate safety/tolerability, pharmacokinetic, pharmacodynamic and anti-tumor activity of inupadenant in adult patients with solid tumors who have exhausted standard treatment options. In addition, tumor biomarkers, including adenosine-pathway markers by immunohistochemistry (IHC), are being evaluated. We present updated results of the dose escalation, new results from the monotherapy expansion and new analysis of tumor biomarkers. **Results:** Overall, 42 patients (21 patients in the dose escalation and an additional 21 patients in a monotherapy expansion) with a median of 3 prior regimens were treated as of the data cut off (DCO, 30Nov20).The dose levels investigated, along with the most frequent (>20%) treatment-emergent adverse events (TEAEs) across all dose levels are presented in the table. 7 AEs led to discontinuation; 2 (atrial fibrillation and myocardial infarction) were considered possibly study drug-related by the investigator. No dose reductions were required. Two partial responses (PRs) were reported: melanoma (NRAS-mutant; received prior immunotherapy), and prostate cancer (received antiandrogen and chemotherapy). At the DCO, both PRs were ongoing with a duration of response >230 days. 12 patients had stable disease (SD) as best response and SD >6 months was observed in 3 patients. Response and stable disease were associated with a higher number of cells expressing the A_{2A} receptor within the tumor at baseline, as measured by IHC. **Conclusions:** Inupadenant monotherapy was generally well-tolerated as of the DCO at a dose of 80 mg twice daily with initial evidence of clinical benefit, including 2 durable PRs in patients who have exhausted standard treatment options. Analysis of pre-treatment tumor biopsies has identified the A_{2A} receptor as a biomarker which may be associated with clinical benefit. Clinical trial information: NCT03873883. Research Sponsor: iTeos Therapeutics.

Most frequent TEAEs (>20%) in dose escalation and monotherapy expansion.

	Patients N (%)					
Preferred Term	20 mg QD (N=3)	40 mg QD (N=3)	40 mg BID (N=3)	80 mg BID (N=27)	160 mg BID (N=6)	Total (N=42)
Fatigue	1 (33.3)	2 (66.7)	1 (33.3)	9 (33.3)	4 (66.7)	17 (40.5)
Anemia	0 (0)	2 (66.7)	0 (0)	11 (40.7)	1 (16.7)	14 (33.3)
Decreased appetite	2 (66.7)	1 (33.3)	1 (33.3)	6 (22.2)	3 (50.0)	13 (30.9)
Constipation	2 (66.7)	1 (33.3)	0 (0)	7 (25.9)	1 (16.7)	11 (26.2)

2563 **Poster Session**

Tumor-selective activity of XTX202, a protein-engineered IL-2, in mice without peripheral toxicities in nonhuman primates. *First Author: Jennifer O'Neil, Xilio Therapeutics, Waltham, MA*

Background: High-dose recombinant human interleukin-2 (aldesleukin) elicits anti-tumor immunity and is approved for the treatment of renal cell carcinoma and melanoma based on durable complete remissions. However, use of aldesleukin is limited due to treatment-related life-threatening toxicities. Recent second-generation efforts to alleviate toxicities have largely focused on eliminating binding to IL-2Rα, often with half-life extension. We have determined that mice and non-human primates (NHPs) treated with a second generation IL-2 surrogate still experience characteristic dose-limiting toxicities, including vascular leak syndrome. To overcome these toxicities and improve the therapeutic index (TI) of IL-2 as an anti-tumor immunotherapy, we employed protein engineering to generate XTX202, a highly potent third generation masked IL-2. XTX202 is unmasked in the tumor microenvironment by proteolytic activation resulting in full restoration of binding to IL-2Rβ without binding to IL-2Rα. The current study characterizes the therapeutic index of XTX202 versus aldesleukin and a second generation IL-2 surrogate. **Methods:** XTX202 bioactivity was measured using STAT-5 phosphorylation in human PBMCs and reporter cell lines. Anti-tumor efficacy and peripheral immune activation were evaluated in mice bearing syngeneic tumor models. Safety was evaluated in rodents and Cynomolgus monkeys. XTX200, an unmasked half-life extended IL-2 that does not bind to IL-2Rα, was used as a surrogate second generation IL-2. **Results:** Masked XTX202 showed limited IL-2R-dependent STAT-5 signaling *in vitro*. Proteolytic activation of XTX202 resulted in $CD8^+$ T and NK cell activation and over 1000-fold reduction in Treg activation as compared to WT IL-2. XTX202 achieved potent tumor growth inhibition in syngeneic mouse models as a single agent with no evidence of toxicity or peripheral immune activation, thus demonstrating tumor selective activity. XTX202 efficacy in mice at 2 mg/kg dose was equivalent to that achieved with the MTD dose of 0.5 mg/kg of a second generation IL-2 surrogate. XTX202 was well tolerated in NHPs in a 4-week repeat dose study at doses up to 30 mg/kg QW whereas a second generation IL-2 surrogate was not tolerated beyond 0.7 mg/kg QW. Based on these data, XTX202 has a 10 fold improvement in TI vs second generation IL-2. Based on comparative efficacy studies with aldesleukin and literature NHP tolerability data, XTX202 is projected to have a ≥150 fold greater TI than aldesleukin. **Conclusions:** XTX202, a third generation, tumor-selective IL-2, inhibits tumor growth and is well tolerated in repeat dose studies in NHPs at high doses. GLP toxicity studies with XTX202 are underway and first-in-human studies are expected to initiate this year. XTX202 has the potential to be a best-in-class IL-2 immunotherapy by expanding the curative anti-tumor activity of IL-2 while minimizing dose-limiting toxicities. Research Sponsor: Xilio Therapeutics.

2564 **Poster Session**

Antitumor activity of dostarlimab in patients with mismatch repair-deficient/microsatellite instability–high tumors: A combined analysis of two cohorts in the GARNET study. *First Author: Dominique Berton, GINECO & Institut de Cancerologie de l'Ouest, Centre René Gauducheau, Saint-Herblain, France*

Background: Dostarlimab is an investigational, humanized programmed death 1 (PD-1) receptor monoclonal antibody that blocks interaction with the PD-1 ligands, PD-L1 and PD-L2. GARNET (NCT02715284) is a phase 1 study assessing the antitumor activity and safety of dostarlimab monotherapy in patients with solid tumors. **Methods:** This multicenter, open-label, single-arm study is being conducted in 2 parts: dose escalation and expansion. Here we report on the 2 expansion cohorts that enrolled mismatch repairdeficient/microsatellite instabilityhigh (dMMR/MSI-H) patients. Cohort A1 enrolled patients with advanced or recurrent dMMR/MSI-H endometrial cancer (EC), and cohort F enrolled patients with advanced or recurrent dMMR/MSI-H or $POL\varepsilon$-hypermutated non-EC solid tumors, mainly gastrointestinal (GI) tumors (99 [93.4%] had GI tumors, including 69 [65.1%] with colorectal cancer). Patients received 500 mg IV of dostarlimab every 3 weeks for 4 cycles, then 1000 mg IV every 6 weeks until disease progression or discontinuation. The primary endpoints were objective response rate (ORR) and duration of response (DOR) by RECIST v1.1. Here we report ORR and DOR, by individual cohort and as an overall population, in patients with dMMR tumors identified by immunohistochemistry testing. **Results:** For this interim analysis, an efficacy analysis was performed for the patients who had baseline measurable disease and ≥6 months of follow-up in the study (N = 209). The ORR was 41.6% (95% CI, 34.9%48.6%) for the combined A1+F dMMR cohorts (Table). Responses were durable, and median DOR has not been reached in either cohort (median follow-up: cohort A1, 16.3 months; cohort F, 12.4 months). A total of 267 patients were included in the safety population (all patients who received ≥1 dose; cohort A1, N = 126; cohort F, N = 141). Treatment-related adverse events (TRAEs) were consistent across tumor types. Overall, the most frequently reported any-grade TRAEs were asthenia (13.9%), diarrhea (13.5%), and fatigue (11.2%). The most common grade ≥3 TRAEs were anemia (2.2%), lipase increased (1.9%), alanine aminotransferase increased (1.1%), and diarrhea (1.1%). No deaths were attributed to dostarlimab. **Conclusions:** Dostarlimab demonstrated durable antitumor activity in patients with dMMR solid tumors, with consistent antitumor activity seen across endometrial and nonendometrial tumor types. The safety profile was manageable, with no new safety signals detected. Most TRAEs were low grade and were similar across cohorts. Clinical trial information: NCT02715284. Research Sponsor: GlaxoSmithKline.

		Confirmed ORR (RECIST v1.1)	
dMMR solid tumors	N	n (%)	95% CI[a]
Cohort A1 (EC)	103	46 (44.7)	34.9–54.8
Cohort F (non-EC)	106	41 (38.7)	29.4–48.6
dMMR overall	209	87 (41.6)	34.9–48.6

[a]Exact, 2-sided 95% CI for the binomial proportion.

2565 **Poster Session**

Pembrolizumab in microsatellite instability high (MSI-H)/mismatch repair deficient (dMMR) cancers: Updated analysis from phase 2 KEYNOTE-158 study. *First Author: Michele Maio, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy*

Background: Approval of pembrolizumab for the treatment of unresectable or metastatic MSI-H/dMMR solid tumors that have progressed on prior therapy was supported by data from KEYNOTE-158 (NCT02628067). At the data cutoff of Dec 6, 2018, the ORR was 34.3% among 233 patients (pts) with MSI-H/dMMR solid tumors enrolled in all cohorts of KEYNOTE-158, 77.6% had duration of response (DOR) ≥24 mo, median PFS was 4.1 mo, and median OS was 23.5 mo. We present results from 351 pts enrolled in KEYNOTE-158 cohort K at the data cutoff of Oct 5, 2020. **Methods:** Cohort K of this phase 2, open-label study enrolled adults with any previously treated advanced noncolorectal MSI-H solid tumor, measurable disease per RECIST v1.1, and ECOG PS of 0–1. MSI-H/dMMR status was assessed locally from a tumor tissue sample and defined as ≥1 of 4 MMR proteins absent by immunohistochemistry or as ≥2 allelic loci size shifts of 5 microsatellite markers by PCR. Pts received pembrolizumab 200 mg Q3W for up to 35 cycles or until PD, unacceptable toxicity, investigator decision, or withdrawal of consent. The primary endpoint was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints were DOR and PFS per RECIST v1.1 by BICR, OS, and safety. Efficacy was assessed in all pts who received ≥1 dose of treatment with ≥6 mo follow-up; safety was assessed in all treated pts. **Results:** 351 pts were enrolled in KEYNOTE-158 cohort K across multiple tumor types, including endometrial (22.5%), gastric (14.5%), small intestine (7.4%), ovarian (7.1%), cholangiocarcinoma (6.3%), and pancreatic (6.3%). 41.0% had 1 prior line of therapy; 55.6% had ≥2 prior lines. Median time from first dose to database cutoff (Oct 5, 2020) was 37.5 (range, 0.2–55.6) mo; 16.0% were continuing treatment. The ORR among the 321 eligble pts was 30.8% (CR, 27; PR, 72); median DOR was 47.5 mo (Table). Treatment-related AEs occurred in 64.7% of pts (grade 3–5, 12.0%), led to discontinuation in 6.6%, and led to death in 3 pts (myocarditis, pneumonia, and Guillain-Barre syndrome). Immune-mediated AEs and infusion reactions occurred in 20.2% of pts (grade 3–4, 4.3%) and led to death in 2 pts with no other contributing factors (myocarditis [AE start, day 26; death, day 33] and Guillain-Barre syndrome [AE start, day 22; death, day 41]). **Conclusions:** Pembrolizumab demonstrated a high ORR (30.8%), durable clinical benefit, and a manageable safety profile in this heavily pretreated advanced MSI-H/dMMR noncolorectal pan-tumor population. Clinical trial information: NCT02628067. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	KEYNOTE-158 Cohort K N = 321
Confirmed ORR, % (95% CI)	30.8 (25.8 to 36.2)
Median DOR, mo (range)	47.5 (2.1+ to 51.1+)
- ≥24 mo, %	74.1
- ≥36 mo, %	70.1
Median PFS, mo (95% CI)	3.5 (2.3 to 4.2)
- 36-mo rate, %	24.0
Median OS, mo (95% CI)	20.1 (14.1 to 27.1)
- 36-mo rate, %	39.1

CI, confidence interval. "+" indicates no progressive disease by the time of last disease assessment.

2566 **Poster Session**

Efficacy and safety of HLX10, a novel anti-PD-1 antibody, in patients with previously treated unresectable or metastatic microsatellite instability-high or mismatch repair-deficient solid tumors: A single-arm, multicenter, phase 2 study. *First Author: Shukui Qin, Chinese People's Liberation Army Cancer Center of Nanjing Bayi Hospital, Nanjing, China*

Background: Microsatellite instability-high/mismatch repair-deficient (MSI-H/dMMR) in cells render them susceptible to immune checkpoint blockages. This study aimed to evaluate the efficacy and safety of HLX10, a fully humanized monoclonal antibody against PD-1, in patients with unresectable or metastatic MSI-H/dMMR solid tumors who have progressed on or been intolerant to standard therapies. **Methods:** In this single-arm, open-label, multicenter, phase 2 study (NCT03941574), patients (18≤ age ≤75 years) with histologically/cytologically confirmed unresectable or metastatic MSI-H/dMMR solid tumors were recruited to receive 3 mg/kg HLX10 every two weeks intravenously for up to 2 years until disease progression, unacceptable toxicity, or patient withdrawal. The primary endpoint was objective response rate (ORR) assessed by IRRC (evaluated every 6 weeks for the first 48 weeks and every 12 weeks thereafter) per RECIST v1.1. Secondary endpoints included ORR assessed by investigators, duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety. All eligible patients who received at least one dose of HLX10 were included in the safety analyses. **Results:** As of Jan 9, 2021, 108 patients were enrolled and 68 with locally or centrally confirmed MSI-H were included in the main efficacy analysis population. Among the 68 patients, the median follow-up duration was 7.7 (range: 1.1–16.4) months and the median age was 53.0 (range: 23.0–72.0) years. MSI-H tumor types included colorectal cancer (n = 54), endometrial cancer (n = 5), gastric cancer (n = 4), breast cancer (n = 2), small intestine cancer (n = 2) and fallopian tube cancer (n = 1). IRRC and investigator assessed ORR were 38.2% (95% CI: 26.7–50.8%; 2 complete response) and 35.3% (95% CI: 24.1–47.8%) respectively in the main efficacy analysis population. Median DoR, PFS and OS have not been reached. 105 (97.2%) patients experienced treatment-emergent adverse events (TEAEs), most commonly anemia (34.3%), hypoproteinemia (27.8%) and increased aspartate aminotransferase (25.0%). 53 (49.1%) patients had grade 3 or worse TEAEs, most commonly anemia (8.3%), progressive disease (6.5%), increased γ- glutamyltransferase (5.6%) and intestinal obstruction (5.6%). 52 (48.1%) patients had immune-related adverse events (irAEs) while 10 (9.3%) had grade 3 or worse irAEs. 3 (2.8%) deaths (2 PD and 1 intestinal obstruction) that might be related to the study drug were reported. **Conclusions:** HLX10 provides encouraging antitumor activity with a manageable safety profile in patients with MSI-H/dMMR solid tumors who have progressed on or been intolerant to standard therapies. As an effective tissue-agnostic treatment, HLX10 possesses the potential to improve patients' clinical outcomes. Clinical trial information: NCT03941574. Research Sponsor: Shanghai Henlius Biotech, Inc.

2567 **Poster Session**

Multi-center phase 1 safety and efficacy study of nivolumab in renal transplant patients with metastatic malignancy. *First Author: John Raymond Zalcberg, Peter MacCallum Cancer Centre, Melbourne, Australia*

Background: Organ Transplant Recipients (OTR) are generally excluded from trials of immune checkpoint inhibitors (ICI) due to the reported risk of allograft rejection. A recent systematic review of published case series includes only 65 cases. Transplant organ rejection rates of 41% are reported with cancer response rates of 39%. The majority of OTR treated with ICI have had reduction/cessation of immunosuppression (IS) prior to ICI. Isolated IS reduction is associated with organ rejection and therefore either IS manipulation alone and/or ICI could induce organ rejection episodes. **Methods:** Renal OTR with incurable cancer, for whom ICI would normally be used in the general population (without an organ transplant), were eligible if creatinine < 180 umol/l, no donor specific HLA antibodies and ECOG < 2. Treatment was with nivolumab (3mg/kg q 14 days for 5 doses, then 480 mg q 28 days), without manipulation of IS and pre-ICI-exposure alloimmune risk assessment. Treatment continued till progression, patient refusal, or graft rejection. Primary endpoint was rate of irretrievable renal graft rejection. **Results:** 15 patients (9 male:6 female; median age 66.6 years) were enrolled and treated with a median (range) 3(1-42) infusions and with median (range) follow-up of 128 (11-784) days . Tumour types included:1 melanoma; 2 renal tract; 1 hepatocellular carcinoma; 1 Merkel cell; 1 adenocarcinoma lung; 1 MSI high colorectal, 8 squamous cell carcinoma (SCC) head and neck. 2 patients experienced rejection; one at day 28 (2 infusions); one at day 36 (3 infusions). Both had SCC and have had a CR. One is on haemodialysis and alive at 2 years the other a creatinine 450 umol/l. Both rejections treated with steroid, plasma-exchange and anti-thymocyte-globulin (ATG). 1 patient (metastatic bladder cancer) experienced graft loss (at 300 days) due to ureteric-stent bleed and BK-nephritis indirectly related to nivolumab- this patient died of progressive disease at 65 days after nivolumab cessation. Median (range) progression free disease (PD) with ≥ 2 infusions was 300 (68-784+) days. There were 5 CR (1 MSI high colorectal, 4 SCC) median duration of response 13 months and 2 PR (1 SCC 1 bladder)- 1 without PD. **Conclusions:** In this interim analysis, rejection rates in OTR with incurable cancers treated with ICI was 2/15 (13%) when IS is maintained and there is pre exposure alloimmune assessment. The combined CR and PR rate was 7/15 (47%). Clinical trial information: 12617000741381. Research Sponsor: BMS.

2568 **Poster Session**

Phase I dose escalation of KD033, a PDL1-IL15 bispecific molecule, in advanced solid tumors. *First Author: Jason J. Luke, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: IL-2 and IL-15 signal through the shared IL-2/15 βγ receptor, but unlike IL-2, IL-15 does not expand regulatory T cells (Tregs), does not mediate activation-induced cell death and may have an improved therapeutic index. KD033 is a fusion antibody combining a fully human, high affinity anti-human Programmed Death Ligand 1 (PD-L1) IgG1 antibody with the human IL-15 receptor alpha (IL15Rα) sushi domain and human IL-15 (IL-15). KD033 (or its mouse cross reactive surrogate molecule, srKD033) has been extensively characterized in multiple *invitro* and *in vivo* nonclinical studies. The fusion of anti-PD-L1 antibody to IL-15 significantly increases the maximal-tolerated dose (MTD) of srKD033 in mice compared to free IL-15. In addition, srKD033 has exhibited increased efficacy in rejecting tumors in mice as compared to the combination of its individual components, anti-PD-L1 antibody and IL-15. **Methods:** This is a phase 1, open-label, multiple ascending dose, multi-center clinical trial being conducted in patients with metastatic or locally advanced solid tumors (NCT04242147). The primary objective is to determine the safety and tolerability and the MTD of KD033. Secondary objectives include characterization of PK and immunogenicity, evaluation of CD8 T and NK cell activation and assessment of best overall response and duration of response. KD033 is administered by IV infusion over 30 minutes every 14 days. Accelerated intra-patient dose escalation across the initial three dose levels, followed by 3+3 escalation thereafter, is investigating dose ranges from 3 μg/kg to 600 μg/kg. Efficacy evaluation is planned in an expansion cohort of patients with PD-1/L1 refractory tumors. **Results:** A total of 7 patients have received treatment. Three patients were dosed in Cohort 1 and four patients were dosed in Cohort 2. Through two dose escalation cohorts (3 μg/kg – 25 μg/kg), no dose-limiting toxicities have been reported. Grade 1-2 treatment-related toxicities, when observed, resolved within 24 hours with supportive management. 6 patients are evaluable for treatment response with one patient (adenoid cystic carcinoma) in the first cohort having stable disease for more than 6 months. **Conclusions:** KD033 has been well tolerated early in dose escalation with on-mechanism pharmacodynamics consistent with IL-15 agonism. Clinical trial information: NCT04242147. Research Sponsor: None.

2569 **Poster Session**

A phase 2 study of tislelizumab monotherapy in patients with previously treated, locally advanced unresectable ormetastatic microsatellite instability-high/mismatch repair deficient solid tumors. *First Author: Jian Li, Beijing Cancer Hospital, Beijing, China*

Background: Tislelizumab is an anti-programmed cell death protein 1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis. In early phase clinical studies, tislelizumab monotherapy was generally well tolerated and had antitumor activity in patients (pts) with solid tumors, including microsatellite instability-high (MSI-H) or mismatch-repair-deficient (dMMR) solid tumors such as colorectal cancer (CRC). **Methods:** This single-arm, multicenter, open-label, phase 2 study evaluated the efficacy and safety of tislelizumab monotherapy in adult Chinese pts with previously treated, locally advanced, unresectable or metastatic histologically confirmed MSI-H/dMMR solid tumors by central lab. Pts received tislelizumab 200 mg intravenously every 3 weeks until disease progression, unacceptable toxicity, or withdrawal. Radiological imaging was performed at 9 weeks then every 6 weeks for the first year of therapy and every 12 weeks thereafter. The primary efficacy analysis set was all pts who received any dose of tislelizumab with measurable disease per independent review committee (IRC) at baseline. The primary endpoint was IRC-assessed overall response rate (ORR; RECIST v1.1). Secondary endpoints included duration of response (DoR) and disease control rate. Using a binomial exact test, the null hypothesis of ORR=10% (historical rate) was rejected if 1-sided p≤0.025. **Results:** Between Sep 2018-Aug 2020, 80 pts were enrolled (median age 53 years; range 19-81 years) and 74 were included in the primary efficacy analysis set. At median study follow-up of 11.78 months, ORR by IRC was 45.9% (n=34/74; 95% CI 34.3, 57.9) in all tumor types (1-sided p<0.0001), including 4 complete responses (CR) and 30 partial responses (PR). Observed ORR by IRC was 39.1% (n=18/46; 95% CI 25.1, 54.6) in CRC pts and 57.1% (n=16/28; 95% CI 37.2, 75.5) in non-CRC pts. Of 74 pts, 53 (71.6%) had disease control and 39 (52.7%) achieved CR, PR or durable stable disease by IRC ≥24 weeks. Median DoR by IRC has not been reached; no disease progression was reported in the 34 responders (CR+PR), with 33 responders still on treatment (12-month DoR rate=100%). Treatment-emergent adverse events (TEAEs) ≥Grade 3 occurred in 47.5% (n=38/80) pts, of which 21.3% (n=17/80) were lab abnormalities. Immune-mediated TEAEs ≥Grade 3 were 5% (n=4/80). **Conclusions:** Tislelizumab achieved statistical significance and demonstrated clinically meaningful improvement in ORR in pts with previously treated locally advanced unresectable or metastatic MSI-H or dMMR solid tumors. Treatment effect was consistent and durable across tumor types and endpoints. Tislelizumab was generally well tolerated and no new safety signals were identified. The data support tislelizumab as a new treatment option in this population. Clinical trial information: NCT03736889. Research Sponsor: This study is sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Jessica Jones, PhD, and Kirsty Millar, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

2570 **Poster Session**

Mega- and meta-analyses of fecal metagenomic studies in predicting response to immune checkpoint inhibitors. *First Author: Alya Heirali, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: A number of studies have demonstrated that the gut microbiome of responders to immune checkpoint inhibitors (ICI) is compositionally different compared to that of non-responders. However, differences in study design, patient cohorts and bioinformatic analyses make it challenging to identify bacterial species consistently associated with response to ICI across different cohorts and cancer types. **Methods:** We leveraged the statistical power of mega- and meta-analyses to identify bacterial species consistently associated with response to ICI using data from three published fecal metagenomic studies (Gopalakrishnan *et al., Science 2018;* Matson *et al., Science 2018;* Routy *et al., Science 2018).* Metagenomic data was uniformly processed and analyzed using Metaphlan v2.0. We conducted a two-part modelling approach of bacterial species present in at least 20% of samples to account for both prevalence and relative abundance differences between responders/non-responders. **Results:** A total of 190 patients (n = 103 responders; n = 87 non-responders) were included from the three studies. Data from Routy *et al.*, was analyzed as subsets based on tumor type for a total of 4 analyzed cohorts. We identified five species including *Bacteroides thetaiotaomicron*, *Clostridium bolteae, Holdemania filiformis,Clostridiaceae bacterium JC118* and *Escherichia coli* that were concordantly significantly different between responders and non-responders using both meta- and mega-analyses. *B. thetaiotaomicron* and *Clostridium bolteae* relative abundance (RA) were independently predictive of non-response to immunotherapy when data sets were combined and analyzed using mega-analyses (AUC 0.59 95% CI 0.51-0.68 and AUC 0.61 95% CI 0.52-0.69, respectively). **Conclusions:** Despite inter-cohort heterogeneity in tumor type, treatment regimens, and sequencing modalities, meta- and mega analysis of published metagenomic studies identified generalizable bacterial species associated with ICI response or lack thereof. *B.thetaiotaomicron* and *C. bolteae* were predictors of non-response to ICI suggesting the clinical potential of narrow spectrum anti-biotics targeting non-response associated bacterial species to improve outcomes in ICI recipients. Research Sponsor: Princess Margaret Cancer Foundation, Tomcyzk AI and Microbiome Working Group.

2571 **Poster Session**

Phase 2 study of retifanlimab (INCMGA00012) in patients (pts) with selected solid tumors (POD1UM-203). *First Author: Michele Maio, Center for Immuno-Oncology, University Hospital of Siena, Siena, Italy*

Background: Checkpoint inhibitors (CPIs) are an effective treatment (tx) for many tumor types. Retifanlimab, an investigational humanized anti–PD-1 monoclonal antibody, has shown safety, pharmacology, and clinical activity consistent with the class. POD1UM-203 (NCT03679767) assessed efficacy and safety of retifanlimab in pts with selected solid tumors where CPI monotherapy is highly active. **Methods:** Eligible pts (≥18 y) had tx-naïve metastatic non-small cell lung cancer (NSCLC) with high PD-L1 expression (tumor proportion score ≥50%), cisplatin ineligible locally-advanced/metastatic urothelial cancer (UC) with PD-L1 expression (combined positive score ≥10%), unresectable/metastatic melanoma, or tx-naïve locally advanced/metastatic clear-cell renal cell carcinoma (RCC). Measurable disease (RECIST v1.1) was required. ECOG PS >1 and prior PD-1/PD-L1 directed tx were exclusions. Retifanlimab was administered as an IV infusion at 500 mg every 4 wks over 30 min. Primary endpoint was investigator-assessed objective response rate (ORR). Secondary endpoints were duration of response (DOR), disease control rate (DCR), progression-free survival, overall survival, safety, and pharmacokinetics. **Results:** A total of 121 pts (35 melanoma, 23 NSCLC, 29 UC, 34 RCC) received ≥1 dose of retifanlimab and were included in the analyses. Median duration of tx was 169 d (range, 1–442). The efficacy cut-off for the primary analysis occurred once all pts had been followed for at least 6 mo from the time of initial tx. Confirmed RECIST v1.1 responses were observed in all tumor types (Table) and were consistent with published ORR for other CPIs; median DOR was not reached for any tumor cohort and tx was ongoing at the time of data cutoff for 17, 11, 9, and 15 pts with melanoma, NSCLC, UC, and RCC, respectively. The most common tx-emergent AEs (TEAEs, >10% incidence) were asthenia (17.4%), arthralgia (14.9%), decreased appetite (14.0%), pruritus (12.4%), rash (10.7%), and urinary tract infection (10.7%); majority of TEAEs were low grade (≤ grade 2) and none led to tx discontinuation. Immune-related AEs occurred in 23 pts (19.0%), most common (>1% incidence) were hypothyroidism (7.4%), rash (4.1%), hyperthyroidism (2.5%), and pruritus (1.7%).Immune-related AEs led to dose delay in 5 pts (4.1%), but none led to tx discontinuation and/or dose interruption. **Conclusions:** Retifanlimab demonstrated antitumor activity and was generally well-tolerated in pts with melanoma, NSCLC, UC, or RCC comparable with approved CPIs for these tumor types. These results support ongoing further development of retifanlimab. Clinical trial information: NCT03679767. Research Sponsor: Incyte Corporation Inc.

Efficacy summary.

	Melanoma n=35	NSCLC n=23	UC n=29	RCC n=34
ORR, n (%)	13 (37.1)	7 (30.4)	11 (37.9)	8 (23.5)
95% CI	21.5–55.1	13.2–52.9	20.7–57.7	10.7–41.2
DCR, %	54.3	65.2	55.2	64.7
95% CI	36.6–71.2	42.7–83.6	35.7–73.6	46.5–80.3
Median DOR 95% CI	NE	NE	NE	NE
NE, not estimable	NE–NE	1.9–NE	2.2–NE	2.8–NE

2572 **Poster Session**

Efficacy of HX008 in high microsatellite instability/mismatch repair–defificient (MSI-H/dMMR) solid tumors: Results from a multicenter phase II open-label study. *First Author: Jing Huang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: The subsequent treatment choices are limited for the patients with advanced solid tumors who had failed the standard therapies. PD-1 blockade monotherapy demonstrated robust antitumor activity in patients with MSI-H/dMMR. The aim of this study is to identify the efficacy and safety of HX008, an anti-PD-1 monoclonal antibody, in patients with advanced MSI-H/dMMR solid tumors. **Methods:** Eligible patients were age ≥18 years with histologically/cytologically confirmed advanced MSI-H/dMMR solid tumors, who have failed at least one line of standard systemic therapy. MSI-H/dMMR status was assessed centrally. Patients received HX008 200 mg once every 3 weeks until disease progression, unacceptable toxicity, or patient withdrawal. Radiologic imaging was performed 9 weeks after the first treatment, then every 6 weeks for the first year of therapy, and every 12 weeks thereafter. The primary end point was objective response rate (ORR) per RECIST1.1. **Results:** One hundred patients were enrolled from October 2018 to December 2020, with a median age of 53 (range 20-74) years. All of the patients were ≥ second-line patients. The most common cancer types were colorectal cancer (N=74) and gastric cancer (N=10). Median follow-up is 8.97 (range 0.03-25.53) months at the time of data cutoff. Among 86 patients who had reached the initial response evaluation, there were 8 CR, 33 PR, 24 SD, 17 PD and 4 NE. ORR was 47.67% (95%CI 36.79%-58.73%), and DCR was 75.58% (95%CI 65.13%-84.20%). ORR and DCR for the 66 colorectal cancer patients were 50% (95%CI 37.43-62.57%) and 75.76% (95%CI 63.64-85.46%). Median PFS was not reached (95%CI 6.18-NR) for all enrolled patients, while the 6-month and 12-month PFS rates were 62.66% (95%CI 50.98%-72.31%) and 52.70% (95%CI 39.96%-63.94%), respectively. Median OS was not reached. Treatment-related adverse events occurred in 77 patients (77%). Twelve patients (12%) had grade 3 or 4 treatment-related adverse events and there were no grade 5 treatment-related adverse events. The grade 3 or 4 treatment-related adverse events with incidence >1% included anemia (2%) and leukopenia (2%). Immune-related adverse events were observed in 15 patients (15%), including hypothyroidism in 9 patients (all were grade 1-2), and hepatitis, hyperglycemia, myocarditis, creatin kinase/creatin kinase MB increased, hypopigmentation of the vulva, rash, each in 1 patient. **Conclusions:** HX008 as a ≥second-line therapy showed promising efficacy and a manageable safety profile in patients with MSI-H/dMMR advanced solid tumors. Clinical trial information: NCT03704246. Research Sponsor: Taizhou Hanzhong Biomedical Co. LTD.

2573 **Poster Session**

An exploratory study of nivolumab (nivo) with or without ipilimumab (ipi) according to the percentage of tumoral CD8 cells in advanced metastatic cancer. *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Immune checkpoint inhibitors (ICIs) have demonstrated durable clinical responses and improved survival in patients (pts) across numerous indications. Despite this progress, the benefit of ICIs is limited to a minority of overall metastatic cancer patients. There is a critical need for biomarkers agnostic of tumor type to inform which pts will benefit from nivo alone versus ipi/nivo combination treatment. Both pre-treatment tumoral $CD8^+$ cells and recruitment of $CD8^+$ T cells in response to ICIs are associated with improved clinical outcomes in patients treated with anti-PD-1 therapy. [1,2,3,4] Here we report the final results of a prospective clinical study in which pts with varying advanced solid tumors were assigned to nivo, with or without ipi, based on the percentage of tumoral CD8 cells at the time of treatment. **Methods:** We performed a prospective, non-randomized, open-label, multicenter study in which pts with tumoral $CD8^+$ cells $\geq$ 15% ($CD8^+$ high) received nivo 360mg IV Q3W, followed by nivo maintenance 480mg Q4W. Pts with tumoral $CD8^+$ cells $<$ 15% ($CD8^+$ low) received nivo 360 mg IV Q3W, and ipi at 1 mg/kg IV Q3W for 2 doses and then Q6W for 2 doses, followed by nivo maintenance 480 mg IV Q4W until PD or intolerable toxicity. Primary endpoints were Disease Control Rate (DCR: CR, PR, or SD $\geq$ 6 months) and CD8 low to high conversion ($<$ 15% to $\geq$ 15%). Baseline and on-treatment tumor, blood and stool samples were collected for multiomic biomarker analyses. This study was not powered for formal statistical analysis. Up to 200 pts could be enrolled to allow for adaptive exploration of response and CD8 changes. **Results:** N = 79 pts were enrolled:7 in $CD8^+$ high arm (nivo) and 72 in $CD8^+$ low arm (ipi/nivo). The study enrolled a wide variety of primary solid tumors; the most common were gynecological (n = 15), prostate (12), and head and neck (7). DCR was 14% (1/7; 95% CI 1 - 44) and 24% (17/72; 95% CI 15 - 34) in the CD8 high and CD8 low arms, respectively. Of 39 pts in CD8 low arm with an on-treatment biopsy, 14 (36%; 95% CI 22 - 51) had CD8 conversion; 7/14 pts (50%) who converted had DCR. Immune-related AEs (irAEs) were consistent with known safety profile of both drugs. **Conclusions:** Ipi/nivo demonstrated clinical responses and increased CD8% in a range of "cold" tumors with low tumoral CD8 cells. There may be an association between increasing CD8% and response. Baseline high CD8% alone does not appear to be sufficient as a pan-cancer predictive biomarker of response to nivo monotherapy. CD8 conversion, response, and irAEs associated with circulating and stool-based biomarkers are under evaluation as composite biomarkers may improve their predictive value. Clinical trial information: 03651271. Research Sponsor: The Parker Institute for Cancer Immunotherapy.

2574 **Poster Session**

Assessment of cancer-specific microbiome signature of response to immune checkpoint inhibitors. *First Author: Michal Sarfaty, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Clinical and preclinical experiments suggest that the gut microbiome can affect outcome in cancer patients treated with immune checkpoint inhibitors (ICI). Most data to date has been in melanoma, so the relationship of the gut microbiome with treatment outcome in other cancers is poorly understood. Here, we evaluated the microbiome composition in correlation to ICI response in patients with metastatic lung, urothelial, or renal cancer, as well as metastatic melanoma. **Methods:** Fecal microbiome samples were obtained from patients with metastatic melanoma, lung, urothelial, or renal cancer immediately before ICI therapy was initiated. Bacterial genomic DNA was isolated and profiled by whole metagenome sequencing. Sequence data were analyzed using a custom implementation of MetaPhlAn2. Response to ICI was defined as partial or complete response or remaining on therapy for more than 6 months. **Results:** Samples were prospectively collected from 94 patients, including metastatic melanoma (n = 17), lung (n = 44), urothelial (n = 23), or renal cancer (n = 10). Treatment included anti-PD(L)1 monotherapy (n = 51), anti-PD1 + anti-CTLA4 combination therapy (n = 17), or a combination of anti-PD1 and chemotherapy (n = 26). Clinical response was observed in 58% of patients, including partial or complete response (45%) and on treatment for more than 6 months (55%, with 31% on treatment for more than 1 year). Although the variance in the composition of pretreatment microbiome samples did not explain response alone (R vs NR, PERMANOVA, p = 0.273), a significant portion of the variance in microbiome composition was explained by the interaction of cancer type and outcome (PERMANOVA, p = 0.014), suggesting a cancer-specific microbiome relationship. Notably, there was some similarity in the signature of NR across three cancer types (lung, urothelial and melanoma). One sample in this NR cluster was from a patient whose metastatic NSCLC was nonresponsive to pembrolizumab and carboplatin/pemetrexed. This microbiome sample was evaluated *in vivo* using subcutaneous MC38 and CT26 tumor models in germ-free mice. In contrast to mice colonized with stool from a healthy donor, mice colonized with stool from this patient yielded a nonresponsive result upon treatment with anti-PD1 or anti-PD-L1 in combination with anti-CTLA4. **Conclusions:** Analysis of the fecal microbiome composition from patients with metastatic lung, urothelial, renal cancer, and melanoma identified a cancer-specific signature of R and NR to ICI. Across three cancer types, a consistent signature of NR was identified and corroborated experimentally in preclinical models. Research Sponsor: Seres therapeutics, U.S. National Institutes of Health.

2575 **Poster Session**

CheckMate 8KX: Phase 1/2 multitumor preliminary analyses of a subcutaneous formulation of nivolumab (± rHuPH20). *First Author: Sara Lonardi, Veneto Institute of Oncology (IOV)-IRCCS, Padua, Italy*

Background: Immunotherapy has transformed cancer survival expectations. Nivolumab (NIVO), a programmed death-1 inhibitor, is approved for intravenous (IV) administration across multiple cancers. BMS is developing a subcutaneous (SC) NIVO formulation with a permeation enhancer, recombinant human hyaluronidase PH20 enzyme (rHuPH20), to allow for more rapid delivery and the potential to decrease treatment burden. We report the first data on pharmacokinetics (PK), pharmacodynamics, safety, and immunogenicity for SC NIVO + rHuPH20. **Methods:** CheckMate 8KX is a phase 1/2 study in checkpoint inhibitor-naïve patients (pts) who were $\geq$ 18 years of age, ECOG PS 0–1, with metastatic/unresectable solid tumors and measurable disease. The primary objective was to describe SC NIVO PK; secondary objectives were safety and immunogenicity. Additional analyses compared exposures to historical IV NIVO (Zhao X, et al. *J Clin Oncol* 2020;31:302–309). In cycle 1, pts in Part A received SC NIVO 720 mg + rHuPH20, and pts in Part B received SC NIVO 720 mg, SC NIVO 960 mg + rHuPH20, or SC NIVO 960 mg. For cycles 2+, pts in Parts A and B received IV NIVO 480 mg every 4 weeks (Q4W). Pts still on study switched to Part C, SC NIVO 1200 mg + rHuPH20 until end of therapy. In Part D, pts received de novo SC NIVO 1200 mg + rHuPH20 Q4W. **Results:** Patient characteristics varied by age, weight, tumor type, and prior treatment. NIVO exposures increased with increasing SC dose (Table). For 960 mg and 1200 mg NIVO + rHuPH20, Cavg and Ctau were above geometric mean exposures for IV NIVO 3 mg/kg every 2 weeks (Q2W), and Cmax was below IV NIVO 10 mg/kg Q2W. In Part C (n = 28), 13 (46.4%) pts experienced any-grade TRAEs with no new/worsening grade 3+ TRAEs or TRAEs leading to discontinuation/death; 7 (25.0%) reported grade 1 local site reactions. In Part D (n = 36), 27 (75.0%) pts experienced any-grade TRAEs, 4 (11.1%) grade 3/4 TRAEs, 2 (5.6%) serious grade 3/4 TRAEs with 1 leading to discontinuation, and no treatment-related deaths; 10 (27.8%) reported grade 1 local site reactions. Anti-NIVO antibodies (Ab) were observed with SC NIVO but not associated with altered PK/safety, or neutralizing Ab. Exploratory biomarker data found increased CD8+ tumor-infiltrating lymphocytes and PD-L1 tumor expression in post-treatment biopsies, similar to IV NIVO. **Conclusions:** Exposures associated with SC NIVO + rHuPH20 doses investigated in CheckMate 8KX were well tolerated, with a safety profile consistent with IV NIVO. Data support evaluation of SC NIVO + rHuPH20 in a phase 3 study. Clinical trial information: NCT03656718. Research Sponsor: Bristol Myers Squibb, Professional medical writing assistance was provided by Katherine Groschwitz, PhD, and Jay Rathi, MA, of Spark Medica Inc, funded by Bristol Myers Squibb.

NIVO exposures by dose with rHuPH20.

Geometric mean NIVO concentration, μg/mL (range)	Ctau	Cavg	Cmax
NIVO 720 mg SC (n = 20[a])	22.2 (4.76–59.6)	36.6 (16.5–76.3)	54.8 (19.9–114)
NIVO 960 mg SC (n = 9)	39.5 (8.06–67.6)	62.2 (26.8–93.3)	84.8 (42.7–128)
NIVO 1200 mg SC (n = 25[b])	51.3 (18.4–96.5)	77.5 (39.1–141)	105 (40.0–245)

[a]n = 22 for Cmax [b]n = 26 for Cmax Ctau = concentration at the end of the dosing interval.

2576 **Poster Session**

Final results of a phase I "RadVax" trial of hypofractionated radiation combined with pembrolizumab in patients with metastatic solid tumors. *First Author: John Nicholas Lukens, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: Many patients treated with anti-PD-1 therapy do not show a clinical response. Preclinical studies suggest that adding hypofractionated radiotherapy (HFRT) to anti-PD1 can increase the efficacy of immunotherapy through several mechanisms including increased antigen presentation. We conducted a prospective trial testing the combination of pembrolizumab and HFRT in patients with metastatic solid tumors. **Methods:** This prospective single-institution phase I trial tested pembrolizumab in combination with HFRT in patients with metastatic cancers (NSCLC, melanoma, pancreas, breast, others) and an ECOG performance status of 0-1. Melanoma and NSCLC patients were required to have progression of disease on anti-PD1, having received $\geq$ 2 doses of anti-PD1 and progression documented by RECIST v1.1. Patients were required to have an index lesion $\geq$1 cm that was amenable to HFRT and at least one other lesion that was not irradiated and could be followed for response using RECIST criteria. Pembrolizumab 200 mg IV every 3 weeks was administered beginning 1 week prior to the first fraction of radiation. The HFRT dose was 8 Gy x 3 fractions or 17 Gy x 1 fraction, determined by randomization during the Expansion phase. The primary objective was the safety of HFRT combined with pembrolizumab, with dose-limiting toxicity (DLT) defined as Grade $\geq$ 3 non-hematological toxicity related to the combination of Pembrolizumab and HFRT. The secondary objective was the radiographic response of metastatic lesions outside the radiation field as measured by RECIST. **Results:** 59 patients aged 27-90 years (median 60) were enrolled from March 2015 to December 2018 (24 in the Safety Phase and 35 in Expansion Phase). 40 patients (67.7%) had treatment-related AEs, of which 4 were grade 3 and none were grade 4. One patient experienced hepatitis, classified as DLT. While most patients did not have a radiologic response, in patients with metastatic melanoma, 7 of 16 (43.8%, exact 95% CI 19.8-70.1%) had an objective response to HFRT + pembrolizumab, including 3 complete and 4 partial responses. Responses are durable with 3/3 complete responders alive with no progression, and 3/4 partial responders alive with 2 having no evidence of progression. Among melanoma patients, only 2 of 7 (29%) responders received ipilimumab prior to enrollment, compared to 8 of 9 (89%) non-responders (p = 0.035). An increase in Ki67+ PD-1+ non-naïve CD8 T-cells was observed in the blood 2 weeks after HFRT, but the magnitude did not correlate with likelihood of response. Responses were observed after either 17 Gy x 1 fraction or 8 Gy x 3 fractions, with no difference in response rate by fractionation. **Conclusions:** This study suggests that HFRT administered with concurrent pembrolizumab is associated with acceptable toxicity and that in patients with metastatic melanoma progressing on anti-PD-1 therapy, this approach yields an ORR of 44%. Clinical trial information: NCT02303990. Research Sponsor: Merck, U.S. National Institutes of Health.

2577 **Poster Session**

A first-in-human phase I dose escalation of YH001, an anti-CTLA-4 monoclonal antibody (mAb) in combination with toripalimab (anti-PD-1 mAb) in patients with advanced solid tumors. *First Author: Vinod Ganju, Peninsula and Southeast Oncology, Frankston, VIC, Australia*

Background: YH001 is a humanized anti -hCTLA-4 IgG1 mAb that relieves CTLA-4-mediated immunosuppression, and thereby enhances the T-cell-mediated antitumor immune response. Pre-clinical data have shown potent anti-cancer activity when combined with anti-PD-1 mAb. **Methods:** This is an ongoing phase 1 dose-escalation study. Patients (pts) with advanced solid tumors received YH001 by IV administration at 0.05 to 6.0 mg/kg for 1 cycle (21 days) then in combination with Toripalimab (anti-PD-1 mAb) at 240 mg Q3W for 4 cycles. An accelerated titration method followed by the standard "3+3" design was utilized to evaluate safety, tolerability and preliminary efficacy. **Results:** As of 31-Dec-2020 data cut-off, 10 pts were enrolled and treated at 0.05 mg/kg (n = 2), 0.1 mg/kg (n = 3), 0.3 mg/kg (n = 3) and 1 mg/kg (n = 2). The median age was 62 years (range 46-74). Baseline ECOG scores were 0 (n = 8), 1(n = 2) with all pts progressed after a median of 2 prior lines of available standard therapy (range 1-4) including 1 pt progressed after immunotherapy of pembrolizumab. There were no dose limiting toxicities (DLT) observed. No severe adverse events (SAEs), Grade (G) 3 or above adverse events (AEs) and AEs leading to treatment discontinuation were reported. Twelve drug related AEs were all G1/2 events including 2 G2 AEs (1 rash maculopapular at 0.05mg/kg, 1 hypothyroidism at 0.1mg/kg), 10 G1 AEs (1 hypotension, 1 dry skin, 1 pruritus at 0.05mg/kg; 1 rash, 1 rash macular, 1 hyperthyroidism, 2 rash pruritus at 0.1mg/kg, 2 fatigues at 0.3mg/kg). Among 7 patients having imaging tumor assessment by RECIST v1.1, there were 4 SD, including 1 at 0.05 mg/kg with tongue carcinoma at week 8 assessment, 1 at 0.1 mg/kg with nasopharyngeal carcinoma at week 8 and 15 assessment, 2 at 0.3 mg/kg with gastroesophageal junction cancer and uterus leiomyosarcoma at week 8. **Conclusions:** YH001 combined with Toripalimab is safe and tolerable up to 1 mg/kg dose level. Updated safety and preliminary efficacy data will be presented. Clinical trial information: NCT04481009. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

2578 **Poster Session**

Phase I/II study of nivolumab plus vorolanib in patients with thoracic malignancies: Interim efficacy of the SCLC and primary refractory NSCLC cohorts, and safety data across all cohorts. *First Author: Selina K. Wong, Vanderbilt University Medical Center, Nashville, TN*

Background: Combination strategies to improve the efficacy of single agent immune checkpoint inhibitors (ICIs) are increasingly being explored, with one strategy being the addition of vascular endothelial growth factor (VEGF) inhibition. Having shown promise in the treatment of hepatocellular carcinoma and renal cell carcinoma, NCT03583086 is a multi-institutional, phase I/II study of combination vorolanib and nivolumab in both naïve and refractory thoracic tumors that progressed on at least one prior line of platinum-based chemotherapy. Though structurally similar to the tyrosine kinase inhibitor, sunitinib, vorolanib was designed to have a more favorable safety profile with comparable efficacy. Here we present safety data across all cohorts and interim efficacy analyses of the SCLC and NSCLC with primary resistance to ICI-based therapy cohorts, both of which have now completed enrolment. **Methods:** The maximum tolerated dose determined in phase I was vorolanib 200mg daily and nivolumab 240mg q2 weeks. Phase II uses a two-stage MinMax design across 5 cohorts with objective response rate (ORR) as the primary endpoint: NSCLC (ICI naïve, primary refractory, and acquired resistance), SCLC, and thymic carcinoma. Primary refractory is defined as radiographic progression of disease within 12 weeks of ICI initiation. **Results:** As of January 2021, 75 patients have been enrolled across all cohorts. Stage 1 of the SCLC and primary refractory NSCLC cohorts have completed accrual at 18 and 15 patients, respectively. In the SCLC cohort, disease-control rate (DCR) was 7% and no objective responses were achieved among 14 evaluable patients. In the primary refractory NSCLC cohort, DCR was 57% and ORR 7% (1 partial response) among 14 evaluable patients. A total of 140 treatment-related adverse events (TRAEs) have been reported, 13 (9%) were grade 3 and there were no grade 4/5 events. Fatigue (9%), nausea (6%), diarrhea (6%), ALT elevation (5%), and AST elevation (5%) were the most common all grade TRAEs. The most common grade 3 TRAEs were ALT elevation and hypertension. **Conclusions:** This therapeutic strategy of nivolumab plus vorolanib appears to be a well-tolerated combination with a manageable safety profile. Adding VEGF inhibition may offer additional disease control in the setting of NSCLC with primary resistance to ICIs, but neither the SCLC or primary refractory NSCLC cohorts achieved the pre-determined target number of objective responses for progression to stage 2 of the study. Enrolment in the other 3 cohorts as well as exploratory correlatives are ongoing. Clinical trial information: NCT03583086. Research Sponsor: Bristol Myers Squibb, Xcovery.

2579 **Poster Session**

Phase Ib study of BI 836880 (VEGF/Ang2 nanobody) plus ezabenlimab (BI 754091; anti-PD-1 antibody) in patients (pts) with solid tumors. *First Author: Nicolas Girard, Institut Curie, Institut du Thorax Curie-Montsouris, Paris, France*

Background: In preclinical studies, the combination of anti-VEGF/Ang2 and anti-PD-1 therapy has been shown to promote an immunopermissive state, which is supportive of T-cell-mediated tumor cell destruction. BI 836880 is a humanized bispecific nanobody that targets VEGF and Ang2, and ezabenlimab (BI 754091) is an anti-PD-1 antibody. Phase I studies investigating each as monotherapies have reported safety and preliminary antitumor activity. This ongoing Phase Ib study is evaluating the combination of BI 836880 and ezabenlimab in pts with advanced solid tumors. In Part 1 (dose escalation), the combination was feasible in pts with advanced NSCLC, with a recommended Phase II dose (RP2D) of BI 836880 720 mg + ezabenlimab 240 mg IV q3w. Here, we report updated results from Part 2 (expansion phase), which is assessing the antitumor activity and safety of the RP2D. **Methods:** Seven cohorts are currently recruiting pts in Part 2: metastatic (m) NSCLC after checkpoint inhibitor (CPI) monotherapy (Cohort A); mNSCLC after chemotherapy (CT) + CPI (Cohort B); mSCLC after CT ± CPI (Cohort C); 1st and 2nd recurrences of glioblastoma (GBM; Cohort D); immunotherapy-resistant m-melanoma (Cohort E); hepatocellular carcinoma (HCC) after prior sorafenib or lenvatinib ± CPI (Cohort F); and previously untreated/unresectable HCC (Cohort G). Primary endpoint is objective response rate (complete response + partial response [PR]). **Results:** As of January 2021, 196 pts have received BI 836880 plus ezabenlimab (14 in Part 1, 182 in Part 2 [Cohort A, 26; B, 30; C, 19; D, 31; E, 32; F, 28; G, 16]). 134 (68%) pts were male, median age was 63 years and 102 (52%) had prior CPI use. Any grade and ≥G3 adverse events (AEs; any cause) were reported by 160 (82%) and 62 (32%) pts, most commonly (all%/≥G3%) hypertension (20/8), asthenia (20/3), diarrhea, decreased appetite, and nausea (all 11/1). 95 (48%) pts had a drug-related AE, most commonly hypertension and asthenia (both 11%). 6 pts had a G4 AE (non-related: hyperkalemia + cardiac arrest, laryngospasm, gastrointestinal perforation; drug-related: anaphylactic reaction, acute pancreatitis, transaminases increased); 8 pts had a G5 AE (non-related: general physical health deterioration, epilepsy, hemoptysis, cardio-respiratory arrest, hepatic failure, intracranial hemorrhage, COVID-19 pneumonia; drug-related tracheal hemorrhage). 30 (15%) pts had immune-related AEs (3% ≥G3), including hypothyroidism (3%). 11 (6%) pts had an AE leading to discontinuation. Overall, 145 pts were evaluable for response: 9 pts achieved confirmed PR (2 pts in Part 1 and 7 in Part 2 [NSCLC, n = 3; SCLC, n = 1; GBM, n = 1; melanoma, n = 1; and 2nd-line HCC, n = 1]), 87 pts had stable disease and 49 pts had progressive disease. 111 pts remain on treatment. **Conclusions:** BI 836880 plus ezabenlimab had a manageable safety profile. The combination showed preliminary antitumor activity in a range of tumor types. Clinical trial information: NCT03468426. Research Sponsor: Boehringer Ingelheim.

2580 **Poster Session**

Phase I open-label, dose escalation of YH003, an anti-CD40 monoclonal antibody in combination with toripalimab (anti-PD-1 mAb) in patients with advanced solid tumors. *First Author: Jermaine Coward, ICON Cancer Care, South Brisbane, QLD, Australia*

Background: YH003, a recombinant, humanized agonistic anti-CD40 IgG2 monoclonal antibody (mAb) specifically recognizes and agonizes CD40 on the antigen-presenting cells to enhance immune responses. Preclinical data have shown potent anti-cancer activity when combined with anti-PD-1 antibodies. **Methods:** This is an ongoing phase 1 dose-escalation study. Patients with advanced solid tumors receive YH003 by IV administration Q3W as monotherapy at 0.03 to 3.0 mg/kg for the first cycle (21 days) then in combination with Toripalimab at 240 mg Q3W for the 4 subsequent cycles in an accelerated "3+3" design. The safety, tolerability and preliminary efficacy data will be analyzed. **Results:** As of 31 Dec 2020 data cutoff, 9 patients (pts) were enrolled and treated at 0.03 mg/kg (n = 3), 0.1mg/kg (n = 3), and 0.3mg/kg (n = 3). The median age was 63 years (range 33-68). Baseline ECOG scores were 0 (7 pts) and 1 (2 pts) with a median of 2 prior lines therapy (range 1-7). 5 pts had received prior immunotherapy (PD-1/PD-L1 or PD-1+CTLA-4). As of data cutoff, no dose limiting toxicities (DLT) were observed. No Serious Adverse Event (SAE) or AEs leading to treatment discontinuation were reported. Four drug related AEs were reported including one Grade 1 (G1) choroidal thickening (related to YH003) at 0.03 mg/kg, one G1 fatigue (related to YH003) at 0.1 mg/kg, two G1 febrile episodes (one related to YH003 and the other related to combination treatment) at 0.3 mg/kg. Among 5 patients assessable for response, there were 2 SD (one with anti-PDL1 refractory Merkel cell carcinoma at 0.03 mg/kg and one with anti-PD1 refractory NSCLC at 0.1 mg/kg) and 1 PR with anti-PD1/anti-CTLA4 refractory ocular melanoma at 0.1 mg/kg. **Conclusions:** YH003 was well tolerated up to 0.3 mg/kg dose levels when combined with Toripalimab and has shown encouraging antitumor activity in patients with advanced solid tumors. Clinical trial information: NCT04481009. Research Sponsor: Eucure (Beijing) Biopharma Co., Ltd.

2581 **Poster Session**

Anlotinib enhanced penpulimab efficacy through remodeling of tumor vascular architecture and immune microenvironment in hPD-L1/hPD-1 humanized mouse model. *First Author: Yunlong Shan, China Pharmaceutical University, Nanjing, China*

Background: Even though immune checkpoint inhibitor (ICI) such as anti-PD-1 mAb has emerged as effective treatment for tumor regression, the response rate of ICI monotherapy in solid tumor is low. Many studies have demonstrated that the efficacy of combination therapy of ICI and anti-angiogenesis was superior to monotherapy. Penpulimab (AK105), a humanized IgG1 mAb that blocks PD-1 binding to PD-L1, engineered to eliminate FcγR binding and ADCC/ADCP completely. Here, we explore a new combined therapy of penpulimab and anlotinib, an oral multi-targeted tyrosine kinase receptor inhibitor. **Methods:** MC38-hPD-L1 tumor-bearing B-hPD-1 humanized mouse model were conducted to investigate the effects of anlotinib (1 mg/kg, every day, p.o) or penpulimab (5 mg/kg, twice a week, i.p) alone or in combination. Immunofluorescence was applied to elucidate tumor vessel normalization. *In vivo* imaging was conducted to detect the distribution of AF647-labelled penpulimab after anlotinib treatment. Flow cytometry and other techniques were performed to investigate intratumoral immune cells. **Results:** After 3-week treatment, immunotherapeutic administration of anlotinib or penpulimab showed moderate inhibition of tumor growth (tumor volume: 66.5% and 58.4% of control group, respectively), while combined treatment of anlotinib with penpulimab significantly decreased tumor volume to 36.5% of control group. Tissue pathological and blood biochemical results showed no significant toxic and side effects. Immunohistochemistry revealed that anlotinib induced tumor vascular normalization, indicated by decreased $CD31^+$ area, increased α-SMA around tumor vessels and reduced $GLUT1^+$ area. Furthermore, anlotinib markedly enhanced the delivery of AF647-penpulimab into tumors. Combining anlotinib with penpulimab also promoted infiltration and activity of anti-tumoral immune cells by reducing the level of immune checkpoint TIM3 and increasing the IFNγ secretion from T cells. **Conclusions:** Our work provides a strong scientific rationale for the combination therapy of anlotinib and penpulimab to improve tumor microenvironment and immunotherapy, which highlights the clinical potential for this new combined therapy. Research Sponsor: None.

2582 **Poster Session**

Platform trial of ezabenlimab (BI 754091), an anti-PD-1 antibody, in patients (pts) with previously treated advanced solid tumors: Combination with BI 836880, a VEGF/Ang2-blocking nanobody. *First Author: Maen A. Hussein, Florida Cancer Specialists, Lady Lake, FL and Sarah Cannon Research Institute, Nashville, TN*

Background: The combination of anti-PD-1 antibodies with other immunomodulatory or targeted therapies has the potential for synergistic effects. This open-label, Phase II platform trial is assessing ezabenlimab, an anti-PD-1 antibody, in combination with other agents. Here, we report preliminary data from Module C, which assesses ezabenlimab in combination with BI 836880, a humanized bispecific nanobody that targets vascular endothelial growth factor (VEGF) and angiopoietin-2 (Ang2). VEGF and Ang2 play key roles in tumor angiogenesis and have an immunosuppressive effect in the tumor microenvironment. Combining anti-VEGF/Ang2 with an anti-PD-1 therapy promotes an immunopermissive state supportive of T-cell-mediated tumor cell death. **Methods:** Pts are being enrolled into 5 cohorts: locally advanced/metastatic gastric or gastroesophageal adenocarcinoma with $\geq$1 prior treatment (anti-PD-[L]1 naïve; Cohort 1); any advanced/metastatic solid tumor (excluding non-squamous NSCLC or melanoma) with prior anti-PD-(L)1 treatment, which progressed after achieving at least stable disease (SD) for $\geq$4 months (Cohort 2); advanced/metastatic solid tumors with no benefit from prior anti-PD-(L)1 treatment (SD or progressive disease [PD] in $<$ 4 months; Cohort 3); locally advanced/metastatic microsatellite stable (MSS) colorectal cancer with $\geq$1 prior treatment (anti-PD-[L]1 naïve; Cohort 4); advanced MSS and mismatch repair-proficient endometrial carcinoma, which progressed after 1 line of chemotherapy (anti-PD-[L]1 naïve; Cohort 5). Pts will receive BI 836880 720 mg and ezabenlimab 240 mg IV every 3 weeks. The primary endpoint is investigator-assessed objective response (complete response [CR] or partial response per RECIST v1.1). Safety is also being assessed. **Results:** As of Jan 2021, 29 pts have received ezabenlimab plus BI 836880; 26 pts remain on treatment. Cohorts 1/2/3/4/5 included 0/6/3/19/1 pts; median age 63 yrs; 20 (69%) pts were male. Overall, 22 (76%) pts experienced an adverse event (AE; any-cause), most commonly (all%/G3%) nausea (31/3), hypertension (28/7) and fatigue (21/0). No G4/5 AEs were reported; 5 (17%) pts experienced serious AEs. One pt had an immune-related AE (G1 rash). Eighteen (62%) pts had a drug-related AE, most commonly nausea (24%), vomiting, fatigue, and hypertension (all 14%). Three pts had infusion-related reactions (G1, n = 2; G2, n = 1) and 1 pt had an AE that led to treatment discontinuation (non-related G3 bile duct stone). Of 7 pts evaluable for response prior to cycle 3, 5 have SD (Cohort 2, n = 2; Cohort 4, n = 3), and 2 have PD (Cohorts 3 and 4, n = 1 each). Updated data will be presented. **Conclusions:** These preliminary data suggest that ezabenlimab in combination with BI 836880 has a manageable safety profile. Cohorts are continuing to recruit (approximately 30 pts per cohort). Clinical trial information: NCT03697304. Research Sponsor: Boehringer Ingelheim.

2583 **Poster Session**

AdvanTIG-105: Phase 1 dose-escalation study of anti-TIGIT monoclonal antibody ociperlimab (BGB-A1217) in combination with tislelizumab in patients with advanced solid tumors. *First Author: Sophia Frentzas, Medical Oncology, Monash Health, Melbourne, Victoria, Australia, School of Medical and Health Sciences, Monash University, Melbourne, VIC, Australia*

Background: Anti-programmed death 1 (PD-1) therapy has improved clinical outcomes for patients (pts) with advanced solid tumors but unmet needs remain. T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) is a co-inhibitory, immune checkpoint receptor. Ociperlimab (OCI; BGB-A1217) is a novel, humanized, monoclonal antibody that binds to TIGIT with high affinity and specificity. OCI has demonstrated competent binding with C1q and all Fcγ receptors and induces antibody-dependent cellular cytotoxicity. Preclinical studies demonstrated dual targeting with OCI and tislelizumab (TIS), an anti-PD-1 antibody, produces synergistic immune cell activation and enhanced anti-tumor activity. **Methods:** AdvanTIG-105 is a phase 1, open label, multicenter, dose-escalation study (NCT04047862) that assessed the safety and preliminary antitumor activity of OCI plus TIS in pts with advanced, metastatic, unresectable solid tumors, for which standard therapy was ineffective or unavailable. Eligible pts had an Eastern Cooperative Oncology Group performance score $\leq$1 and no prior therapy targeting TIGIT. Pts received OCI intravenously (IV) on Day 1 of Cycle 1 and TIS 200 mg IV on Day 8. Pts were monitored for dose-limiting toxicities (DLTs) until Day 28. If tolerated, OCI and TIS were administered sequentially on Day 29 and every 3 weeks (Q3W) thereafter. Pts received escalating doses of OCI (50-900 mg) plus TIS 200 mg. The study objective was determination of recommended phase 2 dose (RP2D) of OCI plus TIS. Study endpoints included assessment of adverse events (AEs), pharmacokinetics and antitumor activity. Data cut-off was October 12 2020. **Results:** 24 pts with various advanced solid tumors received OCI plus TIS. At baseline, pts had undergone a median of 2 prior treatment regimens; 9/24 (37.5%) pts had received prior immunotherapy. Median follow-up time was 17 weeks. No DLTs were observed. 20 pts had $\geq$1 treatment emergent AE (TEAE) and most TEAEs were grade $\leq$2; fatigue (6 pts) and diarrhea (4 pts) were most commonly reported. No pts had grade $\geq$4 TEAEs or TEAEs leading to death. There were 2 grade 3 immune related AEs (colitis and low cortisol). One pt on OCI 450 mg achieved partial response and 9 pts had stable disease. The longest duration of stable disease was 36 weeks (1 pt on OCI 150 mg). After administration, serum concentration of OCI decreased in a biphasic manner. Exposure to OCI increased proportionally with dose, and TIGIT receptor occupancy was sustained at $\geq$50 mg doses. **Conclusions:** OCI in combination with TIS was well tolerated across all doses in pts with advanced solid tumors. The RP2D was OCI 900 mg plus TIS 200 mg Q3W. Clinical trial information: NCT04047862. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Stephanie Pruden, BSc (Hons), of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

2584 **Poster Session**

IFN-α, IFN-γ, IL-2 combined with TNF-α for predicting efficacy of PD-1 inhibitors combination therapy in patients with solid cancers. *First Author: Penghui Xing, Department of Neurosurgery, Fourth Hospital of Hebei Medical University, Shijiazhuang, China*

Background: PD-1 inhibitors have transformed the treatment landscape for patients (pts) with many advanced malignancies. Combination therapy with PD-1 inhibitors for cancer is a trend. However, Biomarkers for the efficacy of combination therapy remains unknown. In order for the benefited population to be screened out, biomarkers need to be established. we will conduct the following study, to explore the IFN-α, IFN-γ, IL-2 combined with TNF-α for predicting efficacy of PD-1 inhibitors combination therapy. **Methods:** Using postoperative without lesions as control group (n=7). Pts with lesions as the experimental group (n=66). 27 of 66 pts received chemoradiotherapy (group A), 39 of 66 pts received PD-1 inhibitors combined with therapy (group B). IFN-α, IFN-γ, IL-2, TNF-α in peripheral blood of all pts were measured using flow cytometry. **Results:** 1) There was significant difference in proportion above normal concentrations (ANCs) of IFN-α between two groups (57.1% vs 43.5%, $P<0.05$), but there was no significant difference in IFN-γ, IL-2 and TNF-α between two groups (IFN-γ 57.1% vs 52.2%, IL-2 14.3% vs 5.8%, TNF-α 42.9% vs 43.5%, $P>0.05$). 2) The normal ratios of IFN-α, IFN-γ and TNF-α in group B was significantly higher than that in group A (IFN-α 64.1% vs 51.9%, IFN-γ 59% vs 37%, TNF-α 69.2% vs 44.4%, $P<0.05$). The proportion ANCs of IFN-α, IFN-γ, and TNF-α were lower in group A (IFN-α 35.9% vs 63%, $P>0.05$; IFN-γ 41% vs 63%, $P<0.05$; TNF-α 30.8% vs 55.6%, $P<0.05$). However, the proportion ANCs of IL-2 detection was lower (7.4% vs 5.1%). 3) In group B, 21 of 39 pts were evaluable. ORR was 52.4% (11/21) and DCR was 85.7% (18/21). The proportion ANCs of IFN-α, IFN-γ and TNF-α in the pts with PR was higher than that with SD (IFN-α 37.5% vs 28.6%, IFN-γ 37.5% vs 28.6%, TNF-α 50% vs 38.8%, $P<0.05$). 4) We found that the coincidence rate of IFN-α+ IFN-γ and IFN-α+ IFN-γ+TNF-α was higher in group B (Table). **Conclusions:** Our results suggest that the proportion ANCs of IFN-α, IFN-γ, and TNF-α in the pts with lesions were lower than that without lesions, it may be the decrease of immune function with lesions. There was positive correlation between proportion ANCs of IFN-α, IFN-γ and TNF-α and efficacy in these pts. IL-2 was not used as a routine detection indicator. The coincidence rate of IFN-α, IFN-γ combined with TNF-α was higher, it may help predict the outcome of PD-1 inhibitors combination therapy in pts with solid cancers, and helpful to screen the benefit population. Further study is needed. Research Sponsor: None.

Coincidence rate of IFN-α, IFN-γ and TNF-α after treatment in different patients.*

	Non-coincidence rate (%)	Coincidence rate (%)
IFN-α+IFN-γ	14.8	85.2
IFN-α+IFN-γ (+)	15.4	84.6
IFN-α+IFN-γ (+SD)	0	100
IFN-α+IFN-γ (+PR)	0	100
IFN-α+IFN-γ+TNF-α	29.6	70.4
IFN-α+IFN-γ+TNF-α (+)	28.2	71.8
IFN-α+IFN-γ+TNF-α (+SD)	0	100
IFN-α+IFN-γ+TNF-α (+PR)	100	87.5

*IFN-α+IFN-γ, IFN-α+IFN-γ+TNF-α: group A; others: group B.

2585 **Poster Session**

A phase 1 dose-escalation study of a PD-L1xCD27 bispecific antibody CDX-527 in patients with advanced malignancies. *First Author: Rachel E. Sanborn, Earle A. Chiles Research Institute, Providence Cancer Institute, Portland, OR*

Background: CDX-527 is a bispecific antibody (BsAb) targeting PD-L1 and CD27 that is designed to block immune checkpoint PD-L1/PD-1 interactions while providing immune costimulation through CD27 signaling. CD27 is a key immunostimulatory molecule that enhances T cell activation, effector function, and survival. Combining anti-PD-L1 and anti-CD27 mAbs synergize in preclinical studies, activating complementary cytotoxic and proliferative gene expression profiles, respectively. Clinical studies demonstrated the safety and biological activity of combining varlilumab, an agonist anti-CD27 mAb, with nivolumab or atezolizumab, along with modest clinical activity of the combinations. CDX-527 is a novel human BsAb containing a neutralizing, high affinity IgG1k PD-L1 mAb and the single chain Fv fragment (scFv) of an agonist anti-CD27 mAb genetically attached to the C-terminus of each heavy chain, thereby making CDX-527 bivalent for each target. Pre-clinical studies demonstrated enhanced T cell activation by CDX-527 and anti-tumor activity of a surrogate bispecific compared to individual mAb combinations. **Methods:** CDX527-01 is a phase 1 first-in-human, open-label, multi-center, dose-escalation (DE) and expansion study evaluating safety, pharmacokinetics (PK), pharmacodynamics (PD), and clinical activity of CDX-527 in patient with advanced solid tumors that have progressed on standard-of-care therapy. The primary study objective is to characterize the safety and tolerability of CDX-527. CDX-527 is administered intravenously Q2W with doses ranging from 0.03 mg/kg up to 10.0 mg/kg or until the maximum tolerated dose. The first 2 cohorts of the DE phase initiate with single patients and subsequent DE cohorts will be conducted in 3+3 manner. Tumor-specific expansion cohorts may be enrolled to further characterize the safety, PK, PD, and efficacy of CDX-527. Tumor assessments are performed Q8W by the investigator per iRECIST. Biomarker assessments include characterizing the effects on peripheral blood immune cells and cytokines, and for the expansion cohorts, the impact of CDX-527 on the tumor microenvironment in paired tumor biopsies. **Results:** To date, 8 patients have received CDX-527 in doses ranging from 0.03 mg/kg to 1 mg/kg and 3 are still on treatment. There has been no drug related SAEs, DLTs or discontinuations due to an AE. Most common treatment related AEs were influenza-like illness, fatigue, and arthralgia (all at 25%). All drug related AEs have been grade 1 or 2. **Conclusions:** Preliminary results indicate that the novel anti-PD-L1xCD27 bispecific antibody CDX-527 up to and including the 1 mg/kg dose level has been well tolerated. Additional data will be presented, including the safety profile at higher dose levels along with clinical activity, as well as PK and PD data. Clinical trial information: NCT04440943. Research Sponsor: None.

2586 **Poster Session**

The predictive values of loss-of-function variants in histone methyltransferases for response to immune checkpoint inhibitors in solid tumors. *First Author: Naixin Liang, Department of Thoracic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: Dysregulation of histone methyltransferases (HMTs) has been reported to play critical roles in cancer development. Previous studies showed that many HMTs were recruited to DNA damage sites where they posttranslationally modified chromatin to regulate chromatin-based DNA damage repair (DDR) activities. We hypothesized that loss-of-function (LOF) variants of HMTs may associate with genome instability and tumor mutational burden (TMB). Thus, we explored the associations of LOF variants in some HMTs with TMB and benefit from immune checkpoint inhibitors (ICIs) in solid tumors. **Methods:** An ICIs treatment cohort from the Memorial Sloan Kettering Cancer Center (MSKCC) was analyzed. The following solid tumor types were enrolled: NSCLC (n = 350), colorectal cancer (n = 110), bladder cancer (n = 215), breast cancer (n = 44), esophagogastric cancer (n = 126), head and neck cancer (n = 139), glioma (n = 117), melanoma (n = 320), and renal cell carcinoma (n = 151). We evaluated 15 HMTs (KMT2A, KMT2B, KMT2C, KMT2D, SETD2, SETD8, EZH1, EZH2, PRDM1, PRDM14, SMYD3, NSD1, WHSC1, WHSC1L1, and DOT1L). **Results:** The data revealed that LOF variants of *KMT2D*, *SETD2*, and *KMT2C* were more frequent in pan-cancer dataset. Furthermore, we found that LOF variants of 7 HMTs, including *KMT2A*, *KMT2B* , *KMT2C*, *KMT2D, NSD1*, *SETD2*, and *EZH2*, were associated with higher TMB ($P < 0.0001$). Then we analyzed the associations between LOF variants and overall survival (OS) after ICIs therapy. The results indicated that LOF variants of *KMT2A* (P = 0.0295), *KMT2B* (P = 0.0329), *KMT2C* (P = 0.0122), and *SETD2* (P = 0.0004) were significantly associated with prolonged median OS for all the enrolled patients. In this cohort, LOF variants of *KMT2A*, *KMT2B*, *KMT2C*, and *SETD2* were most common in bladder cancer, colorectal cancer, colorectal cancer, and renal cell carcinoma, respectively. Then we assessed the predictive values of these four genes for each type of cancer. It was noteworthy that *KMT2C* LOF variants were significantly correlated with longer median OS in colorectal cancer (P = 0.0171), but not in other cancer types. Surprisingly, we did not observe the predictive roles of LOF variants in *KMT2A*, *KMT2B*, and *SETD2* genes for response to ICIs therapy in any types of cancer. **Conclusions:** In pan-cancer dataset, we found that LOF variants of 4 HMTs, such as *KMT2A*, *KMT2B*, *KMT2C*, and *SETD2*, were correlated with better outcomes of ICIs treatment. However, for different types of cancer, only *KMT2C* LOF variants were associated with longer median OS in colorectal cancer, suggesting that it may be used as a predictive biomarker for ICIs efficacy in colorectal cancer. Because the sample sizes of patients with *KMT2A*, *KMT2B*, or *SETD2* LOF variants were small, we did not find the predictive values of LOF variants in these three genes for different types of cancer. Next, we will enroll more patients to address this question. Research Sponsor: None.

2587 **Poster Session**

Association of *KMT2C/D* loss-of-function mutations with tumor infiltrating lymphocytes and response to immune checkpoint inhibitors in solid tumors. *First Author: Ruiqi Liu, Department of Radiation Oncology, Sun Yat-Sen University Cancer Center, Guangzhou, China*

Background: Dysregulation of HMTs plays an important role in tumorigenesis. KMT2C and KMT2D are enzymatically active scaffold proteins that form the core of mammalian COMPASS complexes, which methylate the histone 3 lysine 4. Both KMT2C and KMT2D are involved in the regulation of gene expression. Therefore, we explored the associations of *KMT2C/D* loss-of-function (LOF) mutations with the expression of immune-related genes, the levels of tumor infiltrating lymphocytes (TILs), and response to immune checkpoint inhibitors (ICIs). **Methods:** *KMT2C/D* LOF mutations were defined as nonsense, frameshift, splice site variants within consensus regions, start lost, and stop lost/gained variants. An ICIs treatment cohort from the MSKCC was used for exploring the associations between *KMT2C/D* LOF mutations and ICIs efficacy. The RNA-Seq data obtained from the TCGA cohort was used for analysis of gene expression and the levels of TILs using *CIBERSORT*. **Results:** In MSKCC pan-cancer dataset, patients with *KMT2C/D* LOF mutations had a relatively longer median overall survival (OS) compared to those with non-LOF mutations, although the result did not reach statistical significance (P = 0.0832). Then we analyzed the predictive roles of *KMT2C/D* LOF mutations for each cancer type. The results showed that the predictive role of *KMT2C/D* LOF mutations for the clinical efficacy of ICIs therapy was only observed in colorectal cancer (P = 0.045). However, we did not find the associations of *KMT2C/D* LOF mutations with ICIs efficacy in bladder cancer, breast cancer, melanoma, glioma, head and neck cancer, renal cell carcinoma, NSCLC, and esophagogastric cancer. Consistently, analysis of TILs in colorectal cancer revealed that *KMT2C/D* LOF was associated with increased infiltration of several types of immune cells, such as CD8+ T cells (P = 0.0001), activated NK cells (P = 0.0001), M1 macrophage (P = 0.0005), M2 macrophage (P = 0.0115), and neutrophils (P = 0.0209). Meanwhile, regulatory T cells (Tregs) (P = 0.0048) and M0 macrophage (P = 0.0043) were dramatically decreased in *KMT2C/D* LOF group for colorectal cancer. Moreover, there were no significant relationships between *KMT2C/D* LOF and the levels of TILs in other cancer types. Our data also demonstrated that KMT2C and KMT2D could regulate the expression of more than 30 immune-related genes in colorectal cancer. **Conclusions:** Our data indicated that *KMT2C/D* LOF mutations were significantly correlated with better outcomes of ICIs therapy in colorectal cancer, suggesting it can be as a useful predictor for response to ICIs in colorectal cancer. Meanwhile, we found the associations of *KMT2C/D* LOF with the levels of TILs in colorectal cancer, but not in other cancer types, indicating that the efficacy of ICIs was consistent with the levels of TILs. Research Sponsor: None.

2588 **Poster Session**

Risk of immunosuppression and hospitalization after checkpoint inhibitor therapy in patients with cancer and radiation therapy. *First Author: Kate E Lee, Columbia University Vagelos College of Physicians and Surgeons, New York, NY*

Background: Immune checkpoint inhibitors (ICIs) are potent new cancer therapies but can cause serious immune-related adverse events. Radiation therapy (RT) also induces systemic immunologic effects, and data on the interaction and safety of combining ICIs and RT are limited. **Methods:** In this retrospective cohort study using a large medical claims database from 2010 to 2017, we ascertained the risk of immunosuppressive steroid therapy as well as the risk of hospitalization within 180 days of treatment with an ICI in patients with diagnoses of malignant melanoma or lung cancer. Patients were stratified by use of RT within 30 days before and after ICI therapy. ICIs included pembrolizumab, nivolumab, and ipilimumab, while immunosuppressive agents included oral prednisone and intravenous methylprednisolone. **Results:** 2020 patients (218 with RT, 1802 without RT) met inclusion criteria for prednisone analysis, while 3519 patients (361 with RT, 3158 without RT) met inclusion criteria for all other analyses. On univariable analysis, RT was not associated with need for prednisone or methylprednisolone (RR 1.2, 95%CI 0.8-1.9 and RR 1.2, 95%CI 0.7-2.1 respectively). When assessing hospitalization, RT was significantly associated with hospitalization following ICI therapy for certain cancer/drug combinations (RR 1.4, 95%CI 1.2-1.6, $p<0.001$ for lung cancer/PD-1 inhibitors, RR 2.0, 95%CI 1.0-3.5, $p=0.03$ for melanoma/ipilimumab). **Conclusions:** In patients treated with ICIs, receiving RT was not associated with a higher risk of requiring immunosuppressive steroid therapy as compared to not receiving RT. However, in those with ICIs, RT was associated with a higher risk of hospitalization as compared to no RT, though this may be a result of underlying differences in patent severity (more severe disease may require ICI and RT). Research Sponsor: Barry Neustein and Polyflex Inc. to the lung cancer research program in Radiation Oncology at Columbia University, Other Foundation, Louis V. Gerstner, Jr. Scholar Award.

Risk of corticosteroid treatment after ICI treatment across cancer type, ICI, and RT.[a,b]

	Oral Prednisone			IV Methylprednisolone		
	RT	No RT	Relative Risk (95% CI)	RT	No RT	Relative Risk (95% CI)
Melanoma PD-1 Inhibitors	13.6% (3/22)	10.7% (35/326)	1.3 (0.4, 3.8)	0.0% (0/33)	1.4% (7/501)	1.0 (0.1, 16.9)
Lung Cancer PD-1 Inhibitors	10.2% (18/176)	8.4% (96/1145)	1.2 (0.8, 2.0)	4.7% (12/257)	4.9% (78/1591)	1.0 (0.5, 1.7)
All Cancers PD-1 Inhibitors	10.6% (21/198)	8.9% (131/1471)	1.2 (0.8, 1.8)	4.1% (12/290)	4.1% (85/2092)	1.0 (0.6, 1.8)
Melanoma Ipilimumab	5.0% (1/20)	5.4% (18/331)	0.9 (0.1, 6.5)	2.8% (2/72)	1.3% (14/1066)	2.1 (0.5, 9.0)
Melanoma Ipi-Nivo Combo	40.0% (4/10)	32.2% (46/143)	1.2 (0.6, 2.8)	21.1% (4/19)	22.1% (44/199)	1.0 (0.4, 2.4)
All Cancers All ICIs	10.1% (22/218)	8.3% (149/1802)	1.2 (0.8, 1.9)	3.9% (14/362)	3.1% (99/3158)	1.2 (0.7, 2.1)

[a]No values were significantly different at $p<0.05$. [b]The patient populations for prednisone and methylprednisolone are not identical because the separate analyses required distinct inclusion criteria.

2589 **Poster Session**

Phase Ia/Ib dose-escalation study of IBI110 (anti-LAG-3 mAb) as a single agent and in combination with sintilimab (anti-PD-1 mAb) in patients (pts) with advanced solid tumors. *First Author: Cai Zhou, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China*

Background: Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor protein that functions to control T cell response, activation and growth. Dual inhibition of PD-1 and LAG-3 may improve anti-tumor effect synergistically. In this first-in-human dose-escalation study, we report the preliminary safety and anti-tumor activity of IBI110 ± sintilimab in pts with advanced solid tumors. **Methods:** Enrolled pts, ECOG PS 0-1, had locally advanced, recurrent or metastatic solid tumors for whom standard therapy had failed. Pts received escalating doses of IBI110 (0.01/0.1/0.3/1/3/10/20mg/kg) IV Q3W in phase Ia and escalating doses of IBI110 (0.3/0.7/1.5/3/5 mg/kg) in combination with sintilimab 200 mg IV Q3W in phase Ib. Crossover from mono to combo was allowed at progression. The objectives were safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor activity of IBI110 alone or IBI110+sintilimab (per RECIST v1.1). **Results:** Phase Ia: 21 pts (median age: 62 yr [range 43-72]; ECOG PS: 0 [n = 11], 1 [n = 10]) were enrolled. Dose escalation has completed and no dose-limiting toxicity (DLT) was observed in all dose cohorts. The most common treatment-related adverse event (TRAE) was anaemia (19.0%). TRAEs ≥G3 included anaemia (4.8%), ascites (4.8%) and hepatic function abnormal (4.8%). By investigator-assessment, best response was 1 confirmed partial response (PR) (ovarian cancer, 3 mg/kg IBI110 single agent) and 5 stable disease (SD) in monotherapy. After crossing from mono to combo at progression, 5 pts were observed to have SD. Phase Ib: 12 pts (median age: 60 yr [range 33-72]; ECOG PS: 0 [n = 7], 1 [n = 5]) were enrolled. All dose cohorts in dose escalation except IBI110 5mg/kg+ sintilimab have completed DLT observation and no DLT was observed. The most common TRAE was AST increased (41.7%). TRAEs ≥G3 included hyperglycaemia (8.3%), bilirubin conjugated increased (8.3%) and hepatic function abnormal (8.3%). By investigator-assessment, best response was 2 PR (small cell lung cancer and endometrial cancer) and 6 SD. **Conclusions:** IBI110 alone or plus sintilimab has acceptable toxicity and shows preliminary antitumor activity. Clinical trial information: NCT04085185. Research Sponsor: Innovent Biologics, Inc.

2590 **Poster Session**

A phase I trial evaluating NBTXR3 activated by radiotherapy in combination with nivolumab or pembrolizumab in patients with advanced cancers. *First Author: Colette Shen, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Immune checkpoint inhibitors (ICIs) targeting PD-1 are an effective treatment for a variety of cancers. However, the majority of patients (pts) exhibit resistance to ICIs. Overcoming this resistance represents a major challenge in immuno-oncology. Emerging evidence suggests radiation therapy (RT) produces an immunomodulatory effect that may act synergistically with ICIs. However, RT dose and ultimate efficacy are limited by toxicity to surrounding healthy tissues. NBTXR3, a novel radioenhancer administered by direct intratumoral injection (ITI), is designed at the nanoscale to increase RT dose deposit within tumor cells and subsequent tumor cell killing, without increasing toxicity to surrounding healthy tissue. Preclinical data suggest NBTXR3/RT can trigger a local and systemic anti-tumor immune response and overcome anti-PD-1 resistance. NBTXR3/RT combined with anti-PD-1 may prime the immune system to increase the proportion of ICI responders, or convert ICI non-responders to responders. **Methods:** This is a multicenter, open-label, phase I trial [NCT03589339] to evaluate NBTXR3/RT/anti-PD-1 in 3 cohorts: (1) Locoregional recurrent or recurrent and metastatic head and neck squamous cell carcinoma (HNSCC) amenable to HN re-irradiation, and metastases from any primary cancer eligible for anti-PD-1 (nivolumab or pembrolizumab) treatment specifically localized in the lung (2) or liver (3), respectively. Stereotactic body RT (SBRT) is delivered at tumor-site selective doses per standard practice. The primary objective is NBTXR3/RT/anti-PD-1 recommended phase 2 dose in each cohort. Secondary objectives are anti-tumor response (objective response rate), safety and feasibility of NBTXR3 injection. **Results:** Nine pts have been treated: 3 HNSCC, 4 lung, 2 liver. 7/9 pts were anti-PD-1 non-responders. Overall tumor regression was observed in 8/9 pts. NBTXR3/RT/anti-PD-1 resulted in tumor regression in 6/7 pts who had progressed on prior anti-PD-1. A complete response in the injected lymph node lasting over 1 year was observed in 1 anti-PD-1 naïve pt. 2 SAEs related to anti-PD-1 and possibly related to NBTXR3 (G5 pneumonitis, G4 hyperglycemia) were observed in 1 anti-PD-1 naïve HNSCC pt and considered DLTs. This pt also experienced 2 other SAEs related to anti-PD-1 (G4 diabetic ketoacidosis, G4 acute kidney injury). SBRT-related safety profile was as expected. Updated results will be presented. **Conclusions:** Data from this first-in-human phase I trial evaluating NBTXR3/RT/anti-PD-1 in pts with advanced cancers, show NBTXR3 ITI is feasible and well-tolerated. NBTXR3/RT/anti-PD-1 demonstrated promising signs of efficacy. Of particular interest, NBTXR3/RT can overcome ICI resistance in pts having progressed on prior anti-PD-1, supporting further development of NBTXR3 in combination with anti-PD-1 as well as other ICIs. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix.

2591 **Poster Session**

Overcoming resistance to anti-PD-1 with tumor agnostic NBTXR3: From bench to bed side. *First Author: Tanguy Y. Seiwert, The University of Chicago Medicine, Chicago, IL*

Background: Despite recent advances, resistance to immune checkpoint inhibitors (ICI), observed in over 80% of treated patients, is currently the main challenge in immuno-oncology. Intense efforts are being made to identify combination therapies that could improve ICI response rates. NBTXR3, a novel radioenhancer administered by direct intratumoral injection (ITI), is designed at the nanoscale to increase radiation therapy (XRT) dose deposit within tumor cells and subsequent tumor cell killing, without increasing toxicity to surrounding healthy tissue. Here we present evidence that NBTXR3 activated by XRT primes the immune system, producing an anti-tumor response, including activation of the cGAS-STING pathway, that overcomes anti-PD-1 resistance both in mice models and patients. **Methods:** Abscopal assays were conducted in immunocompetent mice. Anti-PD-1 sensitive or resistant tumor cell lines, were injected in both flanks of mice. Intratumoral injection of NBTXR3 (or vehicle) followed by XRT was performed in right flank (primary) tumors only. Some mice also received anti-PD-1 injections. Tumor growth was monitored, and tumor immune cell infiltrates analyzed by immunohistochemistry (IHC). Separately, in the phase II/III randomized Act.in.Sarc [NCT02379845] trial patients with locally advanced soft tissue sarcoma (STS) received either NBTXR3+XRT or XRT alone followed by tumor resection. Pre- and post-treatment tumor samples from patients in both groups were analyzed by IHC and Digital Pathology for immune biomarkers. The safety and efficacy (RECIST 1.1/iRECIST) of NBTXR3 plus stereotactic body radiotherapy (SBRT) in combination with anti-PD-1 is being evaluated in three cohorts of patients with advanced cancers [NCT03589339]. **Results:** Pre-clinical studies demonstrated that NBTXR3+XRT induces an immune response not observed with XRT alone and enhances systemic control. IHC showed significant increase of CD8+ T-cell infiltrates in both NBTXR3+XRT treated and untreated tumors compared to XRT alone. Similarly, increased CD8+ T-cell and decreased FOXP3+ Treg density (pre- vs post-treatment) was observed in tumor tissues from STS patients treated with NBTXR3+XRT. Furthermore, NBTXR3+XRT in combination with anti-PD-1 improved local and systemic control in mice bearing anti-PD-1 resistant lung tumors, as well as reduced the number of spontaneous lung metastases. Preliminary efficacy data from the first in human trial of NBTXR3+XRT in combination with anti-PD-1 showed tumor regression in the majority of patients (8/9). Of note, tumor regression was observed in 6/7 pts who had progressed on prior anti-PD-1. **Conclusions:** The clinical efficacy of NBTXR3+XRT has been demonstrated as a single agent. We now demonstrate that it potentiates anti-PD-1 treatment to overcome resistance mechanisms. These results highlight the potential of NBTXR3+XRT to positively impact the immuno-oncology field. Clinical trial information: NCT03589339. Research Sponsor: Nanobiotix.

2592 **Poster Session**

A phase 1/2 study of intratumoral INT230-6 alone (IT-01) or in combination with pembrolizumab [KEYNOTE-A10] in adult subjects with locally advanced, unresectable and metastatic solid tumors refractory to therapy. *First Author: Anthony B. El-Khoueiry, University of Southern California, Los Angeles, CA*

Background: Study IT-01 (KEYNOTE-A10) evaluates INT230-6, a novel formulation of cisplatin (CIS) and vinblastine (VIN) with an amphiphilic cell penetration enhancer designed for intratumoral (IT) administration, alone or in combination with pembrolizumab (PEM), an antibody to PD-1. INT230-6 dosing is set by a tumor's volume. In preclinical studies, INT230-6 increases drug dispersion throughout the tumor, allows drug diffusion into cancer cells and recruits dendritic, CD4 and CD8 T cells. The addition of PEM has been shown to improve these responses in models. Phase 1 data indicated INT230-6 alone induced tumor regression in both injected and non-injected lesions. Considering the large volume of drug injected and retained in the tumor, coupled with immune infiltration on biopsies, RECIST response methodology may not capture the benefit of INT230-6 treatment. **Methods:** IT-01 is an open-label phase 1/2 study, currently enrolling adult subjects with solid tumors in phase 2. INT230-6 was administered IT Q2W for 5 doses alone or with PEM 200mg Q3W. The study seeks to assess the safety and efficacy of IT INT230-6 alone and in combination with PEM. **Results:** 67 subjects have been enrolled (58 mono and 12 INT230-6 + PEM (3 started in mono, then received combo)) having a median of 3 prior therapies (0, 10). Median age was 60 (42, 85). 20+ cancer types were accrued; breast cancer and sarcoma were the most frequent. Over 500 image guided INT230-6 IT injections were given (253 to deep tumors) at doses of 0.3 to 172mL (86 mg CIS, 17.2 mg VIN) in a single session, which are higher amounts than typical IV doses. PK shows that 95% of INT230-6 active agents remain in the tumor. The most common (> 20%) related TEAEs for INT230-6 alone were localized pain (57%), nausea (36%), fatigue (29%) and vomiting (24%); with grade 3 TEAEs (> 1) of localized pain (5%) and anemia (3%). The safety in the combination was similar. There were no related grade 4 or 5 TEAEs. In evaluable monotherapy subjects (n = 43), the disease control rate (DCR) was 65% vs. 100% in PEM subjects (n = 5). Given the range of dose and entering tumor burden, an exploratory analysis of dose relative to tumor burden (TB) showed that subjects receiving a dose of INT230-6 < 50% of their reported TB (n = 30) had a mOS of 3.5 months. While in subjects receiving a dose of INT230-6 to ≥50% of TB (n = 37), mOS has not yet been reached after a median follow up of 9.5 months (HR: 0.26 (0.13,0.51)). **Conclusions:** INT230-6 is well tolerated when administered IT as monotherapy and combined with PEM. Given the challenge in assessing overall response rate following IT delivery, an exploratory analysis suggests prolonged survival for subjects receiving an INT230-6 dose ≥50% of their tumor burden compares favorably to the < 50% group and to literature accounting for prognostic factors (ECOG, LDH, # of metastatic sites). Clinical trial information: 03058289. Research Sponsor: Intensity Therapeutics, Inc.

2593 **Poster Session**

Nivolumab/ipilimumab primed immunotransplant in post-CAR-T and post-ASCT DLBCL. *First Author: Bailey Gleason Fitzgerald, The Tisch Cancer Institute at Mount Sinai Health System, New York, NY*

Background: Patients with refractory diffuse large b cell lymphoma (DLBCL) have poor outcomes with < 30% surviving for 12 months and especially poor outcomes for those who progress after chimeric antigen receptor T cells (CAR-T) or autologous stem cell transplant (ASCT). These therapies utilize lymphodepleting chemotherapy which induces homeostatic T cell proliferation. We have demonstrated these expanding T cells express high levels of PD1 and CTLA4. In pre-clinical models, addition of dual checkpoint blockade (DCB) with anti-PD1/anti-CTLA-4 to adoptive T cell transfer after lymphodepletion achieved a synergistic anti-tumor effect. Based on these studies, we developed a phase Ib/II study of Nivolumab/Ipilimumab primed "immunotransplant" for relapsed/refractory (R/R) DLBCL (NCT03305445). **Methods:** Phase Ib of the trial enrolled 6 patients with progressive disease following at least one line of standard therapy. Patients received two cycles of DCB with ipilimumab (1mg/kg) and nivolumab (3mg/kg) given at three-week intervals followed by immunotransplant (i.e. peripheral blood T cell harvest, lymphodepletion with fludarabine/cyclophosphamide, T cell reinfusion), followed by two further cycles of DCB and nivolumab maintenance. **Results:** Five patients received at least two cycles of DCB and the autologous T cell transfer, while one patient had progressive disease during initial DCB and required salvage chemotherapy. Treatment emergent AE (TEAE) occurred in 100% of patients. As expected with lymphodepleting chemotherapy, the most common TEAE were neutropenia (66.7% grade 1, 66.7% grade ≥ 3), fatigue (83.3%, 16.7%), fever (66.7%, 0%), and dyspnea (66.7%, 0.0%). One patient (16.7%) died during the intervention period (grade 5 TEAE), though relation to study drug is unclear. Three patients (50.0%) experienced clinical benefit with immunotransplant. One patient (a 58yo M with progression after seven lines of therapy including ASCT and CAR-T) is experiencing partial metabolic response after 4 months on protocol. One 77yo F with multiple prior lines of therapy including ASCT has experienced an extended complete metabolic response, currently 31 months post immunotransplant. A third (a 50yo F) experienced mixed radiographic response, and has not received subsequent therapy 30 months following immunotransplant. **Conclusions:** Nivolumab/Ipilimumab primed immunotransplant is well tolerated in patients with R/R DLBCL for whom there are few treatment options. Preliminary results demonstrate remissions in heavily pre-treated patients, including prior ASCT and CAR-T. Pre-clinical models in melanoma, non-small cell lung cancer, and T cell lymphoma all demonstrate synergy when DCB is administered with lymphodepletion and autologous T cell transfer. These data support further investigation of DCB-primed immunotransplant. Clinical trial information: NCT03305445. Research Sponsor: Bristol Myers Squibb.

2594 **Poster Session**

Safety, pharmacokinetics, pharmacodynamics profiles and preliminary antitumor activity of phase 1b/2a study of NT-I7, a long-acting interleukin-7, plus pembrolizumab in patients with advanced solid tumors: The phase 1b data report. *First Author: Aung Naing, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: NT-I7 (efineptakin alfa) is the first-in-class long-acting IL-7 which can increase the number and functionality of T cells in the peripheral blood (PB) of patients (pts). The combination of NT-I7 and pembrolizumab (pembro), a PD-1 Checkpoint Inhibitor (CPI), may augment and broaden the efficacy of CPIs. **Methods:** This is an open-label, phase 1b/2a study in pts with relapsed/refractory (R/R) advanced solid tumors. In the phase 1b (Dose Escalation), which followed the 3+3 design, pts received NT-I7 intramuscularly (IM) at 3 dose levels (DLs): 480, 960, and 1200 μg/kg every 6 weeks (Q6W) plus pembro 200 mg intravenously (IV) Q3W. The objectives of the phase 1b were to evaluate Dose Limiting Toxicity (DLT), determine the Maximum Tolerated Dose (MTD) and/or the Recommended Phase 2 Dose (RP2D), and assess pharmacokinetics (PK), pharmacodynamics, and preliminary antitumor activity. **Results:** As of 12 January 2021, 12 pts were enrolled in the phase 1b: DL1 (n=3), DL2 (n=3) and DL3 (n=6). Median age 58.0 years [43-77], ECOG PS 0 (50%), PS 1 (50%), median number of prior therapies 4 [1-8]. MTD was not reached. One DLT (Grade [G] 3 ALT increased) was reported in DL3. Treatment-related adverse events (AEs) occurred in 11 (91.7%) pts, 11 (91.7%) G1-2 and 4 (33.3%) G3; no G4 or G5 AEs reported. Common treatment-emergent AEs were injection site reaction (n=8, 66.7%), chills (n=7, 58.3%), nausea (n=6, 50%) and pyrexia (n=6, 50%). Preliminary PK analysis showed T_{max} = 24 hours and $T_{1/2}$ = 123 hours for NT-I7 at DL3. NT-I7 + pembro induced dose-dependent lymphocyte proliferation in the PB, with ~ 3-fold increase at DL3, and a corresponding decrease in neutrophil to lymphocyte ratio at 14 days after the 1st treatment. Importantly, increased number of T cells in the tumor microenvironment (TME) was also observed (Table). One pt with metastatic mucosal melanoma who had not responded to prior combination of nivolumab and ipilimumab had a rapid, confirmed partial response with 46% tumor reduction. Patient follow-up continues and updated data will be presented. The combination of NT-I7 1200 μg/kg IM Q6W + pembro 200 mg IV Q3W has been selected as the RP2D. **Conclusions:** The combination of NT-I7 + pembro was well tolerated in pts with R/R advanced solid tumors. NT-I7 + pembro significantly increased T cell numbers in both the TME and the PB, and there was encouraging antitumor activity with the combination in this pt population. These results support continued evaluation of NT-I7 in combination with pembro in pts with R/R advanced solid tumors. The phase 2a of the study is enrolling pts with either CPI-pretreated or CPI-naïve solid tumors (NCT04332653). Clinical trial information: NCT04332653. Research Sponsor: NeoImmuneTech, Inc.

Increased lymphocytes in the TME on treatment (OT) compared to baseline (BL).

	% lymphocyte			
	Stroma		Tumor	
DL	BL	OT	BL	OT
DL2	2	7	0	<1
DL3	3	20	1	<1
DL3	13	16	<1	<1
DL3	15	20	6	20

2595 **Poster Session**

Phase II trial of MEDI0457 and durvalumab for patients with recurrent/metastatic HPV-associated cancers. *First Author: Van K. Morris, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Infection with human papillomavirus (HPV) types 16 or 18 drives oncogenesis for the majority of patients (pts) with cervical, anal, and some penile cancers via viral oncoproteins E6 and E7. While anti-PD1/PD-L1 antibodies have activity in pts with HPV-associated cancers, the majority do not derive benefit from these agents as monotherapy. MEDI0457, a therapeutic DNA vaccine containing plasmids for E6 and E7 oncogenes for HPV-16/18 and IL-12 adjuvant, has been shown to be safe and to provoke an immune response against the expressed antigens. We tested MEDI0457 with the anti-PD-L1 antibody durvalumab for pts with recurrent or metastatic HPV-associated cancers with the goal of improving anti-tumor activity. **Methods:** Pts with HPV-16/18 cervical cancer or rare (anal, penile, vaginal, or vulvar) HPV- associated cancers that were recurrent and/or metastatic following standard therapies were eligible. No prior immunotherapy was allowed. Pts received 7 mg of MEDI0457 intramuscularly (weeks 1, 3, 7, 12, and every 8 weeks thereafter) and durvalumab 1500 mg intravenously every 4 weeks starting at week 4. The primary endpoint was best overall response according to RECIST 1.1. Adverse events (AE) were assessed using CTCAE v4.03. A Simon two-stage phase 2 trial (Ho: p < .15; Ha: p≥.35) using a one-sided alpha = .05 and beta = .20 was conducted. ≥2 responses were needed in both the "cervical" and non-cervical cohorts during the first stage in order for the trial to proceed. Median progression-free survival (PFS) and overall survival (OS) were estimated via Kaplan-Meier. **Results:** 41 pts were screened between 11/2018-10/2020. 21 pts (12 cervical, 7 anal, 2 penile) were treated. All 21 were evaluable for toxicity and 19 for response. Median age was 49 years (range, 29-75), and 18 (86%) were female. There were 17 squamous cell carcinomas (SCC) and 4 cervical adenocarcinomas. Grade ≥3 AEs occurred in 3 (14%) pts and included transaminitis, elevated lipase/amylase, hyponatremia, and neutropenia. No AE required study discontinuation. Overall response rate (ORR) was 21% (95% CI, 6-46%) and disease control rate (DCR) was 42% (95% CI, 20-67%). There was one patient with a complete response, 3 with partial response, and 4 with stable disease. All responses were noted among SCCs (1 cervical, 2 anal, 1 penile). Median duration of response among responders is 16 months (range, 11-27). Median PFS was 3.7 months (95% CI, 2.8-9.2), and median OS was 13.5 months (95% CI, 10.1-NA). 6-month PFS rate was 36% (95% CI, 20-65). **Conclusions:** The combination of MEDI0457 and durvalumab demonstrated acceptable safety/tolerability in pts with advanced HPV-16/18 cancers. Despite a clinically meaningful DCR, the low ORR among pts with cervical cancer led to study discontinuation for futility. Correlative studies are ongoing to characterize pts with prolonged disease control with study treatment. Clinical trial information: NCT03439085. Research Sponsor: AstraZeneca.

2596 **Poster Session**

Preliminary data from QUILT 3.055: A phase 2 multi-cohort study of N803 (IL-15 superagonist) in combination with checkpoint inhibitors (CPI). *First Author: John M. Wrangle, Johns Hopkins Univ School of Medcn, Baltimore, MD*

Background: There is currently a paucity of treatment options for checkpoint relapsed patients who have had an initial response but subsequently progress. N803, a novel IgG1 Fc-engineered IL-15-complexed protein may rescue checkpoint activity in a checkpoint independent manner via its selective enhancement of natural killer cell (NK) and CD8+ T cell number and function, without stimulation of T regs and MDSCs. **Methods:** QUILT 3.055, (NCT03228667) a phase 2b study of N803 plus investigator choice CPI in 11 tumor types: NSCLC, SCLC, Urothelial carcinoma, HNSCC, Merkel cell carcinoma, Melanoma (single PD-1/PD-L1 CPI or w/ ipilimumab), Renal cell carcinoma (RCC), Gastric cancer, Cervical cancer, Hepatocellular carcinoma, Microsatellite instability-high (MSI-H)/ mismatch repair deficient (dMMR) solid tumors, with a heterogeneous mix of prior therapies. We present interim data for 135 patients treated with CPI alone or in combination with chemotherapy as their most recent prior therapy. Trial inclusion required investigator assessed progression on last line of therapy, patients had either CR with relapse or partial response or stable disease for 6 months with progression as their most recent result of checkpoint therapy. Patients with hyperprogression or best initial response of progression were excluded. Subjects received N803 15mck/kg SC q 3 weeks in combination with the same checkpoint inhibitor on which they had their most recent progression. **Results:** Preliminary data from 135 patients (60% NSCLC) with treatment with checkpoint and N-803 following progression on the same checkpoint show CR 0%, PR 8%, Stable Disease 51%, Progression 29%, response unevaluable 12% to date. A PR or SD was seen in all subgroups. Median PFS 3.9 months (95% CI: 2.6,5.0). Median OS 13.8 months (95% CI: 11.8, 16.3) N-803 is well tolerated with grade 1-2 common N-803 treatment related adverse events (TRAE) were injection site reaction (68%), chills (32%) fatigue (26%), pyrexia (26%), flu-like illness (14%), nausea (12%) and no other individual AE > 10%. Grade 3 N-803 TRAE were 12% but no individual grade 3 AEs were greater than 5%. **Conclusions:** N803 demonstrates low toxicity in patients previously treated with CPI and promising efficacy of cessation of progression and induction of response and durable stable disease in patients who had previously progressed on a CPI containing regimen in multiple tumor types and different CPIs. Clinical trial information: NCT03228667. Research Sponsor: ImmunityBio.

2597 **Poster Session**

Evaluating the role of immune-checkpoint inhibitor (ICI) combinations in patients (pts) with unselected "cold" tumors enrolled in early clinical trials (CT). *First Author: Omar Saavedra, Department of Medical Oncology, Vall d'Hebron Institute of Oncology (VHIO), Barcelona, Spain*

Background: In order to improve the expected response rate (ORR) of less than 10% in cold tumors, several ICI combinations are being evaluated in clinical trials. However, most of these trials don't require any biomarker and pts are included based solely in histology. We aimed to assess the benefit of ICI combinations in pts with unselected cold tumors included in early CT. **Methods:** ICI naïve pts with cold tumors treated from 2015 to 2021 with ICI combinations in early CT at VHIO were reviewed. Clinico-pathological data and anti-tumor activity were extracted from a prospective database. ORR was defined as per RECIST v1.1 and clinical benefit rate (CBR) as complete/partial response (CR/PR) + stable disease (SD) for ≥ 4 months (m). Kaplan Meier estimates of progression-free survival (PFS) and overall survival (OS) were calculated and a Cox model according to LIPI (Lung Immune Prognostic Index = baseline LDH and derived neutrophil to lymphocyte ratio) was constructed. Immune-related adverse events (irAE) were classified as per CTCAE v.4.03. Hyperprogressive disease (HPD) was evaluated using RECIST v1.1 (Matos *et al,* 2020). **Results:** Out of 97 pts, median age was 62y, 61% had ECOG 0 and 29.8% had LIPI 0 (good prognostic score). Most pts had microsatellite stable (MSS) colorectal cancer (60.8%) or ovarian cancer (14.4%). Regimens included anti-PD1/L1 + another ICI in 69% (most commonly anti-LAG3 [26,8%] and CD40 agonist [20.9%]), anti-PD1/L1 + other molecule in 21.7% (most commonly SHP2 inhibitor [33.3%] and anti p53-HDM2 [28.5%]) and bispecific antibodies in 9.3% (anti-PD1/L1 + anti-LAG3 or CD137 agonist). No patient achieved a response. CBR was 15.3% (11 pts with MSS colorectal cancer, 2 ovarian cancer, 1 olfactory neuroblastoma, 1 paraganglioma). 33 pts (34%) presented irAE, 15 pts (15.5%) had irAE ≥ G2, 4 pts (4.1%) had G3 irAE (dry mouth, hypertransaminasemia, myocarditis and neutrophils count decreased) and 1 patient (1%) had G4 hyperglicemia. 58 pts (59.7%) had progressive disease (PD) as best response, 19 of these pts (32.7%) presented irAE. Overall, 20 pts (20.6%) met definition of HPD, representing 34.4% of pts with PD as best response. Median PFS for overall and CBR population were 1.9 m (CI95% 1.7-2.0) and 5.9 m (5.4-NR), respectively. Median OS for overall population was 7.6 m (5.9-9.5), with a trend for improved OS if LIPI good score vs. others (12.6 m vs. 6.2 m, hazard ratio 1.9, (CI 95% 1.1-3.3), p = 0.02). Among hyperprogressors, median OS was 5.33 m (3.39 - NR) and significantly worse LIPI scores (intermediate [1] or poor [2]) were observed as compared to pts with CBR (75% vs 53.3% p = 0.001). **Conclusions:** ICI combinations demonstrated very limited activity in pts with unselected cold tumors. However, the risk for irAE and HPD remain substantial. Further drug-biomarker co-development strategies are urgently needed to increase the risk benefit ratio for these pts. Research Sponsor: BBVA Foundation.

2598 **Poster Session**

A pan-cancer analysis of MUC family genes as potential biomarkers for immune checkpoint therapy. *First Author: Yang Li, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China*

Background: Mucin (MUC) is a family of high-molecular weight glycoproteins and increased mucin production occurs in many malignant tumors. Recent studies have found relationship between mutations of some MUC family genes and efficacy of immunotherapy. Here, we explored the associations of MUC family genes (MUC2, MUC3A, MUC4, MUC5B, MUC6, MUC12, MUC16, MUC17, MUC19) mutation with ICI response based on multidimensional data from multiple solid tumors. **Methods:** 15 solid tumor types of TCGA genomic data for 6138 patients was used to evaluate tumor mutational burden (TMB) differences between MUC family genes mutation group and wildtype group. TMB was calculated as the total count of nonsynonymous mutations in coding sequence. Neoantigens of 3039 samples across 11 solid tumor types were obtained from The Cancer Immunome Atlas. A pan-cancer immunotherapy cohort (Broad/Dana-Farber, Nat Genet 2018, N = 249) was used to explore the relationship between mutations of MUC family genes and its efficacy of immunotherapy. **Results:** The most common mutated MUC genes (frequency > 5%) were MUC16 (25.3%), MUC17 (10.8%), MUC5B (10.5%), MUC4 (8.6%), and MUC2 (5.1%). The data between MUC mutation group and wild type group showed a significant difference ($P < 0.01$) in TMB. Median TMB across fifteen tumors in MUC mutation group and wild type group is 7.04 mutations per Mb and 2.07 mutations per Mb, separately. The TNB between two group is also showed a significant difference ($P < 0.01$). Median TNB across nine types tumor in MUC mutation group and wild type group is 121.5 neoantigens and 34.0 neoantigens, separately. A multivariable analysis across the pan-cancer cohort using Cox proportional-hazards regression demonstrated that KMT2C mutation was associated with better OS (hazard ratio, 0.66; 95%CI, 0.45-0.99; P = 0.042), adjusting for sex and cancer type. **Conclusions:** The results indicated that MUC family genes mutation was associated with a higher TMB and TNB. Analysis of immunotherapy cohort data showed MUC family was associated with better OS. These findings indicate that these genes mutation may serve as a predictive biomarker for ICI in solid tumor patients. Research Sponsor: None.

2599 **Poster Session**

Real-world pan-cancer landscape of frameshift mutations (FSM) and their role in predicting responses to immune checkpoint inhibitors (ICI) in patients (pts) with tumors with low tumor mutational burden (TMB). *First Author: Vaia Florou, Huntsman Cancer Institute University of Utah, Salt Lake City, UT*

Background: Pembrolizumab was recently approved in tumors with TMB ≥10 mut/Mb. FSM can complement TMB in predicting ICI responses. We obtained a real-world dataset of genomic alterations from 250,813 samples to examine the distribution of TMB and FSM across a variety of malignancies. We then conducted a multi-institutional retrospective review of pts treated with ICI. **Methods:** Database samples were sequenced by Foundation Medicine using hybrid capture genomic profiling to evaluate all classes of genomic alterations in at least 315 genes. The clinical cohort included pts with metastatic solid malignancies who received ICI and had undergone commercial next-generation sequencing (NGS). Pts were classified into four distinct groups: TMB-L (< 10mut/Mb)/ FS-A (absent FSM), TMB-H (≥10mut/Mb)/ FS-A, TMB-L /FS-P (present, ≥1 FSM) and TMB-H/FS-P. Progression-free survival (PFS), overall survival (OS), and response rate (RR) were compared between the groups. **Results:** 246,252 MSS and 4,561 MSI-High samples were segregated by histology and divided into four distinct groups based on the TMB and FSM. For the MSS cohort the distribution was: TMB-L/FS-A (N = 111,065, 45%), TMB-H/FS-A(N = 15,313, 6%), TMB-L /FS-P (N = 98,389, 40%) and TMB-H/FS-P (N = 21,485, 9%). In the ICI-treated clinical cohort, there were 230 pts in 12 histology groups; 212 had information on TMB and FSM. The most common primary sites were GI (N = 39), melanoma (N = 37), GU (N = 32) and H&N cancer (N = 21). 159 pts received single ICI and 53 dual ICI. 196 tumors were MSS, 11 MSI, and 5 unknown. Group distribution: TMB-L/FS-A 80 pts (38%), TMB-L/FS-P 57pts (27%), TMB-H/FS-A 36pts (17%), TMB-H/FS-P 39pts (18%). FS-P was associated with higher RR 23.81 vs. 12.8 % (p = 0.02). Regardless of TMB, the median PFS for FS-P vs. FS-A was 7.9 and 4.0 mo, respectively ($p < 0.01$). TMB-L/FS-P had superior PFS (5.1 mo) compared to TMB-L/FS-A (3.6 mo) group ($p < 0.01$). The 15-month PFS probability was 12% for TMB-L/FS-A vs. 38% for TMB-L/FS-P. No statistically significant difference was detected in OS between the groups. From the pan-cancer cohort, histologies with more than 40% of samples in the TBM-L/FS-P (MSS) group were: CRC, RCC, PDAC, biliary, breast, esophageal, and endometrial cancers. Additional genomic data will be presented. **Conclusions:** FSM are frequently found on commercial NGS testing in tumors that are MSS and TMB-L. The presence of FSM may complement TMB in predicting benefit from immunotherapy. If validated in additional cohorts, FSM presence could be utilized to identify pts that may benefit from ICI, particularly for tumors with low TMB. Research Sponsor: None.

2600 **Poster Session**

Association of KMT2C mutations with favorable outcomes with immune checkpoint inhibitors across multiple tumor types. *First Author: Chunling Liu, The Affiliated Tumor Hospital of Xinjiang Medical University, Urumchi, China*

Background: The KMT2 (lysine methyltransferase) family of histone modifying proteins play important roles in regulating developmental pathways, and mutations in the genes encoding these proteins have been strongly linked to many solid tumor cancers. Recently, there is emerging evidence that KMT2 family genes are involved in sensitivity to immune checkpoint inhibitors (ICIs) by modulating the immune environment. Here we explored the relationship between KMT2C mutation and its efficacy of immunotherapy. **Methods:** 1661 patients with next-generation sequencing (NGS) and immunotherapy data obtained from MSKCC clinical cohort were used to explore the association with KMT2C mutation and TMB and efficacy of ICIs. TMB was defined as the total number of somatic nonsynonymous mutations in the coding region. NGS data of 6624 pan-cancer patients who also detected MSI and PD-L1 expression from the Chinese clinical dataset were also analyzed relevance of mutation and these immune-related indicators. **Results:** In total, 9.81% (163/1661) patients in MSKCC cohort harbored KMT2C mutation. In the Chinese cohort, the KMT2C mutation ratio (11.19%, 741/6624) was similar to MSKCC. The TMB level of KMT2C mutation group in both MSKCC cohort and Chinese pan-cancer patient cohort was significantly higher than wild-type group ($P < 0.001$). A multivariable analysis across the pan-cancer cohort using Cox proportional-hazards regression demonstrated that KMT2C mutation was significantly associated with better OS (hazard ratio, 0.69; 95%CI, 0.52-0.90; P = 0.006), and association remained significant with bladder (P = 0.039), colorectal (P = 0.024), melanoma ($P < 0.001$) and renal ($P < 0.001$), adjusting for cancer age, sex, metastases or primary. In addition, in Chinese cohort, KMT2C mutation was associated with higher PD-L1 positive expression (≥1%) (P = 0.01203) and MSI-H ($P < 0.001$). **Conclusions:** KMT2C mutation shows impressive association with efficacy of ICIs. Meanwhile, KMT2C-mutant group has a higher TMB, PD-L1 expression and MSI-H. These results indicated that KMT2C mutation may serve as a good potential biomarker of ICI benefit in patients with multiple cancer types. Research Sponsor: None.

2601 **Poster Session**

MSIFinder: A python package for detecting MSI status using random forest classifier. *First Author: Tao Zhou, AcornMed Biotechnology Co., Ltd., Beijing, China*

Background: Microsatellite instability (MSI) is a common genomic alteration in several tumors, such as colorectal cancer, endometrial carcinoma, and stomach, which is characterized as microsatellite instability-high (MSI-H) and microsatellite stable (MSS) based on a high degree of polymorphism in microsatellite lengths. MSI is a predictive biomarker for immunotherapy efficacy in advanced/metastatic solid tumors, especially in colorectal cancer (CRC) patients. Several computational approaches based on target panel sequencing data have been used to detect MSI; However, they are considerably affected by the sequencing depth and panel size. **Methods:** We developed MSIFinder, a python package for automatic MSI classification, using random forest classifier (RFC)-based genome sequencing, which is a machine learning technology. We included 19 MSI-H and 25 MSS samples as training sets. First, RFC model were built by 54 feature markers from the training sets. Second. The software was validated the classifier using a test set comprising 21 MSI-H and 379 MSS samples. **Results:** With this test set, MSIFinder achieved a sensitivity (recall) of 0.997, a specificity of 1, an accuracy of 0.998, a positive predictive value (PPV) of 0.954, an F1 score of 0.977, and an area under curve (AUC) of 0.999. We discovered that MSIFinder is less affected by low sequencing depth and can achieve a concordance of 0.993, while exhibiting a sequencing depth of 100×. Furthermore, we realized that MSIFinder is less affected by the panel size and can achieve a concordance of 0.99 when the panel size is 0.5 m (million base). **Conclusions:** These results indicated that MSIFinder is a robust MSI classification tool and not affected by the panel size and sequencing depth. Furthermore, MSIFinder can provide reliable MSI detection for scientific and clinical purposes. Research Sponsor: None.

Summary of classification performance of MSIFinder, mSINGS and MSIsensor.

Tools	Sen.	Spe.	Acc.	PPV	F1	AUC
MSIFinder	0.997	1.000	0.998	0.954	0.977	0.9999
msings	0.983	0.950	0.981	0.730	0.826	0.985
MSIsensor	0.959	0.944	0.958	0.586	0.723	0.985

Sen: Sensitivity; Spe: Specificity; Acc: Accuracy; PPV: positive predictive value; F1: F1 score; AUC: Area Under Curve.

2602 **Poster Session**

A cancer organogram test as a guide for oncology treatments in SOLID tumors: An analysis of 628 tests in 419 patients. *First Author: Astrid Margossian, SEngine Precision Medicine, Seattle, WA*

Background: A CLIA-certified organoid based drug sensitivity assay (a cancer organogram) has been developed for all solid tumors. An actionable report of organogram sensitivities to endocrine, chemotherapy and targeted agents, produced a drug sensitivity score as a tool to inform therapy decision making. Objectives: To evaluate the success rate of organoid derivation, the organogram drug responses across cancer types and to analyze the impact of the organogram report on therapeutic decision making. **Methods:** From 2016 to 2020, 628 cancer organograms were performed, with 513 tumor samples from 419 cancer patients. Within 48 hours of collection, fresh samples of tumor cells obtained from core biopsies, surgical excisions, or fluids were cultured, the majority as 3D organoids. Drug screens were performed with a library of up to 220 drugs, and dose-response was evaluated across a range of concentrations for each drug. Organogram sensitivity was ranked as response in five categories based on SPM Score: Exceptional (SPM15/14), Good (13/12), Moderate to Low (11/9), and None(< 9). 118 drugs on average were tested per screen (range: 68-152), so in a total of 628 organograms, more than 70,000 individual drug trials have been performed. The median turnaround time was 28 days (range: 19.5-51.5). **Results:** Of the 513 collected samples, 314 were fresh specimens: 96 core biopsies, 151 surgical specimens, and 67 fluids (pleural effusions or ascites), with an organoid derivation success rate of 58.3%, 78%, and 88%, respectively. Overall success rate in organoid derivation was 70.2%. Samples with poor viability and low tumor cell count (22%) were rejected. The primary cancer types tested were ovarian (n = 92, 17.9%), breast (n = 73, 14.2%), colorectal (n = 70, 13.6%), pancreatic (n = 51, 9.9%), cholangiocarcinoma (n = 42, 8.1%), and other solid tumors (n = 185, 36%). Median age of patients was 56 years old (range: 5-83), most of them heavily pretreated. 20.45% of drugs screened had exceptional and good responses (SPM score 15-12) (SD: 17.92%). We reviewed genomic data from 374 third-party genomic reports. The most frequent genomic alterations found were *TP53* (n = 143, 38.2%), *BRCA1* and *BRCA2* (n = 47, 12.5%) *CDKN2A* (n = 42, 11.2%), *FGFR1/2/3/4* (n = 41, 10.9%), and *PIK3CA* (n = 38, 10.1%). Post-test treatment information is available for a subset of 61 patients. The treating physician made an organogram-guided therapeutic decision in 32/44 patients with post test treatment drugs scored (72%). **Conclusions:** The cancer organogram test has a high rate of success in generating an actionable report that identifies therapies for patients with limited therapeutic options, including those with no known genomic biomarkers. The organogram guided selection of therapeutics for a significant subset of patients, nearly 4 times the rate reported with genomic testing alone. Research Sponsor: Sengine Precision Medicine.

2603 **Poster Session**

Relationship between DICER1 mutations and immunotherapy biomarkers in solid tumors. *First Author: Jie Gao, The Department of Hepatobillary Surgery, Peking University People's Hospital, Beijing, China*

Background: Dicer1 functions as a tumor suppressor in mouse models. In humans, somatic mutations are associated with many cancers in adults, and patients with DICER1 syndrome with *DICER1* germline mutations are susceptible to childhood cancers. *DICER1* is the core caner-intrinsic CTL-evasion gene, especially positive correlate with innate anti-PD-1 resistance signature or IPRES signature and hERV expression which involved in sensitivity and resistance to ICIs. Nevertheless, the association between mutations in *DICER1* and the Chinese patients, the relationship between *DICER1* mutations with immunotherapy biomarkers are unknown. **Methods:** NGS and clinical data were collected from 10953 Western pan-cancer patients (TCGA cohort). A 539-gene panel targeted sequencing assay was performed on FFPE tumor samples from 3514 Chinese pan-cancer patients (Chinese cohort). Both *DICER1* mutation ratio and TMB were calculated on the two cohorts following the same criteria.DNA NGS testing (MSI-high vs low/stable (MSS)) in Chinese cohort were included. NGS data of 3514 patients who also detected PD-L1 expression from Chinese clinical dataset were analyzed to explore the association with mutation and PD-L1. The survival information was collected from 1661 pan-cancer patients to analyze the association between *DICER1* mutation and efficacy of immunotherapy (MSKCC cohort). **Results:** In total, 2.91% (319/10953) patients in TCGA harbored *DICER1* mutation; in the Chinese cohort, the *DICER1* mutation ratio (2.67%, 94/3514) was similar to TCGA. The top 5 mutant *DICER1*-associated cancer types in Chinese cohort were lung cancer, colon adenocarcinoma, liver cancer, uterine corpus endometrial carcinoma , melanoma. In both cohorts, TMB level of mutation group was significantly higher than wild-type group ($p < 0.001$). The ration of mutation group in MSI-H (50%) and MSI-L (23.53%) was significantly higher than wild-type group in Chinese cohort (2.17%) ($p < 0.001$). In addition, the ratio of PD-L1 positive expression ($\geq$1%) in mutation group (48.94% , 46/48) was significantly higher than wild-type in Chinese cohort (38.48% ,1316/2104) ($p < 0.05$). The survival probability of mutation group was significantly longer than wild-type group in immunotherapy. **Conclusions:** The results indicated that *DICER1* mutation was associated with a higher TMB, MSI-H and PD-L1 expression level in Chinese patients. Patients with *DICER1* mutations may benefit more from ICIs. Research Sponsor: None.

2604 **Poster Session**

YAP1 mutation as a novel predictor of response to anti-PD-1/PD-L1 treatment in pan-cancers. *First Author: Wei-guo Xu, Department of Respiratory and Critical Care Medicine, Mianyang Central Hospital, Mianyang, China*

Background: YAP1 is the main downstream target of the Hippo pathway and acts as a transcriptional coactivator to regulate development processes. YAP1 amplification is a potentially useful biomarker for predicting treatment outcomes and identifying patients with a high risk of relapse who should be closely monitored in nonsurgical esophageal squamous cell carcinoma (ESCC). YAP1 overexpression has been identified in multiple solid cancers, which consistently correlated with unfavorable clinical outcomes. Previous work suggested that YAP1 alterations may enrich for responses to immune checkpoint inhibitors (ICI), validation of these findings in needed. **Methods:** Using 539-gene target-capture next generation sequencing, we analyzed the YAP1 mutation in 3547 tumor tissue or plasma ctDNA samples from different patients, and the public database of TACG was also compared. Data from MSK-IMPACT study (n = 1661, anti-PD-(L)1/CTLA-4 mono/ combined therapy) was retrieved and analysed. In survival analysis, Kaplan-Meier curves were compared by log-rank test, and the hazard ratio (HR) was determined through a multivariable Cox regression model. **Results:** In clinical cohort, the frequency of YAP1 mutation in 3547 tumor tissue or plasma ctDNA samples from different patients was 0.62 % (22 in 3547). Meanwhile, the frequency of YAP1 mutation in TCGA cohort was 0.90 % (99 in 10953). We further analyzed Kaplan-Meier curves from MSK-IMPACT study (n = 1661, anti-PD-(L)1/CTLA-4 mono/ combined therapy). In MSK-IMPACT cohort, mutation of YAP1 was associated with higher TMB ($P = 0.022$) and higher mutation count ($P = 0.017$) in pan-cancers. YAP1 mutation was associated with prolonged overall survival (OS) trend compared with YAP1 wt in pan-cancers ($P = 0.15$; HR, 2.209, 95% CI, 0.7109-6.8639). **Conclusions:** In our study, the frequency of YAP1 mutation was investigated in clinical and TCGA cohort, which might provide useful information to guide precision medicine. YAP1 mutation may serve as a novel predictor of response to anti-PD-1/PD-L1 treatment in pan-cancers via upregulating TMB and mutation count. Research Sponsor: None.

2605 **Poster Session**

Pan-cancer analysis of *CD274* (PD-L1) mutations in 314,631 patient samples and subset correlation with PD-L1 protein expression. *First Author: Richard S.P. Huang, Foundation Medicine, Inc, Cambridge, MA*

Background: The effects of non-amplification short variant (SV) mutations in *CD274 (PD-L1)* on PD-L1 protein expression and immune checkpoint inhibitor (ICPI) therapy are unknown. Here, we present a retrospective analysis of *CD274* mutations detected by comprehensive genomic profiling (CGP) and correlate these results with tumor-cell PD-L1 immunohistochemistry (IHC)-based expression assessment to better understand the relationship between mutations and protein expression of PD-L1. **Methods:** FoundationOne CGP was performed on hybridization-captured, adaptor ligation-based libraries using DNA and/or RNA extracted from 314,631 tumor samples that were sequenced for up to 406 cancer related genes and select gene rearrangements. PD-L1 IHC was performed on a subset of cases (n = 213) using the DAKO 22C3 PD-L1 IHC assay and scored with the tumor proportion score (TPS). **Results:** Overall, the prevalence of *CD274* SV mutations was low (0.3%, 1,081/314,631) with 577 unique variants. The most common *CD274* SV mutations were R260H (n = 51), R260C (n = 18), R125Q (n = 12), C272fs*13 (n = 11), R86W (n = 10), and R113H (n = 10). The prevalence of *CD274* mutations varied depending on tumor type with diffuse large B-cell lymphoma (1.9%, 19/997), cutaneous squamous cell carcinoma (1.6%, 14/868), endometrial adenocarcinoma (1.0%, 36/3740), unknown primary melanoma (0.9%, 33/3679), and cutaneous melanoma (0.8%, 32/3874) having the highest frequency of mutations. Ultraviolet exposure was likely a mechanism for *CD274* SV mutations in cutaneous tumors with high frequencies of ultraviolet mutational signatures (cutaneous squamous cell carcinoma [84.6%, 11/13], cutaneous melanoma [93.8%, 30/32], and unknown primary melanoma [100%, 32/32]), and microsatellite instability (MSI) was likely a mechanism for development of *CD274* mutations in non-serous endometrial adenocarcinoma. Of the R260H cases concurrently tested with PD-L1 IHC, most (81.8%, 9/11) had no PD-L1 expression, which contrasts to the five E237K cases where most (80%, 4/5) had PD-L1 expression. This difference in protein expression of these two mutations was significantly different (p = 0.036). It was notable that nearly all samples (88.9%, 16/18) with a clonal truncating variant (nonsense or frame shift indel) and PD-L1 testing showed a PD-L1 TPS score $\leq$1, whereas three of four samples with sub-clonal truncating variants had TPS scores $\geq$5. **Conclusions:** We defined the landscape of *CD274* mutations in a large cohort of tumor types that can be used as a reference for examining *CD274* mutations as potential resistance biomarkers for ICPI. Furthermore, we presented novel data on the correlation of *CD274* mutations and PD-L1 protein expression, providing important new information on the potential functionality of these mutations and can serve as a basis for future research. Research Sponsor: None.

2606 **Poster Session**

Investigating the various predictive values of *POLE/POLD1* mutations for response to immune checkpoint inhibitors (ICIs) in different solid tumors. *First Author: Yanling Niu, Genetron Health (Beijing) Technology, Co. Ltd., Beijing, China*

Background: Both POLE and POLD1 encode the catalytic subunit of polymerase enzyme complexes involved in DNA replication and repair. The mutations of *POLE* and *POLD1* have been shown to be oncogenic and lead to DNA repair defects and elevated tumor mutation burden (TMB). And patients with *POLE/POLD1* mutations are more likely to benefit from ICIs therapy. Previous studies have shown that TMB has divergent predictive value for response to ICIs therapy in different cancer types. We hypothesized that the associations between *POLE/POLD1* mutations and ICIs efficacy are also varied in different solid tumors. Therefore, we explored the prediction values of *POLE/POLD1* mutations in some cancer types. **Methods:** The ICIs treatment cohort from Memorial Sloan Kettering Cancer Center (MSKCC) was selected to analyze the association of *POLE/POLD1* mutations with ICIs efficacy. TCGA cohort was enrolled for characterizing tumor infiltrating lymphocytes (TILs) with CIBERSORT. The patients were classified into two groups: *POLE/POLD1* mutations (Mut) and wildtype (WT). Overall survival (OS) after ICIs therapy was estimated with Kaplan-Meier method. **Results:** In MSKCC pan-cancer dataset, patients with *POLE/POLD1* mutations had significantly longer median OS after ICIs therapy (34.00 vs 19.00 months, P = 0.0143), indicating that *POLE/POLD1* mutations were associated with better immunotherapy outcomes. Then we analyzed the predictive roles in each cancer type. Notably, we found the associations of *POLE/POLD1* mutations with longer median OS in NSCLC (Undefined vs 12.00 months, P = 0.05) and esophagogastric cancer (27.00 vs 15.00 months, P = 0.05). However, the associations between *POLE/POLD1* mutations and ICIs efficacy were not observed in bladder cancer, melanoma, glioma, head and neck cancer, renal cell carcinoma, and colorectal cancer. Furthermore, our data showed that the median TMB was significantly higher in the Mut group for NSCLC (20.2 vs 6.9 muts/Mb, P $<$ 0.0001) and esophagogastric cancer (21.4 vs 5.6 muts/Mb, P $<$ 0.0001). In TCGA esophagogastric cancer cohort, *POLE/POLD1* mutations were correlated with decreased naive B cells (P = 0.0306) and increased activated memory CD4+ T cells (P = 0.0224). In TCGA NSCLC cohort, *POLE/POLD1* mutations were correlated with elevated gamma delta T cells (P = 0.0219). These data suggested that *POLE/POLD1* mutations were also involved in the infiltration of some immune cells. **Conclusions:** Although *POLE/POLD1* mutations were associated with better ICIs efficacy for all the enrolled patients, the prolonged OS was only found in the Mut group for NSCLC and esophagogastric. These data suggested that *POLE/POLD1* mutations may be a useful predictor for ICIs efficacy in these two types of cancer. Moreover, *POLE/POLD1* mutations were correlated with the level of TILs in NSCLC and esophagogastric. The finding was consistent with the efficacy of immunotherapy. Research Sponsor: None.

2607 **Poster Session**

Artificial intelligence-powered spatial analysis of tumor-infiltrating lymphocytes predicts survival after immune checkpoint inhibitor therapy across multiple cancer types. *First Author: Jeanne Shen, Department of Pathology, Stanford University School of Medicine, Stanford, CA*

Background: Tumor infiltrating lymphocytes (TIL) are a potential tumor-agnostic biomarker for immune checkpoint inhibitor (ICI) therapy. We previously reported the clinical application of an artificial intelligence-powered spatial TIL analyzer, Lunit SCOPE IO, for predicting ICI treatment outcomes in advanced non-small cell lung cancer (NSCLC). Here, we expand the clinical application of Lunit SCOPE IO as a tumor-agnostic ICI biomarker across multiple cancer types. **Methods:** Lunit SCOPE IO was trained and validated with a 2.8 x 10^9 micrometer^2 area and 5.9 x 10^6 TILs from 3,166 H&E Whole-Slide Images (WSI) of multiple cancer types, annotated by 52 board-certified pathologists. The Inflamed Score (IS) was defined as the proportion of all tumor-containing 1 mm^2-size tiles within a WSI classified as being of the inflamed immune phenotype (high TIL density within cancer epithelium). We first evaluated the correlation between the IS and TMB, MSI-H, and immune cytolytic activity (*GZMA* and *PRF1*) across 22 cancer types from The Cancer Genome Atlas (TCGA, n = 7,467). Subsequently, the correlation between the IS and overall survival after ICI treatment was evaluated in a real-world dataset of patients with 9 different tumor types (n = 1,013), retrospectively collected from Stanford University Medical Center, Chonnam National University Hospital, Samsung Medical Center, and Seoul National University Bundang Hospital. **Results:** Lunit SCOPE IO accurately detected CE, CS, and TILs with an area under the receiver-operating-characteristic curve of 0.970, 0.949, and 0.925, respectively. In the TCGA pan-cancer cohort, Lunit SCOPE IO's IS correlated significantly with immune cytolytic activity (Spearman rho = 0.504, $p < 0.001$), TMB-high ($\geq$ 10 mutations/Mb, fold change 1.39, $p < 0.001$) and MSI-H (fold change 1.45, $p < 0.001$). The IS-positive proportions of microsatellite-stable (MSS) and TMB-low cases were 42.5% and 17.1%, using the thresholds of IS $\geq$ 20% and $\geq$ 50% as presumptive clinical cutoffs. In the real-world ICI clinical dataset (n = 1,013), an IS $\geq$ 20% correlated significantly with favorable overall survival after ICI treatment (cancer type-adjusted hazard ratio [HR] 0.70, 95% confidence interval [CI] 0.59-0.83, $p < 0.0001$). Furthermore, this association remained significant after the exclusion of NSCLC patients (n = 519) (adjusted HR 0.68, 95% CI 0.53-0.86, $p = 0.0016$) indicating that the effect was not driven solely by one major tumor type. **Conclusions:** The Inflamed Score (IS), as evaluated by Lunit SCOPE IO, correlates with favorable overall survival after ICI treatment across multiple tumor types. AI-powered spatial TIL analysis of the tumor microenvironment may be able to detect a significant proportion of ICI responders, and offers promise as a new companion diagnostic, particularly in patients with MSS/TMB-low tumors. Research Sponsor: Lunit Inc.

2608 **Poster Session**

Awareness and utilization of tumor mutation burden (TMB) as a biomarker for administration of immuno-oncology (I-O) therapeutics by practicing community oncologists in the United States (U.S.). *First Author: Kristin M. Zimmerman Savill, Cardinal Health, Dublin, OH*

Background: TMB, a measurement of the number of mutations carried by tumor cells, is emerging as a biomarker for the identification of patients who may benefit from certain I-O-based therapies. TMB-high (TMB-H) tumors, defined by the detection of $\geq$10 mutations/megabase (mut/Mb) in tumor cells using a tissue-based assay such as the FoundationOneCDx (F1CDx) assay (Foundation Medicine, Inc.), may be more likely to respond to some I-O therapies. Higher neoantigen loads of TMB-H tumors have been proposed to contribute to increased responsiveness of TMB-H tumors to certain I-O therapeutics. Pembrolizumab was approved by the FDA on June 16, 2020 for the treatment of adult and pediatric patients with unresectable or metastatic TMB-H tumors, as determined by F1CDx, based on results from the KEYNOTE-158 trial (NCT02628067), which demonstrated that 50% of patients with TMB-H tumors had response durations of $\geq$24 months, with objective response rates in TMB-H vs. non-TMB-H patients of 29% and 6%, respectively (Marabelle et al, The Lancet Oncology, 2020). This survey-based study aimed to evaluate awareness and utilization of TMB as a biomarker for I-O therapeutics among practicing community oncologists in the U.S. **Methods:** Questions related to awareness and utilization of TMB as a biomarker for I-O therapeutics were developed by two medical oncologists (AG and BF) and presented to community oncologists in a web-based survey prior to virtual meetings held between October and November 2020. Descriptive statistics were used to analyze the results. **Results:** Of the 193 participating providers geographically distributed across the U.S., 15% reported being unaware of either the concept of TMB in I-O therapy or how to use the information clinically. 39% of these providers reported testing $\leq$25% of patients with advanced cancer for TMB, including 8% who do not test for TMB at all. Misconceptions regarding TMB identified among participating providers included the belief that high TMB is considered to be $>$ 5 mut/Mb among 20% of providers, that TMB is essentially the same as MSI-high among 8% of providers, and that there are no therapies with FDA approval based on TMB among 15% of providers. Further, 37% of the participants did not identify pembrolizumab as an agent approved for the treatment of solid tumors based on TMB-H status. **Conclusions:** These findings demonstrate that there is a knowledge gap regarding the definition of TMB, testing for TMB, as well as implementation of TMB status in clinical decision making. Education directed towards community oncology providers regarding TMB and its use as a predictive biomarker for I-O therapy may improve its utilization and adoption in solid tumors to improve patient outcomes. Research Sponsor: Cardinal Health.

2609 **Poster Session**

Comprehensive genomic and transcriptomic profiling (CGTP) to predict pembrolizumab (P) benefit in patients (pts) with advanced solid tumors (STs). *First Author: Dan Rhodes, Strata Oncology, Ann Arbor, NC*

Background: P is approved in many ST types, however predictive biomarkers and the proportion of pts who benefit vary widely. Biomarkers beyond PD-L1 immunohistochemistry and comprehensive genomic profiling (CGP) based tumor mutation burden (TMB) may improve benefit prediction. We determined if treatment data and CGTP collected in an ongoing observational trial (NCT03061305) could predict pan-ST P benefit. **Methods:** Eligible advanced ST pts had QC-passing TMB and expression data from multiplex PCR based tissue CGTP on FFPE tissue (StrataNGS and an investigational test) and documented P treatment $>$ 1 month. Real-world time to next treatment (TTNT) was defined as time in months from therapy start to new therapy start (after stopping initial therapy) or death. TMB and gene expression biomarker association with P TTNT was evaluated. Backward stepwise regression was performed to fit a multivariate Cox proportional hazards model; pts were assigned to four score groups (IRS 1-4) based on overlapping TTNT curves from 8 equal bins. P TTNT were compared between IRS groups by log-rank test. A chemotherapy (C) comparator cohort was established from C TTNT for pts in this cohort. Results were stratified by ST type, P mono vs. C combo, and TMB status. **Results:** 610 pts (254 [41.6%] NSCLC; 356 [58.4%] from 23 other ST types) with CGTP and P treatment were identified; P TTNT was highly correlated to overall survival (n=146; Pearsons r^2=0.75). By univariate analysis of TMB and 9 expression biomarkers, TMB, two independent *PD-L1* expression amplicons, and *PD-L2* expression were significantly associated with P TTNT (all $p \leq 0.002$). The most significant multivariate model included 5 variables, with 1) increasing TMB, *PD-L1*, and *PD-L2*, and 2) decreasing *TOP2A* (proliferation) and *GZMA* as P TTNT predictors. Median P TTNT, but not C TTNT (345 courses from 254 pts), differed significantly by IRS group (Table). Median P TTNT by IRS group did not significantly differ by non-small cell lung vs. other ST type or P mono vs. C combo (both $p > 0.05$); excluding TMB-high patients, median P TTNT was still significantly longer in IRS groups 3/4 vs. 1/2 (p = 5.0e-4). Across 19,623 total evaluable pts in NCT03061305, 12.2% were in IRS groups 3/4 and outside of P approved ST types/TMB-low. **Conclusions:** CGTP in an observational trial cohort demonstrated that TMB, *PD-L1* and *PD-L2* independently predicted pan-ST P benefit as assessed by OS-validated TTNT. A multivariate CGTP signature predicted P benefit relative to C across ST types. If further validated, such a signature may enable improved P benefit prediction. P versus C TTNT by IRS group. Clinical trial information: NCT03061305. Research Sponsor: Strata Oncology.

	P			C				
IRS Group	**n**	**%**	**Median TTNT**	**n**	**%**	**Median TTNT**	**HR (95% CI)**	**p-val**
1	73	12%	7	66	19%	7	0.97 (0.65–1.47)	0.894
2	138	23%	8.7	111	32%	7	0.71 (0.52–0.98)	0.037
3	233	38%	13	112	32%	7	0.51 (0.38–0.69)	1.1E-05
4	166	27%	>24	56	16%	6	0.26 (0.17–0.4)	2.9E-09
	610	100%		345	100%			

HR - hazard ratio; log-rank P-value.

2610 **Poster Session**

YAP1 transcription factor expression to define subsets of cancers with T-cell inflamed phenotype in a pan-tumor analysis across 33 tumor types. *First Author: Bhakti Dwivedi, Emory University Department of Biostatistics and Bioinformatics, Atlanta, GA*

Background: Immune checkpoint blockade (ICB) has become an established treatment option for the majority of solid tumors. PD-L1 expression, tumor mutation burden (TMB) and mismatch repair (MMR) deficiency are established but suboptimal predictive markers to select patients for ICB therapy. The identification of better predictive biomarkers to complement existing biomarkers is an area of need. We previously identified Yes Associated Protein 1 (YAP1) gene expression as a marker of inflamed tumor phenotype in small cell lung cancer. We sought to elucidate the role of YAP1 as a tumor agnostic biomarker of inflamed tumor phenotype. **Methods:** We obtained the publicly available TCGA normalized RSEM expression data (version dated September 29, 2019) from the GDC legacy archive (https://portal.gdc.cancer.gov/legacy-archive) for this analysis. We used the shinySISPA method (https://bbisr.shinyapps.winship.emory.edu/shinySISPA/) to classify the primary tumor samples into YAP1 high or low on the basis of the normalized expression profile for YAP1 gene. The T-cell–inflamed gene expression profile score for each sample was calculated as weighted sum of the normalized expression values of the 18 genes (*PSMB10, HLA-DQA1, HLA-DRB1, CMKLR1, HLA-E, NKG7, CD8A, CCL5, CXCL9, CD27, CXCR6, IDO1, STAT1, TIGIT, LAG3, CD274, PDCD1LG2, CD276*) as originally published in the Patent filed under "WO201609437" and validated as a predictor of clinical efficacy in patients treated with anti PD1 immunotherapy drug, pembrolizumab. **Results:** A total of 11283 samples from 33 different histologic tumor types contained in the TCGA database were included in this analysis. A small but meaningful subset of cases 271 (2%) were classified as YAP1 high with a wide range in proportion of YAP1 high tumors of 0.67% to 12.09% across the 33 histologic tumor types. Adrenocortical, cholangiocarcinoma, chromophobe RCC, DLBCL, and mesothelioma had a high rate of YAP1 high tumors ($>$ 10% of cases) . Overall trend showed a higher median interferon gamma GEP score in YAP1 high versus YAP1 low tumors with a GEP score of 11.2 vs. 10.7 respectively. A minority of histologic tumor subtypes (HNSCC, clear cell RCC, sarcoma, uterine carcinosarcoma, testicular GCT, melanoma, mesothelioma and ovarian cancer) showed a reverse trend of lower GEP score in association with YAP1 high status. Ongoing validation of these findings in an independent cohort of clinical samples and correlation of YAP1 status with other predictive biomarkers (TMB, PD-L1 and MSS status) will be presented at the meeting. **Conclusions:** YAP1 is highly expressed in a small but meaningful subsets of cancers and is associated with the inflamed phenotype in the majority of cancers. YAP1 expression is most common in rarer tumor types and in histologic types where currently available biomarkers have not been shown to predict the benefit of ICB. Research Sponsor: U.S. National Institutes of Health.

2611 **Poster Session**

Therapeutic effect of DDR pathway with different functional annotations for immune checkpoint inhibitor. *First Author: Wei Nie, Shanghai Chest Hospital, Shanghai, China*

Background: DNA damage response and repair (DDR) pathway-related gene mutations have been reported to predict the efficacy of immune checkpoint inhibitor (ICI). However, therapeutic effect of DDR pathway with different functional annotations is not fully studied. Here we explore the relationship of DDR pathway with different functional annotations and clinical outcomes in public cohorts of immunotherapy and chemotherapy. **Methods:** Genetic testing and clinical outcomes data were obtained from the public clinical cohorts across 10 tumor types. 232 DDR pathway-related gene were assigned to eight pathway according to the literature. Nine predictive models for the mutation pathogenicity were included in the analysis, of which at least five returned positive results were defined as deleterious mutations. All annotations were according to the American College of Medical Genetics (ACMG) standards and guidelines. To explore the association between DDR pathways and ICI, DDR pathway mutation is grouped. Patients, who harbored mutations in two or more DDR pathways and meanwhile had deleterious mutation in at least one DDR pathway, were enrolled in group A. Patients, who harbored deleterious mutations in only one DDR pathway or had only uncertain significance mutations, were enrolled in group B. Patients with no DDR gene mutations were enrolled in Group C. We analyzed relation of the group and survival outcomes in four public cohorts. **Results:** Of 4 clinical cohort analyzed, the group A treated with ICI has the best PFS or OS outcomes. However, the comparison of group B and group C is not coincide across different cohorts. Treatment is the key factor that influents the relation of DDR pathway mutations and clinical outcomes. As shown in POPLAR/OAK cohort, patients in group C has the best PFS (p=0.0381) or OS (p=0.0350) outcome when treated with chemotherapy, but patients in group A has the best PFS (p=0.0083) or OS (p=0.0222) outcome when treated with ICI. **Conclusions:** When treated with ICI, patients with at least one deleterious mutation and another deleterious or uncertain significance mutation has the best PFS or OS outcomes, but not for chemotherapy. Our study suggested that DDR pathway with deleterious mutations might be a potential predictive factor for immunotherapy. Research Sponsor: None.

Cohort	**PFS sorting**	**OS sorting**
Oak poplar-chemotherapy	C vs A vs B (p=0.0381)	C vs A vs B (p=0.0350)
Oak poplar-ICI therapy	A vs C vs B (p=0.0083)	A vs C vs B (p=0.0222)
MSKCC-NSCLC	A vs B vs C (p=0.0003)	
MSKCC cohort	A vs C vs B (p=0.0090)	
Mskccmbdata-mutations-mskcc.hg19		A vs B vs C (p<0.0001)

2612 **Poster Session**

First-in-human, phase I study of PF-06753512, a vaccine-based immunotherapy regimen (PrCa VBIR), in biochemical relapse (BCR) and metastatic castration-resistant prostate cancer (mCRPC). *First Author: Karen A. Autio, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Therapeutic vaccines targeting PC-associated antigens represent attractive approaches in combination with immune checkpoint inhibitors (ICI). Safety/antitumor activity of PF-06753512 (PrCa VBIR) was evaluated in a phase I, dose-escalation and expansion study in patients (pts) with BCR prior to ADT and in pts with mCRPC either prior to or after failure of novel hormone therapy. PrCa VBIR consists of: 1) priming immunization with a replication-deficient adenoviral vector (AdC68) expressing PSA, prostate-specific membrane antigen and prostate stem cell antigen; 2) boosts with plasmid DNA (pDNA) encoding the same antigens by IM electroporation; 3) ICI given subcutaneously, including anti CTLA-4 antibody tremelimumab (TRM) and anti PD-1 antibody sasanlimab (SSL). **Methods:** AdC68 ± ICI(s) were given on months (mos) 1 and 5 and pDNA ± ICI(s) on mos 2–4 and 6–8. After 8 mos, maintenance pDNA + ICI(s) were given every 1 or 2 mos. In Part A (6 escalation cohorts), pts with mCRPC received AdC68 (4 or 6x10e11 viral particles) + pDNA 5 mg ± ICIs (TRM alone 80 mg; TRM 40 or 80 mg + SSL 130 or 300 mg). In Part B (3 expansion cohorts), pts with mCRPC received AdC68 6x10e11 + pDNA 5 mg + TRM 80 mg + SSL 300 mg; pts with BCR received similar vector and pDNA + TRM 80 mg ± SSL 130 mg. Primary objectives: Assess overall safety (CTCAE v4.03), determine expansion dose. Secondary objectives: Anti-tumor activity (RECIST v1.1, Prostate Cancer Working Group 3, PSA 50 response) and immune response. (Note: Database remains open, some queries pending). **Results:** As of Sept 15, 2020, 91 pts were treated in dose-escalation (n=38) and expansion (n=53; BCR=35, mCRPC=18). Immune responses (ELISpot) were positive in some pts. Grade (G) 3 or 4 treatment-related adverse events (TRAEs) developed in 38.5% (35/91) of pts. G5 TRAEs occurred in 2 pts (n=1 G4 myasthenia gravis + G5 pulmonary embolism; n=1 G5 myocarditis). irAEs were more frequent in BCR compared to mCRPC. See the table for efficacy data. **Conclusions:** Vaccination with PrCa VBIR had a manageable safety profile. TRAEs increased when 2 ICIs were given. Some pts with BCR experienced durable PSA-50 responses without ADT; patients with mCRPC had few objective tumor responses, but had prolonged median rPFS. PrCa VBIR appears to stimulate antigen-specific immunity and results in noticeable antitumor activity, particularly in androgen sensitive disease. Clinical trial information: NCT02616185. Research Sponsor: Pfizer.

Efficacy			
mCRPC (N)	**PSA-50 n, (%)**	**ORR (%) [95% CI]**	**rPFS, mos, median [95% CI]**
AdC68+pDNA+TRM 80+SSL 300 (32)	2 (6.3)	9.4 [2, 25]	9.2 [2, not reached]
BCR (N)	**PSA-50 n, (%)**	**Duration of PSA-50 response, mos median (range)**	
AdC68+pDNA+TRM 80 (20)	5 (25.0)*	10.2 (6.9 – 24.9)	
AdC68+pDNA+TRM 80 +SSL 130 (15)	4 (26.7)	3.9 (1.9 – 4.2)	

*Associated with G1 hypopituitarism in 1 pt.

2613 **Poster Session**

Long term results from a phase 1 trial of GEN-009, a personalized neoantigen vaccine, combined with PD-1 inhibition in advanced solid tumors. *First Author: Maura L. Gillison, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: GEN-009 is an adjuvanted personalized cancer vaccine containing up to 20 neoantigens selected by ATLAS, an *ex vivo* bioassay screening autologous T cells for immune responses against both neoantigens as well as Inhibigens. Inhibigen-specific T cells suppress immunity and have been shown to accelerate tumor progression in mice and are avoided in GEN-009. In cohort A, all patients immunized in the adjuvant setting with GEN-009 monotherapy developed immune responses. Nearly all (99%) of selected peptides were immunogenic: *ex vivo* $CD4^+$ and $CD8^+$ fluorospot responses specific for 51% and 41% of immunized peptides, respectively. Seven of 8 patients continue without progression with a median follow up of 18 months. **Methods:** GEN-009 is being evaluated in patients (pts) with advanced cancer who received standard-of-care (SOC) PD-1 inhibitor as monotherapy or in combination therapy during vaccine manufacturing. Five vaccine doses were administered over 24 weeks in combination with a PD-1 CPI. Patients who progressed prior to vaccination received alternative salvage therapy followed by GEN-009 in combination. Peripheral T cell responses were measured by fluorospot assays in *ex vivo* and *in vitro* stimulation. **Results:** 15 pts received GEN-009 in combination with a PD-1 inhibitor; 1 patient received GEN-009 monotherapy. Median number of neoantigens per vaccine was 14 (5-18). GEN-009-related adverse events were limited to vaccine injection site reactions and mild myalgias or fatigue. Longitudinal evaluation of *ex vivo* T cell responses revealed that sequential vaccination with GEN-009 had an overall additive effect on the robustness of IFNγ secretion and responses were persistent for at least 6 months in some patients. Epitope spread was detected in CPI sensitive patients, but not in CPI refractory patients receiving salvage therapy. Three patients who responded to PD-1 inhibition followed by disease stabilization then demonstrated further reduction after GEN-009 vaccination that could represent vaccine effect. Eight of 9 CPI responsive patients are progression-free from 3 to 10 months after first vaccine dose. Four of 7 CPI refractory patients have experienced unexpected prolonged stable disease after vaccination of up to 8 months after vaccination. 2 of 2 patients with available samples lost all evidence of circulating tumor DNA including non-targeted neoantigens. **Conclusions:** Vaccination with GEN-009 in combination with anti-PD-1 CPI in patients with advanced solid tumors shows little additive toxicity. Preliminary data demonstrate induction of broad neoantigen-specific immune responses and epitope spreading in the presence of PD-1 CPI. Broad immunity against tumor specific targets and encouraging patient outcomes support further study. Clinical trial information: NCT03633110. Research Sponsor: Genocea Biosciences.

2614 **Poster Session**

Phase I trial to determine safety and immunogenicity of amplivant, a synthetic toll-like receptor 2 ligand, conjugated to two HPV16 E6 synthetic long peptides. *First Author: Frank M. Speetjens, Leiden University Medical Center, Department of Medical Oncology, Leiden, Netherlands*

Background: Therapeutic vaccines based on synthetic long peptides (SLPs) have a great potential for immunotherapy of cancer patients as these SLPs include both human leukocyte antigen (HLA) class I and II epitopes and no patient selection for HLA types is required. The antigen-induced immune response can be strengthened with immune stimulating additives. Amplivant (AV) is a synthetic Toll-like receptor 2 ligand which can be directly conjugated to tumor peptide antigens. In preclinical studies, AV-conjugation to antigens led to both enhanced antigen presentation by dendritic cells and T-cell priming and caused superior induction of effective anti-tumor responses. Moreover, AV-conjugated SLPs showed a 100 times higher immune response compared to unconjugated SLP. The current study is a first-in-human trial to investigate safety and immunogenicity of AV-conjugated human papillomavirus (HPV)16-SLPs. **Methods:** A dose escalation phase I trial was performed in 24 patients with HPV16 positive (pre-) malignant lesions. AV was conjugated to two SLPs derived from the most immunodominant regions of the HPV16 E6 oncoprotein. Four dose groups (1, 5, 20 or 50 μg of each peptide) in 6 patients each were studied. The vaccine was injected three times intradermally in DMSO / water with a three-week interval. Adverse events (AE) were collected according to CTCAE v4.0 up to 26 weeks. Peptide-specific T-cell immune responses were determined in blood samples taken before and after vaccination using complementary immunological assays (proliferation assay, IFNγ-ELISPOT and cytokine bead array). **Results:** Toxicity after three AV-conjugated HPV16-SLP vaccinations was limited to CTCAE grade 1 or 2, with predominantly inflammation at the vaccination site and sometimes flu-like symptoms, which generally resolved within one day. Dose increase resulted from no AE in the lowest dose group to mild/moderate AE in all vaccinated persons in the highest dose group. In the lowest dose group, minor vaccine-induced T-cell responses were observed in three of six vaccinated persons. In the highest dose group, all patients displayed a strong HPV16-specific T-cell response after vaccination. The induced T-cell response against HPV16 lasted until the end of the trial. **Conclusions:** This first-in-human study showed that AV conjugated to SLPs can safely be used as an intradermal therapeutic vaccine. AV-conjugated HPV16-SLP was able to induce robust HPV16-specific T-cell immunity in patients treated for HPV16 positive (pre-) malignancies without any other vaccine adjuvant or formulation. Increase in dose resulted in both a higher number of mild adverse events as well as stronger T-cell immunity. Clinical trial information: NCT02821494. Research Sponsor: None.

2615 **Poster Session**

A phase 1b study of personalized neoantigen vaccine plus pembrolizumab in adults with advanced cancer. *First Author: Aaron Miller, UCSD Moores Cancer Center, La Jolla, CA*

Background: Neoantigens (NeoAg) are key targets for personalized immunotherapy but efficient methods for their systematic identification and therapeutic targeting remain elusive. We developed a methodology to reliably identify and verify somatic alteration-derived neoantigens based on natural T cell responses against them which formed the basis of an individualized therapeutic vaccine strategy. **Methods:** This is a phase Ib study to assess the immunogenicity, safety and early clinical activity of personalized synthetic long peptides (PSLP) cancer vaccines in combination with pembrolizumab for patients with treatment refractory metastatic solid tumors or PSLP vaccine alone as an adjuvant treatment with patients with no evidence of disease (NED) that incorporates patient-specific NeoAg identified by an HLA-agnostic, functional T-cell assay (see table). **Results:** At the time of data cutoff, a total of 5 patients had been treated on ARM-A, 5 patients on ARM-C and 2 patients on ARM-D. AES possibly attributed to personalized vaccine (PSLP), or pembrolizumab, or both include: Grade 1: Arthralgia (1); Diarrhea (1); Fever (4); Fatigue (7); Generalized muscle weakness (1); Headache (2); Nausea (1); Confusion (1); Injection site reaction (5); Rash maculo-papular (3); Flu like symptoms (5); Myalgia (1); and Grade 2: Diarrhea (1); Fatigue (1); Hyperhidrosis (1); Hypothyroidism (1); Injection site reaction (1); Proteinuria (1); Renal and Urinary – other (1); and Grade 3: Colitis (1). For the 9 patients with at least 1 radiographic assessment at the time of analysis 6 had a best response of stable disease (SD) and 3 had progressive disease (PD). Immune monitoring of peripheral blood specimens consistently demonstrated that NeoAg-specific T cell responses were enhanced following administration of PSLP vaccine. On-treatment biopsies demonstrated immune-editing with the variant allele frequency of targeted mutations decreasing following administration of the PSLP vaccine. **Conclusions:** Taken together, these data meet the trial primary endpoint by demonstrating PSLP vaccines targeting NeoAg identified using the HLA-agnostic pipeline augment effector T cell function against these targets. Clinical trial information: NCT02287428. Research Sponsor: None.

ARM	PSLP	Adjuvant	Vaccinations	Pembrolizumab
A	5 NeoAg (max)	Montanide	3 doses SQ every 3 weeks	200 mg every 3 weeks
C	24 NeoAg (max)	Hiltonol	3 weekly IM doses then 6 doses every 3 weeks	200 mg every 3 weeks
D	24 NeoAg (max)	Hiltonol	3 weekly IM doses then 6 doses every 3 weeks	None

2616 **Poster Session**

A phase 1 study of an off-the shelf, multi-neoantigen vector (ADXS-503) in subjects with metastatic non-small cell lung cancer (NSCLC) progressing on pembrolizumab as last therapy. *First Author: Missak Haigentz, Atlantic Health System Cancer Care, Morristown, NJ*

Background: ADXS-503 (A503) is an off-the-shelf, attenuated Listeria monocytogenes (Lm)-based immunotherapy bioengineered to elicit potent T cell responses against 22 tumor antigens commonly found in NSCLC (i.e., 11 hotspot mutations and 11 tumor-associated antigens, TAAs). Pembrolizumab (Pembro) is a programmed death receptor-1 (PD-1)- blocking antibody approved for the treatment of advanced lung cancer. A503 and Pembro have complementary mechanisms of immune activation and reversal of immune tolerance. **Methods:** A phase 1 study of A503 ± Pembro has been conducted in patients (pts) with metastatic squamous or non-squamous NSCLC. In dose-escalation part B, A503 was added-on to Pembro within 12 weeks of the first scan showing disease progression per RECIST criteria v1.1. Both, A503 (1 $x10^8$ CFU) and Pembro (200 mg) were infused by IV every 3 weeks until disease progression or limiting toxicity. The dose-escalation cohort has established safety, tolerability and immunogenicity of the combination therapy and it has been further expanded to evaluate efficacy (Goldman JW *et.al.*, SITC 2020). **Results:** Nine pts have been treated and evaluated in Part B. Pembro + A503 combo has been well tolerated and without immune related AEs. Of the nine evaluable pts, one has achieved partial response (PR) and 3 stable disease (SD), yielding an overall response rate (ORR) of 11% and disease control rate (DCR) of 44%. Two patients have had clinical benefit for over 12 months (i.e., one PR and one SD) and both of them had been on Pembro therapy for 2 years before enrollment. The two other pts with SD have sustained it for almost 6 months thus far. Seven pts have been evaluated for immunogenicity. In all pts there was a transient release of pro-inflammatory cytokines and proliferation of cytotoxic- and memory-CD8+ T cells. Seven evaluable pts had antigen-specific T cells within 1-2 weeks after starting therapy and 4/7 showed antigen spreading. **Conclusions:** ADXS-503 as an add-on therapy to Pembro at disease progression has been well tolerated and it has induced antigen specific-T cell responses and durable disease control in 44% of pts. Part B cohort is currently enrolling additional pts to further explore the potential reversal of Pembro resistance with ADXS-503. Clinical trial information: NCT03847519. Research Sponsor: ADVAXIS INC.

2617 **Poster Session**

A phase 1 open label trial of intravenous administration of MVA-BN-Brachyury vaccine in patients with advanced cancer. *First Author: Peter Joseph DeMaria, Genitourinary Malignancy Branch, NCI, NIH, Bethesda, MD*

Background: Brachyury is a member of the T-box family of transcription factors which is overexpressed in several tumor types and has been associated with treatment resistance, epithelial to mesenchymal transition and metastatic potential. MVA-BN-Brachyury vaccine is a vector-based therapeutic cancer vaccine which demonstrated immunogenicity and safety in previous clinical trials. Preclinical studies suggested that IV administration of vaccines can induce superior CD8 + T-cell responses as compared with SC or IM routes. This is the first-in-human study to evaluate safety and tolerability of IV administration of this vaccine. **Methods:** Patients with metastatic or unresectable locally advanced malignant solid tumors were treated with MVA-BN-Brachyury vaccine in a phase 1, open-label, 3+3 dose-escalation study. Eligible patients received a total of three vaccine doses intravenously Q3W at $1x10^7$ (DL1), $1x10^8$ (DL2), or $1x10^9$ infections units (Inf.U) (DL3). Patients were admitted for 48 hours for observation after each dose and had imaging at baseline and 1 and 3 months after the last vaccine dose. Primary objective was to determine the safety and tolerability and establish the recommended phase 2 dose (RP2D). Immune assays were performed in the first 10 enrolled patients. **Results:** In 13 patients (10 chordoma, 1 small cell breast, 1 prostate, 1 colorectal cancer), no dose-limiting toxicities were observed. Right upper quadrant abdominal pain was the only grade 3 TRAE. All other TRAEs were grade 1 or 2; most common was cytokine release syndrome (four grade 2 and one grade 1. As of Feb 2021, 9 patients completed treatment and two planned restaging scans: 5 patients had PD (3 in DL1 and 2 in DL2), 3 had SD (2 in DL2 and 1 in DL3) and 1 had PR (DL3) as their best treatment response per RECIST 1.1. One patient with advanced sacral chordoma had significant reduction of ulcerated skin metastases after 2 doses, followed by 33% shrinkage at the end of trial. Two chordoma patients with SD reported significant pain improvement. Multifunctional Brachyury, CEA, and MUC1 specific T cells were increased after vaccination in in 60%, 67%, and 50% of patients, respectively. **Conclusions:** MVA-BN-Brachyury IV vaccine is safe across all tested dose levels and suggesting activity in chordoma at DL3 for which this vaccine was granted FDA orphan drug designation. Mild cytokine release syndrome (rigors, chills, fever and hypotension) has been observed in 5 patients and managed with IV fluids and steroids in 2 patients. A dose 1×10^9 Inf.U (DL3) was selected for RP2D based upon available safety data. Further research is pending to evaluate clinical benefit and immunogenicity. Clinical trial information: NCT04134312. Research Sponsor: U.S. National Institutes of Health, CRADA with Bavarian Nordic, Inc.

2618 **Poster Session**

Long-term follow up of patients with mesothelioma treated with dendritic cell therapy in three phase I trials. *First Author: Daphne W Dumoulin, Department of Pulmonary Medicine, Erasmus MC Cancer Institute, University Medical Center, Rotterdam, Netherlands*

Background: Immunotherapy targeting PD-(L)1 has become indispensable in the treatment of many malignant tumors. Recently, checkpoint inhibition using anti-PD-1 in combination with anti-CTLA-4 was proved to be effective in patients with malignant pleural mesothelioma (MPM). However, the minority of patients benefit from this treatment. The lack of immunotherapy efficacy in the majority of patients with mesothelioma can be explained by the fact that mesothelioma is a tumor with an "immune-desert" phenotype, meaning a non-inflamed tumor characterized by low T-cell infiltration. By administration of dendritic cells (DCs), which were cultured, activated, and exposed to antigens ex-vivo, this "immune-desert" phenotype might be turned into an "inflamed" phenotype. Previously, we performed and published three phase I trials using activated DCs, which support this concept. Here, we report the long-term survival of the patients treated with DCs in these three phase 1 studies. **Methods:** We collected the survival data of the phase 1 trials using DC therapy in patients with MPM. In the first two trials, DCs loaded with autologous tumor lysate were used, while in the third allogeneic tumor lysate was used to load the DCs (Mesopher). **Results:** Between 2006 and 2015, in the three studies combined, 29 patients with MPM were treated with DC vaccination. At data cut-off, the median OS was 27 months (95% confidence interval (CI): 21 – 47 months). OS at 2 years was 55.2% (95% CI: 39.7%-76.6%), OS at 5 years was 20.7% (95% CI: 10.1%-42.2%). **Conclusions:** The long-term follow up of MPM patients treated with DC vaccination in the three separate phase 1 trials show a promising signal, with a 2-year OS of over 50% and a 5-year OS of over 20%. In addition, 2 patients are alive after 10 years of treatment. In our opinion, these findings show the potency of DC vaccination therapy in long-term activation of the immune system. DC vaccination therapy in patients with MPM is currently being investigated in a large, randomized phase II-III trial (NCT03610360) and in pancreatic cancer. Additional biomarker studies, as well as treatment combinations with for example ICI, could further improve the outcomes of DC-vaccination therapy. Clinical trial information: NCT02395679. Research Sponsor: Dutch Cancer Society (to KWF) and ZonMW (grant number 95104006).

Overall survival analysis based on the Kaplan Meier curves.

	Median OS (95% CI)	OS – 2 years (95% CI)	OS – 5 years (95% CI)
Overall	27 months (21 - 47)	55.2% (39.7% - 76.6%)	20.7% (10.1% - 42.2%)
Study 1	15 months (15 - Inf)	20.0% (5.8% - 69.1%)	10.0% (1.6% - 64.2%)
Study 2	26 months (20 - Inf)	60.0% (36.2 – 99.5%)	30.0% (11.6% - 77.3%)
Study 3	31 months (28 - Inf)	88.9% (70.6% - 100%)	22.2% (6.6% - 75.4%)

2619 **Poster Session**

Final report and long-term outcomes: Phase I trial of a HER2 intracellular plasmid-based vaccine in HER2+ advanced stage breast cancer. *First Author: Mary L. Disis, University of Washington, Seattle, WA*

Background: Vaccination with the intracellular domain (ICD) of HER2 in pre-clinical models is both immunogenic and protective against the development of mammary tumors. This study (NCT00436254) was designed to examine the safety and optimal immunogenic dose of a DNA-based vaccine encoding the HER2 ICD in subjects with HER2+ breast cancer. **Methods:** Sixty-six patients with stage III or IV HER2 + breast cancer in remission or with stable bone only disease were enrolled into three vaccine arms: 1 (10mcg dose of plasmid), 2 (100mcg) and 3 (500mcg). Vaccines were administered i.d. monthly for three immunizations. Endpoints included safety and optimal dose. HER2 specific IFN-gamma immune responses were evaluated and DNA persistence at the vaccine site was assessed. Toxicity and clinical outcomes were followed for 10 years. **Results:** The majority of vaccine-related toxicity was grade 1 (89%) and grade 2 (11%) and was not significantly different between the three dose arms. All Arms developed HER2 ICD immunity after vaccination, however, patients in Arm 2 and Arm 3 had significantly better immune responses (of higher magnitude and at most time points) than patients in Arm 1 ($p=0.003$ and $p<0.001$, respectively) after adjusting for baseline factors. At 60 weeks, the number of patients who maintained the greatest fold-difference in HER2 ICD immune responses from their baseline was highest in Arm 2 (73%) when compared to Arm 1 (47%) and Arm 3 (45%). Associations between ICD responses and plasmid DNA persistence at the vaccine site were estimated via linear regression models. HER ICD immunity after the end of immunizations, relative to baseline, was significantly lower in patients with DNA persistence at week 16 compared to those without persistence ($p=0.02$). Patients at the highest dose demonstrated the greatest incidence of plasmid persistence (92%) as compared to 33% in Arm 1 and 10% in Arm 2. The median time of follow-up was 118.6 months (Arm 1), 99.7 months (Arm 2), and 73.5 months (Arm 3). The median OS and PFS has not been reached in any Arm and did not differ with respect to treatment arm (Log-rank p-value 0.36 for OS, and 0.63 for PFS). However, we observed a separation of Kaplan-Meier curves for OS from about 40 months and curves for PFS from about 30 months, and the separation maintained until the end of the study for Arm 2 versus Arm 1 and Arm 3. One patient in Arm 2 developed lymphocytic colitis 2.2 years from enrollment deemed possibly related to vaccination. **Conclusions:** An intermediate dose (100mcg) of vaccine was immunogenic and associated with persistence of immunity at 60 weeks. A randomized phase II trial of the HER2 ICD plasmid-based vaccine in the neoadjuvant setting is in development. Clinical trial information: NCT00436254. Research Sponsor: U.S. National Institutes of Health.

2620 **Poster Session**

A phase I clinical trial investigating the telomerase vaccine UV1 in combination with pembrolizumab in patients with advanced melanoma. *First Author: Yousef Zakharia, University of Iowa and Holden Comprehensive Cancer Center, Iowa City, IA*

Background: UV1, a telomerase peptide-based vaccine, consists of 3 long peptides (15-30 aa) representing a 54 aa sequence in the catalytic unit of the reverse transcriptase subunit of telomerase (hTERT). UV1 contains both CD4 and CD8 epitopes, and immunogenicity is shown in 78% of HLA unselected patients (pts.) in prior studies. UV1 induced expansion of hTERT specific CD4+ T cells that might be relevant in tumors expressing telomerase, theoretically enabling enhanced checkpoint efficacy in pts. with insufficient spontaneously primed T cells. Reciprocally, checkpoint inhibitor may support the UV1-induced T cells and provide increased effector activity, as these cells may be restricted by intrinsic and tumor-induced suppressor mechanisms. **Methods:** UV1 was combined with standard of care pembrolizumab in pts. with advanced melanoma. The primary objective of this phase I, multicenter study (NCT03538314), was to evaluate safety and tolerability of UV1 in combination with standard pembrolizumab. Secondary objective was evaluation of response rate (RR) according to iRECIST. Pts. received, in a serial manner, adjuvant GM-CSF and UV1 (300μg) intradermally followed by pembrolizumab. The first 3 UV1/GM-CSF doses were given during week 1, and from week 2 in combination with pembrolizumab (Q3W). Two different doses of GM-CSF were investigated: 37.5μg (20 pts. cohort 1) and 75μg (10 pts. cohort 2). Totally 8 UV1/GM-CSF vaccinations per pt. were planned (14 weeks). **Results:** In total 30 pts. were enrolled; cohort 1 (N = 20); cohort 2 (N = 10). The abstract reports cohort 1 results. The majority of adverse events (AEs) reported was grade 1 or 2 (48%, 41%). Main AEs were fatigue (8%), injection site reaction (5%), diarrhea (4%) and pyrexia (3%). 18% and 30% of AEs were possibly/definitely related to UV1 or pembrolizumab, respectively. Three patients experienced SAE, one (inflammatory arthritis) was considered possibly related to UV1. No severe allergic reactions were observed. Pembrolizumab was continued after completion of UV1 treatment in 14 pts. for a mean of 8.2 months (range 3-21). Four pts. discontinued pembrolizumab due to PD, one for irAE and one for unknown reason. The RR was 60%, with 5 CRs, and the 1-year survival rate 85 %. **Conclusions:** Results from cohort 1 (N = 20) show that the treatment of UV1 together with pembrolizumab was safe and well tolerated in patients with advanced melanoma. Updated data with minimum 18 months follow-up will be presented at the conference. Cohort 2 results will be presented at a later stage. Clinical trial information: NCT03538314. Research Sponsor: Ultimovacs ASA.

Male /female	13/7
Median age (range)	70 (31-82)
ECOG 0/1	15/5
Stage IIIb, IIIc, IV	2 /8 /10
Elevated LDH	5
UV1/GM-CSF doses (pts.)	8 (17) 7 (2) 6 (1)
RR*	5 iCR (25%) 7 iPR (35%) 1 iSD (5%) 7 iUPD/iCPD (35%)
Survival rate*	80%
mPFS (1 yr.)	NR

*Median follow-up 18.3 months.

2621 **Poster Session**

Adverse effects of COVID-19 vaccination among cancer patients: Results from an Internet-based survey. *First Author: Brian Loew, Inspire, Arlington, VA*

Background: The rapid development of safe and effective vaccines against SARS-CoV-2 may stem the global COVID-19 pandemic. However, since individuals with cancer were under-represented during clinical vaccine trials, experience with COVID-19 vaccines among cancer patients is limited. **Methods:** An internet-based survey was conducted January 15 - February 10, 2021 among members of the Inspire online health community. The 63-item survey was emailed to members of the Inspire community who had opted-in for research. **Results:** Out of 19,152 respondents, 4895 (25%) self-reported a cancer diagnosis. Of these, 1337 (27%) were receiving active therapy. Cancer respondents were 66% female, 77% white, 44% college educated, with a median age range 55-65 years. 88% had solid tumors and 12% hematologic malignancies. 241 (5%) had prior COVID-19 and 148 (3%) thought they had had it but were not tested. Among cancer patients with COVID-19 approximately 30% reported ongoing late symptoms. At the time of survey, 1335 (27%) cancer patients had received a COVID-19 vaccine (Moderna 51% Pfizer-BioNTech 46%, Astra-Zeneca 3%, Other/unknown >1%). Following the first injection, 63% had local adverse events (AEs): injection site pain (51%), swelling (8%), redness (6%), and itching (4%). 34% reported systemic AEs including myalgia (32%), fatigue (18%), headache (12%), joint pain (5%), and chills (5%). 199 (15%) had received the second (booster) vaccination. 76% reported local AEs including pain (69%), swelling (14%), itching (8%), and redness (7%). 67% reported systemic AEs including fatigue (49%), myalgia (30%), headache (29%), chills (23%), fever (16%), joint pain (15%), and nausea (12%). AEs were comparable to the clinical trial results obtained from the general population (fda.gov/media/144245/download & 144434/download). **Conclusions:** In this internet-based survey drawn from the Inspire online health community 1335 cancer patients reported receiving COVID-19 vaccinations. By self-report the vaccines were well tolerated with AEs patterns mimicking clinical trial results conducted in the general population. These safety results should be reassuring to cancer patients although attention to COVID-19 vaccine efficacy is required (and will be studied during follow-up surveys). Research Sponsor: Inspire.

	Pfizer clinical trial	Moderna clinical trial	Cancer with Pfizer	Cancer with Moderna
First dose local AEs	79%	84%	58%	68%
First dose systemic AEs	59%	55%	36%	33%
Second dose local AEs	73%	89%	73%	79%
Second dose systemic AEs	70%	79%	60%	74%

2622 **Poster Session**

Risk factors for immune mediated adverse events with immune checkpoint inhibitors. *First Author: Ari Pelcovits, Brown University, Providence, RI*

Background: Immune checkpoint inhibitors (ICIs) are associated with unique toxicity - immune-related adverse events (irAEs). irAEs are common, occurring in nearly 30 % of patients (pts) in clinical trials. Risk factors for irAEs remain largely unknown, with limited evidence to guide risk stratification for these pts. **Methods:** In this historical cohort study, we identified 400 pts receiving ICIs at our institution between 1/1/2015 - 12/31/2019 and followed them until progression, death, or study end date. Using modified Poisson and multinomial logistic regression we assessed irAEs (yes/no; none/grade 1-2/grade 3-4) as a function of independent risk factors in separate models. These included age, PDL-1%, steroid use in the 2 weeks (S2wks) prior to ICI, concurrent chemotherapy, combination ICI use, and pre-ICI creatinine (Cr) and absolute lymphocyte count. We constructed sample weights using sociodemographic and clinical factors to account for confounding by indication and mortality-related censoring. **Results:** 367 pts (median age: 68 yrs) had complete data for analysis comprising 55% men and 89% white. 111 (31%) experienced an irAE during the study period (median time to first event: 81 days). Risk was greatest for the youngest and oldest pts on ICI. In weighted models, Pts ≤59 yrs were 3 times as likely to experience an irAE relative to those aged 60-68 (95% CI: 1.18,7.41; Table). Additionally, for each 1 unit increase in Cr, risk of irAE increased by 19% (95% CI: 1.08,1.28). Precision of weighted estimates was impacted by limited pt comparability across factors of interest and overall sample size. While not statistically significant (RR: 2.04;95% CI:0.92,4.53) 70.6% of pts on combination ICIs experienced an irAE compared with 20.3% on one ICI. Similarly, while not statistically significant, 15.4% of pts with PDL-1 >49% experienced a grade 3/4 irAE compared with 7.7% of pts with PDL-1<1%. **Conclusions:** In this real-world analysis of irAEs, younger age and elevated creatinine were risk factors for development of irAEs. Further research leveraging larger data sources is needed to examine PDL-1% as a potential risk factor of irAE. Research Sponsor: None.

	irAE vs. No irAE[1] RR (95% CI)	Grade 1/2 irAE vs. No irAE[2] OR (95% CI)	Grade 3/4 irAE vs. No irAE[2] OR (95% CI)
Age (Ref: 60-68 yrs)	**2.95 (1.18,7.41)**	7.42 (0.83,66.10)	1.55 (0.31,7.83)
27-59 yrs			
69-76 yrs	1.40 (0.77,2.57)	1.26 (0.51,3.12)	2.29 (0.56,9.44)
77-93 yrs	1.33 (0.71,2.50)	1.37 (0.55,3.44)	2.18 (0.66,7.30)
PDL-1 (Ref <1%)	1.36 (0.70,2.64)	1.22 (0.40,3.73)	2.67 (0.62,11.46)
1-49%			
>49%	2.27 (0.98,5.26)	5.08 (0.66 (38.96)	1.59 (0.38,6.59)
Initial Cr	**1.18 (1.08,1.28)**	**1.54 (1.05,2.27)**	0.92 (0.38,2.19)
Concurrent Chemotherapy (Ref: No)	0.73 (0.34,1.60)	0.77 (0.22,2.72)	0.42 (0.14,1.22)
S2wks (Ref: No)	1.00 (0.61,1.65)	0.69 (0.24,1.98)	1.90 (0.76,4.75)
Combination ICIs (Ref: One ICI)	2.04 (0.92,4.53)	2.27 (0.27,18.84)	7.08 (0.88,56.67)

[1]Weighted modified Poisson. [2]Weighted multinomial logistic.

2623 **Poster Session**

Safety, pharmacokinetics, efficacy, and preliminary biomarker data of first-in-class BI 765063, a selective SIRPα inhibitor: Results of monotherapy dose escalation in phase 1 study in patients with advanced solid tumors. *First Author: Stéphane Champiat, Gustave Roussy Cancer Campus, Department of Drug Development (DITEP), Villejuif, France*

Background: BI 765063 is a humanized IgG4 monoclonal antibody antagonist of SIRPα (Signal Regulatory Protein α), which blocks the "don't eat me" signal of the SIRPα/CD47 axis, a critical innate immune checkpoint. SIRPα is expressed on myeloid cells. BI 765063 binds to the V1 SIRPα allele with high affinity and to the V2 SIRPα allele with low affinity. BI 765063 lacks SIRPγ binding to preserve T-cell activation. We report results of the completed BI 765063 monotherapy dose escalation in patients with advanced solid tumors. **Methods:** This study involves a step 1 dose escalation to determine the dose-limiting toxicities (DLT) and maximum tolerated dose (MTD), then a step 2 dose-confirmation expansion at recommended phase 2 dose. In Step 1, BI 765063 ascending doses, given IV every 3 weeks, were tested using a Bayesian Logistic Regression Model (BLRM) approach with overdose control. The endpoints were safety, pharmacokinetics, receptor occupancy (RO) in peripheral $CD14^+$ monocytes and efficacy (RECIST 1.1). **Results:** Fifty patients (26 V1/V1, 24 V1/V2) received at least one dose of BI 765063. The most frequent tumors were ovarian (9), colorectal (8), lung (5), breast (4), melanoma (3), and kidney (3). No DLTs were reported up to the highest dose tested. MTD was not reached. The most frequent related adverse events were infusion related reaction (IRR) (46%), fatigue (12%), headache (10%), arthralgia and diarrhea (8% each). All related adverse events were mild to moderate, except one case of IRR Grade 3. No related anemia nor thrombocytopenia were observed. BI 765063 showed dose proportional exposure and full RO saturation in Cycle 1 after the fourth dose level. Clinical benefit was observed in 21/47 (45%) patients evaluable per RECIST 1.1. One patient with hepatocellular carcinoma (HCC) with liver and lung metastases and 7 prior lines of therapy showed a durable partial response maintained for 27 weeks treatment (ongoing). The baseline tumor biopsy of this patient showed high CD8 T-cell and macrophage infiltration. There was an increase in CD8 T-cell infiltration and activation on treatment. An increase in PD-L1 expression on tumor cells 2 weeks after first dosing was also observed. Analysis of paired tumor biopsies in other patients is ongoing. **Conclusions:** The first-in-class SIRPα inhibitor BI 765063 was well-tolerated, showed monotherapy activity, and sustained RO saturation. A durable partial response was observed in an advanced HCC patient. The on-treatment biopsy of the responder showed an increase in CD8 T-cell infiltration and activation. PD-L1 expression on tumor cells also increased. BI 765063 dose escalation in combination with ezabenlimab (anti-PD1 antibody) is ongoing. Clinical trial information: NCT03990233. Research Sponsor: OSE Immunotherapeutics; Boehringer Ingelheim.

2624 **Poster Session**

A phase 1/2 open-label study of KY1044, an anti-ICOS antibody with dual mechanism of action, as single agent and in combination with atezolizumab, in adult patients with advanced malignancies. *First Author: Manish R. Patel, Sarah Cannon Research Institute, Florida Cancer Specialists, Sarasota, FL*

Background: KY1044, is a fully human IgG1 anti ICOS antibody designed to stimulate Teffs and to deplete ICOS high Tregs in the tumor microenvironment. **Methods:** Patients with advanced/metastatic malignancies received escalating doses of KY1044 as a single agent and in combination with atezolizumab 1200 mg by IV infusion every 3 weeks until disease progression or unacceptable toxicity. Dose escalation was guided by a modified toxicity probability interval design. The primary objective was to determine safety, tolerability, and maximum tolerated dose. Cohorts that were tolerated were later enriched with more subjects. AEs were classified according to CTCAE v5 and efficacy measures performed according to RECIST v1.1 every 8 weeks for the first 16 weeks and then every 12 weeks. **Results:** As of 16-Dec-2020, a total of 103 patients have been enrolled in the study (38 patients as monotherapy in 6 cohorts at doses ranging from 0.8 to 240 mg and 65 in combination with atezolizumab in 5 cohorts at doses 0.8 – 80 mg). 63% and 55% of patients received ≥4 prior anti-cancer therapies in the single agent and combination cohorts, respectively. All cohorts were completed without DLTs during the first 21 days of treatment. In the KY1044 single agent cohorts, 47.4% of patients experienced treatment-related AEs (TRAEs), all were grades 1 or 2. In the combination cohorts, TRAEs were observed in 58% of patients. Most of the TRAEs were grade 1 or 2 apart from 8 TRAEs that were ≥grade 3 occurring in <8% of patients. Infusion-related reactions, pyrexia and lymphopenia were the most commonly occurring TRAEs in ≥10% of patients. TRAE leading to dose interruptions occurred in 1 patient in the single agent cohort and in 4 patients in the combination cohort. Only 1 patient discontinued treatment due to myositis that was considered related to the combination. Preliminary KY1044 PK data from 69 patients agree with the PK model predictions. Median treatment duration for all enrolled patients was 9 weeks. Treatment duration ≥16 weeks was observed in 24% (9/38) and 27% (17/64) patients in the single agent and combination cohorts, respectively. Five objective responses, including 1 CR in triple negative breast cancer (TNBC) and 4 PRs in TNBC, head and neck squamous cell carcinoma, penile and pancreatic cancer were observed. Four of the 5 responding patients were still on treatment at the data cut, with 3 patients on treatment for >43 weeks (range 45 to 66 weeks). **Conclusions:** KY1044 is well tolerated as single agent and in combination with atezolizumab. Objective responses have been observed in this phase 1 part of the study. The phase 1 expansion and phase 2 part of the study is ongoing. Clinical trial information: NCT03829501. Research Sponsor: Kymab.

2625 **Poster Session**

Real world experience with standalone immunotherapy regimens: Immune-related adverse events, healthcare utilization and cost among patients with commercial or Medicare Advantage insurance. *First Author: Krishna Soujanya Gunturu, Lahey Hospital and Medical Center, Burlington, MA*

Background: Immunotherapy is a fast growing class of cancer therapy. We evaluated the rates of immune-related adverse events (irAEs), healthcare utilization, and costs up to 1 year post-index among patients using monotherapy (PD-1/PD-L1 inhibitor) and combination therapy (PD-1/PD-L1 with CTLA-4 inhibitors). **Methods:** We reviewed claims from the HealthCore Integrated Research Database (HIRD), which contains commercially insured/Medicare Advantage members and captures clinical, utilization, and cost measures. We analyzed both the monotherapy (M) and combination therapy (C) cohorts focusing on members with ≥ 6 months of baseline continuous medical and pharmacy coverage. Descriptive and multi-variate analyses were performed. **Results:** The C cohort had 904 and M had 9,084 patients, with mean ages of 58 and 64 years, respectively. Prominent cancer types were melanoma for C and lung for M. The most common incident irAEs (%) for C vs. M were: endocrinopathies (27.7, 14.7), hepatitis (17.1, 7.7), nephritis (21.0, 14.0), neuropathy (6.6, 7.0), followed by colitis, dermatitis, and myocarditis. After adjustment, C therapy showed greater risk of all-cause inpatient admissions (OR 2.27, 95% CI 1.93, 2.66), all-cause emergency department (ED) visits (OR 1.55, 95% CI 1.33, 1.81) and irAE-related visits (See table). Mean adjusted all-cause cost difference for C vs M was +$43,747 (95% CI $38,440, $49,427). In age ≥65 subset, 222 received C and 4,208 received M. C therapy patients had more irAE-related hospitalizations (45.3% vs. 57.7%, p=0.0004). Costs were similar to the main cohort. **Conclusions:** C therapy showed greater incident irAE rates, increased utilization and medical costs compared to M therapy. Limitations include less precise ascertainment of irAEs in claims data and generalizability only to those with commercial or Medicare Advantage insurance. Our study highlights the increased toxicity and cost tradeoffs involved in choosing combination immunotherapy over monotherapy. Research Sponsor: Anthem Inc.

	Monotherapy (n/mean/%/SD)	Combination Therapy (n/mean/%/SD)	OR/Adjusted Mean Difference (95% CI)	Adjusted p-value/ Unadjusted p-value*
All-cause				
Inpatient Stay, n (%)	5,028 (55.4%)	593 (65.6%)	2.27 (1.93, 2.66)	<0.0001
ED visit, n (%)	3,059 (33.7%)	374 (41.4%)	1.55 (1.33, 1.81)	<0.0001
Outpatient visit, n (%)	9,076 (99.9%)	902 (99.8%)	-	0.2274*
Total medical cost PMPM, mean (SD)	$26,741 ($55,623)	$67,877 ($237,854)	$43,747 ($38,440, $49,427)	<0.0001
irAE-related				
Inpatient stay, n (%)	3,826 (42.1%)	499 (55.2%)	2.17 (1.87, 2.53)	<0.0001
ED visit, n (%)	1,430 (15.7%)	205 (22.7%)	1.64 (1.36, 1.97)	<0.0001
Outpatient visit, n (%)	6,653 (73.2%)	729 (80.6%)	1.31 (1.09, 1.58)	0.0038
Total medical cost PMPM, mean (SD)	$7,837 ($30,841)	$22,626 ($165,487)	$19,224 ($14,911, $24,246)	<0.0001

2626 **Poster Session**

KY1044 to target the ICOS pathways inducing intratumoral Treg depletion and agonism of effector T cells: Preliminary pharmacodynamic markers from a phase 1/2 multicenter trial. *First Author: Chia-Chi Lin, National Taiwan University Hospital, Taipei, Taiwan*

Background: Inducible T-cell co-stimulator (ICOS) is an important co-stimulatory receptor on effector T cells (Teffs) that also promotes tumor growth due to its high expression on regulatory T cells (Tregs). KY1044 is a fully human IgG1 that targets ICOS, acting via a dual mode of action (MoA) by depleting $ICOS^{high}$ Tregs and stimulating $ICOS^{Low}$ Teffs. A Phase 1/2 clinical trial (NCT03829501) is currently assessing the safety and preliminary efficacy of KY1044, as a single agent and in combination with atezolizumab, in subjects with advanced relapsed/refractory malignancies. Using longitudinal blood samples and tumor biopsies, we aim to correlate KY1044 target engagement levels with pharmacodynamic (PD) properties (e.g. dual MoA) in the tumor microenvironment (TME) and the circulation. **Methods:** Phase 1 subjects were enrolled in dose escalation and enrichment cohorts to evaluate the effect of KY1044 as monotherapy (0.8 – 240 mg) Q3W and in combination (0.8 – 80 mg) with atezolizumab (1200 mg) Q3W. PBMCs, plasma and tumor biopsies were collected over the first 3 cycles to confirm target engagement and KY1044 MoA. The sample analysis included: immunohistochemistry (IHC) of tumor samples (ICOS, FOXP3 and CD8); circulating T cell immunoprofiling and receptor occupancy by chip-cytometry; PBMC and tumor sample pre- and post-treatment transcriptomic analysis; and the assessment of circulating cytokines (e.g. GM-CSF). **Results:** As assessed in PBMCs, full/prolonged ICOS target engagement on T cells was confirmed in subjects receiving a flat dose of 8 to 240 mg, while partial/transient saturation was observed at lower doses (0.8-2.4 mg). The target engagement was not affected by atezolizumab. The immune cell profiling showed changes in some populations, but there was no significant depletion of peripheral $ICOS^+$ cells. In contrast, pre- and post-treatment IHC analysis of $ICOS^+/FOXP3^+$ cells in tumor biopsies confirmed a KY1044-dose dependent reduction of $ICOS^+$ Tregs and maintenance of $CD8^+$ T cells in the TME. Together, this resulted in an increased intratumoral $CD8^+/ICOS^+$ Treg ratio at all doses, plateauing from subjects receiving a flat KY1044 dose of 8 mg. KY1044-dependent agonism was indirectly assessed by measuring circulating cytokine levels. A post-dosing transient induction of GM-CSF was evident in subjects dosed with KY1044 at the 0.8 and 2.4 mg dose, whereas minimal induction was observed at dose of 8 mg and higher. **Conclusions:** LongitudinalPDdata confirmed the expected KY1044 MoA, namely ICOS Treg depletion and increased CD8/ICOS Treg ratio in the TME as well as T cell co-stimulation. The observed PD responses are currently being further explored in a more homogenous patient population. Research Sponsor: Kymab.

2627 **Poster Session**

Association and prevalence of venous thromboembolism in cancer patients with COVID-19: A single healthcare system experience. *First Author: Aneesha Ananthula, Louisiana State University, New Orleans, LA*

Background: There are increasing reports of thromboembolic complications in patients with COVID-19 infection. According to a meta-analysis of 28,173 patients, the prevalence of venous thromboembolism (VTE) in hospitalized COVID-19 patients ranges from 7.9% to 22.7% based on the severity of COVID-19. Cancer and anti-cancer therapies are known risk factors for thrombosis. Another study based on registry data reported the overall prevalence of VTE in hospitalized COVID-19 patients with cancer to be 14.5%. Our study aimed to assess the prevalence of VTE in cancer patients diagnosed with COVID-19 as well as the association between VTE and cancer in the setting of COVID-19 infection in a large predominantly urban healthcare system. **Methods:** We utilized a cohort data query tool in the electronic medical record at University Medical Center in New Orleans, Louisiana to identify patients >17 years of age with a hospital or clinic visit in the LCMC Health system between March 1, 2020 and December 31, 2020 which were considered the base population for the study. Cancer patients were identified via the cancer registry tool. Patients with COVID-19 were identified using the abnormal COVID-19 PCR test result search field. An encounter diagnosis of deep venous thrombosis (DVT) or pulmonary embolism (PE) was used to identify patients with VTE. Odds ratios, p-values, and corresponding confidence intervals (CI) were calculated using 2x2 contingency tables. **Results:** In our database, we identified 3,807 patients with a diagnosis of COVID-19 and 9,560 with a cancer diagnosis. 158,812 patients had neither COVID-19 nor cancer. There were statistically significant greater odds of developing VTE in all subgroups compared: COVID-19 alone vs neither (OR 2.43), cancer alone vs neither (OR 3.8), and COVID-19 and cancer vs neither (OR 10.65). **Conclusions:** COVID-19 and cancer are both risk factors for VTE. Based on our study, appears that cancer has the greater effect on VTE compared with COVID-19 infection. Also, there is possibly a synergistic effect between COVID-19 and cancer, which further increases the likelihood of VTE. This study is a preliminary analysis. Further investigation is warranted in the form of either variable adjusted analysis of the same data, individual chart review, or a prospective study. Research Sponsor: None.

Cohort [VTE n = prevalence%]	Odds ratio	CI	P value
COVID-19 [84 = 2.29%] vs none [1520 = 0.96%] *cancer excluded	2.43	1.95–3.04	<0.0001
Cancer [334 = 3.54%] vs none [1520 = 0.96%] *COVID-19 excluded	3.8	3.37–4.29	<0.0001
COVID-19 and cancer [14 = 9.33%] vs neither [1520 = 0.96%]	10.65	6.13–18.51	<0.0001

2628 **Poster Session**

Priming immunotherapy with radiotherapy (RT) in advanced non-small cell lung cancer (NSCLC) and head and neck squamous cell cancer (HNSCC): Interim analysis of phase II clinical trial. *First Author: Aasems Jacob, University of Kentucky, Lexington, KY*

Background: Preclinical models demonstrate that combined RT with immune checkpoint inhibitor (ICI) results in specific CD8+ T-cell phenotype associated with a tumor-reactive population resulting in significant tumor response. Sequential treatment could allow radiation to release tumor antigens from immune inaccessible areas and provide robust anti-tumor immune response with ICI. We report an interim analysis of the phase II clinical trial evaluating the efficacy and safety of the combination. **Methods:** Advanced NSCLC and HNSCC patients who had initiated on FDA approved single-agent ICI were eligible. Patients were given SBRT (BED >100Gy) or 30 Gy fractionated RT delivered as a 3-dimensional dose to a single metastatic site within 14 days of the first ICI dose. Primary objective was 6-month PFS and secondary objectives were safety and tolerability, 1Y PFS and OS. This interim analysis was done after enrollment of 43 patients. **Results:** Between 10/2017 to 1/2021, 43 patients were enrolled, and 38 included in this analysis. Median age was 62 years; 26 patients were male. 9 patients received ICI for NSCLC as first-line, 7 for NSCLC second-line and 22 for HNSCC second-line. 24 patients received pembrolizumab and 14 nivolumab; 21 had SBRT and 17 fractionated RT. Median follow up duration was 11.8m (range: 2.7 - 31.4m) for patients without progressive disease (PD). 10 patients were off-study, 7 continuing treatment. 15 died and 26 had PD. 14 patients died of malignancy and cause of death for one patient was unknown. 6-month PFS was 49.19% with median PFS of 5.5 months. (table) Fifty-two grade-3-5 adverse events (AEs) were reported among 21 subjects. Most common were transaminitis (n=15), lymphopenia (n=8), and GI side effects (n=4). Treatment related AEs included 19 grade-3 events, and none were grade 4/5. Two grade-5 AEs were from PD (oral bleeding and unspecified). There were 20 grade-1/2 and 3 grade-3 immune related adverse events (IRAEs). No grade-4/5 IRAEs were reported. Two patients discontinued treatment due to grade 3 transaminitis. **Conclusions:** Interim analysis shows that 6m PFS was acceptable with majority of patients being second-line metastatic HNSCC who historically had mPFS of 2.1-2.3 months and mOS 7.7-8.4 months in Checkmate-141/KEYNOTE-040 trials. Hence, the combination is of further interest and accrual will continue to reach the goal. The combination therapy was tolerable without unexpected AEs. Majority of deaths were from disease progression. No treatment related grade 4/5 adverse events were reported. Two patients discontinued treatment due to grade-3 IRAE. Clinical trial information: NCT03313804. Research Sponsor: University of Kentucky Markey Cancer Center's Cancer Center Support Grant.

Median PFS, OS and survival probabilities in the study population.

	PFS	OS
Median follow-up duration	11.8m	11.5m
Median	5.5m	19.27m
Survival Probability		
6m	49.19%	77.68%
12m	32.20%	57.37%
24m	21.46%	40.16%

2629 **Poster Session**

The Tim3-galectin-9 interactions in the tumor microenvironment of nasopharyngeal cancer. *First Author: Dora Lai Wan Kwong, The University of Hong Kong, Hong Kong, China*

Background: The complex cell interactions within the tumor microenvironment (TME) have become a crucial point in cancer research. Yet, the cell interactions might not only depend on the frequency of immune cells, but also on the inter-individual distances as cells might interact via soluble factors and/or cell-cell contact. Accordingly, the mapping of TME has recently gained importance. The aim of this study is to investigate the alternations between galectin-9 (G9) and its natural immunosuppressive receptor, T cell immunoglobulin and mucin domain 3 (Tim3) in nasopharyngeal cancer (NPC). **Methods:** Using multiplexed quantitative immunofluorescence, we measured the levels of G9 and Tim3 in 95 NPC patients cancerous and 8 normal specimens in tissue microarray format. Cell densities and cell-to-cell distances were quantified. The interaction between G9-expressing tumor cell lines and T cells were also studied. **Results:** G9-expressing tumor cells were detected in all NPC cases and were significantly higher than normal tissue. Elevated G9 was associated with shorter overall survival (OS: 89% vs 70.5% at 7 years, p: 0.019). Incremental percentages of $Tim3^+$ cells were shown in top 10% cases strongly positive for G9-expressing tumor cells. The number of $Tim3^+$ cells was calculated at 15μm intervals from the nearest G9-expressing tumor cells, of which a significant difference of $Tim3^+$ cells was observed at the 0-15μm distance from G9-expressing cell in cancerous compared to normal tissues. Epithelial short distances were associated with a unfavourable prognosis. Observed short distance were hypothesized to represent $Tim3^+$ cells actively interacting with G9-expressing tumor cells. Accordingly, *In vitro* cocultured of G9-ovexpressing NPC cell lines induced Tim3 expression on T cells which suppressed the T-cell mediate cytotoxicity on tumor cells. **Conclusions:** Our findings indicate a specific preexisting profile of $Tim3^+$ and G9-expressing tumor cells and demonstrated that $Tim3^+$ cells were mainly found intratumorally within 15μm of a NPC cell. The relevance of $Tim3^+$ and $G9^+$ distances reflect a potential marker of their functional interaction. Our results could have important implications for clinical therapeutic strategies. Since high G9 expression have poorer OS, they would deserve a different therapeutic strategy. Research Sponsor: Health and Medical Research Fund.

NPC (cases).

Total_G9-expressing tumor cells (Tc)	Top10% G9-expressing Tc	$Tim3^+$ within Top10% G9-expressing Tc	$Tim3^-$ within Top10% G9-expressing Tc	10-50% G9-expressing Tc	$Tim3^+$ within 10-50% G9-expressing Tc	$Tim3^-$ within 10-50% G9-expressing Tc
95	9	6	3	33	7	26
Cell densities (%)						
$Tim3^+$ cells within Top10% G9-expressing tumor cells	$Tim3^-$ cells within Top10% G9-expressing tumor cells	$Tim3^+$ cells within 10-50% G9-expressing tumor cells	$Tim3^-$ cells within 10-50% G9-expressing tumor cells			
30.62	69.38	19.54	80.46			
Distance to G9-expressing Tc (median; um)						
$Tim3^+$ cells	$Tim3^-$ cells					
7.62	11.34					

2630 **Poster Session**

Safety of AK117, an anti-CD47 monoclonal antibody, in patients with advanced or metastatic solid tumors in a phase I study. *First Author: Hui Kong Gan, Austin Health, Heidelberg, VIC, Australia*

Background: AK117 is a novel humanized IgG4 monoclonal antibody (mAb) targeting CD47, a macrophage immune checkpoint that allows tumor cells to evade immune destruction by phagocytic cells. CD47 is a target expressed in many cancers. However, the initial dose of anti-CD47 therapy may be limited by severe anemia due to ubiquitous CD47 expression on senescent red blood cells (RBCs). Here, we present encouraging preliminary AK117 safety and receptor occupancy (RO) data from an ongoing dose-escalation study in patients (pts) with advanced or metastatic solid tumors. **Methods:** This is a first-in-human, phase 1a/1b, multicenter, open label, single arm, dose escalation and dose expansion study of AK117 administered intravenously to adult pts with resistant/refractory advanced or metastatic solid tumors or lymphomas. In the dose escalation phase (phase 1a), an accelerated titration followed by a 3+3+3 design was used to assess the safety and tolerability of AK117 monotherapy (dose range 0.3 mg/kg to 45 mg/kg); and determine the maximum tolerated dose (MTD). AK117 was administered QW on a 28-day treatment cycle and dose limiting toxicity (DLT) observation period. Tumor assessments per RECIST v1.1 were performed once every 8 weeks (2 cycles). **Results:** As of 15 Feb 2021, 15 pts were enrolled in phase 1a with DLT evaluation of the 30 mg/kg cohort currently in progress. There were no DLTs up to 20 mg/kg QW AK117, inclusive. Five treatment-related adverse events (TRAEs) occurred in 4 subjects as shown in the table below. All pts with TRAEs continue to receive AK117, except the pt on 1 mg/kg AK117 who discontinued due to disease progression. G2 anemia and G1 thrombocytopenia occurred after Cycle 1 in a pt (liposarcoma, 10 mg/kg cohort), who had a medical history of anemia (hemoglobin 119 g/L at screening). No hematological TRAEs were seen in other pts, including those who received 20 mg/kg AK117 QW. There were no infusion-related reactions (IRRs) or grade ≥ 3 TRAEs. Target engagement in the periphery was confirmed by measuring CD47 RO of AK117 on RBCs and T lymphocytes. 100% RO on RBCs and T lymphocytes was achieved after the first dose and continued to Day 8 (prior to second dose) in the 10 mg/kg and 20 mg/kg cohorts. **Conclusions:** AK117 is safe and well-tolerated up to 20 mg/kg QW, inclusive, with no IRRs or severe TRAEs observed. There were no hematological TRAEs, except in a pt with baseline G1 anemia receiving 10 mg/kg AK117. Unlike other anti-CD47 therapies, AK117 does not require a lower 'priming' dose to prevent anemia. Safety evaluation of the 30 mg/kg dose level is in progress. Full and durable RO in the periphery was seen at 10 mg/kg and above. Further evaluation of AK117 in combination with AK104, an anti-PD-1/CTLA-4 bispecific antibody, shall commence imminently. Clinical trial information: NCT04349969. Research Sponsor: Akeso Biopharma, Inc.

Dose Level	AE	CTCAE Grade
1 mg/kg	Rash	1
3 mg/kg	Nausea	1
10 mg/kg (same pt)	Anemia	2
	Thrombocytopenia	1
20 mg/kg	Headache	1

2631 **Poster Session**

Phase 1 dose escalation study of MGC018, an anti-B7-H3 antibody-drug conjugate (ADC), in patients with advanced solid tumors. *First Author: Sekwon Jang, Inova Schar Cancer Institute, Fairfax, VA*

Background: MGC018 is an investigational ADC with a duocarmycin payload linked to an anti-B7-H3 monoclonal antibody (mAb). B7-H3 is expressed on multiple solid tumors with limited normal tissue expression. It is hypothesized that MGC018 may exert activity against B7-H3-expressing tumors with an acceptable safety profile. Studies demonstrate that B7-H3 is a significant factor in progression and events of metastasis of multiple tumor types, including melanoma. **Methods:** This phase 1 study characterizes safety, maximum tolerated or maximum administered dose, pharmacokinetics, immunogenicity, and tumor response per RECIST v1.1 of MGC018 in a 3+3+3 dose escalation design in patients with advanced solid tumors. MGC018 was administered intravenously (IV) every 3 weeks. **Results:** The study enrolled 29 patients of multiple tumor types, which included 3 melanoma patients refractory to ≥2 prior lines of checkpoint therapy. The study completed 5 of 6 planned dose cohorts (0.5 mg/kg - 4 mg/kg) as of the data cutoff of 21 January 2021. The final cohort of 4 mg/kg has 3 patients with ongoing treatment and follow-up at the date of submission. Dosing MGC018 IV every 3 weeks resulted in minimal serum accumulation. At least 1 treatment emergent adverse event occurred in 29 patients (100.0%); most common (≥25%) were anemia, neutropenia, fatigue, hyperpigmentation, infusion related reaction, nausea, and palmar plantar erythrodysesthesia. Two dose-limiting toxicities occurred; one grade 4 neutropenia (2 mg/kg) and one grade 3 fatigue lasting 7 days (4 mg/kg). No febrile neutropenia was reported. The 3 melanoma patients had reductions in target lesion sum of 24.4%, 27.5%, and 35% (unconfirmed partial response) and remain on treatment as of the data cutoff. The recommended phase 2 dose was determined to be 3 mg/kg. **Conclusions:** Results to date demonstrate a manageable safety profile, with early evidence of clinical activity in pretreated metastatic melanoma. Cohort expansion is ongoing using a recommended phase 2 dose of 3 mg/kg IV every 3 weeks. The planned enrollment includes advanced metastatic castrate-resistant prostate cancer, melanoma, triple-negative breast cancer, and non-small cell lung cancer. Clinical trial information: NCT03729596. Research Sponsor: MacroGenics, Inc.

2632 **Poster Session**

Comparison of checkpoint inhibitor treatment-related cutaneous adverse events in racial and ethnic minority and Caucasian cohorts at Memorial Sloan Kettering Cancer Center. *First Author: Amaris Geisler, CUNY School of Medicine, New York, NY*

Background: Immune-related cutaneous adverse events (irCAEs) are the most common and often the first toxicity of immune checkpoint inhibitors (CPIs). In the general population, irCAEs occur on average within 3.6 weeks of treatment initiation and most commonly manifest as maculopapular rash, lichenoid rash, and pruritus. Less is known about these irCAEs in racial and ethnic minority patients. The purpose of this study is to compare the irCAEs of cohorts of Caucasian and racial and ethnic minority patients at Memorial Sloan Kettering Cancer Center. **Methods:** Herein, we conducted a retrospective chart review of racial and ethnic minority patients treated with CPIs between 2012-2019 at Memorial Sloan Kettering Cancer Center. irCAEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) v5.0. These were compared to a Caucasian cohort matched by demographics and cancer therapy regimen. **Results:** One hundred ten racial and ethnic minority patients presented to dermatology for irCAEs. Our population consisted of 59 (53.6%) females and 51 (46.4%) males with a mean age of 59 (range 20-85). Of the patients who were seen by dermatology, 63/110 were Asian (57.3%) followed by 34/110 African American (30.9%), and 1 Native American. Twelve patients were of Hispanic ethnicity (10.9%), which included those of both African American and Caucasian race. The 110 patients that were evaluated by dermatology had 221 cutaneous adverse events. Rash (96, 43.4%), pruritus (40, 18.1%), and xerosis (23, 10.4%) were most frequently diagnosed (average time from treatment start to presentation was 125 days). Dermatology identified 87 (39.3%) grade 1, 103 (46.6%) grade 2, 30 (13.5%) grade 3, and 1 (0.4%) grade 4 events. There were 17 (15.5%) treatment interruptions, including 7 patients who required permanent discontinuation. In the Caucasian cohort, mean time to onset was 228 days (range 1-1500). Dermatology identified 48 (43.6%) grade 1, 44 (40.0%) grade 2, 18 (16.4%) grade 3, and 0 (0.0%) grade 4 events, with maculopapular rash (55, 50.0%) and pruritus (25, 22.7%) most frequently diagnosed. **Conclusions:** Our findings suggest that irCAEs occur frequently in cancer patients from racial and ethnic minority groups, with similar grade and morphology as Caucasian patients. When irCAEs develop in this population, the diagnosis occurred later than what has previously been reported, possibly due to these patients seeing MSK oncologists with an established dermatology consultation system and insight into how to manage these patients on their own. Prospective evaluation of underrepresented minorities receiving CPI therapy is warranted in order to identify risk factors and therapeutic strategies for these untoward events, so that optimal cancer care may be delivered. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health.

2633 **Poster Session**

Proton pump inhibitor use (PPI) in patients treated with immune checkpoint inhibitors (ICI) for advanced cancer: Survival and prior therapy.

First Author: Marium Husain, The Ohio State University Medical Center, Columbus, OH

Background: Emerging data suggest that concomitant medications (CM) influence response to ICI. CM impact the host microbiome which may mitigate tumor-immune responsiveness. PPI use in patients treated with ICI has been associated with worse survival. Few data exist regarding the effects of PPI use in terms of prior chemotherapy or in risk for immune related adverse events (irAE) (e.g., colitis). **Methods:** This retrospective study of patients with advanced cancer treated with ICI between 2011 and 2019 was conducted at The Ohio State University. Patients who received ICI as either single agent or combination were included. Clinical data was abstracted from chart review, including CM, toxicity, and survival. Overall survival (OS) was evaluated to date of death or last contact. Associations between OS and proton pump inhibitor (PPI) use were studied using log-rank tests and Cox regression analyses overall and by the groups of whether prior chemotherapy was administered and timing from chemotherapy to ICI. The associations between PPI and incidence of irAE (overall and colitis) were assessed by chi-square tests. **Results:** We identified 1,091 patients treated with ICI, of whom 415 (38%) received PPI at time of ICI. Most common cancers were NSCLC and melanoma; most common therapy was PD1/L1 (Table). PPI use was associated with shorter OS in patients treated as first line therapy (HR = 1.46, 95% CI = [1.11, 1.91], p=0.006) and in second line and beyond (HR = 1.30, 95% CI = [1.10, 1.53], p=0.002). PPI use was associated with shorter OS in patients treated with ICI for those without prior chemotherapy (HR = 1.47, 95% CI = [1.17, 1.86], p=0.001). When evaluated by timing from chemotherapy to ICI, PPI use was associated with shorter OS only in patients where last chemotherapy was $>$ 1 year from ICI (HR = 1.99, 95% CI [1.15, 3.45], p=0.014) but not for patients with chemotherapy within 1 year of ICI (HR = 1.01, 95% CI = [0.79, 1.29], p=0.960). The use of PPI was not associated with incidence of irAE (p=0.317) or colitis in particular (p=0.781). **Conclusions:** PPI use was associated with shorter survival in patients treated with ICI across a broad variety of cancers and in first line of therapy or beyond. In patients with recent chemotherapy ($<$1 year), PPI use was not associated with survival, which may be due to disruption of the microbiome by chemotherapy. Further study is needed to determine the impact of CM (e.g, PPI), on outcomes of patients treated with ICI. Research Sponsor: U.S. National Institutes of Health.

Patient Characteristics	No PPI	PPI	P value
N = 1091	676	415	
Age (mean (SD))	61.64 (13.73)	62.36 (11.88)	0.381
Female	280 (41.4)	164 (39.5)	0.577
ECOG PS (%)			0.026
0	254 (41.6)	130 (33.7)	
1	252 (41.2)	177 (45.9)	
2	91 (14.9)	61 (15.8)	
>2	14 (2.3)	18 (4.7)	
Immunotherapy (%)			0.602
PD1/L1	476 (70.4)	294 (70.8)	
CTLA4	116 (17.2)	78 (18.8)	
PD1/L1 + CTLA4	51 (7.5)	29 (7.0)	
Other	33 (4.9)	14 (3.4)	

2634 **Poster Session**

Initial findings of the first-in-human phase I study of AGEN2373, a conditionally active CD137 agonist antibody, in patients (pts) with advanced solid tumors.

First Author: Anthony W. Tolcher, NEXT Oncology, San Antonio, TX

Background: CD137 is a member of the tumor necrosis factor receptor superfamily that functions as a potent co-stimulator of both adaptive and innate immune cells, thus making it an attractive target for cancer immunotherapy. The development of first-generation anti-CD137 antibodies has been hampered by limited clinical activity or dose-limiting hepatotoxicity. AGEN2373 is a novel, conditionally active CD137 agonist antibody designed to selectively enhance tumor immunity while mitigating side effects associated with systemic activation of CD137. Here we report the initial findings from the first-in-human evaluation of AGEN2373 in pts with advanced solid cancers. **Methods:** Pts received AGEN2373 on day 1 of a 28-day cycle (Q4W dosing), with cycles repeated until progression, intolerable toxicity or investigator/patient decision. Dose-escalation followed a standard 3+3 scheme, with planned dosing of 0.03, 0.06, 0.3, 1.0, 2.0, and 3.0 mg/kg. The primary objective was to determine the safety, tolerability, and dose-limiting toxicity (DLT) of AGEN2373 as monotherapy. Secondary objectives included pharmacokinetics (PK) and preliminary clinical activity. Adverse events (AEs) were reported per CTCAE v5.0 and DLTs evaluated within a 28-day window. For PK analyses, serum AGEN2373 concentrations determined using a validated bioanalytical assay and simultaneously analyzed by an NLME model. Antitumor activity was assessed using RECIST v1.1. **Results:** As of January 21 2021, 19 pts (median age 54.4 years, range 33-74; 11 men, 8 women; 7 with prior immunotherapy) have been treated with AGEN2373 Q4W at escalating doses from 0.03 – 2.0 mg/kg across 5 cohorts. Eleven pts (57.9%) experienced treatment-related AEs; none were grade 3 or higher. The most common events were fatigue (4 pts, 21.1%) and nausea (2 pts, 10.6%). No DLTs have been observed. Importantly, no drug-related elevations in liver transaminases (ALT, AST) or bilirubin beyond 1 grade have been seen. AGEN2373 PK were consistent with linear elimination. Prolonged disease stabilization as best response occurred in 5 pts (26.3%; range, 6-41 weeks); three of which were seen in heavily pretreated pts with metastatic leiomyosarcoma, including one who had progressed on prior combination checkpoint immunotherapy. Enrollment into the 3.0 mg/kg cohort is continuing. **Conclusions:** AGEN2373 demonstrates good tolerability in pts with advanced solid tumors, with a safety profile characterized by a lack of hepatotoxicity frequently observed with CD137-targeting antibodies. These findings underscore the suitability of AGEN2373 as a potential partnering agent for other immunomodulatory agents, including planned expansion as combination therapy with balstilimab (anti-PD-1). Clinical trial information: NCT04121676. Research Sponsor: Agenus Inc.

2635 **Poster Session**

Late immune-related adverse events with immune checkpoint inhibitors.

First Author: Andrew Ip, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ

Background: Immune Checkpoint Inhibitors (ICIs) are associated with unique immune-related adverse events (irAEs). IrAEs can occur at any timepoint of ICI treatment. Late irAEs are not well reported in the literature. Herein, we attempt to characterize irAEs that occur 6-month, one year and two years after ICI treatment initiation. **Methods:** We identified patients treated with ICIs (anti-CTLA-4, anti-PD(L)-1 either alone or in combination or with chemotherapy) across Hackensack Meridian Health hospital and MedStar Georgetown University Health systems from 12011 to 4/2018. Patients' baseline demographics, treatment history, and irAEs were collected from EHR. CTCAE V4.03 was used to grade irAEs. **Results:** We identified 1332 patients treated with 1443 unique ICIs. The ICI therapies were nivolumab 38% (543), pembrolizumab 23% (332), ipilimumab plus nivolumab 12% (180), ipilimumab 11% (161), Atezolizumab 3% (47) and others 13% (180). Tumor types were lung cancer 34% (496), melanoma 27% (389), GI cancers 6% (92), kidney cancer 6% (87), and other cancers 26% (379). The median age was 66 (21-87), age $>$75 37% (541), Caucasian 67% (970). We identified a total of 911 any grade irAEs among 37% (552) therapies. Among, 911 irAEs, grade 1-2, grade $\geq$3 and unknown grade irAEs were 39% (572), 12% (182) and 11% (157), respectively. The most common any grade irAEs were skin rash 22% (202), colitis 13% (120), and hepatitis 12% (108). 84% of all irAEs and 85% of $\geq$ Grade 3 irAEs occurred within 6 months of treatment initiation. Of the 350, patients on active treatment at six months, 37 % (132) and 7% (26) developed any grade and grade $\geq$3 irAEs, respectively. irAEs that had $>$ 10% of their occurrences after six months were skin rash and colitis 14% each. Other common irAEs were hypothyroidism, hepatitis, joint pain, pruritis and pneumonitis at 7% each. Among 170 patients on active treatment at one year, 37% (62) and 7% (12) developed any grade and grade $\geq$3 irAEs respectively. irAEs with $>$10% incidence after one year of treatment were rash 19% and hepatitis 13%. **Conclusions:** Our RWE findings suggest although 85% irAEs occurs within the first six months of treatment, late irAEs can occur with ICI treatment. The incidence and pattern of late irAEs appears similar to early irAEs, (e.g., skin rash, colitis, hypothyroidism and hepatitis) with pneumonitis being a notable exception. It is uncertain if these results will be influenced by changing patterns of ICI use (e.g. different diseases and/or regimens) over time. Research Sponsor: U.S. National Institutes of Health.

Pattern of any grade, grade $\geq$ 3, and select irAEs over time.

	Any grade irAEs % (N=911)	Grade $\geq$ 3 irAEs % (N=182)	Any grade Colitis % (120)	Any grade Hepatitis % (108)	Any grade Rash % (202)	Any grade Pneumonitis % (54)
Less Than 3 months	72 (659)	75% (137)	72 (87)	86 (86)	80 (161)	67 (36)
4-6 months	12 (113)	10 (19)	11 (13)	12 (12)	10 (21)	15 (8)
7 -12 months	8 (70)	8 (14)	10 (12)	2 (2)	4 (8)	11 (6)
Over 1 year	5 (44)	5 (9)	4 (4)	2 (2)	4 (8)	6 (3)
Over 2 years	2 (18)	2 (3)	1 (1)	6 (6)	2 (4)	2 (1)

2636 **Poster Session**

Cardiovascular toxicity incidence following immune checkpoint inhibitors in randomized clinical trials: A systematic review and meta-analysis.

First Author: Camila Bragança Xavier, Hospital Sírio-Libanês, São Paulo, Brazil

Background: Immune checkpoint inhibitors (ICIs) are widely used in oncology and may be associated with a variety of immune-related toxicities. Cardiovascular (CV) adverse effects (AEs) are underreported in randomized clinical trials (RCTs), and the real risk associated with ICIs use has yet to be defined. Therefore, we aimed to investigate the incidence and risk of cardiovascular toxicities in patients receiving ICIs, using an up-to-date meta-analysis of prospective RCTs. **Methods:** We conducted a systematic search of the literature from January 1st, 2010 until July 1st, 2020 to identify RCTs testing ICIs for solid tumors, either in monotherapy or in combination between them. Our initial search yielded a total of 21,249 relevant publications. For CV AEs incidence estimation, we included phase III RCTs testing PD-1, PD-L1, CTLA-4 inhibitors or any combination of these agents. For relative risk (RR) assessment, we included phase II or phase III RCTs testing the same agents and with placebo or best supportive care (BSC) as the comparator. Data were extracted by independent reviewers following *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) guidelines. CV AEs were categorized based on the *Common Toxicity Criteria* (CTCAE) and stratified by ICIs type. Analyses were conducted using random effects model. **Results:** After screening and eligibility assessment, a total of 21,118 patients (67 cohorts from 57 trials) were available for this meta-analysis. We categorized the cohorts by ICIs regimen as monotherapy with a PD-1 inhibitor (35 cohorts; 10,241 patients), PD-L1 inhibitor (12 cohorts; 3,755 patients), CTLA-4 inhibitor (11 cohorts; 4,135 patients), and combination therapy (9 cohorts; 2,987 patients). Incidence measures are described in the table. Deaths from any CV cause occurred in 0.20% of the patients (95%CI 0.10%; 0.20%). For RR analysis, we included 12 cohorts from 11 RCTs. Risk of experiencing all grade AEs was numerically higher among patients who received ICIs than placebo or BSC (RR 1.16; 95%CI 0.98; 1.37; p=0.09). When only grade 3-5 CV AEs were considered, ICIs were associated with increased risk (RR 1.36; 95%CI 1.06; 1.73; p= 0.01). Additional analyses were conducted to estimate the RR of individual CV AEs including arrhythmia, cardiac arrest, heart failure, stroke, hypertension, myocardial infarction, myocarditis, pericardial events, and thromboembolic events. None of the analysis identified a significant additional risk. **Conclusions:** This meta-analysis corroborates the preclinical rationale of worsen CV risk related to ICIs use. Research Sponsor: None.

ICI TYPE	ALL GRADE CV AEs (95% CI)	HIGH GRADE CV AEs (95% CI)
CTLA-4 inhibitor	8.30% (7.50%–9.10%)	4.80% (4.20%–5.50%)
PD-1 inhibitor	10.50% (10.00%–11.00%)	5.00% (4.50%–5.40%)
PD-L1 inhibitor	10.40% (9.50%–11,5%)	5.50% (4.80%–6.30%)
COMBINATION	15.87% (14.60%–17.20%)	6.30% (5.50%–7.20%)

2637 **Poster Session**

Infections in cancer patients treated with immune checkpoint inhibitors: Data from randomized trials. *First Author: Cinzia Solinas, Azienda Tutela della Salute Sardegna, Nuoro, Italy*

Background: Febrile neutropenia and infections are well studied complications of chemotherapy (CT) and some targeted agents employed in oncology. Less is known about the risk of infection associated with the use of immune checkpoint inhibitors (ICIs) in cancer patients. The present systematic review and meta-analysis was performed to address this question in patients diagnosed with solid tumors enrolled in randomized trials employing ICIs as experimental treatment. **Methods:** The Cochrane Library, EMBASE, and Pubmed databases were searched from inception through December 1st, 2020. Randomized clinical trials comparing any ICI alone, with CT, or with other agents *vs* CT, placebo, or other agents in patients with solid tumors were included. Two independent reviewers used a standardized data extraction and quality assessment form. Discordant cases were discussed with a third independent investigator. The following information was extracted: baseline study characteristics, including the primary tumor, author, year of publication, type of trial, type of disease, and the type of therapy (experimental and control arms); and the incidence of any-grade (grades [G] 1–5), low-grade (G1–2), and high-grade (G3–4), fatal event (G5) infections, and type of event. Random or fixed-effect models were used according to the statistical heterogeneity. **Results:** 36 randomized clinical trials were deemed eligible. The total population reached 21451 patients. In the pooled analysis, the use of ICIs was associated with a similar risk of all-grade infections (relative risk, RR = 1.02; 95% CI 0.84–1.24; P = 0.85) compared to non-ICI treatments (G1-5 events: 9.6 *vs.* 8.3%). When the ICIs alone arms were compared to CT, the experimental arms were associated with a 42% less risk of all-grade infections (RR = 0.58, 95% CI 0.4–0.85; P = 0.01; N = 18 studies). Compared to CT, the combination of ICIs and CT increased the risk of all-grade infections (RR = 1.37, 95% CI 1.23–1.53; P < 0.01; N = 13 studies) and severe infections (RR = 1.52, 95% CI 1.17–1.96; P < 0.01; N = 12 studies). Fatal infections were similar in the experimental and control arms (0.5%). **Conclusions:** In patients with advanced solid tumors, when ICIs were administered with CT, the risk of all-grade and G3-5 infections was significantly increased. Compared to CT alone, ICIs were safer and their use should be recommended for frail patients. Further studies are required to identify high-risk patients and evaluate the need for CT dose reduction or prophylactic myeloid growth factors use. Research Sponsor: None.

2638 **Poster Session**

Age affects the efficacy of immune checkpoint inhibitors in patients with advanced cancer. *First Author: Yongjie Wang, The Affiliated Hospital of Qingdao University, Qingdao, China*

Background: Immune checkpoint inhibitors (ICIs), such as programmed death(ligand)1 (PD-(L)1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitors, have dramatic effects on treatment in patients with various malignancies. High tumor mutation burden (TMB) is predictive of clinical response to ICI in multiple cancer types. Although age-related immune dysfunction might induce difference on the efficacy of ICIs between younger and older patients, the potential effect of age on the efficacy of ICIs remains little known and controversial. Herein, we aimed to analysis the association between age and the efficacy of ICIs based on MSKCC cohort. **Methods:** We screened out 1661 patients having complete information with advanced cancer, whose tumors underwent next-generation sequencing (NGS) detection and who were treated with at least one dose of ICI in MSKCC cohort. All patients were divided into two groups according to age, the younger group (age ≤50-year old) and the older group (age > 50-year old). We further analyzed the differences in overall survival (OS) and TMB between the two groups. The pooled hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated via Cox regression model for OS and P-values were calculated via the Wilcoxon sign test for TMB. We analyzed the effect of age on ICI in lung cancer using the same way. **Results:** In 1661 patients with cancer in our study, 312 (19%) younger and 1349 (81%) older patients were found. The pooled HRs for OS was 1.28 (95% CI: 1.09-1.52) in younger group compared with older group. In 1661 patients with cancer, there was 350 (21%) patients with lung cancer, including 30 (9%) younger and 320 (91%) older patients. The pooled HRs for OS was 1.45 (95% CI: 0.95-2.23) in younger group compared with older group in lung cancer. In addition, TMB in older group was higher than in younger group and significant difference of TMB was found via the Wilcoxon sign test (p = 2.6e-10) between the two groups, especially in lung cancer (p = 1e-4). **Conclusions:** Our study assessed the impact of age on the efficacy of ICIs using the threshold of 50 years old for the first time and we founded that patients in older group had higher TMB and longer OS than younger group. Research Sponsor: None.

2639 **Poster Session**

Improving tolerability of pembrolizumab with weight based dosing: A meta-analysis. *First Author: Nabeela Khan Patail, Stony Brook University Hospital, Stony Brook, NY*

Background: Pembrolizumab, a PD-1 immune checkpoint inhibitor (ICI), has demonstrated significant clinical activity in various cancers. Despite a favorable toxicity profile, discontinuation due to adverse events including immune related adverse events (irAE) has been reported. We conducted a meta-analysis of published clinical trials to evaluate the tolerability of pembrolizumab in cancer patients. **Methods:** A systematic review was conducted of relevant studies from the databases of PubMed and abstracts presented at American Society of Clinical Oncology (ASCO) from June 2015 until September 2020. Eligible studies included prospective clinical trials that reported a discontinuation rate due to adverse effects. Incidence, relative risk and 95% confidence intervals (CI) were calculated by employing fixed or random effects models. **Results:** A total of 6,380 patients with a variety of hematologic and solid malignancies from 20 studies of pembrolizumab were included for analysis. The overall rate of pembrolizumab discontinuation due to adverse events was 8.2% (95% CI: 6.4-10.4%). The discontinuation rate of pembrolizumab was not significantly lower than the chemotherapy controls, with RR of 0.84 (95% CI: 0.58-1.12, p = 0.33). However, the discontinuation rate of pembrolizumab was significantly higher compared to placebo control with RR of 2.20 (95% CI: 1.36-3.54, p < 0.001), and significantly lower compared to ipilimumab with RR of 0.58 (95% CI: 0.34-0.99, p = 0.04) respectively. The discontinuation rate varied widely among different tumor types with the lowest rate of 0.8% (95% CI: 0.2-3%) in gastric cancer, and the highest of 13.5% (95% CI: 10.8-16.8%) in head and neck squamous cell carcinoma. Interestingly, the discontinuation rate varied with pembrolizumab dosing, with the fixed dosing of 200mg being 9.2% (95% CI: 6.9-12%) and the weight-based dosing being 6.5% (95% CI: 4.8-8.8%). The weight-based dosing was associated with a significantly lower discontinuation rate compared to controls with RR of 0.62 (95% CI: 0.47-0.81, p < 0.0001), while the fixed dosing had similar discontinuation rate with RR of 1.03 (95% CI: 0.89-1.20, p = 0.67). **Conclusions:** The tolerability of pembrolizumab may be comparable to chemotherapy in cancer patients and may vary with its dosing. Future studies are warranted to evaluate the impact of different dosing. Research Sponsor: None.

2640 **Poster Session**

Pan-Canadian cohort of immune checkpoint inhibitor-induced insulin-dependent diabetes mellitus (CANDIED). *First Author: Thiago Pimentel Muniz, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Endocrine immune-related adverse events (irAEs) are frequent with immune checkpoint inhibitors (ICIs); however, ICI-related insulin-dependent diabetes mellitus (IDDM) is a rare but serious endocrine irAE. We describe the characteristics of patients who developed ICI-related IDDM across five academic Canadian cancer centres. **Methods:** In this multicentre, retrospective study, we included both patients who developed IDDM and patients with non-IDDM (NIDDM) or pre-DM who became insulin-dependent while on treatment with ICI. We collected data on primary tumor type, ICI regimen (single agent or combination), time to development of IDDM from ICI initiation, comorbidities, laboratory parameters at the time of IDDM diagnosis, tumor response and survival. A p value < 0.05 was considered statistically significant. **Results:** We identified 27 patients between July 2016 and August 2019. Median age was 60 (39-79) years, 20 (74%) were male, 15 (55%) had melanoma and 4 each (15%) non-small cell lung cancer (NSCLC) and renal cell carcinoma. Seven (26%) patients had prior NIDDM or pre-DM; 5 (18%) had an auto-immune disease (2 psoriasis, 2 inflammatory bowel disease, and 1 systemic lupus erythematosus). Laboratory parameters at presentation and management of IDDM are presented in the Table. Mean A1c was not statistically different between patients with or without prior NIDDM or pre-DM (8.4% vs. 8.6%; $p = 0.9$). All IDDM events were irreversible; 1 (4%) patient died of diabetic ketoacidosis. At time of IDDM diagnosis, 17 (63%) patients were receiving single agent anti-PD1 and 10 (37%) anti-PD1-based combinations (7 anti-CTLA-4, and 3 other compounds). Median time for development of IDDM from ICI initiation was 2.7 months (95% CI 0.2-5.3). Patients receiving combination ICI developed IDDM earlier than those treated with single agent (1.4 vs 4.8 months; $p = 0.05$). Amongst patients with metastatic disease (n = 24), 9 (38%) had a complete response and 7 (29%) had a partial response. Two patients (8%) were treated in the adjuvant setting; 1 (4%) received consolidation ICI. IDDM led to ICI discontinuation in 12 (44%) patients. After a median follow up of 21 months from ICI initiation, median survival was 30 months (95% CI NE) and was not reached in patients with melanoma and NSCLC. **Conclusions:** ICI-related IDDM is a rare and typically irreversible irAE that occurs early in the course of treatment and develops earlier with combination ICI. In this cohort, patients who developed ICI-related IDDM had a high tumor response rate and prolonged survival, especially melanoma and NSCLC patients. Prospective evaluation of autoantibodies to predict development of IDDM is ongoing. Research Sponsor: None.

Glucose, mean (SD)	33 μmol/L (15.6)
A1c (17 patients), mean (SD)	8.5% (1.9)
C-peptide decreased (12 patients)	8 (67%)
Diabetic ketoacidosis	14 (52%)
Management	
Insulin Replacement	27 (100%)
Hospital Admission	18 (67%)
Steroids	4 (15%)
Infliximab	1 (4%)

2641 **Poster Session**

Real-world outcomes of treatment with immune checkpoint inhibitors in unique patient cohorts: Elderly, non-caucasian race, poor performance status, obese, chronic viral infections, and autoimmune diseases. *First Author: Neil J. Shah, Memorial Sloan Kettering Cancer, New York, NY*

Background: Immune Checkpoint Inhibitors (ICI) have revolutionized current cancer treatment. Nevertheless, outcomes data across various patient cohorts are lacking. To address this knowledge gap, we conducted a comprehensive analysis of real-world data (RWD) that included patient cohorts traditionally underrepresented in clinical trials. **Methods:** We identified patients (pts) treated with ICI (anti-CTLA-4, anti-PD(L)1 or their combination at 6 US academic and community hospitals from 1/2011 – 4/2018. Clinical data obtained from EHR and CTCAE V4.03 was used to define immune-related adverse events (irAEs). **Results:** A total of 1332 pts treated with 1443 unique ICI treatments were included in the cohort. The median age was 66 (21-87), Male 58% (827), Caucasian 70% (1004), African American (AA) 16% (232), other race 14% (207), ECOG PS 0,1 79% (1130), chronic viral infection 5% [hepatitis B (24), hepatitis C (32) and HIV (17)], with BMI > 30 22% (287) and autoimmune disease (AID) 15% (215). Lung cancer (NSCLC) 34% (423), and melanoma 27% (389) were top 2 tumor types and nivolumab 38% (544), pembrolizumab 23% (332), and ipilimumab plus nivolumab 12% (180) were the most common ICI treatments. Overall survival (OS) was worse for patients with ECOG ≥2 (0.34 - 0.63) vs. ECOG 0,1 (1.27 - 1.73, P <0.001), and better with AID (1.21 - 2.63) vs. no AID (0.90 - 1.24, P=0.01) and Caucasian (1.02 - 1.45) vs AA (0.72 - 1.30, P=0.02). No difference in OS was noted for sex, other races, h/o chronic viral infection or obesity. We performed an analysis of OS and irAEs restricted to NSCLC patients (n=423); (N=447 unique ICI treatments); age >75 27% (120), AA 28% (124), Female 50% (224), ECOG PS ≥2 23% (104), BMI >30 15% (62), chronic viral infections 10% (44), and AID 14% (62). The ICI therapies were nivolumab 55% (245), pembrolizumab 23% (102), and atezolizumab 6% (27) and 16% (others). Data is contained in the table. **Conclusions:** Overall, in our RWD, OS appeared to be similar across above cohorts except poor OS for pts with ECOG ≥2. irAEs also appeared to be similar across cohorts except less with ECOG ≥2. In NSCLC cohort, we noted similar findings except less irAEs in Male cohort. Prospective studies are needed to confirm the above findings. Research Sponsor: U.S. National Institutes of Health.

NSCLC (N=447)	Overall survival Hazard Ratio	P value	Any grade IrAEs	P value univariate	Adj. P value multivariable
18-75 vs. Age > 75	0.90	0.5	29% vs. 40%	0.03	0.078
Male vs. Female	0.87	0.33	26% vs. 38%	0.01	0.046
Caucasian vs. AA	0.76	0.08	35% vs. 24%	0.08	N/A
No Chronic viral infections vs. Yes	1.19	0.48	31% vs 41%	0.23	N/A
No autoimmune disease vs. Yes	0.68	0.07	30% vs 45%	0.03	0.07
ECOG PS 0,1 vs. ECOG PS ≥2	1.96	0.01	36% vs. 20%	0.005	0.004
BMI 12 -30 vs. >30-60	1.10	0.60	30% vs. 36%	0.47	N/A

2642 **Poster Session**

Maintenance immunosuppressive therapy with resumption of immune checkpoint inhibitor treatment to reduce recurrence of immune-mediated colitis. *First Author: Hamzah Abu-Sbeih, University of Missouri, Kansas City, MO*

Background: Immune-mediated colitis (IMC) may limit immune checkpoint inhibitors (ICI) treatment. Current guidelines recommend consideration of resuming ICI when IMC symptoms subside to ≤ grade 1. We aimed to investigate the effect of maintenance immunosuppressive therapy (IST) on the outcome of IMC in patients who resume ICI therapy. **Methods:** We retrospectively studied patients who resumed ICI therapy after adequate treatment of IMC from March 2015 to June 2020 at MD Anderson Cancer Center. Relevant demographic, oncologic, and ICI data were collected and analyzed. Univariate logistic regression analysis was conducted to assess risk factors of IMC recurrence. **Results:** We included 102 patients with a median age of 61 years. 66% were males and 97% were Caucasians. 48 patients (47%) received IST maintenance in conjunction with ICI resumption and 54 patients did not. Symptoms of IMC recurred in 28 patients, 8 (17%) in the concurrent IST group and 20 (37%) in the other group. Compared to no concurrent IST group, patients on concurrent IST were more likely to have received combined ICI regimen (60% vs 41%, p = 0.003) and more initial ICI doses (9 vs 5 doses, p = 0.030). Concurrent IST group had significantly longer ICI treatment duration on resumption (72 vs 62 days, p = 0.023), more ICI resumed doses (5 vs 4 doses, p = 0.038), and lower IMC recurrence (17% vs 37%, p = 0.027). Patient who received more IST doses, both therapeutic and prophylactic, had lower rate of IMC recurrence (OR 0.72, p = 0.012; table). IST maintenance treatment (OR 0.34, p = 0.024) was associated with lower IMC recurrence rate after ICI resumption. Vedolizumab was the predominant IST used. Overall survival was comparable among the two groups (p = 0.934). **Conclusions:** Concurrent IST treatment with ICI resumption after IMC was associated with significantly lower IMC recurrence and more extended ICI treatment while reserving similar overall survival to patients without IST maintenance therapy. Future prospective randomized trial of concurrent IST is still merited for further clarification. Research Sponsor: None.

Univariate logistic regression analysis for risk factors of IMC recurrence.

Characteristic	OR (95% CI)	*P*
Initial ICI type		
CTLA-4	Reference	
PD-(L)-1	0.58 (0.15-2.18)	0.419
Combination	0.68 (0.19-2.34)	0.548
Use of IST for the initial IMC	0.86 (0.29-2.50)	0.776
Dose of IST for initial IMC	0.73 (0.46-1.17)	0.733
Corticosteroids duration for initial IMC	0.98 (0.96-1.02)	0.376
Total number of IST doses	0.72 (0.55-0.94)	0.012
IST Concurrent treatment	0.34 (0.13-0.87)	0.024
Concurrent treatment		
Infliximab	0.68 (0.19-2.47)	0.556
Vedolizumab	0.23 (0.07-0.74)	0.014
None	Reference	
Type of ICI resumed		
PD-(L)1	Reference	
CTLA-4 based	1.75 (0.71-4.68)	0.252
Median duration from last ICI to resumption	1.01 (0.99-1.02)	0.742

IST: immunosuppressive therapy.

2643 **Poster Session**

Outcomes of immune checkpoint inhibitor-mediated colitis: Multicenter cohort study. *First Author: Hamzah Abu-Sbeih, University of Missouri, Kansas City, MO*

Background: Immune checkpoint inhibitor (ICI)-mediated colitis (IMC) is a common and serious adverse event. Although small series have described the clinical presentation of IMC, large multicenter series that integrate clinical, endoscopic, and histologic findings are lacking. **Methods:** We retrospectively assessed patients who received ICI and had endoscopically confirmed IMC from 2010 to 2019. IMC was graded based on the CTCAE version 5.0 criteria. Multivariate logistic regression analyses were conducted to assess factors associated with recurrence of IMC symptoms and long duration of corticosteroids use (> 70 days). **Results:** 675 patients were included. 387 patients were males (57%). Median age was 63 years. Melanoma was the most common cancer type (327; 48%). Most (365; 54%) patients received CTLA-4 inhibitor ICI, as monotherapy or in combination with PD-(L)1. Median time from ICI therapy to IMC was 62 days. IMC was grade 2 in 335 (50%) patients, Grade 3 in 181 (27%), and grade 4 in 16 (3%). 155 (23%) patients had mucosal ulceration on endoscopy, 91 of them had severe features (deep, large, or multiple ulcers); 336 (50%) patients had non-ulcerative inflammation. The rest had normal endoscopic findings with histologic inflammation. Most patients were admitted to the hospital for management of IMC (405; 60%) and 16 (3%) needed ICU-level of care. Treatment included corticosteroids in 577 (85%) patients (median duration 52 days), TNF inhibitor in 245 (36%), and vedolizumab in 90 (13%). 202 (32%) patients had recurrent IMC after resolution of symptoms. On multivariate logistic regression, factors associated with IMC recurrence and long (> 70 days) duration of corticosteroid therapy were grade of IMC (p = 0.049), treatment with infliximab or vedolizumab (p = 0.044), presence of mucosal ulceration (p = 0.034), or features of active histologic inflammation (p = 0.076). Of note, patients with mucosal ulceration received infliximab or vedolizumab more frequently ($p < 0.001$). For patients with grade 2 IMC, mucosal inflammation on endoscopy and delay in performing endoscopy with time from IMC onset to endoscopy more than a month were associated with IMC recurrence and longer duration of corticosteroid use (p = 0.029 and $p < 0.001$, respectively). 16 (3%) patients had colonic perforation, 7 of them underwent surgical resection. No IMC-related death occurred. **Conclusions:** IMC is a clinically significant adverse event that can lead to premature termination of ICI therapy with high rates of hospital admission. Rarely, it results in colonic perforation requiring surgical intervention and ICU admission. Our data suggest that there is a utility of endoscopic and histologic evaluation in the prediction of worse outcomes from IMC. This finding is particularly important for grade 2 IMC as current guidelines do not recommend endoscopic evaluation for this group. Research Sponsor: None.

2644 **Poster Session**

Pancreatic volumes in immune checkpoint inhibitor-induced diabetes. *First Author: Rebecca Jeun, Baylor College of Medicine, Houston, TX*

Background: Immune checkpoint inhibitor-mediated insulin dependent diabetes (ICI-DM) is a rare and irreversible adverse event often presenting with life-threatening diabetic ketoacidosis (DKA). Pancreatic volume changes have been studied in classic Type 1 and Type 2 diabetes as a surrogate for functional β-cell mass. In this study, we investigate longitudinal changes in pancreatic volumes in patients who develop ICI-DM. **Methods:** Among patients with ICI-DM seen at our institution between 2014 and 2020, 20 patients who had serial CT scans of the abdomen and pelvis before and after ICI DM diagnosis were identified for inclusion in this study. Demographic data and clinical variables were obtained from the electronic medical record. Weight-adjusted pancreatic volumes were calculated from CT scans at three time points. The most recent CT scan prior to ICI initiation was used as baseline, the CT scan immediately prior to ICI DM diagnosis was used as a midpoint, and the most recent CT scan prior to the end of the study period was used as the final time point for comparison. **Results:** Median age was 63 years old (range 35 to 83). Renal cell carcinoma and melanoma were the most common cancer types. Male gender predominated (80%). 18/20 patients were on a PD-1 inhibitor with the remaining two on a PD-L1 inhibitor. After initiation of ICI therapy there was a variable response in pancreatic volumes prior to the diagnosis of ICI-DM with 20% patients experiencing a volume loss of > 10% and 25% experiencing a volume gain of > 10%. Volume loss nor volume gain prior to diabetes diagnosis was associated with presentation with DKA. 9/13 (69%) of patients who had pancreatic enzymes checked at diagnosis of ICI-DM had elevated levels. Pancreatic atrophy with a median volume loss of 41% was seen in all patients at a median of 14.9 months (range 3-77 months) after ICI-DM diagnosis. Most had more than 20% volume loss from baseline to most recent scan with no correlation in degree of volume loss with the time interval. There was no evidence of pancreatic ductal dilation, increased pancreatic fat nor any changes consistent with chronic pancreatitis. **Conclusions:** This study shows a variable response in pancreatic volumes after initiation of ICI in patients who progress to developing ICI-DM, though most had a significant decline in volume after the diagnosis of ICI-DM with long-term pancreatic atrophy. As β-cell mass is thought to comprise 1-2% of the pancreas, these findings may suggest both endocrine and exocrine compartment changes because of ICI-DM, though exocrine dysfunction has not been clinically described in this patient population. As these patients receive frequent imaging during treatment, fluctuations in pancreatic volumes with new or worsening hyperglycemia may portend the onset of ICI-DM and clinicians should have a low threshold to screen for this diagnosis as many will present with life-threatening DKA. Research Sponsor: None.

2645 **Poster Session**

Incidence of hepatitis associated with addition of immune checkpoint blockade to conventional solid tumor therapy: A meta-analysis of phase 3 randomized clinical trials. *First Author: Yu Fujiwara, Department of Medicine, Icahn School of Medicine at Mount Sinai, Mount Sinai Beth Israel, New York, NY*

Background: Immune checkpoint blockade (ICB) has emerged as a promising treatment strategy for many solid tumors. Although safe for many patients, ICB causes immune-related adverse events (irAEs) including hepatitis, which may result in morbidity and treatment disruption. Severe hepatitis requires immunosuppression, including corticosteroids and mycophenolate mofetil. We conducted a meta-analysis of clinical trials to investigate the effect of adding ICB to conventional solid tumor therapy on the incidence of hepatitis. **Methods:** Phase 3 randomized clinical trials (RCTs) comparing ICB and conventional therapy to conventional therapy alone were chosen by database search on PubMed, Embase, Web of Science, and Cochrane Library. The odds ratios [OR] of any-grade and grade ≥3 hepatitis, elevated aspartate aminotransferase (AST), and elevated alanine aminotransferase (ALT) were calculated. Meta-analysis was conducted to determine the incidence of hepatitis, elevated AST, and elevated ALT among patients receiving ICB and those receiving conventional therapy alone. Subgroup analysis based on the mechanism of ICB (Cytotoxic T-lymphocyte-associated protein 4 [CTLA-4] inhibitor, programmed cell death protein 1 [PD-1] inhibitor, and programmed death-ligand 1 [PD-L1] inhibitor) was also conducted. **Results:** A total of 29 randomized controlled trials (RCTs) enrolling 18,829 participants were analyzed. Incidence of hepatitis was derived from 24 RCTs enrolling 15,183 patients, and incidence of grade ≥3 hepatitis was derived from 22 RCTs enrolling 13,846 patients. Incidence of elevated AST was extracted from 18 RCTs, and incidence of elevated ALT was extracted from 20 RCTs. Addition of ICB to conventional therapy was associated with an increase in incidence of any-grade hepatitis (OR 2.54, 95% confidence interval [CI] 1.82-3.55) and grade ≥3 hepatitis (OR 4.22, 95% CI 2.51-7.11). The addition of ICB was also associated with an increase in incidence of elevated AST (any grade: OR 2.19, 95% CI 1.59-3.03; grade ≥3: OR 3.18, 95% CI 1.85-5.48) and elevated ALT (any grade: OR 2.08, 95% CI 1.47-2.92; grade ≥3: OR 2.41, 95% CI 1.40-4.14). Subgroup analysis based on the mechanism of ICB demonstrated increased incidence of grade ≥3 hepatitis associated with CTLA-4 inhibitor, PD-1 inhibitor, and PD-L1 inhibitor therapy (OR 2.78, 95% CI 1.26-6.14; OR 6.30, 95% CI 2.23-17.78; OR 4.73, 95% CI 1.83-12.23, respectively). No significant difference of heterogeneity was observed among subgroups (I^2= 0%, p = 0.43). **Conclusions:** Addition of ICB to conventional solid tumor therapy was associated with increased incidence of any-grade and severe hepatitis, and elevations of AST and ALT, regardless of the mechanism of ICB. Clinicians should weigh the risk of liver toxicity when considering addition of ICB therapy in patients with solid tumors. Research Sponsor: None.

2646 **Poster Session**

A first-in-human, multicenter, open-label, phase 1 study of ATOR-1017, a 4-1BB antibody, in patients with advanced solid malignancies. *First Author: Gustav J. Ullenhag, Akademiska Sjukhus, Uppsala, Sweden*

Background: ATOR-1017 is a human agonistic IgG4 antibody targeting the co-stimulatory receptor 4-1BB (CD137). It is developed to activate T cells and natural killer cells in the tumor environment, leading to immune-mediated tumor cell killing. This is a first-in-human, multicenter, phase 1 study (NCT04144842). **Methods:** In this study, ATOR-1017 is administered intravenously every 21 days as a single agent to patients with solid malignancies. ATOR-1017 is administered until confirmed progressive disease, unacceptable toxicity or withdrawal of consent. The primary objective of the study is to determine the maximum tolerated dose, assessed by adverse events (AEs) and dose limiting toxicities (DLTs), and the recommended phase 2 dose. Secondary objectives include pharmacokinetics, immunogenicity and clinical efficacy, assessed with CT scans using response criteria for use in studies testing immunotherapeutics (iRECIST). The study uses a single cohort design for doses up to 40 mg, and thereafter a modified 3+3 design. **Results:** The first patient was dosed in December 2019; by 22 Jan 2021, twelve patients have been exposed to ATOR-1017. The following dose levels have been evaluated; 0.38 mg; 1.5 mg; 5 mg; 15 mg; 40 mg and 100 mg. Dose escalation is ongoing, and the 200 mg dose level is under evaluation. The maximum tolerated dose has not been reached. The following cancer types are included; ovarian cancer (n = 1), choroidal melanoma (n = 3), anal cancer (n = 1), cholangiocarcinoma (n = 1), gastrointestinal stromal tumor (n = 1), breast cancer (n = 1), pancreatic cancer (n = 1), adenoid cystic cancer (n = 1), malignant melanoma (n = 1), colorectal cancer (n = 1). Drug-related AEs were reported in 5 out of 12 patients; one patient experienced a grade 3, all others were grade 1 or 2. There have been two episodes each of chest pain (grades 2 and 3) and headache (grades 1 and 2). Single cases of pyrexia, upper abdominal pain, mouth ulceration, nausea, leukopenia, neutropenia, cytokine release syndrome (CRS), arthralgia, neck pain, and rash were also reported. No DLTs have been observed in the study to date. The median age of the patients were 48.5 years (range 34-76). Patients received a median of 2 prior lines of therapy (range 1-4). The median time on study were 15 weeks (range 0.14-51). Six patients are on study, and six patients have discontinued treatment. Reasons for discontinuation include; investigator decision (n = 1), confirmed disease progression (n = 1), withdrawal of consent (n = 1), death due to disease progression (n = 1) and other reason (n = 2). Preliminary PK data show dose-proportional kinetics up to 100 mg. Best response has been stable disease. **Conclusions:** ATOR-1017 is safe and well-tolerated up to 100 mg. Dose escalation continues and the current dose level is 200 mg. Clinical trial information: NCT04144842. Research Sponsor: Alligator Bioscience.

2647 **Poster Session**

Consensus disease definitions for the spectrum of neurologic immune related adverse events. *First Author: Amanda C Guidon, Harvard Medical School, Boston, MA*

Background: Expanding FDA-approved indications for immune checkpoint inhibitors in patients with cancer has resulted in both therapeutic success and immune related adverse events (irAEs). Neurologic irAEs (irAE-Ns) have an incidence of 1-12% and a high fatality rate relative to other irAEs. Lack of standardized disease definitions and accurate phenotyping leads to syndrome misclassification and impedes evidence-based treatments and research progress. The objectives of this study were to develop consensus guidance for an approach to irAE-Ns including disease definitions and severity grading. **Methods:** A working group of 4 neurologists drafted irAE-N consensus guidance and definitions, which were reviewed by the Neuro irAE Disease Definition Panel, consisting of neurologists, oncologists, neuro-oncologists and irAE subspecialists. A modified Delphi consensus process was used, with 2 rounds of anonymous ratings by panelists and 2 virtual meetings to discuss areas of controversy. Panelists rated content for usability, appropriateness and accuracy on 9-point scales in electronic surveys and provided free text comments. The working group aggregated survey responses and incorporated them into revised definitions. Consensus was based on numeric ratings using the RAND/UCLA Appropriateness Method with prespecified definitions. **Results:** Twenty-seven panelists from 15 academic medical centers voted on a total of 53 rating scales (6 general guidance, 24 central and 18 peripheral nervous system disease definition components, 3 severity criteria and 2 clinical trial adjudication statements); of these, 77% (41/53) received first round consensus. After revisions, all items received second round consensus. Consensus definitions were achieved for 7 core disorders: irMeningitis, irEncephalitis/Encephalomyelitis, irDemyelinating disease, irVasculitis, irNeuropathy, irNeuromuscular junction disorders and irMyopathy. For each disorder, 6 sub-classifications are described: disease subtype, diagnostic certainty, severity, autoantibody association, exacerbation of pre-existing disease or de novo presentation and present or absent concurrent irAE. **Conclusions:** These disease definitions standardize irAE-N classification. They are being incorporated into a multi-institutional registry that our group has initiated to study irAEs. Given consensus on their accuracy and usability from a representative panel group, we anticipate that they can be used broadly across clinical and research settings. Research Sponsor: Support from the non-profit Project Data Sphere.

2648 **Poster Session**

A risk stratification model for toxicities in phase 1 immuno-oncology (P1-IO) trials. *First Author: Alberto Hernando-Calvo, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*

Background: Despite an exponential increase in the number of potential targets in the immuno-oncology (IO) field, lack of risk models to predict toxicities remains a challenge in early drug development. We proposed a risk stratification strategy and investigated whether different IO classes may be associated with incremental risk of toxicities. **Methods:** A systematic search for IO studies from 01/2014 to 10/2020 was conducted. Among the 12053 abstracts screened, 254 reporting phase I-IO trials were selected. Type of IO treatment (IO monotherapy [mono] vs IO combination [comb]), therapeutic class (e.g. IO, molecularly targeted agents [MTA]), and dose escalation method (rule-based, model-based and model-assisted) were collected. A risk scoring model was developed after expert consensus: treatment-related deaths (1:yes, 0:no), incidence of G3/G4 treatment related adverse events (TRAE) or treatment emergent adverse events (TEAE) (0 if 1-29%,1 if ≥30-49%, 2 if ≥50%), incidence of ≥G2 cytokine release syndrome (1:yes, 0:no), incidence of ≥G2 encephalopathy (1:yes 0:no) and incidence of dose-limiting toxicity (DLT) (0:no, 1:lab, 2:clinical). Risk categories were defined by summing all points (0 = low, 1-2 = intermediate, 3+ = high) and were correlated with type of IO treatment, therapeutic class and dose escalation method. **Results:** Of 254 P1-IO trials reviewed, 228 (90%) were scorable, 26 were not (25 due to lack of AE data). Up to 10/26 (38%) of non-scorable studies were cell therapies. Among the 228 scorable studies, 120 (53%) scored 0, 65 (28%) scored 1-2, 43 (19%) scored 3+; 24 (11%) and 125 (55%) did not provide no. of pts with G3/G4 TRAEs or TEAEs respectively. A significant association was observed between risk categories and therapeutic class ($p<0.001$) (see table). Additionally, IO-MTA and IO-IO were both associated with an increased risk of toxicity as compared to IO-mono (OR=3.91 (95%CI 1.7-9.2), p=0.002) and (OR=2.79 (95%CI 1.2-6.5), p=0.02) respectively. There was no association between dose escalation method and risk of toxicity (p=0.95), but 182 (92%) used rule-based methods. **Conclusions:** Our results suggest that different IO classes are associated with different risks of toxicity. This risk classification strategy may guide future clinical trial design. Additionally, standards for reporting toxicities in P1-IO trials are urgently needed. Research Sponsor: None.

IO class	N	Score = 0	Score = 1-2	Score = 3+
AntiPD-1/PD-L1 (mono)	20	11 (55)	7 (35)	2 (10)
AntiPD-1/PD-L1 (comb)	22	5 (23)	9 (41)	8 (36)
AntiCTLA-4	8	1 (13)	4 (50)	3 (37)
Co-stimulatory mAbs	12	4 (33)	4 (33)	4 (33)
Cytokines	18	3 (17)	7 (39)	8 (44)
BITE	4	0 (0)	0 (0)	4 (100)
Cell therapy (no conditioning)	13	11 (85)	2 (15)	0 (0)
Cell therapy (conditioning regimen)	8	1 (13)	3 (37)	4 (50)
Oncolytic virus	9	4 (44)	4 (44)	1 (11)
Vaccines	79	66 (83)	10 (13)	3 (4)
Other immunodulators	35	14 (40)	15 (43)	6 (17)

2649 **Poster Session**

Prevalence of hyperprogressive disease (HPD) mutations and correlations to immune-related biomarkers in a large pan-cancer Chinese cohort. *First Author: Shengli Yang, Department of Thoracic Surgery, Foshan First People's Hospital, Foshan, China*

Background: Immune checkpoint blockade (ICI) therapies have demonstrated inspiring clinical efficacy in multiple types of cancer. However, a subset of patients suffered rapid tumor growth after ICI treatment, which is known as hyperprogressive disease (HPD). Although the mechanism of HPD has not been fully elucidated, some genomic alterations, such as CDKN2A/CDKN2B loss and MDM2/MDM4 amplification were reported to occur in tumors with ICI-related HPD. We analyzed the prevalence of these four "HPD mutations" and their association with PD-L1 expression, TMB, and occurrence of driver gene mutations in a large pan-cancer Chinese cohort. **Methods:** Patients whose tumor tissues were subjected to molecular profiling using targeted next-generation sequencing from January 2017 – November 2020 were included. Single nucleotide variants (SNV), copy number variants (CNV), insertion/deletions (indels) and fusions were called. PD-L1 expression was stratified by CPS 5. Fisher's exact test were conducted to compare the frequencies of biomarkers and Mann-Whitney U test was used to compare the TMB level between the "HPD mutations" group and their wild-type counterpart. **Results:** 45,785 patients of 22 types of cancer were queried. Across all 22 cancers, CDKN2A loss and CDKN2B loss were most commonly seen in ESCA (23.3%, 19.8%), while with the lowest frequency in PRAD (0.18%, 0.18%). MDM2 gain and MDM4 gain occurred most frequently in SARC (14.6%) and BRCA (3.3%), respectively, with the lowest frequency in COAD (0.05%, 0.07%). PD-L1 positive (CPS≥5) rates were similar in CDKN2A/B loss, MDM2/4 amp and wild-type groups in the whole cohort (26.1%, 25%, 27.7%). Enrichment of PD-L1 positivity was not observed in HPD-mutant groups in a specific cancer type. Compared with wild-type group, CDKN2A/B loss significantly correlated with higher TMB levels in NSCLC and SARC ($p < 0.05$) while MDM2/4 amp correlated with lower TMB levels in NSCLC, BTC, and STAD ($p < 0.05$). In NSCLC, SNV in EGFR, TP53, KEAP1, NFE2L2, STK11, PIK3CA, and SMARCA4 genes were significantly enriched in the CDKN2A/B loss group, while SNV in EGFR, RBM10, AR, KDR genes, and fusion in RET were significantly enriched in MDM2/4 amp group. **Conclusions:** HPD mutations were significantly associated with TMB level and occurrence of some driver genes, but were not correlated with PD-L1 expression. Our results revealed the immune-related molecular characteristics in tumors with HPD mutations, providing more insights into the exploration for mechanism of HPD. Research Sponsor: None.

2650 **Poster Session**

Pembrolizumab patient reported benefits: A perspective based on multiple tumors. *First Author: Elise Wu, Merck, North Wales, PA*

Background: Pembrolizumab is a programmed death ligand receptor-1 (PD-L1) treatment indicated for multiple tumors. Patient-reported outcomes (PRO) benefit has only been reported at the tumor level, while a holistic review of PRO effects across tumor types has been missing. We performed a systematic review of PRO to assess the overall health-related quality of life (HRQoL) among cancer patients treated with pembrolizumab across multiple tumors. **Methods:** We systematically searched PRO evidence published from January 2014 to April 2020 across approved pembrolizumab indications using Embase, MEDLINE, and CENTRAL. Eligible studies were required to assess cancer patients treated with pembrolizumab (200 mg or 2mg/kg Q3W) and report PROs and/or HRQoL. The PRO evidence was summarized into three categories: short-term (≤Week 12), mid-term (Week 13-Week 24), and long-term (Week 25-Week 52). A clinically meaningful difference in HRQoL is defined as at least a 10 points improvement or deterioration relative to baseline; a change between ± 10 points is defined as stable. **Results:** We screened 1,262 citations, of which 16 publications reported EORTC QLQ-C30 data; 10 (9 trial-based studies; 1 observational study) of 16 publications reported global health status (GHS) mean change from baseline (CFB) across six indications. Within trial based studies in first-line setting (n=3 studies), the short-term, mid-term, and long-term GHS changes from baseline vary from 0.5 to 2.1, 1.2 to 8.4, and 1.6 to 2.5, respectively. For second-line plus setting (n=6 studies), GHS changes vary from -3.3 to 8.6, -1.0 to 10.9, and -0.9 to 9.2, respectively. Eight trial-based publications reported EORTC QLQ-C30 domain data as CFB. Short- or mid-term mean changes in functioning domain data showed improvement or stability in emotional, cognitive, role, and social functioning. Short-term deterioration in physical functioning was observed for 1 study, whereas physical functioning remained stable for other studies. For symptom domains, deterioration was not observed in any studies; mid-term improvement was reported by one study each in fatigue, dyspnea, and appetite loss; 2 studies reported mid-term improvement in pain. **Conclusions:** This is the first study that presented pembrolizumab PRO evidence at the product level. This study suggests that most pembrolizumab-treated patients maintained or improved HRQoL relative to baseline at pre-defined timepoints. This review's limitations include potential publication bias and lack of meta-analytic methods in reporting results. Nevertheless, these findings provide additional information about pembrolizumab's benefits to physicians and patients from a patient-centric perspective. Research Sponsor: Merck.

2651 **Poster Session**

Pseudoprogression and cancer immunotherapy: A seven year retrospective study of rate, temporal course, and predictive markers in an Irish tertiary referral center. *First Author: Kate McKendry, Department of Medical Oncology, Dublin, GA, Ireland*

Background: Immunotherapy is a relatively new treatment strategy which has achieved unprecedented clinical efficacy in many advanced malignancies. However, the pattern of tumour response to immunotherapy is distinct from other therapies and poses major challenges to clinicians. One such challenge is pseudoprogression. The aim of this study was to assess the current management of patients on immunotherapy with radiological evidence of disease progression at first restaging imaging in an Irish cancer centre, and to determine the rate, time course, and predictive markers of pseudoprogression in those patients treated beyond progression (TBP). **Methods:** Patients treated with immunotherapy for metastatic malignancy in MMUH between March 2013 and September 2020 were retrospectively drawn. Inclusion required follow-up restaging imaging every 4-12 weeks for the duration of treatment. Patterns of response during immunotherapy were established from radiology reports and categorized as stable (SD), response (R), mixed disease (MD), or progressive disease (PD). Pseudoprogression was defined as progression/ mixed disease at first restaging compared to baseline followed by subsequent response/stable disease. **Results:** The cohort of 228 patients was comprised of 80 NSCLC, 74 melanoma, 25 RCC, 19 gynaecological, 14 gastrointestinal, 6 breast, 1 ESSCLC, and 9 other cancer patients. Median age was 61.16 (IQR 49.47-69.44). Therapeutic agents were anti-PD1 alone (176) or in combination with targeted therapy (6) or CTLA4 (13), CTLA4 alone (15), and anti-PD-L1 alone (13) or in combination with chemotherapy (5). At first restaging, the number (%) classified as SD, R, MD, and PD, respectively, was 29 (12.8), 62 (27.2), 16 (7), and 76 (33.3). Treatment was stopped prior to restaging in 44 (19.3) cases. Of the 92 patients with mixed/ progressive disease, 41 were TBP and 51 were not treated beyond progression (NTBP). Evidence of radiological progression and worsening performance status (PS) were the most common reasons given by clinicians for NTBP. Of those TBP, 20 had subsequent response/stable disease, occurring at a median of 105.50 (range 58.0-420) days after the initial restaging scan and giving an overall pseudoprogression rate of 8.8%. At one year, 100% of the pseudoprogression group was alive. The neutrophil-lymphocyte ratio (NLR) was significantly lower in the pseudoprogression group compared to those with true progression ($p = 0.006$). There was no significant difference in performance status between the two groups. **Conclusions:** Pseudoprogression on cancer immunotherapy is real but uncommon, with an overall incidence of 8.8%. It can occur any time up to 420 days after initial progression and indicates a high likelihood of > 1 year survival. A low NLR may be a useful predictor of pseudoprogression but a technological solution is likely needed. Research Sponsor: None.

2652 **Poster Session**

Proton pump inhibitors and antibiotics impact on toxicities and clinical outcomes in cancer patients treated with immunotherapy. *First Author: Haniel alves Araujo, Instituto do Càncer do Estado de São Paulo (ICESP), São Paulo, Brazil*

Background: Gut microbiome dysbiosis impairs systemic immune responses and recent evidence suggests its critical role in patients (pts) treated with immune checkpoint inhibitors (ICI). Proton pump inhibitors (PPI) and antibiotics (ATB) may alter the microbiome and their impact on clinical outcomes and toxicities requires further investigation. **Methods:** This retrospective cohort included consecutive metastatic cancer pts treated with ICI with palliative intent. We reviewed pts' records, concomitant medication and toxicities graded by CTCAE 4.0. Pts with PPI or ATB exposure were analyzed according to previous use (pPPI and pATB, ≤60 days to ICI) and concomitant use (cPPI and cATB). We estimated median overall survival (mOS) and progression free survival (PFS) by Kaplan–Meier and used a Cox proportional-hazards model to adjust for differences in baseline characteristics. Toxicities and ATB/PPI interaction was calculated using Pearson Chi-square method. **Results:** We enrolled 216 pts with a median age of 59 years, mostly ECOG-PS 0 (34%) or 1 (58%). ICI employed were mostly anti-PD-1 (60.2%), anti-CTLA-4 (16.2%) and anti-PD-L1 (12.5%). Most frequent primary tumor sites were lung n = 39 (18.1%), gastrointestinal n = 34 (15.7%) and melanoma n = 33 (15.2%). Half of the pts (108) received ATB and 114 (52.8%) PPI. Compared to control, pPPI group n = 57 (26.4%) had shorter mOS (11.6m vs 19.7m, $p < 0.001$) and PFS (2.8m vs 8.5m, $p < 0.001$), but no statistically significant difference in toxicities grade ≥3 and/or leading to ICI discontinuation (36% vs 29.1%; p = 0.29). cPPI n = 100 (46.3%) depicted a negative impact on mOS (12.1m vs 17.0m; p = 0.01), PFS (4.3m vs 7.1m; p = 0.04) and augmented toxicities (42% vs 19%; $p < 0.001$). pATB n = 34 (15.7%) had shorter OS (6.9m vs 19.3m, $p < 0.001$) and PFS (3.2 vs 7.2m, p = 0.005) and higher incidence of toxicities (45.9% vs 28.1%; p = 0.04). cATB use n = 92 (42.6%) did not impact OS (12.1m vs 15.6m; p = 0.32) or PFS (5.5m vs 5.9m; p = 0.82), but had a higher incidence of toxicities: 37% vs. 24.2% (p = 0.05). Multivariate analyses confirmed that pATB therapy and pPPI respectively remained as independent prognostic variables associated with OS (HR 2.39; 95% CI, 1.60-3.59; $P < .001$ and HR 1.73; 95% CI 1.23-2.44; P = 0 .002) and PFS (HR 1.72; 95% CI, 1.14-2.61; P = 0.01 and HR 2.36; 95% CI 1.67 - 3.34; $P < 0$ .001) adjusted by performance status, age and line of treatment. **Conclusions:** These data suggest that concomitant use of PPI and ATB is associated with increased toxicities in ICI treated pts. pPPI and pATB can negatively impact OS and PFS and merit clinician's attention. Research Sponsor: None.

2653 **Poster Session**

Impact of pharmacodynamic biomarkers in immuno-oncology (IO) phase 1 clinical trials. *First Author: Abdulazeez Salawu, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*

Background: Pharmacodynamic biomarkers (PD) are considered fundamental for go/no-go decisions in phase 1 trials. Despite an increase in the availability of blood-based biomarker assays, the requirement of invasive non-diagnostic research tumor biopsies for trial eligibility remains common. In the immuno-oncology (IO) era, the impact of PD analysis for the confirmation of biologic activity and recommended phase 2 dose (RP2D) has not been investigated. **Methods:** Phase 1 studies from 01/2014 to 12/2018 were reviewed. Among 12053 abstracts screened, a total of 143 phase I-IO trials were identified. Characteristics of studies that included on-treatment PD biomarkers (tissue-derived, blood-based and radiomic) were extracted and analyzed. Outcomes from the biomarker data in terms of proof of mechanism/biologic activity and statistically significant correlation with clinical benefit (objective response or survival) were collected. Authors' statements on the influence of PD results on RP2D were also noted. **Results:** Out of 143 phase 1 IO trials, 107 (75%) were monotherapy. The most frequent IO evaluated were vaccines (41%), cell therapy (16%), immunomodulators (13%) and cytokines (7%). Of the 36 combination studies, 20 (61%) included a second IO drug while 16 (39%) included molecular-targeted agents. Only 18 of 143 studies (12%) did not report any PD data. Of the remaining 125 studies, tissue-derived PD (t-PD) biomarkers alone, blood-based PD (b-PD) biomarkers alone, both t-PD and b-PD biomarkers, and imaging biomarkers were tested in 3 (2%), 97 (78%), 25 (20%), and 7 (6%), respectively. Demonstration of proof of mechanism/biologic activity only were reported in 16/28 (57%), 80/122 (66%) and 4/7 (57%) of the t-PD, b-PD and imaging biomarker studies, respectively. Significant correlation with clinical benefit was reported in 2/28 (7%), 7/122 (6%) and 0/7 (0%) of the t-PD, b-PD and imaging biomarker studies, respectively; these involved 4 vaccines (1 in combination with PD1 blockade), 1 cell therapy and 1 oncolytic virus (in combination with CTLA4 blockade). Among 35 b-PD studies with negative results, 5 also performed t-PD biomarkers, all with negative results. Notably, 3 out of 10 t-PD studies with negative results reported concurrent positive b-PD results. Based on the published reports, authors stated that biomarker results helped with RP2D determination in 16/28 (57%) of t-PD and 78/122 (64%) of b-PD studies. **Conclusions:** Our results suggest that in the IO era, most studies perform PD analysis, with similar proportions of t-PD and b-PD showing proof of mechanism/biologic activity. IO PD biomarkers have limited correlation with clinical benefit. Many authors considered IO PD biomarkers to be relevant in RP2D decisions, but this needs confirmation by other measures of impact. With continued technological developments utilizing circulating biomarkers, b-PD may ultimately replace many t-PD tests in future IO studies. Research Sponsor: None.

2654 **Poster Session**

Impact of multidisciplinary severe immunotherapy complication service on outcomes for cancer patients receiving immune checkpoint inhibition. *First Author: Leyre Zubiri, Massachusetts General Hospital, Boston, MA*

Background: The exponential increase in FDA-approved indications for immune checkpoint inhibitors (ICI) in cancer care has resulted in therapeutic success but also in the occurrence of immune-related adverse effects (irAEs) that can represent a significant clinical challenge. On October 3 2017, the Massachusetts General Hospital (MGH) implemented the Severe Immunotherapy Complications (SIC) Service, a multi-disciplinary care team for patients hospitalized with irAEs. The objectives of this study were to evaluate the impact of SIC Service on 1) healthcare utilization and 2) patients outcomes. **Methods:** Using pharmacy and hospital admission databases, a list of patients was identified that both received ICI for a malignancy and were hospitalized with severe irAEs in the period prior to initiation of the SIC service and after SIC initiation. The pre-SIC period was defined as an admission between 4/2/2016 through 10/3/2017, and the post-SIC period as an admission from 10/3/2017 through 10/24/2018. The rate of readmission after the index hospitalization was the primary outcome. Secondary outcomes included lengths of stay (LOS) for both initial irAE admissions and readmissions, use of corticosteroids and non-steroidal second-line immunosuppression, ICI discontinuation, and inpatient mortality in the pre- and post-SIC periods. **Results:** Among 1169 patients treated in the pre-SIC service intervention period; 127 were hospitalized for irAE. Among 1159 patients treated in the post-SIC intervention 122 were hospitalized for irAE. SIC Service implementation was associated with a significant reduction in irAE readmission rates (post-SIC 14.8% vs. pre-SIC 25.9%; odds ratio [OR], 0.46; 95% CI, 0.22-0.95; p=0.036). The length of stay, rates of corticosteroid use, second-line immunosuppression, and ICI discontinuation for irAE, as well as inpatient mortality rates were not significantly different before and after SIC Service implementation. **Conclusions:** This is the first study to report that establishing a highly subspecialized care team focused on irAEs can be associated with improved clinical outcomes for patients receiving ICI therapy. Such care teams may play an essential part in optimizing irAE care. Research Sponsor: None.

2655 **Poster Session**

Patients with steroid-refractory toxicity following immune checkpoint inhibitors: Frequent hospitalizations and long duration of illness. *First Author: Mia Bothwell, Massachusetts General Hospital, Boston, MA*

Background: Immune checkpoint inhibitors (ICIs) have revolutionized the treatment of cancer with significantly improved outcomes, but these agents have a unique spectrum of toxicities known as immune-related adverse events (irAEs). The recommended treatment for non-endocrine toxicities is steroid based. However, a subset of patients (pts) is steroid-refractory and requires second-line immunosuppression. There is very little evidence regarding this population. In this retrospective study we report the 1) incidence 2) type of treatment used 3) natural history and 4) potential predictors of steroid-refractory irAE at a major academic medical center. **Methods:** The Research Patient Database Registry at Mass General Brigham was used to identify pts treated with an ICI from 1/5/2017 to 6/1/2019. Pharmaceutical records identified a subset of the cohort received a second-line immunosuppressive agent within a 15-month period after ICI. For pts with steroid-refractory irAE additional information was collected: demographics, ICI regimen, type/#/and severity of irAE, clinical characteristics, # of admissions, length of stay (LOS), amount and duration of steroid therapy, second line immunosuppression type, treatment discontinuation rates, response, and outcome of re-challenge. Multivariate logistic regressions were used to predict risk of refractory toxicity and study the association of different variables (age, sex, race, marital status, cancer and ICI types) with refractory toxicities. **Results:** We identified 61 pts (1.4%) with steroid-refractory irAEs (48 colitis, 4 myocarditis, 6 pneumonitis, 3 neurologic) out of the total ICI cohort (N=4,325). 60.7% received ICI monotherapy. 24.6% received ICI in the adjuvant setting. Median length of steroid duration was 68 days with max of 1135 days. Despite use of second line immunosuppression, 25.8% of pts were never able to discontinue steroids. Majority of pts (72.1%) had at least one hospitalization with median LOS of 7.5 days. 93.4% of pts permanently discontinued the ICI responsible for the irAE. Thirteen pts (21.3%) were later re-challenged with ICI and 7 (53.8%) of these developed a subsequent irAE. Anti-CTLA-4 therapy was associated with a 10-fold risk of refractory toxicity compared to PD-1 ($p<.05$). Best tumor response was complete response in 21.3% and partial response in 26.2%. Among different cancer types, melanoma was most strongly associated with refractory events (OR 2.97 in comparison to thoracic malignancy). **Conclusions:** Refractory toxicity is uncommon but leads to high rates of ICI discontinuation, frequent hospitalizations, and a long duration of illness with exposure to prolonged and high-doses of steroids. There is an urgent need for further investigation into predictive factors for steroid-refractory toxicity given that ICI is being used more frequently and in earlier lines of treatment. Research Sponsor: None.

TPS2656 **Poster Session**

Zanidatamab, an anti-HER2 bispecific antibody, plus chemotherapy with/without tislelizumab as first-line treatment for patients with advanced HER2-positive breast cancer or gastric/gastroesophageal junction adenocarcinoma: A phase 1B/2 trial-in-progress. *First Author: Keun Wook Lee, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, South Korea*

Background: Zanidatamab is a novel HER2-targeted antibody that binds two distinct extracellular domains of HER2, allowing for multiple mechanisms of action including enhanced binding, clustering, receptor internalization and downregulation; this results in inhibition of ligand-dependent and -independent proliferation and potent activation of antibody-dependent cellular cytotoxicity. Zanidatamab monotherapy is well tolerated and has shown promising anti-tumor activity in patients (pts) with pre-treated advanced HER2-positive cancers, and was well tolerated in a Phase I trial (NCT02892123). Tislelizumab is an investigational anti-programmed death-1 (PD-1) antibody engineered to minimize binding of $Fc\gamma R$ on macrophages in order to abrogate antibody-dependent phagocytosis, which is a potential mechanism of T-cell clearance and resistance to anti-PD-1 therapy. Tislelizumab is well tolerated and has anti-tumor activity alone and in combination with chemotherapy in pts with advanced solid tumors. The highly immunogenic nature of HER2 tumors has led to the development of therapies combining anti-HER2 therapies with immune checkpoint blockade. **Methods:** This open-label, two cohort Phase 1B/2 study (NCT04276493) is designed to evaluate zanidatamab as a first-line therapy with chemotherapy in pts with HER2-positive metastatic breast cancer (mBC; cohort 1) or with chemotherapy + tislelizumab in pts with HER2-positive advanced gastric/gastroesophageal junction adenocarcinoma (GC/GEJC; cohort 2). Weight-based dosing (cohorts 1a and 2a) and flat dosing (cohorts 1b and 2b) regimens of zanidatamab are being investigated. In cohort 1 (n = 20), pts with treatment-naïve HER2-positive (IHC3+ or ISH amplified) mBC will receive intravenous (IV) zanidatamab 30 mg/kg (cohort 1a) or 1800 mg (cohort 1b), plus IV docetaxel 75 mg/m^2 once every 3 weeks (Q3W). In cohort 2 (n = 30), treatment-naïve pts with HER2-positive (IHC3+ or IHC2+ with ISH amplification) advanced GC/GEJC will receive IV zanidatamab 30 mg/kg (cohort 2a), or 1800 mg (pts $<$ 70kg; cohort 2b) or 2400 mg (pts $\geq$ 70kg; cohort 2b), plus IV tislelizumab 200 mg and chemotherapy (CAPOX regimen: oral capecitabine 1000 mg/m^2 twice daily [days 1–14] and IV oxaliplatin 130 mg/m^2 [day 1]) Q3W. For cohort 2 there is a six pt safety lead-in phase, followed by dose expansion after approval by the safety monitoring committee. Primary endpoints are the safety profile and objective response rate. Secondary endpoints include duration of response, time to response, progression-free survival, disease control rate, and overall survival. Clinical trial information: NCT02892123. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Shannon Galgani, MSci, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

TPS2657 **Poster Session**

SGNTGT-001: A phase 1 study of SEA-TGT, an effector-function enhanced monoclonal antibody (mAb), in advanced malignancies (trial in progress). *First Author: Elena Garralda, Hospital Vall d'Hebron, Barcelona, Spain*

Background: T-cell immunoreceptor with Ig and ITIM domains (TIGIT) is an inhibitory immune checkpoint receptor expressed on subsets of T cells and NK cells. SEA-TGT is an effector-function enhanced human mAb that targets TIGIT with pico-molar affinity and blocks TIGIT's interaction with CD155 and CD112. SEA-TGT was developed to have amplified binding to and engagement of Fcγ receptors. Enhanced effector function increases TIGIT+ T-regulatory cell depletion, enhances innate immune cell activation, and augments naïve and memory CD8+ T-cell responses. Preclinically, SEA-TGT elicits superior anti-tumor immune responses compared to other TIGIT mAbs without effector-enhanced backbones, with curative anti-tumor activity as monotherapy and in combination with other immune-modulators. **Methods:** This phase 1, open-label, multicenter, dose-escalation/expansion study (NCT04254107) is assessing the safety, tolerability and preliminary activity of SEA-TGT monotherapy in up to 205 adults (≥18 years) with histologically or cytologically confirmed relapsed, refractory, or progressive metastatic solid tumors (non-small cell lung, gastric/GE junction carcinomas, cutaneous melanoma, head and neck squamous cell carcinoma, bladder cancer, ovarian cancer or triple-negative breast cancer) or lymphomas (classical Hodgkin lymphoma, diffuse large B-cell lymphoma, or peripheral T-cell lymphoma, not otherwise specified). SEA-TGT will be infused on Day 1 of 21-day cycles. In Part A, the safety and tolerability of SEA-TGT will be assessed in ~25 subjects to identify the maximum tolerated dose and recommended phase II dose (RP2D). In Part B, the safety and antitumor activity of the RP2D will be assessed in ~180 subjects in disease-specific expansion cohorts. Primary endpoints are adverse events, laboratory abnormalities, dose-limiting toxicities, and dose-level safety and activity. Secondary endpoints are objective response (OR) rates, duration of OR, complete response, progression-free survival, overall survival, PK, and antidrug antibodies. Exploratory biomarkers of SEA-TGT-mediated pharmacodynamic (PD) effects, PK-PD correlations, and correlative analyses of predictive and PD measurements with response, toxicity, and resistance will be explored. The study was opened April 2020 and is enrolling across sites in North America and Europe. Clinical trial information: NCT04254107. Research Sponsor: Seagen Inc.

TPS2658 **Poster Session**

A phase I, first-in-human clinical trial of the GDF-15 neutralizing antibody CTL-002 in subjects with advanced-stage solid tumors (ACRONYM: GDFATHER). *First Author: Ignacio Melero, Universidad de Navarra, Center for Applied Medical Research (CIMA), Pamplona, Spain*

Background: Growth and differentiation factor 15 (GDF-15) is a TGF-β superfamily member physiologically expressed mainly in placenta and linked to feto-maternal tolerance. Under pathophysiologic conditions, prevention of excessive immune cell infiltration during tissue damage and cachexia induction have been ascribed to GDF-15. A recent study [Haake et al. AACR2020; Abstract #5597] elucidated a mechanism by which GDF-15 inhibits LFA-1 activation on CD8+ T cells, thus interfering with effector T cell recruitment to tissues. Importantly, several cancer entities secrete high levels of GDF-15, correlating with poor prognosis and reduced overall survival [reviewed in Front Immunol 2020 May 19;11:951]. To block this effect the GDF-15 neutralizing antibody CTL-002 was generated. In preclinical models CTL-002 demonstrated potent effector T cell shifting into tumor tissue by neutralizing GDF-15. **Methods:** This is a phase 1, first-in-human (FIH), two-part, open-label clinical trial of intravenous (IV) administration of CTL-002 given as monotherapy and in combination with an anti-PD-1 antibody in subjects with advanced-stage, relapsed/refractory solid tumors who relapsed post or were refractory to a prior anti-PD-1/PD-L1 therapy. Eligible subjects have exhausted all available approved standard treatments. Further key eligibility criteria include having received at least one prior anti-PD1/-PD-L1 treatment and having relapsed on or after it or having been refractory to it, and presenting with a biopsy-accessible tumor for serial biopsy taking. The trial is termed GDFATHER, for "GDF-15 Antibody-mediaTed Effector cell Relocation". Main endpoints are safety of CTL-002 monotherapy and CTL-002 combination with an anti-PD-1 antibody, pharmacokinetics, pharmacodynamics (e.g. degree of GDF-15 neutralization achieved and change in immune-cell number and composition in the tumor tissue) as well as preliminary clinical efficacy (tumor mass reduction; anticachexia effect) In part A of the trial (dose escalation) up to 24 subjects will receive escalating doses of CTL-002 IV (0.3 – 20 mg/kg) in a ,,mono-followed-by-combination"-design with CTL-002 given as monotherapy and followed by combination with an anti-PD-1 checkpoint inhibitor. In part B (expansion) up to 5 cohorts with up to 25 subjects per cohort with defined tumor entities expected to be GDF-15 dependent will be treated to determine the recommended phase 2 dose (RP2D) and further evaluate safety and preliminary efficacy of CTL-002 monotherapy and the combination. The study was initiated in December 2020 and enrolled the first patient on Dec 09, 2020. Cohort 1 has been completed without DLT and enrollment for cohort 2 began in February 2021. Clinical trial information: NCT04725474. Research Sponsor: CatalYm GmbH.

TPS2659 **Poster Session**

A phase 1/2, open-label, dose-escalation, safety and tolerability study of NC410 in subjects with advanced or metastatic solid tumors. *First Author: Martin Gutierrez, John Theurer Cancer Center at Hackensack University Medical Center, Hackensack, NJ*

Background: Leukocyte-Associated Immunoglobulin-like Receptor (LAIR)-1 and LAIR-2 are members of the Leukocyte Receptor Complex (LRC) (An & Brodsky, 2016). LAIR-1 is a co-inhibitory receptor expressed on several subsets of immune cells, and functions to delimit immune responses (Meyaard et al., 1997). LAIR-2 is a secreted protein with homology to the transmembrane protein LAIR-1 (Lebbink et al., 2008). In cancer, it is hypothesized that LAIR-1 expression on several subsets of leukocytes prevents optimal immune responses by limiting both innate and adaptive immune functionality. LAIR-1 serves to suppress anti-tumor immunity through the inhibition of stimulatory signaling pathways. Specifically, LAIR-1 is a checkpoint and adhesion receptor on T cells that limits T cell activation and increases adhesion to collagens (Meyaard, 2008). LAIR-2 is capable of blocking LAIR-1 functional interactions with ligands, resulting in improved immune function on multiple immune cell subsets. Dysregulation of LAIR-1 ligands in the tumor microenvironment results in excessive production of collagens and complement C1q as well as altered forms of collagens, that leads to immune inhibition through binding to LAIR-1+ immune cells . NC410 is a dimeric form of the LAIR-2 protein fused to a human Fc domain of the immunoglobulin (Ig) subtype IgG1. The rationale for developing NC410 as a cancer therapeutic is based on nonclinical data demonstrating LAIR-1 signaling blockade can improve the immune response. Because LAIR-2 binds to ligands shared with LAIR-1 with increased affinity, NC410 acts as a decoy receptor for LAIR-1 ligands releasing suppression from myeloid cells and T cells and promoting anti-tumor immunity. NC410 may also mediate remodeling of the tumor extracellular matrix, further contributing to anti-tumor activity. **Methods:** This is a multi-center, first in human, phase 1/2, open-label, single-armed study to determine the safety and tolerability, define maximum tolerated dose (MTD) and/or pharmacologically active dose, assess preliminary efficacy, and explore predictive and pharmacodynamic biomarkers of NC410 in subjects with advanced or metastatic solid tumors. Key eligibility criteria include measurable disease based on RECIST v1.1 and being able to consent for collection of biopsies at screening and on treatment. Phase 1 is a classic 3+3 dose escalation design to determine the safety, tolerability, DLT, MTD and recommended phase 2 dose (RP2D) (NCT04408599). Ongoing exploratory analyses include the assessment of predictive biomarkers associated with treatment benefit, and pharmacodynamic markers associated with study drug activity. Phase 2 is going to enroll ovarian, colorectal, NSCLC, H&N, and gastric carcinomas and other tumors depending on biomarker data available from the Phase 1 part of the study. Clinical trial information: 04408599. Research Sponsor: NextCure Inc.

TPS2660 **Poster Session**

A phase 1, first in human study of adenovirally transduced autologous macrophages engineered to contain an anti-HER2 chimeric antigen receptor (CAR) in subjects with HER2 overexpressing solid tumors. *First Author: Joshua Bauml, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

Background: Adoptive T cell therapies have led to remarkable advances among patients with hematologic malignancies, but not in those with solid tumors. Macrophages are actively recruited into, and abundantly present in the solid tumor microenvironment (sTME). Tumor- associated macrophages typically evince immunosuppressive behavior, but when engineered to be proinflammatory, may be an ideal vector to administer adoptive cellular therapy in solid tumors. Furthermore, insertion of a CAR confers on the macrophages the ability to selectively recognize and phagocytose antigen overexpressing cancer cells. Additionally, CAR macrophages reprogram the sTME and present neoantigens to T cells, leading to epitope spreading and immune memory. Human Epidermal Growth Factor Receptor 2 (HER2) is overexpressed in many cancers, including but not limited to breast and gastroesophageal cancers (Table). CT-0508 is a cell product comprised of autologous monocyte-derived pro-inflammatory macrophages expressing an anti-HER2 CAR. Pre-clinical studies have shown that CT-0508 induced targeted cancer cell phagocytosis while sparing normal cells, decreased tumor burden and prolonged survival in relevant models. CT-0508 cells were safe and effective in a semi-immunocompetent mouse model of human HER2 overexpressing ovarian cancer. **Methods:** This is a FIH phase 1 study to evaluate safety, tolerability, cell manufacturing feasibility, trafficking, and preliminary evidence of efficacy of investigational product CT-0508 in approximately 18 subjects with locally advanced (unresectable) or metastatic solid tumors overexpressing HER2 who have failed available therapies including anti-HER2 therapies when indicated. Filgrastim will be used to mobilize autologous hematopoietic progenitor cells for monocyte collection by apheresis. The CT-0508 CAR macrophage product will be manufactured, prepared and cryopreserved from mobilized peripheral blood monocytes. The study is enrolling Group 1 subjects, who will receive CT-0508 infusion split over D1, 3 and 5. Subjects will be continually assessed for acute and cumulative toxicity. Dose limiting toxicities will be observed and addressed by a Safety Review Committee. Group 2 subjects will follow, and will receive the full CT-0508 infusion on D1. Pre and post treatment biopsies and blood samples will be collected to investigate correlates of trafficking, persistence, TME modulation, immune response and safety. Clinical trial information: NCT04660929. Research Sponsor: Carisma Therapeutics.

HER2 positivity frequencies across tumor types.

Tumor	HER2 positive %*
Bladder	8–70
Breast	11.0–25.0
Cervical	2.8–3.9
Colorectal	1.6–5.0
Esophageal	12.0–14.0
Cholangiocarcinoma	6.3–9.0
Gallbladder	9.8–12.8
Gastric	7.0–34.0
Ovarian	26
Salivary mucoepidermoid	17.6
Salivary duct	30–40
Testicular	2.4
Uterine	3.0

*References available upon request.

TPS2661 **Poster Session**

Master protocol to assess safety and recommended phase 2 dose of next generation NY-ESO-1–specific TCR T-cells in HLA-A*02 patients with synovial sarcoma or non-small cell lung cancer (Substudies 1 and 2). *First Author: Adam Jacob Schoenfeld, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell therapy using a genetically modified T-cell receptor (TCR) to improve recognition of cancer cells expressing NY-ESO-1/LAGE-1a. Next generation NY-ESO-1 TCR T-cell therapies, such as GSK3901961 and GSK3845097, integrate added genetic modifications to enhance anticancer activity. GSK3901961 co-expresses the CD8α chain to stabilize TCR-human leukocyte A (HLA) class I interactions on CD4+ T cells, improving T-cell persistence and helper functions such as Type 1 T-helper antitumor responses. GSK3845097 co-expresses a dominant negative transforming growth factor-β (TGF-β) type II receptor to reduce TGF-β pathway activation and maintain T-cell proliferation, cytokine production, and cytotoxicity in the tumor microenvironment. A first-time-in-human master protocol (NCT04526509) will evaluate safety, tolerability, and recommended phase 2 dose (RP2D) of these and possible subsequent therapies. Substudy 1 will assess GSK3901961 in patients (pts) with advanced non-small cell lung cancer (NSCLC) or synovial sarcoma (SS). Substudy 2 will assess GSK3845097 in pts with advanced SS. **Methods:** Each substudy includes a dose confirmation stage to assess RP2D and a dose expansion stage. Key inclusion criteria are age $\geq$18 y; measurable disease per RECIST v1.1; HLA-A*02:01, A*02:05, or A*02:06 positivity; NY-ESO-1/LAGE-1a tumor expression; advanced (metastatic/unresectable) SS with t(X;18) translocation and anthracycline-based therapy receipt/completion/intolerance (SS only); and Stage IV NSCLC, receipt of $\geq$1 prior line(s) of standard of care (SOC) therapy including programmed death receptor- or ligand-1 inhibitors, and SOC chemotherapy receipt/intolerance (Substudy 1 only). Key exclusion criteria are prior malignancy that is not in complete remission or clinically significant systemic illness; prior receipt of gene/NY-ESO-1–specific therapy or allogenic stem cell/solid organ transplant; central nervous system metastases (SS only); and actionable genetic aberration and receipt/failure of $\geq$3 systemic therapy lines (Substudy 1 only). Primary endpoints are safety (adverse events) and tolerability (dose-limiting toxicities). Secondary endpoints include investigator-assessed overall response rate, duration of response, and maximum expansion/persistence and phenotype of infiltrating transduced T cells. Exploratory endpoints include laboratory parameters, overall survival, and anti-GSK3901961 or -GSK3845097 titers as applicable. Analyses will be descriptive. The substudies are enrolling. Funding: GSK (209012; NCT04526509). Editorial support was provided by Eithne Maguire, PhD, of Fishawack Indicia, part of Fishawack Health; funded by GSK. Previously presented at AACR 2021 (CT219). Clinical trial information: NCT04526509. Research Sponsor: GlaxoSmithKline (209012).

TPS2662 **Poster Session**

A phase 1 study to evaluate chimeric antigen receptor (CAR) T cells incorporating a chlorotoxin tumor-targeting domain for patients with MMP2+ Recurrent or progressive glioblastoma (NCT04214392). *First Author: Behnam Badie, City of Hope National Medical Center, Duarte, CA*

Background: Glioblastoma (GBM) is the most common and most aggressive primary brain tumor. Around 294,900 new cases are diagnosed globally with 241,000 deaths each year. The 5-year survival is only 5%. Median overall survival from first recurrence is only 5-8 months. There is no established standard of care for recurrent GBM. City of Hope (COH) has developed and optimized a CAR T cell therapy utilizing the chlorotoxin peptide (CLTX) as the CAR's tumor recognition domain against GBM. CLTX-CAR T cells specifically and broadly target GBM through recognition of a receptor complex including membrane-bound matrix metalloprotease 2 (MMP-2). CLTX-CAR T cells do not exhibit off-tumor recognition of normal human or murine cells and tissues in preclinical models. In *in vitro* studies, COH evaluated patient-derived brain tumor (PBT) cell lines for CLTX binding and expression of IL13Rα2, HER2 and EGFR, three targets of CAR T cell trials for GBMs. Strong CLTX binding to tumor cells was observed in of the majority of primary GBM lines, independent of these other antigens. In preclinical studies using *in vivo* mouse models, a single intratumoral (ICT) injection of CLTX-CAR T cells (1×10^6 CAR+ T cells) exhibited robust anti-tumor activity against ffLuc+ PBT106 tumors orthotopically-engrafted in NSG mice. Overall, when compared to mice treated with mock-transduced Tn/mem (no CAR) T cells, the CLTX(EQ)28ζ/CD19t+ T cells reduced tumor burden and significantly increased survival. Taken together, these preclinical findings support the potential safety and efficacy of CLTX-CAR T cells, and provide the rationale for clinical testing of this therapy. As cellular heterogeneity intrinsic to GBM likely contributes to resistance to therapy and limited response rates, CLTX-CAR T cells may provide greater tumor eradication in a higher proportion of patients with GBM. **Methods:** This study is a phase 1, single center, safety and maximum tolerated dose (MTD) finding study of CLTX-CAR T cells for subjects with MMP2+ recurrent or progressive GBM. A safety lead-in of 3−6 participants receiving CLTX-CAR T cells by ICT delivery will be completed first. Subsequently, subjects would receive cells administered through both ICT and intraventricular (ICV catheters) (i.e. dual delivery) in two dose schedules. Subjects will be evaluated for safety and tolerability, and may continue to receive treatment until disease progression. Time to progression, overall survival, and disease response by Response Assessment in Neuro-Oncology (RANO) criteria, will be evaluated and descriptively compared to historical data. The study is actively enrolling patients. Clinical trial information: NCT04214392. Research Sponsor: U.S. National Institutes of Health.

TPS2663 **Poster Session**

Phase I study of adoptive immunotherapy for advanced MUC1* positive breast cancer with autologous T cells engineered to express a chimeric antigen receptor, huMNC2-CAR44 specific for a cleaved form of MUC1 (MUC1*). *First Author: Jennifer M. Specht, University of Washington, Seattle, WA*

Background: Chimeric antigen receptor (CAR) T cell therapy targeting CD19 results in marked tumor regression for patients with CD19+ malignancies. It would be ideal to extend the success of CAR-T cell therapy to epithelial cancers. MUC1* is a post-translationally modified/cleaved form of mucin 1 (MUC1) that is frequently expressed on breast tumors, functions as a growth factor receptor, and a promising antigen for CAR-T cell therapy. Minerva Biotechnologies developed a CAR (huMNC2-CAR44) which recognizes MUC1* and does not bind to full-length or MUC1* negative cells. huMNC2-CAR44 product consists of autologous T cells transduced with a lentiviral vector encoding humanized MNC2-scFv (MUC1* targeting head), sequences from CD8 ? leader, hinge and transmembrane domains, 4-1BB and CD3ζ domains. **Methods:** NCT04020575 is a phase I study evaluating the safety of adoptively transferred autologous T cells genetically modified to express huMNC2-CAR44 in patients with metastatic MUC1* positive breast cancer. After screening, leukapheresis is performed, CD8+ and CD4+ T cells are selected, transduced with huMNC2-CAR44, expanded, and antigen stimulated *in vitro*. Lymphodepletion with cyclophosphamide and fludarabine is followed by infusion of huMNC2-CAR44 CAR-T cells in escalating doses (3.3×10^5 CAR+ T cells/kg – 1×10^7 CAR+ T cells/kg). Key inclusion criteria include metastatic breast cancer of known ER, PR and HER2 status, MUC1* membrane expression $>$ or = 30% with 2+ staining by IHC, measurable or evaluable disease, receipt of standard systemic therapies known to confer benefit, age $>$ 18, informed consent, adequate organ function, and KPS $>$ or = 60%. Patients with active autoimmune disease, uncontrolled infection, anticipated survival $<$ 3 months, and/or untreated CNS metastases are not eligible. The primary objective is to identify the maximum tolerated (MTD) dose of huMNC2-CAR44 T cells by CTCAE v5 and Lee criteria. Secondary objectives include persistence and phenotype of adoptively transferred huMNC2-CAR44 T cells and preliminary antitumor activity. Exploratory objectives include trafficking of huMNC2-CAR44 T cells to tumor sites, effector function of huMNC2-CAR44 T cells *in vivo*, association between tumor MUC1* expression and huMNC2-CAR44 T cell persistence and response, change in tumor immune microenvironment by multiplex IHC in pre- and post-treatment tumor biopsies. Dose escalation is completed using a "3+3" design. Once the MTD has been determined, up to 15 more patients will be enrolled in each of 3 expansion cohorts (Luminal, HER2 positive, and TNBC) to inform future huMNC2-CAR44 T cell trials. Study is open to screening and enrollment in dose escalation. Up to 69 patients may be enrolled in dose escalation and expansion phases. Clinical trial information: NCT04020575. Research Sponsor: Minerva Biotechnologies, Other Foundation.

TPS2664 **Poster Session**

A phase 1 study of RTX-321, an engineered red blood cell as an artificial antigen-presenting cell expressing HLA-A*02 with the HPV-16 E7 peptide and 4-1BB ligand with membrane-bound IL-12 for the treatment of HPV 16-positive cancers. *First Author: Johanna C. Bendell, Sarah Cannon Research Institute/Tennessee Oncology PLLC, Nashville, TN*

Background: High-risk strains of HPV (HPV 16/18) have been associated with the development of multiple cancers, and the associated viral antigens are validated targets from immunotherapy approaches. We engineered red blood cells into allogeneic, off-the-shelf, artificial antigen-presenting cells (aAPCs) that express a human papillomavirus (HPV) 16 E7 peptide bound to human leukocyte antigen (HLA)-A*02:01, the costimulatory molecule 4-1BB ligand (L), and the cytokine interleukin (IL)-12 on the cell surface. This aAPC, RTX-321, activated HPV specific T-cells and promoted effector function *in vitro.* In animal models using a murine surrogate system, this aAPC approach resulted in robust antigen-specific T-cell expansion, NK cell expansion, tumor control, memory formation and antigen spreading, which led to a broad and robust antitumor immune response. The presence of 4-1BBL and IL-12 induced minimal toxicities in these models due to restriction of the biodistribution of the aAPC to the vasculature and spleen. RTX-321 is a potential *in vivo* cellular immunotherapy for treating HPV 16-positive cancers including cervical, head and neck and anal cancers. **Methods:** The RTX-321-01 study is a phase 1 multi-center, dose-escalation study of RTX-321 administered intravenously every 3 weeks in HLA-A*02:01-positive patients with relapsed or refractory HPV 16-positive cancers of the cervix or anal canal, or squamous cell cancers of the head and neck (HNSCC). Patients with cervical cancer or HNSCC will undergo testing for the presence of the HPV 16 virus or provide confirmation from archival tumor tissue prior to enrollment. Patients with anal cancer will not be required to have prospective determination of HPV 16-positive status prior to enrollment given the high incidence in this indication (approximately 80-85 percent of anal cancers). Approximately 18 patients will be enrolled across dose level cohorts to identify the recommended phase 2 dose (RP2D) of RTX-321, followed by RP2D expansion cohorts in specific indications. The starting dose is 1 billion ($1x10^9$) cells administered intravenously every 3 weeks (Q3W) and the dose will escalate by half-log increments, following a Bayesian logarithmic regression model (BLRM) with overdose control. Translational studies will investigate the activation and expansion of HPV16 E7 antigen-specific responses as well as broad innate and adaptive responses in multiple peripheral blood samples over the first 3 cycles of therapy as well as in optional paired tumor biopsies. At this time, the study is open and enrolling patients in the first dose escalation cohort (NCT04672980). Clinical trial information: NCT04672980. Research Sponsor: Rubius Therapeutics.

TPS2665 **Poster Session**

Identification of a microbiome signature predicting immune checkpoint inhibitor outcomes across multiple cancer types in the MITRE study. *First Author: Philippa Gail Corrie, Department of Oncology, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

Background: The gut microbiome is implicated as a biomarker of response to immune checkpoint inhibitors (ICIs), based on preclinical mouse models and preliminary observations in limited patient series. Furthermore, early reports suggest faecal microbial transfer may have therapeutic potential, converting ICI non-responders to responders. So far, identification of specific responsible bacterial taxa has been inconsistent between published studies, which limits future application. By culturing and metagenomic sequencing of stool sample bacteria, our group has identified a unique microbiome signature, which appears to be predictive of response to ICIs across all key published series as well as our own melanoma patient series (Robinson M *et al*, J Immunother Cancer 2020;8(suppl 3):A404). Because the patient numbers in all published series remain low, we are now further exploring and validating this microbiome signature in a larger scale study across several different cancer types. **Methods:** MITRE (Microbiome Immunotherapy Toxicity and Response Evaluation) is a UK NIHR portfolio multi-centre prospective study funded jointly by Cancer Research UK and Microbiotica (NCT04107168). Up to 1800 patients receiving ICIs will be recruited over a 5-year period. In the first stage, 300 patients with advanced melanoma (cohort 1: anti-PD1 monotherapy, cohort 2: anti-PD1+anti-CTLA-4 combination), renal cancer (cohort 3: anti-PD(L)1+kinase inhibitor, cohort 4: anti-PD1+anti-CTLA-4 combination) and non-small cell lung cancer (cohort 5: anti-PD(L)1 monotherapy, cohort 6: anti-PD(L)1+chemotherapy+anti-angiogenic) are being recruited, 50 patients to each cohort. A cohort-specific, simulation-based power calculation will then be performed, guiding subsequent recruitment. Stool and blood are collected prior to treatment, at 3, 6 and 12 months, or disease progression (whichever is sooner), as well as after any grade >3 immune-related adverse events. Patients collect and freeze their own stool samples which are cultured and subjected to shotgun metagenomic sequencing. Plasma, whole blood, buffy coat, RNA and PBMCs are being stored, for correlative studies. Any tumour, or organ biopsies, taken prior to and during treatment are also being collected. Clinical data collection includes treatment, disease response (using RECIST criteria) and toxicity. The primary outcome measure is 1 year progression-free survival. Patients are also asked to invite a household member to be part of the study control group. Recruitment started in July 2020. The Covid-19 pandemic hindered recruitment last year, but the protocol was amended to incorporate a Covid-19 substudy (to document testing, infection and vaccination) and adapt processes for remote trial delivery as much as possible. As of February 2021, 7 sites have opened, 17 patients and 5 household controls have been recruited. Clinical trial information: NCT04107168. Research Sponsor: Cancer Research UK, Pharmaceutical/Biotech Company.

TPS2666 **Poster Session**

Phase I/Ib study with INT-1B3, a novel LNP-formulated micro-RNA (miR-193a-3p mimic) therapeutic for patients with advanced solid cancer. *First Author: Nuria Kotecki, Institut Jules Bordet, Bruxelles, Belgium*

Background: MicroRNAs (miR) are naturally-occurring small non-coding RNA molecules involved in the regulation of gene expression and their dysregulation plays a fundamental role in several pathological conditions including cancer. The miR-193a-3p acts as a tumor suppressor and is downregulated in many cancer types. INT-1B3 is a novel lipid-nanoparticle (LNP) formulated 1B3, a 22-nucleotide double stranded chemically-modified miR-193a-3p mimic. INT-1B3 showed significant tumor growth inhibition in a large panel of human and syngeneic tumor models. It directly targets tumor cells and the tumor microenvironment by specific modulation of multiple signaling pathway components. Furthermore, in syngeneic mice models for e.g. TNBC (4T1) and HCC (H22), INT-1B3 was able to modulate the immune tumor microenvironment by turning 'cold' tumors into 'hot' tumors *via* upregulation of cytokines (e.g., IL-2 and IFN-g), decreasing immunosuppressive cells/Treg (e.g., CD4+ /LAG3+ and CD3+ /FoxP3+) and triggering cytotoxic CD8+ T cell-mediated long-term memory immune protection against rechallenge with tumor cells. These preclinical results suggest potential clinical benefit in a broad range of cancer indications, and a reduced potential to develop drug resistance due to its multi-targeted mode of action. **Methods:** This is a 2-part, multi-center, open-label, multiple ascending dose, first-in-human, clinical study to evaluate the safety, pharmacokinetics, pharmacodynamics, and preliminary efficacy of INT-1B3 in the treatment of patients with advanced solid tumors. The phase 1 part follows a 'hybrid' 3+3 study design in 'all-comer' cancer patients enrolled and treated in cohorts to define the recommended phase 2 dose (RP2D). Upon completion of the dose escalation phase of the study, 2 expansion cohorts are planned to further confirm the safety, tolerability, and preliminary efficacy of the RP2D of INT-1B3 in patients with hepatocellular carcinoma and triple negative breast cancer. Major eligibility criteria include evaluable disease according to RECIST 1.1 and no more than one prior line of anti-PD-1/PD-L1 therapy. Patients will receive INT-1B3 *via* 60-min i.v. infusions twice a week in 21-day cycles. The first patient was enrolled on January the 14th 2021. Clinical trial information: NCT04675996. Research Sponsor: InteRNA Technologies BV.

TPS2667 **Poster Session**

Phase 1/2 study of the novel SUMOylation inhibitor TAK-981 in adult patients (pts) with advanced or metastatic solid tumors or relapsed/refractory (RR) hematologic malignancies. *First Author: Arkadiusz Z. Dudek, University of Minnesota, Department of Medicine, Division of Hematology, Oncology, and Transplantation, Minneapolis, MN, Regions Cancer Care Center, HealthPartners, Saint Paul, MN*

Background: SUMOylation, a posttranslational modification analogous to ubiquitination, attaches a small, ubiquitin-like modifier (SUMO) to target proteins. SUMOylation plays a central role in regulating type I interferon (IFN-I)-dependent innate response and functions to constrain the innate immune response, which can impair tumor immune surveillance. TAK-981 is a first-in-class, small-molecule inhibitor of SUMO-activating enzyme subunit 2 (SAE2). Inhibition of SAE2 by TAK-981 disrupts SUMOylation, thereby allowing innate immune system activation. In *ex vivo* assays, TAK-981 increased phagocytic activity of monocyte-derived macrophages, increased natural killer cell cytotoxicity, and induced markers of dendritic cell activation and maturation via IFN-I signaling. In syngeneic mouse models, TAK-981 resulted in antitumor activity, including complete remissions, and a sustained, protective antitumor immune response. **Methods:** This first-in-human study of single-agent TAK-981 comprises two parts. Phase 1 primary objectives are to determine safety and tolerability, and to select a recommended phase 2 dose (RP2D); secondary objectives are to assess preliminary antitumor activity, characterize pharmacokinetics (PK), and explore pharmacodynamic (PD) biomarkers. This phase will enroll ~70 pts with untreatable locally advanced or metastatic solid tumors or RR lymphoma. The phase 2 primary objective is to evaluate preliminary efficacy at the RP2D in ~132 pts with non-squamous non-small cell lung cancer, cervical cancer, microsatellite-stable colorectal cancer, or CD20+ RR diffuse large B-cell lymphoma or follicular lymphoma. Pts receive TAK-981 via a 1-hour intravenous infusion on days 1, 4, 8, and 11 in 21-day cycles until unacceptable toxicity, pt withdrawal, or death. Dose escalation is proceeding from 3 mg, guided by an adaptive 3+3 design combined with Bayesian logistic regression modelling with overdose control, plus consideration of other safety, clinical, PK, and PD data. The RP2D will be based on the maximum tolerated dose (MTD) or on a biologically effective dose (BED) that is ≤MTD. The BED is defined as a dose at which there is evidence of drug-target engagement and inhibition of SUMOylation, plus: induction of cytokines/chemokines and/or IFN-I signature in tumor or blood; evidence of increased T cell infiltration in tumor; or antitumor activity. PK/PD modeling in the BED range is ongoing and will be used in RP2D determination. Clinical trial information: NCT03648372. Research Sponsor: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

TPS2668 **Poster Session**

Association of combined phase I/II study of a novel bicyclic peptide and MMAE conjugate BT8009 in patients with advanced malignancies with Nectin-4 expression. *First Author: Meredith McKean, Sarah Cannon Research Institute and Tennessee Oncology, PLLC, Nashville, TN*

Background: BT8009 is a Bicycle Toxin Conjugate (BTC), a novel class of chemically synthesized molecules, comprising a bicyclic peptide targeting Nectin-4 tumor antigen, linked to cytotoxin (monomethyl auristatin E [MMAE]) via a valine-citrulline (val-cit) cleavable linker. Nectins (Nectin-1, -2, -3, and -4) and nectin-like molecules (Necl) are Ca2+ independent immunoglobulin-like cell adhesion molecules. Recent studies have shown the importance of Nectin-4 in several human cancers, including lung, ovarian, breast and bladder cancer; however, the precise roles and clinical relevance of Nectin-4 in tumors remain largely unknown. The Nectin-4 targeted enfortumab vedotin, linked to MMAE via a val-cit linker, is highly active in late-stage bladder cancer and demonstrates notable additional clinical activity as a single agent and in combination with pembrolizumab[1]. Skin toxicities, bone marrow suppression, peripheral neuropathy and diabetes have been associated with enfortumab, with some of these toxicities already noted with MMAE-bearing antibody therapies. We anticipate a similar toxicity profile for BT8009 in clinical studies. BT8009 exhibited a favorable preclinical profile and was effective in a range of cell-derived xenograph tumor models. **Methods:** Study BT8009-100 (NCT04561362) will evaluate safety and tolerability of weekly and every other week BT8009 administration, alone and in combination with q4w nivolumab. Determination of both a realistic phase 2 dose and a sequence will also be key to further exploration of safety and efficacy signals, along with an early examination of the role of baseline immunohistochemistry-ascertained levels of tumor Nectin-4. Patients will be recruited with advanced solid tumors associated with Nectin-4 expression after exhausting SOC options (i.e., bladder, breast, pancreatic, head and neck, gastric, esophageal and ovarian). Patients must have available tumor tissue, acceptable hematologic and other critical organ function and be willing to participate. Appropriate ethical and regulatory approvals and advice will be in place and adhered to. Exclusion criteria include uncontrolled brain metastases, uncontrolled hypertension, concomitant CYP3A4 inhibitors and significant history of autoimmune disease for the nivolumab cohorts. PK serial collections will be taken on D1 through D15. Radiologic tumor assessments for response per RECIST will be taken every two months. 1. Enfortumab Vedotin. FDA_data. 761137Orig1s000MultiDisclipline R.pdf (fda.gov). Clinical trial information: NCT04561362. Research Sponsor: Bicycle Therapeutics.

TPS2669 **Poster Session**

Trial in progress: A phase 1b study of sotorasib, a specific and irreversible KRAS^{G12C} inhibitor, as monotherapy in non-small cell lung cancer (NSCLC) with brain metastasis and in combination with other anticancer therapies in advanced solid tumors (CodeBreaK 101). *First Author: David S. Hong, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Kirsten rat sarcoma viral oncogene homolog(*KRAS*) p.G12C mutation is an oncogenic driver mutation in several solid tumors. Sotorasib is a specific, irreversible, small molecule inhibitor of KRAS^{G12C} that has demonstrated durable clinical benefit in NSCLC, with mild and manageable toxicities. The combination of sotorasib with other anticancer therapies may enhance antitumor efficacy. This master protocol is designed to evaluate safety, tolerability, pharmacokinetics (PK), and efficacy of multiple sotorasib combinations in patients (pts) with *KRAS*p.G12C mutated solid tumors. Herein, we overview 1 monotherapy and 11 combination cohorts. **Methods:** This is a phase 1b, open-label study evaluating sotorasib alone and in combination regimens (Table) in pts with advanced *KRAS* p.G12Cmutated solid tumors. Dose exploration will evaluate the safety and tolerability of sotorasib alone and in combination regimens; dose expansion will then verify the safety and tolerability profile of sotorasib regimens and assess antitumor efficacy. Key eligibility criteria include locally-advanced or metastatic solid tumor with *KRAS* p.G12C mutation identified through molecular testing in pts who have received ≥1 lines of prior systemic therapy. Primary endpoints include dose-limiting toxicities and treatment-emergent or treatment-related adverse events. Secondary endpoints include PK profile of combination regimens and efficacy (eg, objective response, disease control, duration of response, progression-free survival, and duration of stable disease assessed per RECIST 1.1). Enrollment began in December 2019 and is ongoing. Clinical trial information: NCT04185883. Research Sponsor: Amgen Inc.

Advanced tumor types	Treatment arms
NSCLC with brain metastasis	Sotorasib monotherapy
NSCLC	Sotorasib + TKI
	Sotorasib + anti-PDL1 therapy
	Sotorasib + chemotherapeutic regimen
	Sotorasib + anti-PD1 therapy
Colorectal cancer	Sotorasib + anti-VEGF therapy + chemotherapeutic regimen
All solid tumors	Sotorasib + MEK inhibitor ± EGFR inhibitor
	Sotorasib + anti-PD1 therapy
	Sotorasib + SHP2 inhibitor
	Sotorasib + anti-EGFR therapy ± chemotherapeutic regimen
	Sotorasib + CDK inhibitor
	Sotorasib + mTOR inhibitor

CDK = cyclin-dependent kinase; EGFR = epidermal growth factor receptor; MEK = mitogen-activated protein kinase; mTOR = mammalian target of rapamycin; PD1 = programmed cell death protein-1; PDL1 = programmed death-ligand 1; SHP2 = Src homology region-containing protein tyrosine phosphatase 2; TKI = tyrosine kinase inhibitor; VEGF = vascular endothelial growth factor.

TPS2670 **Poster Session**

A phase 1 dose-escalation study of intravenously (IV) administered TAK-676, a novel STING agonist, alone and in combination with pembrolizumab in patients (pts) with advanced or metastatic solid tumors. *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute at HealthONE, Denver, CO*

Background: Immuno-oncology therapies, including immune checkpoint inhibitors (CPIs), are revolutionizing cancer treatment. However, primary and secondary resistance to CPIs remains a significant challenge. CPI resistance has been associated with reduced interferon (IFN) signaling, altered antigen presentation, and an immunosuppressive tumor phenotype. Stimulating innate immune cells to develop a proinflammatory tumor environment that activates IFN signaling and downstream adaptive antitumor immune mechanisms is predicted to overcome such resistance. Stimulator of Interferon Genes (STING) is a key mediator of type 1 IFN-dependent innate immune modulation. Most STING agonists evaluated clinically have required intratumoral administration, which has significant logistical challenges and excludes many pts whose tumors are not accessible for injection. TAK-676 is a novel STING agonist under clinical investigation as an IV administered systemic therapy in pts with solid tumors. **Methods:** The primary objective of this study is to determine the safety and tolerability of TAK-676 alone and in combination with pembrolizumab. Secondary objectives are to: determine the pharmacologically active dose and recommended phase 2 dose; characterize TAK-676 pharmacokinetics; assess preliminary antitumor activity; and assess STING agonism gene signature induction. An exploratory objective is to assess immune cell activation and clinical response. The study comprises a single-pt safety lead-in with single-agent (SA) TAK-676 0.1 mg IV, followed by dose escalation using Bayesian Logistic Regression Model design. Dose escalation will start in the combination arm when ≥2 dose levels in the SA arm have been evaluated and considered safe. In both arms, pts will receive TAK-676 on days 1, 8, and 15 in 21-day cycles for up to 1 year. In the combination arm, pts will also receive pembrolizumab 200 mg IV on day 1 of each cycle. Adult pts with histologically confirmed advanced or metastatic solid tumors who have no standard therapeutic options or are intolerant to them, with an Eastern Cooperative Oncology Group (ECOG) performance status 0–1, and ≥1 Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1- evaluable lesion are eligible; pts with tumors that have relapsed, are refractory or naïve to anti-programmed death 1 (PD-1) or anti-programmed death ligand 1 (PD-L1) therapy are eligible for the combination arm. Planned enrollment is ~76 pts; recruitment is ongoing. Clinical trial information: NCT04420884. Research Sponsor: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

TPS2671 **Poster Session**

Trials in progress: A phase 1, open-label, dose-escalation, pharmacokinetic, safety and tolerability study of the selective TAM kinase inhibitor PF-07265807 in patients with advanced or metastatic solid tumors. *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MERTK is a receptor tyrosine kinase from the tumor-associated macrophage kinase (TAMK) family that regulates key aspects of immune homeostasis and responses to infection. MERTK inhibition may lower the threshold for immune activation thereby promoting antitumor activity. Agents with some degree of MERTK inhibitory activity have been investigated in the clinic, but are limited by poor potency in patients (pts) and significant off-targets effects. PF-07265807 (ARRY-067) is a selective small-molecule inhibitor of the TAMKs MERTK and AXL. In preclinical models, PF-07265807 monotherapy shows antitumor activity that results in long-term cures and resistance to tumor re-challenge when combined with anti-programmed cell death protein 1/programmed death-ligand 1 (anti-PD-1/PD-L1) antibodies. This first-in-human study will evaluate the safety, tolerability, pharmacokinetics (PK) and preliminary anti-tumor activity of PF-07265807 in pts with selected advanced or metastatic solid tumors. This study will also explore the potential utility of PF-07265807 in combination with anti-PD-1/PD-L1 antibodies. **Methods:** This is a phase 1, open-label, multi-center, dose-escalation study (NCT04458259) to evaluate the safety, PK and tolerability of PF-07265807. Eligible participants will be adult pts with selected advanced or metastatic solid tumors who are intolerant or resistant to standard therapy. Other key eligibility criteria: measurable disease by RECIST 1.1 or non-measurable disease; Eastern Cooperative Oncology Group performance status 0–2; adequate bone marrow, renal and liver function; and resolved acute effects of any prior therapy. Successive cohorts of pts will receive escalating doses of PF-07265807 starting from 25 mg QD. Each cycle will be 21 days in duration (14 days on/7 days off). Study drug treatment will continue until disease progression or unacceptable toxicity, whichever occurs first. For dose escalation, a Bayesian logistic regression model will be used to model the relationship of dose-limiting toxicities (DLTs) to PF-07265807 dose. This model, along with escalation with overdose control, will guide the dose escalation of PF-07265807 after the completion of the DLT observation period (first two cycles of treatment, i.e. 42 days) of each cohort, until determination of the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D). After the MTD/RP2D is identified, the safety and efficacy of combined PF-07265807 and anti-PD1/PD-L1 treatment will be explored. Primary endpoints: incidence of DLTs, treatment-emergent adverse events and laboratory abnormalities. Secondary endpoints: PK parameters of PF-07265807, objective response rate and duration of response. The study began enrolling pts in September 2020 and is still recruiting. Clinical trial information: NCT04458259. Research Sponsor: Pfizer.

TPS2672 **Poster Session**

Phase 1, first-in-human trial of JTX-8064, an anti-LILRB2/ILT4 monoclonal antibody, as monotherapy and in combination with anti-PD-1 in adult patients with advanced solid tumors (INNATE). *First Author: Kyriakos P. Papadopoulos, START-San Antonio, San Antonio, TX*

Background: Leukocyte Immunoglobulin-like receptor B2 [LILRB2; immunoglobulin-like transcript 4 (ILT4)] is an immunoinhibitory protein expressed on the surface of myeloid cells and is a therapeutic target of interest in immuno-oncology. Published data showed that antagonism of LILRB2 resulted in the repolarization of human macrophages from an M2 (suppressive) to M1 (pro-inflammatory) phenotype, and enhancement of anti-tumor immunity in a mouse model (Chen 2018). JTX-8064 is a novel humanized IgG4 monoclonal antagonist antibody that selectively binds LILRB2 and prevents it from binding its ligands, classical and non-classical MHC I molecules. By blocking the ability of LILRB2 to bind HLA-A/B and/or HLA-G, a marker of immunotolerance on cancer cells, JTX-8064 has been shown to enhance pro-inflammatory cytokine production in macrophages (Cohen 2019). Additionally, blocking HLA-A/B-LILRB2 binding with JTX-8064 may augment antigen presentation and has been shown to lead to enhanced T cell activation and IFNg production (McGrath 2021). Using an ex vivo tumor explant model, we observed an IFNg-associated pharmacodynamic response in tumor tissue treated with JTX-8064 and a PD-1 inhibitor (PD-1i) that was not observed with PD-1i alone. Biomarkers were identified that predicted this JTX-8064 driven response (Hashambhoy-Ramsay 2020). It is hypothesized that JTX-8064 is a novel macrophage immune checkpoint inhibitor that may overcome mechanisms of resistance to PD-1i in tumors not responsive to JTX-8064 or PD-1i alone. **Methods:** The primary objectives of this open-label, phase 1, first-in-human, multicenter trial are to determine the safety and tolerability, and the recommended phase 2 dose (RP2D) of JTX-8064 as a monotherapy and in combination with a PD-1i, JTX-4014 (a Jounce investigational agent) or pembrolizumab, in patients with advanced solid tumors (NCT04669899). The INNATE study will consist of 4 stages: 1) JTX-8064 monotherapy dose escalation, 2) JTX-8064 dose escalation in combination with a PD-1i, 3) JTX-8064 monotherapy in indication-specific expansion cohorts and 4) JTX-8064 in combination with a PD-1i in indication-specific expansion cohorts. Stages 1 and 2 will employ an innovative interval i3 + 3 design with Bayesian decision framework to guide dose escalation. Safety, pharmacokinetic and receptor occupancy data will be considered during dose escalation. INNATE will assess pharmacodynamic and potential predictive biomarkers of response, and the expansion cohorts will explore multiple patient populations, including PD-(L)1i sensitive and PD-(L)1i-resistant (primary or acquired) patients to address current unmet medical needs. Enrolment in INNATE began in January 2021. Clinical trial information: NCT04669899. Research Sponsor: Jounce Therapeutics.

TPS2673 **Poster Session**

A phase 1, multicenter, open-label, dose-escalation, safety, pharmacodynamic, pharmacokinetic study of Q702 with a cohort expansion at the RP2D in patients with advanced solid tumors. *First Author: Angela Tatiana Alistar, Atlantic Health System, Morristown, NJ*

Background: Immune checkpoint inhibitors directly targeting T cell activation have been successfully used in the treatment of various malignancies, nevertheless, the durable ORRs are low for certain indications. The low ORRs have been attributed to the immune suppressive tumor microenvironment (TME), composed of innate immune suppressive components such as tumor associated macrophages (TAM) and myeloid-derived suppression cells (MDSC). The potential contributions of innate immune modulation to anti-tumor immunity, suggest the need for the novel strategies to elicit a more efficient/robust immune response against the targeted malignant cells. Axl, Mer and CSF1R receptor tyrosine kinases play vital roles in promoting an immune suppressive TME by affecting TAM and MDSC populations and by decreasing antigen presentation on tumor cells. Q702 is a novel Axl/Mer/CSF1R inhibitor, able to modulate the TAM and MDSC population leading to CD8+ T cell activation and to increase antigen presentation of the tumor cells in syngeneic animal models. Q702, as a monotherapy, shows significant tumor growth inhibition in multiple syngeneic tumor models, and demonstrates synergistic effects with anti-PD-1 treatment particularly in high myeloid containing tumor models. Interestingly, intermittent administration of Q702 monotherapy demonstrates a more favorable immune cell population changes, possibly through preventing immune exhaustion secondary to negative feedback with continuous activation. These results suggest that Q702 monotherapy or in combination with existing therapies have a good potential to become a novel treatment strategy for patients with advanced solid tumors. **Methods:** "A Phase 1, Multicenter, Open-label, Dose-Escalation, Safety, Pharmacodynamic, Pharmacokinetic Study of Q702 with a Cohort Expansion at the RP2D in Patients with Advanced Solid Tumors. (NCT04648254)" is open and recruiting patients at 4 US investigative sites. Patients with histologically or cytologically confirmed advanced or metastatic solid tumors, that have progressed following SOC or for which there is no SOC which confers clinical benefit are being enrolled in this study. The study follows a standard dose escalation. The study will enroll up to 78 patients. The primary endpoint is to establish safety, PK profile and define the recommended phase 2 dose. The secondary and exploratory endpoints include establishing pharmacokinetic/pharmacodynamic relationship, potential biomarkers and preliminary anti-tumor activity. Clinical trial information: NCT04648254. Research Sponsor: Qurient Co. Ltd.

TPS2674 **Poster Session**

Phase 1 first-in-human study of ABBV-184 monotherapy in adult patients with previously treated acute myeloid leukemia or non-small cell lung cancer. *First Author: Abraham Avigdor, Institute of Hematology, Sheba Medical Center, Ramat Gan, Israel, and Sackler Faculty of Medicine, Tel Aviv University, Tel-Aviv, Israel*

Background: Survivin, a member of the inhibitor of apoptosis protein family, is an attractive therapeutic target in cancer, due to its broad expression in solid tumors and hematologic malignancies but limited expression in normal tissues. Elevated survivin expression is associated with an increased invasive phenotype and worse clinical outcomes. ABBV-184 is a first-in-class T-cell receptor (TCR)/anti-cluster of differentiation 3 (CD3) bispecific molecule. It is composed of a soluble TCR that binds to a survivin-derived peptide bound to the class I MHC allele HLA-A2:01 expressed on tumor cells and to the CD3 receptor on T cells. Preclinical data have demonstrated that treatment with ABBV-184 results in T-cell activation, proliferation, and redirected cytotoxicity of HLA-A2:01–positive target cell lines. This first-in-human trial evaluates ABBV-184 monotherapy in patients with previously treated acute myeloid leukemia (AML) or non-small cell lung cancer (NSCLC). **Methods:** Patients (≥18 years, Eastern Cooperative Oncology Group performance status ≤2, HLA-A2:01 restricted genotype) with relapsed or refractory AML or NSCLC are currently enrolling in this phase 1 multicenter, open-label trial (NCT04272203), which includes parallel dose-escalation and dose-expansion phases for both diseases. Primary objectives are to determine the recommended phase 2 dose (RP2D) of ABBV-184 (dose escalation) and to assess its preliminary efficacy (dose expansion). Secondary objectives include safety, tolerability, pharmacokinetics (PK), and immunogenicity assessments (dose escalation and dose expansion) and duration of response (dose expansion). Patients will receive intravenous infusion of ABBV-184 once weekly. Dose escalation of ABBV-184 is guided by a Bayesian optimal interval design and the RP2D will be determined on the basis of clinical safety, PK, and pharmacodynamic data. For patients with AML, disease assessment is performed according to modified European LeukemiaNet-International Working Group criteria. For patients with NSCLC, response will be assessed using Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 and immune RECIST. Treatment can continue until disease progression or intolerable toxicity. Biomarker assessments will include longitudinal profiling of peripheral blood immune cells and cytokines, analysis of HLA-A2 and survivin levels on AML bone marrow blasts and NSCLC tumor biopsies, and retrospective correlations of biomarker data with antitumor activity. Enrollment initiated in Sep 2020, with 7 patients enrolled as of Jan 2021. Clinical trial information: NCT04272203. Research Sponsor: AbbVie, Inc.

TPS2675 **Poster Session**

A phase I study of AK119, an anti-CD73 monoclonal antibody, in combination with AK104, an anti-PD-1/CTLA-4 bispecific antibody, in patients with advanced or metastatic solid tumors. *First Author: Ben Markman, Alfred Hospital, Melbourne, Australia*

Background: AK119 is a humanized IgG1 monoclonal antibody (mAb) that selectively binds to and inhibits the ectonucleotidase activity of CD73, a cell surface enzyme that converts adenosine monophosphate (AMP) into adenosine. Adenosine has been shown to facilitate tumor-mediated evasion. CD73 inhibition may therefore reduce adenosine accumulation and promote anti-tumor immunity. AK104 is a recombinant humanized IgG1 bispecific antibody that simultaneously binds to programmed cell death protein 1 (PD-1) and cytotoxic T- lymphocyte-associated antigen protein 4 (CTLA-4). Preliminary data from phase I and II studies suggest that AK104 has encouraging anti-tumor activity in selected tumor types and an improved safety profile compared to the co-administration of anti-PD-1 plus anti-CTLA-4 mAbs. Preclinical studies show that CD73 inhibition synergistically increases the anti-tumor activity of PD-1 and CTLA-4 immune checkpoint inhibitors (ICIs). Published early clinical data suggests that anti-CD73 therapy in combination with ICIs produces improved clinical outcomes. Thus, AK119 plus AK104 is postulated to have synergistically enhanced anti-tumor activity compared to the administration of anti-CD73 monotherapy or ICIs alone. **Methods:** This is a phase 1a/1b, first-in-human, multicenter, open-label study in patients with advanced solid tumors that are refractory to standard therapies. The primary objective is to assess safety, tolerability and dose limiting toxicity; and to determine the Maximum Tolerated Dose (MTD) or Maximum Administered Dose (MAD) of AK119 in combination with AK104. Secondary objectives are to evaluate antitumor activity, PK and AK119 immunogenicity. The dose-escalation phase will evaluate 5 dose levels of AK119 (1mg/kg to 40 mg/kg Q2W IV) in combination with 6mg/kg AK104 Q2W IV using a 3+3+3 study design. Eligible pts will receive a single dose of AK119 on COD1 of a 14-day "lead-in" period. Thereafter, from C1D1 pts will receive AK119 in combination with AK104 on a 28-day cycle, until unacceptable toxicity, confirmed progressive disease, subject withdrawal, or for a maximum of 24 months. The "lead-in" period is only applicable for dose-escalation cohorts. Any dose-escalation cohort not exceeding the MTD may be expanded to a maximum of 18 subjects with selected solid tumor types for further evaluation of safety, PK/ PD, immunogenicity, and preliminary anti-tumor activity. Cohort 1 is currently in progress with the first patient enrolled in January 2021. For the dose-expansion phase, cohorts of pts with advanced/metastatic pancreatic cancer or MSS/pMMR colorectal cancer will be enrolled. Cohorts of other tumor types may be added based on emerging pharmacodynamic and anti-tumor response data. Clinical trial information: NCT04572152. Research Sponsor: Akeso Biopharma, Inc.

TPS2676 **Poster Session**

A phase 1b study of nivolumab in patients with autoimmune disorders and advanced malignancies (AIM-NIVO). *First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Nivolumab is an anti-PD1 monoclonal antibody approved for treatment of an increasing number of solid tumors and hematological malignancies. However, patients (pts) with history of autoimmune disorders are excluded from the majority of clinical trials testing immune-checkpoint inhibitors (ICI) such as anti-PD1/anti-PD-L1 antibodies. Consequently, the risks of flare ups, worsening of pre-existing autoimmune disorders or risk of de-novo immune related adverse events (irAEs) in pts with dysfunctional immune systems and tumor types who otherwise stand to benefit from ICI therapy are largely unknown, posing a challenge for oncologists. We are conducting a phase Ib study to test the hypothesis that nivolumab can be safely administered to pts with varying severity of Dermatomyositis, Systemic Sclerosis, Rheumatoid Arthritis, Systemic Lupus Erythematosus, Inflammatory Bowel Disease, Multiple Sclerosis and other autoimmune disorders (AIM-Nivo). **Methods:** AIM-Nivo is an open-label, multi-center ongoing phase Ib study with nivolumab 480mg IV every 28 days in pts with autoimmune diseases and advanced malignancies (NCT03816345). The study has autoimmune disease-specific cohorts overseen by a multidisciplinary group of experts. The primary objective is to assess the overall safety and toxicity profile of nivolumab in pts with autoimmune disorders and advanced malignancies. Secondary objectives are to evaluate the antitumor efficacy; the impact of nivolumab on the autoimmune disease severity indices; and to explore potential biomarkers of response, resistance, or toxicity for each of the autoimmune disease-specific cohorts. Key overall inclusion criteria include age ≥18 years, histologically confirmed advanced or metastatic malignancies in which ICI are approved or have shown clinical activity. Key overall exclusion criteria include prior therapy with anti-PD-1/PD-L1 antibodies. Specific eligibility criteria are defined for each disease-specific cohort. For each autoimmune disorder, severity level of the disease as defined by disease-specific severity indices will be assessed, and up to a total of 12 pts will be included in each disease cohort at each severity level (max 36 pts per cohort). Primary endpoints are dose-limiting toxicities, adverse events (AEs) and serious AEs. Continuous monitoring of toxicity will be conducted. Key secondary endpoints are best objective response per RECIST1.1; progression free and overall survival; and cohort specific tumor tissue, blood, and non-tumor tissue-based biomarkers. The AIM-Nivo trial opened in May 2019 and is enrolling pts through the National Cancer Institute Experimental Therapeutics Clinical Trials Network (ETCTN), Early Drug Development Opportunity Program (EDDOP), and Create Access to Targeted Cancer Therapy for Underserved Populations (CATCH-UP) sites. Clinical trial information: NCT03816345. Research Sponsor: U.S. National Institutes of Health.

TPS2677 **Poster Session**

An open-label phase 1b/2 study of surufatinib in combination with tislelizumab in subjects with advanced solid tumors. *First Author: Arvind Dasari, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Surufatinib (S) is an inhibitor of VEGFR1, 2, & 3; FGFR1; and CSF-1R. In two phase 3 randomized trials (SANET-ep; NCT02588170 & SANET-p; NCT02589821) S demonstrated a manageable safety profile and statistically significant efficacy. Patients (pts) with extrapancreatic neuroendocrine tumors (epNETs) achieved a median progression free survival (PFS) of 9.2 v 3.8 months (mo) (hazard ratio [HR] 0.334; p<0.0001), and pts with pancreatic NETs (pNETs) achieved a median PFS of 10.9 v 3.7 mo (HR 0.491; p=0.0011), with S v placebo, respectively. S was recently approved for the treatment of pts with epNET in China. Tislelizumab (T) is a humanized immunoglobulin G4 anti-PD-1 monoclonal antibody engineered to minimize binding to Fc-gamma-receptor on macrophages. T is approved in China in combination with chemotherapy for squamous non-small cell lung cancer and has conditional approval for Hodgkin's lymphoma and locally advanced or metastatic urothelial carcinoma with PD-L1 high expression. The objective of this study is to evaluate the safety and efficacy of combination therapy with S and T, which may have synergistic effects, where inhibition of angiogenesis along with stimulation of an immune response may enhance the overall antitumor activity. **Methods:** This study (NCT04579757) will include pts, ≥18 years of age, with advanced metastatic solid tumors, who have an Eastern Cooperative Oncology Group performance status of 0 or 1 and have progressed on or are intolerant to standard therapies. The primary objective of part 1 (dose escalation) will be to evaluate the safety and tolerability of S and T to determine the recommended phase 2 dose of the combination. The starting dose in part 1 will be 250 mg of S, orally, daily, and 200mg of T, intravenously, every 3 weeks. The dose of S will be escalated during part 1, while the dose of T will remain fixed. Endpoints include dose limiting toxicities, treatment emergent adverse events, serious adverse events, adverse events leading to discontinuation, electrocardiograms, clinical laboratory abnormalities and vital signs. Antitumor activity will be evaluated as a secondary objective. Six to 12 pts will be enrolled. The primary objective of part 2 (dose expansion) will be to evaluate the objective response rate (ORR) of S in combination with T per RECIST v1.1. The endpoint will be ORR at 12 weeks. Key secondary endpoints include PFS, disease control rate, duration of response, safety endpoints, and PK parameters. Approximately 95 pts with indications of interest will be enrolled: colorectal cancer, neuroendocrine tumors (thoracic and gastroenteropancreatic), small-cell lung cancer, gastric cancer, and soft tissue sarcoma (undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma). Enrollment in the United States is open and ongoing, and enrollment in Europe is planned for fourth quarter 2021. Clinical trial information: NCT04579757. Research Sponsor: Hutchison MediPharma Limited.

TPS2678 **Poster Session**

Combination of atezolizumab and pirfenidone in second-line and beyond NSCLC: A phase I/II study. *First Author: Takefumi Komiya, Hematology/Medical Oncology, Parkview Cancer Institute, Fort Wayne, IN*

Background: Checkpoint inhibitors (CPI) targeting the PD1/PD-L1 axis significantly improved patient outcomes in stage IV non-small cell lung cancer (NSCLC). However, these patients will eventually develop resistance and progression. There is a need to identify novel treatment options. Poor response to PD-L1 antibody was correlated with increase in cancer-associated fibroblasts (CAF), which is known to interact with cytotoxic T cells (CTLs) by suppressing their function in a manner similar to regulatory T cells (Tregs). Production of cytokines by CAFs leads to impaired antitumor immunity by impairing CTL function (TGF beta) and prevent recruitment/mobilization of CTLs into tumors. These effects suggesting that CAF can be a therapeutic target in lung cancer resistant to checkpoint inhibitors. Pirfenidone (P) is approved to treat pulmonary fibrosis with anti-fibrotic effect by blocking the differentiation of fibroblasts into CAFs and suppress the production of TGF beta and TGF beta-induced signaling pathways/collagens. Atezolizumab is a humanized immunoglobulin (Ig) G1 monoclonal antibody that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (CD80), both of which function as inhibitory receptors expressed on T cells. We proposed a phase I/II trial to test the combination of atezolizumab (A) with P in patients with recurrent non-small cell lung cancer (NSCLC) after progression with CPI. The primary objective of phase I is to determine the maximum tolerated (MTD) dose of P in combination with A and assess the safety and tolerability of this combination. The secondary objective is to determine the efficacy of AP in all NSCLC participants treated in this study. Exploratory objectives include the measurement of circulating levels of TGF beta and research in expression of CAF related proteins. **Methods:** The initial phase I will enroll 3 patients using P at 801 mg po TID. A will be at 1200mg iv every 3 weeks. If there is ≤ 1 DLT, the study will proceed to phase II If there are 2- 3 DLT, P will be reduced to 534 mg TID. If there is ≤ 1 DLT, then this dose will proceed to phase II. If there is 2-3 DLT, then the study will be terminated. The phase II will enroll 16 patients to assess efficacy. Main inclusion criteria are patients with recurrent NSCLC after progression with first-line therapy CPI with or without chemotherapy, measurable disease, ECOG 0-2, and adequate organ function. Clinical trial information: NCT04467723. Research Sponsor: Genentech.

TPS2679 **Poster Session**

Immune Resistance Interrogation Study (IRIS): A prospective comprehensive multi-omic analysis in patients with intrinsic and acquired resistance to immunotherapy. *First Author: Sofia Genta, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Immune checkpoint inhibitors (ICI) have demonstrated efficacy in a wide variety of cancers. Nevertheless, only a small proportion of patients derive a durable benefit. Mechanisms underlying primary and acquired resistance are still incompletely understood. They comprise tumor-intrinsic factors such as genomic and transcriptomic changes; upregulation of immunosuppressive subsets; T cell exhaustion; and promotion of an immune-tolerant tumor microenvironment. The collection of tumor biopsy at disease progression (PD) is challenging both in clinical and research settings as this often occurs at the time of treatment discontinuation. However, the analysis of these samples can lead to novel strategies to prevent or reverse immune resistance. Thus, the current approach to begin a profiling study with patients at the time of PD on ICI enables access and interrogation of such samples. **Methods:** IRIS is a prospective, investigator-initiated trial at the Princess Margaret Cancer Centre that aims to extensively characterize the genomic, transcriptomic, epigenetic and immunophenotypic profiles of tumors with primary versus acquired resistance to ICI-based therapy. Primary resistance is defined as PD at the first on-treatment imaging, whereas acquired resistance is defined as PD occurring after an initial partial or complete response or following disease stability lasting ≥6 months. Additional objectives include the evaluation of radiomic parameters on standard radiological imaging, investigation of fecal microbiome, generation of patient-derived organoids and facilitation of data and sample sharing with the research community. The planned samples size is 100 patients. A one-time fresh tumor biopsy, blood and stool samples and archival tissue (when available) are collected at the time of PD on ICI (baseline) from all the participants. Longitudinal blood samples are obtained every 2-3 months (around the time of tumor imaging) until PD in patients receiving a subsequent treatment. Subjects who are not amenable for therapy undergo blood collections at the time of further PD. Molecular characterization of tumor samples includes: DNA/RNA sequencing, Assay of Transposase Accessible Chromatin (ATAC)-sequencing, Cellular Indexing of Transcriptomes and Epitopes (CITE)-sequencing, multiplexed immunohistochemistry and flow cytometry. Results of NGS performed on the first biopsy core are returned to patient and physician. Key eligibility criteria include diagnosis of solid tumor, progression to ICI as the most recent line of treatment and disease amenable to core needle biopsy. The IRIS trial, activated in October 2020, is currently open to enrollment. As of January 2021, 21 patients have been enrolled and a total of 92 tissue cores, 42 blood and 20 stool samples have been collected. Clinical trial information: NCT04243720. Research Sponsor: Princess Margaret Cancer Center institutional founding.

TPS2680 **Poster Session**

Personalized DNA neoantigen vaccine in combination with plasmid IL-12 and pembrolizumab for the treatment of patients with advanced hepatocellular carcinoma. *First Author: Mark Yarchoan, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: Hepatocellular carcinoma (HCC) is the fourth most common cause of cancer-related death. Immune checkpoint inhibitors targeting PD-1 have limited activity in HCC as monotherapy, with response rates ranging from 14-17%. Tumor neoantigens derived from tumor-specific mutations can be incorporated into personalized therapeutic cancer vaccines to prime T cell responses, potentially enhancing responses to anti-PD1 therapy. DNA vaccines have been shown to elicit strong CD8 and CD4 T cell responses in preclinical and clinical trials. In preclinical studies, DNA-encoded neoantigen vaccines have shown induction of CD8 T cells against 50% of predicted high affinity epitopes with the ability to impact tumor growth. GNOS-PV02 is a personalized DNA vaccine, encoding up to 40 patient-specific neoantigens. In the GT-30 trial, it is used in combination with INO-9012 (plasmid-encoded IL-12) and pembrolizumab for the treatment of advanced HCC. **Methods:** The GT-30 trial (NCT04251117) is a single-arm phase I/II clinical trial to assess the safety, immunogenicity, and preliminary efficacy of GNOS-PV02 in combination with INO-9012 and pembrolizumab in patients with advanced HCC. Twenty-four patients are anticipated to be enrolled. Patients are recruited upon diagnosis or during first-line treatment with tyrosine kinase inhibitors (TKI). Tumors are biopsied for exome and transcriptome sequencing. The tumor specific vaccine is designed, optimized and manufactured during first-line therapy. Each vaccine encodes up to 40 neoantigens, which includes all detected neoantigens for the majority of HCC patients. After progression or intolerance with first-line therapy, patients can commence trial therapy with concurrent personalized vaccine and pembrolizumab. GNOS-PV02 + INO-9012 are administered Q3w for the first 4 doses and Q9w thereafter until disease progression. Pembrolizumab is delivered Q3w until disease progression. Immunogenicity of each of the vaccine epitopes will be determined by ex vivo ELISpot and flow cytometry. Clinical activity is assessed by RECIST1.1 at baseline and every 9 weeks. Serial biopsies will be obtained at 9 weeks and upon disease progression to evaluate changes in the exome, transcriptome and changes to the tumor microenvironment. Clinical trial information: NCT04251117. Research Sponsor: Geneos Therapeutics.

TPS2681 **Poster Session**

Phase I study investigating the safety of stereotactic body radiotherapy (SBRT) with anti-PD-1 and anti-IL-8 for the treatment of multiple metastases in advanced solid tumors. *First Author: Lilit Karapetyan, UPMC HCC, Pittsburgh, PA*

Background: Anti-PD-(L)1 immunotherapy improves outcomes for patients across various cancers; however, many patients do not benefit. Previous studies combining multi-site SBRT with anti-PD1 have confirmed feasibility and revealed induction of interferon signaling by SBRT. Elevated levels of serum IL8 (sIL8) associate with lack of response to anti-PD1 and we have observed that elevated IL8 is strongly associated with lack of response to immunotherapy and SBRT combinations. Overcoming IL8 induced epithelial-mesenchymal transitioning and trafficking of myeloid derived suppressor cells in tumor microenvironment therefore represents a promising strategy to overcome resistance. BMS-986253 is a fully human neutralizing antibody that binds to sIL8. The combination of BMS-986253 and nivolumab was safe in patients with advanced solid tumors. The present study aims to evaluate safety and preliminary efficacy of combining BMS-986253 with nivolumab and SBRT in patients with advanced solid tumors, Melanoma (MEL) and Renal Cell Carcinoma (RCC). **Methods:** This is a phase 1 open label single arm study (CT.gov: NCT04572451) which will include safety and efficacy cohorts. Patients will receive SBRT in 1-4 tumor lesions, in 3 or 5 fractions, at the total of 30 or 45 or 50 Gy based on the irradiated organ site. This will be followed by intravenous (IV) nivolumab (480mg q4 weeks (W)) and IV BMS-986253 (2400mg q2W) within seven days of completing SBRT. In the initial safety portion of the clinical trial, we will include 30 patients with advanced/metastatic solid tumors in order to evaluate safety. The primary endpoint of dose limiting toxicity will be assessed by continual Bayesian monitoring. The toxicities will be attributed to combination of SBRT/Immunotherapy as opposed to individual components. The secondary objective of the study is efficacy with an endpoint of objective response rate (ORR) as assessed by RECIST v1.1 in Mel and RCC. We will include 20 patients with MEL and RCC and compare against a historical benchmark of 20% ORR as sufficient signal of activity for further study. ORR will be assessed for association with serum IL-8 levels and radiation-induced changes in peripheral blood T cell populations. Clinical trial information: NCT04572451. Research Sponsor: Bristol Myers Squibb.

3000 **Oral Abstract Session**

A first-in-human phase 1 study of a novel PARP7 inhibitor RBN-2397 in patients with advanced solid tumors. *First Author: Gerald Steven Falchook, Sarah Cannon Research Institute, Denver, CO*

Background: Targeting cytosolic nucleic acid sensing pathways and the Type I interferon (IFN) response is an emerging therapeutic strategy in oncology. PARP7 is a member of the monoPARP class of enzymes and a newly identified negative regulator of nucleic acid sensing in tumor cells. PARP7 expression is increased by cellular stress and aromatic hydrocarbons, and the *PARP7* gene is amplified in multiple cancers. RBN-2397 is a potent, selective inhibitor of PARP7. In preclinical models, RBN-2397 restored Type I IFN signaling in tumors, caused complete tumor regressions, and induced adaptive immunity. **Methods:** Patients (pts) with advanced solid tumors were treated with RBN-2397 on either a continuous or 14-of-21-day intermittent schedule using a 3+3 dose escalation design. Primary objective: establish MTD and/or RP2D. Secondary obj.: safety, activity, PK of unmicronized/micronized tablets. Exploratory obj.: Pd. **Results:** As of 4 January 2021, 47 pts were treated: 25 pts in the intermittent schedule (25 to 500 mg BID) and 22 patients in the continuous schedule (100 to 400 mg BID). The most frequent RBN-2397-related AEs (all grades) were dysgeusia (26%), decreased appetite (13%), fatigue (11%), and diarrhea (11%). Gr 3/4 RBN-2397-related AEs all occurred in 7 pts (15%) at doses $\geq$ 200 mg: diarrhea (2 pts, 4%), increased ALT, AST, and bilirubin (1 pt, 2%), and fatigue, anemia, neutropenia, and thrombocytopenia in 1 pt (2%) each. The 2 DLTs were Gr 3 febrile neutropenia (400 mg continuous schedule) and Gr 4 increase in ALT/AST (500 mg intermittent schedule). Plasma exposures generally increased dose dependently with the majority at or above the projected efficacious range based on animal studies. All evaluable baseline tumor biopsies showed evidence of PARP7 expression as measured by mRNA in situ hybridization (n = 11; Median tumor H score: 128). In 5 evaluable tumor biopsy pairs, increases in interferon-stimulated gene expression were observed post RBN-2397, consistent with activation of Type I IFN. CXCL10 mRNA increased in all evaluable on-treatment biopsies (1.5 to 8-fold). Several on-treatment biopsies showed enrichment for immune response gene sets that was accompanied by an increase in CD8+ T cells and Granzyme B expression, evidence for induction of an adaptive immune response post RBN-2397. This increase in immune response related genes and CD8+ T cells was observed in a pt with metastatic squamous NSCLC who has been on study for 16+ months. 1 pt with HR+, HER2- breast cancer achieved a confirmed PR at 100 mg and 8 pts had SD for $\geq$18 weeks (RECIST 1.1). **Conclusions:** To date, RBN-2397 is well tolerated and demonstrates dose dependent increases in plasma exposures, evidence of target inhibition, and preliminary signs of clinical activity. Determination of MTD/RP2D is imminent and study expansion is planned to evaluate safety and efficacy in squamous NSCLC, HNSCC, HR+ breast cancer, and PARP7 amplified tumors. Clinical trial information: NCT04053673. Research Sponsor: Ribon Therapeutics Inc.

3001 **Oral Abstract Session**

First-in-human biomarker-driven phase I trial of the potent and selective glutaminase-1 (GLS1) inhibitor IACS-6274 (IPN60090) in patients (pts) with molecularly selected advanced solid tumors. *First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Glutamine metabolism is frequently deregulated in different cancers, including tumors harboring *KEAP1*/*NFE2L2* mutations or those expressing low Asparagine Synthetase (ASNS) levels. IACS-6274 is a potent oral GLS1 inhibitor discovered at MD Anderson Cancer Center with excellent pharmacokinetics (PK) and antitumor activity in biomarker-defined preclinical models. **Methods:** Pts with advanced solid tumors received IACS-6274 BID at escalating doses using a phase 1 BOIN design. PK and pharmacodynamic (PD) studies were conducted in serial tumor and/or blood samples. Peripheral glutamine metabolism was assessed in peripheral blood mononuclear cells (PBMC) to assess glutamine metabolism via 13C-isotope labelling. Predictive biomarker studies included tumor analyses for *KEAP1*, *NFE2L2*, *STK11*, *NF1* mutations and IHC for ASNS loss. **Results:** 22 pts with advanced ovarian (n=8), NSCLC (n=7), melanoma (n=2), leiomyosarcoma, gastric, anal, endometrial and HNSCC (all n=1) received IACS-6274 at 20 (n=1), 40 (n=1), 80 (n=1), 120 (n=4), 180 (n=11) or 240 (n=4) mg BID. Molecular alterations assessed included pts with ASNS loss (n=6), *STK11* (n=5), *KEAP1* (n=5), *NFE2L2* (n=4) and *NF1* (n=1). Prior lines of therapies: 2-4 (n=12); $\geq$5 (n=10). Common IACS-6274-related adverse events included G1-2 photopsia (n=7), photophobia (n=7), increased creatinine (n=4) and AST (n=4). Less common G3 toxicities at 180 and 240 mg included reversible nausea (n=3), vomiting and fatigue (n=2). Dose-limiting toxicities of G3 acute renal failure and PRES syndrome were seen in one patient at 240mg BID, which fully resolved. Plasma exposures showed a dose-dependent increase across doses with observed half-life ~12 hrs. Patients at 180mg displayed steady-state exposures at C1D14 with Cmax of 45.8 μM +/- 18.6 μM and average AUC(0-12hrs) of 382.48 h*μM +/- 159.27 h*μM. Glutamate to glutamine ratios decreased in PBMC samples in pts at C1D14 vs baseline; pts at 120, 180 and 240 mg had inhibition of 82.5% ($P<0.0001$), 83.9% ($P<0.0001$) and 85.3% ($P<0.0001$), respectively, exceeding doses predicted to be efficacious in preclinical models. A robust PK/PD relationship was established across doses ($P<0.0001$). The recommended phase 2 dose was 180mg BID. Best RECISTv1.1 response was stable disease (SD) in 17 of 20 evaluable pts. Disease control rate at 12 weeks was 60%. Durable RECISTv1.1 SD $\geq$6 months +/- tumor regression were seen in pts with advanced ASNS-loss ovarian cancer (n=2), PD-1/L1-exposed melanoma (n=2) and *NF1* mutant leiomyosarcoma (n=1). **Conclusions:** IACS-6274 was well tolerated at biologically active doses with good human PK, significant PD target modulation and preliminary antitumor activity observed. The clinical trial assessment of rational combinations to maximize benefit in molecularly-selected pts is initiating. Clinical trial information: NCT03894540. Research Sponsor: Commonwealth Foundation for Cancer Research, The University of Texas MD Anderson Cancer Center.

3002 **Oral Abstract Session**

Phase 2 study of DRD2 antagonist/ClpP agonist ONC201 in neuroendocrine tumors. *First Author: Peter Meade Anderson, Cleveland Clinic Foundation, Cleveland, OH*

Background: ONC201, an imipridone with specificity for the dopamine-like DRD2 receptor and the mitochondrial protease ClpP, imparts anti-cancer effects via up-regulation of TRAIL/DR5, dual AKT/ERK pathway inhibition, and promotion of an integrated stress response. Select neuroendocrine tumors are known to secrete dopamine and harbor elevated DRD2 expression, which is most pronounced in pheochromocytoma-paraganglioma (PC-PG). **Methods:** This investigator-initiated single center trial (NCT03034200) enrolled 10 patients with metastatic PC-PG to cohort A and 12 patients with other neuroendocrine tumors to cohort B. The primary endpoint was response using MRI or CT, PET-CT and/or PET-MRI imaging defined as CR + PR + SD $>$ 3 months by RECIST criteria assessed by investigator. Secondary endpoints included progression-free survival, overall survival and safety. ONC201 was administered at 625 mg by oral capsules once each week. CT scans and tumor markers (plasma chromogranin and metanephrines) were followed at 6 weeks, 3 months and then every 3 months. Patients with clinical benefit could receive stereotactic body radiotherapy (SBRT) for non-indicator (e.g. bone) metastases. The data cutoff for this analysis is December 1, 2020. **Results:** In Arm A (n = 10; all paraganglioma) 5 patients exhibited a PR and 2 additional patients exhibited SD $>$ 3 months. Median duration of therapy for patients was 9 months (range: 1.5-33) with 5 patients $>$ 1 year. In Arm B (n = 12) there were 1 PR and 2 SD $>$ 3 months. Median duration of therapy was 3 months (range: 1-33). The partial response occurred in a patient with desmoplastic small round cell tumor who remains on treatment for $>$ 2 years. There was no instance of dose modification or discontinuation due to treatment-related adverse events. **Conclusions:** ONC201 is well tolerated at 625mg weekly in adults with advanced neuroendocrine tumors and is associated with clinical benefit that includes tumor response, particularly in paraganglioma patients. A more intense schedule of 2 daily doses each week is under evaluation, in addition to other neuroendocrine tumors. Clinical trial information: NCT03034200. Research Sponsor: Anderson Sarcoma Research Funds (T56428).

3003 **Oral Abstract Session**

Efficacy and safety of zenocutuzumab in advanced pancreas cancer and other solid tumors harboring NRG1 fusions. *First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: NRG1 fusion proteins are oncogenic drivers in pancreas cancer and other solid tumors. They bind HER3, leading to HER2/HER3 heterodimerization and oncogenic transformation. The activity of zenocutuzumab (MCLA-128; zeno), a bispecific antibody targeting NRG1 fusion signaling in *NRG1* fusion positive (*NRG1+*) cancers, is being evaluated in the ongoing global multicenter phase 2 part of the eNRGy study and a global early access program (EAP). **Methods:** Enrolled patients (pts) have advanced *NRG1+* pancreas cancer, non-small cell lung cancer (NSCLC), and other solid tumors previously treated with standard therapy, are $\geq$ 18 years-old, have ECOG $\leq$1, adequate organ function, and measurable disease (RECIST v1.1). Zeno dosing: 750 mg IV every 2 weeks until progression or unacceptable toxicity. Primary endpoint: investigator (INV)-assessed objective response rate (ORR). Secondary endpoints: ORR per central independent radiologist review, duration of response (DOR), and safety. Tumor imaging is conducted every 8 weeks. **Results:** 51 pts with *NRG1+* cancer have received zeno, 37 in the eNRGy study and 14 pts in the EAP. As of 12 Jan 2021, treatment is ongoing in 27/51 pts (8/13 pancreas, 10/25 NSCLC, 9/13 other solid tumors). Among the 51 pts, 10 pts with pancreas cancer, 18 pts with NSCLC, and 5 pts with other solid tumors had measurable disease and had the opportunity for $\geq$1 tumor assessment (TA) and are included in this analysis. Among the 10 pts with pancreas cancer, median age was 49 y (range 34-72), 50% were male, 6/4 pts had ECOG 0/1, and all had metastatic disease and were *KRAS* wild-type. The median number of prior therapies was 3 (range 1-6). The INV-assessed confirmed ORR was 40% (4/10; 90% CI, 15;70), and for this cohort of pts, responses occurred at the first TA. Tumor regression was seen in 7/10 pts, and the disease control rate was 90% (90% CI, 61-100). A CA 19-9 decline of $\geq$ 50% was observed in 9/9 (100%) pts. DOR is pending. In the overall *NRG1+* population, tumor regression was observed in 25 of 33 pts and confirmed INV-assessed responses were seen in 9 of 33 pts (ORR 27%; 90% CI, 15;43), including in pts who previously received afatinib. Zeno was well tolerated with no pts requiring dose reduction for toxicity. Across all cohorts, for individual AEs, grade 3 events were reported in $\leq$5% of pts, and there was a notable lack of cardiotoxicity and severe gastrointestinal or skin toxicity. Updated data from all cohorts (pancreas, NSCLC, other solid tumors) will be presented. **Conclusions:** Zeno induces rapid and major radiologic tumor regression and biomarker responses in heavily-pretreated metastatic *KRAS* wild-type *NRG1+* pancreas cancer, with minimal toxicity. Zeno is a promising novel targeted therapeutic option for pts with *NRG1+* cancers. Clinical trial information: NCT02912949. Research Sponsor: Merus NV.

3004 **Oral Abstract Session**

MyPathway HER2 basket study: Pertuzumab (P) + trastuzumab (H) treatment of a large, tissue-agnostic cohort of patients with HER2-positive advanced solid tumors. *First Author: Funda Meric-Bernstam, Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *HER2* (*ERBB2*) amplification and/or overexpression is observed in 2–3% of solid tumors, and is often associated with more aggressive disease. Thus far, HER2-targeted therapies are FDA-approved only for breast, gastric, and gastroesophageal cancers. MyPathway (NCT02091141) is a non-randomized, phase 2a multi-basket study assessing the activity of FDA-approved targeted therapies in non-indicated advanced solid tumors with relevant molecular alterations. We report results from the MyPathway HER2 basket, comprising a large, tissue-agnostic cohort of patients (pts) with HER2-altered tumors treated with P + H. **Methods:** Pts in this analysis were aged ≥18 years and had HER2-amplified and/or overexpressed tumors. Pts received P (840-mg IV loading dose, then 420-mg every 3 weeks [q3w]) + H (8-mg/kg IV loading dose, then 6-mg/kg q3w). The primary efficacy endpoint was investigator-assessed objective response rate (ORR). Other endpoints included disease control rate (DCR, defined by objective response or stable disease >4 mos) and duration of response (DOR). Subgroup analyses were completed by tumor type and *KRAS* status. **Results:** Pts were fully enrolled from April 14, 2014 to June 15, 2020. By January 22, 2021, 260 pts were efficacy-evaluable. Confirmed ORR (cORR) was 23.1% (60/260, including 5 complete responses; 95% confidence interval [CI] 18.1–28.7), DCR was 44.2% (115/260, 95% CI 38.1–50.5), and median DOR was 7.9 mos (95% CI 6.2–9.3). In 199 pts with wild-type *KRAS* tumors, cORR was 25.6% (51/199, 95% CI 19.7–32.3), DCR was 48.7% (97/199, 95% CI 41.6–55.9), and median DOR was 8.3 mos (95% CI 6.2–10.8). In comparison, in 26 pts with *KRAS*-mutated tumors, cORR was 3.8% (1/26, responder had colorectal cancer; 95% CI 0.1–19.6), DCR was 3.8% (1/26, 95% CI 0.1–19.6), and DOR was 2.7 mos. *KRAS* status was unknown in 35/260 pts (cORR 22.9% [8/35, 95% CI 10.4–40.1]; median DOR 6.7 mos [95% CI 2.5–12.7]). Clinical outcomes by tumor type are shown in the Table. **Conclusions:** P+H was active in a wide variety of *KRAS* wild-type HER2-amplified/overexpressed tumor types, but had limited activity in *KRAS*-mutated tumors. Clinical trial information: NCT02091141. Research Sponsor: F. Hoffmann-La Roche/Genentech.

Tumor type	cORR n/n (%) 95% CI	cORR: KRAS WT n/n (%) 95% CI	DOR: KRAS WT Median mos 95% CI
Colorectal	22/84 (26.2)	21/68 (30.9)	5.9
n=84	17.2–36.9	20.2–43.3	4.2–8.5
Biliary	9/40 (22.5)	9/35 (25.7)	8.5
n=40	10.8–38.5	12.5–43.3	7.0–18.9
Non-small cell lung	7/27 (25.9)	5/20 (25.0)	8.3
n=27	11.1–46.3	8.7–49.1	5.6–not evaluable [NE]
Uterine	1/23 (4.3)	1/16 (6.3)	15.4 (1 responder)
n=23	0.1–21.9	0.2–30.2	
Urothelial	4/22 (18.2)	3/18 (16.7)	24.2
n=22	5.2–40.3	3.6–41.4	7.9–44.9
Salivary	11/18 (61.1)	7/11 (63.6)	8.4
n=18	35.7–82.7	30.8–89.1	6.9–NE
Ovarian	1/12 (8.3)	1/10 (10.0)	6.9 (1 responder)
n=12	0.2–38.5	0.3–44.5	
Pancreas	1/10 (10.0)	1/3 (33.3)	19.3 (1 responder)
n=10	0.3–44.5	0.8–90.6	
Other	4/24 (16.7)	3/18 (16.7)	11.3
n=24	4.7–37.4	3.6–41.4	9.3–20.7

3005 **Oral Abstract Session**

Initial results from a dose finding study of TNO155, a SHP2 inhibitor, in adults with advanced solid tumors. *First Author: Irene Brana, Vall d'Hebron University Hospital, Vall d'Hebrón Institute of Oncology, Barcelona, Spain*

Background: SHP2 transduces signals from activated receptor tyrosine kinases to downstream pathways including MAPK. TNO155 is a selective, allosteric, oral inhibitor of SHP2. **Methods:** CTNO155X2101 (NCT03114319) is an ongoing first-in-human, open-label dose escalation/expansion trial of TNO155 in adults with advanced solid tumors. The primary objective is to characterize the safety and tolerability of TNO155 and identify regimen(s) for future study. Secondary assessments included pharmacokinetics, pharmacodynamics, and preliminary clinical efficacy. Here we present data from TNO155 single agent escalation. **Results:** As of 10/26/2020, 118 patients received TNO155 in variable schedules: once (QD; 1.5–70 mg; n = 55) or twice daily (BID; 30–50 mg; n = 25) in a 2 weeks on/1 week off (2w/1w) cycle; or QD in a 3w/1w cycle (30–60 mg; n = 32), or continuously (40 or 50 mg QD; n = 6). The most common cancer diagnoses treated were colorectal (54%), gastrointestinal stromal tumor (16%), non-small cell lung (12%), and head & neck (8%). The median number of prior antineoplastic therapies was 4 (range 1–10). Overall 109 patients (92%) have discontinued study treatment, 94 (80%) for progressive disease and 6 (5%) for adverse events (AEs). TNO155 showed rapid absorption (median day 1 T_{max} ~1.1 hours), an effective median $T_{1/2}$ of ~34 hours, and near dose-proportional exposure at day 14 (power model: AUC_{τ} beta = 1.09 [90% CI 1.02–1.16]). AEs were mostly Grade 1/2 and generally consistent with on-target effects of SHP2 inhibition. The most common treatment-related AEs (all grades) were increased blood creatine phosphokinase (n = 33, 28%), peripheral edema (n = 31, 26%), diarrhea (n = 31, 26%), and acneiform dermatitis (n = 27, 23%). The most common treatment-related Grade ≥3 AEs were decreased platelets (n = 5, 4%), increased aspartate aminotransferase, diarrhea, and decreased neutrophils (each n = 4, 3%). The best observed response was stable disease (SD) per RECIST 1.1, reported in 24 (20%) patients, with a median duration of SD of 4.9 months (range 1.7–29.3). Evidence of SHP2 inhibition, as measured by change in *DUSP6* expression by qPCR in paired pre- vs. on-treatment tumor samples, was seen in the majority of patients treated with TNO155 doses ≥20 mg/day (≥25% reduction, 38/42 [90%]; ≥50% reduction, 25/42 [60%]). Analysis of tumor whole-transcriptome RNA sequencing data is ongoing. **Conclusions:** TNO155 shows favorable pharmacokinetic properties and promising early safety and tolerability data at doses with evidence of target inhibition. The optimal dose using several schedules is still under evaluation. Studies of TNO155 in combination with other agents, including nazartinib (mutant-selective EGFR inhibitor[i]), adagrasib (KRAS G12Ci), spartalizumab (anti-PD-1 antibody), ribociclib (CDK4/6i), and dabrafenib (BRAFi) with LTT462 (ERKi), are ongoing (NCT03114319, NCT04330664, NCT04000529, NCT04294160). Clinical trial information: NCT03114319. Research Sponsor: Novartis.

3006 **Oral Abstract Session**

First-in-human phase I/II study of CYT-0851, a first-in-class inhibitor of RAD51-mediated homologous recombination in patients with advanced solid and hematologic cancers. *First Author: Ryan Lynch, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Homologous recombination (HR) is an essential, high-fidelity mechanism to repair DNA double strand breaks (DSBs). Inhibition of HR in cancer cells leads to accumulation of unrepaired DSBs and tumor cell death. This is the first reporting of the first-in-human study of CYT-0851, an oral, first-in-class, small molecule inhibitor of RAD51-mediated DNA repair. **Methods:** Patients (pts) with advanced hematologic and solid tumors were treated with continuous 28-day cycles of increasing doses of CYT-0851 with an accelerated titration and 3+3 trial design. Primary objectives included safety, maximum tolerated dose (MTD), recommended Phase 2 dose (RP2D) (Phase 1), and antitumor activity (Phase 2). Secondary and exploratory objectives included pharmacokinetics (PK), pharmacodynamics (PD) and predictive biomarkers of response. **Results:** As of an 8 Dec 2020 data cutoff (DCO), 23 pts with advanced cancers (Sarcoma n = 8, Breast n = 4, Non-Hodgkin's Lymphoma n = 5; Pancreas n = 3; Ovarian n = 2; mucoepidermoid carcinoma n = 1) were enrolled in 6 cohorts (15 mg, 20 mg, 30 mg, and 45 mg BID; 90 mg and 130 mg QD). No pts experienced a dose-limiting toxicity and escalation continues per protocol to identify the MTD. 6 pts (26.1%) experienced a CYT-0851-related adverse event with only Gr 1/2 nausea (n = 3, 13%) and constipation (n = 2, 8.7%) occurring in > 1 pt. There has been no reported CYT-0851-related myelosuppression, serious adverse events, study discontinuation, or death. Preliminary PK analyses showed dose proportional systemic exposure with a half-life of ~3 days supporting transition from BID to QD dosing. PD effects were observed with increases in γH2AX in on-treatment circulating tumor cells compared to baseline at exposures associated with preclinical anti-tumor activity. Ten pts were response evaluable prior to the DCO. Two partial responses by Lugano and RECIST v1.1 criterion were achieved in pts with DLBCL (-74%) and myxofibrosarcoma (-30%) at 45 mg BID with treatment ongoing at 126+ and 250+ days. An additional two pts, with pancreatic cancer (-19%) and follicular lymphoma (-42%) had stable disease with tumor shrinkage at 45 mg BID for 111 and 99+ days. **Conclusions:** CYT-0851, a first-in-class inhibitor of RAD51-mediated HR, is well tolerated, with linear PK, target-directed PD effects and promising antitumor activity across different tumor types. CYT-0851 is the first DNA-damage repair (DDR) therapeutic with demonstrated clinical activity in both hematologic malignancies and solid tumors. Dose escalation continues to establish the RP2D, with planned expansion in 7 disease-specific cohorts in hematologic and solid cancers. Clinical trial information: NCT03997968. Research Sponsor: Cyteir Therapeutics.

3007 **Oral Abstract Session**

A phase Ib trial of belvarafenib in combination with cobimetinib in patients with advanced solid tumors: Interim results of dose-escalation and patients with NRAS-mutant melanoma of dose-expansion. *First Author: Sang Joon Shin, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*

Background: Belvarafenib, a potent, selective RAF dimer (type II) inhibitor, exhibits clinical activity in $BRAF^{V600E}$- and NRAS-mutant (NRASm) melanoma patients. The combination of belvarafenib and cobimetinib more potently and durably suppressed MAPK pathway output and tumor growth than currently approved BRAF/MEK inhibitors in RAS- or RAF-mutant tumor xenograft models. This interim results of phase 1b trial evaluated the safety, tolerability, pharmacokinetics, and anti-tumor activity of belvarafenib in combination with cobimetinib in dose-escalation and NRASm melanoma patients among the 9 indication-specific expansion cohorts. **Methods:** Patients with locally advanced or metastatic solid tumors harboring RAS or RAF mutation were enrolled in the dose-escalation stage, and the recommended doses were explored in the indication-specific expansion stage. Patients in the dose-escalation stage were given belvarafenib (100–300mg BID) in combination with cobimetinib (20–40mg QD) and the dose of subsequent cohorts was decided by a traditional 3+3 design and safety profile. Primary objectives were to evaluate the safety and tolerability, to estimate the maximum tolerable dose, and to identify the RP2D of the combination. **Results:** A total of 32 patients enrolled were evaluated for safety analysis; 19 were enrolled in 4 cohorts in the dose-escalation stage and 13 NRASm melanoma patients were enrolled in the indication-specific expansion stage (cut-off date: 2020-7-24). There were 3 DLTs (G3 colitis, G3 diarrhoea, G3 nausea) in 2 patients at the starting dose of belvarafenib 200mg BID continuously and cobimetinib 40mg QD 21/7 schedule. Belvarafenib dose was escalated to 300mg BID with cobimetinib 20mg QD, which did not result in DLTs. The most common treatment-emergent adverse events that occurred in ≥30% of 32 patients were dermatitis acneiform, diarrhoea, constipation, and increase in blood creatine phosphokinase. Two combination doses were explored in the indication-specific expansion stage. Out of the 9 indication-specific expansion cohorts, NRASm melanoma patients exhibited promising efficacy signal; 5 patients reached partial responses (PRs) out of 13, giving a response rate of 38.5%. Among them, 11 had been previously treated with checkpoint inhibitors (CPIs), including 5 (45.5%) who achieved PR. The median PFS was 7.3 months and 5 patients remained on the treatment at the cut-off date. **Conclusions:** Belvarafenib in combination with cobimetinib showed acceptable tolerability and encouraging efficacy in NRASm melanoma, and in those with prior CPI treatment. Further research is ongoing in other cohorts (Clinicaltrial.gov, NCT03284502) and in NRASm melanoma (reference GO42273 by clinicaltrials.gov ID number). *S.J.S and J.L contributed equally to this work. Clinical trial information: NCT03284502. Research Sponsor: Hanmi Pharm.

3008 **Oral Abstract Session**

BOS172738, a highly potent and selective RET inhibitor, for the treatment of *RET*-altered tumors including *RET*-fusion+ NSCLC and *RET*-mutant MTC: Phase 1 study results. *First Author: Patrick Schoffski, Department of General Medical Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium*

Background: *RET* (REarranged during Transfection) gene alterations (mutations and fusions) leading to constitutive kinase activity are identified as drivers of disease progression in multiple tumor types, including non-small cell lung cancer (NSCLC) and medullary thyroid cancer (MTC). BOS172738 is an investigational, potent, selective oral RET kinase inhibitor. This next-generation inhibitor was designed with nanomolar potency against RET and >300-fold selectivity against vascular endothelial growth factor receptor 2, to maximize the potential therapeutic window. **Methods:** NCT03780517 is a phase 1 study consisting of a dose-escalation and dose-expansion phase. During the escalation, 67 patients with *RET*-altered advanced solid tumors received once-daily oral doses of BOS172738 (10-150 mg). Intra-patient dose escalation was allowed as was over-accrual to dose levels deemed to be safe. Study endpoints were safety (CTCAE v. 4.03), tolerability and confirmed overall response rate (ORR; RECIST 1.1). The data cutoff was Dec. 11, 2020. **Results:** BOS172738 exhibited a favorable safety profile (n=67) for long-term administration with most treatment-emergent adverse events (TEAEs) classified as grade ≤2 and deemed unrelated to drug. The most common TEAEs were creatinine phosphokinase (CPK) increase (54%), dyspnea (34%), facial edema, aspartate aminotransferase elevation, anemia (25% each), neutropenia, diarrhea (22% each), fatigue (21%), and constipation (20%). BOS172738 was not associated with hypertension or significant hepatoxicity. BOS172738 demonstrated broad anti-tumor activity with an investigator-assessed ORR of 33% (n=18/54), a NSCLC ORR of 33% (n=10/30), MTC ORR of 44% (n=7/16, including 1 complete response) and one patient with *RET* fusion+ pancreatic cancer reported a partial response. Responders included patients with brain metastases with one patient whose brain lesion decreased by 43%. The median duration of response has not been reached. Many patients remain on study, including the longest of 659 days, at data cutoff. BOS172738 exhibited dose-dependent exposure (AUC, C_{max}), rapid absorption (median T_{max} 1 to 4.5 h), and an extended half-life (approximately 65 hours) maximizing target coverage. **Conclusions:** BOS172738 is a highly potent and selective RET inhibitor with a differentiated safety profile and clinical activity against *RET*-altered tumors, including patients with brain metastases. BOS172738 continues to be evaluated in patients with NSCLC, MTC, and in patients previously treated with other selective *RET* inhibitors. Clinical trial information: NCT03780517. Research Sponsor: Boston Pharmaceuticals.

3009 **Poster Discussion Session**

Prevalence of inferred clonal hematopoiesis (CH) detected on comprehensive genomic profiling (CGP) of solid tumor tissue or circulating tumor DNA (ctDNA). *First Author: Emmanuel S. Antonarakis, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: The increased use of ctDNA CGP has paralleled increased detection and interest in CH, which can confound CGP results from ctDNA or tissue, and can be associated with hematologic and cardiovascular morbidity. However, paired-depth sequencing of white blood cells (WBC) for confirmation of CH is not widely available. We here study the prevalence of inferred CH (iCH), which refers to incidental detection on routine clinical CGP of variants attributable to CH due to their known CH association and their negligible prevalence in solid tumors. **Methods:** A database of clinical CGP results was reviewed, including two 324-gene NGS panels for tumor tissue (FoundationOne CDx) and plasma ctDNA (FoundationOne Liquid CDx). Analysis was limited to NSCLC, breast, prostate, colorectal, and pancreatic cancers. iCH was defined as any pathogenic mutation in *ASXL1*, *DNMT3A*, and *TET2*, and prespecified mutations in *JAK2*, *SF3B1*, *U2AF1*, *MYD88*, *IDH2*, *MPL*, *CBL*. Variant allelic frequency (VAF) > 2% was considered clinically significant and VAF > 10% was considered high risk. **Results:** 100,905 total cases were studied; median age was 65 for tissue CGP and 68 for ctDNA. iCH was more commonly detected in ctDNA (1468/2891, 51%) than in tissue (9416/97993, 10%). Among cases with any iCH detected, multiple iCH mutations were seen more commonly in ctDNA (640/2891, 22%) than in tissue (987/98014, 1%). Focusing on clinically significant iCH (> 2% VAF), prevalence remained higher in ctDNA (22%, 637) than in tissue (8%, 7878), while the higher sensitivity of ctDNA testing identified more low level iCH (< 2% VAF, 40% in ctDNA, 2% in tissue). Across cancer types, iCH > 2% was consistently more common in ctDNA (Table). As expected, prevalence of iCH > 2% increased with age (continuous variable, $p < 0.001$). High risk iCH (> 10% VAF) was seen in 4% of total cases (most commonly *ASXL1*, *TET2*, *DNMT3A*); 1% of all cases had multiple clinically significant iCH variants (> 2% VAF). Focusing on a subset of 439 cases with both tissue and ctDNA results (median 1.5 months between samples), 290 iCH mutations were detected in ctDNA (median VAF 1%) but only 38 in tissue (median VAF 9%). **Conclusions:** Inferred CH is common on somatic CGP of cancer patients, with a high prevalence in ctDNA likely due to the deeper sequencing depth and WBC contamination. For the minority of patients with high VAF iCH, further research is needed to understand whether this might be representative of an occult hematologic condition deserving of further evaluation. Research Sponsor: Foundation Medicine, Inc.

	Tissue				Liquid			
	N	Median age	iCH	iCH 2% VAF	N	Median age	iCH	iCH 2% VAF
NSCLC	34536	68	4486 (13%)	3698 (11%)	1386	70	753 (54%)	351 (25%)
CRC	23360	61	1959 (8%)	1712 (7%)	433	63	168 (39%)	65 (15%)
Breast	19260	59	1211 (6%)	998 (5%)	372	64	180 (48%)	68 (18%)
Pancreatic	12176	66	1094 (9%)	909 (7%)	231	67	99 (43%)	35 (15%)
Prostate	8682	67	666 (8%)	560 (6%)	469	74	268 (57%)	118 (25%)

3010 **Poster Discussion Session**

Interim results of PATHFINDER, a clinical use study using a methylation-based multi-cancer early detection test. *First Author: Tomasz M. Beer, Knight Cancer Institute, Oregon Health & Science University, Portland, OR*

Background: PATHFINDER (NCT04241796) is an interventional, prospective study evaluating implementation of a blood-based multi-cancer early detection (MCED) test that uses targeted methylation-based cfDNA analysis to detect multiple cancer types and simultaneously predict cancer signal origin (CSO). We present a prespecified interim analysis of PATHFINDER evaluating an MCED test in a clinical setting. **Methods:** Participants (pts; ≥50y) were enrolled into 2 risk cohorts: non-elevated and elevated (smoking history, prior cancer [> 3y post treatment], or genetic predisposition). MCED test results (cancer signal detected/not detected) were returned to investigators; pts with a signal detected also received a CSO prediction and underwent further diagnostic testing by their medical team. The primary objective was to assess the extent of diagnostic testing needed to achieve diagnostic resolution (eg, time to resolution, number/type of tests). Secondary endpoints included positive predictive value (PPV) and a measure of test satisfaction (following diagnostic resolution [signal detected] and post test [signal not detected]). **Results:** PATHFINDER consented 6796 pts before closing accrual on 12/4/20; as of October 6, 2020, 4086 consented, 4047 enrolled, and 4033 analyzable pts were included in the interim analysis (62.4% female, 92.1% white). Two study-related adverse events (anxiety of mild severity) were reported. Cancer signal was detected in 1.5% (62/4033) of pts; 40/62 reached diagnostic resolution to date. Kaplan-Meier estimate of median time to resolution was 78 (95% CI, 54-151) days. Among 40 pts that reached diagnostic resolution, ≥1 imaging test was performed in 93% (37/40); ≥1 invasive procedure was performed in 72% (13/18) versus 18% (4/22) of pts with diagnostic resolution of cancer versus no cancer, respectively. Based on results to date, PPV was 45% (95% CI, 30.7-60.2%; 18/40). Of 18 cancer diagnoses, 11 were solid tumors (3 stage IV, 6 stages I-III, 1 metastatic recurrence, 1 missing stage), and 7 were hematologic malignancies (1 stage IV, 4 stages I-III, 2 without AJCC stage). Accuracy of the top CSO prediction in true positives was 82.4% (95% CI, 59.0-93.8%; 14/17). Most pts were satisfied with the test (43.7% extremely satisfied, 30.7% very satisfied, 14.6% satisfied). Signal detection rate and test satisfaction were similar in the 2 risk cohorts; PPV tended to be higher in the elevated risk cohort, as expected. **Conclusions:** An interim analysis of this return of results study demonstrated promising MCED test results. Of 40 pts achieving diagnostic resolution, nearly half had a diagnostic workup confirming cancer; CSO was predicted with high accuracy for detected cancers. Taken together with the rarity of adverse events and high test satisfaction, these results support the feasibility of clinical implementation. Full enrollment cohort data will be available at the meeting. Clinical trial information: NCT04241796. Research Sponsor: GRAIL, Inc.

3011 **Poster Discussion Session**

Circulating tumor DNA to investigate resistance mechanism and clone evolution of ALK TKI treated lung adenocarcinoma. *First Author: Gang Hua, Department of Cardiothoracic Surgery, HwaMei Hospital, University of Chinese Academy of Sciences, Ningbo, China*

Background: Sequential treatment with first-, second-generation ALK TKI followed by third-generation TKI (lorlatinib) have been widely applied to *ALK*-positive lung cancer. However, acquired resistance is often driven by secondary *ALK* mutations, which are needed to be further explored. Circulating tumor DNA, a non-invasive approach, can detect tumor-derived DNA from multiple metastatic sites and has become a promising strategy for assessing the genetic evolution of tumors and analyzing TKI resistance. **Methods:** Post-progression plasma specimens were collected and sequenced with a targeted gene panel from a total of 116 patients underwent *ALK* TKI treatment with from February 2014 to April 2020. The ALK TKIs administrated in this cohort included crizotinib (first-generation), ceritinib (second-generation), alectinib (second-generation), brigatinib (second-generation), ensartinib (second-generation) and lorlatinib (third-generation). **Results:** In this *ALK*-positive lung adenocarcinoma cohort, 49.1% were female and the rest were male with a median age of 52 (range 20 to 79). More than half of patients received more than one line of ALK TKI treatment. The most frequent *ALK* fusion type is *EML4-ALK* including *EML4-ALK* v1(E13; A20, 37/116, 31.9%) and *EML4-ALK*v3(E6a/b; A20, 49/116, 42.2%). *TP53* (29.1%, 41/141) was the most frequently mutated gene other than *ALK*. Frequently identified secondary mutations in patients progressing on *ALK* inhibitors were *ALK* mutations L1196M and G1202R. *ALK* G1202R was more common in patient with v3 fusion than in v1 (25.8% vs 0%; P< .001) while *ALK* L1196M was more common in v1 than in v3 (20.8% vs 3.2%; P= .005). Meanwhile, G1202R was identified at higher ratio in patients progressed on second-generation ALK TKI than first- and third-generation ALK TKI (11.3% vs 0% and 9.1%) whereas L1196M was more found in patients progressed on first-generation ALK TKI (9.1% vs 1.9% and 4.5%). Other identified secondary mutations were *ALK* F1174C/V/L, E1210K/Q, D1269A, D1203N and L1122M/V. Compound *ALK* mutations (≥2 concurrent *ALK* mutations) were more common in patients relapsed on third-generation ALK TKI lorlatinib (36.4%) compared to first- (12.1%) and second-generation (20.8%) ALK TKIs. Using serial plasma specimens, clone evolution analysis showed that five patients developed compound *ALK* mutations after sequential ALK TKI treatments and two novel *ALK* compound lorlatinib-resistant mutations D1203N+I1171N and F1174C+G1202R were identified. **Conclusions:** Genotyping of sequential post-progression plasma specimens reveals that treatment with sequential first-, second-, and third-generation ALK inhibitors can accelerate the accumulation of ALK resistance mutations and may lead to treatment-refractory compound ALK mutations. The selection for optimal first-line TKI is very important to achieve a more efficacious long-term strategy and prevent the emergence of on-target resistance. Research Sponsor: None.

3012 **Poster Discussion Session**

BRCA reversion mutations in a pan-cancer cohort to reveal _BRCA_-dependence in select noncanonical _BRCA_-mutant histologies. *First Author: Yonina R. Murciano-Goroff, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Loss of *BRCA1/2* function leads to homologous recombination deficiency (HRD) and can enhance platinum and PARP inhibitor sensitivity in breast, pancreas, prostate, and ovarian cancers. In *BRCA*-associated cancers, resistance can result from the development of *BRCA1/2* reversion mutations, which restore *BRCA1/2* function. By contrast, a *BRCA* mutation may be an incidental finding in other tumor histologies. **Methods:** To determine the distribution of reversion mutations in a pan-cancer cohort, the MSK-IMPACT clinical sequencing cohort was mined to identify patients who had both a germline *BRCA1/2* mutation and a frameshift somatic reversion mutation that restored *BRCA1/2* function. Whole exome resequencing was used to detect HRD signatures. Chart review enabled collection of data on treatment history in patients consented to germline testing. **Results:** Of the 33,277 patients with matched tumor and normal sequencing profiled in this study, 861 patients were found to have germline pathogenic *BRCA1/2* alterations, including 347 (40%) in *BRCA1* and 514 (60%) in *BRCA2*. Somatic *BRCA1/2* driver alterations were also found in tumor tissue from an additional 447 patients, with 156 (35%) having *BRCA1* mutations, and the remainder having alterations in *BRCA2* (65%). Among the 1,308 germline or somatic *BRCA1/2* mutant tumors, we identified reversion mutations in 12 patients, all of whom were germline carriers of *BRCA1/2*, comprising 3 *BRCA1* and 9 *BRCA2* tumors. 7 patients consented to germline testing enabling review of clinical characteristics and treatment history, 5 of whom received PARP inhibitor or platinum-therapy prior to reversion detection. Ten of 12 tumors with reversion mutations were in canonical *BRCA*-associated cancers. Interestingly, reversion mutations were also found in patients with lung adenocarcinoma (n=1) and gastroesophageal junction adenocarcinoma (n=1). In both these non-canonical histologies, the reversion was detected following progression on platinum-based therapy. Whole exome resequencing of the lung tumor revealed the classic somatic molecular phenotypes of HRD that are characteristic of *BRCA*-dependent tumors, including in terms of large-scale transitions, HRD-loss of heterozygosity, signature 3, and the number of telomeric allelic imbalance score. **Conclusions:** Matched tumor and normal sequencing from a large cohort of patients with diverse cancer histologies reveals that reversion mutations are found across *BRCA*-associated cancer types. In rare cases, reversionmutations in *BRCA1/2* following platinum-based therapy may be indicative of prior *BRCA*-dependence in select non-canonical tumor histologies. Research Sponsor: U.S. National Institutes of Health.

3013 **Poster Discussion Session**

Feasibility of whole-genome sequencing in routine clinical practice. *First Author: Kris Samsom, Netherlands Cancer Institute, Department of Pathology, Amsterdam, Netherlands*

Background: In the next few years numerous drugs will be approved for defined genomic targets, most of these in a tumor agnostic manner. Identifying patients who can benefit from this is critical for the future success of precision medicine, ideally using a single comprehensive test to detect all possible biomarkers. The WIDE study (WGS Implementation in standard cancer Diagnostics for Every cancer patient) aimed to evaluate the feasibility, clinical validity (primary endpoints) and added value (secondary endpoint) of clinical grade Whole Genome Sequencing (cWGS) in routine clinical practice. **Methods:** cWGS was prospectively performed on 1,200 consecutive patients with (suspected) metastatic cancer. Tumor material was obtained during routine clinical procedures for both Standard-Of-Care (SOC) and cWGS. Next to securing a high quality specimen for SOC diagnostics, multiple frozen sections per patient were evaluated to identify the sample most suitable for WGS. cWGS was conducted independently of, but in parallel with SOC diagnostics, which included SOC molecular diagnostics (MolDx) for 48% of patients. cWGS and MolDx results were compared and discussed in a dedicated tumor board. Additional tests for resolving discordances were applied when needed. **Results:** cWGS was successfully performed in 69% (841/1217) of samples with a technical success rate of 97% (841/871). An insufficient amount of tumor cells ($< 20\%$) was the main reason for not completing cWGS (25%, 310/1217). cWGS turn-around-time (TAT), due to continuous improvements to the clinical procedure and cWGS pipeline over the course of the study, decreased to 10 working days. A total of 856 genomic biomarkers identified by SOC MolDx could be compared to cWGS results. Initial analyses of discordances revealed an error rate of 2.1% (18/856) for cWGS compared to a 1.0% (8/856) error rate for SOC MolDx. After optimizing cWGS and SOC pipelines based on these findings, error rates dropped to 0.6% (5/856) and 0.7% (6/856) for cWGS and SOC MolDx, respectively. Overall, cWGS identified clinically actionable (routine practice and experimental) biomarkers in 71% of all patients tested. Compared to SOC MolDx, cWGS identified one or more additional clinically actionable biomarkers in 54% (446/832) of patients. Interestingly, in patients who were not tested by SOC MolDx, actionable variants were identified by cWGS in 54% (153/282). **Conclusions:** The WIDE study has shown that cWGS is feasible in routine clinical practice in a comprehensive cancer center setting, using tumor material obtained during routine procedures. Furthermore, cWGS showed added value by identifying one or more additional clinically actionable biomarkers in 54% of patients including patients who had not received SOC MolDx. These outcomes have led to the successful adoption of cWGS at the Netherlands Cancer Institute as part of routine care, which will further facilitate precision medicine for cancer patients. Research Sponsor: The Netherlands Organisation for Health Research and Development, Hartwig Medical Foundation.

3014 **Poster Discussion Session**

Racial and ethnic disparities among participants in precision oncology clinical studies. *First Author: Christopher M. Aldrighetti, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA*

Background: Precision medicine has revolutionized oncologic care in the United States (US) in the past two decades. While the US cancer population is rapidly diversifying, enrollment of a diverse patient population into clinical trials lags behind. In particular, it is unclear whether minority patients are adequately represented in precision oncology trials. Herein, we report racial/ethnic representation in precision oncology studies spanning four common cancer types (breast, lung, prostate, colorectal cancers). **Methods:** Completed US clinical studies incorporating precision medicine objectives based on a set of 12 precision oncology search terms (including tumor biomarker, whole exome sequencing, tumor mutation testing, gene expression signatures, tumor microarray, tumor genomics, et cetera) were identified from Clinicaltrials.gov. Studies were reviewed for reporting race/ethnicity for inclusion in the analysis. The Surveillance, Epidemiology, and End Results (SEER) database was used to determine incidence of race/ethnicity in the US cancer population, correlated with disease site and median year of enrollment for each trial. The difference in incidence (D-I) was defined as the median absolute difference in study racial enrollment and SEER incidence, with a negative value corresponding to underrepresentation. Wilcoxon signed-rank test was used to compare median D-I to a value of 0 by racial/ethnic subgroups. **Results:** Overall, 156 studies were identified; 40.3 and 27.5% studies enrolling from 2000 through 2020 met the inclusion criteria for racial and ethnic subgroups reporting, respectively. Of 4,418 total enrollees, 82.5% were White, 10.5% Black, 3.8% Asian, and 0.4% American Indian/Alaskan Native (AIAN). Ethnically, 6.4% were Hispanic. The D-I was +2.2% for Whites (interquartile range (IQR) = -43.7% to 25.4%; $P < 0.013$), -0.74% AIAN (IQR = -0.8% to +5.9%; $P < 0.001$), -2.5% Asians (IQR = -4.1% to 30.4%; $P < 0.152$), -4.6% Blacks (IQR = -20.1% to +45.0%; $P < 0.001$), and -8.1% Hispanics (IQR = -14.8% to + 29.6%; $P < 0.001$). By disease site, Blacks were significantly underrepresented proportional to their cancer incidence among prostate (D-I of -11.8%, $p = 0.009$) and lung studies (D-I of -5.9%, $p = 0.013$), while prostate studies significantly overrepresented Whites (D-I +14.0%, $p = 0.005$). Lung studies overrepresented Asians (D-I +0.49%) consistent with the prominent role of targetable oncogene drivers in this population. **Conclusions:** Results demonstrate an underrepresentation of minority racial groups and an overrepresentation of Whites in precision oncology studies. Increased emphasis on equitable enrollment onto these studies is critical, as resulting precision Omic conclusions are used to stratify populations and personalize treatments. A continued lack of diversity among enrollees may further leave behind vulnerable minority populations in the era of precision oncology. Research Sponsor: None.

3015 **Poster Discussion Session**

A first-in-human study of mirzotamab clezutoclax as monotherapy and in combination with taxane therapy in relapsed/refractory solid tumors: Dose escalation results. *First Author: Anthony W. Tolcher, Next Oncology, San Antonio, TX*

Background: Mirzotamab clezutoclax (ABBV-155) is a first-in-class antibody drug conjugate comprised of a BCL-X_L (B-cell lymphoma - extra long) inhibitor, solubilizing linker, and a monoclonal anti-B7H3 antibody. **Methods:** Patients (pts) with relapsed and/or refractory (R/R) solid tumors were administered mirzotamab clezutoclax with or without paclitaxel. Dose escalation of mirzotamab clezutoclax was guided by Bayesian continual reassessment. Primary outcomes were to determine the maximum tolerated dose (MTD) and the recommended phase 2 dose (RP2D). Secondary outcomes: safety, pharmacokinetics, and overall response rate per RECIST v1.1. **Results:** As of November 6, 2020, 31 pts received mirzotamab clezutoclax monotherapy (monoTx) and 28 pts received combination therapy with paclitaxel (comboTx). Overall demographics: median age 62 years (range 25–79); 61% female; 86% white; 24% ECOG 0, 76% ECOG 1; 51% had > 3 prior systemic therapies. The median duration of mirzotamab clezutoclax exposure was 3 cycles (range 1–14) for monoTx and 5 cycles (range 1–14) for comboTx. There were no dose limiting toxicities (DLT) reported with monoTx. In comboTx, 2 pts experienced a DLT: Grade 4 neutrophil count decreased and Grade 3 lymphocyte count decreased considered related to paclitaxel. 97% of all pts had adverse events (AEs). The most common AEs (in $\geq$20% of pts) overall were fatigue (39%), nausea (25%), diarrhea and arthralgia (22% each), vomiting and hypokalemia (20% each). AEs in $\geq$5 pts related to mirzotamab cleuzutoclax were fatigue (27%), diarrhea (12%), and nausea (9%). Related Grade 3/4 AEs overall (in > 1 patient) included anemia, lymphocyte count decreased, fatigue, and diarrhea (3% each). One patient on monoTx experienced a fatal cardiac arrest. No fatal AEs occurred on comboTx. Responses were observed with comboTx as shown in the Table. **Conclusions:** Mirzotamab clezutoclax as monotherapy and with paclitaxel demonstrates a tolerable safety profile (MTD not reached) with anti-tumor activity in R/R solid tumors. Further investigation in prospectively-selected B7H3 positive tumors as monoTx in pts with R/R small cell lung cancer and with paclitaxel in pts with R/R breast cancer and docetaxel in pts with R/R non-small cell lung cancer in the dose expansion phase is ongoing. Clinical trial information: NCT03595059. Research Sponsor: AbbVie.

Efficacy, n (%)	MonoTx N = 31	ComboTx N = 28
Objective response (confirmed CR or PR) [95% CI]	0	4 (14%) [4–33%]
Clinical benefit rate (CR + PR + SD) [95% CI]	16 (52%) [33–70%]	19 (68%) [48–84%]
Best Response*:		
Partial response	0	6 (21%)
Stable disease	16 (52%)	13 (46%)
Progressive disease	12 (39%)	3 (11%)
Missing post-baseline assessment	3 (10%)	6 (21%)

CI, confidence interval; CR, complete response; PR, partial response; SD, stable disease.
*Best response includes unconfirmed responses.

3016 **Poster Discussion Session**

A phase I dose-escalation study of the MDM2-p53 antagonist BI 907828 in patients (pts) with advanced solid tumors. *First Author: Patricia LoRusso, Yale University School of Medicine, Yale Cancer Center, New Haven, CT*

Background: BI 907828, a highly potent and orally administered MDM2-p53 antagonist, showed antitumor efficacy *in vivo*, especially in *TP53* wild-type MDM2-amplified de-differentiated liposarcoma (DDLPS) patient-derived xenografts and syngeneic models. **Methods:** NCT03449381 is a phase I study of BI 907828 in pts with solid tumors. The objectives of the dose-escalation part were to determine the maximum tolerated dose (MTD) based on the frequency of pts with dose-limiting toxicities (DLTs) during cycle 1, determine the recommended dose for expansion, and evaluate the safety and tolerability of two dosing schedules: BI 907828 given on day 1 of 21-day cycles (Arm A) or days 1 and 8 of 28-day cycles (Arm B). Dose escalation was guided by a Bayesian logistic regression model. The secondary objectives include pharmacokinetics (PK), pharmacodynamics and antitumor activity. **Results:** At January 15, 2021, 54 pts with advanced solid tumors (median of 2 lines of prior systemic therapies; range 0–11) were treated with BI 907828 (Arm A, 29 pts, dose range 10–80 mg; Arm B, 25 pts, dose range 5–60 mg). In Arm A, 5 pts experienced DLTs in cycle 1, including one Grade (Gr) 3 Nausea and one Gr 3 Thrombocytopenia at 45 mg, one Gr 3 Enterocolitis at 60 mg, and one Gr 4 Neutropenia and one Gr 4 Thrombocytopenia at 80 mg. In Arm B, 3 DLTs were reported: one Gr 4 Thrombocytopenia at 45 mg, one Gr 4 Neutropenia associated with Gr 4 Thrombocytopenia, and one Gr 3 Neutropenia at 60 mg. The most common Gr 3/4 treatment-related adverse events (AEs) were Thrombocytopenia (28.6%), Neutropenia (10.7%) and Nausea (10.7%) in Arm A, and Thrombocytopenia (16.6%) and Neutropenia (12.5%) in Arm B. Preliminary PK data indicate that BI 907828 reaches T_{max} at 4–6 h. Mean plasma exposures (C_{max} and $AUC_{0\text{-}inf}$) increased with dose. The geometric mean (gMean) Clearance/F was 5–19 mL/min and the gMean apparent volume of distribution was 23–57 L. The gMean half-lives estimated after the 1st dose were 26–55 h. Inter-patient variability in exposure was moderate. An increase in the target engagement biomarker GDF-15 in plasma was observed. The mean fold-change from baseline ranged from 8 to 49. Antitumor activity was seen in both schedules. In Arm A, a confirmed PR was seen in 2 pts with MDM2-amplified LPS (one PR lasted $>$ 2 years) and SD in 17 pts. In Arm B, 2 pts had PR (one confirmed in MDM2-amplified LPS and one not yet confirmed in MDM2-amplified pancreatic adenocarcinoma) and 14 had SD. Of note, 5 of 10 pts with DDLPS were progression-free for $\geq$9 months. **Conclusions:** BI 907828 showed a manageable safety profile, favorable PK properties and early signs of efficacy, especially in MDM2-amplified tumors. With both dosing regimens, DLTs were Neutropenia and Thrombocytopenia. Non-hematologic AEs, mainly gastrointestinal, were mostly low-grade and not dose-limiting. The MTD of 60 mg in Arm A (day 1 of 21-day cycles) and 45 mg in Arm B (days 1 and 8 of 28-day cycles) are awaiting confirmation. Clinical trial information: NCT03449381. Research Sponsor: Boehringer Ingelheim.

3017 **Poster Discussion Session**

Phase I study of mTORC1/2 inhibitor sapanisertib (TAK-228) in combination with metformin in patients (pts) with *mTOR/AKT/PI3K* pathway alterations and advanced solid malignancies. *First Author: Niamh Coleman, The University of Texas MD Anderson Cancer Center, Houston*

Background: Sapanisertib (TAK-228) is a potent, selective ATP-competitive, dual inhibitor of mTORC1/2. Metformin is thought to inhibit the mTOR pathway through upstream activation of AMPK suggesting combination therapy may enhance anti-tumor activity of TAK-228. We report preliminary safety, tolerability and efficacy from the dose escalation study of sapanisertib in combination with metformin in patients with advanced solid tumors. **Methods:** Pts with advanced metastatic solid tumors resistant or refractory to standard treatment, with and without *mTOR/AKT/PI3K*pathway alterations, received sapanisertib 3mg or 4mg daily together with metformin once to three times daily(500mg - 1500mg). All patients underwent 14-day titration period for metformin in cycle 1. Tumor measurements were performed following cycle 2 and subsequently every 8 weeks. Data cut-off date was December 31 2020. **Results:** 30 pts were enrolled across 4 cohorts (3mg/500mg; 3mg/1000mg, 4mg/1000mg; 4mg/1500mg). 19 were female (63%), median age was 57 (range: 30–77), all were ECOG PS 1. Tumor types included sarcoma (6), breast (4), ovarian (4), head and neck (3), colorectal (2), lung (2), renal cell (2), endometrial (2), gastro-esophageal junction (1), prostate (1), stomach (1), urachus (1) and cervical cancer (1). Median number of prior lines of therapy was 4. Most common genomic alterations included *PIK3CA* (27%), *PTEN*(17%), *AKT1/2* (10%), *mTOR* (10%). Of 30 pts evaluable for response, 4 pts achieved partial response (PR); 14pts achieved stable disease (SD) as best response. Disease control rate (CR+PR+SD) was 60%. Of the responders in PR, 3/4pts had documented*PTEN*mutations (3/5 pts enrolled with*PTEN*mutation had PR); 2/4 of pts in PR had co-mutations (pt with leiomyosarcoma had both *PTEN*and *TSC*;pt with breast cancer had both *PTEN*and *STK11*); 1/4 pts in PR had *AKT*and *mTOR*mutation; tumor types included leiomyosarcoma (n = 2), breast (n = 1) and endometrial cancer (n = 1).Most common treatment-emergent adverse events included nausea, anorexia, diarrhea, and rash. Grade (G) 3-5 treatment-related adverse events included hyperglycemia (4/30; 13%) fatigue (2/30; 7%) hypertriglyceridemia (1/30; 3%) rash (2/20; 7%), diarrhea (2/30; 7%), creatinine increase (1/30; 3%), acidosis (1/30; 3%). No dose-limiting toxicities (DLTs) were reported in the 3mg/500mg cohort. 1/6 pt had DLT in the 3mg/ 1000mg cohort (G3 diarrhea) and 2/11pts had DLTs in the 4 mg/1500mg cohort (G3 fatigue, G3 rash). 4mg/1000mg was defined as the maximum tolerated dose. **Conclusions:** The safety profile of mTORC1/2 inhibitor sapanisertib in combination with metformin was generally tolerable, with anti-tumor activity observed in patients with advanced malignancies harboring *PTEN* mutations and *AKT/mTOR* pathway alterations. Clinical trial information: NCT03017833. Research Sponsor: None.

3018 **Poster Discussion Session**

Phase 1b/2a study of PLX2853, a small molecule BET inhibitor, in subjects with advanced solid tumors and lymphoma. *First Author: Michael S. Gordon, HonorHealth Research Institute, Scottsdale, AZ*

Background: PLX2853 is a potent, orally active small molecule BET inhibitor. Its unique pharmacokinetic (PK) profile is associated with less thrombocytopenia and improved tolerability by allowing transient target engagement with a prolonged pharmacodynamic (PD) response and time for recovery after dosing. **Methods:** We conducted a first-in-human 3+3 Ph1b/2a study of PLX2853 in adults with relapsed or refractory solid tumors and lymphoma to determine the safety, PK and recommended phase II dose (RP2D) (NCT03297424). Secondary endpoints included efficacy and PD. **Results:** As of 2 February 2021, 44 subjects (median age 65, range 39 - 84) received PLX2853 in escalating doses from 5mg to 120mg QD and 40mg to 60mg BID. Ovarian cancer (n = 11), uveal melanoma, colorectal, and prostate (n = 5 each) were the most represented tumor types. Adverse events (AE) occurring in $\geq$15% of subjects included nausea (41%), decrease appetite (39%), fatigue (27%), vomiting (25%), diarrhea (25%), dysgeusia (25%), dehydration (23%), anemia (20%), dry mouth (18%), dizziness (16%), abdominal pain (16%), and pyrexia (16%). Thrombocytopenia occurred in 11% of subjects. Most AEs ($>$ 85%) were grades (G) 1-2. Of all AEs, 40% were related. There were 5 treatment-related serious AEs in 2 subjects (n = 1 G4 thrombocytopenia, G4 ischemic stroke, G3 subarachnoid hemorrhage [SAH], and G3 thromboembolic event; n = 1 G3 vomiting). Dose-limiting toxicities were observed at 120mg QD (G4 thrombocytopenia, G4 ischemic stroke, G3 thromboembolic event, and G3 SAH; asymptomatic G4 thrombocytopenia), 60mg BID (G3 thrombocytopenia with recovery $>$ 7 days), and 40mg BID (dose reduction for transient G3 fatigue). PLX2853 systemic exposure was dose-proportional up to 120mg with a short terminal half-life ($<$ 3.5 hr). Plasma concentrations were above the IC_{90} in the MYC-responsive reporter assay for 9 hr at 80mg or higher doses. RNA-seq analyses of peripheral blood mononuclear cells showed a dose-dependent modulation of BET target gene expression. One complete response (ongoing 9+ months) was seen in a patient with DLBCL, two patients had partial responses (1 uveal melanoma, 1 primary peritoneal cancer), and 14 patients had stable disease. The median PFS was 82.5 days (range: 51 – 209 days). **Conclusions:** PLX2853 shows encouraging signs of clinical activity and is well tolerated at the anticipated RP2D of 80 mg/day. PLX2853 is being evaluated as monotherapy and in combination. Clinical trial information: NCT03297424. Research Sponsor: Plexxikon.

3019 **Poster Discussion Session**

PF-06939999, a potent and selective PRMT5 inhibitor, in patients with advanced or metastatic solid tumors: A phase 1 dose escalation study. *First Author: Jordi Rodon Ahnert, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Protein arginine methyltransferase 5 (PRMT5) methylates multiple substrates known to be dysregulated in cancer, including components of the spliceosome machinery. PF-06939999 is a selective small-molecule inhibitor of PRMT5. Here we report the safety, PK, PD, and preliminary activity of PF-06939999 in patients (pts) with selected advanced/metastatic solid tumors. **Methods:** This phase 1 dose escalation trial (NCT03854227) enrolled pts with solid tumor types marked by potential frequent splicing factor mutations, including advanced/metastatic endometrial cancer, head and neck squamous cell carcinoma (HNSCC), non-small cell lung cancer (NSCLC), urothelial cancer, cervical cancer, or esophageal cancer. PF-06939999 monotherapy was continuously administered orally QD or BID in 28-day cycles. A Bayesian Logistic Regression Model was used to inform dose level decisions. Primary objectives were to assess dose limiting toxicities (DLTs), AEs and laboratory abnormalities. Tumor response was assessed using RECIST v1.1. PK and PD were assessed by determining PF-06939999 plasma concentration after dosing and changes in plasma levels of symmetric di-methyl arginine (SDMA), the product of PRMT5 enzymatic activity. **Results:** 28 pts received PF-06939999 at doses from 0.5-12 mg daily (QD or BID) during dose escalation. Median number of cycles was 2 (range, 1-13) . Most were female (54%) with a median age of 61.5 (range, 32-84) y. Median number of prior therapies was 4. Overall, 4/24 (17%) pts reported DLTs: thrombocytopenia (n=2, 6 mg BID); anemia (n=1, 8 mg QD); and neutropenia (n=1, 6 mg QD). Treatment-related AEs occurred in 24 (86%) pts. Most common ($\geq$20%) treatment-related AEs across all cycles were anemia (43%), thrombocytopenia (32%), dysgeusia, fatigue and nausea (29% each). Grade $\geq$3 treatment-related AEs included anemia (25%), thrombocytopenia (21%), fatigue, neutropenia and lymphocyte count decreased (4% each). One pt (6mg BID) had Grade 4 treatment-related thrombocytopenia. All cytopenias were dose-dependent and reversible with dose modification. No pts discontinued treatment for treatment-related toxicity. There were no treatment-related deaths. Exposure to PF-06939999 increased with doses in the dose range tested. Plasma SDMA was reduced at steady state (58.4-87.5%), indicating robust PD target inhibition. Two pts had confirmed partial response (HNSCC and NSCLC). 6 mg QD was identified as the recommended monotherapy dose for expansion. **Conclusions:** PF-06939999 showed dose-dependent and manageable toxicities in this phase 1 dose escalation study. Objective tumor responses were observed in pts with HNSCC and NSCLC. Analysis of archival tissue for the presence of splicing factor mutations and other potential predictive biomarkers is ongoing. Enrollment to part 2 dose expansion is ongoing in pts with NSCLC, HNSCC and urothelial cancer. Clinical trial information: NCT03854227. Research Sponsor: Pfizer.

3020 **Poster Discussion Session**

Phase 1 study of CB-103, a novel first-in-class inhibitor of the CSL-NICD gene transcription factor complex in human cancers. *First Author: Elena Lopez Miranda, Medical Oncology, Hospital Universitario Ramón y Cajal, Madrid, Spain*

Background: CB-103 selectively inhibits the CSL-NICD interaction leading to down-regulation of CSL-NICD mediated oncogenic pathway activation downstream of NOTCH receptor/ligand signaling, and has shown potent anti-cancer activity as single agent and in combination with targeted/chemotherapies in preclinical models. The aim of this dose escalation/expansion phase 1/2a study is to assess safety, maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D), preliminary activity, pharmacokinetics and pharmacodynamics of CB-103. **Methods:** Eligible were adult patients (pts) with advanced or recurrent selected solid tumors. Tumor tissue, where available, was retrospectively tested for NOTCH pathway activating mutations and surrogate tissues were evaluated for gene expression of related target genes. CB-103 was given orally in 28 days cycles at escalating doses until disease progression or toxicity. In a dose confirmatory cohort, NOTCH activation will be prospectively assessed to determine eligibility. **Results:** Forty-one pts (19 adenoid cystic carcinoma (ACC), 16 colorectal and 4 breast cancer, 2 prostate cancer) were assigned to increasing dose levels starting from 15mg once daily (OD). Median age was 55 years (range 25-76). Median number of prior lines of therapy was 2 (range 0-7). Thirty-two pts in 8 escalation groups completed the 28-day DLT window. One DLT (asymptomatic grade (G) 3 GGT increase) was observed at the highest dose (600mg). Related treatment emergent adverse events (AE) occurring in >10% of pts were nausea (24%), diarrhea (20%), dyspepsia (15%), fatigue (12%) and vision blurred (12%), all G 1/2. No discontinuations occurred due to treatment-related AEs. The MTD has not been reached. Several pts reported vision changes that improved over time and were fully reversible after stopping the drug. Median time on treatment for all pts was 52 days (range 5-249). Best response was stable disease (SD). For ACC pts, preliminary median PFS was 21.7 weeks (95% confidence interval (CI) 13.7-22.4 weeks) and disease control rate (DCR) was 79% at week 8 and 58 % at week 20. Three pts with ACC harboring activating NOTCH alterations had radiologically confirmed stable disease (SD) > 6 months. Importantly, in 3 pts with NOTCH positive disease a temporary stop of tumor growth was observed. One pt showed a reduction in size of a liver lesion up to 25% before progression due to new lesions. Mechanistically, strong on-treatment downregulation of NOTCH target genes was observed. The dose of 600mg CB-103 OD was declared the RP2D. **Conclusions:** CB-103 is the first drug to effectively control the CSL-NICD transcription complex. CB-103 is well tolerated in pts with advanced tumors and, as expected on the basis of mechanistic studies, in the absence of the typical toxicities associated with Notch targeting GSIs or mABs. The RP2D has been established for advancing clinical development into phase 2. Clinical trial information: NCT03422679. Research Sponsor: Cellestia Biotech AG.

3021 **Poster Session**

A phase 1 trial of FID-007, a novel nanoparticle paclitaxel formulation, in patients with solid tumors. *First Author: Jacob Stephen Thomas, University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: FID-007 (FID) consists of paclitaxel encapsulated in a polyethyloxazoline (PEOX) polymer excipient designed to enhance PK, biodistribution, and tolerability. In addition to allowing the drug to remain in solution until it can enter a cancer cell, the PEOX nanoparticle preferentially delivers paclitaxel to the tumor through the leaky hyperpermeable vasculature. In xenograft studies, FID reduced or limited tumor growth in multiple tumor types including lung, gastric, breast, pancreatic, and ovarian cancer. FID was more effective at lower or comparable taxane doses with fewer side effects. We present the first-in-human trial of FID. **Methods:** The study is evaluating the safety, PK, and efficacy of FID in pts with advanced solid tumors. The primary objective is to determine the MTD and RP2D. Pts received FID in doses between 15mg/m^2 and 125mg/m^2 using a standard 3+3 dose escalation design. FID was given IV on Days 1, 8, and 15 of a 28-day cycle. Eligibility included ECOG 0-2, adequate organ function, and no more than 3 prior lines of cytotoxic therapy for advanced disease. **Results:** Twenty-five pts were treated across 6 dose levels. Median age was 62 (44-76). ECOG PS was 2 in 1 pt and 1 in 64%. Median number of cycles was 2 (1-16). There were 2 DLTs of grade 3 rash at 100 mg/m^2. Given the transient nature of the rash and response to topical therapy, DLT definition was modified to exclude grade 3 rash that lasts $\leq$ 7 days and additional patients were treated at 100 mg/m^2 which was deemed tolerable. There was 1 DLT of grade 3 neutropenia at 125 mg/m^2. All grade treatment related adverse events (TRAEs) in $\geq$ 25% of pts were rash (64%), alopecia (52%), pruritus (44%), anemia (44%) leukopenia, fatigue (40% each), dysgeusia, anorexia, nausea (32% each), and neutropenia (28%). Grade 3/4 TRAEs occurring in > 1 pt were anemia (20%), neutropenia, leukopenia, and maculopapular rash (16%). There were no treatment discontinuations due to toxicity. Twenty-two pts were evaluable for response by RECIST 1.1 with a PR rate of 14% (PR in pancreatic, biliary tract and NSCLC) and disease control rate of 59%. PK is linear and dose proportional. There is no paclitaxel accumulation after weekly dosing, and the $t_{1/2}$ is between 18-26 hours. **Conclusions:** FID has a manageable safety profile with MTD not reached. Accrual is continuing at 125 mg/m^2. PK is linear, dose proportional and comparable to that of nab-paclitaxel. There is preliminary evidence of anti-tumor activity in heavily pre-treated pts across different tumor types. Enrollment in dose escalation continues. Combination studies with immunotherapeutic agents are planned. Clinical trial information: NCT03537690. Research Sponsor: Fulgent.

3022 **Poster Session**

Bosutinib in combination with pemetrexed in patients with selected metastatic solid tumors: A phase I study (NCT03023319). *First Author: Nagla Fawzy Abdel Karim, Augusta University-Georgia Cancer Center, Augusta, GA*

Background: Activation of the *Src* kinase pathway has been observed in about 50% of cancers of the colon, liver, lung, breast and pancreas. Ceppi, *et al*, explored that *Src* inhibitors *might* be synergistic in combination with pemetrexed. Bosutinib is an approved oral ATP-competitive *Bcr-Abl* tyrosine-kinase inhibitor with an inhibitory effect on *Src* kinases. **Methods:** In this phase 1, dose-escalation study, we enrolled 10 patients with advanced metastatic solid tumors who progressed on standard of care chemotherapy, 9 of whom were evaluable, to receive bosutinib and pemetrexed. Bosutinib was administered once daily in a 3 + 3 dose-escalation study design where the first cohort started at an oral dose of 200 mg daily with I.V. pemetrexed 500 mg/m2 on a three weekly schedule. The primary objective was to determine the dose-limiting toxicity (DLT), and maximum tolerated dose (MTD) of bosutinib with pemetrexed, and the type and frequency of adverse events. Secondary objective(s) were to estimate tumor response rate (RR), progression-free survival (PFS), and overall survival (OS). **Results:** All patients had progressed on prior chemotherapy and included 9 patients with adenocarcinoma of the lung, and 1 patient with metastatic adenocarcinoma of the appendix. Two patients (22%) had prior pemetrexed exposure. Median age was 62 years (range, 58-44). The median number of bosutinib and pemetrexed cycles received was 2 (range, 1-4). Nine patients were evaluable. The MTD of bosutinib was 300 mg daily in this combination as 2 out of the 3 patients who received 400 mg experienced elevated liver transaminases (>CTCAE Grade 3) and one patient experienced grade 3 fatigue. Two patients (22%) had a partial response, and 6 patients (67%) had stable disease, including 2 patients with prior pemetrexed exposure, and 1 patient had disease progression. The two responders and the subject with the longest stable disease duration demonstrated Src overexpression on immunohistochemical staining of their tumor. Two patients died of sepsis; both had stable disease. Median PFS was 4.1 months (range, 1.2-11.6), and the median OS was 11.9 months (range, 4-36.7). Adverse events included pneumonia/sepsis, diarrhea, fatigue, rash, weakness, transaminitis, hypertension, and thrombocytopenia. **Conclusions:** The MTD of oral bosutinib was 300 mg daily in combination with pemetrexed 500 mg/m2 every 3 weeks. Despite the limitations of this phase I study there appears potential efficacy of this combination in pretreated patients. We are currently enrolling patients in the expansion cohort. Clinical trial information: NCT03023319. Research Sponsor: Pfizer.

3023 **Poster Session**

Profiling 523 cancer associated genes in circulating tumor DNA of children with CNS tumors. *First Author: Erin R. Bonner, Children's National Health System, Washington, DC*

Background: Pediatric central nervous system (CNS) cancers often pose unique challenges including tumor 'invisibility', where surgical resection is restricted due to the sensitive tumor location and tissue biopsy is not always feasible. Detecting cancer associated mutations and copy number variations (CNV) at diagnosis is increasingly important, as the WHO classification of pediatric CNS cancers has incorporated molecular signatures with tumor grade. To achieve CNS tumor molecular 'visibility', we previously established a liquid biopsy platform for detecting single nucleotide variants in circulating tumor DNA (ctDNA). However, our method was limited by the restricted number of genes that can be monitored and the inability to detect genomic events including CNVs. To address this, we developed a deep sequencing liquid biopsy approach to profile alterations across selected genes. Our platform provides an opportunity for multi-gene monitoring, to assess tumor subclonal evolution and response to treatment in the absence of repeat tissue biopsies. **Methods:** We tested the performance of our platform using paired tissue, CSF, and plasma/serum from 10 children with diffuse midline glioma (DMG). ctDNA was analyzed using the TruSight Oncology 500 (TSO500) ctDNA targeted panel covering 523 genes. Matched tumor, CSF, and blood were assessed for concordance and sequencing results were compared to digital droplet PCR (ddPCR) detection of H3K27M mutation. **Results:** The median exons with ^{3}500X coverage was 96% for 7 CSF samples with optimal input (^{3}60ng), 0.01% for 3 CSF samples with < 5ng input, and 74.5% for plasma/serum samples. ctDNA was more readily detectable in CSF, yet concordance between paired tumor, CSF and plasma/serum was observed. DMG associated mutations in genes including *H3F3A, HIST1H3B, TP53,* and *ACVR1* were detected in ctDNA. Of 9 H3K27M mutations identified in tumor, 8 were present in CSF and 3 in plasma/serum, for a positive percent agreement of 89% and 33%, respectively, with the tumor results. Among CSF samples, H3.3K27M was detected in 6/6 cases, and H3.1K27M in 2/3 cases, with variant allele frequencies comparable to ddPCR results. CNVs including *PDGFRA/B* and *MDM4* amplifications were present in CSF and confirmed by analysis of paired tumor. Additional events, including *PIK3CA* p.E545Q, *PPM1D* truncation, and *KRAS* amplification, were detected in CSF but absent from paired tumor, indicating tissue heterogeneity. Strategies to optimize ctDNA detection, including optimization of ctDNA isolation and adjustment of library QC metrics, were identified. **Conclusions:** This proof-of-concept study demonstrates the feasibility of our high depth, targeted sequencing approach for detecting clinically relevant mutations in ctDNA from children with CNS tumors. This approach may aid in diagnosis of CNS tumor molecular subtype, and monitoring of tumor evolution and response to therapy in serially collected ctDNA. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency.

3024 **Poster Session**

Interleukin-1-beta concentration and neutrophil-lymphocyte ratio as possible predicting biomarkers of response to therapy with checkpoint inhibitors. *First Author: Rashida Orlova, Saint-Petersburg State University, Saint-Petersburg, Russian Federation*

Background: One of the discussed predictive markers of the immune therapy efficacy is the index of neutrophils to lymphocytes ratio in peripheral blood (NLr), which reflects the activity of adaptive immunity and correlates with the level of tumor-infiltrating lymphocytes (TILs). High NLr and low TILs are associated with disease progression. Interleukin-1-beta (IL-1β) is one of the main cytokines produced by the tumor microenvironment (TMO). Overexpression of the cytokine leads to a local immunosuppression. For some tumors, elevated serum IL-1β levels have been associated with a poor prognosis. The aim of this work is to analyze the serum IL-1β level as a marker of TMO activity and the NLr as a marker of adaptive immunity activity in relation to the response to therapy with checkpoint inhibitors in patients with various solid tumors. **Methods:** The study involved 63 patients with various solid tumors who were treated at the City Oncological Dispensary and were prescribed checkpoint inhibitors (nivolumab (n = 33), pembrolizumab (n = 23), ipilimumab + nivolumab (n = 7)). The determination of the level of IL-1β was performed using the ELISA method ("Interleukin-1-beta, ELISA-best", Novosibirsk), a clinical blood test was performed in a dispensary. The response to treatment was assessed 3-6 months after the start of therapy. Statistical analysis was carried out in GraphPad Prism. **Results:** Among the examined patients 49.21% (31/63) achieved partial regression or stabilization of the process (group I), and 50.79% (32/63) progressed (group II). The mean concentration of IL-1β before treatment in group I was 2.21±0.3 pg/ml, in group II - 0.98±0.2 pg/ml. NLr was increased in 7 patients from group I and in 9 patients from group II, with the mean index level being 2.9±0.39 and 3.2±0.5, respectively. There was no statistically significant difference in the concentration of IL-1β and the NLr between the studied groups. In group II, the number of patients undergoing systemic anticancer therapy before immune therapy (n = 18) was statistically significantly higher than in group I (n = 8), p = 0.033. There was no statistically significant difference in IL-1β concentration and NLr relative to previous treatment. **Conclusions:** Our study showed that the level of IL-1β corresponds to that of healthy donors and its isolated determination has no prognostic value. The NLr in most patients from the progression group was higher than normal, in contrast to group I, which is confirmed in the literature. The presence of previous systemic anticancer therapy was found to be associated with disease progression. The described feature can be explained by the fact that patients who received therapy before, already have a longer period of illness, a more severe clinical condition. The presence of systemic anticancer therapy does not affect the level of IL-1β and NLr. Research Sponsor: RFBR, project number 20-015-00498.

3025 **Poster Session**

Genes copy number as a marker of low-invasive assessment of rectal tumors radiotherapy effectiveness. *First Author: Marina A. Gusareva, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Radiotherapy (RT) is a key component of rectal cancer (RC) treatment, however, nonresponsiveness in patients to preoperative RT is very common, usually due to the tumor cells radioresistance, mediated by their molecular characteristics, such as gene expression. The features of mRNA rapid degradation in extracellular environment make this indicator unsuitable for low invasive diagnostics. The solution to this problem is possible by switching to a more stable marker - the copy number variation (CNV), which can be determined in the extracellular DNA (cfDNA) circulating in the blood plasma. Therefore, the aim of the study was to identify the relationship between the level of genes CNV in the cfDNA of blood plasma with the effectiveness of rectal tumors RT. **Methods:** We used cfDNA preparations from blood plasma obtained before RT from 200 patients with RC, as well as from blood plasma of 50 apparently healthy donors (AHD, without cancer). RT was carried out on a linear accelerator Novalis TX (SFD = 2.4 Gy, TFD = 54.0 Gy). Blood samples were separated into plasma and cell fraction by centrifugation. Isolation of cfDNA from blood plasma was performed using the phenol-chloroform method. Determination CNV of 5 genes (BRCA2, H2AX, CASP9, RBBP8 and BCL2) was performed using Real-Time qPCR method. Differences were assessed using Mann-Whitney test; the Bonferroni correction was used to correct multiple comparisons. **Results:** RT results for 200 patients allowed them to be divided into 2 groups. After RT, 120 patients showed complete tumor regression (group 1), 50 patients showed insignificant tumor regression and 30 patients did not regress (group 2). In cfDNA of group 1 patients was found CNV decrease ($p < 0.05$) of H2AX and RBBP8 genes by 2.5 and 2.0 times, respectively, relative to AHD group. In the cfDNA of group 2patients an increase ($p < 0.05$) of BRCA2, H2AX, RBBP8 and BCL2 genes CNV was found by 2.0, 2.2, 2.0 and 2.0 times, respectively, relative to AHD group. Only 2 genes CNV differed in group 1 from group 2: the CNV of H2AX and RBBP8 was 5.4 and 4.0 times less respectively ($p < 0.005$). **Conclusions:** Thus, it has been found that increased CNV of genes BRCA2, H2AX, BCL2, RBBP8 in blood plasma cfDNA is associated with low efficiency of RT. At the same time, the CNV of H2AX and RBBP8 genes in cfDNA of patients with RC has the greatest potential as a marker of the RT effectiveness. Research Sponsor: Ministry of Health of the Russian Federation.

3027 **Poster Session**

Liquid biopsy testing: Impact on treatment assignment and survival in a community-based oncology practice—A real-world experience. *First Author: Khalil Choucair, Kansas University School of Medicine, Wichita, KS*

Background: Liquid biopsy is a promising, rapid and minimally invasive genetic test examining circulating tumor DNA. It offers a significant potential in selecting signal-matched therapeutic options. **Methods:** A retrospective chart review was conducted on adult patients with advanced solid cancer whose tumors were tested with the Guardant 360® (Guardant Health) assay between December 2018 and 2019. A follow-up analysis (censor date: 01/06/2021) was carried to assess the actual impact of testing results on treatment assignment and survival. **Results:** A total of 178 patients underwent testing. Mean age at diagnosis was 65 years. Median (m) Karnofsky Performance Scale was 90% and the majority of patients (89.9%) had ≥ stage III-B disease. Lung (LCa; 50.56%), breast (BCa; 17.42%) and colorectal (CRCa; 7.87%) cancers were the most common cancer types. A positive test was reported in 140/178 patients (78.7%); of those, 105/140 (75%) had an actionable mutation, either with an FDA-approved target-matched therapy (n = 32/105; 30.5%) or with a therapy outside current FDA indication (n = 73/105; 69.5%). In patients with no actionable mutation (n = 35/140; 25%), 85.7% (n = 30/35) had a signal-based clinical trial opportunity. The actual overall signal-based matching rate was 17.8% (24/135; vs. 82.2% no-match rate). Within candidates for FDA-approved treatment, 50% (16/32) received targeted therapy while only 6.9% (5/73) were treated with targeted agents outside current FDA indication: mean matching score (number of matched drugs/number of actionable mutations) was 0.6 (range: 0.33-2) and 0.8 (range: 0.17-2), respectively. Only 10% (3/30) were referred to signal-based clinical trials. Survival analysis of LCa, BCa and CRCa patients with actionable mutations who actually received any therapy (n = 66) revealed post-testing survival advantage for target-matched therapy (n = 22) compared to unmatched therapy (n = 44): overall survival (OS) was longer in the matched cohort (mOS: 13.3 months; 95% CI: 11.8-14.8 vs. 10.7 months; 95% CI: 9-12.4 in unmatched) but did not reach statistical significance ($P = 0.09$). Progression free survival (PFS) was significantly longer in patients who received matched therapy (mPFS: 11.3 months; 95% CI: 9.9-12.7 vs. mPFS: 6.8 months; 95% CI: 5.1-8.5 in unmatched; $P < 0.05$). **Conclusions:** Implementation of liquid biopsy testing is feasible in community practice and impacts therapeutic choices in patients with advanced malignancies. Receipt of liquid biopsy-generated signal-matched precision therapies conferred added survival benefit compared to unmatched therapy. Larger sample size studies are needed to validate these findings. Research Sponsor: None.

3028 **Poster Session**

Circulating tumor DNA as markers of dynamic recurrence risk and adjuvant chemotherapy benefit in resected non-small cell lung cancer. *First Author: Wei Guo, Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: A significant proportion of non-small cell lung cancer (NSCLC) patients relapse after surgical resection with or without adjuvant therapy. The detection of molecular residual disease (MRD) has great potentials to stratify postoperative risk and facilitate early recurrence diagnosis. Here, we aim to evaluate the clinical utility of serial plasma circulating tumor DNA (ctDNA) in MRD detection, adjuvant therapy guidance, and recurrence risk prediction in resected NSCLC patients. **Methods:** This prospective cohort study recruited 116 patients with NSCLC following surgery and/or adjuvant therapy. Thirteen patients discontinued, leaving 103 patients for analysis. Tumor samples were obtained at surgery. Plasma samples were collected at baseline, after surgery, after adjuvant therapy and every 3 months thereafter and were analyzed by ultradeep (30000×) next-generation sequencing with molecular barcode and in-silico error correction. **Results:** Pretreatment ctDNA was detected in 69.8% of patients. ctDNA positivity after surgery and after completion of adjuvant chemotherapy (ACT) were significantly associated with worse recurrence-free survival (RFS) (HR: 4.0; 95% CI: 2.0-8.0; $P < .001$ and HR:3.2; 95% CI: 1.3-8.2; $P < .05$, respectively). In stage II-III patients who were positive for ctDNA after surgery, ACT-treated patients had a better RFS than those without ACT ($P < .05$), whereas ACT did not confer significant clinical benefits in patients with negative postsurgical ctDNA. During surveillance after definitive therapy, ctDNA positivity was associated with worse RFS (HR: 8.5, 95% CI: 3.7-20, $P < .001$) and preceded radiological recurrence by a median of 88 days. Using joint modeling of serial ctDNA and time-to-recurrence, we accurately predicted patients' 12-month and 15-month recurrence status, with areas under receiver-operating characteristics curves (AUROC) of 0.88 and 0.84, respectively. **Conclusions:** These results indicate that ultradeep ctDNA sequencing could sensitively detect MRD, thus identifying patients with high recurrence risk and guiding the adjuvant therapy decision in resected NSCLC. We also demonstrate that joint modeling of serial ctDNA levels and time to recurrent can provide an accurate dynamic risk prediction for NSCLC patients during surveillance. Clinical trial information: ChiCTR1900024656. Research Sponsor: National Key R&D Program of China, Other Foundation, Innovation team development project of Ministry of Education.

3029 **Poster Session**

Plasma hPG_{80} circulating prograstin levels in cancer patients in Nigeria: Prolevcan study. *First Author: Omolara A. Fatiregun, Lagos State University Teaching Hospital, Ikeja, Nigeria*

Background: Progastrin is a tumor-promoting peptide which is detectable in the blood of patients with different cancers. hPG_{80} (circulating progastrin) is produced by cancer cells. Recently it was reported that hPG_{80} is detected in the blood of cancer patients, suggesting its potential utility for cancer detection. In this Nigerian study, we assessed the performance of hPG80 in diagnosed cancer patients versus healthy volunteers. **Methods:** Plasma samples of 50 patients with breast (n = 41) and colorectal (n = 9) cancer, aged from 26 to 70 years, were assayed for hPG_{80} levels with the DxPG80 kit from ECS-Progastrin. The diagnostic performance (ROC AUC) of hPG_{80} was assessed compared to 50 healthy volunteers aged from 21 to 38 years. **Results:** Plasma hPG_{80} levels were significantly higher in cancer patients compared to controls (median values: 4.59 pM (IQR: 2.02-8.27 pM) vs 1.37 pM (IQR: 0-3.11 pM), $p < 0.0001$). The median value of hPG_{80}level was 3.96 pM (IQR: 1.61-7.89 pM) for breast cancers and 6.43 pM (IQR: 2.80-15.86 pM) for colorectal cancer patients. ROC AUC for all cancers, breast cancer and colorectal cancer were 0.75, 0.74 and 0.82 respectively. There was no correlation between hPG_{80} blood levels with age or CA15.3 levels. **Conclusions:** Plasma hPG_{80} is a simple and relatively affordable blood test, it shows potential utility as a biomarker for cancer detection, monitoring and treatment assessment. Further prospective studies are needed to explore and confirm its potential. Research Sponsor: None.

3030 **Poster Session**

Genetic predictor of severe sorafenib-induced diarrhea and hand-foot syndrome (HFS). *First Author: Julia C. F. Quintanilha, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: Diarrhea, HFS, and hypertension are common toxicities of sorafenib. No markers are validated to predict patients at risk of these toxicities. This study aimed to identify genetic predictors of sorafenib-induced toxicities. **Methods:** A two-step, discovery-validation approach was used. The discovery set included 140 renal cell carcinoma patients from the TARGET study treated with sorafenib (400 mg twice daily) and genotyped for 1040 single-nucleotide polymorphisms (SNPs) in 56 genes. The three most statistically significant SNPs associated with grade ≥2 composite toxicity (either hypertension, diarrhea, HFS, or other skin toxicities, CTCAE v.3.0) were tested for association with grade 3 composite toxicity (either hypertension, diarrhea, or HFS, CTCAE v.4.0) in a validation set of 240 hepatocellular carcinoma patients from Alliance/CALGB 80802 treated with sorafenib (400 mg twice daily) alone or with doxorubicin. Associations between SNPs and composite toxicity was performed by logistic regression, with adjusting covariates (age, gender, race, and treatment arm, the latter two covariates for the validation set only). A meta-analysis odds ratio (OR) of each SNP-grade 3 toxicity association between the discovery and validation sets was obtained by inverse variance to point toward effects specific to a type of toxicity. **Results:** In the discovery set, the top three SNPs associated with grade ≥2 composite toxicity were rs12366035 (C>T, minor allele frequency, MAF 0.34) in *VEGFB* (p 0.0007), rs4035887 (G>A, MAF 0.49) in *EPAS1* (p 0.0021), and rs4864950 (T>A, MAF 0.23) in *KDR* (p 0.0058). These SNPs were genotyped in the validation set and only rs4864950 in *KDR* was replicated. No grade 4 toxicities were reported. Similar to the discovery set (OR 2.41, 95% CI 1.29-4.51), the A allele of rs4864950 increased the risk of grade 3 composite toxicity (p 0.032, OR 2.12, 95% CI 1.70-4.27) in the validation set. Grade 3 toxicity prevalence in the discovery and validation sets were 3.6% and 7.4% diarrhea, 8.6% and 12.3% HFS, 3.6% and 8.8% hypertension, respectively. The meta-analysis of the two datasets showed that the A allele of rs4864950 increased the risk of grade 3 diarrhea (p 0.045, OR 3.09, 95% CI 1.03-9.29), grade 3 HFS (p 0.012, OR 2.57, 95% CI 1.24-5.37), but not grade 3 hypertension (p 0.207, OR 0.51, 95% CI 0.18-1.45). **Conclusions:** We provide the first evidence of clinical validity of a marker of sorafenib-induced diarrhea and HFS. Sorafenib inhibits VEGFR2 (coded by *KDR*), leading to epithelial hypoxia and causing diarrhea and HFS. Variant rs4864950 might affect the function VEGFR2, which, during VEGFR2 inhibition, increases the risk of diarrhea and HFS. This SNP is common and can be genotyped in patients before receiving sorafenib for a better risk assessment. Support: U10CA180821, U10CA180882, U24CA196171; https://acknowledgments.alliancefound.org ClinicalTrials.gov Id: NCT01015833. Research Sponsor: U.S. National Institutes of Health.

3031 **Poster Session**

Tumor-educated platelets for breast cancer detection: Biological and technical insights. *First Author: Marte C. Liefaard, Department of Molecular Pathology, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Mammographic screening has enabled early detection of breast cancer, both in a general population and in women with increased risk of breast cancer. However, mammography yields many false positive results, leading to unnecessary invasive diagnostic procedures, and has limited sensitivity, particularly in women with high breast density. Blood-based markers may improve breast cancer screening, but no marker has proven sufficiently sensitive and specific for this purpose thus far. The mRNA repertoire in blood platelets (tumor educated platelets, TEPs) differs between patients with cancer and healthy controls. In this study, we aimed to train a classification algorithm on TEP mRNA profiles to distinguish patients with breast cancer from healthy controls. **Methods:** Platelet mRNA was sequenced from 266 women with stage I-IV breast cancer and 214 female asymptomatic controls from six different hospitals. First, a particle-swarm optimized support vector machine (PSO-SVM) classifier was trained (Best et al., Nature Protocols, 2019). To this end, 71% of the dataset was randomly allocated to train the algorithm, while the remaining 29% was used for internal validation. Second, an alternative classifier was trained on the same samples as in the PSO-SVM using elastic net (EN) regression. Reproducibility of classifier performance was evaluated in a single-center, independent, blinded set, consisting of cases (n = 37) and age-matched controls (n = 36). Post-hoc analyses were performed to assess the influence of hospital of origin and other factors on TEP gene expression and classifier performance. **Results:** Performance of both classifiers in the internal validation set was adequate with an area under the curve (AUC) of 0.86 for the PSO-SVM and 0.87 for the EN classifier. A strong correlation was observed between case control status and hospital of origin (Fisher's exact test, $p < 0.001$). Performance in the single-center, independent set was poor with an AUC of 0.57 and 0.60 for the PSO-SVM and EN, respectively. Post-hoc analyses indicated that 25% of the variance in gene expression was associated with hospital of origin, 6% with case control status, whereas 69% remained unexplained. Gene expression related to platelet activity was significantly different between the two hospitals that contributed most samples, and between cases and controls. **Conclusions:** We were unable to successfully validate two TEP RNA based classifiers for breast cancer detection in a single-center, independent, blinded set, regardless of the algorithm employed. Gene expression was severely influenced by hospital of origin and other factors unrelated to case-control status, suggesting that the wet lab protocol is highly sensitive to within-protocol variations in execution. Therefore, we suggest that thorough revision of the protocol is necessary before TEP RNA based classifiers can be reconsidered for breast cancer detection in the future. Research Sponsor: European Research Council, Other Government Agency, Dutch Cancer Society.

3032 **Poster Session**

Detection of prognostic cancer-specific circular RNA in plasma. *First Author: Jason Brown, Department of Internal Medicine, University of Michigan, Ann Arbor, MI*

Background: Earlier detection of cancer could lead to improved outcomes. Non-invasive biomarkers are integral for early detection, and protein and DNA-based assays have been previously described for this purpose. Evaluation of highly expressed circulating RNA would improve upon existing methods by allowing for quantitation, however RNA expression in plasma is low. Circular RNA (circRNA) is formed by alternative backsplicing and provide resistance to exoribonclease-mediated degradation. Therefore, circRNA is more stable in plasma and could potentially be more easily detected non-invasively. Here, we report results from a novel assay that identifies and quantitates expression of circRNA in cancer plasma. **Methods:** Cancer-specific circRNA targets were identified by analyzing differential expression and abundance based on capture RNA sequencing in tissues. CircRNA-specific probes were designed and validated by stable expression with RNAse R incubation. Expression of selected circRNA isoforms were measured using a quantitative PCR-based assay. For breast cancer specimens, plasma was collected from a cohort of 36 patients and 12 normal female controls without known cancer diagnosis. Expression was determined by normalizing signal to two averaged universally expressed circRNAs. Differential expression for each target was determined for cancer vs. normal and stratified based on ER and HER2 positivity as well as stage. **Results:** Normalized expression of seven proposed breast cancer-specific circRNA targets was determined for all patients in the cohort. All targets demonstrated resistance to RNAse R-mediated degradation in breast cancer cell lines. In the breast cancer cohort, CircTRPS1 expression was higher in cancer plasma than normal, trending toward significance. Expression of circTRPS1 was significantly more common in ER-negative than ER-positive breast cancer ($p = 0.02$). CircPDHX expression was elevated in normal plasma compared to cancer and relatively higher in ER-positive than ER-negative cancer ($p = 0.05$). Median expression in plasma was elevated in cancer specimens compared to normal for CircVAV3, circDNAH14, and circCDYL. CircERBB2 expression was also relatively higher in HER2-positive cancer when compared to other targets. Higher expression significantly positively correlated with metastatic disease for circERBB2 ($p = 0.01$) and circCDYL ($p = 0.005$) and negatively correlated with metastasis for circWDR78 ($p = 0.02$). **Conclusions:** CircRNA are promising biomarkers for early non-invasive detection of cancer. We identified seven circRNA biomarkers in breast cancer plasma which correlated with clinical characteristics. Three circRNAs were significantly prognostic for metastatic breast cancer. Identification of additional cancer-specific targets and multiplexing markers is underway. This assay is generalizable to other cancers, and similar studies in prostate and bladder cancer are in progress. Research Sponsor: Early Detection Research Network (EDRN).

3033 **Poster Session**

Prognostic value of plasma hPG_{80} (circulating progastrin), alone or in combination with Alpha-fetoprotein (AFP) in patients with hepatocellular carcinoma. *First Author: Alexandre Prieur, ECS-Progastrin, Prilly, Switzerland*

Background: Alpha-fetoprotein (AFP) is the most widely used biomarker for hepatocellular carcinoma (HCC) prognosis since it is expressed in the advanced stages of the disease. Consequently, AFP is not useful in establishing a prognosis for patients with a tumor in the early stages of the disease. hPG_{80} (circulating progastrin), a new drug target for cancer treatment which plays a pivotal role in tumorigenesis, is present in the blood of multiple types of cancers at early stages including HCC. The purpose of this study was to evaluate the prognostic value of plasma hPG_{80} in patients with HCC, in combination or not with AFP. **Methods:** A total of 168 HCC patients (BCLC from 0 to D) managed with local or systemic treatments, ("Liverpool" biobank) were enrolled prospectively and analyzed retrospectively. hPG_{80} was quantified using $DxPG_{80}$ Lab kit (ECS-Progastrin) and AFP was quantified using Cobas E411 in the blood of HCC patients. An optimal cutoff value of hPG_{80} was identified at 4.5 pM by calculating the minimal p-value based on the log-rank method. For AFP, a cutoff of 100 ng/mL was used as for liver transplantation (Notarpaolo, 2016). The prognostic impact of hPG_{80} and AFP levels on patient survival was assessed using Kaplan-Meier curves and log-rank tests. **Results:** The median overall survival (OS) of the full cohort is 20.9 months. HCC patients with high hPG_{80} levels (hPG_{80}+: >4.5 pM, 105/168) had significantly lower median OS compared to patients with low hPG_{80} levels (hPG_{80}-: <4.5 pM, 63/168) (12.4 months versus undefined respectively, $p < 0.0001$). Patients with high AFP (AFP+: >100 ng/mL, 69/165) had significantly lower median OS compared to patients with low AFP (AFP: <100 ng/mL 96/165) (7.2 months versus undefined, $p < 0.0001$). To improve the stratification, the patients were further categorized into four groups: hPG_{80}-/AFP- (n = 42), hPG_{80}+/AFP- (n = 54), hPG_{80}-/AFP+ (n = 21) and hPG_{80}+/AFP+ (n = 48). In the AFP- group, hPG_{80}+ patients exhibited a significantly worse prognosis than those with hPG_{80}- (26.3 months versus undefined, p=0.0087). Similarly, in the AFP+ group, patients with hPG_{80}+ had a significantly worse survival compared to hPG_{80}- patients (5.7 months versus 13.4 months, p = 0.0391). Finally, we evaluated the median OS of AFP+ patients according to BCLC staging. Interestingly, in the group BCLC 0 to B, hPG80+ had a significantly worse prognosis than those with hPG_{80}- (15.8 months versus 40.25 months, p=0.0317). **Conclusions:** Our findings show that hPG_{80} could serve as a new prognostic biomarker in HCC. Used in combination with AFP, it improves the stratification of the patients in good and worst prognosis, especially for those patients with negative AFP and early-stage HCC. Research Sponsor: None.

3034 **Poster Session**

Detection of any-stage cancer using plasma and urine glycosaminoglycans. *First Author: Francesco Gatto, Chalmers University of Technology, Gothenburg, Sweden*

Background: Non-invasive liquid biopsies promise to enable early cancer detection and improve patient outcomes. However, virtually all liquid biopsies rely on genomic biomarkers, with limited sensitivity to early-stage tumors and poor detection of cancers shedding little cell-free DNA, like genitourinary or brain tumors. Here, we explored the use of plasma and urine glycosaminoglycan (GAGs) profiles, or GAGomes, as biomarkers reflective of tumor metabolism to serve as an alternative pan-cancer liquid biopsy. **Methods:** In this case-control study, we enrolled retrospective and prospective cohorts from Sweden and Italy. Included cases were treatment-naïve early-stage/low-grade cancers or metastatic/high-grade cancers across 14 histological types. Included controls were healthy 22-78 y/o adults with no history of cancer. We measured GAGomes – encompassing 17 chondroitin sulfate (CS), heparan sulfate (HS), and hyaluronate (HA) disaccharides - using a standardized UHPLC-MS/MS-based kit in a central blind laboratory. We tested the top GAGome features different in cancer using Bayesian estimation. These were used to design one plasma and one urine GAG score for the binary classification of cancer vs. control in a discovery set. We computed the area-under-the-curve (AUC), and sensitivity at 98% specificity of each GAG score in the validation set. A subset analysis was performed in early-stage/low-grade cancers only. In the subset of cases with survival records, we used multivariable Cox regression to estimate the hazard ratio (HR) for overall survival (OS) on each GAG score adjusted for cancer type, age, and gender. **Results:** GAGomes were measured in 753 plasma samples (460 cancers across 14 types, median age = 66 y/o, 51% female vs. 293 healthy adults, median age = 58 y/o, 57% female) and 559 urine samples (219 cancers across 5 types, median age = 69 y/o, 23% female vs. 340 healthy adults, median age = 56 y/o, 60% female). In the discovery set, the urine GAG score had an AUC = 0.80 (95% CI: 0.74-0.85, 124 cancers across 5 types vs. 184 controls) while the plasma GAG score had an AUC = 0.82 (95% CI: 0.78-0.86, 153 cancers across 14 types vs. 282 controls). In the validation set, the urine GAG score had an AUC = 0.78 (95% CI: 0.71-0.84, 95 cancers across 5 types vs. 156 controls) with 35% sensitivity at 98% specificity. The plasma GAG score had an AUC = 0.84 (95% CI: 0.79-0.88, 178 cancers across 14 types vs. 140 controls) with 41% sensitivity at 98% specificity. In the subset of early-stage/low-grade cancers, the AUC was 0.78 and 0.72 in plasma and urine, respectively. The plasma and urine GAG scores were independent predictors of OS regardless of cancer type (HR = 1.39, $p = 0.005$ in plasma [$N = 283$, 11 types, 67 deaths, median follow-up 17 months] and HR = 1.53, $p = 0.016$ in urine [$N = 161$, 4 types, 32 deaths, median follow-up 15 months]). **Conclusions:** GAGomes were sensitive non-invasive metabolic biomarkers for any-stage cancer, including genitourinary and brain tumors. Research Sponsor: Knut and Alice Wallenberg and Cancerfonden.

3035 **Poster Session**

Dynamics of circulating tumor DNA in patients with advanced solid tumors treated with cediranib and olaparib. *First Author: Yiduo Hu, Yale New Haven Hospital, New Haven, CT*

Background: Circulating tumor DNA (ctDNA) has emerged as a potential biomarker to monitor treatment response in solid tumors. Our group previously showed that changes in ctDNA levels were predictive of radiographic response and survival in NSCLC patients receiving immunotherapy. Here we evaluated whether ctDNA dynamics could similarly be used to assess response in a PARP inhibitor-based therapy. **Methods:** A total of 122 patients with NSCLC, TNBC, PDAC or SCLC received cediranib (C) 30mg daily and Olaparib (O) 200mg twice daily in a phase II study NCI9881. Using a multigene NGS assay, ctDNA was measured longitudinally at baseline (T_0), after 3 to 7 days of C monotherapy (T_1), after 1 week of C+O combination (T_2), after 4 weeks of C+O (T_3), and every 4 weeks (T_{4+}) thereafter. The first radiographic assessment was done after 8 weeks of C+O and every 8-12 weeks thereafter. CtDNA was quantified by determining the allele fraction of cancer-associated somatic mutations in plasma. We defined an early ctDNA response *(e-ctDNA-R)* as a >10% decrease in mutant allele fraction from T_0 to T_2, and an early ctDNA progression *(e-ctDNA-P)* as a > 10% increase; otherwise, it was stable ctDNA *(e-ctDNA-S)*. **Results:** In total, 493 samples were analyzed from 94 patients, and 40 unique patients had both T_0 and T_2 ctDNA measurements, as well as corresponding radiographic assessments. These included 10 NSCLC, 17 TNBC, 3 SCLC and 10 PDAC. Of these patients, 4, 21, and 15 patients had PR, SD, and PD as best overall radiographic response respectively. Twenty-three (57.5%) patients had either *e-ctDNA-R* (17, 42.5%) or *e-ctDNA-S* (6, 15.0%), 18 (78.3%) of whom subsequently had either radiographic partial response (PR) or stable disease (SD). Seventeen (42.5%) patients had *e-ctDNA-P*, 10 (58.8%) of whom then had PD. A fair agreement was observed between *e-ctDNA-R/S* or *e-ctDNA-P* and radiographic PR/SD or PD with Cohen's k 0.38 (70% agreement). The correlation between early ctDNA changes and PFS/OS are summarized in the table. All 25 patients with PR/SD eventually progressed. Of these, 17 (68%) had >10% increase in ctDNA from the nadir prior to disease progression (median 94.6%, 95%CI 38.2%-389.1%). The time between ctDNA progression and ctDNA nadir was significantly shorter (median 21 days, 95%CI 21-28) than the time between radiographic/clinical progression and initial PR/SD (median 107 days, 95%CI 56-204, P=0.0015). **Conclusions:** Longitudinal ctDNA measurements could enable early assessment of treatment response, resistance, and disease progression in patients treated with PARP inhibitor-based therapy. However, in this study, tumor responses and ctDNA changes were generally not as robust as have been observed with other classes of therapy. Research Sponsor: U.S. National Institutes of Health.

Early ctDNA changes and clinical outcomes.

	e-ctDNA-R/S	e-ctDNA-P	
median PFS (days)	116	61	P=0.8402, ratio=1.902 (95% CI 1.016-3.559)
median OS (days)	220	173	P=0.4472, ratio=1.272 (95% CI 0.4841 to 3.341)

3036 **Poster Session**

Correlation between different levels of HER2 expression in circulating tumor cells (cHER2 ratio) and metastatic behavior in $stageIV_{aggressive}$ breast cancer. *First Author: Paolo D'Amico, Northwestern University, Feinberg School of Medicine, Chicago, IL*

Background: The presence of HER2 expressing (HER2+) circulating tumor cells (CTCs) occurs often in metastatic breast cancer (MBC) patients (pts). We have previously showed that the ratio among CTCs expressing high level of HER2 and the total number of HER2+ CTCs (circulating HER2 ratio, cHer2 ratio) has a prognostic role in MBC patients. Here we further investigate the role of the cHER2 ratio in the process of metastatic spread. **Methods:** Under IRB-approved study we prospectively analyzed blood samples of patients with MBC enrolled before starting a new line of therapy. Samples were collected from pts treated at Northwestern University (Chicago, IL) between 2016 and 2020. CTCs were enumerated through CellSearch (Menarini Silicon Biosystems, Bologna, Italy) and characterized for HER2 expression using the CellSearch CXC Kit. HER2+ CTCs were divided in 3 different categories (1+,2+,3+) leaning on fluorescence intensity. Pts with <5 CTCs (stage $IV_{indolent}$) were excluded from the analysis. The cHER2 ratio, defined as the sum of 2+ CTCs and 3+ CTCs divided by the total number of HER2+ CTCs, was used to split the remaining pts in 2 different cohorts: cHER2 ratio high (> 0.75) ($cHER2_{high}$) and cHER2 ratio low (≤0.75) ($cHER2_{low}$). The frequency of each metastatic site (i.e. liver, lung, central nervous system, bone, lymph nodes, skin/soft tissue, serosa) and the total number of different sites involved (1-7, ≤2 and >2 sites) were compared among the two sub-populations and analyzed through Fisher exact test. **Results:** Out of 98 pts enrolled, 77 were classified as $cHER2_{low}$ and 21 as $cHER2_{high}$. We observed a higher frequency of oligometastatic pts (≤2 sites involved) in the $cHER2_{high}$ cohort (16, 76%), compared to only 29 (37%) in the $cHER2_{low}$ ($p<0.005$). Moreover, the cHER2 ratio was associated with a tropism toward specific sites of disease spread with higher incidence of liver, lung and lymph nodes metastases in the $cHER2_{low}$ cohort ($p<0.05$). No other statistical associations were observed in respect of specific organ tropism. The frequency of involvement for each metastatic site among the two cohorts are reported in the table. **Conclusions:** Measuring CTCs enumeration and HER2 expression we identified two cohorts, $cHER2_{high}$ and $cHER2_{low}$, associated with distinct patterns of metastatic spread. The $cHER2_{low}$ pts were correlated to multiple sites of metastatic involvement, with particular tropism toward liver, lung and lymph nodes. These results confirm the prognostic role of the cHER2 ratio, suggesting a peculiar biological meaning of the HER2+ 1+ CTCs. Research Sponsor: None.

		Liver	Lung	CNS	Other	Bone	Lymph Nodes	Skin/soft tissue	Serosa
$cHER2_{low}$	77	33 (43%)	34 (44%)	13 (17%)	4 (5%)	64 (83%)	40 (52%)	20 (26%)	11 (14%)
$cHER2_{high}$	21	3 (14%)	4 (19%)	1 (5%)	1 (5%)	15 (71%)	4 (19%)	2 (10%)	2 (10%)
p value		0.0207	0.0444	0.2898	1	0.2301	0.0120	0.1447	0.7285
Total	98	36	38	14	5	79	44	22	13

3037 **Poster Session**

Machine learning-based multiple cancer detections with circulating miRNA profiles in the blood. *First Author: Juntaro Matsuzaki, Division of Pharmacotherapeutics, Keio University Faculty of Pharmacy, Tokyo, Japan*

Background: Early detection of cancer is one of the most important unmet clinical demands. A wide variety of circulating microRNAs (miRNAs) that specifically indicate many types of cancer have been identified, and their miRNA expression profiles are considered as potential biomarkers. Therefore, circulating miRNAs may serve as a non-invasive liquid biopsy diagnostic tool for early detection of many types of cancer. Here, a novel blood-based diagnostic method combined with machine learning techniques is developed using the entire circulating miRNA expression repertoire in serum without prior selection of miRNA marker sets. **Methods:** To validate this diagnostic method, clinical serum samples from cancer patients with five types of cancer (breast cancer(272), colorectal cancer(239), lung cancer(223), stomach cancer(221) and pancreatic cancer(100)) and 289 non-cancer volunteers were collected. Serum samples were immediately processed and their small RNAs were extracted. The entire miRNA expression profile is analyzed via next generation sequencers. The resulting total miRNA expression profile was used to train machine learning models, including deep learning techniques, without prior selection of miRNAs by human intervention. The machine learning model was trained with a training set to test set ratio of 4:1 and was carefully monitored by 5-fold cross-validation to avoid overfitting. **Results:** The diagnostic model provided 88% accuracy for all five cancer types (mean). The overall average AUROC was 0.954. Especially for breast cancer, the machine learning model provided 90% accuracy and 91 % sensitivity at 90% specificity. The overall AUROC was 0.966. High sensitivity was obtained regardless of the stage of the cancers, indicating that the possibility of early detection of cancer is kept high. **Conclusions:** Circulating miRNAs can be informative biomarkers for the earliest cancer detection in combination with machine learning. Unlike other cancer diagnostic methods where only a handful number of biomarkers are considered, this novel miRNA diagnostic platform method that uses machine learning reads a large set of miRNA expression profiles and automatically extracts the specific patterns of miRNA expression for early detection of multiple cancer types. In addition, the main advantage of miRNA-based cancer diagnosis is that they are more sensitive even in the early stages of cancer, compared to other diagnostic methods, such as cell-free DNA diagnostics, where the sensitivity of many types of cancer in the early stages still remains low. This approach could be easily expanded to other cancer types. Given the potential value of early detection in fatal malignancies, further validation studies are justified in future population-based studies. Many cancer research institutes are currently conducting further clinical trials to validate this early cancer diagnosis based on miRNA expression profiles. Research Sponsor: Preferred Medicine, Inc.

3038 **Poster Session**

A single institution experience with droplet digital polymerase chain reaction (dd-PCR) liquid biopsy (LB) for therapeutic decision in advanced solid tumors. *First Author: Andre Marcio Murad, Personal. Oncologia de Precisao e Personalizada, Belo Horizonte, Brazil*

Background: Droplet digital polymerase chain reaction (ddPCR) is a promising method for analyzing minor amounts of cell-free circulating free nucleic acid (DNA and RNA) due to its high sensitivity, low cost, and fast reading, since it dispenses bioinformatics, making it an appropriate alternative to new generation sequencing (NGS) for the detection of biomarkers to guide molecularly targeted cancer therapy. The assay covers main actionable hotspot alterations across many actionable genes: EGFR(mutations), ALK (fusion, mutations), ROS1(fusion), BRAF(mutations), KRAS (mutations), NRAS(mutations), PIK3CA (mutations), ERBB2(CNV- copy number variation), ESR1(mutations), KIT(CNV) and PDGFRA(CNV). Therefore, our genes can be used in panels, both in therapeutically applied genotyping and in detecting molecular responses as well as in secondary resistance to tumors such as NSCLC, breast, cervix. rectal, GIST, melanoma and pancreas. **Methods:** dd-PCR was performed using the QX200 system (BIO-RAD, Hercules). The extraction of DNA and RNA was done using the magnetic beads technique of Thermofisher's MagMAX Kit. All samples were tested in duplicate. Up to now, 108 metastatic cancer patients were tested: NSCLC - 28 (26%), breast - 22 (20%), colorectal - 22(20%), melanoma - 18(17%), pancreas - 8(7%), ovarian - 6(6%), salivary glands - 2 (4%) and GIST 2(4%). **Results:** Significant genomic alterations were detected in 38(35%) patients: 10 (9%) mutations in the KRAS G12V gene (all in colorectal cancer), 10 (9%) ERBB2 amplification (breast cancer), 4 (3.65%) EGFR L858R mutations (NSCLC), 4 (3.5%) EGFR del19 mutations (NSLC), 4 (3.5%) EGFR T790M mutations (NSCLC), 4 (3.5%) BRAF-V600E mutations (colon and melanoma), 2 (1.8%) ALK-EML4 fusion (NSCLC). The MAF (Mutant Allele Fraction) ranged from 0.9% to 24%. In all cases, the results were decisive for the indication or change of a targeted therapy. Median turnaround time was 36 hours and the average cost of the panels was around 500 USD (median of 4 genes per panel). **Conclusions:** Our results suggest that dd-PCR is a highly sensitive method and could be used for a routine laboratory detection of the important genomic variations to determine the targeted therapy in patients with varied advanced solid tumors. Research Sponsor: None.

3039 **Poster Session**

Hyper engorged cancer associated macrophage-like cells in circulation predict for multi-organ metastatic disease in solid tumors. *First Author: Daniel J Gironda, Rutgers, the State University of New Jersey, New Brunswick, NJ*

Background: Patients with multiple organ metastases have poorer prognoses than those with a single organ metastasis, are frequently associated with drug resistance, and have higher tumor burden. Engorged (≥50um) Cancer Associated Macrophage-Like Cells (CAMLs) are a circulating stromal cell subtype detected in the blood of patients with solid tumors at high risk for recurrence or progression. While numerous studies have shown that ≥50um CAMLs predict poor clinical outcomes, meta-analysis of these studies have also suggested that hyper engorged CAMLs ≥100um (heCAMLs) may be associated with multifocal metastatic disease and even worse outcomes. In this prospective study, we evaluated the presence of heCAMLs in patients with metastatic disease and demonstrated a strong relationship with multi organ spread, which also correlated with shorter Progression Free Survival (PFS) and Overall Survival (OS). **Methods:** We prospectively recruited 151 patients with metastatic (m) mbreast (n = 58), mlung (n = 34), mprostate (n = 39), and mrenal (n = 20) cancers. Peripheral blood was collected prior to the induction of new treatment for metastatic cancer. Cells were isolated following standard CellSieve techniques, then imaged and measured in ZenBlue. Multi organ metastasis was defined as spread to ≥2 distant organ sites, or any spread to the brain. Single factor ANOVA was conducted to compare heCAML presence in multi organ metastatic patients versus patients with single organ site metastasis. Univariate and multivariate analysis was run to evaluate for PFS and OS against heCAMLs, and all known clinical parameters. **Results:** 150 viable samples (excluding 1 failed sample) were obtained. Multi organ metastases were present in 55% (n = 83/150) of patients. heCAMLs were found in 59% (n = 49/83) of the multi organ metastatic population, but only in 16% (n = 11/67) of the single site metastatic cohort ($p < 0.001$). heCAML presence appeared to differentiate multi organ vs single organ metastases in mbreast (85% vs. 52%, p = 0.006), mlung (71% vs. 26%, p = 0.025), mprostate (75% vs. 37%, p = 0.029), and mRCC (88% vs. 36%, p = 0.025). Further, in all n = 150 patients, heCAML presence predicted a significantly shorter median PFS of 4.5 versus 7.2 months, 24 month PFS (HR = 1.67, 95%CI = 1.13-2.45, p = 0.013), and significantly shorter median OS of 13.1 versus 20.4 months, 24 month OS (HR = 2.05, 95%CI = 1.24-3.39, p = 0.008). **Conclusions:** We examined a non-invasive prognostic blood based assay to determine its relationship to multi organ metastatic spread as well as its prognostic value in several solid cancers. These results showed patients with heCAMLs had higher rates of multi organ metastases, and appear to predict for shorter PFS and OS. Studies of larger cohorts are needed for prospective validation of these initial findings. Research Sponsor: Department of Defense (DARPA), U.S. National Institutes of Health.

3040 **Poster Session**

Blood-based tumor mutational burden from circulating tumor DNA (ctDNA) across advanced solid malignancies using a commercially available liquid biopsy assay. *First Author: Leylah Drusbosky, Guardant Health, Inc., Redwood City, CA*

Background: Pembrolizumab was recently FDA approved across solid tumors for TMB scores ≥ 10mut/Mb as assessed by next-generation sequencing (NGS) of tissue (tTMB). A prior study of advanced cancer patients treated with immunotherapy found that higher somatic TMB, as defined by the 80th percentile in each histology, was associated with better overall survival. Previously, bTMB assessed by ctDNA from patients with newly diagnosed advanced NSCLC at a score of 16 mut/MB correlated with a tTMB score of 10 mut/MB. TMB levels vary by cancer type, line of treatment, and therapy received; the distribution of bTMB scores across solid tumor types has not been well characterized. Here we report the distribution of bTMB scores in patients with advanced malignancies. **Methods:** We queried 5,610 samples from patients with different cancer types undergoing clinical cell-free DNA testing (Guardant360; Redwood City, CA) and assessed bTMB scores from October 2020 - January 2021. bTMB score was derived via a previously described computational algorithm examining the total number of synonymous and non-synonymous SNVs and indels across a 1.0MB genomic footprint. We assessed the success rate of bTMB evaluation, overlap with microsatellite instability (MSI) status, and defined the distribution of bTMB levels across indications in this dataset. **Results:** bTMB score was successfully assessed in 4,275/5,610 (76.3%) samples (Table). The majority of samples (58%) were tested at disease progression as compared to initial diagnosis (42%). The median turnaround time from sample receipt to clinical reporting was 11 days and decreased to 9 days over the course of the study. For the majority of cancer types the 80th percentile TMB was ≥ 16 mut/MB tissue equivalency. **Conclusions:** Our analysis demonstrates the feasibility of measuring bTMB using a commercially available liquid biopsy assay. bTMB scores trended higher than tTMB previously reported in these cancer types, reflecting the ability of ctDNA to better capture tumor heterogeneity. cfDNA may allow for exploration of bTMB evolution throughout treatment. TMB should be interpreted in the context of disease, treatment, and method; these data establish a pan-cancer benchmark for bTMB which will serve as a resource for further studies. Research Sponsor: None.

Tumor Type	Male %	Mean age	ctDNA tested at diagnosis	ctDNA tested at disease progression	80th %ile (mut/MB)	MSI-H and TMB ≥ 80th %ile	bTMB Success Rate
Melanoma	52%	62.9	47%	53%	23.8	0%	74%
Colorectal	56%	61.5	30%	70%	20.1	16%	84%
Lung	48%	69.3	58%	42%	20.2	3%	77%
Bladder	83%	70.9	46%	54%	20.1	13%	82%
Head & Neck	67%	65.6	38%	51%	17.4	7%	66%
GYN	0%	70.0	32%	68%	17.2	62%	70%
Breast	1%	61.7	22%	78%	15.3	7%	79%
Prostate	100%	72.6	16%	84%	13.4	18%	80%
Pancreatic	49%	67.1	48%	52%	11.4	6%	72%

3041 **Poster Session**

Single cell RNA-sequence analysis to identify transcriptomic differences associated with treatment outcome and ethnicity in circulating tumor cells (CTCs) from patients (pts) with metastatic colorectal cancer (mCRC). *First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: CTCs are a promising diagnostic and prognostic biomarker in colorectal cancer. The analysis of CTCs at the single-cell level may allow to capture tumor heterogeneity and identify novel prognostic and predictive markers in mCRC. Our aim was to evaluate whether the transcriptome profile of CTCs was associated with progression-free survival (PFS) in pts receiving treatment for mCRC and whether we could identify significant differences based on pts' ethnicity. **Methods:** Single CTCs were prospectively collected from 25 pts undergoing treatment for mCRC at the USC/Norris Comprehensive Cancer Center between April and October 2019. Pre-treatment peripheral blood was processed using CTC-FIND comprised filter separation and immunomagnetic depletion of CD45/50-expressing cells to collect ultra-pure CTCs samples. After isolation to single cell, CTCs were processed by single cell RNA-sequence (scRNAseq). Principal component analysis was used for clustering expression data. DESeq2 was used to identify differentially expressed genes between pts with short ($<$ 150 days) and long term ($>$ 150 days) PFS, as well as between Hispanic and non-Hispanic ethnicity with control for FDR ($Q < 0.1$). Ingenuity pathway analyses (IPA) of enriched pathway networks were performed. **Results:** Main pts characteristics were as follow: median age = 52 years; M/F = 18/7; Hispanics/non-Hispanics = 7/18; treatment line (n pts) = 1st (5), 2nd (11), $\geq$ 3rd (9). We identified 59 single CTC and CTC cluster from 22/25 pts (range 1-9, median = 2/pt). scRNAseq analysis identified two separate clusters of pts based on PFS (short term vs long term). Hispanic pts were mainly distributed within the short term PFS cluster. The IPA of the network of top 40 enriched pathways showed several pathways related with metabolism, such as Sirtuin signaling, mitochondrial dysfunction and oxidative phosphorylation, and IL6/JAK/STAT signaling pathways in pts with short term PFS ($Q < 0.05$). When comparing Hispanic vs non-Hispanic pts, we detected enrichment of neuroinflammation signaling pathway in Hispanics, including *CXCL8* (fold change, FC: 11.04), *GAD2* (FC: 4.77), *IRAK3* (FC: 17.06), *PLCG2* (FC: 4.65) and *TYROBP* (FC: 8.43) (all $Q < 0.05$). **Conclusions:** In our study CTCs transcriptome profiles showed an association with PFS in pts receiving treatment for mCRC, with an enrichment in mitochondria-related pathways and IL6/JAK/STAT signaling in the CTCs of pts with shorter PFS. Additionally, CTCs scRNAseq identified differentially expressed genes in Hispanic pts, displaying enrichment in neuroinflammation signaling. These results highlight the potential of CTCs molecular profiling as a tool to identify novel prognostic and predictive biomarkers in mCRC and actionable molecular pathways which may impact tumor spread and treatment response Research Sponsor: NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Victoria and Philip Wilson Research Fund, San Pedro Peninsula Cancer Guild, Daniel Butler Research Fund.

3042 **Poster Session**

Targeted ctDNA sequencing analysis reveals concurrent genomic alterations and its impact on TKI and immune checkpoint inhibitor therapy in advanced NSCLC from Asian population. *First Author: Wei Wu, University of California, San Francisco, San Francisco, CA*

Background: For advanced non-small cell lung cancer (NSCLC), liquid biopsy followed by targeted DNA sequencing is used in the clinical setting for driver-gene identification in circulating tumor DNA (ctDNA), tumor evolution and treatment monitoring. To understand the complexity and diversity of genetic alterations in advanced NSCLC, we examined the genetic landscape of late-stage NSCLC from an Asian population and its association with tyrosine kinase inhibitor (TKI) or immune checkpoint inhibitor (ICI) treatment. **Methods:** Plasma cell-free DNA (cfDNA) from 142 Asian patients with advanced NSCLC underwent real-world testing in a CAP-accredited and CLIA-certified central laboratory. We analyzed genetic alterations in cfDNA using an amplicon-based next-generation sequencing assay that covers 61 NSCLC related genes. 88 patients (62%) had received one or more lines of treatment. A similar cohort from Caucasian NSCLC was used for comparison (Blakely et al. *Nat Genet* 2017). Systematic co-mutation analysis, functional annotation and pathway enrichment analysis were performed. **Results:** The top 10 mutated genes in the Asian cohort were *EGFR* (66.2%), *TP53* (48.6%), *KRAS* (11.3%), *BRCA2* (7%), *CTNNB1* (6.3%), *PIK3CA* (6.3%), *SMAD4* (5.6%), *BRCA1* (4.9%), *MET* (3.5%) and *RB1* (3.5%). *EGFR* mutations occurred at hotspots in exons 18 – 21, with exon19 deletion, L858R, T790M, C797S, and G719A being the top-ranking alleles, similar to the Caucasian NSCLC cohort. Concurrent *KRAS* and *EGFR* mutations were higher in Asian cohort (8.5%) than in Caucasian cohort (0.56%). A rare PD-L1 structural variant (1.1%), reported to be related to immune evasion in other cancers (Kataoka et al. *Nature* 2016), was detected in the *EGFR*-mutated subgroup. Within the first line TKI-treated group, responders (CR+PR) harbored more alterations than non-responders ($p < 0.017$). Among ICI-treated NSCLC patients (anti-PD-1/PD-L1 mono- or polytherapy), responders from 1st line or 2nd line ICI treatment harbored fewer mutations than non-responders, but the distribution of mutational allele frequency (MAF) in responders was shifted to the right (more clonal than subclonal mutations). Functional annotation suggests that concurrent mutated genes and copy number alterations in advanced *EGFR*-mutant NSCLC were enriched in cell cycle, DNA repair, PI3K-AKT signaling pathways. **Conclusions:** We characterized the ctDNA-derived genetic landscape of advanced NSCLC from an Asian population and dissected mutated genes with the outcome of TKI or ICI treatment. We also report a rare PD-L1 structural variant in the *EGFR* mutated subgroup, which could be associated with immune evasion. Our analyses support the occurrence of clonal and subclonal driver co-alterations in *EGFR*-driven NSCLC, underlining the clinical utility of ctDNA detection for NSCLC diagnosis and treatment selection. Research Sponsor: Lucence Diagnostics.

3043 **Poster Session**

A dual target sequencing solution to assess genomic and epigenomic alterations in cell-free DNA with no sample splitting. *First Author: Grace Q. Zhao, Avida Biomed Inc., Fremont, CA*

Background: Assessing the genomic and epigenomic changes on plasma cell-free DNA (cfDNA) using next-generation sequencing (NGS) has become increasingly important for cancer detection and treatment selection guidance. However, two major hurdles of existing targeted NGS methods make them impractical for the clinical setting. First, there is no comprehensive, end to end, kit solution available for targeted methylation sequencing (TMS), let alone one that analyzes both mutation and methylation information in one assay. Second, the low yield of cfDNA from clinical blood samples presents a major challenge for conducting multi-omic analysis. Thus, an assay that is capable of both genomic and epigenomic analysis would be advantageous for clinical research and future diagnostic assays. **Methods:** Here, we report the performance of Point-n-SeqTM dual analysis, a kit solution that can provide in-depth DNA analysis with highly flexible and customizable focused panels to enable both genomic and epigenomic analysis without sample splitting. With custom panels of tens to thousands of markers designed with $>$ 99% first-pass success rate, we conducted both performance validation and multi-center, multi-operator, reproducibility studies. Using spike-in titration of cancer cell-line gDNA with known mutation and methylation profiles, Point-n-Seq assay achieved a reliable detection level down to 0.003% of tumor DNA with a linear relationship between the measured and expected fractions. Benchmarked with conventional targeted sequencing and methylation sequencing, Point-n-Seq solution also demonstrated improved performance, speed and shortened hands-on time. **Results:** In a pilot clinical study, a colorectal cancer (CRC) TMS panel covering 560 methylation markers and a mutation panel with $>$ 350 hotspot mutations in 22 genes were used in the dual assay. Using 1ml of plasma from late-stage CRC patients, cancer-specific methylation signals were detected in all samples tested, and oncogenic mutations. In an early-stage cohort (33 stage I/II CRC patient), comparison of the analysis between tumor-informed, personalized-mutation panels (~100 private SNVs) for each patient and the tumor-independent CRC methylation panels were conducted. The initial results showed that tumor-independent TMS assay achieved a comparable detection compared to the personalized tumor-informed approach. Moreover, cfDNA size information (fragmentome) is also integrated into the analysis of the same Point-n-Seq workflow to improve the assay sensitivity. **Conclusions:** Point-n-Seq dual analysis is poised to advance both research and clinical applications of early cancer detection, minimal residual disease (MRD), and monitoring. Research Sponsor: Avida Biomed seed fund.

3044 **Poster Session**

Genome-wide 5hmC profiles to enable cancer detection and tissue of origin classification in breast, colorectal, lung, ovarian, and pancreatic cancers. *First Author: David Haan, Bluestar Genomics, San Diego, CA*

Background: Epigenomics assays have recently become popular tools for identification of molecular biomarkers, both in tissue and in plasma. In particular 5-hydroxymethyl-cytosine (5hmC) method, has been shown to enable the epigenomic regulation of gene expression and subsequent gene activity, with different patterns, across several tumor and normal tissues types. In this study we show that 5hmC profiles enable discrete classification of tumor and normal tissue for breast, colorectal, lung ovary and pancreas. Such classification was also recapitulated in cfDNA from patient with breast, colorectal, lung, ovarian and pancreatic cancers. **Methods:** DNA was isolated from 176 fresh frozen tissues from breast, colorectal, lung, ovary and pancreas (44 per tumor per tissue type and up to 11 tumor tissues for each stage (I-IV)) and up to 10 normal tissues per tissue type. cfDNA was isolated from plasma from 783 non-cancer individuals and 569 cancer patients. Plasma-isolated cfDNA and tumor genomic DNA, were enriched for the 5hmC fraction using chemical labelling, sequenced, and aligned to a reference genome to construct features sets of 5hmC patterns. **Results:** 5hmC multinomial logistic regression analysis was employed across tumor and normal tissues and identified a set of specific and discrete tumor and normal tissue gene-based features. This indicates that we can classify samples regardless of source, with a high degree of accuracy, based on tissue of origin and also distinguish between normal and tumor status.Next, we employed a stacked ensemble machine learning algorithm combining multiple logistic regression models across diverse feature sets to the cfDNA dataset composed of 783 non cancers and 569 cancers comprising 67 breast, 118 colorectal, 210 Lung, 71 ovarian and 100 pancreatic cancers. We identified a genomic signature that enable the classification of non-cancer versus cancers with an outer fold cross validation sensitivity of 49% (CI 45%-53%) at 99% specificity. Further, individual cancer outer fold cross validation sensitivity at 99% specificity, was measured as follows: breast 30% (CI 119% -42%); colorectal 41% (CI 32%-50%); lung 49% (CI 42%-56%); ovarian 72% (CI 60-82%); pancreatic 56% (CI 46%-66%). **Conclusions:** This study demonstrates that 5hmC profiles can distinguish cancer and normal tissues based on their origin. Further, 5hmC changes in cfDNA enables detection of the several cancer types: breast, colorectal, lung, ovarian and pancreatic cancers. Our technology provides a non-invasive tool for cancer detection with low risk sample collection enabling improved compliance than current screening methods. Among other utilities, we believe our technology could be applied to asymptomatic high-risk individuals thus enabling enrichment for those subjects that most need a diagnostic imaging follow up. Research Sponsor: None.

3045 **Poster Session**

Multiomic, plasma-only ctDNA NGS assay for minimal residual disease (MRD) detection in solid tumors. *First Author: Jessica Kurata, Guardant Health, Redwood City, CA*

Background: Detection of minimal residual disease (MRD) by circulating tumor DNA (ctDNA) post-curative intent treatment is predictive of recurrence in many solid tumors. Due to biological challenges with low ctDNA shed in early-stage disease and potential to detect non-tumor derived alterations in plasma (e.g. CHIP), most ctDNA MRD assays are dependent on *apriori* knowledge of genomic alterations from tumor tissue to achieve high sensitivity and specificity. Tissue-dependent methods limit the clinical application of a MRD assay, especially in cancer types where tissue biopsy is challenging, neoadjuvant therapy (NAT) is standard of care, and/or rapid turnaround times are needed for clinical decision making. We previously validated an assay (Guardant Reveal) that combines somatic and epigenomic analysis to detect ctDNA from early-stage colorectal tumors without tumor tissue or peripheral blood cells. Here we describe the expansion of this assay to detect MRD across multiple tumor types. **Methods:** Cell-free DNA (cfDNA) fragments are extracted from patient plasma, partitioned based on methylation fraction, enriched using a panel to target informative genomic and epigenomic regions, barcoded, and pooled for sequencing. Methylation status is determined non-destructively and with minimal loss of molecules, allowing sensitive genomic and epigenomic analysis of the same cfDNA fragments. A single assay with a total panel size of 5.3 Mb was developed for MRD analysis in multiple cancer types, including CRC, Lung and Bladder. A "ctDNA detected" result is defined by the de novo identification of tumor-derived somatic variants and/or the observation of a tumor-specific methylation profile exceeding predefined thresholds. **Results:** The assay performance was tested using 163 pre-treatment clinical samples from patients with early-stage non small cell lung cancer (NSCLC) and bladder cancer and 133 self-declared healthy donors. Sensitivity for pre-treatment detection in NSCLC was 68.9% at 95% specificity (20/42 Stage I: 47.6%, 25/30 Stage II: 83.3%, 19/21 Stage III: 90.5%). Sensitivity for bladder cancer was 44.2% at 95% specificity (13/43 NMIBC: 30.2%, 18/27 MIBC: 66.7%). Additional development from larger cohorts and other tumor types is ongoing and data will be presented as available. **Conclusions:** Using cancer-specific genomic and epigenomic signals combined with learning-based classifiers, we developed a highly specific method for detecting the presence of ctDNA in early-stage NSCLC and bladder cancer patients from plasma without the need for tumor tissue but with comparable sensitivities to tissue-dependent approaches. A plasma-only MRD assay will allow for greater clinical impact by overcoming the challenges of tissue procurement, particularly following NAT, and enabling faster time to results. Research Sponsor: Guardant Health.

3046 **Poster Session**

Addition of selpercatinib to overcome osimertinib resistance in non-small cell lung cancer (NSCLC) with acquired RET fusion detected in ctDNA at very low allele frequency. *First Author: Leeseul Kim, Developmental Therapeutics Institute, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Osimertinib, a highly selective third generation EGFR tyrosine kinase inhibitor (TKI) became the standard front-line therapy for EGFR-mutant NSCLC. However, therapeutic options are limited for TKI resistance which commonly occurs. Therefore, overcoming acquired resistance to osimertinib remains an important high unmet need in the field of precision oncology. Herein, we present the first case of advanced adenocarcinoma of the lung that showed notable response with the addition of selpercatinib after acquired resistance to osimertinib monotherapy. **Methods:** Case presentation. **Results:** A 37-year-old woman with stage IVB adenocarcinoma of lung with osseous, hepatic and brain metastases initially received one cycle of carboplatin, pemetrexed and pembrolizumab. Based on the EGFR exon19 deletion detected from ctDNA NGS assay (Guardant 360) [variant allele frequency (VAF) 62.7%], the treatment regimen was changed to osimertinib monotherapy (80mg PO daily). Bevacizumab was empirically added given CNS involvement. She maintained overall stable disease for 10 months before subsequent CT showed disease progression. The treatment regimen was switched to atezolizumab, bevacizumab, paclitaxel and carboplatin combination therapy. She tolerated 6 cycles of the regimen in 4 month before a subsequent brain MRI revealed progression of the metastatic brain disease with new leptomeningeal disease. Whole brain radiotherapy was performed and decision was made to start combination TKI treatment of selpercatinib (120mg BID) added to the osimertinib (80mg daily) monotherapy based on her repeat ctDNA NGS assay result showing concurrent acquired CCDC6RET fusion (VAF 0.05%) and EGFR exon 19 deletion (VAF 10.0%). The 6 week follow-up CT demonstrated significant decrease in the largest lung mass (33.95*24.22mm->32.50*16.07mm). Repeat ctDNA NGS assay at one week after selpercatinib use showed disappearance of RET fusion and significant decrease in EGFR clone (VAF 10.0% to 0.05%). **Conclusions:** It has been reported that co-occurring RET fusions in NSCLC patients with EGFR mutations may contribute to acquired resistance to EGFR inhibitors. Several successful cases of cabozantinib, a non-selective RET inhibitor, or pralsetinib, a selective RET inhibitor combined with EGFR inhibitor, have been reported to aid in overcoming the acquired resistance to EGFR inhibitors. To date, there has been no report of clinical benefit in adding a RET inhibitor based on ctDNA detection of RET fusion with minute variant allele frequency. We for the first time report the case of overcoming acquired resistance to osimertinib by adding selpercatinib, a selective RET inhibitor in NSCLC patients with acquired RET fusion detected in ctDNA at VAF of 0.05%. Research Sponsor: None.

3047 **Poster Session**

Concordancy of immunocytochemistry profiling of circulating tumor cells with immunohistochemistry for analysis of therapeutically relevant biomarkers. *First Author: Dadasaheb B Akolkar, Datar Cancer Genetics, Nasik, India*

Background: Immunohistochemistry (IHC) profiling of tumor tissue is the present standard for evaluation of therapeutically relevant biomarkers such as ER, PR, HER2, AR, ARv7, PD-L1 and MMR for selection of targeted, endocrine and checkpoint inhibitor therapy selection. However, this critical analysis is dependent on availability of tumor tissue obtained by an invasive biopsy. Challenges to this analysis include insufficient tumor tissue and inability to perform a repeat biopsy to obtain fresh tumor tissue. We have previously described an approach for negative enrichment of Circulating Tumor Cells (CTCs) from peripheral blood and for Immunocytochemistry (ICC) profiling of these CTCs for detection of diagnostically relevant tissue of origin and subtype specific markers, concordant with tumor tissue analysis. **Methods:** In the present study, we determined concordance between tumor tissue (HPE) and CTCs (ICC) for ascertaining the status of therapeutically relevant markers ER, PR, HER2, AR, ARv7 PD-L1 and MMR. We evaluated 201 matched pairs of tumor tissue (FFPE blocks) and CTCs obtained from peripheral blood. **Results:** Among the 743 paired assays on matched tumor tissue and CTCs, concordance (positive or negative) was observed in 651 matched pairs (87.6%). The concordance was 82.9% for ER, 100% for PR, 90.2 % for Her2, 93.8% for AR, 90% for Arv7, 85.1% and 87.6% for PD-L1 clones 22c3 and 28-8, and 85.6% for MMR (MLH1, MSH2, MSH6, and PMS2). **Conclusions:** The study findings indicate that ICC analysis of CTCs may be able to substitute IHC analysis of tumor tissue for profiling of therapeutically relevant markers. This approach may have application in cases where tumor tissue may be limiting and / or where an invasive biopsy to obtain tumor tissue may be unviable. Research Sponsor: None.

3048 **Poster Session**

Development of extracellular vesicles-based classifier for detection of early-stage bladder, ovarian, and pancreatic cancer. *First Author: Juan Pablo Hinestrosa, Biological Dynamics, San Diego, CA*

Background: Many cancers are lethal because they present with metastatic disease. Because localized/resectable tumors produce vague symptoms, diagnosis is delayed. In pancreatic cancer, only ~10% of patients survive five years, and it will soon become the second leading cause of cancer-related deaths in the USA. For patients with metastatic disease, the 2- and 5-year survival is $< 10\%$ and ~3%, respectively. For the few patients with local disease, 5-year survival is ~40%. Many other cancers have comparable differences between early- and late-stage disease. It is apparent a diagnostic assay for early-stage cancers would transform the field by minimizing the need for aggressive surgeries and other harsh interventions, and by its potential to increase survival. Identifying cancer-specific aberrations in blood-based "liquid" biopsies offers a prospect for a non-invasive cancer detection tool. In the bloodstream, there are extracellular vesicles (EVs) with cargoes including membrane and cytosolic proteins, as well as RNA and lipids derived from their parent cells. **Methods:** We used an alternating current electrokinetics (ACE) microarray to isolate EVs from the plasma of stage I and II bladder (N = 48), ovarian (N = 42), and pancreatic cancer patients (N = 44), and healthy volunteers (N = 110). EVs were analyzed using multiplex protein immunoassays for 54 cancer-related proteins. EV protein expression patterns were analyzed using stepwise logistic regression followed by a split between training and test sets (67%/33% respectively). This process enabled biomarker selection and generation of a classifier to discriminate between cancer and healthy donors. **Results:** The EV protein-based classifier had an overall area under curve (AUC) of 0.95 with a sensitivity of 71.2% (69.4% – 73.0%, at 95% confidence interval) at $> 99\%$ specificity. The classifier's performance for the pancreatic cancer cohort was very strong, with overall sensitivity of 95.7% (94.6% – 96.9%, at 95% confidence interval) at $> 99\%$ specificity. **Conclusions:** EV-associated proteins may enable early cancer detection where surgical resection is most likely to improve outcomes. The classifier's performance for the initial three cancers studied showed encouraging results. Future efforts will include examining additional cancer types and evaluating the classifier performance using samples from donors with related benign conditions with the aim of a pan-cancer early detection assay. Research Sponsor: Biological Dynamics.

3049 **Poster Session**

Dermatologic adverse events of brentuximab vedotin: Characteristics, management, and their relationship with dose regimen. *First Author: Yuna Oh, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Owing to its high efficacy and tolerability, brentuximab vedotin (BV) is increasingly being favored over other aggressive systemic therapies for the treatment of various CD30+ Hodgkin and non-Hodgkin lymphomas, including peripheral T-cell lymphoma and cutaneous T-cell lymphomas. Dermatologic adverse events (dAE) are one of the most common toxicities associated with BV but data regarding their characteristics including correlation to dose, time to occurrence, and management is scarce. We aim to describe the clinical and pathologic characteristics of dAEs associated with BV, their relationship with administered dose regimen, and available management strategies. **Methods:** An IRB-approved retrospective analysis was conducted for all patients who had received at least one cycle of BV from Memorial Sloan Kettering Cancer Center in 2009-2020. Logistic regression, χ^2, student's t-test were performed for univariate analyses. Kaplan-Meier survival and multivariate Cox proportional hazard model evaluated dAE occurrence stratified by 5 major dose regimens (single cycle, 1.2mg q1w, 1.2mg q2w, 1.2mg q3w, 1.8mg q3w). **Results:** Of 611 patients, 201 experienced dAE with median time-to-event of 24 days and 29% experiencing $>$ 1 dAEs. Rash was the most common (62%; 142/230), followed by alopecia (20%) and xerosis (13%). For rash, 50% reported involvement of only the extremities and/or acral sites compared to 25% who had generalized rash. Of those reported (111), 68 patients had grade 1 dAE (61%), 38 grade 2 (34%), and 5 grade 3 (5%)-all grade 3 were rash (maculopapular/morbilliform). 14 cases (7%) resulted in treatment interruptions and 6 in discontinuations due to dAEs (3%). Pathology were often nonspecific consistent with a hypersensitivity reaction: spongiotic/psoriasiform dermatitis with perivascular lymphocytic infiltrates. Patients undergoing weekly regimen were at a statistically and clinically significantly higher risk of dAE during the first 100 days of BV treatment (p = 0.001). Between the two most frequently administered dose regimens (1.8mg vs. 1.2mg, q3w), the higher dose carried 105% higher risk for dAE (HR: 2.047, p = 0.053). Those who had received a single cycle of BV had the lowest risk compared to all other regimen (1/42, p = 0.001). Topical and/or systemic steroids were most frequently prescribed (43%) with 12% of patients requiring systemic steroids. Other treatments varied ranging from antihistamines to moisturizers. **Conclusions:** Understanding of the detailed characteristics, management strategies, dose-dependent effects associated with BV is critical to provide clinical guidance for primary providers and minimize treatment interruptions or discontinuations. The results overall suggest that the risk for dAEs is dose-dependent with those undergoing frequent dosing regimens having a greater risk, although most dAEs remain mild or low-grade. Research Sponsor: None.

3050 **Poster Session**

A phase 1 study of TAK-164, an anti-guanylyl cyclase C (GCC) antibody-drug conjugate (ADC), in patients (pts) with advanced gastrointestinal (GI) cancers expressing GCC. *First Author: Richard D. Kim, Moffitt Cancer Center, Tampa, FL*

Background: TAK-164 is a second-generation ADC comprising a human IgG1 monoclonal antibody targeting GCC conjugated to a DNA-damaging alkylating agent by a peptide linker. TAK-164 demonstrated cytotoxic and antitumor activity in GCC-expressing cells and xenograft mouse models. This first-in-human study investigated the safety, pharmacokinetics (PK), and preliminary efficacy of TAK-164. **Methods:** Adult pts with GCC-positive, advanced/metastatic GI cancers received TAK-164 intravenously on day 1 of a 21-day cycle (Q3W). Dose escalation proceeded based on cycle 1 safety data via a Bayesian model of modified toxicity probability interval starting at 0.004 mg/kg. **Results:** Thirty-one pts were enrolled. Median age was 58 years (range 32–72), 58.1% of pts were female and 64.5% had colon carcinoma. The median number of prior lines of therapy was 4 (range 2–9). TAK-164 was given at 0.004 (n = 1), 0.008 (n = 1), 0.016 (n = 1), 0.032 (n = 5), 0.064 (n = 7), 0.12 (n = 7), 0.16 (n = 2), 0.19 (n = 3), 0.25 (n = 3) and 0.32 mg/kg (n = 1). No pts had dose-limiting toxicities (DLT) in cycle 1 up to 0.32 mg/kg. Three pts had adverse events (AEs) after cycle 1 considered to be DLTs: 1 pt receiving 0.19 mg/kg (grade 3 pyrexia and grade 5 hepatic failure) and 2 pts receiving 0.25 mg/kg (1 pt had grade 3 nausea, and grade 4 platelet count decrease and neutrophil count decrease; 1 pt had grade 4 hepatic failure and grade 4 platelet count decrease). Dosing was capped at 0.19 mg/kg due to hepatic toxicity and the recommended phase 2 dose (RP2D) was determined as 0.064 mg/kg based on safety and tolerability beyond cycle 1. Overall, pts received a median of 2 (range 1–8) treatment cycles. TAK-164-related treatment-emergent AEs (TEAEs) reported in 77.4% of pts included platelet count decrease (58.1%), fatigue (38.7%), and anemia (32.3%). TAK-164-related grade $\geq$3 TEAEs reported in 32.3% of pts included platelet count decrease (12.9%), alanine aminotransferase increase, aspartate aminotransferase increase, fatigue, and anemia (all 9.7%). Three pts discontinued due to TAK-164-related TEAEs. There was a dose-dependent increase in TAK-164 maximum plasma concentration and exposure over the range 0.016–0.32 mg/kg, with no meaningful accumulation in PK with repeat Q3W dosing. One pt receiving TAK-164 0.19 mg/kg showed γH2AX induction via immunohistochemistry in a post-treatment biopsy, demonstrating target engagement. One pt with low baseline GCC expression who received 5 cycles of TAK-164 0.008 mg/kg had an unconfirmed partial response at cycle 4; 11 of 25 (44.0%) evaluable pts had a best overall response of stable disease. **Conclusions:** TAK-164 appeared to have a manageable safety profile up to 0.064 mg/kg in pts with advanced GI cancers; hepatic toxicity was identified as a potential risk. The RP2D was determined as 0.064 mg/kg but was considered insufficient to derive significant clinical benefit. Clinical trial information: NCT03449030. Research Sponsor: Millennium Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

3051 **Poster Session**

Phase I study of mesothelin-targeted immunotoxin LMB-100 in combination with tofacitinib in patients with advanced pancreatobiliary cancer. *First Author: Nebojsa Skorupan, National Cancer Insititute, Bethesda, MD*

Background: LMB-100 recombinant immunotoxin consists of a mesothelin-binding Fab for targeting a modified *Pseudomonas* exotoxin A payload to tumors. Previous clinical trials demonstrated that almost all patients formed anti-drug-antibodies (ADAs) to LMB-100 that made administration beyond cycle 2 ineffective. Tofacitinib is an oral JAK inhibitor that prevented formation of ADAs against a closely related immunotoxin in pre-clinical studies. The primary objective of the dose escalation cohort was assessment of safety and tolerability of LMB-100 given with tofacitinib to patients with mesothelin-expressing solid tumors. The primary objective of the expansion cohort was to determine whether co-administration of tofacitinib delays formation of neutralizing LMB-100 ADAs. **Methods:** Patients (n = 13) with pancreatic adenocarcinoma and other mesothelin-expressing solid tumors (n = 3; cholangiocarcinoma, appendix, cystadenocarcinoma) were treated for up to 3 cycles with LMB-100 as a 30-minute infusion on days 4, 6, and 8 at two dose levels (100 and 140 mcg/kg) and co-treated with oral tofacitinib for the first 10 days of the cycle (10 mg BID). **Results:** Dose level 1 of LMB-100 was started at 100 mcg/kg one dose level below the single agent MTD. Dose escalation to 140 mcg/kg (dose level 2) resulted in DLTs in 2 of the 3 patients treated: grade 3 cardiac toxicity and grade 4 hyponatremia, both attributed to capillary leak syndrome. Ultimately, 7 patients were treated at dose level 1 without DLTs and 100 mcg/kg was chosen as the LMB-100 dose for the expansion cohort. The last of 6 patients treated in the expansion cohort developed grade 4 pericardial effusion leading to early closure of the study for toxicity. No objective responses were seen. Of the 8 patients who received two cycles of treatment at MTD, 4 met prespecified criteria for ADA prevention, and 2 patients who went on to receive cycle 3 had detectable LMB-100 plasma drug levels after administration. **Conclusions:** LMB-100 was unable to be co-administered safely with tofacitinib. ADA formation was prevented in 2 patients through 3 cycles, a rare occurrence. Clinical trial information: NCT04034238. Research Sponsor: U.S. National Institutes of Health.

3052 **Poster Session**

RNA sequencing effectively identifies gene fusions undetected by DNA sequencing in lung adenocarcinomas. *First Author: Ruiying Zhao, Department of Pathology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China*

Background: Next-generation sequencing of DNA, which can provide valid information for clinical therapeutic decision-making, has been widely used in the management of lung cancer especially adenocarcinoma. However, due to its technical limitations for detecting certain alterations such as gene rearrangement, the DNA-based sequencing (DNA-seq) may miss the actionable alteration in some cases, who would have benefited from targeted therapy. The study aimed to evaluate the capability of RNA sequencing (RNA-seq) in identifying DNA-seq undetectable gene alterations in lung adenocarcinomas. **Methods:** A total of 219 lung adenocarcinomas, which had no driver alteration detected by DNA-seq (OncoScreen Plus, Burning Rock Biotech) and had a max AF $\geq$5%, underwent capture-based RNA-seq using a custom panel (OncoRNA, Burning Rock Biotech) spanning full transcripts of 115 genes commonly involved in cancer genomic rearrangements. Furthermore, an independent cohort of 100 DNA-seq driver–negative lung adenocarcinomas were also subjected to RNA-seq with the same panel. **Results:** In the discovery cohort, 166/219 samples (75.8%) generated qualified RNA-seq data for subsequent analyses. RNA-seq identified 44 previously undetected alterations (26.5%), including 40 gene fusions (24.1%), 1 *MET* exon14 skipping variant (*MET*ex14, 0.6%) and 3 other alternative splicing variants (1.8%). Among them, 14 (8.4%) were potential actionable alterations, consisting of *MET*ex14 and in-frame fusions containing functional domain of the driver gene (4 *ROS1* fusions, 3 *BRAF* fusions, 2 *NRG1* fusions, 2 *EGFR* fusions, 1 *ALK* fusion and 1 *MET* fusion). In the validation cohort, 69/100 samples (69.0%) generated qualified data. RNA-seq identified 22 DNA-seq undetected alterations (31.9%), with 7 of them being potential actionable fusions (10.1%). *ROS1* fusion remained as the most common actionable alteration (n = 3), followed by *ALK* fusion (n = 2), *EGFR* fusion (n = 1) and *MET* fusion (n = 1). Further analyses of the two datasets revealed that lacking sufficient coverage spanning the rearrangement breakpoint in the DNA-seq panel mainly accounted for the failure of DNA-seq on detecting these fusions. This can be improved by increasing the corresponding probe coverage in the DNA-seq panel. In addition, complex genomic rearrangement at DNA level and the presence of repetitive sequence in the intronic region spanning or adjacent to the breakpoint might lead to missed calling of canonical fusions by DNA-seq. **Conclusions:** Targeted RNA-seq can effectively identify genomic rearrangements that are undetectable by DNA-seq and provide lung adenocarcinoma patients with more opportunities for targeted therapy. Therefore, it should be recommended for all patients, in whom DNA-seq fails to detect driver alteration. Research Sponsor: None.

3053 **Poster Session**

Sputum supernatant as a viable alternative for liquid biopsy in advanced non-small cell lung cancer. *First Author: Chengzhi Zhou, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*

Background: Sputum has previously attracted attention as a potential medium for detecting genetic and epigenetic alterations in early-stage lung cancer. Recent progress in advanced non-small cell lung cancer (aNSCLC) has highlighted plasma as an option in scenarios where tissue specimens are unavailable. In this study, we investigated the feasibility of mutation profiling with sputum from aNSCLC patients. **Methods:** Matched tissue (TIS), whole blood, and either induced or spontaneous sputum were collected from 42 prospectively enrolled, previously untreated patients with stage IIIB-IV NSCLC. Eight and two milliliters of whole blood and sputum were respectively used for preparation of plasma (PLA) and sputum supernatant (SPU). Capture-based targeted sequencing of TIS, PLA and SPU samples was performed with a panel of 520 cancer-related genes. **Results:** The cohort had a median age of 59 (range 26-79) with a majority of men (31/42). Thirty-five patients were diagnosed with lung adenocarcinoma (LUAD) and the remaining seven with squamous cell carcinoma (LUSC). There were more non-smokers (26/42) than smokers. Most patients (34/42) had metastatic disease. First, we assessed the performance of three sample types in terms of key quality control indices. PLA and SPU showed maximum allelic fraction that were both significantly smaller than that of TIS. Subsequently compared was positive detection rate, TIS, PLA, and SPU achieved respective rates of 92.9%, 71.4%, and 59.5%, revealing comparable levels between PLA and SPU samples ($p = 0.36$). Rates of detection were highly similar between induced (54.6%) and spontaneous sputum (61.3%), but were higher in LUSC (85.7%) than in LUAD patients (54.3%) although this difference was not statistically significant ($p = 0.21$). Furthermore, detection rates rose in smokers (81.3% for PLA and SPU, 100% for TIS). Next, using TIS as the gold standard, we compared the sensitivity of detecting eight established driver alterations in NSCLC with the two liquid biopsies. SPU and TIS achieved respective levels of 50.0% and 70.0%, which, similar to detection rate, improved to 88.9% (8/9) and 77.8% (7/9) in the smokers subgroup. Importantly, detection of altered *KRAS* and *ALK* was more sensitive with SPU (6/6, 2/3, entire cohort) than with PLA (5/6, 1/3). For *EGFR* mutation, which occurred mainly in nonsmokers, the sensitivity was considerably lower in SPU (4/14, entire cohort) than in PLA (12/14). Detection of mutant *MET*, however, appeared difficult for both biopsies (0/4). In addition, there was a high level of correlation between estimates of tumor mutational burden based on PLA and on SPU (Pearson $r^2 = 0.58$). **Conclusions:** Our study demonstrated that for aNSCLC patients, sputum supernatant demonstrates comparable performance as plasma. Sputum is therefore a viable alternative for profiling for established driver alterations in aNSCLC, especially in smokers. Research Sponsor: None.

3054 **Poster Session**

Novel imaging biomarkers predict progression-free survival in stage 3 NSCLC treated with chemoradiation and durvalumab. *First Author: Khalid Jazieh, Cleveland Clinic Foundation, Cleveland, OH*

Background: The current management of stage III non-small cell lung cancer (NSCLC) is chemoradiation followed by durvalumab consolidation. There are no robust biomarkers that predict benefit from this regimen. We evaluated the utility of novel imaging biomarkers (radiomics) to distinguish patients with stage III NSCLC who will benefit from treatment from those likely to progress despite therapy. **Methods:** Patients with stage III NSCLC treated at our center with chemoradiation and durvalumab from July 2017 - July 2019 were identified. We collected patient clinical outcomes, subtype of NSCLC, and PD-L1 expression as well as pre-treatment CT images. Images were split into training and test sets. Lung tumors were contoured on 3D-Slicer software and 1542 radiomic features capturing both intra- and peritumoral texture patterns were extracted. The primary endpoint of this study was progression-free survival (PFS), and the secondary objective was difference in PFS within high PD-L1 ($\geq$50%) and low PDL1 ($<$50%) groups. We used the least absolute shrinkage and selection operator (LASSO) Cox regression model to build the radiomic signature for PFS. A risk score was computed according to a linear combination of selected features and their corresponding coefficients. High- and low-risk groups were defined based on median radiomics risk score. Multivariable Cox regression analysis was performed to evaluate the effect of each factor on PFS. We performed Kaplan–Meier survival analysis and log-rank tests to assess prognostic ability of the features. **Results:** We identified 118 patients who fit our criteria with available CT images and randomly divided them into a training (n=59) and a test set (n=59). The radiomic risk score was calculated using a linear combination of the top six selected features with corresponding coefficients. In a multivariable analysis using clinicopathologic and radiomic signatures, the radiomics risk-score and PD-L1 expression were found to be significantly associated with PFS in training (risk-score: HR = 2.3, 95% CI: [1.46 – 3.63], P = 0.0003; PD-L1: HR = 0.31, 95% CI: [0.081 – 0.96], P = 0.038) and test sets (risk-score: HR= 2.56, 95% CI: [1.75 – 4], P = 8.7e-05; PD-L1: HR = 0.27, 95% CI: [0.048 – 0.58], P = 0.005). Kaplan-Meier analyses showed a significantly shorter PFS in the high-risk radiomics group versus the low-risk group ($P < 0.0001$). The radiomics risk scores were also predictive of significant differences in PFS within both the low (p=0.0005) and high (p=0.0007) PD-L1 groups. **Conclusions:** Radiomic biomarkers from pre-treatment CT images in stage III NSCLC patients were predictive of PFS to chemoradiation followed by durvalumab and could predict outcomes regardless of PD-L1 level. Pre-treatment radiomics may allow early prediction of benefit and expedite more aggressive treatment for high-risk patients. Additional validation of these imaging biomarkers is warranted. Research Sponsor: None.

3055 **Poster Session**

Differences of US-FNA BSRTC class, postoperative pathology, and mutation landscape of thyroid nodules between China and other countries. *First Author: Yuntao Song, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Head and Neck Surgery, Peking University Cancer Hospital and Institute, Beijing, China*

Background: Ultrasound and ultrasound-guided fine needle aspiration (US-FNA) are the first choice for judging benign and malignant thyroid nodules. This study will report on the differences of US-FNA BSRTC class, postoperative pathology and mutation landscape of thyroid nodules between China and other countries. **Methods:** We conducted a prospective study containing 383 FNA samples of thyroid nodules. For most of these FNA samples, genomic DNA and RNA were extracted and sequenced with FSZ-Thyroid NGS Panel V1, and postoperative pathology were followed up. Moreover, we also compared results of this study with those of West China Hospital in China, Yamashita Thyroid Hospital in Japan, and Cleveland Clinic in the United States. **Results:** Among the 383 FNA samples, the proportions of BSRTC class I to VI were 10.7%, 6.3%, 18.8%, 3.7%, 12.3%, and 48.3% respectively. Compared with study in other countries, the proportion of class II was significantly lower than that in Japan and the United States. Meanwhile, the proportion of class V and VI were significantly higher than the above two countries. Subsequently, 232 thyroid nodules were surgically removed. Postoperative pathology showed that the proportion of malignant tumors (85.3%) was also significantly higher than reported in Japan and the United States. But compared with other studies in China, there was no significant difference. Most of the malignant tumors were papillary thyroid cancer (PTC, 96%), accompanied with 2 follicular thyroid cancer (FTC), 3 medullary cancer (MTC) and 3 anaplastic thyroid cancer (ATC). Compared with study in the United States, the proportion of PTC and FTC were elevated (96% vs. 85.3%) and reduced (1% vs. 9.3%) respectively. At last, we also analysis the mutation landscape of 180 malignant tumors. Compared with TCGA study, the frequency of BRAF V600E in PTC in our study was significantly higher than that of TCGA (73.3% vs. 58%), and the frequency of RAS mutation was significantly lower (1.2% vs. 12.6%). And compared with an institutional experience of ThyroSeq v3 for Bethesda III and IV at the University of Pittsburgh Medical Center, the frequency of BRAF V600E and RAS mutation in Bethesda III-IV malignant tumors was also significantly higher (45.8% vs. 1.4%) and lower (8.3% vs. 47.1%). **Conclusions:** There were significant differences in BSRTC class and postoperative pathology between China and other countries, such as Japan and the United States. The possible reasons included that the indications for FNA in China were different. For example, most of patients who underwent FNA in this study had suspicious clinical/ultrasound features. So the proportion of BSRTC class V and VI as well as the malignant rate were elevated. On the other hand, more BRAF V600E and less RAS mutations were detected in malignant tumors in this study which might result from racial differentiation and discrepancy in proportion of PTC and FTC. Research Sponsor: genetronhealth.

3056 **Poster Session**

Circulating genetically abnormal cells combined with artificial intelligence for accurate and non-invasive early detection on NSCLC. *First Author: Han Yang, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China*

Background: Non-small-cell carcinoma (NCSLC) is the most common type of early lung cancer. Early detection of NSCLC is still a diagnostic challenge. Current clinical management of patients with pulmonary nodule is inefficient and may lead to misclassification, thus increasing healthcare expenses. Further, a few previous studies showed liquid biopsy and artificial intelligence (AI) platform on computed tomography (CT) imaging contributes to early NSCLC detection. Still, there is something lacking in a precise and authorized lung nodule classifier to minimize discomfort of patients. This study aims to evaluate the possibility and effectiveness of combining circulating genetically abnormal cells (CACs) with an AI platform on CT imaging to improve the diagnostic route for NSCLC. **Methods:** A prospective cohort of 101 in-patients was enrolled from Sep. 1, 2020 to Jan. 15, 2021, with non-calcified pulmonary nodules, ranging from 0.5 to 3 cm in diameter, indicated by CT. The participants' pulmonary nodules will be assessed by two evaluation tools: CAC detection on full blood and AI platform on CT imaging. The diagnostic performances of the two tools were evaluated in a blinded validation study respectively and combined in an open-label retrospective analysis. **Results:** 68 of enrolled patients were confirmed as NSCLC by pathology. The diagnostic performance of CACs for NSCLC detection was 80.9% for sensitivity and 87.3% for positive predictive value (PPV) while overall accuracy reaches 79.2%. AI platform showed a slight disadvantage as 78.6% for PPV and 73.5% for accuracy. 9 false-negative patients on CAC results could be reversed with a combination of AI platform on CT imaging, while sensitivity rises to 94.1%. However, of 33 benign nodules patients, 8 wrong diagnoses by CAC detection could decrease to 2 when combined with the results from the AI platform, which may avoid unnecessary biopsies. **Conclusions:** Coupling CAC with an AI platform on CT imaging could be a useful strategy to improve the diagnostic route for NSCLC and avoid unnecessary biopsies. Research Sponsor: None.

	Sensitivity (%)	95% CI (%)	PPV (%)	95% CI (%)	+LR (%)	95% CI (%)
CAC	80.9	69.5–89.4	87.3	78.8–92.7	3.34	1.8–6.2
AI-CT	78.6	63.1–89.7	78.6	67.9–86.4	2.25	1.3–3.9
Combined	94.1	85.6–98.4	96.8	89.3–99.2	15.5	4.1–59.6

3057 **Poster Session**

Prediction of adenocarcinoma among other subtypes of lung cancer from CT using deep learning. *First Author: Noah Waterfield Price, Optellum, Oxford, United Kingdom*

Background: Determination of histological subtype is a crucial step in the management of patients with lung cancer as it informs prognosis and management. The identification of adenocarcinoma (AC) is particularly important with new targeted treatments becoming available. Although the gold standard for diagnosing histological subtype is pathological analysis of tissue samples, interventions can present a risk of complication. Imaging-based, computational approaches to distinguishing malignant from benign lesions have shown promising results. A similar approach may also be applied to determining histological subtype, which could provide an early, non-invasive alternative or complimentary method to biopsy. Here, we investigate an imaging and machine learning method to predict the subtype of a malignant lung lesion. **Methods:** A dataset of 1493 primary lung cancer patients was collected, of which 943 were diagnosed with AC. The histological subtypes of the non-AC patients were, squamous-cell carcinoma (158), large-cell carcinoma (69), small-cell carcinoma (33), other subtypes (27), or unreported non-AC subtype (253). This consists of retrospectively collected CT images and demographic data from both screening and clinical settings, across 41 academic and community centres from the USA (35 centres), and Europe (6 centres). All patients included were aged $\geq$ 18 with no history of cancer in the last 5 years. Each CT was manually curated. Given a CT-image of a lung nodule, a Convolutional Neural Network (CNN) was trained to classify nodules as AC or non-AC, using 8-fold cross-validation. A logistic-regression model based on clinical parameters was also trained using the same data and cross-validation. Classification performance was evaluated using the Area-Under-the-ROC-Curve (AUC), sensitivity, and specificity. Confidence intervals and *P* values were calculated by nonparametric bootstrapping. **Results:** The median age of AC patients was 66 yr (non-AC 67 yr) and 62.3% of them were male (non-AC 57.8%). The median pack years for AC patients was 38.4 p.yr (non-AC 50.0 p.yr). For AC tumours, the median diameter was 14.0 mm (non-AC 14.0 mm) and the mean diameter was 15.0 mm (non-AC 16.4 mm). The AC-classification results are tabulated below. The CNN classification performance is significantly better than the logistic-regression baseline across all three measures of performance $P < .001$. AC classification results. All values are given in % with 95% confidence interval bounds in parentheses. **Conclusions:** We find that the CNN significantly outperforms a logistic model in identifying AC from other histological subtypes. With further development, this algorithm could prove a useful tool to aid management of lung cancer patients. Research Sponsor: None.

	AUC	Sensitivity	Specificity
CNN	74.3 (71.5, 76.3)	66.7 (64.5, 68.8)	67.1 (64.1, 69.8)
Logistic regression with clinical data	59.8 (57.5, 62.0)	52.6 (50.1, 54.8)	62.7 (59.7, 65.9)

3058 **Poster Session**

Modeling cell-free DNA fragment size densities for non-invasive detection of cancer. *First Author: Jacob Carey, Delfi Diagnostics, Baltimore, MD*

Background: Circulating cell-free DNA (cfDNA) is largely nucleosomal in origin with typical fragment lengths of 167 base-pairs reflecting the length of DNA wrapped around-the histone and H1 linker. Given the nucleosomal origin of cfDNA, we have previously used low coverage whole genome sequencing to evaluate DNA fragmentation profiles to sensitively and specifically detect tumor-derived DNA with altered fragment lengths or coverage. **Methods:** Here we evaluate the use of Bayesian finite mixtures to model the fragment length distribution and demonstrate how the parameters from these models can be useful to distinguish between individuals with and without cancer. We examined the number of cfDNA fragments by size ranging from 100-220bp and approximated the mixture component location, scale, and weight using Markov Chain Monte Carlo. The performance of the method was determined using a ten-fold, ten repeat cross-validation of Gradient Boosted Machine model using 1) our previously described genome-wide fragmentation profile approach, 2) the parameters from the mixture model and 3) a combination of approaches 1) and 2) as features. **Results:** In this study of 215 cancer patients and 208 cancer-free individuals, we observed cross-validated AUCs of 1) 0.94, 2) 0.95, and 3) 0.97 among the three approaches. **Conclusions:** Our findings indicate that parsimonious mixture models may improve detection of cancer in conjunction with fragmentation profile analyses across the genome. Research Sponsor: Nicholas Dracopoli.

3059 **Poster Session**

Advanced imaging to assess longitudinal vascular changes in brain metastases treated with checkpoint inhibition. *First Author: Albert Eusik Kim, Massachusetts General Hospital, Boston, MA*

Background: Immune checkpoint inhibitors (ICI) have recently been shown to be effective for brain metastases (BM) in melanoma and lung cancer. Several studies demonstrate that 20-50% of BM patients respond to ICI. The reasons behind this wide variability in treatment response is not clear. Therefore, using physiologic imaging, we seek to identify the longitudinal biological changes exerted on BM as a result of ICI administration. **Methods:** Given the importance of aberrant tumor vasculature in cancer proliferation, we have focused on assessing changes in vascular physiology. We analyzed standard post-contrast and dynamic susceptibility contrast (DSC) MRI to identify characteristic vascular signatures as part of an ongoing Phase 2 study of pembrolizumab for patients with untreated or progressive, previously treated BM from any histology. Tumor volume measurements were calculated by summating all enhancing voxels. As per modified RECIST and RANO criteria for immunotherapy, volumetric increase of $>$ 40% was defined as progressive disease (PD), a decrease of $>$ 60% as partial response (PR), and stable disease (SD) as between -60% and +40%. **Results:** 35 patients, out of the total cohort of 60, have undergone DSC-MRI analysis. Histologies include 15 with breast cancer, 6 with non-small cell lung cancer, 4 with melanoma, and 10 with other cancers. At baseline, the total number of BM was 1-50+ per patient. Based on summing the entire enhancing intracranial disease burden, best volumetric responses for the 35 evaluable patients include 4 PR, 12 SD, and 19 PD. Thus far, we found that ICI-resistant BM had a 50% increase in cerebral blood flow (CBF), 105% increase in cerebral blood volume (CBV), a 15% increase in mean transit time (MTT), and an 80% increase in vessel caliber at 6 weeks post-treatment. On the other hand, ICI-responsive BM had no change in CBF, a 33% increase in CBV, a 10% decrease in MTT, and no change in vessel caliber. Ongoing analysis to uncover additional vascular changes (e.g. tumor oxygenation, vessel size index) within BM to ICI are pending. **Conclusions:** Our data provides evidence that effective ICI for BM is associated with unique intra-tumoral vascular physiology. With final analysis, we will uncover other facets of vascular physiology that correlate with ICI response, and may reveal mechanisms of response/resistance within tumors to ICI. Research Sponsor: None.

3060 **Poster Session**

Genetic profiling across multiple cancer types using molecular prescreening comprehensive gene panels offered by clinical trials (CT). *First Author: Iván Victoria, Hospital Clínic de Barcelona, Barcelona, Spain*

Background: Genetic profiling (GP) is essential not only for understanding tumor biology but also helps to identify potential genes for targeted therapies. At the same time, selected CT provide an individual genomic profile panel during the pre-screening phase. Here, we demonstrate our experience using these panels. **Methods:** We selected 14 CT from our Early Drug Development Clinical Trial Unit at Hospital Clinic of Barcelona that included analysis of gene panels in tumor (Foundation One, ArcherDX, Therascreen and Sophia Genetics) or plasma (Resolution Bioscience ctDx). These panels analyzed mutations, fusions, amplifications, microsatellite instability (MSI) and tumor mutational burden (TMB), among others. We collected information about types of cancers, molecular alterations and therapies chosen according to the results of GP. The platform OncoKB (Chakravarty JCO PO, 2017) was used to define genes with potential target therapies and levels of evidence (LE) for those targets (from LE 1 –FDA-recognized biomarker predictive of response to an FDA-approved drug- to LE 4 –Compelling biological evidence supports the biomarker as being predictive of response to a drug). Descriptive statistics were used. **Results:** From March 2017 to January 2021 we analyzed samples from 410 patients (pts) with CNS (19.3%), urothelial (18.3%), prostate (17.6%), breast (15.4%), ovarian (9.3%), esophageal and gastric (5.4%), colorectal (4.4%), pancreas (2.7%), endometrial (2.4%), cholangiocarcinoma (1.2%), cervix (1%), HNSCC (1%), renal (1%), lung (0.5%), liver (0.2%) fallopian tube (0.2%) and paraganglioma (0.2%). 352 pts (85.8%) had at least 1 genetic alteration. The most frequently altered genes were TP53 (153 pts, 46.2%), INSR (19 pts, 22.8%), TERT (76 pts, 22%), CDKN2A (65 pts, 19.9%), FAM175A (11 pts, 19.3%), CDKN2B (54 pts, 18.1%), MLL2 (53 pts, 17.7%), PTEN (52 pts, 16%), MTAP (45 pts, 15.7%), PIK3CA (52 pts, 15%) and ATM (55 pts, 14.4%). TMB ranged from 0 to 76.9 mut/Mb (median 2.5 mut/Mb). MSI was found in 3 pts (1.5%). 196 pts (47.1%) had an OncoKB LE 1 alteration, 105 pts (25.6%) if we restrict the options to their specific cancer type. 16 pts (3.9%) received a matched therapy: 6 pts received an off-label drug, 6 pts were included in the same CT for which the pre-screening was performed and 4 pts were included in a different CT. Additionally, 13 pts (3.2%) received a matched therapy either with OncoKB LE 4 (5 pts received an off-label drug and 3 were included in a different CT) or not included in OncoKB (8 pts included in the same CT of the pre-screening). As a whole, 29 pts (7.1%) received a matched drug according to their genomic results. **Conclusions:** Comprehensive gene panel testing offered through CT allows the identification of targets to enroll pts, although the recruitment was 1.5%. However, 7.1% of the pts received a matched therapy due to the molecular information of these gene panels. Research Sponsor: None.

3061 **Poster Session**

Machine learning models to quantify HER2 for real-time tissue image analysis in prospective clinical trials. *First Author: Benjamin Glass, PathAI, Inc, Boston, MA*

Background: Patient eligibility for HER2-targeting treatments is commonly informed by testing tumor HER2 expression using immunohistochemistry. As HER2 expression is visually assessed by pathologists, inter- and intra-rater variability might affect treatment decisions. Here, we report the development of an automated machine learning (ML)-based algorithm to quantify HER2 cell membrane expression across a diversity of breast cancer phenotypes as a clinical tool for monitoring HER2 testing quality. **Methods:** A total of 689 breast cancer tissue samples were either procured (Avaden Biosciences) or were anonymized samples from the AstraZeneca biobank comprising tissues from primary and metastatic tumors, core needle biopsies and surgical resections, lobular and ductal carcinomas, across tumor grades and HER2 expression levels. Samples were stained for HER2 detection (Ventana HER2 (4B5) Assay) and digitized (Leica Biosystems) across 5 laboratories in the US. Whole-slide images (WSIs) were stratified into training (n = 407), validation (n = 110), and test sets (n = 172). Multiple convolutional neural network based ML models (PathAI, Boston, MA) were trained using 190,000 manual annotations provided by 30 board-certified pathologists to identify artifacts, invasive tumor, identify individual cancer cells and measure tumor cell membrane HER2 expression as partial or complete, and negative, weak-or-moderate, or intense. Cell-level scores were validated against a consensus of manual cell counts from 5 independent pathologists in 320 representative regions of test set WSIs. HER2 scores were generated by automatically applying rules derived from 2018 ASCO/CAP guidelines and then compared in the test set with consensus scores from 3 independent pathologists. **Results:** Cell counts provided by the ML model were strongly consistent with cell counts obtained by pathologist consensus in all cell-types except for faintly positive HER2 cells where ML-based quantification identified more cells on average. Automatically generated ML-ASCO/CAP HER2 scores using WSI showed substantial consistency across IHC categories with the consensus of pathologists (ICC 0.88, 95%CI 0.82-0.92) in the test set and improved further when ML models were trained to agree with pathologists by adjusting cut offs (ICC 0.91, 95%CI 0.89-0.94). The ML-based model was deployed through the PathAI cloud platform to calculate HER2 testing quality control metrics in real-time in multicentric clinical trials. **Conclusions:** Automated image analysis of HER2-stained breast cancer tissues using ML-based models is consistent with pathologist consensus across breast cancer tissue types. The results support evidence that ML-based algorithms can help pathologists assess HER2 testing reproducibility in clinical trials. Research Sponsor: AstraZeneca R&D.

3062 **Poster Session**

Comprehensive molecular profiling of advanced cancers in a real-world setting using an ultrasensitive amplicon-based next-generation sequencing (NGS) liquid biopsy assay. *First Author: Jonathan Poh, Lucence Diagnostics, Singapore, Singapore*

Background: Molecular profiling of circulating tumor DNA (ctDNA) by NGS has demonstrated the value of liquid biopsy in informing treatment decisions and monitoring disease progression in cancer patients. Here we report results from the real-world clinical application of an ultrasensitive amplicon-based NGS liquid biopsy assay for advanced cancers. **Methods:** Plasma cell-free DNA (cfDNA) from 1,338 consecutive samples (51.3% lung, 15.6% breast, 8.4% colorectal, 26.8% from 18 other cancer types; 86.3% of cancer samples were metastatic) underwent real-world testing in a Singapore-based, CAP-accredited, CLIA-certified laboratory from Jan 2018 – Nov 2020. Genomic alterations were analyzed using an amplicon-based NGS assay that detects alterations in 80 cancer-related genes, microsatellite instability (MSI) and cancer-causing viruses, with previously validated cfDNA detection limits of 0.1% variant allele frequency (VAF) for SNPs and indels, 5% tumor fraction, and 2 IU/mL plasma, respectively. **Results:** ctDNA was successfully detected in 70.0% of cancer samples (76.3% from metastatic and 24.7% from localized tumors) for a total of 977 unique variants. Across ctDNA-positive samples the median VAF was 1.4%, and 8.5% of all reported variants had VAFs between 0.01 – 0.09%. The most frequently altered genes were *TP53* (48.8%), *EGFR* (36.9%), *KRAS* (17.4%), *PIK3CA* (15.3%), and *APC* (9.5%). In ctDNA-positive lung cancer, 74.6% of samples (66.5% *EGFR*+) harbored ≥1 actionable target, with 29.9% of patients treated with a first- or second-generation EGFR tyrosine kinase inhibitor harboring an EGFR T790M resistance mutation. Among breast cancers, *ESR1* or *PIK3CA* alterations predicting drug resistance/response were detected in 44.2% of HR+ cases. In colorectal cancer, alterations implicated in anti-EGFR resistance (*NRAS*, *KRAS*, *BRAF*, *ERBB2*) were found in 50.0% of samples. Profiling of cfDNA also enabled cancer monitoring, even among cancers with low genetic biomarker prevalence. 50% of nasopharyngeal cancer samples were Epstein-Barr virus-positive while 35.7% of liver cancer samples were Hepatitis B virus-positive, enabling an additional yield of 14.3% and 7.1% respectively, over ctDNA detection. cfDNA profiling of cancers of unknown primary origins informed potential tumor origins via the detection of tumor type-specific alterations such as mutations in *AR*, *ESR1*, *GNAS*,*EGFR* genes, viral biomarkers, and MSI. **Conclusions:** The use of a comprehensive pan-cancer liquid biopsy panel with rational inclusion of actionable and driver genes resulted in detection of ctDNA in the vast majority of clinical cases processed routinely. These findings support the utility of ultrasensitive amplicon-based NGS liquid biopsy assays in probing cancer drug sensitivity/resistance, tumor burden monitoring, and molecular characterization of tumors. Research Sponsor: Lucence Diagnostics.

3063 **Poster Session**

Feasibility and clinical utility of cancer whole genome and transcriptome sequencing for pediatric and young adult solid tumors. *First Author: Neerav Shukla, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Next generation sequencing (NGS) assays have accelerated the identification of mutations and potential matched targeted therapies for patients with cancer. However, a significant proportion of patients do not derive clinical benefit from targeted panel sequencing approaches. Cancer whole genome and transcriptome sequencing (cWGTS) offers the opportunity to fully characterize tumors, but are challenged by significant cost and computational resource requirements, concerns of assay sensitivity, and the need to deliver curated results within clinically relevant time frames. We performed a prospective study to evaluate the feasibility and utility of cWGTS in pediatric and young adults with solid tumors. **Methods:** We developed an automated analytical workflow (Isabl) for the QC and processing of cWGTS data to include ensembl variant calling for germline and somatic substitutions, indels, and structural variants; fusion genes; gene expression; and mutation signatures. Treatment biomarkers were annotated using OncoKB with generation of a clinical prototype report. We tested the feasibility of cWGTS implementation, evaluated its analytical validity compared to standard diagnostic assays, and characterized the clinical utility of incremental findings in a prospective study of children and young adults treated at Memorial Sloan Kettering Cancer Center. **Results:** A total of 114 patients were enrolled. Standard NGS assays (MSK-IMPACT, MSK-Fusion) identified clinically relevant biomarkers in 22% of cases. The cWGTS process was completed, from sample acquisition to summary report, in less than 12 days. Comparison against clinically reported NGS results demonstrated high precision and recall for reported mutations (98.8%) with high concordance across variant allele representations ($r^2 > 0.73$). cWGTS identified additional oncogenic mutations not captured by targeted sequencing in 49% of patients. Furthermore, incremental findings, beyond those identified by NGS assays, of direct clinical relevance (diagnostic, prognostic, therapy guiding) were identified in 26% of patients. Importantly, < 5% of the incremental findings would have been captured by whole exome or transcriptome sequencing alone. Of possible therapeutic relevance, cWGTS analyses revealed a significantly higher tumor mutation burden than previously reported (range: 0 - 11.23). **Conclusions:** We demonstrate feasibility, analytical validity and clinical utility of cWGTS approaches in pediatric and young adult cancer patients, with nearly half of all patients having incremental findings that were not captured by standard targeted NGS approaches. Research Sponsor: The Scarlett Fund, Olayan Fund for Precision Pediatric Cancer Medicine.

3065 **Poster Session**

Improving differential diagnosis of pulmonary large cell neuroendocrine carcinoma (LCNEC) and small cell lung cancer via a transcriptomic, biological pathway-based ridge regression model. *First Author: Jun Hong, Department of Pathology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China*

Background: In clinics, it can be challenging to make correct diagnosis of LCNEC, Small cell lung cancer (SCLC), if tissues, like needle biopsies, are insufficient or morphology was poorly preserved. In this study, a reliable classifier was constructed based on transcriptome data and machine learning (Ridge regression) to improve the diagnostic accuracy for LCNEC and SCLC. **Methods:** RNA-Seq data obtained from 3 public cohorts were collected as training set, including 60 NSCLC cases from The Cancer Genome Atlas (TCGA), 66 LCNEC cases from Julie George et al., Nature Communications 2018, and 33 SCLC cases from Julie George et al., Nature 2015. Another 80 NSCLC, 30 LCNEC and 15 SCLC cases published by Martin Peifer et al., Nature Genetics 2012 were used as validation set. Additionally, RNA-Seq data of 27 borderline samples which were hard to make diagnosis based on histology and Immunohistochemistry were used to test the accuracy of the prediction model. **Results:** 13,959 genes mapped to 186 Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways were included. Gene Set Variation Analysis (GSVA) algorithm was used to enrich and score each KEGG pathway. A prediction model based on GSVA score of each pathway was constructed via Ridge regression. This GSVA Score Model achieved ROC-AUC 0.949 and concordant rate of 0.75 for the entire prediction efficiency. Of the 27 borderline samples which were hard to make confirmed diagnosis, 17/27 (63.0%) were predicted as LCNEC, 7/27 were predicted as SCLC, and the remainder were predicted as NSCLC. While only 8 (29.6%) cases with LCNEC were diagnosed by pathologists, which was significantly lower than the results predicted by the model. Furthermore, cases with model predicted LCNEC had a significant longer disease-free survival than that with model predicted SCLC (median DFS,59 months for LCNEC vs 5 months for SCLC, $p = 0.0043$), which was in parallel with currently known prognostic difference of these two types of neuroendocrine tumors. **Conclusions:** This GSVA algorithm-based prediction model was able to make accurate diagnosis of LCNEC and SCLC. And it may provide valuable information for clinics to choose optimal therapeutic approach for patients with pulmonary neuroendocrine tumors. Research Sponsor: Shanghai Municipal Commission of Health and Family Planning (No. 20184Y0222), "Dream Mentor" training program of Shanghai Pulmonary Hospital (No. fkxr1903).

	Model Prediction			
Pathological Diagnosis	**LCNEC**	**SCLC**	**NSCLC**	**Total**
LCNEC	28	0	2	30
SCLC	0	13	0	13
NSCLC	15	0	67	82
Total	43	13	69	125
AUC		0.949		
κ-value		0.75		

3066 **Poster Session**

Validation of FAPi PET biodistribution by immunohistochemistry in patients with solid cancers: A prospective exploratory study. *First Author: Christine Mona, UCLA Ahmanson Translational Theranostics Division, Los Angeles, CA*

Background: Fibroblast activation protein (FAP)-expressing cancer-associated fibroblasts (CAF), a major component of tumor stroma, confer treatment resistance, promote local progression, metastasis and immunosuppression. Because FAP is selectively expressed in the tumor stroma of many cancers, radiolabeled small molecule ligands targeting FAP are being explored for their use as pan-cancer theranostic agents. The objective was to establish the spectrum of FAP expression across various cancers by immunohistochemistry (IHC) and to explore whether 68Ga-FAPi-46 PET image biodistribution faithfully reflects tumor FAP expression from resected tumor and non-tumor specimens. **Methods:** This study was a prospective, exploratory, imaging trial in cancer patients. Referred volunteer patients scheduled to undergo surgical resection of the primary tumor and/or metastases were eligible. Patients underwent one whole body 68Ga-FAPi-46 PET/CT scan. Subsequently, patients underwent surgical resection of the primary tumor and/or metastasis. The outcome measure was the correlation of 68Ga-FAPi-46 PET maximum standardized uptake value (SUVmax) with FAP IHC score in patient-matched cancer and non-cancer tissue. **Results:** The frequency of FAP expression across 14 cancers on tissue microarrays ranged from 25 to 100% (mean 76.6±25.3%). For imaging and IHC correlation, fifteen patients with the following cancer types were prospectively included: colorectal (n = 4), head and neck (n = 3), pancreas (n = 2), breast (n = 2),stomach (n = 1), esophagus (n = 2) and uterus (n = 1). All 15 patients underwent surgery following their 68Ga-FAPi-46 PET scan within a mean time interval of 16.1±14.4 days (range 1 – 50 days). For two patients the tumor was deemed unresectable. 68Ga-FAPi-46 SUVmax and IHC scores were higher in cancer tissue than in normal tissue: mean 68Ga-FAPi-46 SUVmax 7.4±4.6 (range 1.5-15.9) vs 1.6±1.2 (range 0.4-5.1), ($p < 0.001$) and mean FAP IHC score 2.38±0.65 vs 0.54±0.66 ($p < 0.001$), respectively. The FAP IHC scores strongly correlated with 68Ga-FAPi-46 SUVmax ($p = 0.001$, repeated measures correlation $r = 0.85$ (95% CI 0.53-0.95), $p < 0.001$). **Conclusions:** 68Ga-FAPi-46 PET biodistribution across multiple cancers strongly correlates with FAP tissue expression as measured by IHC. This translational validation paves the way for large scale prospective trials on the use of 68Ga-FAPi-46 PET/CT as a biomarker and stratification tool for FAP-targeted therapies. Clinical trial information: NCT04147494. Research Sponsor: Education and Research Foundation for Nuclear Medicine and Molecular Imaging (ERF), Society of Nuclear Medicine and Molecular Imaging (SNMMI), 2019 Molecular Imaging Research Grant for Junior Academic Faculty #20194491.

3067 **Poster Session**

Safety profile and disease stabilization in late stage, heavily pretreated, solid tumor patients in a first-in-human (FIH) study of ATX-101, a drug targeting proliferating cell nuclear antigen (PCNA). *First Author: Charlotte Rose Lemech, Scientia Clinical Research, Randwick, Australia*

Background: PCNA is a conserved scaffold protein orchestrating DNA replication, repair or bypass pathways as well as cellular signaling and apoptosis. More than 500 protein-PCNA interactions have been identified which are mediated via two binding motifs, the PIP-box and APIM. Cellular stress, to which cancer cells and cells of tumor microenvironment are exposed, increases the affinity of the APIM motif. APIM-containing proteins bind to PCNA and mediate processes of escape mechanisms and survival of cancer cells. ATX-101 is a cell penetrating peptide containing APIM. It inhibits protein binding via APIM, resulting in cancer cell death and altered cellular signaling. Anticancer effects of ATX-101 have been demonstrated *in vitro* and *in vivo*. **Methods:** A FIH study using a 3+3 dose escalation design was conducted. Patients with late-stage solid tumors received weekly infusions of 20, 30, 45 and 60 mg/m^2 over 6 weeks. Primary objective was safety, secondary objectives were PK and efficacy. Patients with stable disease (SD) after 6 weeks could continue treatment in a long-term follow-up (LTFU) study. **Results:** As of January 2021, 22 patients have been treated. All patients received in average 3.8 [1-9] prior treatment lines, all but one had progressive disease at study entry and 80% were refractory to the last therapy. No dose limiting toxicity or death and no treatment related Grade 3/4 or serious adverse events were reported. The maximum tolerated dose was not reached. Mild to moderate infusion related reactions (IRR) were observed in 73% of patients. They were not dose dependent and resolved completely after treatment interruption and/or symptomatic treatment. IRRs occurred despite premedication and could cause infusion interruptions with extended infusion duration. Experiments in dogs indicate that transiently increased histamine levels may cause IRRs. However, elevated histamine and tryptase levels could not be measured in patients so far. ATX-101 exposure was dose-dependent. Cmax was reached either at the middle or at the end of infusion. ATX-101 disappeared quickly from plasma and was not detectable 5 - 60 minutes post infusion. 13 patients finished the FIH study, 10 had SD after 6 weeks. 9 of 10 patients moved into the LTFU study. The treatment duration in the LTFU study varied from 2.1 to 15.6 months (median 4.2 months). **Conclusions:** ATX-101 is well tolerated at all dose levels with IRRs being the most frequent AEs. Drug exposure is dose dependent with rapid plasma clearance, which confirms *in vivo* data demonstrating the quick uptake by cells of all organs. The observed duration of SD may be attributed to ATX-101 activity. Proof of concept combination studies are being initiated. Clinical trial information: 375262. Research Sponsor: Therapim PTY LTD.

3068 **Poster Session**

Association of low RKIP expression with poor prognosis in non-small cell lung cancer. *First Author: Lingbin Meng, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Raf1 kinase inhibitor protein (RKIP) is able to bind Raf1 to inhibit Ras-Raf-MEK-ERK signaling, a major oncogenic pathway. It has been reported that reduced RKIP expression associates with poor prognosis in many cancers, including gastric adenocarcinoma, gliomas and bladder cancer. However, there are only several studies on its role in non-small cell lung cancer (NSCLC) and the conclusion is still controversial. Hence, we performed this study to assess the prognostic significance of RKIP in our NSCLC population. **Methods:** Between June 2017 and June 2020, 156 NSCLC patients treated at our hospital were included for the present study. None of the patients had received chemotherapy, radiotherapy or surgery before. Their tumor tissues and surrounding normal lung tissues were collected for immunostain and western blot analysis of RKIP expression and ERK signaling. We collected information about gender, age, histological differentiation, tumor size, TNM stage, and lymph node status. Survival curves were analyzed using the Kaplan-Meier method. Cox proportional hazards model was used to determine the prognostic value of various variables in a univariate and multivariate setting. **Results:** Immunostain and western blot results showed a lower RKIP expression and a higher p-ERK level in cancer tissues compared with the surrounding normal tissues. A reduced RKIP expression with high level of p-ERK was also observed in TNM stages III and IV as compared with I and II. Pearson's chi-squared test confirmed low RKIP expression associated with poorer TNM stage ($p< 0.001$) and N-stage ($p< 0.05$). No significant correlation was observed between RKIP expression level and gender, age, histological type or tumor size. Kaplan-Meier survival analysis revealed that patients with low RKIP expression had significantly worse overall survival than patients with high RKIP expression ($p= 0.019$, log-rank). This conclusion was consistent in the stage I&II patients ($p= 0.011$, log-rank) but not in the stage III&IV patients ($p= 0.711$, log-rank). Univariate Cox proportional hazards regression analysis indicated Tumor size, TNM stage and RKIP expression significantly affected overall survival of the NSCLC patients. Multivariate Cox proportional hazards regression analysis confirmed RKIP expression remained a significant predictor of survival after correcting for the effects of Tumor size and TNM stage (hazard ratio = 1.730, 95% confidence interval = 1.017 – 2.942, $p = 0.043$). **Conclusions:** In this study, low RKIP expression was a poor prognostic indicator in NSCLC as it significantly correlated with poorer TNM stage, N-status, and overall survival. Our findings suggest that by inhibiting Ras-Raf-MEK-ERK pathway RKIP may play an anti-tumor role in NSCLC. Research Sponsor: Natural Science Foundation of Anhui Province.

3069 **Poster Session**

Mutational analysis of rare insertions and deletions in exon 18 and 19 of HER2 in Chinese patients with different cancer types. *First Author: Jianwen Qin, Tianjin Chest Hospital, Tianjin, China*

Background: *HER2* belongs to the same family with *EGFR* and is known as an important cancer driver gene. Kinase domain insertions and deletions (KD indels) are frequent driver mutations in both *EGFR* and *HER2*. The most common *HER2* KD indels are the exon 20 insertions while others are rarely reported. Our study aimed to investigate the role of less common *HER2* KD indels in solid tumors. **Methods:** This study was performed in 63,267 Chinese patients including 53,591 patients with lung cancer, 5,888 patients with colorectal cancer, 3,774 patients with breast cancer and 14 patients with renal pelvis cancer. Tissue or plasma samples from the patients were subjected to capture-based targeted sequencing covering *HER2* and other cancer related genes. The sequencing data of each patient were retrospectively collected and analyzed. The *HER2* exon 18/19 indels identified in our study were compared with data from COSMIC and MSKCC. In vitro analysis in Ba/F3 cell lines was performed to assess drug response of different *HER2* exon 18/19 indels. **Results:** We identified recurrent *HER2* KD indels in exon 18 and 19, with a frequency of 0.04% (25/63,267). The data from COSMIC and MSKCC reported the prevalence of *HER2* exon 18/19 indels ranging from 0.04% to 0.23% among breast, cervical, and pancreatic cancers. In our study, *HER2* exon 18/19 indels were identified in 20 patients with lung cancer (0.037%), two with colorectal cancer (0.034%), two with breast cancer (0.053%) and one with renal pelvis cancer (7.143%). Only two patients (8%) harbored concurrent actionable driver mutations including *EGFR* mutation and *MET* amplification. Meanwhile, high level of normalized allelic frequency of *HER2* exon 18/19 indels was presented in most patients (22/25, 88%). In lung cancer, the presence of *EGFR* driver mutation was less common in patients with *HER2* exon 18/19 indels than wild type *HER2* (5% vs. 47.4%, $p < 0.01$). The rates of concurrent driver mutations in lung cancer were comparable between *HER2* exon 18/19 indels and the two established *HER2* drivers, exon 20 insertions and S310 mutations. The in vitro proliferation assay demonstrated that E698_P699insLL mutation in *HER2* exon 18 and L755_E757delinsPQ mutation in *HER2* exon 19 both conferred a survival advantage to Ba/F3 cells. Dose-response curves showed inhibitory effects on cell viability of several HER2 tyrosine kinase inhibitors including neratinib, lapatinib, poziotinib and afatinib. In particular, lapatinib, poziotinib and afatinib demonstrated comparable or stronger inhibitory ability toward the two *HER2* mutants than wild type *HER2* in terms of IC50. **Conclusions:** Our study revealed a novel class of *HER2* KD indels in exon 18/19 that may act as driver mutations in several cancer types. The drug response observed in vitro indicated the potential to use anti-*HER2* targeted therapies for *HER2* exon 18/19 indels. Further studies on this rare type of *HER2* mutation are warranted. Research Sponsor: None.

3070 **Poster Session**

A prespecified interim analysis of the PATHFINDER study: Performance of a multicancer early detection test in support of clinical implementation. *First Author: Tomasz M. Beer, Knight Cancer Institute, Oregon Health & Science University, Portland, OR*

Background: A multi-cancer early detection (MCED) test that uses targeted methylation-based cfDNA technology to detect cancer and predict cancer signal origin (CSO) has potential to efficiently identify malignancies for which effective screening modalities do not exist. A previous version of a blood-based MCED test demonstrated favorable classification and test characteristics. Samples from the ongoing PATHFINDER study were reanalyzed in a prespecified interim analysis to evaluate performance of a more recent version of the test with an updated classifier (eg, updated CSO localization, hematological signal threshold) that is planned for clinical implementation as a general multi-cancer screening tool. **Methods:** PATHFINDER (NCT04241796) is an interventional, prospective study in which results (cancer signal detected/not detected and predicted CSO) using a previous version of the MCED test are returned to investigators, and those with a signal detected undergo further diagnostic testing. In this prespecified interim analysis, samples from those enrolled as of October 6, 2020 were reanalyzed with the more recent version of the MCED test (these results were not returned to investigators). The positive predictive value (PPV) for cancer detection, overall CSO accuracy, and concordance between the two test versions were assessed. **Results:** A total of 4011/4047 (99%) participants (pts) were analyzable (mean [SD] age 63.9 [8.7] years, 62% female, 92% white, 24% with prior cancer history, 39% ever smoker [4% current], 6% with genetic cancer predisposition). Cancer signal was detected in 0.95% (38/4011). A total of 27/38 also had signal detected by the previous version of the MCED test, including 19 who reached diagnostic resolution (13 with cancer diagnosis and 6 without); 11/38 were discordant positives. Nine different cancer types were detected in the 13 pts (2 stage I, 3 stage II, 2 stage III, and 3 stage IV); 1 had no AJCC stage expected, 1 metastatic recurrence and 1 stage evaluation underway. A conservative minimal PPV assuming all discordant positives are false positives, was 43.3% (13/30, 95% CI 27.4-60.8%) based on 19 pts with diagnostic resolution and 11 discordant positives. High negative percent agreement (PA) 99.7% (99.5-99.8%) between the two test versions was observed. Positive PA of 43.5% (95% CI, 31.9-55.9%) was consistent with the more stringent threshold for hematologic signal in the recent MCED version, as most discrepant cases had hematologic CSO with the previous MCED test. Among 13 detected cancers, accuracy of the top CSO prediction was 92.3% (12/13, 95% CI 66.7-99.6%). **Conclusions:** In this prespecified interim analysis, the more recent version of the MCED test detected cancers with high PPV and high accuracy of CSO prediction, supporting readiness for use in clinical practice. Full enrollment cohort data will be available at the meeting. Clinical trial information: NCT04241796. Research Sponsor: GRAIL, Inc.

3071 **Poster Session**

Performance of a targeted methylation-based multi-cancer early detection test by race/ethnicity. *First Author: Wai Hong Wilson Tang, Cleveland Clinic, Cleveland, OH*

Background: Disparities in cancer screening and outcomes based on factors such as gender, socioeconomic status, and race/ethnicity are well documented.[1] The Circulating Cell-free Genome Atlas study (CCGA; NCT02889978) was designed to develop and validate a blood-based multi-cancer early detection (MCED) test analyzing plasma cell-free DNA (cfDNA) to detect cancer signals across multiple cancer types and simultaneously predict cancer signal origin. Findings stratified by race/ethnicity from the third and final CCGA validation sub-study are reported. **Methods:** CCGA is a prospective, multicenter, case-control, observational study with longitudinal follow-up (overall N = 15,254). In this pre-specified exploratory analysis from the third substudy, key objectives were to evaluate test performance for cancer signal detection (specificity, overall sensitivity, and sensitivity by clinical stage) among racial/ethnic groups. Plasma cfDNA from evaluable samples was analyzed using a targeted methylation bisulfite sequencing assay and a machine learning approach. Overall, 4077 participants comprised the independent validation set with confirmed status (cancer: n = 2823; non-cancer: n = 1254). The groups stratified by race/ethnicity were White Non-Hispanic, Black Non-Hispanic, Other Non-Hispanic (including but not limited to Asian, Native Hawaiian, Pacific Islander, American Indian, Alaska Native), Hispanic (all races), and Other/unknown. The study was not powered to detect statistical differences between groups. **Results:** Cancer and non-cancer groups were predominantly White (2316/2823, 82.0% and 996/1254, 79.4%, respectively). Across racial/ethnic groups, specificity for cancer signal detection was 99.6% (White Non-Hispanic: 992/996, 95% confidence interval [99.0-99.8%]), 100.0% (Black Non-Hispanic: 85/85 [95.7-100.0%]), 100.0% (Other Non-Hispanic: 33/33 [89.6-100.0%]), 98.1% (Hispanic: 101/103 [93.2-99.5%]), and 100% (Other/unknown: 37/37 [90.6-100.0%]). Despite slight differences in cancer type and staging across racial/ethnic groups, overall sensitivity for cancer signal detection among groups ranged from 43.9% to 63.0% (White Non-Hispanic: 50.5%, 1169/2316 [48.4-52.5%], Black Non-Hispanic: 53.9%, 104/193 [46.8-60.8%], Other Non-Hispanic: 43.9%, 25/57 [31.8-56.7%], Hispanic: 63.0%, 121/192 [56.0-69.5%], and Other/unknown: 52.3%, 34/65 [40.4-64.0%]). For all racial/ethnic groups, sensitivity generally increased with clinical stage (with limited exceptions at Stage IV in some groups with small sample sizes). **Conclusions:** The MCED test demonstrated consistent specificity and sensitivity across racial/ethnic groups, though results are limited by sample size for some groups. These findings indicate broad applicability and support clinical implementation of this MCED test on a population scale. 1. Zavela et al. Brit J Cancer 2021. Clinical trial information: NCT02889978. Research Sponsor: GRAIL, Inc.

3072 **Poster Session**

Detection of cancer signal for over 50 AJCC cancer types with a multi-cancer early-detection test. *First Author: Habte Aragaw Yimer, The U.S. Oncology Network, Tyler, TX*

Background: The Circulating Cell-free Genome Atlas study (CCGA; NCT02889978) previously demonstrated that a blood-based multi-cancer early detection (MCED) test utilizing cell-free DNA (cfDNA) sequencing in combination with machine learning could detect cancer signals across multiple cancer types and predict cancer signal origin. Cancer classes were defined within the CCGA study for sensitivity reporting. Separately, cancer types defined by the American Joint Committee on Cancer (AJCC) criteria, which outline unique staging requirements and reflect a distinct combination of anatomic site, histology and other biologic features, were assigned to each cancer participant using the same source data for primary site of origin and histologic type. Here, we report CCGA 'cancer class' designation and AJCC 'cancer type' assignment within the third and final CCGA3 validation substudy to better characterize the diversity of tumors across which a cancer signal could be detected with the MCED test that is nearing clinical availability. **Methods:** CCGA is a prospective, multicenter, case-control, observational study with longitudinal follow-up (overall population N = 15,254). Plasma cfDNA from evaluable samples was analyzed using a targeted methylation bisulfite sequencing assay and a machine learning approach, and test performance, including sensitivity, was assessed. For sensitivity reporting, CCGA cancer classes were assigned to cancer participants using a combination of the type of primary cancer reported by the site and tumor characteristics abstracted from the site pathology reports by GRAIL pathologists. Each cancer participant also was separately assigned an AJCC cancer type based on the same source data using AJCC staging manual (8th edition) classifications. **Results:** A total of 4077 participants comprised the independent validation set with confirmed status (cancer: n = 2823; non-cancer: n = 1254 with non-cancer status confirmed at year-one follow-up). Sensitivity was reported for 24 cancer classes (sample sizes ranged from 10 to 524 participants), as well as an "other" cancer class (59 participants). According to AJCC classification, the MCED test was found to detect cancer signals across 50+ AJCC cancer types, including some types not present in the training set; some cancer types had limited representation. **Conclusions:** This MCED test that is nearing clinical availability and was evaluated in the third CCGA substudy detected cancer signals across 50+ AJCC cancer types. Reporting CCGA cancer classes and AJCC cancer types demonstrates the ability of the MCED test to detect cancer signals across a set of diverse cancer types representing a wide range of biologic characteristics, including cancer types that the classifier has not been trained on, and supports its use on a population-wide scale. Clinical trial information: NCT02889978. Research Sponsor: GRAIL, Inc.

3073 **Poster Session**

Preliminary efficacy from an ongoing phase 1 dose escalation study of seclidemstat (SP-2577) in patients (pts) with advanced solid tumors (AST). *First Author: Sant P. Chawla, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: Lysine-specific demethylase 1 (LSD1) is an epigenetic enzyme that is aberrantly expressed in many solid tumors. High levels of LSD1 expression are often correlated with poor patient prognosis due to LSD1's role in cancer cell proliferation, metastasis, and chemoresistance. Seclidemstat is a novel, selective, reversible and oral LSD1 inhibitor capable of inhibiting both LSD1's catalytic and scaffolding functions. We report preliminary efficacy in AST from an ongoing phase 1 trial. **Methods:** SALA-003-AC19 (NCT03895684) is a phase 1 trial of single agent SP-2577 in pts with AST. All pts had progressive disease (PD) at time of study entry. Pts received oral SP-2577 twice a day under fasting condition, in 28-day cycles (C). The primary objective is safety and tolerability. Secondary objectives are to determine maximum-tolerated dose, preliminary efficacy, pharmacokinetics, and pharmacodynamics. **Results:** As of December 30, 2020, 19 pts with AST (10 sarcoma, 2 prostate, 2 ovarian, 2 pancreatic, 1 renal, 1 cervical, 1 breast) were enrolled. Pts received escalating doses of SP-2577 from 150 to 600 mg BID and the dose escalation is ongoing. The median age was 63 years (range, 21–79). 42% were male, and pts had received a median of 4 (range, 1–8) prior systemic therapies. The most common (>5%) grade 3 treatment-related adverse events were GI related including diarrhea (5.3%) and abdominal pain (5.3%). No grade 4 events were reported and there were no treatment-related deaths. Safety data will be presented after completion of phase 1. Three pts had at least one dose reduction. Among the 13 pts who were evaluable for response at end of C2, 7 pts (54%) had best response of stable disease (SD) with median time to progression (TTP) of 4.3 months (range, 2.1–11.5). Four of the 7 pts had genetic abnormalities that may demonstrate increased sensitization to SP-2577 according to preclinical studies. Characteristics of 7 pts with SD at C2 and beyond are shown in the table. **Conclusions:** Seclidemstat has shown activity among advanced sarcoma pts with a manageable safety profile. The dose escalation is ongoing and preliminary clinical data supports further exploration in FET-translocated sarcoma as single agent and in combination therapy. Clinical trial information: NCT03895684. Research Sponsor: Salarius Pharmaceuticals Inc.

Diagnosis	Genetic Abnormality	# prior systemic treatments	Dose level (mg BID)	Best overall response	TTP (months)
Myxoid liposarcoma	FET-translocation: FUS-DDIT3	7	300	SD	7.2
Desmoplastic small round cell tumor	FET-translocation: EWSR1-WT1	5	600	SD	4.3
Extra-skeletal myxoid chondrosarcoma	FET-translocation: TAF15-CHN	1	600	SD	NA - not progressed at 5.7
Ovarian	Mutation in SMARCA4	5	600	SD	3.9
Leiomyosarcoma[1]	–	2	300	SD	11.5
Pleomorphic sarcoma[2]	–	1	600	SD	2.1
Prostate	–	5	300	SD	2.6

[1]Underwent wedge resection of target lung lesion after C2 and other residual lung lesions did not progress until 11.5 months.
[2]No PD, discontinued SP-2577 due to adverse events.

3074 **Poster Session**

First-in-human phase I study of the bifunctional EGFR/TGFβ fusion protein BCA101 in patients with EGFR-driven advanced solid cancers. *First Author: Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Therapeutic targeting of EGFR has demonstrated efficacy in common advanced malignancies such as colorectal cancer (CRC), squamous cell of the head and neck (SCCHN), and non-small cell lung cancer (NSCLC). TGFβ has protumorigenic effects on migration, invasion and tumor-specific immunosuppression, which may enhance the oncogenic effects of activated EGFR. Inhibition of EGFR signaling can lead to TGFβ upregulation as a resistance mechanism. BCA101 is a bifunctional recombinant fusion protein consisting of a chimeric anti-EGFR antibody and an extracellular domain (ECD) of human TGFβRII which demonstrated anti-tumor activity in several preclinical models. **Methods:** Patients with EGFR-driven advanced solid cancers refractory to standard therapies received BCA101 at escalating doses from 64 mg to 1000 mg intravenously (IV) weekly across 6 dose levels using a 3+3 design to determine dose limiting toxicities (DLT, established within 21 days of initial dosing), maximum tolerated dose (MTD) and/or recommended dose (RD). Secondary endpoints include detailed pharmacokinetic (PK), pharmacodynamic (PD) studies in serial tumor and/or blood samples and assessment of anti-tumor activity. **Results:** As of 2/11/2021, 21 patients received single agent BCA101 at 64 (n = 3), 240 (n = 7), 500 (n = 2), 750 (n = 3), 800 (n = 3) or 1000 (n = 3) mg IV weekly, including patients with CRC (n = 6), SCCHN (n = 5) uveal melanoma (n = 2), ovarian cancer (n = 2), glioblastoma multiforme (n = 2), conjunctival melanoma, chordoma, pancreatic cancer and anal squamous cell carcinoma (all n = 1). These patients had 1-7 prior lines of antineoplastic therapy (median 4), including 3 patients with prior EGFR inhibitor exposure. Adverse events (AE) related to BCA101 observed in >1 patient included grade (G) 1-2 rash (n = 9), G 1-2 lipase elevation (n = 2). G3 vitreous hemorrhage at the 240 mg dose level has been the only DLT. The MTD has not been reached and the RD will be based on safety, exposure and pending PD data. Saturation of the clearance was observed at doses above 500mg. Dose proportional increase in Cmax and AUC were observed with doses of 750-1000mg. Best RECISTv1.1 response was stable disease (SD) in 3/10 evaluable patients, with 1 patient on drug $\geq$4 months. **Conclusions:** BCA101 is well tolerated at biologically active doses. BCA101 is now being tested in combination with the PD-1 antibody pembrolizumab in patients with SCCHN and anal carcinoma. Clinical trial information: NCT04429542. Research Sponsor: Bicara Therapeutics.

3075 **Poster Session**

Phase 1 study of OKI-179, an oral class 1-selective depsipeptide HDAC inhibitor, in patients with advanced solid tumors: Final results. *First Author: Jodi A. Kagihara, University of Colorado, Aurora, CO*

Background: OKI-179 is a novel, oral pro-drug analog of largazole, a compound in the romidepsin-depsipeptide class of natural products. OKI-006, the active metabolite of OKI-179, inhibits HDAC 1,2,3 (IC_{50} = 1.2, 2.4, 2.0 nM, respectively), with no significant inhibition of Class IIa HDACs and has shown promising activity in preclinical models of solid tumors. We conducted a first-in-human dose escalation study of OKI-179 in patients with advanced solid tumors. **Methods:** Patients with advanced solid tumors, ECOG $\leq$1, normal QTc, and disease refractory to or with no available standard therapy options were treated with OKI-179 with either intermittent dosing (once daily for 4 days on 3 days off) or continuous dosing (once daily). Dose escalation was conducted using a standard 3+3 design. Pharmacokinetic (PK) and pharmacodynamic (PD) testing was performed at various time points after dosing. **Results:** As of Feb 4, 2021, 26 patients (19 female, 7 male) were enrolled with mean age of 63 (range 41-83). Patients received a median of 5 (range 1-11) prior lines of therapy and most common tumor types included pancreatic (N = 5), breast (N = 4), lung (N = 4), and ovarian cancer (N = 4). Twenty patients were treated in intermittent dosing cohorts from 30-450 mg. One DLT (Grade 2 [G2] thrombocytopenia) occurred in the 450 mg cohort which was expanded to 6 patients without subsequent DLTs. Six patients were treated in 2 continuous dosing cohorts of 200 mg and 300 mg. Two of 3 patients in the 300 mg cohort had DLTs of G3-4 thrombocytopenia and no DLTs were observed in 3 patients treated at 200 mg PO daily. The most common adverse events (AEs) were nausea (62%), fatigue (42%), anemia (39%), anorexia (27%), and vomiting (23%). These AE's were G1-2 except for G3 anemia (12%), G3 fatigue (12%), and G3 anorexia (4%). No other G4-5 treatment-related AEs occurred. Median time on study was 79 days and best response was stable disease (SD) in 10 of 24 patients evaluable for efficacy (42%). Prolonged SD was observed in patients with platinum-resistant serous ovarian cancer (446 days) and adenoid cystic nasopharyngeal carcinoma (256 days). OKI-006 achieved consistent exposure with $C_{max} > 2{,}000$ ng/ml and AUC $>$ 8,000 hr*ng/ml, well above the targeted exposure for efficacy based on pre-clinical studies in murine models. T_{max} was 2 hours and $T_{1/2}$ was 6-8 hours. OKI-179 treatment resulted in $>$ 3X increased T cell histone H3K9 and H3K27 acetylation within circulating PBMCs at doses of 180 - 450 mg. **Conclusions:** OKI-179 has a manageable safety profile, with thrombocytopenia being the on-target DLT. It has a favorable PK profile and demonstrated on-target PD effects at tolerable doses. The MTD and RP2D for OKI-179 was 450 mg daily for intermittent dosing and 200 mg daily for continuous dosing. Phase 2 studies are being designed, with a focus on combination with endocrine therapy in ER+ breast cancer and in NRAS-mutant melanoma. Clinical trial information: NCT03931681. Research Sponsor: OnKure, Inc, CU Cancer Center.

3076 **Poster Session**

Patient-derived micro-organospheres recapitulate tumor microenvironment and heterogeneity for precision oncology. *First Author: Shengli Ding, Duke University, Durham, NC*

Background: Preclinical models that can recapitulate patients' intra-tumoral heterogeneity and microenvironment are crucial for tumor biology research and drug discovery. In particular, the ability to retain immune and other stromal cells in the microenvironment is vital for the development of immuno-oncology assays. However, current patient-derived organoid (PDO) models are largely devoid of immune components. **Methods:** We first developed an automated microfluidic and membrane platform that can generate tens of thousands of micro-organospheres from resected or biopsied clinical tumor specimens within an hour. We next characterized growth rate and drug response of micro-organospheres. Finally, extensive single-cell RNA-seq profiling were performed on both micro-organospheres and original tumor samples from lung, ovarian, kidney, and breast cancer patients. **Results:** Micro-organospheres derived from clinical tumor samples preserved all original tumor and stromal cells, including fibroblasts and all immune cell types. Single-cell analysis revealed that unsupervised clustering of tumor and non-tumor cells were identical between original tumors and the derived micro-organospheres. Quantification showed similar cell composition and percentages for all cell types and also preserved functional intra-tumoral heterogeneity.. An automated, end-to-end, high-throughput drug screening pipeline demonstrated that matched peripheral blood mononuclear cells (PBMCs) from the same patient added to micro-organospheres can be used to assess the efficacy of immunotherapy moieties. **Conclusions:** Micro-organospheres are a rapid and scalable platform to preserve patient tumor microenvironment and heterogeneity. This platform will be useful for precision oncology, drug discovery, and immunotherapy development. Funding sources: NIH U01 CA217514, U01 CA214300, Duke Woo Center for Big Data and Precision Health Research Sponsor: U.S. National Institutes of Health, Duke Woo Center.

3077 **Poster Session**

Phase Ia study of CBP-1008, a bi-specific ligand drug conjugate targeting FRα and TRPV6, in patients with advanced solid tumors. *First Author: Jifang Gong, Peking University School of Oncology, Beijing, China*

Background: CBP-1008 is a first-in-class bi-specific ligand drug conjugate targeting folate receptor α (FRα) and vanilloid subfamily member 6 of transient receptor potential channels (TRPV6) with a high potency tublin inhibitor payload, monomethyl auristatin E (MMAE). A first-in-human, multicenter, phase I study of CBP-1008 (NCT 04740398) is ongoing, and we herein report the preliminary result of part A which is to evaluate the safety, tolerability, pharmacokinetics, and antitumor activity of CBP-1008 in solid tumors. **Methods:** Dose escalation commenced in single-patient cohorts for the first 2 planned dose levels and then followed by a standard 3 + 3 scheme. CBP-1008 was administered as intravenous infusion at escalating doses (0.015, 0.03, 0.12, 0.15, and 0.18 mg/kg). The primary endpoints were to determine the safety and maximum tolerated dose (MTD). Adverse events (AEs) and dose-limiting toxicities (DLTs) were evaluated. **Results:** Eighteen patients with advanced solid tumors who had failed multiple systemic treatment regimens were enrolled. The diseases include colorectal cancer (n = 7), breast cancer (n = 5), non-small cell lung cancer (n = 2), ovarian cancer (n = 2), adrenocortical carcinoma (n = 1), and follicular dendritic cell sarcoma (n = 1). The DLTs observed included grade 4 hypophosphatemia (0.15 mg/kg), grade 4 neutropenia (0.12, 0.15, and 0.18 mg/kg), grade 4 febrile neutropenia (FN) (0.18 mg/kg), grade 3 hyperglycemia (0.15 mg/kg), and grade 3 alanine aminotransferase (ALT) elevation (0.18 mg/kg). The most common all grade AEs suspected to be drug-related were fever (83.3%, totally limited to grade 1-2), aspartate aminotransferase (AST) elevation (72.2%, 5.6% evaluated as grade 3-4), leukopenia (66.7%, 27.8% as grade 3-4), neutropenia (66.7%, 38.9% as grade 3-4) and hypohemoglobinemia (55.6%, 5.6% as grade 3-4), with no drug-related deaths. MTD is estimated between 0.15 mg/kg and 0.18 mg/kg Q2W. Best overall response was partial response (PR) in 1 patient at 0.18 mg/kg and 4 patients (22.2%) achieved stable disease (SD). Responses occurred in patients with FRα and/or TRPV6 -positive expression advanced solid tumors. **Conclusions:** CBP-1008 has demonstrated acceptable safety profile. Tumor response correlating with dosing and FRα/TRPV6 receptor expression levels has been well observed. Clinical trial information: 04740398. Research Sponsor: Coherent Biopharma (Suzhou) Co., Ltd.

3078 **Poster Session**

First-in-human study of PM14 in patients with advanced solid tumors. *First Author: Maria Vieito, Hospital Vall d'Hebron, Barcelona, Spain*

Background: PM14 is a new chemical entity that forms DNA adducts which specifically inhibit RNA synthesis and block active transcription of protein-coding genes. Antitumor activity has been demonstrated *in vitro* in several cell lines (e.g. lung, kidney, prostate), and *in vivo* in mice bearing xenografted human-derived tumors (soft tissue sarcoma, small cell lung cancer, ovarian, gastric, breast and renal cancer). **Methods:** Open-label, dose-escalating, phase I trial of PM14 administered as a 3-hour infusion i.v. every 3 weeks (q3wk) in patients (pts) with advanced solid tumors, adequate organ function and ECOG PS score of 0-1. Two schedules were explored: Schedule A (Day 1 [D1], Day 8 [D8]) and Schedule B (D1). **Results:** 37 pts were treated (Schedule A/B: 28/9 pts). Baseline characteristics of pts (A/B): median age 56/47 years; male 57%/56%; ECOG PS 0: 57%/56%; median of prior lines (range): 3 (1-8)/4 (1-10). Most common tumor types (A + B): STS (n=7 pts), ovarian (n=6), pancreatic (n=4), prostate cancer (n=3). The maximum tolerated dose was 4.5 mg/m^2 for A (dose-limiting toxicities [DLTs]: D8 omission due to lack of recovery of lab parameters for re-treatment [n=2 pts]) and 5.6 mg/m^2 (DLTs: G4 febrile neutropenia [n=1], G4 transaminase increase [n=1]) for B. The recommended dose (RD) was 3.0 mg/m^2 on D1,D8 (A), and 4.5 mg/m^2 on D1 (B). No DLTs were present at the RDs. Most common toxicities were hematological abnormalities and transaminase increase. Main toxicities at the RDs are shown below. Antitumor activity comprised stable disease ≥4 months in 7 heavily pretreated pts (6 in A; 1 in B) at all dose levels. Linear pharmacokinetics were observed for PM14 at tested doses (0.25-5.6 mg/m^2), with geometric mean (CV%) total plasma clearance 5.9 L/h (88%), volume of distribution 128 L (81%) and median (range) terminal half-life 15.9 h (7.5-34.3 h). Less than 1.6% of administered dose was recovered in urine. **Conclusions:** RDs were determined for two PM14 schedules in pts with advanced solid tumors. At the RDs, PM14 is well tolerated and has a manageable safety profile. An expansion phase in specific tumor types, with an optional Bayesian continual reassessment method for RD fine-tuning, is ongoing with both schedules. Research Sponsor: PharmaMar SA, CDTI.

	Schedule A (D1, D8 q3wk) 3.0 mg/m^2 (n=9)			Schedule B (D1 q3wk) 4.5 mg/m^2 (n=6)		
	G1-2 n (%)	G3-4 n (%)	All n (%)	G1-2 n (%)	G3-4 n (%)	All n (%)
Anemia[a]	7 (77.8)	1 (11.1)	8 (88.9)	5 (83.3)	.	5 (83.3)
Neutropenia[a,b]	1 (11.1)	2 (22.2)	3 (33.3)	.	2 (33.3)	2 (33.3)
Thrombocytopenia[a]	1 (11.1)	.	1 (11.1)	.	2 (33.3)	2 (33.3)
Transaminase increase[a]	7 (77.8)	1 (11.1)	8 (88.9)	4 (66.7)	2 (33.3)	6 (100)
Fatigue/Asthenia	.	.	.	3 (50.0)	.	3 (50.0)
Nausea	1 (11.1)	.	1 (11.1)	3 (50.0)	.	3 (50.0)
Vomiting	1 (11.1)	1 (11.1)	2 (22.2)	1 (16.7)	.	1 (16.7)
Decreased appetite	.	.	.	1 (16.7)	.	1 (16.7)
Diarrhea	1 (11.1)	.	1 (11.1)	.	.	.

[a]Regardless of relationship.
[b]No cases of febrile neutropenia.

3079 **Poster Session**

Clinical activity and safety of the RET inhibitor pralsetinib in patients with *RET* fusion-positive solid tumors: Update from the ARROW trial. *First Author: Vivek Subbiah, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *RET* fusions are targetable oncogenic drivers in multiple solid tumor types. ARROW study (NCT03037385) data supported the US FDA approval of pralsetinib, a once-daily (QD) oral highly potent and selective RET inhibitor, for *RET*-altered metastatic non-small cell lung cancer (NSCLC) and advanced/metastatic thyroid cancer. Here we provide an update on the clinical activity of pralsetinib in patients (pts) with advanced *RET* fusion-positive solid tumors other than NSCLC and thyroid cancer ("other" *RET* fusion–positive solid tumors). **Methods:** The global ongoing ARROW study (84 sites in 13 countries) includes phase 1 dose-escalation (30–600 mg [QD or twice daily]) and phase 2 expansion cohorts (400 mg QD) defined by tumor type and *RET* alteration status. Primary objectives are overall response rate (ORR; blinded independent central review per RECIST v1.1) and safety. **Results:** Updated analyses were completed as of Nov 6, 2020 (data cut-off) for 21 pts with other *RET* fusion–positive solid tumors enrolled by May 22, 2020 (enrollment cut-off) (lung other than NSCLC, n = 4; pancreatic, n = 3; colon, n = 3; cholangiocarcinoma, n = 3; unknown primary [UP], n = 2; other, n = 6). Overall, 11 (52%) pts received ≥2 prior lines of therapy for metastatic disease. The most common *RET* fusion partners were *CCDC6 and KIF5B* (24% each), *NCOA4* (19%), other (10%), and unknown (24%). Two pts with colon cancer were excluded from efficacy analyses due to other driver mutations (*KRAS*, *PIK3CB*). In 19 evaluable pts, ORR was 53% (95% CI, 29–76) with 2 (11%) complete responses (CR) and 8 (42%) partial responses (PR). Responses occurred across multiple tumor types including 3/3 pts with pancreatic cancer (including a CR ongoing at 20.8 months on treatment), 2/2 pts with UP, 2/3 pts with cholangiocarcinoma, and in pts with mesenchymal, salivary duct, and lung carcinoid tumors. Median duration of response was 19.0 months (95% CI, 5.5–not estimable). Clinical benefit rate (proportion with CR, PR, or stable disease persisting ≥16 weeks) was 68% (95% CI, 43–87). Tumor shrinkage was observed in 89% of 18 evaluable pts with post-baseline tumor assessment. In all pts enrolled in ARROW who received pralsetinib 400 mg QD irrespective of tumor type (n = 471) the most common (≥25%) treatment-related adverse events (TRAEs) were increased aspartate aminotransferase (39%), anemia (35%), increased alanine aminotransferase (28%), constipation (26%), and hypertension (25%). Overall, 6% of pts discontinued treatment due to TRAEs. **Conclusions:** Pralsetinib showed robust, durable antitumor activity in patients with multiple RET fusion–positive, heavily pre-treated, advanced solid tumors, and was well tolerated. These data highlight the need for broad *RET* testing to identify candidates who could benefit from treatment with pralsetinib. Enrollment of patients with other *RET* fusion–positive solid tumors in ARROW is ongoing. Clinical trial information: NCT03037385. Research Sponsor: Blueprint Medicines Corporation.

3080 **Poster Session**

A phase 1/2 trial of ORIN1001, a first-in-class IRE1 inhibitor, in patients with advanced solid tumors. *First Author: Nashat Y. Gabrail, Gabrail Cancer Center Research LLC, Canton, OH*

Background: ORIN1001 is a first-in-class small molecule with a novel, unique enzyme and mode of inhibition that selectively inhibits Inositol Requiring Enzyme 1α (IRE1) RNAse and blocks X-Box Binding Protein 1 (XBP1) activation in the endoplasmic reticulum (ER). IRE1α/XBP1 has been implicated in a host of pathologies, and molecules that modulate it are under intense investigation for the treatment of oncologic, metabolic, neurodegenerative and other diseases. ORIN1001 has demonstrated preclinical anti-tumor activity alone and in combination with standard of care across multiple animal models including breast, prostate, lung, liver, pancreatic, brain, colon, ovarian, esophageal, and hematologic cancers and is now undergoing first-in-human testing. **Methods:** A phase 1, open label, 3+3 dose escalation trial is testing ORIN1001 administered PO daily to patients (pts) with advanced solid tumors (single agent) or relapsed refractory breast cancer (in combination with Abraxane). The phase 1 dose escalation part of the trial evaluates the safety, tolerability, pharmacokinetics and preliminary efficacy of ORIN1001. After identification of the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) for the single agent, the dose expansion part of the trial will test ORIN1001 in combination with Abraxane. **Results:** As of Jan 25, 2021, 22 patients with advanced cancer have received ORIN1001 dosed at 100mg, 200mg or 300mg per day in 21-day continuous cycles with a median age of 61 (range 42-77). The pts had received a median of 4 prior line of treatments. Two DLTs were observed at 200 mg with thrombocytopenia and rash. MTD has not been reached. Common (>15%) treatment-emergent adverse events (TEAEs) included nausea, vomiting, rash, fatigue, and hypokalaemia. The vast majority of these events were Grade 1-2 in severity. Seven (32%) pts had at least 1 TRAE grade≥ 3, the most frequent of which were thrombocytopenia (N=3) and rash (N=3). Preliminary pharmacokinetic analysis showed ORIN1001 exposure to increase in a dose proportional manner. Mean $t_{1/2}$ at steady state was 18 hrs. Thirteen pts were evaluated for preliminary efficacy. Best response, per RECIST 1.1, was stable disease (SD) in 8 pts while 5 pts had progressive disease (PD). For 2 ongoing patients with advanced liver or colorectal cancer, duration of treatment has exceeded 300 days and 570 days, respectively. **Conclusions:** To date, the phase 1 part of the first-in-human trial has demonstrated a reasonable safety and pharmacokinetic profile for ORIN1001 at 100mg and 200mg dose levels. While efficacy data have yet to mature, chronic dosing achieved in pts with heavily treated advanced solid tumors, suggests clinical potential for in the setting of advanced solid cancers. The phase 2 part of the trial testing ORIN1001 in combination with Abraxane is currently enrolling pts with advanced breast cancer. Clinical trial information: NCT03950570. Research Sponsor: Shanghai Fosun Pharmaceutical Industrial Development Co., Ltd.

3081 **Poster Session**

First-time in-human study of VMD-928, an oral allosteric TrkA selective inhibitor targeting TrkA protein overexpression, in patients with solid tumors or lymphoma. *First Author: Vincent Chung, City of Hope, Duarte, CA*

Background: Tropomyosin receptor kinase A (TrkA) is a protein encoded by the NTRK1 gene. Upregulation of TrkA signal transduction pathways, which can be caused by either NTRK1 gene fusions or intact TrkA protein overexpression, are oncogenic for multiple tumor types. This is clinically validated by demonstrated efficacy of ATP-competitive pan-TrkA/B/C inhibitors, larotrectinib and entrectinib for treatment of advanced solid tumors harboring NTRK1/2/3 gene fusions. VMD-928 is the first oral small-molecule TrkA (NTRK1) selective inhibitor with differentiated allosteric (ATP non-competitive) and irreversible mechanisms of action, acting as a molecular glue which sticks two TrkA proteins together and dose-dependently inhibits TrkA functions and downstream effectors, e.g. activated ERK, a hallmark of cancer. We conducted a first time in human phase 1 trial and completed the dose escalation phase. **Methods:** This is an open label, Phase 1 study investigating oral VMD-928 in adults with advanced solid tumors or lymphoma. The primary objective is to assess the safety and tolerability of VMD-928 and determine the recommended phase 2 dose. Secondary objectives include characterizing the pharmacokinetics (PK) and pharmacodynamics as well as assessing antitumor activity. **Results:** Non-biomarker-selected patients (n = 20) were accrued to 4 dose escalation cohorts ranging from 300 mg/day to 2400 mg/day. Three patients were accrued to the 2400 mg dose level with one DLT of elevated bilirubin, AST and ALT. The trough concentrations (Ctrough, ng/mL) ranged from 5.3 to 727. The dose was de-escalated to 1200 mg per day in divided doses and fifteen heavily pretreated patients were accrued with the following tumor types: adenoid cystic carcinoma, cholangiocarcinoma, lung cancer, pancreatic cancer, parotid, and squamous cell carcinoma of head and neck. There were no DLT's at this dose and one patient with adenoid cystic carcinoma had prolonged stable disease. Common adverse events related to therapy were dark stool (35%), elevated liver enzymes (25%, primarily at 2400 mg/day), fatigue, nausea or vomiting, and decreased appetite (20% each). **Conclusions:** VMD-928 was well tolerated with mainly gastrointestinal side effects. The recommended phase 2 dose (RP2D) is 600 mg twice (1200 mg) per day. The study is currently accruing in expansion cohorts to evaluate efficacy in biomarker-selected patients with tumors of TrkA protein overexpression. Tumor types with reported high TrkA protein expression including thymic carcinoma (98% with TrkA protein expression without NTRK1/2/3 gene fusions), mesothelioma (81%), squamous cell carcinoma of head and neck (80%), ovarian (80%), hepatocellular (72%), and squamous cell carcinoma of the lung (71%) are being accrued. Clinical trial information: NCT03556228. Research Sponsor: VM Oncology, LLC.

3082 **Poster Session**

High-intensity focused ultrasound ablation for treatment of chemotherapy-induced thrombocytopenia and hypersplenism. *First Author: Min Yuan, Department of Oncology, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China*

Background: Chemotherapy-induced thrombocytopenia (CIT) contributes to treatment dose delay and/or modification, often resulting in poorer survival and disease progression. Compared with partial splenic embolization (PSE) and drugs, high-intensity focused ultrasound has the advantages as following: (1) it is a noninvasive treatment modality with potentially fewer adverse effects and complications; (2) the hospital stay and recovery time after treatment are short; (3) its cost is relatively low compared to surgery. The purpose of this work was to preliminarily investigate the efficacy and safety of high intensity focused ultrasound treatment of chemotherapy-induced thrombocytopenia (CIT) and hypersplenism. **Methods:** 26 patients with chemotherapy-induced thrombocytopenia and hypersplenism (15 male and 11 female; median age, 56 years; range, 51-66 years) were treated with ultrasound guided high-intensity focused ultrasound. Complications were recorded. Laboratory examination and magnetic resonance imaging were used to evaluate the efficacy. The spleen volume and ablation volume rate of the spleen were calculated by MRI after treatment. They were followed closely for at least 6 months. **Results:** After high-intensity focused ultrasound treatment, the MRI showed that the ablation area had turned into a non-perfused volume, the mean percent spleen ablation volume was 18.76% ± 6.1% (range, 11.17%-32.34%). After 6 months of HIFU ablation, the ablated area shrank evidently; the sunken spleen formed a lobulated shape and the splenic volume decreased. The platelet count increased 3-7 days after treatment and remained for 1-2weeks higher than baseline ($53.33 \pm 15.80 \times 10^9$/L). The white blood cell count and platelet count of the patients were substantially improved during the follow-up period. No substantial difference was observed in RBC counts between baseline and after treatment. In addition, symptoms such as epistaxis and gingival bleeding were ameliorated or even eliminated, and the quality of life was improved. Follow-up imaging showed a nonperfused volume in the spleen. **Conclusions:** For the first time to our knowledge, high-intensity focused ultrasound ablation was used to treat Chemotherapy-induced thrombocytopenia (CIT) and hypersplenism. High-intensity focused ultrasound ablation of the spleen may cause damage to a certain volume of the spleen parenchyma to achieve the purpose of hypersplenism treatment. High intensity focused ultrasound may be an effective and safe alternative for treatment of CIT and hypersplenism. Research Sponsor: None.

3084 **Poster Session**

Phase 1 trial of a novel, first-in-class G protein-coupled estrogen receptor (GPER) agonist, LNS8801, in patients with advanced or recurrent treatment-refractory solid malignancies. *First Author: Carolyn Muller, University of New Mexico, Albuquerque, NM*

Background: The G protein-coupled estrogen receptor (GPER) is a broadly expressed G protein-coupled receptor that is tumor suppressive. LNS8801 is an oral, highly selective small molecule agonist of GPER. GPER activation results in c-Myc depletion, inhibition of tumor proliferation, and enhancement of tumor immune recognition. Preclinically, LNS8801 demonstrates potent single-agent and combinatorial anti-cancer activity and can overcome established resistance to standard-of-care anti-cancer therapies including immune checkpoint inhibitors. **Methods:** The primary objective of this phase 1/1B first-in-human, open-label, multicenter study (NCT04130516) was to determine the safety and tolerability and recommended phase 2 dose (RP2D) of LNS8801 in patients (pts) with locally advanced or metastatic solid tumor malignancies, both as monotherapy and in combination with the anti-PD-1 antibody, pembrolizumab. Dose levels were escalated in a 3+3 fashion and included 10, 40 and 125 mg dosed 3/7, 125 mg daily, and 125 and 250 mg twice daily. Dose limiting toxicity (DLT) was defined via NCI CTCAE v5.0 during the first 21 days of treatment. An increase in prolactin over the initial 12 hrs of dosing was measured to assess systemic GPER signaling. Tumor c-Myc expression was measured as a surrogate of treatment-related biologic response. Radiographic response (RECIST v1.1) was evaluated every 8 weeks until progression. **Results:** 33 pts (19 M/14 F) with median age 58.8 y and 4 (1-9) prior therapies enrolled. Median duration of treatment was 66 d (1–367+). With monotherapy (n = 28), no DLTs, treatment-related SAEs, or treatment-related study discontinuations were observed up through the maximum administered dose (250 mg bid). Possibly related AEs were grade 1 or 2 and did not correlate with dose level. Exposure was above that predicted for efficacy and $t_{1/2}$ was ~10 hr at all doses. Of 26 evaluable monotherapy pts, 8 (27%) experienced stable disease (SD) for up to a year. All SD pts had a prolactin response. Among tumors expressing GPER, c-Myc depletion was observed in 100% (5/5) of paired pre and on-treatment biopsies. In the combination cohort (n = 5), 2/2 evaluable pts demonstrated net tumor reductions on initial f/up scans, including one RECIST partial response. Based on PK/PD data, 125 mg daily has provisionally been identified as the monotherapy and combination RP2D. **Conclusions:** LNS8801 is well tolerated and demonstrates signals of anti-tumor activity when administered both as monotherapy and in combination with pembrolizumab. Confirmation of RP2Ds and updated efficacy data will be presented in June. A phase 2A expansion study to evaluate these RP2Ds in clinical settings of high unmet need is now in development. Clinical trial information: NCT04130516. Research Sponsor: Linneus Therapeutics.

3085 **Poster Session**

A phase II study investigating biological effects of maintenance usage of hydroxychloroquine on Par-4 levels in patients with resected tumors. *First Author: Peng Wang, University of Kentucky Markey Cancer Center, Lexington, KY*

Background: Hydroxychloroquine (HCQ) is an inducer of the tumor suppressor Par-4 (prostate apoptosis response-4) secretion from normal cells. Secreted Par-4 causes paracrine apoptosis of tumor cells in mice. Established dosing of HCQ 200 mg bid induces Par-4 secretion but not the autophagy-inhibition marker p62 and correlates with apoptosis induction in patients' tumors. **Methods:** This is a single-arm, single institute phase II study to characterize the biological effects of 3-months of HCQ at fixed-dose (200 mg p.o. twice a day) on plasma Par-4 levels in adults with resected solid tumors. The primary endpoint is proportion of patients who will exhibit a two-fold increase in Par-4 levels from baseline compared to 3 months of follow-up. 12-month progression free survival (PFS) is one of the secondary endpoints. A Simon's two-stage design was used to test the null hypothesis that the proportion of patients exhibiting a two-fold increase in Par-4 is equal to 50% compared to 70% using a one-sided alternative. These hypothesized assumptions are based on a small pilot human data and from a phase I clinical trial on a small number of patients (n = 9). The first stage of interim analysis will be performed after a total of 15 patients have been accrued. If there are eight or fewer responses occurred, the study will be stopped. Otherwise, 28 additional patients will be accrued for a total of 43 subjects. **Results:** A total of 19 patients were enrolled in the trial. Per protocol, the interim analysis and stopping boundary is based on the first 15 patients. A total of 4 out of 15 patients (26.7%) 95% CI: 8% - 55% exhibited a >2-fold increase in Par-4 levels at 3 months. This did not surpass the stopping bound for futility and thus indicates stopping of patient accrual based on the assumptions used for the Simon's two-stage design. 7 out of 19 patients (36.8%) 95% CI: 16% - 62% who exhibited at least a 2-fold increase at either 2 or 3 months of follow-up, 50% (95% CI: 26% - 74%) and 56% (95% CI: 31% -79%) exhibited a 1.5-fold and 1.25-fold increase respectively. To date, 10/19 patients finished 12-month follow-up, 4/19 and 5/19 finished 6-month and 3-month follow up respectively. 2 of 12 patients with less than 2-fold increase of Par-4 developed disease progression. None of 7 patients with 2-fold increase of Par-4 showed disease progression. **Conclusions:** Despite that the study was terminated prematurely, to our knowledge this is the first study in human to identify dynamic changes of serum Par-4 while on long-term of usage of HCQ. We also demonstrate trend of PFS benefit especially for subjects having 2-fold increase of Par-4 induction. Identification of tumors more Par-4 sensitive and predictive biomarkers of Par-4 induction are necessary to continue our investigation. Clinical trial information: NCT02232243. Research Sponsor: Markey Cancer Center CCSG pilot grant.

3086 **Poster Session**

Safety and preliminary efficacy from the phase 1 portion of MasterKey-01: A First-in-human dose-escalation study to determine the recommended phase 2 dose (RP2D), pharmacokinetics (PK) and preliminary antitumor activity of BDTX-189, an inhibitor of allosteric *ErbB* mutations, in patients (pts) with advanced solid malignancies. *First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: BDTX-189 is an orally available, ATP-competitive and irreversible inhibitor directed against families of allosteric *HER2* and *EGFR* oncogenic mutations. In preclinical studies BDTX-189 achieved potent inhibition of 48 allosteric *HER2* and *EGFR/HER2* exon 20 insertion mutant variants with selectivity versus *EGFR* wild-type (WT) and demonstrated tumor growth inhibition and regression *in vivo*. The primary objective of the Ph 1 portion of this trial (NCT04209465) is to determine the RP2D and schedule of monotherapy BDTX-189 in pts with advanced solid tumors. **Methods:** Eligibility includes pts with relapsed or refractory locally advanced or metastatic solid tumors with no standard therapy available whose tumor harbors an allosteric *HER2* or *HER3* mutation; *EGFR* or *HER2* exon 20 insertion mutation; *HER2* amplification or overexpression; or *EGFR* exon 19 deletion or L858R mutation. BDTX-189 is dosed continuously orally in 3-wk cycles QD and BID in separate dose escalation cohorts. A separate cohort is also evaluating the high- and low-fat food-effect (FE) on BDTX-189 PK. **Results:** As of 1/11/21, 46 pts have been dosed, with 36 in the QD (fasting) schedule (25-1200 mg), including pts from the FE cohort who received 800 mg QD fasting after FE evaluation: 58% female; 67% white; median age 63.5 yrs; 53% received ≥ 3 prior tx lines. Cancer types: 12 NSCLC, 5 breast, 4 ovary, 3 biliary, and 12 other. Genomic alterations: 23 HER2 amplification and the following mutations: 11 allosteric *HER2*, 5 *EGFR* exon 20 insertion, 5 *HER2* exon 20 insertion, 3 *EGFR* exon 19 del./L858R, and 2 *HER3*. At ≥ 800 mg QD, 3 and 2 pts had EGFR or HER2 exon 20 mutations, respectively. The maximum tolerated dose (MTD) for QD (fasting) was 800 mg, with 2/6 pts with DLTs at 1200 mg. DLTs: gastrointestinal (G3 diarrhea; G1/2 nausea/vomiting). The most frequent (≥20%) related adverse events were diarrhea (36%, 8% G3), nausea (28%, 0% G3), and vomiting (25%, 3% G3). The rate of skin disorders was 11% with the highest severity of G2 in 1 pt. Dose-dependent exposure increases were observed, with the exposure at 800 mg QD fasting within the projected efficacious range. Pilot FE data suggest possible increased exposure with food. 27 pts were evaluable for efficacy, 15 at ≥ 800 mg QD, with 2 partial responses observed: 1 PR confirmed and ongoing (800 mg QD, CUP, HER2 amp, 3 prior lines of chemo) and 1 PR unconfirmed (NSCLC with brain mets, 1200 mg QD, HER2 amp + exon 19 del., 2 prior EGFR TKIs). 3 pts had a best response of SD and 10 with progressive disease. **Conclusions:** BDTX-189 has a generally manageable safety profile with early evidence of anti-tumor activity. Enrollment is ongoing in non-fasting QD and BID cohorts, and the FE cohort, prior to RP2D identification. Clinical trial information: NCT04209465. Research Sponsor: Black Diamond Therapeutics.

3087 **Poster Session**

A phase 2 study of defactinib (VS-6063) in patients with NF2 altered tumors: Results from NCI-match (EAY131) subprotocol U. *First Author: David Michael Jackman, Dana-Farber Cancer Institute, Boston, MA*

Background: The NCI-MATCH trial assigns patients (pts) with solid tumors, lymphomas, or multiple myeloma to targeted therapies based on genetic alterations identified in tumor biopsies. Neurofibromatosis 2 (NF2)-inactivated tumors demonstrate increased sensitivity to FAK inhibition in preclinical models. Arm U evaluated the FAK inhibitor defactinib in pts with NF2 altered tumors. **Methods:** Patients found to harbor an inactivating NF2 mutation on NGS were assigned to the ARM U substudy MATCH. Defactinib 400 mg was given by mouth twice daily until progression or intolerable toxicity. The primary endpoint was objective response rate (ORR). Secondary endpoints included toxicity, progression-free survival (PFS), and 6-month PFS. **Results:** Of 5,548 cases with sufficient tissue for genomic analysis, 51 pts were found to have NF2 alterations (< 1% of the total analyzed). While NF2 alterations are known to occur more commonly in meningiomas and mesotheliomas, alterations were also detected in an array of other tumor types, including renal cell carcinomas and ovarian cancers. Thirty-five pts were ultimately enrolled; 33 patients were started on therapy, with 2 of those determined to be ineligible for outcome analysis. All pts had received at least one prior therapy, with 52% (16/31) having received 3 or more prior lines of therapy. Median follow-up was 35.9 months. ORR [90% CI] was 3% (1/31, [0.16, 14.86]), with the one partial response in a pt with choroid meningioma. Of the twelve pts whose best response was stable disease (39%, 12/31), 8 demonstrated some degree of tumor shrinkage (Table) with a disease control rate of 42% (13/31). Median PFS was 1.9 months for the 31 eligible pts who received study treatment, with median PFS of 9.3 months for the 9 patients who had a best response of stable disease or better. Six pts achieved a PFS of greater than 5.5 months. Among all treated pts (n=33), the most common treatment-related toxicities were fatigue (36%), nausea (33%), and hyperbilirubinemia (27%). There were no grade 4 or 5 toxicities; 27% of pts had grade 3 toxicities. No correlation could be made between clinical outcomes and tumor histology or specific NF2 genotype. **Conclusions:** Defactinib monotherapy had limited clinical activity in this cohort of previously treated patients with solid tumors exhibiting NF2 loss. Clinical trial information: NCT04439331. Research Sponsor: U.S. National Institutes of Health.

Patients with any evidence of tumor reduction.

Case	Histology	Maximum tumor reduction (%)	PFS (months)
16490	Choroid meningioma	–30%	14
11705	Papillary renal cell carcinoma	–27%	7
11988	Undifferentiated pleomorphic sarcoma/myxoid	–12%	4
14866	Mesothelioma of pleural	–8%	5
16466	Neoplasm of spinal cord	–6%	27
10366	Serous carcinoma of ovary	–3%	1
16497	Carcinoma of unknown primary site	–3%	2
16058	Meningioma	–3%	3
15738	Schwannoma of right forearm	–2%	21

3088 **Poster Session**

Phase I trial of 5-aza-4'-thio-2'-deoxycytidine (Aza-TdC) in patients with advanced solid tumors. *First Author: James Nguyen, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI), National Institutes of Health (NIH), Bethesda, MD*

Background: The nucleoside analog Aza-TdC inhibits DNA methyltransferase 1 (DNMT1), which regulates methylation-mediated silencing of tumor suppressor genes. Aza-TdC offers an improvement over traditional DNA methyltransferase inhibitors by virtue of a higher incorporation rate into DNA at lower levels of cytotoxicity. Aza-TdC has also shown improved preclinical antitumor activity compared to other hypomethylating agents in some solid tumor xenograft models. In an ongoing phase I trial, we evaluate the safety and activity of Aza-TdC in patients (pts) with advanced solid tumors. **Methods:** Adult pts with solid tumors whose disease has progressed on standard therapy or for which there is no standard therapy were treated with Aza-TdC administered orally once a day for 5 days of each week for 2 weeks in 21-day cycles. The study followed Simon accelerated titration design 3, with 1 pt per dose level at 100% dose increments. Accelerated titration continued until 1 pt experienced a dose-limiting toxicity (DLT) or 2 pts experience drug-related grade 2 toxicity at any dose level, after which, a 3 + 3 dose escalation design was used. Intrapatient dose escalation was allowed. Correlative studies included pharmacokinetic assays and pharmacodynamic assays in circulating tumor cells. **Results:** As of January 2021, a total of 18 pts have been enrolled on study. Median pt age is 61.5 years (range 35-84). Tumor types included colorectal adenocarcinoma (5 pts), sarcoma (3), breast carcinoma (2), and ovarian carcinoma (2). The DLTs at 48 mg were grade 3 rash and grade 3 acute kidney injury in one pt and < 75% of dosing completed in another pt due to grade 3 myelosuppression. Among the 10 pts treated at 32 mg, 1 pt experienced a DLT: grade 4 neutropenia. The maximum tolerated dose (MTD) is 32 mg. Grade 3 or 4 toxicities across all cycles possibly attributable to study drug were leukopenia (6), lymphopenia (6), neutropenia (4), rash (2), febrile neutropenia (1), anemia (1), thrombocytopenia (1), acute kidney injury (1), elevated AST (1), elevated ALT (1), diarrhea (1), and dehydration (1). Of the 14 pts evaluable for response, 11 had a best response of stable disease, and 3 had a best response of progressive disease. Median cycles on study is 4 (range 1-10+). A pt with clear cell ovarian carcinoma has been on study for > 10 cycles with stable disease. **Conclusions:** At the MTD of 32 mg, Aza-TdC is safe and well tolerated with a toxicity profile similar to currently approved hypomethylating agents. Global DNA methylation profiling, RNAseq, and DNMT immunohistochemical analyses of tumor biopsies are planned for the currently accruing dose expansion cohort. Funded by NCI Contract No. HHSN261200800001E. Clinical trial information: NCT03366116. Research Sponsor: U.S. National Institutes of Health.

3089 **Poster Session**

Evaluating clinical activity of MAPK targeted therapies (TT) in cancer patients (pts) with non-V600 BRAF mutations: A systematic scoping review and meta-analysis. *First Author: Matthew Dankner, McGill University, Montréal, QC, Canada*

Background: Oncogenic nonV600 BRAF mutations (muts) can be classified according to distinct molecular characteristics. TT strategies for class 2 and 3 BRAF muts have not been established. In recent years there have been numerous reports of clinical activity for various TT in pts with nonV600 muts. We performed a systematic scoping review and meta-analysis to assess treatment outcomes with MAPK TT according to BRAF class, cancer type and TT type. **Methods:** An extensive literature search was conducted from 2010-20. All studies were independently reviewed and extracted by 2 reviewers and in accordance with PRISMA guidelines. Individual patient level data were collected and analyzed from studies that met the following inclusion criteria: published reports of 1) advanced cancer pts with; 2) class 2 or class 3 nonV600 BRAF muts; 3) who received MAPK TT; 4) with treatment response (TR) data available. Primary outcome was overall TR rate (TRR). To assess differences between groups, odds ratios (OR) were calculated using a multi-level mixed-effects logistic regression model. **Results:** 15,171 studies were screened and 168 were included for data extraction. We identified 100 studies with a total of 396 pts that met inclusion criteria. There were 17 reports (161 pts) of prospective clinical trials and 83 retrospective studies (235 pts). RECIST criteria were used for TR assessment in 183 (46%) pts. The entire study included 280 pts with class 2 and 116 pts with class 3 BRAF muts. Overall, 111 (28%) pts achieved a TR. TRR according to primary tumor type, BRAF class, and TT type is indicated in Table. TRR was lower in reports of prospective studies compared to retrospective studies (OR 0.14, P = 0.002), and in studies that employed RECIST criteria vs. those that didn't (OR 0.29, P = 0.044). TRR was higher among pts with class 2 muts vs. those with class 3 muts (OR 2.21, P = 0.042). **Conclusions:** These data establish that MAPK TT have demonstrated clinical activity in cancers with oncogenic nonV600 mutations, and that BRAF mutation class may dictate responsiveness to different TT strategies. TRR may be over-estimated in the retrospective literature. This analysis will be valuable for molecular tumor boards and to guide future clinical trial design. Prospective clinical trials of TT in this pt population are warranted. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	Melanoma (n = 117)		Lung (n = 62)		Colorectal (n = 78)		CNS (n = 74)		Other (n = 65)	
	Class 2	Class 3	Class 2	Class 3	Class 2	Class 3	Class 2	Class 3	Class 2	Class 3
BRAFi (n = 99)	14% (6/44)	9% (1/11)	5% (1/19)	12.5% (1/8)	0% (0/3)	-	0% (0/5)	-	25% (2/8)	0% (0/1)
BRAFi + MEKi (n = 57)	52% (17/33)	0% (0/1)	50% (5/10)	33% (1/3)	-	0% (0/2)	100% (1/1)	-	20% (1/5)	50% (1/2)
EGFRi +/- MAPKi (n = 11)	-	-	100% (1/1)	100% (1/1)	20% (1/5)	0% (0/4)	-	-	-	-
EGFRi + chemo (n = 61)	-	-	-	-	6% (1/17)	40% (17/43)	-	-	100% (1/1)	-
MEKi or ERKi (n = 168)	58% (14/24)	0% (0/4)	50% (3/6)	0% (0/14)	0% (0/2)	0% (0/2)	30% (20/67)	0% (0/1)	52% (15/29)	0% (0/19)

3090 **Poster Session**

Phase I study of TT-00420, a multiple kinase inhibitor, as a single agent in advanced solid tumors. *First Author: Sarina Anne Anne Piha-Paul, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: TT-00420 is a spectrum-selective multi-kinase inhibitor that targets cell proliferation, angiogenesis, and immune-oncology pathways by inhibiting Aurora kinases A/B and Janus kinases (JAK) involved in cytokine signaling and receptor tyrosine kinases (FGFRs and VEGFRs) involved in the tumor microenvironment. TT-00420 has demonstrated anti-tumor activity in both *in vitro* and *in vivo* preclinical models of solid tumors, including triple-negative breast cancer (TNBC) and cholangiocarcinoma (CCA). **Methods:** The phase I, first-in-human dose escalation and expansion study of TT-00420 is enrolling adult patients with advanced or metastatic solid tumors. TT-00420 capsules in 1 mg or 5 mg formulation are administered orally once daily in 28-day cycles. Dose escalation is guided by Bayesian modeling with overdose control. The primary safety endpoints are to determine dose limiting toxicities (DLTs) and a dose recommended for dose expansion (DRDE). Secondary endpoints include pharmacokinetics (PK) and preliminary efficacy evaluated per RECIST v1.1 criteria. **Results:** As of February 17, 2021, 40 advanced solid tumor patients were enrolled in dose escalation cohorts and received at least one dose of TT-00420 in 7 dose levels: 1 mg *q.d.* (N=1), 3 mg *q.d.* (N=1), 5 mg *q.d.* (N=4), 8 mg *q.d.* (N=10), 10 mg *q.d.* (N=6), 12 mg *q.d.* (N=12), and 15 mg *q.d.* (N=6). DLTs were observed in 3 out of 32 DLT-evaluable patients, including 1 patient at 8 mg *q.d.* who had grade (Gr) 3 palmar-plantar erythrodysaesthesia syndrome and 2 patients at 15 mg *q.d.* who both had Gr 3 hypertension. Suspected adverse events (AEs) reported in ≥ 20% of patients across all tested dose levels include hypertension (any grade: n=17, 42.5%; Gr 3: n=8, 20.0%), diarrhea (n=10, 25.0%; Gr 3: n=1, 2.5%), vomiting (n=9, 22.5%; Gr 3: n=0), palmar-plantar erythrodysaesthesia syndrome (n=9, 22.5%; Gr 3: n=1, 2.5%), and nausea (n=8, 20.0%; Gr 3: n=1, 2.5%). No Gr 4 AEs, regardless of causality, were reported. Out of 26 patients who had at least one post-baseline scan, 4 (15.4%) had a best overall objective response of partial response (PR) and 13 (50.0%) had stable disease (SD). Of the patients who achieved PRs are 2 CCA patients (8 mg *q.d.*, n=1; 10 mg *q.d.*, n=1), 1 HER2-negative breast cancer patient (12 mg *q.d.*), and 1 TNBC (10 mg *q.d.*). Both CCA patients with PRs had disease control for ≥ 8 months. Of the patients who achieved SD, 1 salivary gland patient (5 mg *q.d.*) and 1 CCA patient (10 mg *q.d.*) had disease control for 8 months, and 2 TNBC patients (5 mg *q.d.*, n=1; 8 mg *q.d.*, n=1) had disease control for 6 months prior to disease progression. **Conclusions:** Toxicities observed in dose escalation cohorts were manageable with concomitant treatment and/or dose interruptions of TT-00420. 12 mg *p.o. q.d.* was recommended as the dose for dose expansion cohort for further safety and efficacy evaluation of TT-00420 capsules with focus on enrollment of TNBC and CCA patients. Clinical trial information: NCT03654547. Research Sponsor: Nanjing TransThera Biosciences Co., Ltd.

3091 **Poster Session**

Incidence of *ERBB* gene fusions (*EGFR*, *ERBB2*, *ERBB4*) across tumor types. *First Author: Laura Schubert, University of Colorado School of Medicine, Denver, CO*

Background: Gene fusions often represent critical therapeutic targets across cancer subtypes. Fusions within the ErbB family of receptor tyrosine kinases, including *EGFR*, *ERBB2* (*HER2*) and *ERBB4* (*HER4*), have been previously described and represent potentially actionable alterations. Here, we report the relative incidence and functional characterization of these rare genomic events. **Methods:** Tumor samples (n = 64,354; representing > 40 tumors types) submitted to Caris Life Sciences (Phoenix, AZ) were molecularly profiled by next-generation sequencing of DNA (NextSeq, 592-gene panel; or NovaSeq, whole exome) and RNA (whole transcriptome). Gene fusion partners, in/out-of-frame status, retention of *ERBB* kinase domain, and topology of fusion breakpoints were characterized for each *ERBB* fusion transcript detected. Fusion prevalence was further examined in public data sets (TCGA, MSK-IMPACT and AACR GENIE). **Results:** From the Caris database, a total of 64 *EGFR* fusion isoforms were detected in 59 tumors (incidence 0.09%); 83% were in-frame and 91% retained the *EGFR* kinase domain. 206 *ERBB2* fusion isoforms were detected in 114 tumors (0.18%); 37% were in-frame and 34% retained the *ERBB2* kinase domain. 131 *ERBB4* fusion isoforms were detected in 108 tumors (0.17%); 62% were in-frame and 51% retained the kinase domain. All fusions were detected at low incidence across all tumor types. *EGFR* fusions were most common in high grade glioma (1.7%, n = 35), largely driven by recurrent *EGFR-SEPT14* fusions (n = 20). *ERBB2* fusions were most common in esophageal/gastroesophageal junction carcinoma (1.1%, n = 20), with recurrent fusion to *PGAP3* observed in multiple tumor types (n = 37). *ERBB4* fusions were most common in ovarian (0.7%, n = 40) and bladder (0.7%, n = 15) cancers, which often resulted from recurrent fusion with *IKZF2* (n = 36). *EGFR* and *ERBB2* fusions were generated predominantly (44-48%) from inversion events, while *ERBB4* fusions arose more frequently and at similar rates (27-32%) from deletions, duplications, or translocations. Mining of public data sets corroborated the prevalence of *ERBB* gene fusions: the frequency of *EGFR* fusions was 0.63%, *ERBB2* was 0.14% and *ERBB4* was 0.04%. *TP53* mutations frequently co-occurred with *ERBB2* and *ERBB4* fusions (> 60% average across public data sets), with higher co-mutation rates (> 70%) observed for samples in the Caris database. **Conclusions:** *ERBB* gene fusions are detectable at low frequency in various tumor types and may represent a unique genomic subset of cancer. Identification of novel *ERBB* gene fusions warrants further investigation to determine the potential pathogenicity and actionability of these fusions. Research Sponsor: None.

3092 **Poster Session**

Association of high gene expression levels of *ARF6* with the immune microenvironment and prediction of poor outcomes. *First Author: Natsuko Kawanishi, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: ADP-ribosylation factor 6 (*ARF6*) is a small GTPase in the RAS superfamily, which regulates membrane trafficking, remodeling and tumor progression. Preclinical study shows that *TP53* and *KRAS* cooperatively activate the *ARF6-AMAP1* pathway which serves as a link by which pancreatic driver mutations promote tumor invasion, PD-L1 dynamics and immune evasion properties in pancreatic ductal adenocarcinoma (PDAC). The clinical impact of *ARF6* on cancer progression and prognosis remains unclear. **Methods:** A total of 2,948 PDAC samples were analyzed using next-generation sequencing of RNA (whole transcriptome, NovaSeq) and DNA (NextSeq, 592 genes or NovaSeq, whole exome sequencing) and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ). QuantiSeq (Finotello 2019, Genome Medicine) was used to quantify immune cell infiltration. Overall survival (OS) was obtained from insurance claims, and Kaplan-Meier estimates were calculated for molecularly defined cohorts. Significance was determined as p values adjusted for multiple correction (q) of < .05. **Results:** Median *ARF6* expression was higher in metastases (33.69 transcriptions per million) compared to primary/local tumors (27.59, q< .05). Specific metastatic sites showed higher expression than did primary tumors (q< .05 for liver and p< .05 for skin, bone and lymph nodes). Dividing into quartiles by *ARF6* expression (the highest expression quartile, QH; the lowest, QL), *KRAS* mutations were significantly more prevalent in QH than QL (93.4 vs 87.2%, q< .05), and *TP53* mutations had similar trends (81.0% in QH vs 74.7% in QL, p= .0078). The mutation rates of *KDM6A*, *FANCD2* and *TFEB* amplifications trended higher in QH than QL; the *STK11* mutation rate tended to be lower in QH (p< .05). PD-L1 expression by IHC was significantly higher in QH than QL (20.9 vs 13.1%); immune checkpoint genes by RNA expression: *IFNG*, *IDO1*, *PDCD1G2*, *CD274*, *PDCD1* and *PDCD2L* were significantly higher in QH than QL (all q< .05). Macrophages, neutrophils, NK cells, fibroblasts and endothelial cells were more abundant in QH than QL (all q< .05); whereas CD4+ and CD8+ T cells were lower in QH (q< .05), and monocytes had similar trends (p< .05). High expression of *ARF6* was significantly associated with unfavorable outcomes in OS (HR = 1.83, 95% CI [1.51–2.22], p< .0001); the effect on OS was seen when primary (HR = 1.47, [1.06–2.05], p= .02) and metastatic tumors (HR = 0.608, [1.29–2.10], p< .0001) were investigated separately. **Conclusions:** This is the first report showing that high gene expression of *ARF6* in PDAC indicates a different immune profile, is enriched in cancer metastases, and is associated with poor survival. Our results provide the first clinical evidence supporting the *ARF6* pathway as a major downstream target of *KRAS* and *TP53* mutations promoting immune evasion, suggesting *ARF6* is a novel marker for prognosis and a potential target for immune therapeutic strategies in PDAC. Research Sponsor: None.

3093 **Poster Session**

Optimal dose selection in oncology biologics development: Need for a paradigm shift. *First Author: Rajendar K Mittapalli, Pfizer, Inc., San Diego, CA*

Background: In oncology, the recommended phase 2 dose (RP2D) is typically selected from the first-in-patient (FIP) dose escalation and then carried forward to late stage trials. The RP2D is often informed by limited data from a relatively small number of patients. Further dose optimization in late stage trials is rare as these trials often evaluate only one dose/dosing regimen. Traditionally oncology development relied on establishing an MTD with the expectation this dose would ultimately provide an optimal benefit/risk profile. However, for biologics there are clear examples suggesting a need to reconsider this approach to dose selection during drug development. The present review attempts to evaluate the dose selection approaches for approved oncology biologics to identify opportunities for improved dose optimization of future oncology drugs. **Methods:** The dose selection steps for oncology biologics approved by the USFDA from 2010 to 2020 were reviewed. The primary focus of the review was RP2D selection based on early clinical data, doses tested in pivotal trials, exposure-response and dose justification for the proposed dose, and post-marketing requirements (PMR) or post-marketing commitments (PMC) related to dose optimization. **Results:** The dose selection process for a total of 22 biologics was analyzed. Among these, 17 (77%) did not identify MTD during the FIP trial, and 6 (27%) tested more than one dose in the registration trials. In the initial approval, 2 (10%) had PMR or PMC for further dose optimization. For majority of the biologics the dose justification was based on 1) receptor occupancy 2) biomarker response 3) early clinical activity and 4) target efficacious concentration based on xenograft data. The majority of biologics had shown a shallow exposure-response relationship in safety or efficacy end points which partly can be attributed to the common practice of testing single dose level in the registrational trial. The dose recommended in the FDA label appears to be highly correlated to the RP2D determined in FIP studies. **Conclusions:** Oncology biologics have heavily relied on pharmacodynamic, early signs of efficacy, and safety data from the limited number of patients in the FIP dose escalation to identify the dose for pivotal trials. In most cases, there have been no dose ranging or optimization based on the final therapeutic outcome. While integration of relevant biomarker, PK, and PD data for optimal dose selection is an important aspect, there is a need to change the paradigm to consider more robust dose optimization, especially in early stage development. Dose ranging assessments incorporating therapeutically relevant endpoints and adequate sample size should be considered, ideally prior to pivotal trials. Research Sponsor: Pfizer Inc.

3094 **Poster Session**

Anticancer drugs associated with venous thromboembolic event: Analysis of the WHO pharmacovigilance database. *First Author: Angélique DA Silva, PICARO Cardio-oncology Program, Breast Cancer Unit, Centre François Baclesse, Caen, France*

Background: Venous thromboembolic event (VTE) is a frequent complication of cancer, as of some classical cancer therapy, like chemotherapy and surgery. The advent of new therapies such as immunotherapy and targeted therapies has meant that new therapies may be associated with VTE. Reliable data concerning the association between ADs and VTE are scarce. **Methods:** On March 1st, 2020 we utilized VigiBase (International pharmacovigilance database) and performed a disproportionality analysis using reporting odds ratios (ROR) to determine the association between the 206 FDA- or EMA-labeled ADs and VTE, defined as deep vein thrombosis and pulmonary embolism. RORs were adjusted (aRORs) on population characteristics including the cancer risk of VTE with the primary tumor site according to Khorana classification and metastatic status. **Results:** A total of 50,438 VTE cases associated with at least one AD were identified. Thirteen ADs were associated with higher reporting of VTE of which 2 represented new VTE associations not previously confirmed in the summary of product characteristics or literature including sipuleucel-t and megestrol. ADs more reported with VTE were lenalidomide (n:5,796), bevacizumab (n:2,780) and thalidomide (n:1,700). ADs associated-VTE occurred mainly during the first 6 months after AD initiation. **Conclusions:** Although cancer itself may generate VTE, we identified 13 ADs associated with VTE overreporting. Recognition of AD most likely to cause VTE can help raise practitioner awareness and lead to earlier diagnosis and treatment. Futures studies should include ADs in VTE risk evaluation and evaluate the management of VTE when recurrences occur under AD favoring VTE. ClinicalTrial registration number: NCT04696250. Research Sponsor: None.

3095 **Poster Session**

Does oxaliplatin pharmacokinetics (PKs) explain associations between body composition and chemotherapy toxicity risk in older adults with gastrointestinal (GI) cancers? *First Author: Grant Richard Williams, Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL*

Background: Considerable inter-individual variability in oxaliplatin toxicity exists in older adults with GI cancers. Low lean body mass (LBM), commonly known as sarcopenia, influences toxicity and is not incorporated in standard body surface area-based dosing, which may affect oxaliplatin PK and tolerability, but has not been examined systematically. **Methods:** We examined oxaliplatin PK in 26 older adults (103 concentrations) with GI cancers (NCT03998202). Using the transverse section at L3, skeletal muscle area (SMA) and total adipose tissue (TAT) were quantified (Slice-O-Matic software) and LBM was calculated (LBM = 0.30 × SMA + 6.06). Noncompartmental methods (WinNonlin 7.0) were used for PK estimates and a one compartment population PK model (PopPK) was developed. Covariates included age, sex, LBM, TAT, weight, BMI, creatinine clearance, BSA, serum albumin, and body composition phenotypes (i.e. low LBM-high TAT, etc.). **Results:** Median age was 68yrs, 69% male, 88% white, and mostly colorectal (62%) and pancreatic (27%) cancers. There was wide variability in oxaliplatin volume of distribution (Vd: 12.5-259L), peak concentrations (Cmax: 404-3642ng/mL), and clearance (CL: 26.7-270L/hr). Participants with lower LBM had lower Vd (r = 0.51, $p< 0.01$); those with higher TAT had higher Cmax (r = 0.53, $p< 0.01$). Higher albumin was associated with lower Cmax (r = -0.49, $p= 0.01$) and higher CL (r = 0.47, $p= 0.01$). The phenotype of low LBM + high TAT had the lowest Vd (Relative Risk [RR] 0.32, $p= 0.01$), lowest CL (RR 0.39, $p< 0.01$), and highest Cmax (RR 3.3, 95% CI 1.7-6.5, $p< 0.01$). Eleven patients (44%) had grade 3-5 chemotoxicity. Vd (r = -0.46, $p= 0.02$) and Cmax (r = 0.44, $p= 0.03$) were associated with grade 3-5 chemotoxicity. The phenotype of low LBM + high TAT was associated with a 45% higher risk of grade 3-5 chemotoxicity (RR = 1.45, 95% CI 1.1-2.1, $p= 0.04$), while BSA was not (r = -0.04, $p= 0.9$). In the popPK model, body composition was associated with PK (TAT with Vd [p = 0.006] and CL [$p < 0.001$]), as was albumin (Vd p = 0.004; CL p = 0.002), while BSA was not (Vd p = 0.08; CL p = 0.2). Compared to BSA, an additional 11-17% in oxaliplatin PK variability was explained by LBM (11%), TAT (14%), and albumin (17%). **Conclusions:** Relationships between body composition, oxaliplatin PK, and severe chemotoxicity suggest the need for novel dosing strategies that incorporate body composition to reduce chemotoxicity and improve outcomes. Clinical trial information: NCT03998202. Research Sponsor: U.S. National Institutes of Health.

3096 **Poster Session**

Pre-therapeutic dihydropyridimidine dehydrogenase (DPD) deficiency screening: Impact on fluoropyrimidine dose reduction at the second chemotherapy cycle and on early severe toxicity. *First Author: Côme De Metz, Hôpital Victor Provo, Roubaix, France*

Background: DPD deficiency screening before fluoropyrimidine is a matter of debate. To avoid lethal toxicity, French authorities impose DPD screening before fluoropyrimidine-based chemotherapy by dosing uracilemia since April 2019. **Methods:** We have included all consecutive adult patients receiving 5-fluorouracil (5-FU) or capecitabin from April 2019 to January 2020 in 6 cancer centers. During the study period, different methods for screening had been applied: *DPYD* complete sequencing, phenotype (uracilemia and/or dihydrouracilemia/uracilemia ratio - UH2/U -) or both. All sceening tests were conducted in the same laboratory. Association between the method of DPD screening and fluoropyrimidine dose reduction at second chemotherapy cycle or on severe ≥grade 3 early toxicity (between first and second cycle) was evaluated using multivariate logistic regression. Concordance between genotype and phenotype for DPD deficiency was explored using Cohen Kappa test. **Results:** We included 597 patients, the median age was 63 (range, 55-77). The most prevalent cancers were digestive (68.3%), head and neck (19.4%) and breast (9.2%). 12.3% of patients received capecitabine and 87.3% received polychemotherapy. DPD deficiency screening was done for most of patients (n=519, 86.9%). DPD screening method consisted in full sequencing of *DPYP* (n=41; 7.9%), phenotype analysis (n=44, 8.5%) or both (n=424, 83.6%). We did not identify any complete DPD deficiency. Uracilemia was dosed for 467 patients, the median was 6.5 ng/mL and for 21 patients (4.5%) uracilemia was > 16 ng/mL and/or UH2/U <6, suggesting DPD deficiency. Severe early toxicities were observed for 82 patients (14%), with two patients presenting grade 5 toxicity. Overall DPD screening and method of DPD screening were not associated with fluoropyrimidine dose reduction at second cycle or early severe toxicity. In multivariate analysis, the only predictor for fluoropyrimidine reduction at second cycle (n = 125 patients) was polychemotherapy (OR=2.8; p=0.012). Kappa between uracilemia and UH2/U was 0.23 (poor concordance). Kappa between *DPYP* sequencing and uracilemia or UH2/U was 0.09 (very poor concordance). **Conclusions:** No DPD deficiency screening method was associated with dose adaptation at second cycle or early severe toxicity. The optimal strategy for DPD screening requires further clinical evaluation. Research Sponsor: None.

3097 **Poster Session**

Clinical pharmacokinetics of bdtx-189, an inhibitor of allosteric ErbB mutations, in patients with advanced solid malignancies in MasterKey-01 study. *First Author: Nigel Waters, Black Diamond Therapeutics, Inc, Cambridge, MA*

Background: Allosteric oncogenic mutations occur outside the canonical ATP-binding site of EGFR and HER2, and there are no approved therapies that target such mutations. BDTX-189 is a potent, selective, irreversible inhibitor of 48 allosteric EGFR and HER2 mutant variants under clinical evaluation in the ongoing MasterKey-01 trial (NCT04209465). BDTX-189 was designed to rapidly and irreversibly occupy the active site of targeted ErbB mutants, leading to sustained pharmacodynamic (PD) effects, and with selectivity over EGFR-WT in order to minimize EGFR-WT mediated toxicities. The pharmacokinetic (PK) profile was designed for rapid absorption and fast elimination to maintain target occupancy while minimizing prolonged drug exposure that could contribute to off-target associated toxicities. **Methods:** In MasterKey-01, BDTX-189 was administered orally once daily in continuous 21-day cycles, taken fasted. Dose escalation included cohorts of 1-2 patients receiving doses between 25 and 200 mg QD followed by 5-7 patients receiving 400 mg, 800 mg, or 1,200 mg QD fasted. The possible effects of a high fat meal on the PK of BDTX-189 were assessed in a subset of patients receiving single doses of 400 mg BDTX-189 fasted and immediately after a high-fat breakfast in a randomized crossover fashion with 3 days between doses. In addition, a dose escalation cohort investigating administration of BDTX-189 non-fasted was enrolled at 800 mg QD. Serial blood samples for analysis of plasma BDTX-189 concentrations were collected after each dose on C1D1 and C1D15. BDTX-189 levels were determined using LC-MS, and data analyzed using non-compartmental methods. **Results:** After single and multiple doses, BDTX-189 was rapidly absorbed (median tmax 1-2 h), with an elimination $t_{1/2}$ of 2-6 h. Dose-dependent increases in exposure from 200 to 800 mg QD fasted were observed, with no apparent accumulation or decline in exposures observed at steady-state. Administration of BDTX-189 with a high-fat meal increased AUC approximately 1.7-fold with minimal effect on Cmax, relative to administration in the fasted state. At 800 mg QD, mean AUC was similar in the non-fasting state relative to fasting and was within the target efficacious range defined by mouse models harboring allo-ErbB mutated tumors. Median tmax and $t_{1/2}$ values were similar after administration in the non-fasted and fasted states. **Conclusions:** BDTX-189 demonstrated rapid absorption and a short PK half-life consistent with the desired PK/PD profile, with exposures in the efficacious target range based on preclinical data. The pilot high fat food-effect data and non-fasting QD dosing regimen show similar or improved systemic exposure relative to dosing in the fasted state. The MasterKey-01 trial is ongoing, including refinement of the dosing regimen and identification of the recommended phase 2 dose. Clinical trial information: NCT04209465. Research Sponsor: Black Diamond Therapeutics.

3098 **Poster Session**

A phase I study of a TGF-β receptor I kinase inhibitor YL-13027 in patients with advanced solid tumors. *First Author: Jin Li, Shanghai East Hospital, Shanghai, China*

Background: Transforming growth factor beta (TGF-β) is upregulated in the majority of tumors, promoting tumor cell proliferation, differentiation, and, modulation of the tumor microenvironment. YL-13027, a small molecule inhibitor of type 1 receptor of TGF-β, is a potent highly selective oral agent that downregulates TGFbR1-dependent pathways in tumor cells. YL-13027 dosed into tumor bearing animals drives tumor growth inhibition and interruption of metastasis. In this first-in-human phase1 study, we characterized the safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics (PK) and preliminary efficacy of YL-13027 in patients with advanced solid tumors. **Methods:** YL-13027 tablets were administered orally, twice daily under fasted conditions for 28 days, for at least two 28 day cycles until disease progression, unacceptable toxicity or withdrawal from the study. Starting with an initial dose of 60 mg, dose escalation in a 3+3 design, and pre-determined PK assessments were applied. Adverse events (AEs) were graded by NCI-CTCAE v5.0. PK analysis was performed using a non-compartmental method. Efficacy was evaluated according to RECIST1.1. **Results:** As of January 18th 2021, thirteen patients were enrolled sequentially to Cohort-1 (60 mg, n = 2), Cohort-2 (120 mg, n = 1), Cohort-3 (180 mg, n = 3), Cohort-4 (240 mg, n = 4) and Cohort-5 (300 mg, n = 3), having gastrointestinal (n = 9), esophageal (n = 1), gallbladder (n = 1), lung (n = 1) and breast (n = 1) carcinomas. These patients had prior systemic antitumor standard therapies, including multi-line chemotherapy, radiation therapy, molecular targeted therapy, immunotherapy, or surgery. Twelve patients completed the cycle 1 safety observation period, with no cardiovascular toxicities or other DLTs observed. The MTD was not reached. Twelve patients experienced AEs possibly related to YL-13027. The most frequent related TEAEs (all grades/grade ≥3) were gamma-glutamyltransferase increased (38.5%/7.7%), haemoglobin decreased (38.5%/0%), blood alkaline phosphatase increased (23.1%/7.7%), aspartate aminotransferase increased (23.1%/0%) and blood phosphorus decreased (23.1%/0%). A maximum YL-13027 plasma concentration was reached within 2h post dose, and the mean elimination half-life was 4.2h in the steady state. Six subjects were evaluable for efficacy. One triple-negative breast cancer (TNBC) subject (Cohort-4) acquired a Partial Response (38.8% reduction of the target lesion), with the response exceeding 4 cycles, and YL-13027 treatment is continuing. The TNBC patient's tumor profile indicated genomic mutations of EGFL7p.Q256H(13.50%), TP53p.E51* (10.90%) and NF1p.L21V(8.70%) from the initial tumor specimen at diagnosis. **Conclusions:** YL-13027 is well tolerated and further clinical investigation is warranted. (Sponsor: Shanghai Yingli Pharmaceutical Co., Ltd.) Clinical trial information: NCT03869632. Research Sponsor: None.

3099 **Poster Session**

A phase Ib study of the PI3Kδ inhibitor linperlisib in patients with advanced solid tumors. *First Author: Jin Li, Shanghai East Hospital, Shanghai, China*

Background: Phosphatidylinositol-3 kinase (PI3K) pathways are important elements of tumor survival and progression, and PIK3C genes are often mutated or overexpressed in many cancers. Additionally, PIK3D (PI3Kδ) modulates immune cell functions in tumors, elaborating another PI3Kδ inhibition feature with a potential clinical benefit. Linperlisib, an oral and highly selective PI3Kδ inhibitor, demonstrated potent anti-tumor activity in syngeneic animals from previous research. In this Phase 1b study, the safety, tolerability, and efficacy of linperlisib is under investigation for patients with advanced solid tumors. **Methods:** Linperlisib was given orally once daily (QD) in 28-day cycle until disease progression, unacceptable toxicity, or withdrawal from the study. Adverse events (AEs) were graded by NCI-CTCAE v5.0. Efficacy was assessed according to RECIST1.1 criteria. **Results:** As of December 28, 2020, 70 patients were enrolled in the Phase1b study, with advanced cancers, including colorectal (n = 22), breast (n = 8), lung (n = 8), kidney (n = 5), liver (n = 4), ovarian (n = 1), head and neck (n = 5), and esophageal (n = 1) cancers; sarcomas, (n = 4), small intestinal stromal tumor (n = 3), thymic (n = 2), gallbladder (n = 2), gastric (n = 4), and pancreatic (n = 1) carcinomas. The patients were heavily pretreated with an average of 4 previous lines of therapy. Among the 70 patients, the most common nonhematologic TEAEs (all grades/grade≥3) were proteinuria (37.14%/0%), elevated aspartate aminotransferase (20%/0%), nausea (20%/0%), oral mucositis (2.8%/2.8%), diarrhea (2.8%/2.8%). The most common hematological TEAEs were leukopenia (24.28%/0%) and neutropenia (17.14%/4.28%). There were no unexpected toxicities in this study. Of 42 patients evaluable for response, the overall response rate was 2.38%. Notably, the disease control rate (DCR) was 45.24% from monotherapy treatment. One patient with thymic carcinoma obtained a partial response (80.8% reduction of the target lesion), with a duration of response of more than 6 cycles. The treatment of this subject is continuing. A lung adenocarcinoma subject reached radiological stable disease associated with 13.7% reduction in the target lesion and disease control for approximately 6 months. **Conclusions:** In this study, the PI3K inhibitor, linperlisib exhibited a favorable safety profile as was previously seen in lymphoma patients. Monotherapy treatment with linperlisib was observed to impart a high DCR in advanced solid cancers of many types. Available data from linperlisib and other PI3K inhibitors suggests that linperlisib may limit tumor growth directly, but also by affecting the tumor immune microenvironment. With these promising indications of clinical tolerability and activity, further investigation of linperlisib alone or in key therapeutic combinations is warranted. Sponsor: Shanghai Yingli Pharmaceutical· Clinical trial information: NCT04049929. Research Sponsor: Shanghai Yingli Pharmaceutical Co.,Ltd.

3100 **Poster Session**

Antibiotic use reduces efficacy of tyrosine kinase inhibitors in patients with advanced melanoma and non-small cell lung cancer. *First Author: Nadina Tinsley, Christie Hospital, Manchester, United Kingdom*

Background: Antibiotic (ABX) use and disruption of the gut microbiome has been demonstrated to reduce the efficacy of immune checkpoint inhibitors and chemotherapeutics in cancer patients. Little is known about the impact of ABX use in patients treated with targeted therapies, such as tyrosine kinase inhibitors (TKI). **Methods:** Retrospective data analysis was performed on advanced melanoma and non-small cell lung cancer (NSCLC) patients treated with TKIs between January 2015 and April 2017 at The Christie NHS Foundation Trust, UK. Demographics, prior systemic treatment, extent of disease, lactate dehydrogenase level (LDH), presence of brain metastases, performance status, comorbidities, TKI agent and the use of ABX (class, route, duration) were collected. Progression free survival (PFS) and overall survival (OS) were compared between the ABX+ group (defined as patients treated with ABX within 2 weeks of TKI initiation or 6 weeks after) and the ABX$^-$ group (patients with no ABX during specified period). Statistical analyses were performed with univariate and multivariable models. **Results:** In total, 168 patients were included; 89 patients (53%) with advanced NSCLC and 79 patients (47%) with melanoma. Over a third of patients, (57/168, 34%) received ABX in the specified period (ABX+). On univariable analysis, ABX use was associated with shorter PFS (208 days vs 357 days, p = 0.008) and OS (294 days vs 438 days, p = 0.024). Increased age, poorer performance status, and higher LDH were also associated with shorter PFS and OS. On multivariable analysis, ABX use was independently associated with shorter PFS (HR 1.57, 95% CI 1.05-2.34, p = 0.028) and OS (HR 2.19, 95% CI 1.44-3.32, p = 0.0002). The negative impact of ABX on OS was particularly pronounced for patients with worse performance status (HR 3.82, 95% CI 1.18-12.36, p = 0.025). **Conclusions:** To our knowledge, this is the largest multivariable analysis showing ABX use independently reduces PFS and OS in patients treated with TKIs. It is the first analysis to demonstrate this phenomenon across two distinct tumour sites. The data suggests that ABX use could be an independent predictor of shorter PFS and OS in cancer patients treated with TKIs, and warrants further validation in a larger cohort. Research Sponsor: None.

3101 **Poster Session**

A phase I study of an IDO inhibitor (SHR9146) plus camrelizumab and in combination with/without apatinib in patients with advanced solid tumors: Safety and efficacy analysis. *First Author: Ying Cheng, Jilin Cancer Hospital, Changchun, China*

Background: IDO is an enzyme of interest in immuno-oncology because of the immunosuppressive effects that result from its role in tryptophan catabolism. Clinical trials of IDO inhibitors with immunotherapy are under active investigation. The addition of angiogenesis inhibitor may further enhance the anti-tumor immune responses. Here we report the safety and efficacy results of SHR9146 (IDO inhibitor) plus camrelizumab (PD-1 antibody) with/without apatinib (VEGFR-2 inhibitor) in patients (pts) with advanced solid cancers who failed standard antitumor therapies. **Methods:** This was an open-label, phase I study. Eligible puts would receive SHR9146 (escalated dose) plus camrelizumab (200 mg IV, q2w) alone (Cohort A) or in combination with apatinib (250 mg p.o. qd) (Cohort B). Each cohort was conducted according to a 3+3 dose escalation design. The starting dose of SHR9146 was 100mg bid, followed by 200, 400, 600 mg bid. The two primary endpoints were Dose-limiting Toxicity (DLT) and Maximum Tolerated Dose (MDT). The secondary objective was to analysis the incidence of Adverse Events (AEs) and efficacy. **Results:** As of Oct 31, 2020, 23 pts have been enrolled (Cohort A:14, Cohort B: 9; median age: 54 years; median prior therapies: 2 lines;). Cohort A was escalating at 600mg, and Cohort B was escalating at 400mg. Two pts experienced DLTs: one DLT (G4 hypercalcemia) was observed at 600mg in Cohort A; the other DLT (G3 rash) was observed at 400mg in Cohort B. MDT was not reached and the study was still ongoing. In Cohort A, ORR and DCR in evaluable pts were 21.4% (3/14, all confirmed) and 42.9% (6/14) . Partial response was observed in 3 pts with liver cancer (1/3), renal cancer (1/3), and cervix cancer (1/3). In Cohort B, ORR and DCR in evaluable pts were 33.3%(3/9, all confirmed) and 77.8%(7/9). Partial response was observed in 3 pts with SCLC (1/3), prostate cancer (1/3) and renal cancer (1/3). The incidence of pts with TRAEs and grade>=3 TRAEs were 91.3% (21/23) and 39.1% (9/23) respectively. The most common grade>=3 TRAEs were hypercalcemia (26.1%, 6/23), fatigue (17.4%, 4/23) and nausea (13.0%, 3/23). No fatal AEs were observed. G3 nausea, G3 lipase increased and G2 GGT increased resulted in SHR9146 dose reduction in 3 pts (Cohort A). **Conclusions:** SHR9146 plus camrelizumab in combination with/without apatinib demonstrated promising anti-tumor activity with acceptable safety in pts with advanced solid tumors. Further study is needed to validate the efficacy and safety. Clinical trial information: NCT03491631. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

3102 **Poster Session**

Phase 1b/2 SEASTAR trial: Safety, pharmacokinetics, and preliminary efficacy of the poly(ADP)-ribose polymerase (PARP) inhibitor rucaparib and angiogenesis inhibitor lucitanib in patients with advanced solid tumors. *First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Lucitanib is an oral, potent tyrosine kinase inhibitor that selectively inhibits VEGFR1–3, PDGFRα/β, and FGFR1–3. In preclinical studies, antitumor activity of rucaparib is enhanced by lucitanib through antiproliferative, antiangiogenic, and immunological mechanisms. We hypothesize that combining lucitanib and rucaparib is tolerable and can induce a higher hypoxic state and homologous recombination repair deficiency that may lead to greater sensitivity to PARP inhibition. **Methods:** Patients with advanced solid tumors who had ≥1 prior line of therapy were eligible. Patients with *BRCA1/2*-mutated ovarian cancer must have received prior PARP inhibitor. Rucaparib and lucitanib were escalated using a 3+3 phase 1b dose-escalation design from starting doses of 300 mg BID and 4 mg QD, respectively. Dose-limiting toxicities (DLTs) were assessed during the first 28 days of treatment. Plasma samples were collected for pharmacokinetic analyses. Genomic alterations were identified by local testing, or through central testing of plasma or tumor tissue. **Results:** As of February 1, 2021, 16 patients were treated with rucaparib + lucitanib and included in the analyses (Table). Patients had a median of 4 prior therapies; 1 patient had prior PARP inhibitor (olaparib) treatment. Median time on treatment was 58.5 days, with 2 patients ongoing as of the data cutoff date. A DLT of grade 3 proteinuria was seen in Cohort 1; no other DLTs have been reported. Across all cohorts, the most common any-grade treatment-emergent adverse events were nausea (n=9; grade ≥3, n=1), hypertension (n=8; grade ≥3, n=2) and ALT/AST increased (n=7; grade ≥3, n=3). Initial pharmacokinetic data indicated no drug interactions between the 2 agents. To date, 1 patient in Cohort 1 with *PALB2*-mutated advanced endometrial cancer had a confirmed partial response per RECIST v1.1, lasting 30 weeks; 6 patients had RECIST v1.1 stable disease (SD), including 1 patient each in Cohorts 1 and 3 with SD for ≥16 weeks. In addition, 1 patient in Cohort 2 with *BRCA2*-mutated castration-resistant prostate cancer continued to receive treatment despite initial progressing bone metastases, resulting in a prostate-specific antigen response (≥50% change) lasting 16 weeks and a best change in sum of target lesions of −46.3%. **Conclusions:** Initial findings suggest that rucaparib + lucitanib has an acceptable safety profile. The safety and efficacy of the combination are being further evaluated. Clinical trial information: NCT03992131. Research Sponsor: Clovis Oncology, Inc.

Cohort	n	Rucaparib (BID)	Lucitanib (QD)	HRR gene mutations identified
1	6	300 mg	4 mg	1 BRCA1, 1 BRCA2, 1 ATM, 1 PALB2, 1 RAD51B
2	4	400 mg	4 mg	1 BRCA2
3	3	400 mg	6 mg	2 CDK12
4	3	600 mg	6 mg	None*

*Based on local testing results only. BID, twice daily; QD, daily; HRR, homologous recombination repair.

3103 **Poster Session**

A phase Ib trial of ERK inhibition with ulixertinib combined with palbociclib in patients (Pts) with advanced solid tumors. *First Author: Alison L. Raybould, UNC Lineberger Comprehensive Cancer Center, Chapel Hill, NC*

Background: Activating *KRAS* mutations are the most frequently detected aberrant oncogenes in pancreatic adenocarcinoma. Combination strategies to target the downstream RAF-MEK-ERK effector pathway are a rational approach. Preclinical data with ERK and CDK4/6 inhibition in both pancreatic cancer cell lines and xenografts demonstrates synergistic cell death and tumor growth suppression. Ulixertinib (BVD-523) is an oral small molecule inhibitor of ERK1/2. This phase 1b study evaluated the safety, pharmacokinetics, and early clinical efficacy of ulixertinib when combined with the oral CDK4/6 inhibitor palbociclib in pts with advanced solid tumors. **Methods:** Using a 3+3 design, pts received ulixertinib at a starting dose of 300mg (range 300-600mg) twice daily continuously with palbociclib at a starting dose of 75mg (range 75-125mg) on D1-21 out of a 28 day cycle. The primary objective was to establish the maximum tolerated dose (MTD) of the combination. Secondary objectives included characterizing safety and estimating progression free survival (PFS). Dose limiting toxicities (DLTs) were evaluated during the first cycle of treatment. Adverse events were graded by CTCAE v4.03. Response was evaluated after 2 cycles (8 weeks) by RECIST 1.1 criteria. **Results:** 26 pts were enrolled (13 colorectal, 9 pancreas, 2 melanoma, 1 cholangiocarcinoma, 1 GIST); 16 were evaluable for response. The MTD of the combination was ulixertinib 450mg BID and palbociclib 125mg daily. DLTs included grade 3 fatigue, grade 3 acute kidney injury and grade 3 hyponatremia (Table). Due to toxicity in cohort 3, the protocol was amended to include two additional cohorts (2A and 2B) with a reduced dose of ulixertinib and increasing doses of palbociclib. The most common treatment-related adverse events (TRAEs) (all grades) were fatigue (70%), rash (62%) and nausea (54%). The most common laboratory TRAEs were decreased lymphocyte count (77%), decreased WBC count (73%) and anemia (65%). Grade 3 TRAEs were decreased WBC count, decreased lymphocyte count, anemia and fatigue. No grade 4/5 TRAEs were reported. Three pts demonstrated stable disease (SD). For this heavily pre-treated pt population, PFS was 2.05 months (95% CI 1.87, not determined). PK analysis for ulixertinib and palbociclib was linear and consistent with previously reported data; no drug-drug interactions were observed. **Conclusions:** The MTD of this phase Ib study of advanced solid tumor pts was ulixertinib 450mg BID combined with palbociclib 125 mg daily. At this dosing, 2 pts demonstrated SD, one with pancreatic cancer and one with cholangiocarcinoma. An expansion cohort of metastatic pancreatic cancer pts is ongoing. Clinical trial information: NCT03454035. Research Sponsor: BioMed Valley Discoveries, Inc, Pharmaceutical/Biotech Company.

Dose Level	Ulixertinib (mg)	Palbociclib (mg)	Total Pts	DLT
1	300	75	4	0
2	450	100	3	0
3	600	75	8	2–Gr 3 fatigue Gr 3 AKI
2A	450	100	4	0
2B	450	125	7	1–Gr 3 hyponatremia

3104 **Poster Session**

Phase 1/2 first-in-human (FIH) study of CPI-0209, a novel small molecule inhibitor of enhancer of zeste homolog 2 (EZH2) in patients with advanced tumors. *First Author: Nehal J. Lakhani, START Midwest, Grand Rapids, MI*

Background: Enhancer of Zeste homolog 2 (EZH2) is a histone methyltransferase and the catalytic subunit of Polycomb Repressive Complex 2 (PRC2). EZH2 is frequently overexpressed in cancers and correlates with poor prognosis. CPI-0209 is an oral, small molecule, second-generation, selective inhibitor of EZH2 designed to achieve comprehensive target coverage through extended on-target residence time. The compound demonstrates more potent anti-tumor activity in preclinical cancer models, compared to first-generation EZH2 inhibitors. CPI-0209 is currently being evaluated in a Phase 1/2, open-label, FIH study (NCT04104776). **Methods:** Patients (pts) with advanced tumors were enrolled in a 3+3 design. Primary objective is to determine maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) of CPI-0209. Secondary objectives are to evaluate the safety, PK, and PD in pts who received CPI-0209 QD in 28 days cycles (C). **Results:** As of December 16, 2020, 33 pts were treated: pancreatic cancer (n = 6), mesothelioma, breast, colorectal, and ovarian cancer (n = 5 each), leiomyosarcoma, melanoma, cholangiocarcinoma, prostate, bladder, endometrial clear cell and gastric cancer (n = 1 each). Pts received CPI-0209 at 50 mg (n = 4), 100 mg, 137.5 mg, and 187.5 mg (n = 6 each), 225 mg (n = 7), and 275 mg (n = 4) daily dose. Median treatment duration was 43 days (range 1-239); 4 pts are ongoing. Median age was 64 yrs (range 24-79); 15 (45%) pts were male. Patients were heavily pretreated, with 67% of pts had ≥ 3 prior lines of therapy. No dose limiting toxicities have been observed. The most frequent treatment-emergent adverse events (TEAEs) (≥10%) were fatigue (27%), diarrhea (24%), nausea (21%), abdominal pain, alopecia, anemia, thrombocytopenia, and dysgeusia (15% each), and vomiting, headache, decreased appetite, and alkaline phosphatase increased (12% each); usually grade 1 or 2 in severity. Thrombocytopenia was dose-dependent and not associated with bleeding or clinical sequalae. Three pts (9%) discontinued CPI-0209 due to TEAEs. Comprehensive target engagement (assessed by global reduction in H3K27me3 levels in monocytes) was observed within the first cycle at all dose levels. CPI-0209 also increased the expression of PRC2-controlled gene sets in blood in a dose-dependent manner. Updated safety, PK, PD, and preliminary efficacy results from Phase 1 will be presented. **Conclusions:** CPI-0209 achieved robust PD effects and a PK-PD relationship has been established. CPI-0209 monotherapy was generally well tolerated, and treatment related AEs were manageable and reversible. The MTD has not been reached. Clinical trial information: NCT04104776. Research Sponsor: Constellation Pharmaceuticals.

3105 **Poster Session**

Inhibition of histone lysine demethylases with TACH101, a first-in-class pan-inhibitor of KDM4. *First Author: Chandtip Chandhasin, Tachyon Therapeutics, Houston, TX*

Background: The KDM4 family of histone lysine demethylases consists of four main isoforms (KDM4A, B, C, D), all of which have been identified as key oncogenic drivers. They function as epigenetic regulators and control transitions between transcriptionally silent and active chromatin states via removal of methyl marks on histone H3K9 and histone H3K36. KDM4 isoforms play an important role in the epigenetic dysregulation in various cancers and is linked to more aggressive disease and poorer clinical outcomes. Functional redundancy and cross-activity have been observed across KDM4 family members, thus, selective inhibition of one isoform appears to not be effective. TACH101 is a novel, first-in-class pan inhibitor of KDM4 that simultaneously targets multiple isoforms of KDM4. Here we present data that show TACH101 has promising pre-clinical and pharmacologic properties as a cancer therapeutic. **Methods:** TACH101 was evaluated in *in vitro* and *in vivo* studies including cell-proliferation assays in multiple cancer cell lines, apoptotic and cell cycle analyses, and efficacy studies in various xenograft tumor models and patient-derived organoid models. **Results:** *In vitro*, TACH101 was broadly effective in killing 67% (200 out of 300) of cancer cell lines screened. TACH101 demonstrated potent increase of H3K36me3 levels (EC50 < 0.001 mM, HTRF) in KYSE-150 cell line engineered to overexpress KDM4C and potent anti-proliferative activity in multiple cell lines in OncoPanel. TACH101 treatment increased cancer cell population in S-phase in multiple cancer cell lines indicating cell-cycle arrest. TACH101 induced apoptosis in human colorectal (HT-29), esophageal (KYSE-150), and triple negative breast cancer (MDA-MB-231) cell lines with EC50s ranging from 0.033-0.092 μM. *In vivo*, TACH101 triggered effective tumor control in xenograft models including colorectal, esophageal, gastric, breast, and lymphoma with tumor growth inhibition of up to 100%. Further evaluation using a panel of patient-derived colorectal models and patient-derived organoids showed a strong correlation of TACH101 sensitivity with MSI-H status (IC50 ranges 1-150 nM). TACH101 also reduced tumorigenic potential by 4.4-fold as determined by FACS analysis using sorted CD44High EpCAM+ population in Limiting Dilution Assays *in vivo*, suggesting that reduction of cancer stem cells by TACH101 may be effective in therapy-resistant settings. Pharmacologic studies showed TACH101 demonstrated favorable cell permeability, good oral bioavailability, and high metabolic stability. **Conclusions:** Extensive preclinical work on TACH101 KDM4 inhibitor shows compelling data and broad applicability as a potential anti-cancer agent. Further evaluation is ongoing to advance the molecule into clinical trials. Research Sponsor: Tachyon Therapeutics.

3106 **Poster Session**

WX390, a high-potent PI3K-mTOR dual inhibitor, first-in-human (FIH) phase I study in advanced relapsed or refractory solid tumor, and lymphoma. *First Author: Wenbo Tang, Department of Medical Oncology, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China*

Background: WX390 is a high potent PI3K-mTOR dual inhibitor targeting pan-PI3K and mTOR. WX390 exhibited anti-tumor activity and high potency in xenograft models with inhibition of AKT phosphorylation. **Methods:** Patients (pts) with advanced lymphoma and solid tumors who have failed standard therapies were enrolled in dose escalation cohorts and received WX390 administered daily orally in 28-day cycles until confirmed progressive disease, intolerable toxicity or withdrawal of consent. Plasma samples were collected up to 7 days after the first dose and up to 24 hours at C1D28. **Results:** As of the cut-off date 2021 Feb 10, 25 patients (median age 52 years) were enrolled in 6 dose levels (0.1mg, 0.2mg, 0.4mg, 0.7mg, 1.1mg and 1.4mg) of the dose-escalation cohorts. Cohorts 0.1 mg to 1.1 mg were completed without dose-limiting toxicities (DLT), cohort 1.4 mg was completed with 1 DLT (Diabetic ketoacidosis combined with grade 3 hyperglycemia) out of 4 evaluable patients. Common treatment-related adverse events (TRAEs) (all grades, ≥20%) included hyperglycemia (20 pts, 80%), proteinuria (10 pts, 40%), creatinine increased (11 pts, 44%), hypophosphatemia (10 pts, 25%), anemia (8 pts, 33.3%), thrombocytopenia (7 pts, 29.2%), and aspartate aminotransferase increased (25%). Grade≥3 TRAEs were hyperglycemia (7 pts, 28%, 1 pt combined with diabetic ketoacidosis), hypophosphatemia (2 pts, 8%), neutropenia (2 pts, 8%), dermatitis (1 pt, 4%), and maculopapular rash (1 pt, 4%). PK showed fast absorption (Tmax 0.5-4 h) and dose proportionality for Cmax and $AUC_{0-\infty}$. The mean multiple dose $T_{1/2}$ was approximately 12.4 hours across all cohorts with minimum accumulation. Among 14 tumor response evaluable patients, there were 3 patients with confirmed PIK3CA mutation. All 3 patients experienced tumor shrinkage and were still on treatment by the cut-off date. 2 (1 pt with head and neck cancer and 1 pt with cervical cancer) of them have achieved partial response (PR). The head and neck cancer patient (PR) was treated with WX390 0.7mg/day without any severe AE and the duration of response was beyond 15 months. Stable disease (SD) was observed in 6 patients (n = 5 with unknown PIK3CA mutation status and n = 1 with confirmed PIK3CA mutation). Of note, 1 patient (follicular lymphoma) treated with 0.1mg experienced SD for 14 months. Another patient (SD, head and neck cancer with PIK3CA mutation) experienced tumor shrinkage for more than 8 months and was still receiving WX390 treatment by the cut-off date. **Conclusions:** the PI3K-mTOR dual inhibitor WX390 was well tolerated with manageable safety profile, and showed encouraging antitumor activity. A RP2D of 1.1 mg qd is selected to be explored for different indications in solid tumor clinical studies. Clinical trial information: NCT03730142. Research Sponsor: Shanghai Jiatan Pharmatech CO., LTD.

3107 **Poster Session**

First-in-human dose-finding study of venadaparib (IDX-1197), a potent and selective PARP inhibitor, in patients with advanced solid tumors. *First Author: Yong Man Kim, Asan Medical Center, University of Ulsan, Seoul, South Korea*

Background: Poly ADP-ribose polymerase (PARP) is an enzyme that is central to the repair of DNA replication errors known as single-strand breaks (SSBs). PARP inhibitors are currently approved for ovary, breast, pancreatic and prostate cancers which harbor germline or somatic BRCA1/2 mutations (g/sBRCAmt) and/or homologous recombinant repair mutation (g/sHRRmt). In this phase 1 dose finding study of venadaparib, we determined the maximum tolerated dose for venadaparib monotherapy and explored the safety, tolerability, pharmacokinetics, pharmacodynamics and anticancer efficacy of venadaparib in patients with advanced solid tumor which progressed after an attempt of standard-of-care therapy and for which effective therapy does not exist. **Methods:** Subjects who satisfied all of the inclusion/exclusion criteria and provided written informed consent were enrolled in this study. The investigational product was administered orally once daily continuously in a 3 weekly cycle. Enrolled subjects were assessed for safety and evaluated on tumor response using RECIST 1.1. The study was carried out in a conventional 3+3 design, starting from 2 mg up to 240 mg. Dose limiting toxicities (DLTs) and pharmacokinetics were assessed during the first cycle. **Results:** As of 08 Feb 2021, enrollment is completed with 32 patients enrolled. Most common tumor types enrolled are breast cancer (16 patients) and ovarian cancer (11 patients). Other tumor types include cancers of endometrium, fallopian tube, uterus and prostate. No DLTs were observed up to the maximum tested dose of 240 mg. Frequently observed adverse drug reactions were as follows – Anemia (56%), nausea (38%) and neutropenia (25%). Overall objective response rate (ORR) was 16% and clinical benefit rate (CBR) was 47%. Partial response was observed starting from 40 mg and clinical benefit was observed from the lowest dose of 2 mg. From optional tumor tissue samples, venadaparib exhibited ≥ 90% PAR inhibitory effect in pharmacodynamic analysis from 10 mg. For patients with known germline or somatic BRCA status either from local lab results or examined at a central lab retrospectively, ORR and CBR was 22% and 44% respectively for BRCAm(+) (9) patients. Interestingly, clinical efficacy was observed in BRCAm(-) (18) patients also, with ORR and CBR of 17% and 50% respectively. **Conclusions:** Safety and tolerability of the venadaparib monotherapy was confirmed with preliminary efficacy signals observed, even in BRCAm(-) patients. Clinical benefit was observed from the lowest tested dose, suggesting the potential to combine with other chemotherapeutic agents. Further studies to explore efficacy and safety of venadaparib in other tumor types and combinations, as well as to explore adequate biomarkers are warranted. Clinical trial information: NCT03317743. Research Sponsor: Idience Co. Ltd, Other Government Agency.

3108 **Poster Session**

Long-term efficacy and safety of larotrectinib in an integrated dataset of patients with TRK fusion cancer. *First Author: David S. Hong, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions encode tropomyosin receptor kinase (TRK) fusion proteins, which are oncogenic drivers in various tumor types. Larotrectinib is a first-in-class, highly selective, CNS-active TRK inhibitor approved to treat adult and pediatric patients with TRK fusion cancer. Larotrectinib demonstrated an objective response rate (ORR) of 78% and a median progression-free survival (PFS) of 36.8 months in an integrated analysis of 175 patients with non-primary CNS TRK fusion cancer (McDermott et al, ESMO 2020). We report updated efficacy and safety data with longer follow-up in an expanded dataset. **Methods:** Data were pooled from three clinical trials of patients with non-primary CNS TRK fusion cancer treated with larotrectinib. Larotrectinib was administered until disease progression, withdrawal, or unacceptable toxicity. Response was assessed by investigators using RECIST v1.1. Data cutoff: July 20, 2020. **Results:** As of data cutoff, 218 patients were treated with larotrectinib, of which 206 were evaluable for efficacy. There were 21 different tumor types, the most common being soft tissue sarcoma (STS [46%], including infantile fibrosarcoma [20%] and other STS [26%]), thyroid (13%), salivary gland (11%), lung (9%), and colorectal (5%). The median age was 38.0 years (range 0.1–84.0). Patients were heavily pretreated with 45% having received 2 or more prior lines of systemic therapy; 27% had 0 prior lines of systemic therapy. The ORR was 75% (95% CI 68–81): 45 (22%) complete response, 109 (53%) partial response (PR), 33 (16%) stable disease (SD), and 13 (6%) progressive disease (PD). Nineteen patients had brain metastases at baseline, with 15 evaluable for efficacy. The ORR for patients with brain metastases was 73% (95% CI 45–92): 11 PR, 2 SD, and 2 PD. Among all evaluable patients, the median time to response was 1.8 months (range 0.9–9.1). With a median follow up of 22.3 months, the median duration of response was 49.3 months (95% CI 27.3–not estimable). Treatment duration ranged from 0.03+ to 60.4+ months. Median PFS was 35.4 months (95% CI 23.4–55.7) with a median follow up of 20.3 months. At a median follow-up of 22.3 months, median overall survival (OS) was not reached and 36-month OS was 77% (95% CI 69–84). Treatment-related adverse events (TRAEs) were mainly Grade 1–2, with 18% having Grade 3–4 TRAEs. Only 2% of patients discontinued due to TRAEs. **Conclusions:** These results highlight the importance of testing for *NTRK* gene fusions in patients with cancer because the majority of patients with TRK fusion cancer treated with larotrectinib had long-term clinical benefit. The safety profile continued to be favorable and no new safety signals were identified. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: Bayer HealthCare and Loxo Oncology.

3109 **Poster Session**

PARALLEL 303: Phase 2 randomized study of pamiparib vs placebo as maintenance therapy in patients (pts) with inoperable locally advanced or metastatic gastric cancer that responded to platinum-based first-line (1L) chemotherapy. *First Author: Fortunato Ciardiello, Second University of Naples, Department of Clinical and Experimental Medicine, Naples, Italy*

Background: A subset of gastric cancers exhibits platinum sensitivity and genomic instability that is characteristic of homologous recombination deficiency (HRD). Cells with HRD are sensitive to poly (ADP-ribose) polymerase (PARP) inhibition. PARP inhibitor maintenance therapy following platinum-based chemotherapy has been a successful treatment strategy in pts with ovarian cancer. Pamiparib is an orally administered selective PARP protein 1 and 2 (PARP1/2) inhibitor that has shown potent DNA-PARP trapping activity and crosses the blood brain barrier in preclinical studies. In early phase clinical studies (NCT02361723; NCT03333915), pamiparib showed an acceptable safety profile and promising antitumor activity. PARALLEL 303 compared the efficacy and safety of pamiparib vs placebo as maintenance therapy in pts with inoperable locally advanced or metastatic gastric cancer that responded to platinum-based 1L chemotherapy. **Methods:** The primary endpoint of this double-blind, randomized, global phase 2 study (NCT03427814) was progression-free survival (PFS) as determined by the investigator per RECIST Version 1.1. Key secondary endpoints included time to subsequent treatment, objective response rate, duration of response, time to response, overall survival (OS) and safety. At the time of this analysis, OS data were immature due to the short duration of study. Data presented here will focus on PFS and safety. **Results:** 136 pts were randomized 1:1 to receive pamiparib 60 mg orally (PO) twice daily (BID) (n=71) or placebo PO BID (n=65) in 28-day cycles. The median PFS was longer with pamiparib vs placebo, but did not reach statistical significance (3.7 months; 95% CI, 1.94–5.26 vs 2.1 months; 95% CI, 1.87–3.75 months); hazard ratio 0.799 (95% CI, 0.534–1.193; P=0.1428). Treatment-emergent adverse events (TEAEs) of ≥ Grade 3 were experienced by 29 pts (40.8%) in the pamiparib arm, and 20 pts (30.8%) in the placebo arm. The most common TEAEs of ≥ Grade 3 were blood and lymphatic system disorders in the pamiparib arm, and gastrointestinal disorders in the placebo arm. TEAEs leading to treatment discontinuation were: 8 pts (11.3%) in the pamiparib arm and 2 pts (3.1%) in the placebo arm. TEAEs leading to death were: 2 pts (2.8%; 1 pneumonia, 1 unexplained) in the pamiparib arm, and 2 pts (3.1%; 1 hepatic rupture, 1 sepsis) in the placebo arm. **Conclusions:** Although pamiparib did not meet statistical significance for superiority vs placebo for its primary endpoint, it was generally well tolerated with few treatment discontinuations due to TEAEs. No new safety signals were identified with pamiparib, and its safety profile was consistent with that of other PARP inhibitors. Clinical trial information: NCT03427814. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Yasmin Issop, PhD, and Shannon Galgani, MSci, of Ashfield Medcomms, an Ashfield Health Company, and funded by BeiGene, Ltd.

3110 **Poster Session**

Biomarker results supporting selection of RP2D from a phase 1b study of ORIC-101, a glucocorticoid receptor antagonist, in combination with nab-paclitaxel in patients with advanced solid tumors. *First Author: Anneleen Daemen, 240 E. Grand Ave., South San Francisco, CA*

Background: Preclinical studies have shown that activation of the glucocorticoid receptor (GR) leads to resistance to chemotherapeutics (eg taxanes) and antiandrogens across multiple tumor types, while GR inhibition enhances therapeutic efficacy. ORIC-101 is a potent, selective, and orally bioavailable small molecule GR antagonist undergoing clinical development in combination with nab-paclitaxel in patients with advanced solid tumors and in combination with enzalutamide in patients with metastatic prostate cancer. **Methods:** 21 patients were enrolled in the dose escalation portion of the phase 1b study, which evaluated both intermittent (5 days on, 2 days off for 21 days) and continuous dosing regimens of ORIC-101 across 5 cohorts (NCT03928314). Tumor tissue was obtained pre-treatment for 19 out of 21 patients, and on study or at the end of treatment for 11 patients. GR protein status was retrospectively evaluated using a proprietary IHC assay optimized for staining nuclear GR in the epithelial compartment of major tumor type tissues. Biopsies were also profiled with RNA-seq to evaluate a proprietary GR activation signature as a potentially predictive and pharmacodynamic (PD) biomarker. Blood-derived peripheral blood mononuclear cells (PBMCs) were collected for 20 patients along with the pre-treatment biopsy, in the morning of days 1, 5 and/or 8 of Cycle 1, and 2.5 or 6 hours after ORIC-101 administration. Blood cortisol levels were also simultaneously measured. PD modulation in PBMCs was assessed by RT-qPCR for biomarkers FKBP5, GILZ and PER1, selected for their consistent stimulation by GR and reversal with ORIC-101 in preclinical studies and observed PD modulation in healthy volunteers administered ORIC-101. **Results:** Nuclear GR protein was detected in most pre-treatment biopsies regardless of tumor type, and on treatment reduction of GR protein was observed across dose levels. At physiological systemic cortisol levels, ORIC-101 demonstrated PD suppression in PBMCs on days 1, 5 and 8 in the majority of patients. Cortisol levels increased post-dose in these patients due to negative feedback between cortisol and GR. Steady-state target engagement was not consistently demonstrated with the intermittent regimen. In healthy volunteer studies of ORIC-101, steady-state target suppression was consistently achieved after 7 consecutive daily doses of 200 or 350 mg of ORIC-101. Thus, continuous ORIC-101 administration was selected as the recommended phase 2 dose (RP2D) regimen, aimed at achieving sustained GR suppression for optimal chemotherapy re-sensitization. **Conclusions:** Biomarker data from patients enrolled in the phase 1b study provide evidence of on-target tumor cell eradication and PD modulation and support the RP2D and the tumor types selected for the ongoing dose expansion portion of the study. Clinical trial information: NCT03928314. Research Sponsor: ORIC Pharmaceuticals.

3111 **Poster Session**

Institutional experience with *nab*-sirolimus in patients with malignancies harboring *TSC1* or *TSC2* mutations. *First Author: Mark Andrew Dickson, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *TSC1*/*TSC2* genes are tumor suppressors in the mTOR pathway; mutated at low frequency across tumor types (~1–2%). Retrospective analyses of patients (pts) with mTOR pathway mutations treated with everolimus did not show improved outcomes vs the wild type (Voss et al. Clin Cancer Res 2019. PMID 30327302). In NCT02201212, pts with *TSC1/TSC2* mutations treated with everolimus had a 7% (2/30) response rate. In the AMPECT study, pts with advanced PEComa treated with a novel mTOR inhibitor (mTORi), *nab*-sirolimus (*nab*-S, ABI-009), the subset of pts with *TSC1/TSC2* mutations had a response rate of 64% (9/14) (Wagner et al. CTOS 2020. #3463014). In a xenograft model, *nab*-S showed significantly higher tumor accumulation, target suppression (pS6) and antitumor activity vs everolimus or sirolimus (Hou et al. AACR 2019. #348). In an expanded access program (NCT03817515), pts with advanced tumors bearing *TSC1/ TSC2* mutations were treated with *nab*-S and outcomes in pts with malignancies other than PEComa are reported herein. **Methods:** Eligible pts (ECOG 0–2) received *nab*-S 100 mg/m^2 IV, once weekly for 2 of every 3 weeks at 3 US sites between 7/2019 and 11/2020. **Results:** 7 pts with *TSC1*/*TSC2* mutations have been consecutively enrolled and are reported here. 6/7 pts had multiple prior therapies including 2 pts previously progressing on an mTORi. 4/7 pts had partial response (PR), all in mTORi naïve pts. 2/7 pts had stable disease (SD). In 2 pts previously treated with an mTORi, 1 had SD and 1 came off treatment after 1 cycle (CA125 ↑) with no follow-up scan. Treatment-related serious adverse events (SAEs; hyperglycemia and infection) and dose reduction were reported in 1 pt with metastatic angiosarcoma; SAEs resolved and the pt continued Rx. No other SAE or dose limiting event was reported **Conclusions:** Patients with various malignancies bearing *TSC1* or *TSC2* mutations, most with progression on multiple prior therapies, showed evidence of response and manageable toxicities during treatment with *nab*-S. A basket trial of *nab*-S in malignancies with *TSC1/TSC2* mutations is planned. Clinical trial information: NCT03817515. Research Sponsor: Study sponsored by Aadi Bioscience, Inc.

Pt#	Tumor Type	Relevant mutation	Prior Therapy	Treatment, months	Best Response[1] to nab-Sirolimus
1	Endometrial stromal sarcoma	TSC2	Exemestane, letrozole, fulvestrant	9.8+	PR
2	Epithelial ovarian cancer	TSC1	Cisplatin/paclitaxel, bevacizumab, carboplatin, liposomal doxorubicin, gemcitabine	9.6+	PR
3	Angiosarcoma	TSC1	Doxorubicin, ifosfamide, paclitaxel	5.6+	SD[2]
4	High grade sarcoma	TSC2	Doxorubicin, ifosfamide, gemcitabine, docetaxel, pazopanib, pembrolizumab	4.3+	PR
5	Epithelial ovarian cancer	TSC2	Liposomal doxorubicin, carboplatin, bevacizumab, gemcitabine, enzalutamide, sapanisertib (mTORi)	0.7	No scan
6	Endometrial cancer	TSC2	Anastrozole, leuprolide, sirolimus	2.9+	Mixed response SD
7	Lymphangioleiomyoma	TSC2	None	4.3+	PR

Bold = mTOR inhibitor treatment [1] RECIST 1.1 [2] PR in target lesions, but new lesion in Rx break.

3112 **Poster Session**

Dosing, drug reduction, drug interruption, and drug discontinuation rates among U.S. FDA approved tyrosine kinase inhibitors. *First Author: Neha K. Reddy, Dell Medical School, The University of Texas at Austin, Austin, TX*

Background: The advent of tyrosine kinase inhibitors (TKIs) has altered the therapeutic landscape of multiple hematological and solid malignancies. FDA approved starting doses of TKIs are based on the recommended phase 2 dose (RP2D) in clinical trials. Since many of these drugs are continuously dosed, ongoing toxicities may lead to drug reductions and drug discontinuations. Hence in practice, many patients are started on lower doses due to tolerability concerns or are dose-reduced subsequently for toxicity. Herein, we assessed the dosing, drug reduction rates, and drug discontinuation rates among FDA approved TKIs. **Methods:** We established a database of all FDA approved TKIs from the FDA online label repository. We extracted descriptive data for indications and usage, type of approval, approval dosage, dose reduction recommendation, median age, dose reduction rates, drug discontinuation rates, dose modification, warnings, adverse reactions, clinical trial experience, and geriatric use above 65 yrs and 75 yrs. **Results:** TKIs were approved for 143 different indications, ranging from 1 indication to 11 indications (eg. Imatinib) from data arising from 7 patients to 2816 patients for a specific indication. Among all TKIs, median dose was 150 mg and average dose was 237 mg; 34 (23.8%) were approved bid vs 71 (49.7%) qd. Specifically for oncology, 54 indications were biomarker based (eg. EGFR mutant NSCLC) and 52 were non-biomarker based for specific diseases (eg. metastatic RCC). Among approved indications range of dose reduction rate (DRR), drug interruption rates (DIR), drug discontinuations rates (DDR) were 0.80-89%, 3%-89%, and 1-39% respectively. Most common reasons for DRR, DIR, and DDR were diarrhea, fatigue, nausea, vomiting, hepatotoxicity, rash, and hypertension. Geriatric use was listed in 99 indications ($>$ 65 yrs, 6-68%; $>$ 75 yrs, 0.50-24%). Patient reported outcomes were not available. **Conclusions:** TKIs have a variable dose reduction and drug discontinuation rate. Clinical trials should evaluate multiple dosing regimens and schedules to lessen the toxicity burden and improve QOL in patients. Future studies are warranted to look into flat dosing vs alternative dosing, like weight-based dosing for TKIs, and to report patient reported outcomes. Research Sponsor: None.

3113 **Poster Session**

A phase I dose-escalation and expansion study of JPI-547, a dual inhibitor of PARP/tankyrase in patients with advanced solid tumors. *First Author: Seock-Ah Im, Seoul National University Hospital, Seoul, South Korea*

Background: JPI-547 is an oral inhibitor of PARP 1/2 and Tankyrase 1/2. JPI-547 demonstrated anti-tumor activity in BRCA-deficient xenograft models as a single-agent and in combination with chemotherapy and immune checkpoint inhibitors. **Methods:** This is the first in human (FIH) phase I study of JPI-547 in patients (pts) with advanced solid tumors. For the dose escalation phase, a 3+3 design was used with 4 doses from 50 to 200 mg QD on 21-day cycles. Primary objectives were to assess safety and tolerability to determine RP2D, and secondary objectives included pharmacokinetics and preliminary antitumor activities. DLT monitoring period was 21 days. Pharmacodynamics and information of HRR mutation were also explored. For the dose expansion phase, pts with documented pathogenic germline or somatic BRCA/HRR mutations were enrolled to assess the preliminary efficacy and safety. Tumor response (RECIST 1.1) was evaluated every 6 weeks. Centralized germline BRCA testing was conducted to confirm pathogenic gBRCA mutations. Results available at the cut-off date of 31-Dec-2020 are presented. **Results:** For dose escalation phase, 22 pts were enrolled. JPI-547 was well absorbed with T_{max} of 0.25-8 h post-dose and apparent half-life of 18-31 h. Mean C_{max} and AUC increased proportionally (within the dose range of 50-200 mg). PAR level measured from PBMC was 53% inhibited at C_{max}. One DLTs was observed at 100 mg (elevated ALT, G3) and 200 mg (elevated ALT/AST, G3) respectively. MTD was determined as 200 mg after considering DLTs and myelosuppression observed from cycle 2. RP2D was determined to be 150 mg based on the pharmacokinetic data and safety. Thirteen pts (59.1%) had at least one grade 3/4 TRAE and 12 had dose interruption/reduction due to TRAE. The most common ($>$ 20%) TRAE were anemia, thrombocytopenia and neutropenia. In dose expansion phase, 40 pts were enrolled, and response was evaluable in 39 pts. The best overall responses were 11 confirmed PR (cPR) and 15 SD with ORR of 28.2% (11/39) and DCR of 64.1 % (25/39). The mPFS was 3.5 mos and mDoR was 3.4 mos. At the time of data cut-off, three pts were ongoing as following response and cancer types: cPR (breast, ATMm, 9.0 mos), cPR (NSCLC, gBRCA2m, 3.8 mos) and SD (breast, gBRCAm, 9.3 mos). Five pts (2 ovarian, 3 breast) previously treated with olaparib and discontinued due to progressive disease were enrolled in this JPI-547 trial and one ovarian cancer pt showed cPR with 37% tumor shrinkage. **Conclusions:** These results demonstrate that JPI-547 is adequately absorbed with acceptable safety profile. Preliminary efficacy results suggest that JPI-547 monotherapy is effective in pts with BRCA/HRR mutation. Further investigation is warranted in pts with solid tumor including PARP inhibitor resistant cases. Clinical trial information: NCT04335604. Research Sponsor: National OncoVenture (Korea).

3114 **Poster Session**

Intra-patient comparison from larotrectinib clinical trials in TRK fusion cancer: An expanded dataset. *First Author: David S. Hong, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Larotrectinib is a highly selective, CNS-active tropomyosin receptor kinase (TRK) inhibitor that demonstrated rapid and durable responses in three phase I/II single-arm studies of patients (pts) with TRK fusion cancer. In single-arm studies the growth modulation index (GMI) can be used to provide a comparative analysis. GMI is an intra-patient comparison that uses pts as their own control by comparing progression-free survival (PFS) on current therapy to time to progression or treatment failure (TTP) on the most recent prior therapy; namely the ratio of PFS/TTP (EMA Guidelines. Guideline on the Evaluation of Anticancer Medicinal Products in Man, EMA/CHMP/205/95 Rev.5). A GMI ratio $\geq$1.33 has been used as a threshold of meaningful clinical activity. In a previous analysis of 122 pts with TRK fusion cancer treated with larotrectinib, 84 pts (69%) had a GMI $\geq$1.33. Conversely, 38 pts (31%) had a GMI $<$ 1.33, but of these, 9 pts were ongoing treatment and censored for PFS as of July 2019 (Italiano et al, ESMO 2020). Here, we report the GMI of this initial group with a longer follow-up as well as an expanded dataset to more accurately assess the treatment effect of larotrectinib in pts with TRK fusion cancer previously treated with $\geq$1 line of therapy. **Methods:** Pts with TRK fusion cancer from three clinical trials on larotrectinib treatment with $\geq$1 prior line of systemic therapy were eligible for retrospective GMI analysis. TTP on the prior line of therapy was investigator-assessed. PFS on larotrectinib was determined by independent review committee per RECIST v1.1. Pts who had not progressed were censored as of date of last visit. Kaplan–Meier (KM) analyses were used to estimate median GMI, in addition to median PFS and TTP. The data cut-off was July 2020. **Results:** With an extended follow up of the original 122 pts, 90 (74%) pts had a GMI $\geq$1.33, including 6 of the 9 pts who were previously censored with a GMI $<$ 1.33 and ongoing treatment; 6 pts (5%) had a GMI $\geq$1 to $<$ 1.33 and 26 (21%) had a GMI $<$ 1. The KM estimated median GMI increased from 7.6 (95% CI 5.7–88.0) to 9.5 (95% CI 5.7–17.4). In the expanded dataset of 140 pts, 103 pts (74%) had GMI $\geq$1.33, 7 (5%) had a GMI $\geq$1 to $<$ 1.33 and 30 (21%) had a GMI $<$ 1. Six of the 37 pts with a GMI $<$ 1.33 were censored and still ongoing treatment. The KM estimated median GMI was 8.9 (95% CI 6.2–17.4). Among pts who had received 1, 2, or $\geq$3 prior lines of therapy, 74%, 65%, and 80%, respectively, had GMI of $\geq$1.33. Median TTP on the prior therapy was 3.0 months (95% CI 2.1–3.5) and median PFS on larotrectinib was 33.0 months (95% CI 16.6–34.9). **Conclusions:** With a longer follow-up, nearly three-quarters of pts with TRK fusion cancer treated with larotrectinib had a prolonged PFS compared to their most recent prior therapy. These results further validate the use of larotrectinib in treating patients with TRK fusion cancer. Clinical trial information: NCT02576431, NCT02122913, NCT02637687. Research Sponsor: Bayer HealthCare and Loxo Oncology.

3115 **Poster Session**

Phase I expansion study of the first-in-class monocarboxylate transporter 1 (MCT1) inhibitor AZD3965 in patients with diffuse large B-cell lymphoma (DLBCL) and Burkitt lymphoma (BL). *First Author: Sarah E. R. Halford, Cancer Research UK Centre for Drug Development, London, United Kingdom*

Background: Tumours rely on lactate transporters (MCT1-4) to maintain glycolytic flux and avoid intracellular acidification. In haematological tumours the MCT1 transporter acts as a lactate and pyruvate exporter. AZD3965 is a potent and specific inhibitor of MCT1 causing intracellular lactate accumulation. *In vivo* efficacy was observed in xenografts of DLBCL and BL, expressing high levels of MCT1 and no or low levels of MCT4. In the AZD3965 phase I (NCT01791595) dose-escalation an oral recommended phase 2 dose (RP2D) of 10mg twice-daily (bd) was determined. Pharmacokinetic (PK) showed exposure estimated to produce a minimum MCT1 occupancy of 90% (based on modelling). DLTs were primarily on-target dose-dependent, reversible, asymptomatic alterations in retinal function seen on ERG. **Methods:** This expansion cohort enrolled patients with relapsed/refractory DLBCL and BL. Expression of MCT1/MCT4 was assessed by immunohistochemistry. Pharmacokinetic (PK) sampling was performed and pharmacodynamic assessments included [^{18}F]FDG-PET/CT imaging and plasma/urine metabolomics. **Results:** 11 DLBCL patients were treated with AZD3965 10mg bd. PK showed exposure to be broadly in line with the escalation cohort. No significant ERG changes were observed. One patient experienced a dose-limiting SUSAR of Troponin I increase. MCT1 is expressed in erythrocytes, however no serious events of anaemia were seen, with one non-clinically significant episode of grade 3 anaemia reported. Urine analysis showed increased excretion of lactate and ketone bodies post AZD3965 treatment consistent with renal target engagement. No alteration was detected in plasma. Ongoing stable disease at cycle 5 was observed in one patient and an additional patient had a confirmed complete response (CR) lasting 15 months, with no significant toxicity. In the patient showing CR a reduction in tumour FDG uptake was observed on day 3 of cycle 1. The other four patients who consented to research imaging did not have a clinical response and no changes were observed on FDG-PET. **Conclusions:** AZD3965 can be safely administered at 10mg bd. In one DLBCL patient monotherapy activity was observed with changes in FDG-PET providing evidence indicative of proof of mechanism. These changes in FDG uptake as early as on day 3 in the responding patient warrant further investigation of FDG-PET as a predictive biomarker. Further biomarker analysis and preclinical studies are ongoing to understand the biology and explore effective combinations with other agents targeting tumour cell metabolism Clinical trial information: NCT01791595. Research Sponsor: Cancer Research UK.

3116 **Poster Session**

The next-generation pan-RAF inhibitor, KIN-2787, is active in class II and class III BRAF mutant models. *First Author: Aleksandra Franovic, Kinnate Biopharma Inc., San Diego, CA*

Background: Oncogenic *BRAF* gene alterations, leading to aberrantly activated BRAF monomers (Class I mutations) or dimers (Class II and Class III mutations), are observed in approximately 6% of all human cancers. First-generation BRAF inhibitors targeting Class I BRAF mutants, including dabrafenib, encorafenib, and vemurafenib, provide significant clinical benefit to patients with BRAF V600 mutation-driven melanoma and select solid tumors as monotherapies or in combination with other targeted therapies. The currently approved BRAF inhibitors have not, however, proven to be effective in patients with Class II or III *BRAF* alterations which account for a large proportion (34%) of *BRAF* mutations. KIN-2787 is an orally available, potent and selective small molecule pan-RAF inhibitor specifically designed to inhibit Class II and III BRAF dimers, in addition to Class I mutants. **Methods:** The efficacy and tolerability of the pan-RAF inhibitor, KIN-2787, was evaluated *in vitro* and *in vivo* in Class I, II, and III *BRAF* mutation-driven human cancer models. **Results:** In biochemical assays, KIN-2787 showed low nanomolar to picomolar potency against RAF1, BRAF, and ARAF (IC50 0.06-3.46 nM) with minimal activity towards non-RAF kinases. In cell-based assays, KIN-2787 inhibited RAF activity, as measured by inhibition of downstream ERK phosphorylation (pERK), across multiple BRAF mutant cancer cell lines. Class II and III BRAF mutant cell lines were the most responsive when treated with KIN-2787 (IC50 $<$ 50 nM); 19- and 7-fold more sensitive compared to cells harboring wild-type BRAF, respectively. Dose-dependent inhibition of A-375 (Class I), BxPC-3 (Class II), and WM3629 (Class III) BRAF mutant human xenograft tumor growth was attained with daily KIN-2787 treatment and was well-tolerated. A trend towards greater tumor responses was observed with twice daily (BID) compared to once daily (QD) dosing of KIN-2787; however, the two dosing regimens led to similar tumor growth inhibition (TGI) and regressions (mean TGI up to 101-118%; $p \leq 0.0001$) at equivalent total daily doses. Furthermore, KIN-2787 led to a significant *in vivo* pharmacodynamic response using either regimen, however, prolonged target coverage, as measured by pERK, was achieved with BID dosing. The impact of KIN-2787 treatment on additional biomarkers, including transcriptional changes and MAPK pathway modulation in cell-based models and patient-derived samples, will be presented at the meeting. **Conclusions:** KIN-2787 is a next-generation pan-RAF inhibitor with pronounced *in vitro* and *in vivo* activity against human cancers driven by Class II and III *BRAF* mutations. A phase 1 dose escalation and expansion clinical trial evaluating the safety and efficacy of KIN-2787 monotherapy in patients with advanced or metastatic solid tumors harboring *BRAF* gene alterations, including Class II and III mutations, is expected to initiate in 2021. Research Sponsor: Kinnate Biopharma Inc.

3117 **Poster Session**

Prognostic factors in RET dependent cancers treateded with RET inhibitors in early phase clinical trials. *First Author: Max Gordon, UT MD Anderson Cancer Center, Houston, TX*

Background: Activation of the RET proto-oncogene has been identified in multiple cancer types, for example, gene rearrangements in non-small cell lung cancer (NSCLC) and papillary thyroid cancer (PTC) and activating mutations in medullary thyroid cancer (MTC), amongst others. The recent FDA approval of two highly selective RET inhibitors, selpercatinib and pralsetinib has changed the treatment paradigm of RET-driven cancers, but the significance of historical prognostic factors is unknown. Herein, we analyzed the outcomes of patients with RET-altered cancers enrolled in phase I trials and assess the utility of prognostic scores. **Methods:** A retrospective analysis was performed of patients treated with selective RET inhibitors at the MD Anderson Cancer Center (MDACC). Baseline clinical factors and survival data were assessed. Overall and progression free survival (OS and PFS) were estimated using the Kaplan-Meier method and multivariable Cox models were constructed. For all a p-value of $<$ 0.05 was consider significant. **Results:** Among 126 patients, median age was 58 years (range, 15-82), most with ECOG 0-1 (n = 124). RET-mutant MTC was most frequent (n = 81), followed by RET fusion-positive NSCLC (n = 30) and RET fusion positive thyroid cancer (n = 9). RET fusion partners were KIF5B (n = 17), CCD6 (n = 12) and NCOA4 (n = 7). RET M918T mutation was the most frequent (n = 50, 63%). Most patients were treated in the relapsed/refractory (R/R) setting (n = 85) and received a median of 1 prior line of therapy (range, 0-11). Median follow up was 20 months (range, 1-43). The estimated median PFS and OS were 24 and 35 months, respectively. Overall objective response rate was 64% (81/126), 2 complete response, 79 partial response, 32 had stable disease (25%) and 13 had progressive disease (PD). The following were associated with shorter PFS and OS: age $\geq$50 years ($p < 0.05$), albumin $<$ 4 g/dL ($p < 0.01$), brain metastases ($p < 0.0001$), hemoglobin $<$ 12 g/dL (< 0.05), LDH $>$ normal ($p < 0.05$), WBC $\geq$8 ($p < 0.01$), PD ($p < 0.0001$) and NSCLC ($p < 0.01$). The M918T mutation and ECOG $>$ 0 were associated with shorter OS but not PFS ($p < 0.05$). $>$ 3 metastatic sites and R/R disease were associated with inferior PFS ($p = 0.04$ and $p = 0.01$, respectively) but not OS. The Royal Marsden Hospital (RMH) and MDACC prognostic scores were significantly associated with PFS and OS ($p < 0.01$). In multivariable models including all variables significantly associated with PFS and OS (excluding LDH as this was only tested in 58 patients) albumin $<$ 4 (HR 6.10, $p = 0.013$), brain metastases (HR 4.90, $p = 0.027$) and WBC $\geq$8 (HR 4.67, $p = 0.031$) were associated with inferior OS. NSCLC was significantly associated with inferior PFS (HR 5.45, $p = 0.02$). **Conclusions:** The RMH and MDACC prognostic scores predict OS in RET-aberrant cancers treated on early phase trials. Low albumin, WBC $>$ 8 and brain metastases are significantly associated with inferior survival. Research Sponsor: None.

3118 **Poster Session**

Expression of end-binding protein 1 (EB1), a potential response-predictive biomarker for lisavanbulin, in glioblastoma and various other solid tumor types. *First Author: Magdalena Skowronska, Institute of Pathology, University of Bern, Bern, Switzerland*

Background: EB1, a protein located on the plus-ends of microtubules is involved in microtubule function and has been associated with glioblastoma (GBM) stem-cell-ness and more aggressive disease. Lisavanbulin (BAL101553) is a prodrug of the lipophilic small molecule BAL27862, that promotes tumor cell death by modulating the spindle assembly checkpoint and has been shown in rodents to efficiently penetrate the brain. Data from GBM mouse models and recent phase 1 clinical data (Lopez et al. ESMO 2020) suggest that EB1 is a response-predictive marker for lisavanbulin in GBM. A phase 2 study is ongoing to confirm this hypothesis (NCT02490800). A proof-of-concept in GBM would support an expansion of EB1-directed lisavanbulin clinical development in non-GBM tumors, which requires prevalence estimates of EB1-positivity in non-GBM tumor types. **Methods:** Tissue samples from GBM and other tumor types were stained for EB1 using a CE-marked immunohistochemistry Clinical Trial Assay (Targos Molecular Pathology GmbH, Kassel Germany). EB1-positivity was assessed by a board-certified pathologist based on the percentage of tumor cells showing moderate or strong staining for EB1, using thresholds of $\geq$50%, $\geq$60% and $\geq$70% of tumor cells with EB1 positivity. Whole transcriptome sequencing (WTS) using RNAseq was performed in a subset of tissue samples to develop a potential RNA-based predictive response signature for lisavanbulin. **Results:** 73 GBM tissue samples and 333 tissue samples from 13 other cancer types were stained for EB1. The strongest overall signal for EB1-positivity was obtained for medulloblastoma, neuroblastoma and GBM. In addition, moderate or strong EB1-staining in $\geq$50% of tumor cells was observed in samples from colorectal cancer (CRC), non small-cell lung cancer (NSCLC), metastatic melanoma, small-cell lung cancer (SCLC) and triple-negative breast cancer (TNBC). An expanded staining campaign is ongoing in these cancer types. Initial results from the ongoing WTS analyses show marked differences in gene expression profiles between EB1-positive and -negative cases. **Conclusions:** Strong EB1-positivity is infrequent but occurs in a variety of tumor types, with the strongest signals in medulloblastoma, neuroblastoma and GBM. A phase 2 study is ongoing to assess prospectively whether EB1 is a response-predictive biomarker for lisavanbulin in GBM. Research Sponsor: Basilea Pharmaceutica International Ltd.

		% EB1-positive tissue samples (moderate or strong EB1 staining based on % tumor cells threshold)			
Tumor type	**Ntissue samples**	**≥50%**	**≥60%**	**≥70%**	**Max**
Medulloblastoma	7	14%	14%	14%	100%
Neuroblastoma	13	23%	23%	15%	90%
GBM	73	11%	11%	7%	80%
NSCLC	30	10%	7%	0%	60%
CRC	30	7%	7%	0%	60%
Metastatic melanoma	30	3%	3%	0%	60%
SCLC	13	8%	0%	0%	50%
TNBC	30	3%	0%	0%	50%
Gynecological carcinosarcoma; Hepatocellular carcinoma; Breast cancer (not TNBC); Prostate cancer; Soft tissue sarcoma; Renal cell carcinoma	30 per tumor type	0%	0%	0%	<50%

3119 **Poster Session**

TP53 and CHEK2 germline mutations in malignant solid tumors. *First Author: Zhiye Zhang, The First Affiliated Hospital of Henan University of Science and Technology, Luoyang, China*

Background: Li-Fraumeni syndrome (LFS, OMIM #151623) is an autosomal dominant cancer predisposition syndrome. Typical LFS tumors comprise adrenocortical carcinomas, sarcoma, breast cancer and central nervous system tumors. LFS is also associated with an increased risk of a multitude of other common types of cancer, such as prostate cancer, lung cancer, gastric cancer, colorectal cancer, ovarian cancer, melanoma, etc. TP53 germline mutations are the most common gene with LFS. Germline mutationsof CHEK2 have been identified as another predisposing gene and associated with a range of cancer types. However, the pattern of TP53 and CHEK2 germline mutations in malignant tumors remains unknown. **Methods:** We identified 8535 malignant solid tumors patients without selecting age or family history in a retrospective cohort. Germline mutations were categorized based on ACMG (American College of Medical Genetics and Genomics) guidelines in pathogenicity. The patients were divided into three groups, P group (with pathogenic mutations), LP group (with likely-pathogenic mutations) and Non_P group (neither pathogenic nor likely-pathogenic mutation). Statistical significance was defined as P-value less than 0.05. **Results:** A total of 461 (461/8535) patients carried TP53 or CHEK2 germline mutations were identified, in which 15 patients with pathogenic mutations and 17 patients with likely-pathogenic mutations. One patient with lung cancer in LP group carried TP53 homozygous mutation (p. Ser215Ile), and the remaining 31 patients all carried heterozygous mutations. Among these 31 carriers, 16 (51.6%) carried nonsense or missense mutations (10 for nonsense and 6 for missense mutations). 3 patients in the P group carried CHEK2p. Y139* (one liver cancer patient and two lung cancer patients) were identified. The median age of group P, LP and Non_P was 55 (39 for TP53, 61 for CHEK2), 63 (52 for TP53, 66 for CHEK2) and 59, respectively. Somatic mutation analysis found no significant difference in tumor mutation burden (TMB) among three groups. The SNV/INDEL mutation frequency of LRP1B in the P or LP group was significantly lower than the Non_P group. **Conclusions:** Our data showed that 0.375% (32/8535) malignant solid tumor patients carried TP53 (16/8535) or CHEK2 (16/8535) germline pathogenic or likely-pathogenic mutations. The relationship between germline mutations and cancer susceptibility will be studied in the future. Research Sponsor: None.

Mutation distribution in different cancer types.

Cancer type	Number	TP53 (P Group)	TP53 (LP Group)	CHEK2 (P Group)	CHEK2 (LP Group)
Lung cancer	13	3	4	4	2
Colorectal cancer	5	1	1	2	1
Liver cancer	4	0	0	3	1
Brain tumor	3	1	2	0	0
Sarcoma	2	0	2	0	0
Prostate cancer	3	0	0	0	3
Pancreatic cancer	1	1	0	0	0
Bladder cancer	1	0	1	0	0
Total	32	6	10	9	7

3120 **Poster Session**

A comprehensive landscape of BRCA1 versus BRCA2 associated molecular alterations and survival outcome across 35 cancer types. *First Author: Alberto Puccini, Medical Oncology Unit 1, IRCCS Ospedale Policlinico San Martino, Genoa, Italy*

Background: Poly (ADP-ribose) polymerase inhibitors (PARPi) are effective therapies for some patients with both germline and somatic *BRCA1/2* mutations (MTs) or with homologous recombination repair deficiency (HRD). We aimed to characterize molecular differences between *BRCA1* and *BRCA2* MTs and their prognostic and/or predictive impact on PARPi outcomes in various cancer subtypes using real world data (RWD). **Methods:** Tumor samples obtained from patients with 35 types of cancer were analyzed by whole exome sequencing (WES, Novaseq) at Caris Life Sciences (Phoenix, AZ). High genomic loss of heterozygosity (gLOH-H) was defined as LOH-H in ≥16% of tested loci. MSI/MMR was tested by fragment analysis, IHC, and WES. Overall survival (OS) extracted from insurance claims was calculated from start of treatment or tissue collection until last contact or death using Kaplan-Meier curves. *P*-values adjusted for multiple comparisons (q-value of < 0.05 was considered to be significant). **Results:** In total, 17,640 tumors were included, of which 776 (4.3%) had tumor-based *BRCA1/2* MTs. *BRCA1/2* MTs were most commonly seen in ovarian (N = 221/2187, 10.1%), breast (138/2506, 5.5%), prostate (61/1131, 5.4%), pancreatic (48/1430, 3.4%), and non-small cell lung (100/4046, 2.5%) cancers. *BRCA2* MTs were more frequent than *BRCA1* except in ovarian cancers. *BRCA1* MTs were more common in younger pts (median age, 61 vs 65 years, $p < .001$). When compared to *BRCA2* MTs, *BRCA1* MTs were more often associated with gLOH-H (64% vs 51%, $p < .001$) and *TP53* MT (80% vs 53%, $p < .001$) in all tumor types. In NSCLC, *EGFR* mutations were exclusively seen in *BRCA2* compared to *BRCA*1 (10.3 vs. 0%, P = 0.038). The *EGFR* mutations that co-occurred with BRCA2 mutations were L858R (N = 1), Exon19del (N = 4), and L861Q (N = 1). *KRAS* was more frequently mutated in *BRCA*1-mutated NSCLC (*BRCA1*: 32% vs. *BRCA2*: 16%, p = .056). In univariate analyses, overall *BRCA1/2* MTs were associated with improved OS compared to wild type (HR 1.38, 95% CI [1.31-1.45], $P < .0001$). This effect was seen in ovarian (1.42 [1.29-1.57], $p < 0.0001$) and triple-negative breast cancers (TNBC) (1.18, [1.09-1.28], $p < .001$); but was not observed in prostate, pancreatic, or non-TNBC breast cancer subtypes. In all breast cancers, *BRCA2* MTs had a superior OS (0.68, [0.51-0.89], p = .005) compared to *BRCA*1, while no differences were seen in other cancers. Using RWD, PARPi treated-patients with *BRCA2* MTs had worse OS than *BRCA1* MTs (HR 1.4, [1.09-1.80], p = 0.009); but this was not significant when individual cancers were considered. **Conclusions:** *BRCA1* and *BRCA2* MTs had variable power to be prognostic and predictive for PARPi efficacy among different cancer types using RWD. About 2.5% of NSCLCs harbor BRCA1/2 MT. Additional genomic exploration may refine biomarkers predictive of response to PARPi and may highlight features within the tumor microenvironment of importance in the setting of HRD. Research Sponsor: None.

3121 **Poster Session**

Analysis of the MOSAIC correlative cancer database integrating molecular cancer classification and tumor profiling to identify targeted treatment options for metastatic cancer. *First Author: Li Ma, Biotheranostics, Inc., San Diego, CA*

Background: Unless tumor type and genetic alterations can be identified, metastatic cancer patients with unknown or uncertain diagnoses may be limited to empiric chemotherapy. The 92-gene assay (CancerTYPE ID) is a validated gene expression classifier of 50 tumor types and subtypes for patients with cancer of unknown primary (CUP) or ambiguous diagnoses. Multimodal molecular biomarker testing by next-generation sequencing (NGS), tumor mutational burden (TMB), fluorescent in situ hybridization (FISH), microsatellite instability (MSI), and immunohistochemistry (IHC) can identify genetic targets. A database integrating tumor typing with biomarker analysis in metastatic cases was utilized to identify the most prevalent genetic alterations by tumor type. **Methods:** MOSAIC (Molecular Synergy to Advance Individualized Cancer Care) is an IRB-approved database of cases with CancerTYPE ID testing plus multimodal biomarker testing. The current study determined molecular tumor type followed by molecular profiling by NGS for up to 323 genes, (NeoTYPE profiles, Neogenomics). **Results:** Tumor type was determined in 1992 of 2151 cases (92.7%), comprised of 27 different tumor types. 72% of cases were comprised of the 7 tumor types shown in the table,- which also shows the frequency of the 10 most commonly mutated genes by tumor type. Bolded are genes with actionable genetic mutations for which FDA-approved therapies are not currently indicated in the identified tumor type. **Conclusions:** Precise targeted treatment for many patients with CUP or ambiguous diagnoses requires accurate diagnosis of the cancer origin combined with multimodal molecular testing to identify actionable genetic alterations in the appropriate cellular context. Future studies will evaluate additional biomarker profiles, including TMB, FISH, MSI, and IHC for cases in the MOSAIC database. Research Sponsor: Biotheranostics, Inc.

Tumor type	N (%)	Mutational frequency of the 10 most commonly mutated genes by tumor type									
Pancreaticobiliary[1]	541 (25%)	TP53 37%	KRAS 30%	ARID1A 15%	SMARCA4 15%	BAP1 13%	LRP1B 12%	IDH1 11%	FAT1 11%	KEAP1 11%	KMT2C 11%
Squamous cell carcinoma[2]	274 (12%)	TP53 65%	KMT2D 32%	FAT1 21%	BCORL1 18%	LRP1B 18%	PIK3CA 18%	SMARCA4 17%	NOTCH1 16%	KMT2C 16%	MTOR 16%
Lung	157 (7%)	TP53 66%	KRAS 42%	KEAP1 27%	KMT2D 20%	STK11 16%	ARID2 14%	BRCA2 14%	CHD2 14%	EPHA5 14%	KMT2C 14%
Intestine	134 (6%)	TP53 54%	APC 43%	KRAS 35%	ARID2 17%	KMT2D 17%	LRP1B 17%	NF1 17%	PIK3CA 13%	KMT2C 13%	RANBP2 13%
Gastroesophageal	130 (6%)	TP53 56%	KRAS 36%	KMT2C 24%	ARID1A 21%	FAT1 14%	LRP1B 14%	BRAF 12%	ALK 10%	APC 10%	ATM 10%
Neuroendocrine[3]	112 (5%)	TP53 63%	NBN 29%	APC 24%	KMT2C 24%	LRP1B 24%	RB1 24%	CTNNB1 18%	DICER1 18%	MED12 18%	MTOR 18%
Sarcoma[3]	100 (5%)	TP53 44%	TERT Promoter 43%	KMT2D 24%	FAT1 19%	KRAS 16%	KDR 14%	LRP1B 14%	RAD54L 14%	SPTA1 14%	CDKN2A 12%

[1]Pancreas, bile duct, and gall bladder; [2]Cervix, head & neck/skin, and lung; [3]Multiple subtypes.

3122 **Poster Session**

Temporal and spatial topography of cell proliferation in cancer. *First Author: Sheheryar Kairas Kabraji, Dana Farber Cancer Institute, Boston, MA*

Background: Tumors are complex ecosystems where exogenous and endogenous cues are integrated to either stimulate or inhibit cancer cell proliferation. However, the nature of these complex cell cycle states, their spatial organization, response to perturbation, and implications for clinical outcomes, are poorly characterized in tumor tissues. **Methods:** We used multiplexed tissue imaging to develop a robust classifier of proliferation, the multivariate proliferation index (MPI), using 513 unique tumors across five cancer types. Next, we used dimensionality reduction analysis to assess how the patterns of cell cycle protein expression in tumors were altered in response to perturbation. **Results:** The MPI outperforms single markers, like Ki67, when classifying proliferative index across diverse tumor types and reveals the proliferative architecture of tumors in situ. We find that proliferative and non-proliferative cancer cells are organized across microscopic (cell-to-cell) and macroscopic (tissue-level) scales. Both domains are reshaped by therapy, and local clusters of proliferative and non-proliferative tumor cells preferentially neighbor distinct tumor-infiltrating immune cells. We further phenotyped non-proliferating cancer cells using markers of quiescent cancer cells, cancer stem cells, and dormant cancer cells. We found that these types of non-proliferating cancer cells can occupy distinct regions within the same primary tumor. In high-dimensional marker space, populations of proliferative cancer cells express canonical patterns of cell cycle protein markers, a property we refer to as "cell cycle coherence". Untreated tumors exist in a continuum of coherence states, ranging from optimal coherence, akin to freely cycling cells in culture, to reduced coherence characterized by either cell cycle polarization or non-canonical marker expression. Coherence can be stereotypically altered by induction and abrogation of mitogen signaling in a HER2-driven model of breast cancer. Cell cycle coherence is modulated by neoadjuvant therapy in patients with localized breast cancer, and coherence is associated with disease-free survival after adjuvant therapy in patients with colorectal cancer, mesothelioma and glioblastoma. **Conclusions:** The MPI robustly defines proliferating and non-proliferating cells in tissues, with immediate implications for clinical practice and research. The coherence metrics capture the diversity of post-treatment cell cycle states directly in clinical samples, a fundamental step in advancing precision medicine. More broadly, replacing binary metrics with multivariate traits provides a quantitative framework to study temporal processes from fixed static images and to investigate the rich spatial biology of human cancers. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Ludwig Center at Harvard.

3123 **Poster Session**

Multi-cancer detection and tissue of origin determination based on 5-hydroxymethylcytosine biomarkers in circulating cell-free DNA. *First Author: Zhou Zhang, Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Early detection may reduce cancer mortality. Systematic screening programs are available only for a limited number of cancers (e.g., colorectal cancer). The majority of common cancers are detected after the onset of signs and symptoms, making treatment difficult or less effective. We describe here a multi-cancer epigenetic approach for simultaneous cancer detection of common cancers (~70% of adult cancers) and determination of tissue of origin (TOO) using circulating cell-free DNA (cfDNA) from plasma. **Methods:** A total of 2241 cancer cases, including patients with newly diagnosed primary colorectal, gastric, esophageal, liver, lung, and breast cancer (stages I-III or equivalent) and 2289 non-cancer controls were recruited from participating hospitals in China. Study participants were randomly assigned into a training set (70%) and a testing set (30%), and patients were matched for cancer types and stages. Plasma samples were collected before radical treatment or surgery. The 5hmC-Seal, a highly sensitive chemical labeling technique, was used to profile genome-wide 5-hydroxymethylcytosines (5hmC) in cfDNA from ~5mL of plasma per person, followed by the next-generation sequencing, data summarization at gene-level, and normalization. We applied the elastic net regularization to establish a predictive rule based on the multivariable logistic regression model for cancer detection in the training set as well as a multiclass classification model for determining TOO. The final solution for simultaneous cancer detection and TOO determination was established by integrating the 5hmC-based models and protein markers (e.g., AFP). Overall sensitivity and specificity were computed and reported in the testing set of 670 cancer cases and 686 non-cancer controls. **Results:** For the primary scenario (i.e., stages I-III or equivalent), at specificity of 95%, the overall sensitivity achieved 79.3% for detecting a cancer patient in all six cancer types in the testing set, except stage I lung cancer, for which the multi-cancer detection solution showed a sensitivity of 51%. Notably, for individuals with a negative result from conventional protein markers (e.g., AFP, CEA), the 5hmC-only models showed 67.6% sensitivity at 98.2% specificity in the testing set, representing significant improvement. In the testing set, among the 500 cancer patients who were detected from the multi-cancer detection solution, 435 patients were assigned a TOO; of those, 362 (83.2%) TOO were correctly determined. **Conclusions:** The 5hmC-Seal in cfDNA shows the potential as a non-invasive tool that could be integrated into a screening program for simultaneous detection of common cancers and TOO localization. This approach can be expanded to additional cancer types and is currently undergoing validation in prospectively recruited cohorts. Research Sponsor: Shanghai Epican Genetech, Co. Ltd.

3124 **Poster Session**

Frequency of longitudinal changes in *TP53* mutation status from gene sequencing of serial tumor biopsies from a large cohort of cancer patients. *First Author: D. Allen Allen Annis, Aileron Therapeutics, Inc., Cambridge, MA*

Background: The p53 pathway is one of the most important in cancer biology, with mutation of the *TP53* gene that encodes the p53 tumor suppressor protein observed in ≈50% of all cancers. We evaluated the frequency of changes in *TP53* mutation status in a large cohort of serial tumor biopsies. **Methods:** From a database of >200,000 next-generation gene sequencing results we identified 16,592 samples arising from repeat biopsies from 7840 patients (pts), average 2.12 per pt, 1007 pts with ≥3, max 11; over an interval up to 234 months (mos), average 11.0 mos. *TP53* mutations with known or unknown significance in successive biopsies and changes in assignment from *TP53*-Wild-Type (WT) to Mutant (Mut), or Mut to WT, were evaluated vs. cancer type and time between biopsies. **Results:** Table: N (%) of samples vs. change in *TP53* status from previous biopsy vs. mos from initial biopsy in all samples (7840 initial + 8752 successive, 46% *TP53*-Mut) and the three most represented cancers: non-small cell lung cancer (NSCLC, 1189 initial + 1268 successive, 60% Mut), breast (947 initial + 993 successive, 55% Mut), multiple myeloma (MM, 578 initial + 981 successive, 18% Mut). **Conclusions:** Changes in *TP53* status were rare (<10% of samples). Differences may occur in serial biopsy samples for pathophysiological reasons, e.g., a mutant clone becoming dominant and/or heterogeneity at different tumor biopsy sites, or analytical differences in biopsy tumor content or assay sensitivity between samples. In this analysis, WT-to-Mut changes were more frequent (5.9%) than Mut-to-WT changes (3.3%), suggesting a small selection pressure for *TP53* alterations later in oncogenesis and indicating that these alterations are truncal. Mut-to-WT changes are not readily explained physiologically and may suggest these infrequent changes are mostly due to sampling or analytical variability, and genuine changes in *TP53* mutation status are quite rare. Research Sponsor: Aileron Therapeutics, inc.

		Overall	1-12 mos	13-24	25-36	37-48	49-60	61-240
All	No Change	7950 (90.8%)	3680 (91.2%)	1974 (91.7%)	1014 (90.5%)	521 (89.7%)	298 (91.1%)	463 (86.5%)
	WT to Mut	513 (5.9%)	205 (5.1%)	121 (5.6%)	67 (6%)	42 (7.2%)	20 (6.1%)	58 (10.8%)
	Mut to WT	289 (3.3%)	151 (3.7%)	57 (2.6%)	40 (3.6%)	18 (3.1%)	9 (2.8%)	14 (2.6%)
NSCLC	No Change	1118 (88.2%)	518 (89.2%)	299 (90.3%)	145 (84.3%)	70 (82.4%)	33 (89.2%)	53 (85.5%)
	WT to Mut	83 (6.5%)	29 (5%)	16 (4.8%)	21 (12.2%)	9 (10.6%)	1 (2.7%)	7 (11.3%)
	Mut to WT	67 (5.3%)	34 (5.9%)	16 (4.8%)	6 (3.5%)	6 (7.1%)	3 (8.1%)	2 (3.2%)
Breast	No Change	902 (90.8%)	313 (92.1%)	209 (92.1%)	152 (93.8%)	73 (85.9%)	49 (86%)	106 (86.9%)
	WT to Mut	60 (6.0%)	14 (4.1%)	14 (6.2%)	6 (3.7%)	9 (10.6%)	6 (10.5%)	11 (9%)
	Mut to WT	31 (3.1%)	13 (3.8%)	4 (1.8%)	4 (2.5%)	3 (3.5%)	2 (3.5%)	5 (4.1%)
MM	No Change	892 (90.9%)	523 (90.5%)	253 (90.7%)	77 (95.1%)	25 (92.6%)	13 (86.7%)	1 (100%)
	WT to Mut	62 (6.3%)	38 (6.6%)	20 (7.2%)	2 (2.5%)	1 (3.7%)	1 (6.7%)	0 (0%)
	Mut to WT	27 (2.8%)	17 (2.9%)	6 (2.2%)	2 (2.5%)	1 (3.7%)	1 (6.7%)	0 (0%)

3125 **Poster Session**

A comprehensive literature review and meta-analysis on prognostic value of BRCAm, HRRm and HRD+ across tumor types. *First Author: Changxia Shao, Merck & Co., Inc., Kenilworth, NJ*

Background: Poly (ADP-ribose) polymerase inhibitor (PARPi) may have broad application in the treatment of cancer patients with mutations of BRCA (BRCAm) or other homologous recombination repair genes (HRRm) or HR deficiency positive (HRD+). A literature review and meta-analysis were conducted to evaluate the clinical prognostic outcomes by total BRCAm, HRRm, and HRD+ status across tumor types among patients treated with non-PARPi treatment. **Methods:** Comprehensive searches for eligible studies in Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane reviews were performed in May 2020 to capture studies published in English within 10 years for manuscripts and 3 years for abstracts across geographic regions. A summary estimate with corresponding 95% CI was calculated using random-effects models due to varying effects sizes across studies. **Results:** A total of 135 eligible studies were included. Breast cancer (BC) patients with either BRCA1m or BRCA2m (BRCA1/2m) had a similar overall survival (OS) to those with wild-type BRCA1 and BRCA2 (BRCA1/2wt) across 18 studies reporting data on BRCA1m and BRCA2m. The pooled estimates of hazard ratio (HR) was 1.0 (95% CI: 0.8-1.3) overall and was 1.0 (0.7-1.5) for triple-negative BC (TNBC, 7 studies). Similarly, the HR was 1.1 (0.9-1.3) across all 10 studies reporting BRCA1m data and 1.1 (0.8-1.3) across all 7 studies reporting BRCA2m data. Ovarian cancer (OC) patients with BRCA1/2m had a significantly longer OS than those with BRCA1/2wt across 24 studies reporting BRCA1m and BRCA2m, with a HR of 0.7 (0.6-0.8). The HR was 0.6 (0.4, 0.8) across 4 studies on stage III-IV ovarian cancer. The HR was 0.8 (0.6-1.1) across 13 studies reporting BRCA1m and 0.5 (0.3-0.9) across 8 studies reporting BRCA2m. Less OS data were reported for other tumors, 6 studies for BRCA2m in prostate cancer with a HR of 1.9 (1.1-3.2) and 2 studies for BRCA1/2m in pancreatic cancer with a HR of 1.5 (0.8-3.1). Only 4 studies reported HRD+ by either BRCAm or genomic instability score (GIS) ≥ 42 and OS by HRD status; 3 on TNBC and 1 on high-grade serous ovarian cancer. The HR was 0.67 (0.43-1.02) for OS with HRD+ vs. HRD-. A total of 15 studies reported the association between HRRm and OS of cancers (5 on prostate, 4 on pancreas, 3 on ovary, 2 on breast and 1 on urothelial cancer), in which one or more HRR genes were examined. The HR was 1.0 (0.7-1.4) comparing patients with HRRm to those with HRRwt across tumor types. Due to the limited study number and inconsistent methodology/definitions of HRRm and HRD+, these results should be interpreted with caution. **Conclusions:** The effects of BRCA1/2m on OS in patients treated with chemotherapy varies by cancer type with no effect in BC and a positive association in OC. More study is required in other cancer types. There was no significant association found between HRD+ or HRRm with OS. These findings could help inform evidence-based treatment decisions. Research Sponsor: Merck & Co.

3126 **Poster Session**

The value of defining molecular resistance in patients with progressive *EGFR* and *ALK*-driven lung cancer in a public system. *First Author: Carly C. Barron, University of Toronto, Toronto, ON, Canada*

Background: Repeat molecular profiling, except to detect *EGFR* T790M, is not routinely performed in Canadian patients with lung cancer progressing on *EGFR* tyrosine kinase inhibitors (TKIs). We performed genomic profiling on post-progression biopsies in patients with stage IV non-small cell lung cancer (NSCLC) and known *EGFR/ALK* aberrations treated with TKIs to identify resistance mechanisms, evaluate options for subsequent treatment, and to assess clinical trial eligibility and costs. **Methods:** From Feb 2018-Aug 2020, post-progression tumour biopsies from consenting patients at a major cancer centre underwent genomic profiling (ThermoFisher OCA v3.0 including hotspots, fusions, and copy number variations in 161 cancer-associated genes). Outcomes of interest were the identification of resistance mutations, actionable targets, clinical trial eligibility (per clinicaltrials.gov), and costs. **Results:** Thirty-two patients consented to the study. Most, 84% (n = 27), had successful testing completed while 16% (n = 5) had insufficient tissue. Median age of the cohort was 56 yrs, 59% (n = 16) were female, 74% (n = 20) were never-smokers, 81% (n = 22) had ECOG performance status 0-1, and 67% (n = 18) were Asian. The majority, 81% (n = 22) had *EGFR* mutated NSCLC, and had progressed on EGFR TKIs (15 with previously identified T790M had progressed on osimertinib), and 19% (n = 5) had *ALK* fusions. Patients had received a median of 2 prior lines of targeted therapy prior to re-biopsy (IQR 1.5,3). One patient had evidence of small cell transformation and associated *TP53* and *RB1* mutations, 11% (n = 3) had acquired *EGFR* C797S mutations, and 11% (n = 3) had acquired *ALK* resistance point mutations (G1202R n = 2, I1171N n = 1). Genomic profiling identified additional actionable targets in 19% of patients (n = 5: *MET* exon 14 skip mutation n = 1, *MET* amplification n = 2, *BRAF* V600E n = 2). Overall, 33% (n = 9) patients had management-changing resistance mechanisms identified (small cell transformation n = 1, actionable targets n = 5, *ALK* inhibitor resistance = 3). New clinical trial options based on genomic profiling results were identified for 67% (n = 18) of patients. Incremental costs for repeat genomic profiling were approximately $880 CAD per case. **Conclusions:** Molecular profiling upon development of resistance to targeted therapy in our cohort revealed actionable resistance mechanisms for over a third of patients and clinical trial options for 67%. These incremental benefits for patients highlight the importance of routine molecular profiling in the setting of acquired TKI resistance in lung cancer. Research Sponsor: Princess Margaret Cancer Foundation OSI Pharmaceuticals Foundation Chair.

3127 **Poster Session**

Landscape of *KRAS^{G12C}*, associated genomic alterations, and interrelation with immuno-oncology (IO) biomarkers. *First Author: Mohamed E. Salem, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Sotorasib has shown promising activity in cancer patients (pts) specifically harboring the *KRAS^{G12C}* mutation. Response rates vary significantly by tumor type, suggesting *KRAS^{G12C}* pathogenesis may be cancer-type-dependent. **Methods:** We retrospectively analyzed de-identified records of 79,004 pts with various cancer types that underwent Tempus xT and xF next generation sequencing assays. Fisher's exact test was used to analyze the association between cancer subtypes and *KRAS* variants. Logistic regression was used to study co-mutations between *KRAS^{G12C}* and other oncogenes, as well as the association between *KRAS* variants and IO biomarkers. False discovery rate-adjusted P-value (FDR *P*) was used for multiple testing. **Results:** In total, 13,578 (17.4%) tumors harbored *KRAS* mutations, of which 1,632 were G12C; 750 *KRAS* wild-type (WT) tumors gained *KRAS* mutation on follow-up testing, with 79 harboring G12C. The most frequent *KRAS* variants across all cancers were G12D, G12V, G12C, and G13D (see Table). The distribution of *KRAS* variants significantly varied by cancer type, with G12C and G12D being the most prevalent in non-small cell lung (NSCLC) and colorectal (CRC) cancers, respectively. G12C was most prevalent in NSCLC (9%), appendiceal cancer (3.9%), CRC (3.2%), tumors of unknown origin (1.6%), and pancreatic cancer (1.3%). Compared to non-G12C, G12C was more frequently identified in females (56% vs. 51%, FDR $P = 0.0005$), smokers/prior smokers (85% vs. 56%, FDR $P < 0.0001$), and pts > 60 years of age (73% vs. 63%, FDR $P = 0.0006$). While no G12C tumors exhibited *BRAF^{V600E}* co-mutations, *BRAF$^{non\text{-}V600E}$* co-mutations were seen in 3.1% of pts. Significant differences were observed in genomic alterations co-occurring with G12C compared to non-G12C (e.g., *STK11* (20.6% vs 6%), *KEAP1* (15.4% vs 4.6%), *SMAD4* (7.2% vs 19%), and *PDGFRA* (5.8% vs 3%); FDR $P < 0.0001$). However, G12C and oncogene co-mutations were not significantly different between NSCLC and CRC, except for *KEAP1* (FDR_$P = 0.04$). Compared to non-G12C and WT, G12C tumors were associated with TMB-High and PD-L1 over expression but were less likely to have MSI-H status (FDR $P < 0.0001$; Table). **Conclusions:** Our data suggest that *KRAS* variants significantly differ by cancer type. Tumors harboring KRAS^{G12C} were significantly associated with high TMB and PD-L1 overexpression. KRAS^{G12C} mutation appeared to be associated with smoking status. These results may guide future therapeutic strategies. Research Sponsor: None.

Cancer Type		KRAS Variant	Prevalence (%)	FDR P Value
		G12C	17.9	
	TMB-High (> 10 m/MB)	non-G12C	8.4	< 0.0001
		WT	10.5	
		G12C	54	
	PD-L1 Overexpression	non-G12C	40.4	< 0.0001
		WT	41.5	
All Cancers		G12C	1.2	
	MSI-High	non-G12C	2.9	< 0.0001
		WT	1.9	
		G12D	29.5	
	Top	G12V	23	
	Variants	G12C	11.9	
		G13D	6.5	
		G12C	36.8	
NSCLC	Top	G12V	19.2	< 0.0001*
	Variants	G12D	14.5	
		G12A	6.3	
		G12D	29.9	
CRC	Top	G12V	20	
	Variants	G13D	15.8	
		G12C	7	

Comparison of the *KRAS* variant distribution in NSCLC vs CRC*.

3128 **Poster Session**

The impact of clinical decision making in a molecular tumor board at a tertiary care center. *First Author: Meena Sadaps, Cleveland Clinic, Cleveland, OH*

Background: Multidisciplinary molecular tumor boards were first established with the onset of precision oncology (PO), as many clinicians were unfamiliar with the interpretation and incorporation of the information into clinical practice. PO has since rapidly evolved and integrated itself into standard of care practices for most cancer patients, yet molecular tumor boards have not grown accordingly and in fact some have been discontinued. There remains a paucity of data in regards to the value and impact of molecular tumor board discussions themselves. We previously reported on our longitudinal experiences in PO (*Sadapset al*, 2018), focusing on the therapeutic impact of matched therapy. Here, we report on the utility of our molecular tumor board in clinical decision making. **Methods:** We conducted a retrospective review of patients seen at Cleveland Clinic with a solid tumor malignancy who had large panel, next-generation-sequencing (NGS) performed via any commercial platform from November 2019-January 2021. Cases were filtered through a local therapeutic algorithm and then reviewed individually. Initial review was performed by a core genomics committee comprised of 2 oncologists and 2 genetic counselors. Interesting and/or complex cases were flagged for discussion at our bimonthly molecular tumor board, which is regularly attended by medical oncologists, pathologists, genetic counselors, bioinformaticians, and patient care coordinators. Data analyzed included categorization of treatment recommendations and the percentage of cases for which initial recommendations were changed based on tumor board discussion. **Results:** Of 782 total cases, 575 (73.5%) had a clinically relevant genomics tumor board (GTB) recommendation as compared to 51.7% from our previously reported study. 16.7% of patients had on label recommendation(s) and 86.4% had off label/ clinical trial recommendation(s). 179 (22.9%) patients were recommended for genetic counseling (GC). During our bimonthly GTB, we discussed 173 (22.1%) of these cases. Of the discussed cases, the most common tumor types were hepatobiliary (18.5%), lower gastrointestinal (17.3%), and breast (16.2%). Topics of discussion at GTB included such things as pathologic/histologic/molecular testing, prioritization of available trials, appropriateness of an off label therapy, and need for a genetics consult. Discussion at GTB resulted in a change in treatment recommendation in 63 (36.4%) cases. **Conclusions:** Discussions from multidisciplinary molecular tumor board impacted treatment decisions for our patients. Referral to GC was also common and should be considered an integral part of somatic sequencing review. Molecular tumor boards remain a crucial platform for treatment guidance and clinical management, especially given the increase in "actionability" over the years due to newly discovered targets and targeted therapies in this rapidly evolving field. Research Sponsor: None.

3129 **Poster Session**

The mutational landscape of the sensitivity of cancer to ionizing radiation. *First Author: Priyanka Gopal, Northwestern University, Chicago, IL*

Background: The impact of common or rare gene mutations on the sensitivity of cancers to ionizing radiation remains largely unknown. We conducted a systematic, arrayed (single variant per well) profiling effort to identify gene mutations that alter cellular sensitivity to radiation and validated some of our findings using a clinical cohort of patients who received thoracic radiotherapy alone. **Methods:** Candidate mutations were prioritized on the basis of genotype-phenotype associations from our previously completed large-scale cancer cell line irradiation profiling study (doi: 10.1038/ncomms11428), location within conserved protein domains, and functional impact (MutationAssessor). We used site-directed mutagenesis to generate mutant clones (2 clones per variant) and transferred the ORFs into lentiviral vectors in SV40 lung primary immortalized cells (BEAS2B). For clinical validation, an IRB-approved study was used to identify patients treated with lung radiotherapy alone. 197 patients with primary (stage I–IV) or recurrent lung cancer and patients with other cancer types and solitary metastases or oligometastases to the lung were included. Death without evidence of local failure was treated as a competing event, and Fine and Gray regression modeling was used to examine potential predictors of local failure. **Results:** Over 600 cancer variants were tested in ~1200 experimental replicates, comprising 91 genes. We identified known and new radioresistant and radiosensitive variants involved in several cellular functional categories including cellular signaling, cytoskeleton, cell cycle, apoptosis, DNA methylation, and DNA repair. Variants that conferred resistance in BEAS2B cells were significantly more likely to confer resistance in TERT-HU1 and NCI-H520 cells, suggesting that most functional variants are cellular context indifferent. Variants under somatic oncogenic selection (hotspot mutants) were significantly more likely to confer resistance to radiation. Several infrequent cancer variants (< 1% prevalence in cancer), including those in ERBB3, SMAD4, TGFBR1, VHL, CTNNB1, and MAP2K1, conferred radiation resistance. Some genes (e.g. KEAP1) demonstrated significant intragenic allelic variation in the magnitude of conferred resistance and other genes (e.g. CTNNB1) displayed both resistance and sensitivity in a protein domain-dependent manner. KRAS (resistant; HR 2.23; $P = 0.02$) and CTNNB1 exon 3 (sensitive; HR 0.3; $P = 0.04$) mutants conferred resistance and sensitivity, respectively, to radiotherapy in our clinical cohort. **Conclusions:** We report on a large-scale profiling effort to identify mutant alleles that govern radiation survival. Our results reveal new insights into potentially actionable determinants of tumor sensitivity to radiotherapy and accelerate clinical validation of common and rare gene mutations that impact radiation sensitivity. Research Sponsor: U.S. National Institutes of Health.

3130 **Poster Session**

Clinically advanced pelvic squamous cell carcinomas (pSCC) in men and women: A comprehensive genomic profiling (CGP) study. *First Author: Philippe E. Spiess, Moffitt Cancer Center, Tampa, FL*

Background: Given that the clinical manifestations, disease course, and treatment options for pSCC differ between tumor types, we performed CGP to examine possible genomic differences. **Methods:** 1,741 clinically advanced pSCCs including 230 penile (penSCC), 17 male urethral (murthSCC), 125 male anal (manSCC), 7 female urethral (furthSCC), 263 vulvar (vulSCC), 822 cervical (crvSCC), and 277 female anal SCCs (fanSCC) underwent hybrid capture-based CGP to evaluate all classes of genomic alterations (GAs). Tumor mutational burden (TMB) was determined on up to 1.1 Mb of sequenced DNA and microsatellite instability (MSI) was determined on up to 114 loci. PD-L1 expression was determined by IHC (Dako 22C3). **Results:** HPV-16/18 detection was lowest in murthSCC and vulSCC and highest in manSCC, fanSCC, and crvSCC. *TP53* GAs were inversely associated with HPV status. *PIK3CA* GA frequency varied (22-43%). DNA-damage response (DDR) GAs (e.g., *BRCA1/2*, *ATM*, others) were low (< 1-3%) throughout. Cell-cycle GAs were most frequent in external cases (penSCC, furthSCC, vulSCC). MTOR pathway GAs (*PTEN*, *FBXW7*) were the most frequently identified "actionable" GAs. *FGFR3* GA were present in >5% of murthSCC, crvSCC, and fanSCC; other receptor-tyrosine kinase (RTK) targeted options were 1% in *BRAF*/*ERBB2*. *NOTCH1* GAs were present in > 15% of penSCC and vulvSCC. TMB ≥10 mut/Mb was >15% in manSCC, fanSCC, and crvSCC. PD-L1 low expression was > 25% in all pSCC except crvSCC and high expression was > 18% in all pSCC except urthSCC and manSCC. **Conclusions:** Despite similar histology, pSCC differ widely in GAs and HPV status. *PIK3CA* is the most frequent "targetable" GA followed by MTOR pathway and cell cycle; RTK targets are extremely rare. PARP inhibitor options appear low given the infrequent finding of DDR GAs. Anti-PD(L)1 could be considered in a number of cases based on TMB>10 mut/Mb and PD-L1 expression. Research Sponsor: Foundation Medicine Inc.

	Penile SCC (n = 230)	Male Urethral SCC (n = 17)	Male Anal SCC (n = 125)	Female Urethral SCC (n = 7)	Vulvar SCC (n = 263)	Cervical SCC (822)	Female Anal SCC (n = 277)
Median age (range), yrs	65 (24-92)	63 (40-76)	60 (26-89+)	61 (49-75)	64 (29-89+)	51 (22-89+)	62 (35-89+)
HPV-6/11 (low risk)	3%	0%	6%	0%	1%	< 1%	1%
HPV-16/18 (high risk)	29%	12%	73%	43%	25%	68%	90%
BRCA1	< 1%	0%	3%	0%	2%	1%	2%
BRCA2	3%	0%	3%	0%	2%	3%	1%
***CCND1* amplification**	15%	6%	6%	0%	18%	3%	3%
***CD274* amplification**	6%	0%	2%	0%	5%	4%	4%
***CDKN2A/B* inactivation**	47%/9%	24%/0%	15%/8%	43%/14%	37%/7%	4%/2%	4%/2%
***EGFR* amplification**	14%	12%	1%	0%	10%	3%	2%
FBXW7	8%	6%	15%	29%	7%	14%	16%
FGFR3	3%	6%	2%	0%	1%	5%	5%
NOTCH1	17%	0%	8%	0%	17%	5%	
PIK3CA	22%	30%	34%	29%	23%	43%	38%
***PTEN* inactivation**	4%	6%	7%	0%	5%	13%	18%
***TERT* promoter mutation**	44%	13%	10%	29%	56%	16%	5%
TP53	55%	59%	18%	43%	65%	10%	9%
MSI High	1%	0%	< 1%	0%	< 1%	1%	1%
Median TMB	3.8	3.8	5.0	3.8	3.8	5.0	5.0
TMB >10 mut/Mb	15%	6%	24%	0%	11%	27%	22%
PD-L1 Low Positive (1-49%)	25%	28%	(n = 60) 50%	(n = 4) 75%	(n = 143) 43%	(n = 22) 9%	(n = 112) 48%
PD-L1 High Positive (≥50%)	34%	14%	18%	0%	33%	27%	22%

3131 **Poster Session**

Partitioning of cancer therapeutics in nuclear condensates. *First Author: Isaac Klein, Dana Farber Cancer Institute, Milton, MA*

Background: The molecules of the cell are compartmentalized into membrane- and non-membrane-bound organelles. Many non-membrane-bound organelles are phase-separated biomolecular condensates with distinct physicochemical properties that can absorb and concentrate specific proteins and nucleic acids involved in discrete biochemical processes. We reasoned that selective condensate partitioning might also occur with small molecule drugs whose targets occur within condensates, and that the therapeutic index and efficacy of such compounds might therefore relate to their ability to partition into condensates. **Methods:** To study the behavior of drugs within condensates, these were modeled in cells and in vitro with purified proteins and visualized by fluorescent confocal microscopy. The functional outcomes of condensate partitioning were queried in cells. **Results:** We found that cisplatin, tamoxifen, JQ1, THZ1, and mitoxantrone are concentrated in specific protein condensates in vitro, and that this occurs through physicochemical properties independent of the drug target. A screen of a chemically diverse fluorescent probes and mutant-protein condensates demonstrated that pi-system interactions between aromatic moieties in the protein and small molecule govern concentration in condensates. These results show that clinically important drugs partition into specific protein condensates in vitro by virtue of defined chemical properties, thereby altering their local concentration. In vitro droplet assays revealed that cisplatin is selectively concentrated in transcriptional condensates, and that this ability is required for efficient platination of target DNA. In cell studies revealed that cisplatin preferentially targets DNA contained within MED1 condensates, and disrupts the genetic regulatory elements that compose phase-separated transcriptional condensates. Live cell imaging demonstrated that transcriptional condensates are dissolved by cisplatin, whereas other condensates remain intact. **Conclusions:** Our results show that antineoplastic drugs partition selectively into biomolecular condensates, that this can occur through physicochemical properties independent of their molecular targets, and that drug activity may occur through condensate-related mechanisms. These results have implications for development of efficacious cancer therapeutics; effective target engagement will depend on factors such as drug partitioning in condensates. Assays of the type described here may thus help optimize condensate partitioning, target engagement, and the therapeutic index of drugs for cancer treatment. Research Sponsor: ASCO, NIH, Private, Other.

3132 **Poster Session**

The genomic landscape of gene fusions across solid tumors and clinical outcome of targeted therapies: A real-world retrospective analysis. *First Author: Yumeng Zhang, Hematology/Oncology Fellowship, Moffitt Cancer Center, Tampa, FL*

Background: Oncogenic gene fusions can be observed across numerous solid tumor types with therapies targeting fusion events emerging as important treatment modalities. The occurrence of rare fusion events and response to targeted therapy inclusive of off-label drug use has not been fully elucidated. We describe a real-world (RW) landscape of gene fusions in solid tumors and treatment outcomes of targeted therapies. **Methods:** Patients with solid tumors harboring a gene fusion or rearrangement were retrospectively identified through review of a clinical molecular database housing sequencing data on 6,800 patients from a single-center between 1/1/2015 – 12/31/2019. Patients who received targeted therapy for gene fusions were divided into three arms: off-label, on-label, and clinical trial use. Clinical characteristics were summarized using descriptive statistics. Overall survival (OS) and Progression free survival (PFS) between the three arms were compared using the Kaplan-Meier estimates. **Results:** A total of 336 (4.9%) patients had a fusion positive solid tumor with 197 (2.9%) having a fusion event predicted to be oncogenic and could be targeted with a drug. Thirty different cancer types had targetable fusions with the three most common types being lung adenocarcinoma (41%), glioblastoma (10.2%), and melanoma (7.1%). The most common observed targetable fusions included *ALK* (21.3%), *RET* (11.7%), *ROS1* (9.1%), and *FGFR2* (8.1%). A total of 71 patients received targeted therapy; 37 (52%) received therapies on-label, 20 (28%) off-label, and 14 (20%) on-trial (Table). The median PFS was 4 months for off-label, 16 months for on-label, and 9 months for on trial-therapy (p=0.02). The median OS was 8 months for off-label, 51 months for on-label, and 11 months for on-trial therapy (p=0.001). Seven out of twenty patients (35%) in the off-label group had PFS for at least 6 months. Three patients had a response for more than one year. However, higher toxicity related discontinuation rate was observed (30%, 8%, 7% for off-label, on-label, and on-trial, p=0.03). **Conclusions:** Off-label targeted therapy had shorter PFS and OS when compared to on-label therapy. However, 35% patients in the off-label group had at least 6 months PFS. Off-label therapy remained a valuable option for patients who were not candidate for clinical trials or with rare fusions. Further studies are needed to determine which patients are most likely to benefit from targeting gene fusion events. Research Sponsor: None.

Clinical Factor	Off Label n=20	On Label n=37	On Trial N=14	P value
Male Gender	50%	43.2%	42.9%	0.28
Mean age at the time of therapy	64 (32-81)	53 (27-76)	54 (40-77)	0.012
Former Smokers, %	13 (65)	9 (24.3)	6 (43)	0.03
Median number of prior therapies	2	1	1	0.733
Progression Free Survival (month)	4	16	9	0.02
Overall Survival (months)	8	51	11	0.001
Discontinuation rate due to toxicity	30%	8%	7%	0.03

3133 **Poster Session**

Differential response rates in early-phase cancer clinical trials (EPCCT). *First Author: Rozana Abdul Rahman, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: The primary objective of EPCCT (phase I and non-randomised phase II trials) is to determine the safety and tolerability of new therapeutic agents. Response rates (RR) in these trials have typically been reported at around 10-15%. Increasingly RR and survival outcomes are now investigated in EPCCT as primary or secondary objectives. **Methods:** Retrospective data analysis was performed on patients (pts) enrolled onto an EPCCT between January 2018 and December 2019 at The Christie NHS Foundation Trust, UK. Data on demographics, prior systemic treatment, sites of disease, performance status, comorbidities, types of therapy, RR, progression free survival (PFS), and overall survival (OS) were collected. Statistical analyses were performed with univariable and multivariable models. Objective response rate (ORR) was defined as the proportion of pts with complete response (CR) and partial response (PR). Duration of response (DOR) was from initial response to progressive disease (PD). Disease control rate (DCR) was defined as CR+PR+ stable disease (SD). **Results:** A total of 247 pts were treated across 46 EPCCTs. Median age 61 years; 57% female. Sixty-six percent of pts had ≥2 lines of treatment and the majority were ECOG PS 0/1 (98%). Eighty-one percent of pts had ≥2 sites of metastatic disease, and 13 major tumour types were included. Monotherapy trials (159 pts) were predominantly targeted therapies (TT; 60%), or immunotherapies (IO; 20%). Combination therapy trials (88 pts) were TT-based (68%) or IO-based (32%). Data for RR analyses was available for 231 pts. ORR across all trials was 15% (CR 2%) and DCR was 63%. The median DOR was 8.3 months (mos) (95% CI: 7.0 – 9.7) with 28% of pts responding for >6 mos and 7% for >12 mos. ORR in pooled IO treated pts was 27%, DCR was 65% with sustained response >6 mos seen in 37% of these pts. ORR in pooled TT treated pts was 9.4%, DCR was 60% and sustained response > 6 mos seen in 25% of pts. ORR for IO v TT treated pts was significantly different, p=0.007 (pearson chi square), but no significant difference was seen for DCR. Median PFS for all patients was 5.0 mos (95% CI: 4.1 – 6.0) and OS was 10.4 mos (95% CI: 8.4 – 13.0). OS for those with a PR is not reached (HR for PR v PD, 0.006 (95% CI: 0.002 – 0.18). Pts with SD appear to have significantly better OS compared to those with PD (14.6 v 4.2 mos, HR 0.2 (95% CI: 0.1 – 0.3). Multivariable Cox proportional hazards analysis for OS was significant for male gender (HR 1.9, p=0.002), presence of liver metastasis (HR 2.0, p=0.001), low Hb (HR 0.8, p=0.03) and log (LDH) (HR 1.9, p<0.001). **Conclusions:** Two-thirds of pts enrolled on EPCCTs benefitted in terms of DCR with significant OS improvement in those with PR and SD. Higher ORR were seen in pts receiving IO-based treatments however DCR was similar in IO and TT pts. Gender, presence of liver metastases, Hb count and LDH level contributed significantly to survival differences. Research Sponsor: None.

3134 **Poster Session**

A phase Ib trial of alpelisib and weekly cisplatin in patients with solid tumor malignancies. *First Author: Erica S Tsang, University of California San Francisco, San Francisco, CA*

Background: The PI3K pathway may represent a mechanism to overcome cisplatin resistance, particularly in human papilloma virus (HPV)-associated tumors. We conducted a phase Ib trial of alpelisib and cisplatin for patients with solid tumor malignancies and HPV-associated tumors in the dose expansion cohort. **Methods:** Patients with advanced solid tumors were enrolled in this phase Ib open label study (NCT02620839). Dose escalation followed standard 3+3 design. Two different weekly doses of cisplatin (30 and 35 mg/m^2) were evaluated with escalating doses of alpelisib, administered daily during a 21-day cycle. The primary objective was to determine the maximum tolerated dose (MTD) and recommended phase II dose. Secondary objectives included determining the objective response rate (ORR), median progression-free survival (PFS), and characterizing the safety profile. **Results:** 23 patients were enrolled in this study between September 2016-August 2018. Median age was 57 years (range 37-83), and 57% of patients were female. Tumor sites included prostate (22%), cervical (13%), endometrial (13%), breast (9%), anal (9%), penile (9%), and other (26%). 91% of patients had > 3 lines of prior therapy, with 74% who previously received a platinum. Median duration of treatment was 8.7 weeks (range 1-57.5). The MTD was alpelisib 250 mg daily with weekly cisplatin 30 mg/m^2. 9 patients discontinued the study during cycle 1 due to an adverse event without progression. There were 3 DLTs, all of which were grade 4 hyperglycemia: 2 at alpelisib 250 mg and 1 at alpelisib 300 mg. Treatment-related grade 3-4 toxicities included hyperglycemia (13%), rash (13%), neutropenia (9%), anemia (4%), thrombocytopenia (4%), neuropathy (4%), and diarrhea (4%). Any grade nephropathy occurred in 17%. Dose reductions and/or interruptions were required in 61% of patients. There was a significant decrease in administered cisplatin dose intensity (33.8%) with a planned weekly cisplatin dose of 35 mg/m^2 and alpelisib 250 mg. In contrast, dose intensity ranged from 55-85% for other dose levels with an intended cisplatin dose of 30 mg/m^2. Dose expansion was not conducted due to significant early and cumulative toxicity. Of the 14 patients with post-baseline assessment available, ORR was 29%, with all 4 patients demonstrating partial response and 7 patients (50%) with stable disease. Of the 4 responders, tumor sites included 2 endometrial cancers, cervical neuroendocrine carcinoma, and penile SCC, and 3 were platinum-refractory. Median PFS measured 3.1 months (95% CI 1.3-4.1). 5 of 21 patients had *PIK3CA* mutations, with no difference in PFS (p= 0.76). **Conclusions:** While alpelisib and cisplatin demonstrated responses among patients with solid tumor malignancies, the combined adverse event profile presented significant dose intensity limitations. Future prospective studies are planned using carboplatin and alpelisib to improve the toxicity and tolerability. Clinical trial information: NCT02620839. Research Sponsor: Novartis.

3135 **Poster Session**

Cancer and COVID-19: A proposed mechanism with therapeutic interventions. *First Author: Yan Leyfman, Penn State Hershey College of Medicine, Hershey, PA*

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel betacoronavirus that causes the respiratory illness coronavirus disease 2019 (COVID-19). COVID-19 ranges in severity from an asymptomatic viral infection to life-threatening cases of pneumonia, acute respiratory distress syndrome (ARDS), multi-organ damage and sepsis. Cancer patients are at an increased risk of severe SARS-CoV-2 infection due to their immunocompromised status. We propose a mechanism by which SARS-CoV-2 infection causes multiple organ damage through IL-6-mediated inflammation and hypoxia-induced cellular metabolic alterations leading to cell death. Hypoxia is also induced by malignancy due to alterations in metabolism, resulting in greater IL-6 secretion. **Methods:** To highlight the possible effect of active cancer on the likelihood of hypoxia in COVID-19, we analyzed the correlation between cancer status and the severity of COVID-19 from the COVID-19 and Cancer Consortium data registry. For cancer status, we looked at progressive cancer and remission of cancer only – those being the two extremes of presence and absence of uncontrolled cancer. Similar to prior studies, the severity of COVID-19 was used as an indication of hypoxia. **Results:** We observed a 24% positive deviation between expected and actual number of patients with actively progressing cancer who had hypoxic COVID-19 (moderate to severe), and a 26.9% negative deviation between expected and actual number of patients with active cancer who had no hypoxia with COVID-19 ($p<0.0001$). Conversely, for patients with cancer in remission, there was only a +5.8% and -5.1% deviation between expected and actual number of patients who did not have hypoxia and who had hypoxia, respectively. **Conclusions:** These results suggest that in the presence of poorly controlled malignancy, there is an increased likelihood of hypoxia in patients with COVID-19, thereby exacerbating downstream cytokine release syndrome and contributing to prolonged systemic inflammatory injury. Appreciating this pathway, future therapies can be developed to target the pathogenesis of both diseases and prevent progression, as seen with mesenchymal stem cells, which demonstrated a 91% overall survival and 100% survival in patients younger than 85 years old at one month after a single treatment. Research Sponsor: None.

	Cancer in Remission	Cancer Progressing
Expected Non-Hypoxic	526	113
Actual Non-Hypoxic	557	82
Expected Hypoxic	589	126
Actual Hypoxic	558	157

3136 **Poster Session**

Genome-wide cfDNA fragmentation in patients with cancer and other diseases. *First Author: Jacob Carey, Delfi Diagnostics, Baltimore, MD*

Background: Genome-wide cfDNA fragmentation patterns have previously been demonstrated to distinguish with high sensitivity and specificity between plasma samples from individuals with and without cancer. **Methods:** To further evaluate cfDNA fragmentation as a blood-based screening test for cancer, we have evaluated these genomic features in patients with and without cancer who have been diagnosed with other common comorbidities. For this study, we have used low coverage (1-2x) whole genome sequencing to analyze plasma samples from 412 patients referred to an advanced diagnostic center due to unexplained signs and symptoms associated with cancer. **Results:** Seventy-seven of these patients were ultimately diagnosed with one of sixteen different solid cancers, 68 with cardiovascular disease, 48 with diabetes, as well as other comorbidities. We used the DELFI approach (DNA evaluation of fragments for early interception) to measure the cfDNA fragmentation in plasma from all 412 patients included in the study using a cross-validated machine learning model. Patients with cancer could be distinguished from non-cancer individuals with high sensitivity and specificity (AUC = 0.92), including for common cancers such as colorectal and lung cancer. **Conclusions:** These data support the hypothesis that abnormal cfDNA fragmentation is a consequence of unregulated mitoses in cancer cells and can be distinguished from fragmentation patterns of individuals with co-morbidities. Research Sponsor: Delfi Diagnostics.

3137 **Poster Session**

Outcomes of active cancer patients with COVID-19 infection treated with COVID-19 neutralizing monoclonal antibodies. *First Author: Justin Shaya, University of California San Diego, Moores Cancer Center, La Jolla, CA*

Background: Treatment with COVID-19 (C19) neutralizing monoclonal antibodies (mAbs), including bamlanivimab and casirivimab/imdevimab, has been associated with decreased rates of C19-related hospitalizations in high-risk patients. Patients with active cancer are at high-risk for C19 complications and currently are candidates for C19-mAbs. Little is known about C19-related outcomes with mAb therapy in cancer patients. Here, we examine the outcomes of a cohort of active cancer patients infected with C19 who were treated with C19-neutralizing mAbs. **Methods:** Retrospective, single center cohort of patients with active cancer and mild-moderate C19 infection not requiring hospitalization who were treated with either bamlanivimab or casirivimab/imdevimab. Active cancer was defined as a solid or hematologic malignancy diagnosed within 90 days of C19 diagnosis or recurrent/metastatic disease. The primary endpoint was the rate of C19-related hospitalization. Secondary endpoints included the rate of C19-related mortality and adverse events associated with mAb therapy. **Results:** We identified 38 active cancer patients with C19 who were treated with mAbs. Median age was 65 years (range 20-89) and 47.4% (N = 18) had a hematologic malignancy. Among the cohort, 73.7% (N = 28) were on an anti-cancer therapy at the time of C19 diagnosis: targeted therapy (n = 18), cytotoxic chemotherapy (N = 5), immunotherapy (n = 3), or hormonal therapy (n = 2). 42.1% (N = 16) received bamlanivimab and 57.9% (N = 22) received casirivimab/imdevimab. Median time from C19 diagnosis to mAb infusion was 2 days (range 0-6 days). With a median follow-up of 21 days (range 7-71), 7.9% (N = 3) required hospitalization for C19-related complications. Median time from mAb infusion to hospitalization was 25 days (range 5-29). C19-related deaths occurred in 5.3% (N = 2) of the cohort. No significant adverse events were reported with either mAb formulation. **Conclusions:** Among a cohort of high-risk cancer patients treated with mAbs, rates of hospitalization and mortality due to C19 were low compared to previously described rates among active cancer patients. Key limitations of this analysis include the lack of a control group for comparison and a small sample size given the recent emergency use authorization of these agents. Given the high mortality rate of active cancer patients with C19, these data support the use of mAbs in cancer patients with C19. Research Sponsor: None.

3138 **Poster Session**

Patients with advanced solid cancers treated with ERK inhibitors exhibit pseudo-progession in lymphatic nodes. *First Author: Reem Abo-Zahrah, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: ERK1/2 signaling is often overactivated in cancer, especially in patients with molecular alterations activating the MAPK pathway. MAPK pathway inhibition can result in the increase of CD8+ and CD4+ T-cells and decreased expression of immunosuppressive cytokines. **Methods:** This is a retrospective study of 52 patients with advanced solid cancers and oncogenic alterations in the MAPK pathway, who were treated in phase I/II clinical trials with five different single agent ERK1/2 inhibitors at MD Anderson Cancer Center. We reviewed serial PET and/or CT imaging obtained before therapy, on therapy, and after therapy completion. We evaluated dynamic changes in the lymphatic nodes (LN) in the context of overall response per RECIST 1.1 and other outcomes. **Results:** Of the 52 patients, 19 (37%) patients were evaluated with serial PET/CT and 33 (63%) with serial CT imaging only. Of the 19 patients evaluated with PET/CT, 12 (63%) demonstrated increased FDG uptake in LN compared to pre-treatment imaging (LN enlargement, n = 9; no LN enlargement, n = 3) discrepant from the known target and non-target lesions. These 12 patients were on therapy with ERK inhibitors (11 at doses $>$ recommended phase 2 dose [RP2D]) for a median of 3.6 months (range, 1.8-12 months) with a best response per RECIST 1.1. as follows: partial response, n = 1; stable disease (SD), n = 10; progressive disease (PD), n = 1. Of interest, in 6 of those 12 patients, FDG uptake in LN decreased or resolved after treatment discontinuation. Further, one patient had a biopsy of an emerged LN, which showed lymphocytic infiltrate without tumor cells. Of the 33 patients evaluated with CT only, 5 (15%) demonstrated increased size of LN discrepant from the known target and non-target lesions compared to pre-treatment imaging. These 5 patients were on therapy with ERK inhibitors (all at doses $<$ RP2D) for a median of 1.4 months (range, 1.1-3.5 months) with a best response per RECIST 1.1. as follows: SD, n = 2; PD, n = 3. Of interest, in 2 of those 5 patients, size of LN decreased or resolved after treatment discontinuation. In addition, one patient had a biopsy of an emerged LN, which showed lymphoid aggerates without tumor cells. **Conclusions:** Our data suggest that treatment with ERK inhibitors can result in activation of the lymphatic nodes, which can manifest as pseudo-progression. This can lead to an inconclusive assessment of their therapeutic benefit and further suggests exploration of the potential synergistic effects with immune therapy. Research Sponsor: U.S. National Institutes of Health.

3139 **Poster Session**

Germline polymorphisms in genes maintaining replication fork to predict the efficacy of oxaliplatin and irinotecan in metastatic colorectal cancer (mCRC) patients enrolled in MAVERICC trial. *First Author: Hiroyuki Arai, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Protection of replication forks is critical for the survival of cancer cells. Chemotherapeutic drugs such as oxaliplatin and irinotecan can impede the progression of replication forks by inducing DNA lesions, which cause fork collapse and generate double-strand breaks. We hypothesized that functional genetic variants in genes involved in the maintenance of replication forks may predict the efficacy of cytotoxic drugs in mCRC patients. **Methods:** We analyzed genomic and clinical data from MAVERICC, a phase II trial which compared mFOLFOX6 and FOLFIRI in combination with bevacizumab in untreated mCRC patients. Genomic DNA extracted from blood samples was genotyped using an OncoArray (Illumina, Inc., San Diego, CA, USA). Candidate six missense single nucleotide polymorphisms (SNPs) (*SLFN11* rs9898983, *SLFN11* rs12453150, *RPA1* rs5030749, *MCM3* rs2230240, *TIMELESS* rs2291739, and *TIMELESS* rs774047) were tested for association with progression-free survival (PFS) and overall survival (OS), using Cox proportional hazards model. To confirm the predictive value, the treatment-by-SNP interaction was tested. **Results:** A total of 324 patients were available for the SNP analyses (mFOLFOX6 plus bevacizumab arm [OHP arm]: $n = 161$; FOLFIRI plus bevacizumab arm [IRI arm]: $n = 163$). In the OHP arm, univariable analysis showed a significantly better PFS in patients with G/G genotype of *TIMELESS* rs2291739 compared to those with any A allele, and in patients with T/T genotype of *TIMELESS* rs774047 compared to those with any C allele. However, neither of these SNP's associations were confirmed by multivariable analysis: *TIMELESS* rs2291739 (any A allele vs G/G, hazard ratio [HR] = 0.60, 95% confidence interval [CI] = 0.31–1.17, $p = 0.12$) and *TIMELESS* rs774047 (any C allele vs T/T, HR = 0.74, 95% CI = 0.41–1.36, $p = 0.33$). In the IRI arm, univariable analysis showed a significantly worse OS in patients with G/G genotype of *TIMELESS* rs2291739 compared to those with any A allele, and in patients with T/T genotype of *TIMELESS* rs774047 compared to those with any C allele. Multivariable analysis confirmed the significant associations in these SNPs: *TIMELESS* rs2291739 (any A allele vs G/G, HR = 3.06, 95% CI = 1.49–6.25, $p < 0.01$) and *TIMELESS* rs774047 (any C allele vs T/T, HR = 2.95, 95% CI = 1.43–6.08, $p < 0.01$). Treatment-by-SNP interaction test confirmed the significant predictive value of both SNPs, both on PFS and OS. **Conclusions:** Germline polymorphisms in the *TIMELESS* gene involved in the protection of replication forks may predict efficacy of oxaliplatin and irinotecan in mCRC patients. Our novel findings warrant further validation studies. Research Sponsor: This work was supported by the National Cancer Institute [P30CA 014089 to HJL], Gloria Borges Wunder-Glo Foundation, Dhont Family Foundation, Daniel Butler Memorial Fund, Victoria and Philip Wilson Research Fund, San Pedro Peninsula Cancer Guild.

3140 **Poster Session**

Initiative for Molecular Profiling and Advanced Cancer Therapy (IMPACT2): Challenges and Opportunities in Conducting an MD Anderson Randomized Study in Precision Oncology. *First Author: Henry Hiep Vo, The University of Texas MD Anderson Cancer Center, Department of Investigational Cancer Therapeutics, Houston, TX*

Background: Precision oncology is associated with favorable outcomes in selected patients with cancer. Our first IMPACT trial (IMPACT1) demonstrated that in sequential patients with advanced cancer who had tumor molecular testing and participated in phase I clinical trials, matched targeted therapy (MTT) was associated with superior rates of response, progression-free survival (PFS) and overall survival compared with those of patients who received non-MTT. Despite the statistical significance for these outcomes, the study was non-randomized. Recognizing that it would be difficult to randomize patients we nonetheless undertook IMPACT2, a phase 2 randomized study to determine whether patients treated on the basis of tumor genomic alterations have longer PFS compared to those whose treatment is not selected on the basis of molecular alteration analysis. **Methods:** Patients with metastatic cancer undergo a tumor biopsy and genomic profiling. Patients are presented at tumor board and are offered to be randomized between two arms: MTT or non-MTT, when criteria (biomarker present, available clinical trial, eligibility criteria met, insurance approval) are met. In April 2019, we amended the trial to include a "patient-preference" cohort for each arm. Patients who decline randomization are offered choice of arm (ClinicalTrials.gov: NCT02152254). The primary analysis will use both randomized and patient-preference cohorts based on a Bayesian hierarchical model that "borrows" from the patient-preference cohorts to the extent to which its PFS agrees with that in the randomization cohort. **Results:** The key barriers randomizing patients with actionable molecular alterations are patient-related (advanced, metastatic setting requiring immediate intervening therapy; decline in performance status, organ function; or death); drug-related (FDA-approved drug available; or unavailable MTT against key driver biomarker) or financial (no insurance coverage of MTT; lack of patient resources to participate in trials). As the study spans over a few years, some investigational agents that were considered non-MTT at the time of treatment assignment were later proven to be MTT (e.g., immunotherapeutic agents targeting high tumor mutational burden); and/or were approved by the FDA. **Conclusions:** Although randomized trials have been considered the gold standard in drug development, such studies in the advanced metastatic setting are complicated. The benefit of Precision Oncology has been exemplified in individual patients who were treated with biomarker-selected therapy. The adaptive design of IMPACT2 enables patient randomization despite the evolving tumor biomarkers and the plethora of investigational drugs. IMPACT2 provides insights for the development of cancer genome-based medicine. Outcomesfor randomized patients are awaited. Clinical trial information: NCT02152254. Research Sponsor: Foundation Medicine and Tempus, U.S. National Institutes of Health, Donor funds from Jamie's Hope, Mr. and Mrs. Zane W. Arrott, and Mr. and Mrs. Steven McKenzie for Dr. Tsimberidou's Personalized Medicine Program. This work was also supported in part by the National Institutes of Health/National Cancer Institute award number P30 CA016672 (University of Texas MD Anderson Cancer Center), the Clinical Translational Science Award 1UL1 TR003167; the Cancer Prevention Research Institute of Texas (CPRIT) Precision Oncology Decision Support Core (RP150535), and the Sheikh Khalifa Bin Zayed Al Nahyan Institute for Personalized Cancer Therapy.

TPS3141 **Poster Session**

A phase 2 basket trial of combination therapy with trastuzumab and pertuzumab in patients with solid cancers harboring HER2 amplification (JUPITER trial). *First Author: Ryo Kudo, Tokyo Medical and Dental University hospital, Bunkyo-Ku, Japan*

Background: The human epidermal growth factor receptor 2 (HER2) gene amplification and mutations have emerged as oncogenic drivers and therapeutic targets not limited to breast and gastric cancers, but also in a variety of cancers. However, even if an actionable gene alteration is found, the incidence of HER2 amplification in these cancers is less than 5%. Despite its considerable therapeutic potential, the evidence is not yet mature enough for use as treatment in clinical practice. To address this unmet clinical need, we have designed an organ-agnostic basket trial, which covers a variety of solid cancers harboring HER2 amplification. **Methods:** JUPITER trial is a Japanese multicenter, single-arm, phase 2 basket study of combination therapy with trastuzumab and pertuzumab. Patients with solid cancers harboring HER2 amplification, who have progressed with standard treatment, or rare cancers for which there is no standard treatment, are eligible. Types of cancer include bile duct, urothelial, uterine, ovarian, and other solid cancers that HER2 amplification is detected by comprehensive genomic profiling using next-generation sequencing technology. Target sample size is 38. All enrolled patients receive combination therapy with trastuzumab and pertuzumab every 3 weeks until disease progression, unacceptable toxicity, death, or withdrawal of informed consent. Response assessment using RECIST version 1.1 is performed at weeks 9 and 17, followed by every 12 weeks. The primary endpoint is the objective response rate, and secondary endpoints are progression-free survival, overall survival, duration of response, and safety. In total, 40 patients were enrolled by June 2020. Data fix is scheduled in September 2021. Trial registration: jRCT2031180150 Clinical trial information: jRCT2031180150. Research Sponsor: Japanese Agency for Medical Research and Development.

TPS3142 **Poster Session**

A phase 1b, open-label, single-arm study of cofetuzumab pelidotin (a PTK7-targeting antibody-drug conjugate) in patients with PTK7-expressing, recurrent non-small cell lung cancer (NSCLC). *First Author: Eric S Schaefer, Highlands Oncology Group, Fayetteville, AR*

Background: Protein tyrosine kinase 7 (PTK7) is a highly conserved receptor tyrosine kinase involved in the Wnt signaling pathway and is overexpressed in multiple cancer types, including non-small cell lung cancer (NSCLC). Cofetuzumab pelidotin (ABBV-647) is an anti-PTK7 antibody-drug conjugate comprising the hu6MO24 monoclonal antibody, a cleavable cysteine-reactive linker, and Aur0101 (an auristatin microtubule inhibitor). It has shown promising preclinical anti-tumor effects (Damelin et al. Sci Transl Med 2017;9[372]:eaag2611) and clinical activity with a manageable safety profile in a Phase 1 study in patients with advanced solid tumors, with promising anti-tumor activity noted in NSCLC (Sachdev et al. DOI: 10.1200/JCO.2018.36.15_suppl.5565). **Methods:** This open-label, single-arm, multicenter Phase 1b study (NCT04189614) will assess the anti-tumor activity and safety of cofetuzumab pelidotin in approximately 40 patients with PTK7-expressing, recurrent NSCLC. The primary objective is to assess the objective response rate of cofetuzumab pelidotin according to Response Evaluation Criteria in Solid Tumors version 1.1. Secondary objectives include the duration of response, progression-free survival, overall survival, and safety and tolerability. Pharmacokinetic and biomarker samples will also be collected throughout for analysis. Patients must be aged ≥18 years with an Eastern Cooperative Oncology Group performance status of 0–1 and have recurrent histologically confirmed NSCLC with PTK7-expressing tumor (using a validated immunohistochemistry assay). Patients must have progressed after treatment with a platinum-based chemotherapy doublet and an immune checkpoint inhibitor (for tumors without targetable genetic alterations), or a platinum-based chemotherapy doublet and targeted agent(s) (for tumors with targetable genetic alterations). Patients must also have received ≤2 prior lines of systemic therapy (≤3 prior lines for tumors treated with targeted agent[s] for genetic alterations), including no more than 1 line of systemic chemotherapy. Cofetuzumab pelidotin (2.8 mg/kg) is administered intravenously every 3 weeks until the patient experiences disease progression, intolerable toxicity, or other study treatment discontinuation criteria are met. The study commenced on February 13, 2020 and enrollment is ongoing. Clinical trial information: NCT04189614. Research Sponsor: AbbVie.

TPS3143 **Poster Session**

TCF-001 TRACK (Target Rare Cancer Knowledge): A national patient-centric precision oncology trial for rare cancers. *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Many rare cancers are understudied, and affected patients often have few if any standard treatment options and limited access to clinical trials. Comprehensive genomic profiling (CGP) is a robust tool to efficiently identify the genomic alterations of cancer and can be applied to study rare tumors. The promise of this technology is to simultaneously enhance our understanding of diverse rare tumors and find matched therapies to benefit the individual patient in real-time. The COVID19 pandemic has challenged the "trial-centric" clinical trial infrastructure. Novel "patient-centric" trials are needed, especially for rare cancers. TRACK is a decentralized, patient advocacy-initiated trial that aims to establish whether patients with rare tumors and cancer of unknown primary can benefit from matched molecular therapy as dictated by their CGP results. **Methods:** This is a national open label, non-randomized, multi-center (includes community and academic centers) pragmatic study in rare tumors (<6 cases per 100,000 persons per year) and cancer of unknown primary. All participants will have tumor tissue and blood analyzed by CGP (FoundationOneCDx and FoundationOneLiquidCDx). A Virtual Molecular Tumor Board (VMTB) will convene to identify targeted treatment recommendations for participants with genomic alterations. Overall, 400 participants will be enrolled to achieve the goal of 100 patients matched to genomically informed treatment, utilizing remote consenting to ensure study access regardless of geographic location. The primary feasibility endpoint is the percent of participants who receive a molecularly matched treatment after recommendation from the VMTB. The primary efficacy endpoint is the progression-free survival (PFS) among participants who received the molecularly matched treatment. Secondary endpoints include the percent of participants with genomic alterations, overall response rate, response duration, overall survival, clinical benefit rate (SD > 6 months; PR; CR), and high-grade toxicities (as available) of matched targeted therapy. Exploratory endpoints include matching rates; understanding genomic correlates of response; concordance rates between CGP from tissue and blood, time-to-treatment failure, and the impact of the cancer treatment from the patient perspective (via ESAS-FS, a validated patient-reported outcomes (PRO) instrument). All eligible and enrolled patients, regardless of whether receiving matched treatment or not, will be followed for a minimum of one year in a uniform way such that the treatment efficacy and outcomes can be assessed in standard formats. The study is open with six patients enrolled at time of submission. Clinical trial information: NCT04504604. Research Sponsor: TargetCancer Foundation, Inc, Pharmaceutical/Biotech Company.

TPS3144 **Poster Session**

A phase 1 study of SGN-B6A, an antibody-drug conjugate targeting integrin beta-6, in patients with advanced solid tumors (SGNB6A-001, Trial in Progress). *First Author: Amita Patnaik, START, San Antonio, TX*

Background: The extracellular matrix (ECM) plays an important role in solid tumor pathogenesis and is a major focus of research and therapeutic targeting. Integrin beta-6 is a cell surface receptor that interacts with the ECM to mediate cellular adhesion. Integrin beta-6 is overexpressed in numerous solid tumors and its expression is a negative prognostic marker in cancers including colorectal, non-small cell lung, gastric, and cervical cancers. SGN-B6A is an investigational vedotin, an antibody-drug conjugate directed against integrin beta-6 to selectively deliver the cytotoxic agent monomethyl auristatin E, which binds tubulin and induces apoptosis. In multiple xenograft models, treatment with SGN-B6A resulted in tumor growth delay and regression in tumor volume when compared to non-binding control. **Methods:** SGNB6A-001 (NCT04389632) is a phase 1, first-in-human, open-label, multicenter study designed to evaluate the safety, tolerability, pharmacokinetics (PK), and antitumor activity of SGN-B6A in adults with select advanced solid tumors. Primary objectives are to evaluate the safety and tolerability of SGN-B6A in patients with advanced solid tumors, identify the maximum tolerated dose, and identify a recommended dose and schedule. The study has 2 parts: dose escalation (Part A) and dose expansion with multiple disease-specific cohorts and a biology cohort (Part B). SGN-B6A will initially be given by intravenous infusion on Days 1, 8, and 15 of 21-day cycles. The dose escalation (Part A) will be conducted using the modified toxicity probability interval method to determine a dose that demonstrates a dose-limiting toxicity rate of 25% with a 5% margin. The dose and schedule for Part B will be determined based on evaluation of safety, PK, and pharmacodynamic biomarkers. Response evaluations will be based on RECIST v1.1. Patients must be ≥18 years old and have histologically or cytologically confirmed metastatic or unresectable solid malignancy within one of the following tumor types: non-small cell lung cancer, head and neck squamous cell cancer, breast cancer, esophageal cancer, ovarian cancer, cutaneous squamous cell cancer, exocrine pancreatic adenocarcinoma, bladder cancer, cervical cancer, or gastric cancer. After an appropriate dose and schedule are determined in Part A, safety and preliminary antitumor efficacy of SGN-B6A will be evaluated in indication-specific cohorts (Part B). This study is ongoing in sites across North America and Europe. Clinical trial information: NCT04389632. Research Sponsor: Seagen Inc.

TPS3145 **Poster Session**

Phase I trial of acoustic cluster therapy (ACT) with chemotherapy in patients with liver metastases of gastrointestinal origin (ACTIVATE study). *First Author: Udai Banerji, The Institute of Cancer Research and The Royal Marsden, London, United Kingdom*

Background: Response to existing chemotherapeutics (chemo) can be limited by exposure, itself limited by systemic toxicity. Interstitial fluid pressure can impede transport of drugs with, in some cases, <5% of systemic chemo penetrating the target tumour. ACT is an innovative platform technology using sonopermeation to induce ultrasound (US) mediated targeting of therapeutic agent of choice by co-administration of an emulsion of microbubble-microdroplet clusters (PS101) for intravenous injection. Dual-frequency US is applied to tumor tissue to concentrate the drug through expansion and oscillation of the clusters, increasing tumoral penetration. Early pre-clinical models of ACT indicate significant increase in uptake of co-administered product at the US targeted site and have demonstrated enhanced efficacy outcomes with co-administered ACT across a range of cancer models. All studies showed significant benefit in disease response and tumour regression/inhibition versus drug alone. The combination of US, microbubbles and chemo has been shown to be feasible in a clinical setting using commercially available equipment with no additional toxicities. This first in human study will primarily investigate the safety and tolerability of PS101 in combination with chemo together with any differential response in ACT-treated versus control lesions to identify the phase 2 recommended dose. **Methods:** This is an open label non-randomised study with central blinded assessment of tumor response. The study comprises two parts: Part 1, a dose escalation in a 3+3 design followed by dose expansion in Part 2. Patients with advanced solid tumors with liver metastases for whom FOLFOX/FOLFIRI is considered an appropriate treatment option are eligible for Part 1 (n=6-12); two separate cohorts of patients with liver metastases, one with metastatic colorectal cancer eligible for 1L or 2L standard of care (SOC) FOLFOX/FOLFIRI (n=25) and one with metastatic pancreatic ductal adenocarcinoma (n= 6) eligible for SOC gemcitabine-nab-paclitaxel will be treated in Part 2. The starting dose of PS101 is 20 μL/kg with a maximum feasible dose of 40 μL/kg. In Part 1, after sentinel administration of PS101 for PK profiling and toxicity assessment, patients receive PS101 (given as i.v. bolus x 3) in combination with FOLFOX or FOLFIRI and US (to one target lesion) in four q2w cycles. The DLT evaluation period comprises the PK-assessment period plus two cycles of ACT plus chemo. Patients receive a further two cycles of ACT and chemo prior to evaluation of tumor lesions by CT/MRI at the Week 8 timepoint. Assessment is made of the target lesion and the pre-defined control lesions outside of the US field. Part 1 has enrolled 5 patients without DLT, with part 2 expected to start in mid-2021. Clinical trial information: NCT04021277. Research Sponsor: Exact Therapeutics.

TPS3146 **Poster Session**

First-in-human phase 1 trial (DRAGON) of SRK-181, a potential first-in-class selective latent TGFβ1 inhibitor, alone or in combination with anti-PD-(L)1 treatment in patients with advanced solid tumors. *First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Transforming growth factor-beta 1 (TGFβ1) is a key mediator of primary resistance to programmed cell death protein 1 (PD-1) pathway blockade. SRK-181 is a fully human, highly potent and selective monoclonal antibody that inhibits latent TGFβ1 activation. SRK-181 has minimal or no binding to latent TGFβ2 and TGFβ3 isoforms or to active TGFβ growth factors. In mouse tumor models (bladder, melanoma, and breast cancer), SRK-181 in combination with anti-PD1 therapy overcame primary anti-PD-1 resistance and showed survival benefit. No cardiotoxicities (valvulopathy) were observed with SRK-181 in 4-week GLP nonclinical toxicology studies. Thus, the potency and selectivity of SRK-181 may overcome PD-1 inhibitor resistance and toxicity of non-selective TGFβ pathway approaches. **Methods:** The DRAGON trial NCT04291079 is an ongoing multicenter, open-label, phase 1 study of SRK-181 administered by IV infusion every 3 weeks (Q3W) alone or in combination with anti-PD-(L)1 in patients (pts) with locally advanced or metastatic solid tumors. The study comprises 3 parts: Part A of the study follows a standard 3+3 dose escalation trial design to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antitumor activity of SRK-181 alone (Part A1) or in combination with the anti-PD-(L)1 agent that is approved for the respective tumor indication (Part A2). Part A1 and Part A2 will determine maximum tolerated dose (MTD) or maximum administered dose and Recommended Phase 2 Dose (RP2D) for Part B. Part B (expansion phase) will evaluate combination treatment of SRK-181 with anti-PD-(L)1 in pts with non-small cell lung cancer, urothelial carcinoma (UC), melanoma or other advanced solid tumors, to confirm the tolerability of the RP2D and to evaluate the antitumor activity of combination treatment. Pts in Part A2 and Part B must have previously received an anti-PD-(L)1 therapy approved in their tumor indication and considered non-responders (best response of stable disease or disease progression) to anti-PD-(L)1 monotherapy. Pts in Part B must have received the most recent dose of the prior anti-PD-(L)1 within 6 months of study enrollment (9 months for UC cohort). Safety, PK, PD and efficacy data will be collected and monitored throughout the study. Detailed translational PD and predictive biomarker studies for SRK-181 will include a novel digital pathology analysis of CD8 to assess the alteration of immune profile in tumor microenvironment and TGFb pathway biomarkers, such as quantitative analysis of tumor phospho-Smad2 and circulating levels of TGFb1 ligand. As of Feb 01 2021, dose escalation has proceeded to the highest planned dose of 2400 mg Q3W in Part A1 (monotherapy) and to 800 mg Q3W in Part A2 (anti-PD-(L)1 combination). Additional planned doses in Part A2 are 1600 mg and 2400 mg Q3W. Clinical trial information: NCT04291079. Research Sponsor: Scholar Rock Inc.

TPS3147 **Poster Session**

Phase 1b dose escalation study to evaluate the safety, tolerability, pharmacokinetics, and preliminary efficacy of GS-3583, a FLT3 agonist Fc fusion protein, in patients with advanced solid tumors. *First Author: Joshua Brody, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Productive antitumor immune responses in nonclinical models depend on a type of dendritic cell (DC), conventional DC subtype 1 (cDC1), which in the context of cancer, primes tumor-reactive T cells through presentation of tumor-derived antigens. FMS-related tyrosine kinase 3 ligand (FLT3L) is a hematopoietic growth factor that binds to and activates FLT3 on terminally differentiated DCs. Activated FLT3 promotes proliferation, inhibits cell death, and is required for the differentiation, expansion, and maintenance of DCs in peripheral and lymphoid organs. GS-3583 is a fusion protein composed of the extracellular domain of recombinant human FLT3L fused to an engineered fragment crystallizable (Fc) region of human immunoglobulin G4. GS-3583 has PK properties that support sustained cDC in patients and potential combination with established immunotherapies. This phase 1b, open-label, multicenter, dose-finding study will evaluate safety, tolerability, PK, and preliminary efficacy of GS-3583 monotherapy in patients with advanced solid tumors (NCT04747470). **Methods:** Approximately 33 adults aged ≥18 years with a histologically or cytologically confirmed locally advanced or metastatic malignant solid tumor that is refractory to or intolerant of standard therapy or for which no standard therapy is available will be enrolled. The study employs a 3+3 dose escalation design in which GS-3583 is administered intravenously for up to 52 weeks or until progressive disease or unacceptable toxicity. Up to five dose escalation cohorts have been planned. The maximum tolerated dose is the highest dose with incidence of DLT in < 33% of 6 or more patients in the first 28 days of GS-3583 dosing; recommended phase 2 dose will be determined. Assessments include safety, PK, pharmacodynamics including cDCs, immunogenicity, and efficacy by RECIST 1.1 in CT/MRI imaging conducted every 8 weeks. Accrual at approximately 3-4 centers in the US is ongoing. Clinical trial information: NCT04747470. Research Sponsor: Gilead Sciences, Inc.

TPS3149 **Poster Session**

Phase 1 and phase 2a, first-in-human (FIH) study, of DRP-104, a broad glutamine antagonist, in adult patients with advanced solid tumors. *First Author: Melissa Lynne Johnson, Sarah Cannon Research Institute, Nashville, TN*

Background: Dependence of cancer cells on glutamine has made glutaminolysis an attractive therapeutic target in cancer. Prior clinical trials evaluating glutamine analogues for the treatment of cancer were abandoned due to lack of efficacy and/or tolerability. DON (6-Diazo-5-oxo-L-norleucine) is an irreversible inhibitor of several enzymes that utilize glutamine as a metabolic substrate. In addition to direct anti-tumor efficacy, inhibition of glutamine metabolism in the tumor microenvironment has been shown to improve T-cell activation and tumor infiltration, increasing anti-tumor immune responses. As such, combining DON with an immune checkpoint inhibitor (ICI), has strong preclinical rationale. The investigational product DRP-104 (sirpiglenastat) is an inactive prodrug of DON designed to limit systemic DON exposure while targeting glutamine dependence in tumor cells. **Methods:** A phase 1/2a, FIH, multi-center, non-randomized, multi-cohort, open-label study of DRP-104 is currently open to accrual for patients with advanced solid tumors. This study will be conducted in 4 parts: A) Dose Escalation of IV and subQ DRP-104 (Run-In phase followed by modified Continual Reassessment Method) to define MTD/RP2D. Primary objective of dose escalation is to assess the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary antitumor activity of DRP-104 as a single agent; B) Dose Expansion of IV and subQ DRP-104 for safety assessment while primary objective is to select and recommend phase 2 DRP-104 route of administration; C) Phase 2a at recommended MTD/RP2D of selected route of DRP-104 in 2 patient cohorts: patients with locally advanced/metastatic NSCLC with KEAP1, NFE2L2 and/or STK11 mutation and patients with unresectable or metastatic SCCHN, in order to assess the safety, tolerability and preliminary antitumor activity of DRP-104 as a single agent; D) Phase 2a at recommended MTD/RP2D of selected route of DRP-104 in combination with atezolizumab in adult patients with advanced solid tumors previously treated with an ICI, in order to assess the safety, tolerability and preliminary antitumor activity of DRP-104 in combination with atezolizumab; DRP-104 IV is infused TIW over 1 hour infusion for 2 consecutive weeks followed by 1 week off. DRP-104 subQ is administered BIW weekly. Study is currently open with 6 IV patients (Run-In Phase completed and at Dose Level 4) and 3 subQ patients at Dose Level 1 at time of submission. Clinical trial information: NCT04471415. Research Sponsor: Dracen Pharmaceuticals, Inc.

TPS3150 **Poster Session**

Subcutaneous delivery of amivantamab in patients with advanced solid malignancies: PALOMA, an open-label, multicenter, dose escalation phase 1b study. *First Author: Matthew Krebs, Division of Cancer Sciences, Faculty of Biology, Medicine and Health, The University of Manchester and The Christie NHS Foundation Trust, Manchester Academic Health Science Centre, Manchester, United Kingdom*

Background: Amivantamab, an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity, targets activating/resistance EGFR mutations and MET mutations/amplifications. Amivantamab has demonstrated antitumor activity in patients (pts) with EGFR-mutant NSCLC and also in pts with EGFR tyrosine kinase inhibitor-resistant disease. The recommended phase 2 dose (RP2D) is 1050 mg (1400 mg, ≥80 kg) administered as intravenous (IV) infusions weekly (QW) for the first 28-day cycle and every other week (Q2W) thereafter. A subcutaneous (SC) formulation of amivantamab has the potential to reduce pt and physician burden by reducing administration time. The safety and pharmacokinetics (PK) of amivantamab administered SC ± recombinant human hyaluronidase (rHuPH20) will be evaluated. **Methods:** PALOMA is an ongoing phase 1b dose escalation study of amivantamab SC in pts with advanced solid tumors that may derive benefit from EGFR or MET-directed therapy (NCT04606381). Pts must have progressed on standard of care therapy for metastatic disease, be ineligible for, or have refused current standard therapies. The primary endpoints are trough concentration at the end of QW dosing and safety of SC administration. The objective of part 1 is to evaluate the feasibility, safety, and PK of SC administration of a low concentration (50 mg/mL) formulation of amivantamab alone (Ami-LC) or admixed with rHuPH20 (Ami-LC-MD). Approximately 8 pts will be enrolled to receive either 1050/1400 mg amivantamab SC using Ami-LC-MD (Cohort 1a) or Ami-LC (Cohort 1b) QW in cycle 1 and Q2W thereafter. The objective of part 2 is to evaluate the safety and PK of SC administration of a high concentration (160 mg/mL) formulation of amivantamab alone (Ami-HC) or with rHuPH20 (Ami-HC-CF) and to determine a dose, schedule, and formulation for SC administration that achieves similar exposure as observed at the RP2D of amivantamab IV, with acceptable safety. Pts enrolled in part 2 will initially receive 1050/1400 mg amivantamab SC using Ami-HC-CF in Cohort 2a or Ami-HC in Cohort 2b. ≤10 pts may be enrolled in either cohort. Additional cohorts of ≤10 pts may be enrolled to support dose, schedule, and formulation selection as guided by safety and PK observations in earlier cohorts. To mitigate infusion related reactions (IRR), medication with steroid, paracetamol, and antihistamine will be given pre-infusion and as clinically indicated post-infusion. Safety assessments include monitoring adverse events, laboratory abnormalities, vital signs, IRR, and injection site reactions. Blood samples will be collected to assess PK, pharmacodynamics, and immunogenicity. A Study Evaluation Team composed of investigators and sponsor representatives will review safety and PK data to make decisions about dose escalation and cohort expansion throughout the conduct of the study. Clinical trial information: NCT04606381. Research Sponsor: Janssen R&D.

TPS3151 **Poster Session**

SGNTUC-019: Phase 2 basket study of tucatinib and trastuzumab in previously treated solid tumors with HER2 alterations (trial in progress). *First Author: Tom Stinchcombe, Duke Cancer Institute, Durham, NC*

Background: Tucatinib (TUC) is a highly selective HER2-directed TKI approved in combination with trastuzumab (Tras) and capecitabine (Cape) for HER2 overexpressed/amplified (HER2+) metastatic breast cancer (BC), based on a statistically significant and clinically meaningful PFS, OS, and ORR benefit over Tras and Cape. In xenograft models of HER2+ and HER2-mutated (HER2-mut) tumors, dual targeting of HER2 with TUC and Tras showed superior activity to either agent alone. While various HER2-directed agents have been evaluated in HER2+ and HER2-mut tumors, there are no approved HER2 therapies outside of breast and gastric cancers. The SGNTUC-019 basket study is evaluating TUC combined with Tras in patients (pts) with HER2+ or HER2-mut locally-advanced unresectable or metastatic solid tumors. **Methods:** SGNTUC-019 (NCT04579380) is a multi-cohort, open-label, international phase 2 study. Eligible pts must have progressed on or after the last systemic therapy for advanced disease. Metastatic cervical cancer: must have received platinum-based chemotherapy ± bevacizumab; hormone receptor positive (HR+) HER2-mut BC: must have received a prior CDK4/6 inhibitor. Pts must be ≥18 years old, with ECOG PS ≤1, adequate hepatic, hematological, renal, coagulation, and cardiac function, and no prior HER2-directed therapy (except Tras for uterine serous carcinoma). For eligibility, HER2 alterations can be demonstrated by HER2+ in tumor tissue by prior IHC/ISH (IHC 3+/signal ratio ≥2.0 or gene copy number >6), or by HER2 amplification/mutation in a prior or on-study NGS assay of ctDNA or prior tissue NGS assay. Pts with HER2+ disease will be enrolled in cohorts for cervical, uterine, biliary tract, and urothelial cancers, non-squamous NSCLC, and other solid tumors (except GEC, BC, and CRC). Pts with HER2-mut disease will be enrolled in cohorts for non-squamous NSCLC, BC, and other solid tumors. Except for solid tumor and BC cohorts, 12 RECIST 1.1 evaluable pts will be enrolled in each cohort. If ≥2 responses are observed, the cohort will be expanded to a total of 30 pts. Other solid tumor and BC cohorts will enroll 30 pts in a single stage. If justified, additional HER2+ or HER2-mut disease-specific cohorts may be opened. Approximately 162-270 pts are planned. The primary objective is antitumor activity in each cohort, with confirmed ORR per investigator as primary endpoint, and disease control rate, duration of response, PFS, and OS as secondary endpoints. Pts will receive TUC 300 mg orally twice daily and Tras 8 mg/kg IV on Cycle 1 Day 1 and 6 mg/kg q21 days from Cycle 2 Day 1. HR+ BC pts will also receive fulvestrant 500 mg IM every 4 weeks and C1 D15. Disease assessments per RECIST 1.1 will occur q6 weeks for 24 weeks, then q12 weeks. TUC PK will be evaluated in all pts in Cycles 2-6. QoL is evaluated q2 cycle using EQ-5D-5L. Sites are open in the US; EU and Asia will be opened. Enrollment began in Dec 2020. Clinical trial information: NCT04579380. Research Sponsor: Seagen Inc.

TPS3152 **Poster Session**

Trial in progress: Phase 1a/b study of PF-07284890 (brain-penetrant BRAF inhibitor) with/without binimetinib in patients with BRAF V600-mutant solid tumors. *First Author: Vivek Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: BRAF inhibitors have transformed treatment (Tx) for patients (pts) with BRAF V600-mutant cancers, but long-term efficacy is limited by disease progression in the brain, due to poor brain penetration. PF-07284890 is a potent, selective, highly brain-penetrant, small-molecule inhibitor of BRAF V600 mutations. This first in human study will assess the PK, safety, and preliminary clinical activity of PF-07284890, as monotherapy and in combination with binimetinib (MEK inhibitor), in pts with BRAF V600-mutated advanced solid tumors with/without brain metastases. **Methods:** Phase 1a/1b open-label, multicenter, dose-finding study (NCT04543188). Pts will be ≥18 y with a histologically confirmed advanced/metastatic solid tumor including primary brain tumor (PBT), confirmed BRAF V600 mutation, and presence/absence of brain involvement. Pts will have disease progression despite prior Tx without alternative Tx options. Pts with brain metastasis/PBT > 4 cm and/or symptomatic brain disease will be excluded initially, but allowed based on emerging PK. Phase 1a is a dose escalation study of PF-07284890 (monotherapy and combination). ~35 pts will be enrolled to determine maximum tolerated dose (MTD) and/or recommended dose for expansion (RDE) of PF-07284890 (monotherapy and combination). Cohorts of 2-4 pts will be treated at each dose level of PF-07284890 until MTD/RDE determination (PF-07284890 starting dose: 50 mg QD; binimetinib 45 mg BID). Bayesian Logistic Regression Model will be used to inform dose level decisions. At least 6 pts each for monotherapy and combination will be treated at MTD/RDE. Phase 1a primary endpoints: Cycle 1 dose-limiting toxicities; MTD/RDE; AEs; lab abnormalities; and dose interruptions, modifications and discontinuations due to AEs. Secondary endpoints include PK parameters and overall response (RECIST; overall and intracranial; RANO for PBT). Phase 1b is a dose expansion and drug-drug interaction study to further evaluate PF-07284890 + binimetinib. Cohorts 1-4 (~40 pts each) will enroll pts based on tumor type, brain involvement (asymptomatic/symptomatic), and prior Tx. Cohort 5 (~20 pts) will include pts with any solid tumor including leptomeningeal metastases. Cohort 6 (~10 pts) will assess the effect of PF-07284890 + binimetinib on CYP3A activity using midazolam as a substrate. Phase 1b primary endpoint: overall response (RECIST; overall and intracranial; RANO for PBT). Secondary endpoints: duration of response; progression-free survival; disease control rate; time to response; overall survival; AEs; lab abnormalities; and dose interruptions, modifications and discontinuations due to AEs; and PK parameters. For both Phase 1a and 1b, Tx will continue until disease progression, unacceptable toxicity or patient refusal. Study began enrolling pts in January 2021 and is ongoing. Clinical trial information: NCT04543188. Research Sponsor: Pfizer.

TPS3153 **Poster Session**

A first-in-human phase I study of ATR inhibitor M1774 in patients with solid tumors. *First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ataxia telangiectasia and Rad3-related (ATR) protein kinase plays a critical role in the DNA damage response by sensing and responding to DNA replication stress, and by inducing cell cycle arrest to prevent aberrant replication and mitotic catastrophe. Based on extensive preclinical and limited clinical evidence, ATR inhibition is a promising treatment strategy as monotherapy for patients with advanced tumors harboring synthetically lethal conditions, such as alternative lengthening of telomeres (ALT) and inactivating mutations in *ARID1A* and *ATM*. M1774 is a potent, selective, orally administered ATR inhibitor that has been shown to exert antitumor activity in patient-derived xenograft tumors and acute myeloid leukemia xenograft tumors that express the ATR inhibition sensitizing mixed lineage leukemia fusion protein. This study (NCT04170153) aims to evaluate the safety and tolerability, maximum tolerated dose, recommended dose for expansion (RDE) and pharmacokinetics (PK) of M1774 (part A1), the effect of food on M1774 PK (part A2), and the efficacy of M1774 in patients with tumors harboring selected mutations (part A3). An additional objective is to assess the pharmacodynamics of M1774 by measuring relative changes in baseline p-CHK1 and γ-H2AX expression in paired tumor biopsies and serial blood samples. **Methods:** Patients aged ≥18 years, with an Eastern Cooperative Oncology Group performance status ≤1, adequate baseline hematological, renal and hepatic function, and with locally advanced or metastatic disease refractory to standard therapy are eligible. Patients with tumors bearing loss-of-function (LoF) mutations (determined by site testing or a central trial assay) in *ARID1A*, *ATM*, or *ATRX* and/or *DAXX* as ALT status surrogate markers; and measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, will be enrolled in part A3. In the dose escalation phase (part A1 [open]), 18–24 patients are due to receive M1774 at a starting dose of 5 mg once daily. Dose escalation is determined by the safety monitoring committee and guided by a Bayesian 2-parameter logistic regression model. The preliminary food assessment (part A2) will follow a randomized two-sequence two-period crossover design in which ≤12 patients will be randomized (1:1) to receive a single dose of M1774 on Day –7 at the RDE (determined in part A1) in either a fed or fasted condition. After the food assessment, patients will subsequently receive M1774 according to the part A1 dosing schedule. In the preliminary efficacy study (part A3), patients (n = 20–24 for each of the three planned cohorts) with tumors harboring LoF mutations in the genes for *ARID1A, ATM, ATRX* and/or *DAXX*, will receive M1774 at the RDE. The primary efficacy endpoint is overall response (RECIST). The study is open and currently recruiting. Patients have been enrolled to seven cohorts in part A1 with no DLTs observed; dose escalation is ongoing. Clinical trial information: NCT04170153. Research Sponsor: Merck KGaA, Darmstadt, Germany.

TPS3154 **Poster Session**

Tumor-agnostic precision immuno-oncology and somatic targeting rationale for you (TAPISTRY): A novel platform umbrella trial. *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Actionable genomic alterations are found in many solid tumors in pediatric and adult populations. Identifying such alterations can match patients (pts) to genome-driven therapies. Although TRK and immune checkpoint inhibitor therapies have tumor-agnostic approval for *NTRK*-rearranged and tumor mutational burden (TMB)-high cancers, respectively, similar approvals remain an unmet need for other genome-driven cancers, limiting pt access to potentially active therapies. Platform master protocol studies leveraging comprehensive next-generation sequencing (NGS) are a pragmatic means of evaluating multiple genome-driven therapies in rare biomarker-selected populations. Contemporary study designs include adult and pediatric pts to expand care across age groups. **Methods:** TAPISTRY (NCT04589845) is a phase 2, global, open-label, multi-cohort study evaluating the efficacy and safety of targeted therapy or immunotherapy, as single agents or in combination, in pts with unresectable, locally advanced/metastatic solid tumors. Eligible pts have tumors that harbor genomic alterations or are TMB-high by NGS (Foundation Medicine or CLIA/equivalent-certified laboratory). General inclusion criteria: PD on prior treatment/no available acceptable treatment; measurable disease (by RECIST v1.1, RANO, INRC), adequate ECOG/equivalent PS and end organ function. Pts will be assigned to treatment according to eligibility criteria for biomarker-defined cohorts (Table). Pediatric pts may be enrolled if age-appropriate formulations/dosages are established. Samples will be taken for central NGS biomarker testing at baseline (tissue/blood), tumor assessments (blood) and at response/PD (optional tissue/blood). Tumor assessments (CT, MRI, PET) will be completed at baseline then every 6–8 weeks, depending on cohort. Primary endpoint: confirmed ORR by independent review committee (IRC; RECIST v1.1). Key secondary endpoints: ORR (by investigator [INV], per RECIST/INRC); DoR, CBR, PFS, time to CNS PD (by IRC and INV, per RECIST/INRC); intracranial efficacy (Cohorts A–D; per RANO [primary brain tumors]/RECIST [baseline CNS mets]); OS; patient-reported outcomes; safety; pharmacokinetics and immunogenicity (Cohorts D and F). Treatment will continue until PD, loss of clinical benefit, unacceptable toxicity, discontinuation or death. Target enrollment is 650 pts at 100+ sites based on screening 40,000+ pts; 3 pts enrolled as of 9 Feb 2021. Clinical trial information: NCT04589845. Research Sponsor: F. Hoffmann-La Roche Ltd.

Cohort	Biomarker	Drug	Age (yrs)	NSCLC	Primary CNS/mets
A	ROS1-f	Entrectinib	All	N	Y
B	NTRK1/2/3-f	Entrectinib	All	Y	Y
C	ALK-f	Alectinib	≥18	N	Y
D	High TMB	Atezolizumab	All	Y	Y
E	AKT1/2/3-m	Ipatasertib	≥12	Y	N
F	HER2-m	Trastuzumab emtansine	≥12	Y	N
G	MDM2-a, TP53 WT*	Idasanutlin	≥18	Y	N
H	Multiple PIK3CA-m	GDC-0077	≥12	Y	N

*Closed. Cohorts may be added/closed due to new evidence. a, amplification; f, fusion; m, mutation; WT, wild-type.

TPS3155 **Poster Session**

Alpha-T: An innovative decentralized (home-based) phase 2 trial of alectinib in *ALK*-positive (*ALK*+) solid tumors in a histology-agnostic setting. *First Author: Razelle Kurzrock, University of California San Diego, Moores Cancer Center, La Jolla, CA*

Background: Anaplastic lymphoma kinase (*ALK*) fusions are found in 3–8% of non-small cell lung cancers (NSCLC) and ~0.2% of other tumor types. Alectinib is a selective, CNS-active ALK tyrosine kinase inhibitor approved as first-line treatment for adults with advanced *ALK* fusion-positive (*ALK*-fp) NSCLC based on the phase 3 ALEX trial (NCT02075840; PMID 28586279). Preliminary evidence supports investigation of alectinib in a tumor-agnostic setting. ALK inhibitors have shown efficacy in *ALK*-fp tumor types other than NSCLC (PMIDs 29685646; 28977547; 30591488), with alectinib showing efficacy irrespective of *ALK* fusion partner and against *ALK*-activating mutations (PMIDs 29642598; 29559559). **Methods:** Alpha-T is a phase 2 open-label, single-arm trial (NCT04644315) with an innovative home-based remote design, currently enrolling adults with histologically confirmed, locally advanced/metastatic solid tumors (except lung cancer and cancers of unknown primary) harboring *ALK* fusions or selected mutations (*ALK*-mut; R1275Q, F1245C, F1174X). The decentralized design permits enrollment regardless of location, allows most assessments to be home-based and maintains the relationship between patients (pts) and their treating oncologist. Key inclusion criteria: no alternative or unsuitable to receive standard therapy; ECOG PS 0–2; adequate hematologic, renal and hepatic functions; no prior ALK inhibitor; measurable solid tumor (RECIST 1.1) or primary brain tumor (RANO); asymptomatic or stable CNS metastases permitted. Pts are identified via the Foundation Medicine Inc. (FMI) Precision Enrollment service. For any solid tumor identified as *ALK*+ (fusion/selected mutation) by next-generation sequencing in tissue/blood (F1 CDx/F1L CDx, FMI), the ordering oncologist is given trial details and can liaise with a Science 37 investigator. Pts receive 600mg oral alectinib twice a day with food until radiological PD, unacceptable toxicity, withdrawal of consent or death. Home-based assessments (eg, physical examination, blood sampling, questionnaire completion) are conducted in-person by a mobile nurse at baseline and every 4 weeks, with remote support from the Science 37 investigator via their telemedicine platform. Tumor assessments at screening and every 8 weeks are performed at a local radiology facility. Primary endpoint: confirmed ORR by investigator in pts with *ALK*-fp tumors (RECIST 1.1). Secondary endpoints: ORR by independent review facility (IRF); DoR and PFS; intracranial ORR and DoR (IRF); OS and safety. Descriptive analyses are planned for pts with *ALK*-mut tumors and primary brain tumors. Pharmacokinetics and biomarkers will be evaluated. Patient-reported outcomes will be assessed via the EORTC QLQ-C30 and EuroQoL EQ-5D-5L questionnaires. Target enrollment is 50 pts with *ALK*-fp tumors evaluable by RECIST. As of 9 Feb 2021, 1 pt is in screening. Clinical trial information: NCT04644315. Research Sponsor: F. Hoffmann-La Roche.

TPS3156 **Poster Session**

A phase 1/2 study with open-label, dose escalation phase followed by single-arm expansion at the maximum tolerated dose to assess the safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of NT219 injection alone and in combination with cetuximab in adults with advanced solid tumors and head and neck cancer. *First Author: Alberto Bessudo, California Cancer Care Associates for Research and Excellence, Encinitas, CA*

Background: NT219 is a small molecule, dual inhibitor of insulin receptor substrates (IRS) 1/2 and signal transducer and activator of transcription 3 (STAT3), effecting IRS1/2 degradation and inhibiting STAT3 phosphorylation. IRS1/2 and STAT3 are major signaling junctions regulated by various oncogenes, altered during epithelial to mesenchymal transition (EMT) and drug resistance, and play an important role in the tumor and its microenvironment. Patient derived xenograft (PDX) models have shown that inhibition of both IRS and STAT3 is essential to overcome targeted epidermal growth factor receptor inhibitor (EGFRi) resistance, and NT219 has demonstrated efficacy as monotherapy and in combination with immune oncology therapies. Particularly, both pathways have been found to be relevant in resistance to cetuximab in head and neck squamous cell carcinoma (HNSCC) PDX models. **Methods:** This phase 1/2 study (Clinical trial: NCT04474470) began in September 2020. The phase 1 component has a dose escalation arm of NT219 as a single agent at doses ranging between 3mg/kg and 50mg/kg in adult subjects with recurrent and/or metastatic solid tumors enrolled in sequential dose cohorts of 3 to 6 subjects, in a conventional 3+3 design aiming to establish the safety of single agent NT219. Following the conclusion of follow up on the third dose cohort, an additional dose-escalation arm of NT219 in combination with standard dose cetuximab will be opened in patients with recurrent and/or metastatic HNSCC and colorectal cancer, aiming to establish the safety of NT219 when combined with cetuximab. In the expansion phase, 29 patients will be enrolled at the recommended phase 2 dose in combination with standard dose cetuximab in patients with recurrent/metastatic HNSCC. The primary objectives of the trial are safety, tolerability, MTD, and RP2D and preliminary efficacy of NT219 alone and in combination with cetuximab. Measurements of STAT3 and IRS1/2 phosphorylation in biopsy specimens and TILs will be evaluated as potential biomarkers. NT219 provides a first-in-class treatment for patients with resistant neoplastic disease. The current trial will provide important data in patients with recurrent/metastatic cancers, particularly, HNSCC on the effects of the inhibition of STAT3 and IRS1/2 pathways as a novel therapeutic approach. Clinical trial information: NCT04474470. Research Sponsor: Purple Biotech Ltd.

TPS3157 **Poster Session**

Trial in progress: A phase 1-2 multicenter, open-label, dose-escalation and dose-expansion study to evaluate the safety, pharmacokinetics, pharmacodynamics, and antitumor activity of ABN401 in patients with advanced solid tumors. *First Author: Dae Ho Lee, University of Ulsan College of Medicine, Asan Medical Center, Seoul, South Korea*

Background: c-MET (hepatocyte growth factor (HGF) receptor) overexpression, either by gene amplification, or mutation is associated with oncogenic transformation in numerous malignancies including lung, gastric, skin, renal, colorectal, and pancreatic cancers. ABN401 inhibits the activation of c-MET by reversibly interfering with the binding of c-Met tyrosine kinase to adenosine triphosphate (ATP) and blocking the receptor's downstream signaling that has demonstrated efficacy in NSCLC and gastric cancer in mouse xenograft and PDx models. This clinical trial is in progress in patients with advanced cancers. **Methods:** ABN401 is being evaluated in an open-label, non-randomized, dose-escalation (phase 1) study in patients with advanced solid tumors, and dose-expansion (phase 2) in patients with targeted indications and c-MET biomarker expression (NCT04052971). The phase 1 explores ascending daily doses of oral ABN401 monotherapy in 21-day cycles to identify the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D). A preplanned extension (pilot expansion) study has been initiated based on predefined positive efficacy signals at intermediate doses up to 10 NSCLC patients who have c-MET alteration. Once RP2D is determined, the phase 2 expansion of up to 10-29 patients in four specific tumor-type cohorts is planned, utilizing a Simon's optimal two-stage design to evaluate the clinical activity of ABN401. ABN401-001 study began enrolling patients in August 2019 and is ongoing in Korean and Australia. Dose escalation up to cohort 4 has been completed, enrollment to cohort 5 began in November 2020. AEs are assessed according to CTCAE v5. Tumor response is determined according to RECIST 1.1 criteria and safety findings reviewed by the DRC, which will determine the RP2D and MTD. Key Phase 1 eligibility criteria include 1) histological or cytological diagnosis of melanoma or any type of carcinoma or sarcoma and 2) refractory metastatic disease, or refractory locally advanced disease not amenable to local therapy. For the extension (pilot expansion) study, patients must have NSCLC with MET exon 14 skipping, MET amplification and/or c-MET overexpression. An exploratory study is being conducted for co-development of a companion diagnostic (CDx) system including a CTC device and ddPCR kit through liquid biopsy. Clinical trial information: NCT04052971. Research Sponsor: ABION.

TPS3158 **Poster Session**

First-in-man phase I clinical trial evaluating TTI-101, an orally bioavailable, small molecule inhibitor of STAT3, in patients with advanced solid tumors. *First Author: Apostolia Maria Tsimberidou, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that is a key signaling node and a master regulator of the key hallmarks of cancer, including tumor angiogenesis, resistance to apoptosis, metastasis, and immune evasion. STAT3 activation is observed in ~70% of all cancers and up to 95% of hepatocellular carcinomas (HCC). Thus, inhibition of STAT3 signaling is expected to have a therapeutic effect against a wide range of cancers. TTI-101 is a first-in-class, orally bioavailable, selective small molecule that binds STAT3 and prevents phosphorylation, homodimerization, nuclear translocation, and ultimately, STAT3-mediated transcriptional activity. TTI-101 has demonstrated anti-tumor activity across a broad range of preclinical cancer models, including a Hep*Pten*$^{-}$ (hepatocyte-specific deletion of *Pten*) murine model of liver cancer, which recapitulates the pathogenesis of HCC in non-alcoholic fatty liver disease (NAFLD) with chronic inflammation and liver fibrosis leading to cancer at 11 months. TTI-101 treatment starting at 11 months arrested tumor growth as well as reversed liver injury and fibrosis (1). Given these findings, a clinical trial is being conducted examining the effect of this novel, targeted therapeutic agent in patients with advanced solid malignancies. **Methods:** This single-site Phase I trial (NCT03195699) is evaluating TTI-101 as monotherapy in patients with advanced solid tumors who are refractory to prior therapies. The primary objectives of this dose-escalation study include establishing tolerability and safety at each dose level, pharmacokinetics (PK), and establishing the recommended phase 2 dose (RP2D). The secondary and exploratory objectives include assessing clinical outcomes of patients and pharmacodynamics (PD) of TTI-101 via timed, paired tumor biopsies. The initial dose-escalation study is stratified by disease type (HCC and non-HCC) with independent dose-escalation schemas and will be followed by dose expansion cohorts where safety, PK and PD will be evaluated. TTI-101 is administered orally, twice daily for a 28-day cycle. Key eligibility criteria include: 18 years of age or older, having metastatic or unresectable solid tumor refractory to standard therapies, and measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) score of 0-2, and normal organ function. Additional criteria are specified for patients with HCC including Child-Pugh class A. HCC cohorts 1-4 and non-HCC cohorts 1-3 have been completed without dose limiting toxicities (DLTs). Enrollment to the HCC dose expansion began in February 2021. 1. Jung KH, et al. Multifunctional Effects of a Small-Molecule STAT3 Inhibitor on NASH and Hepatocellular Carcinoma in Mice. Clin Cancer Res. 2017;23(18):5537-46. Clinical trial information: NCT03195699. Research Sponsor: Cancer Prevention and Research Institute of Texas, Other Foundation.

TPS3159 **Poster Session**

A multicenter open-label phase 1 study evaluating the safety and tolerability of HMPL-306 in patients with locally advanced or metastatic solid tumors with IDH mutations. *First Author: Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Isocitrate dehydrogenase (IDH) is a rate-limiting tricarboxylic acid cycle enzyme with 3 isoforms. Mutations in IDH1 and IDH2 result in gain-of-function activity that can cause tumor formation and/or progression and have been associated with various tumor types. Therefore, selective, single mutant IDH (mIDH) isotype inhibitors (mIDH1 or mIDH2) can lead to insufficient efficacy and the potential for tumor resistance. HMPL-306 is an innovative, small-molecule, orally available, highly selective, potent inhibitor of both mIDH1 and mIDH2. Clinical development of a compound that concurrently targets, inhibits, and suppresses multiple mIDHs could lead to significant and durable clinical benefit for patients (pts) with solid tumors harboring IDH mutations. **Methods:** This is a phase 1, open-label, dose escalation (Part 1) and dose expansion (Part 2) study to evaluate the safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary efficacy of HMPL-306 in pts ≥18 years with locally advanced or metastatic solid tumors with any IDH mutations. HMPL-306 will be administered orally, once daily in a 28-day continuous dosing treatment cycle. The HMPL-306 dose will be escalated in Part 1 according to the modified toxicity probability interval-2 (mTPI-2) design in 4 cohorts in approximately 15-20 pts: 50, 100, 150, and 200 mg. Eligible pts must have locally advanced or metastatic solid tumors with IDH1 or IDH2 mutations. The primary objectives are to evaluate safety, dose limiting toxicities (DLTs), tolerability, maximum tolerated dose (MTD), recommended phase 2 dose (RP2D), and PK. Approximately 95 pts will be enrolled at the RP2D in Part 2 to further characterize the safety, tolerability, PK, PD, and preliminary anti-tumor activities of HMPL-306. Part 2 will include 5 dose expansion cohorts: cholangiocarcinoma (n = 20), skeletal chondrosarcoma (n = 20), low-grade glioma (n = 20), perioperative low-grade glioma (n = 15), any other solid tumor harboring an IDH1/2 mutation (n = 20). All pts will continue treatment until disease progression, unacceptable toxicity, withdrawal of consent, or at the investigator's discretion. Safety will be assessed based on reports of adverse events including clinical laboratory testing, vital signs, physical examinations, and electrocardiograms. All pts who receive any study treatment will be included in safety and efficacy analyses. Antitumor activity based on investigator-assessed overall response will be evaluated using descriptive analyses. Objective response rate will be calculated with 95% confidence interval using the Clopper-Pearson method. The Kaplan-Meier method will be used to summarize the time-to-event data such as progression-free survival and duration of response. No statistical hypothesis testing is planned. Enrollment started February 2021. Research Sponsor: Hutchison MediPharma Limited.

TPS3160 **Poster Session**

EPIK-P2: A prospective phase 2, double-blind, randomized, placebo-controlled study of alpelisib in pediatric and adult patients (Pts) with *PIK3CA*-related overgrowth spectrum (PROS). *First Author: Guillaume Canaud, Hôpital Necker, Université de Paris, Paris, France*

Background: Somatic gain-of-function mutations in the *PIK3CA* gene, encoding the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) catalytic α subunit (p110α), can result in PI3K pathway hyperactivation. PROS is an umbrella term for rare, phenotypically varied, but overlapping features driven by *PIK3CA* mutations. Disease onset is often congenital or in early childhood; presentation ranges widely from localized overgrowth to pleiotropic, severe overgrowth. Complications depend on anatomical site and extent of overgrowth. Management of PROS currently involves symptomatic treatment of its manifestations; an unmet need exists for targeted, systemic therapies. Alpelisib, a PI3Kα inhibitor, has demonstrated encouraging clinical observations and a promising safety profile; after 6 mo of treatment, pediatric and adult pts with PROS experienced improvements in symptoms without requiring surgery. A low rate of side effects was observed (Venot Q, et al. *Nature.* 2018;558:540-6). **Methods:** EPIK-P2 is a prospective, phase 2, multicenter study with an upfront 16-week, randomized, double-blind, placebo-controlled period. Key eligibility criteria include male or female ≥6 yr of age with PROS and symptomatic and/or progressive overgrowth; ≥1 PROS-related measurable lesion confirmed by a Blinded Independent Review Committee (BIRC) and documented somatic *PIK3CA* mutation. Pts with isolated cases of macrodactyly, epidermal nevus/nevi, or macrocephaly in absence of other PROS-related lesions; previous treatment with PI3K inhibitor(s); or debulking surgery within 3 mo are not eligible. Approximately 138 pts will be enrolled into 2 groups comprising adult (age ≥18 yr) and pediatric (ages 6-17 yr) pts. Pts will be randomized 2:1 to daily oral alpelisib or matching placebo; adults will receive 125 mg and pediatric pts 50 mg. After 16 weeks, pts randomized to placebo will switch to alpelisib in a blinded fashion; pts receiving alpelisib will continue alpelisib. Treatment will continue for up to 5 yr. The primary objective is to demonstrate the efficacy of alpelisib by the proportion of pts randomized to alpelisib with a response at Week 24 in each group. Response is defined as ≥20% volume reduction in the symptomatic target lesion(s) per BIRC. The key secondary objective is to demonstrate efficacy of alpelisib vs placebo based on the proportion of pts in each group with response at Week 16. Other secondary outcomes include safety and tolerability, duration of response, overall clinical response rates, changes in symptoms and comorbidities, patient-reported outcomes, pharmacokinetics, and healthcare utilization. An exploratory group of pts (n = 12) ages 2-5 yr will be later enrolled once a starting dose of alpelisib is confirmed in these pts. Enrollment of 150 pts is anticipated. Clinical trial information: NCT04589650. Research Sponsor: Novartis Pharmaceuticals Corporation.

TPS3161 **Poster Session**

Phase 1/2 study of eprenetapopt (APR-246) in combination with pembrolizumab in patients with solid tumor malignancies. *First Author: Ecaterina Elena Dumbrava, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The p53 pathway has been implicated in antitumor immunity, including antigen presentation and T-cell proliferation. Loss of p53 function can increase resistance to immunotherapy across many tumor types. Eprenetapopt (eprenet) is a small molecule that stabilizes the folded structure of p53, resulting in activation of mutant p53 and stabilization of wild-type (WT) p53. It also targets the cellular redox homeostasis, resulting in induction of apoptosis in tumor cells. *In vivo*, mice carrying supernumerary copies of the *TP53* gene harbor a pro-inflammatory tumor microenvironment, an effect recapitulated in *TP53* normal-copy mice treated with eprenetapopt. Combining eprenetapopt and anti-PD1 or anti-CTLA4 therapy resulted in enhanced tumor growth inhibition and improved survival in *TP53* WT mice inoculated with B16 melanoma and MC38 colon adenocarcinoma cells. Based on these results, we hypothesized that eprenet-induced p53 stabilization may augment response to immunotherapy. To test this hypothesis, we are conducting a phase 1b/2 study of eprenet in combination with pembrolizumab (eprenet+pembro) in pts with solid tumors. **Methods:** The primary objectives are to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) and to assess the safety and tolerability of eprenet+pembro in pts with advanced solid tumors. The secondary objectives are to estimate the anti-tumor activity and to describe the pharmacokinetics of the combination. Exploratory objectives include assessing predictive and pharmacodynamic markers of response. The study includes a safety lead-in with a 3+3 dose de-escalation design for pts with advanced solid tumors with known tumor *TP53* mutation status (*TP53* WT is acceptable) (max 18 pts), followed by expansion cohorts in pts with NSCLC, gastric/GEJ and urothelial cancer (max 100 pts). In expansion, pts with urothelial and gastric cancers must be naïve to anti-PD-1/ L1 therapy. Eprenet is given IV once daily on Days 1–4 while pembro is administered on Day 3 of each 21-day cycle. The RP2D of eprenet+pembro is considered the dose at which ≤ 1 of 6 pts in a cohort has a dose-limiting toxicity (DLT). Primary endpoints are occurrence of DLTs, adverse events (AEs) and serious AEs with eprenet+pembro. Key secondary endpoints are best objective response, progression free survival and overall survival. Exploratory endpoints include gene mutations by next generation sequencing (including *TP53*), mRNA expression, multiplex immunohistochemistry and transcriptomics, multiplex flow cytometry on peripheral blood mononuclear cells and cytokines in serum. Continuous monitoring of toxicity will be conducted. The trial opened in May 2020 and is actively enrolling patients. Clinical trial information: NCT04383938. Research Sponsor: Aprea Therapeutics.

TPS3162 **Poster Session**

A phase 2, multicenter, open-label study evaluating trastuzumab deruxtecan (T-DXd) for the treatment of solid tumors harboring specific HER2-activating mutations (DESTINY-PanTumor01). *First Author: Bob T. Li, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: There are substantial data suggesting that a subset of human epidermal growth factor receptor 2 (HER2)–activating mutations induce ligand-independent constitutive HER2 signaling and promote oncogenesis. Direct therapeutic targeting of HER2 has transformed the treatment of patients with HER2-overexpressing breast and gastric cancers. However, currently no targeted treatments are approved for patients with tumors harboring HER2-activating mutations. T-DXd is an antibody-drug conjugate consisting of an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a membrane-permeable topoisomerase I inhibitor payload that may be selectively internalized in tumors with HER2 mutations (Li BT, et al. *Cancer Discov.* 2020;10:674-687). In a phase 1 study (DS8201-A-J101), T-DXd demonstrated preliminary antitumor activity in patients with tumors harboring HER2 mutations, with confirmed responses observed in 9 of 19 patients (47.4%) (Tsurutani J, et al. *Cancer Discov.* 2020;10:688-701). Here we describe the DESTINY-PanTumor01 trial (NCT04639219). **Methods:** DESTINY-PanTumor01 is an open-label, multicenter, single-arm, phase 2 study evaluating T-DXd for the treatment of patients with unresectable and/or metastatic solid tumors (excluding non-small cell lung cancer) harboring prespecified HER2-activating mutations. Patients (N≈100) are required to have progressed following prior treatment for advanced or metastatic disease or have no satisfactory alternative treatment options. Prior HER2-targeting therapy is allowed. HER2 mutation status will be determined locally using next-generation sequencing or a validated nucleic acid–based methodology. The primary endpoint is confirmed objective response rate according to independent central review per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. Secondary endpoints include duration of response, disease control rate, progression-free survival, investigator-assessed confirmed objective response rate, overall survival, safety, pharmacokinetics, and immunogenicity. Clinical trial information: NCT04639219. Research Sponsor: AstraZeneca.

3500 **Oral Abstract Session**

Final overall survival for the phase III KN177 study: Pembrolizumab versus chemotherapy in microsatellite instability-high/mismatch repair deficient (MSI-H/dMMR) metastatic colorectal cancer (mCRC). *First Author: Thierry Andre, Sorbonne Université and Hôpital-Saint Antoine, Paris, France*

Background: In the phase III, randomized open-label KEYNOTE-177 (NCT02563002) study 1L pembrolizumab (pembro) versus chemotherapy (chemo) provided superior progression-free survival (PFS) at second interim analysis (IA2) in patients (pts) with MSI-H/dMMR mCRC. The study continued to final analysis of overall survival (OS), planned after 190 OS events or 12 months after IA2, whichever occurred first. We present results of the final analysis of OS, 12 months after IA2. **Methods:** A total of 307 pts with MSI-H/dMMR mCRC and ECOG PS 0 or 1 were randomized 1:1 to 1L pembro 200 mg Q3W for up to 2y or investigator's choice of mFOLFOX6 or FOLFIRI Q2W ± bevacizumab or cetuximab. Treatment continued until PD, unacceptable toxicity, pt/investigator decision to withdraw, or completion of 35 cycles (pembro only). Pts receiving chemo could crossover to pembro for up to 35 cycles after confirmed PD. Primary end points were OS and PFS (RECIST v1.1, central review). Secondary end points included ORR, duration of response (DOR) (RECIST v1.1, central review), and safety. For OS significance, the p-value had to meet a prespecified α of 0.0246 (one-sided). Sensitivity analyses to adjust for crossover effect were performed. Data cut-off for final analysis was Feb 19, 2021. **Results:** Median (range) study follow-up was 44.5 mo (36.0-60.3) with pembro vs 44.4 mo (36.2-58.6) with chemo. 56 (36%) pts crossed over from chemo to pembro, with 37 more receiving anti-PD-1/PD-L1 therapies off study (60% effective crossover rate in the ITT). The HR for OS favored pembro vs chemo with a trend toward reduction in the risk of death (HR 0.74; 95% CI, 0.53-1.03; *P*=0.0359; median not reached [NR] vs 36.7 mo); this difference did not reach statistical significance. Sensitivity analysis by the rank-preserving structure failure time model and inverse probability of censoring weighting showed OS HRs of 0.66 (95% CI 0.42-1.04) and 0.77 (95% CI 0.44-1.38), respectively. Pembro vs chemo met the prespecified criteria for PFS superiority at IA2. At final analysis, median PFS was 16.5 mo vs 8.2 mo (HR 0.59; 95% CI, 0.45-0.79), but was not formally tested per analysis plan. Confirmed ORR was 45.1% (20 CR, 49 PR) vs 33.1% (6 CR, 45 PR). Median (range) DOR was NR (2.3+ to 53.5+) vs 10.6 mo (2.8 to 48.3+), respectively. Treatment-related adverse events (TRAEs) occurred in 79.7% vs 98.6% of pts; 21.6% vs 66.4%, respectively, had grade ≥3 TRAEs. **Conclusions**: As 1L therapy for pts with MSI-H/dMMR mCRC, pembro vs chemo provides statistically superior PFS with fewer TRAEs, and is associated with a trend toward reduced mortality that did not meet statistical significance likely due to the high crossover rate from chemo to anti-PD1/PD-L1 therapies. Together these data confirm pembro as a new standard-of-care in the 1L for pts with MSI-H/dMMR mCRC. Clinical trial information: NCT02563002. Research Sponsor: Merck & Co., Inc.

3501 **Oral Abstract Session**

The randomized phase II study of FOLFOXIRI plus cetuximab versus FOLFOXIRI plus bevacizumab as the first-line treatment in metastatic colorectal cancer with *RAS* wild-type tumors: The DEEPER trial (JACCRO CC-13). *First Author: Akihito Tsuji, Department of Medical Oncology, Kagawa University Hospital, Takamatsu, Japan*

Background: Triplet regimens, FOLFOXIRI, combined with bevacizumab (bev) or panitumumab have been shown to be superior in terms of early tumor shrinkage (ETS) and depth of response (DpR) compared to doublet combinations in patients with *RAS* wild-type metastatic colorectal cancer (mCRC), in the TRIBE trial (*N Engl J Med* 2014) or the VOLFI trial (*J Clin Oncol* 2019), respectively. There have been few studies which directly compared cetuximab (cet) with bev when combined with triplet regimen. Therefore, we investigated the efficacy and safety of bev vs. cet in combination with FOLFOXIRI in previously untreated mCRC patients with *RAS* wild-type tumors. **Methods:** This trial was a randomized phase II trial to evaluate modified (m)-FOLFOXIRI (irinotecan 150mg/m^2, oxaliplatin 85mg/m^2, 5-FU 2400mg/m^2) plus cet vs. bev as first-line treatment in terms of DpR during the entire course as the primary endpoint in 360 patients with *RAS* wild-type mCRC. The aim of the trial was to show that median DpR of cet arm was more than 12.5% higher than bev arm, with a power of 85% at a significance level of 0.05. Secondary endpoints included ETS rate at week 8, overall response rate (ORR), progression-free survival (PFS), overall survival (OS), secondary resection rate, and toxicity. **Results:** A total of 359 patients were enrolled between July 2015 and June 2019. For the full analysis set (median age 65y, 64% male, PS0/1: 91%/9%, left/right primary: 83%/17%), 173 and 175 patients were randomly assigned to the cet and bev arms, respectively. On the cutoff date of September 2020, the median number of cycles administered was 10 (range, 1-51) for the cet arm and 12 (range, 1-51) for the bev arm. Safety data was already reported at the ASCO GI symposium 2021 (J Clin Oncol 39, 2021 suppl 3; abstr 86). The primary endpoint was met (p = .001); 57.4% (-15.0~100) for the cet arm versus 46.0% (-0.6~100) for the bev arm. As for primary tumor sidedness, median DpR were 60.3% versus 46.1% (p = .0007) in the left-side and 50.0% versus 41.2% (p = .46) in the right-side. The ETS rate and ORR as the secondary endpoints were 77.8% and 69.1% in the cet arm versus 74.6% and 71.7% in the bev arm, respectively, with no statistical significance. Although the survival data were immature, PFS and OS of both arms were 12.7 months (95%CI 11.5-14.0) and 37.6 months (95%CI 30.8 to 43.0), respectively. **Conclusion:** The mFOLFOXIRI plus cet has been shown to be significantly superior to the mFOLFOXIRI plus bev in terms of DpR as the primary endpoint in first-line treatment for *RAS* wild-type mCRC. Clinical trial information: NCT02515734. Clinical trial information: UMIN000018217. Research Sponsor: Merck Biopharma Co., Ltd.

3502 **Oral Abstract Session**

Randomized study to investigate FOLFOXIRI plus either bevacizumab or cetuximab as first-line treatment of BRAF V600E-mutant mCRC: The phase-II FIRE-4.5 study (AIO KRK-0116). *First Author: Sebastian Stintzing, Medical Department, Division of Hematology, Oncology, and Tumor Immunology (CCM), Charité Universitätsmedizin Berlin, Berlin, Germany*

Background: FIRE-4.5 (AIO KRK-0116) compared FOLFOXIRI plus either cetuximab or bevacizumab in BRAF V600E-mutant metastatic colorectal cancer (mCRC) patients not treated for metastatic disease before. **Methods:** Within this 1:2 randomized, controlled, open-label phase-II study, patients received FOLFOXIRI every two weeks at the following schedule: irinotecan 150mg/m^2 (30-90min, day 1), folinic acid 400mg/m^2 (120min, day 1), oxaliplatin 85mg/m^2 (120 min, day 1), followed by 5-fluorouracil 3,000 mg/m^2, 48h. FOLFOXIRI was combined with either bevacizumab (arm A) at a dose of 5mg/kg body weight, every 2 weeks or cetuximab (arm B) at a loading dose of 400mg/m^2 and subsequent weekly doses of 250mg/m^2. FOLFOXIRI was applied for a maximum of 12 cycles before maintenance treatment was recommended. Primary endpoint was superiority of Arm B with respect to overall response rate (ORR) according to RECIST 1.1 criterions. Secondary endpoints included PFS, OS, and tolerability. **Results:** From November 2016 to December 2020 108 patients were randomized in 90 German and 10 French centers (35 arm A and 73 in arm B). No new or unexpected toxicities were observed. Primary endpoint was not met with an ORR of 66.7% and 52.0% (p =0.23) in the respective arms. Median PFS was significantly longer in arm A vs arm B (8.3 months vs 5.9 months; log-rank p = 0.03; HR 1.8). While OS data is still immature, median OS time are comparable at the time of analysis. Patients with left-sided primary tumors had comparable results with either bevacizumab or cetuximab, whereas those with right-sided primary tumors showed a trend towards better efficacy of the bevacizumab combination. Updated results will be presented at the annual meeting. **Conclusions:** FIRE-4.5 is the first prospective and randomized study investigating efficacy of FOLFOXIRI combined with targeted therapy in the first-line treatment of BRAF V600E-mutant mCRC. FOLFOXIRI plus either bevacizumab or cetuximab have comparable efficacy with differential effects according to primary tumor sidedness supporting the heterogeneity of BRAF V600E-mutant subpopulation of mCRC. Clinical trial information: NCT04034459. Research Sponsor: MERCK.

3503 **Oral Abstract Session**

Maintenance therapy with 5-fluoruracil/leucovorin (5FU/LV) plus panitumumab (pmab) or 5FU/LV alone in RAS wildtype (WT) metastatic colorectal cancer (mCRC) - the PANAMA trial (AIO KRK 0212). *First Author: Dominik Paul Modest, Department of Medicine III, University Hospital, LMU Munich, Munich, Germany*

Background: Planned discontinuation or stop-and-go use of oxaliplatin are established strategies in the systemic therapy of mCRC. Consequently, and irrespective of antibody use, 5FU/LV represents the standard backbone of most maintenance strategies. Unlike VEGF-targeted substances, there is limited evidence that EGFR-antibodies add efficacy to 5FU/LV maintenance in *RAS* wildtype (*RAS* WT) mCRC patients. **Methods:** Following induction therapy with six cycles of 5FU/LV, oxaliplatin (FOLFOX) and pmab, the trial randomized maintenance therapy with 5FU/LV plus pmab vs. 5FU/LV alone in a 1:1 fashion in patients (pts) with *RAS* WT mCRC. The primary endpoint was PFS (progression-free survival: time from randomization until progression or death). With 218 events needed for PFS, the trial was designed to demonstrate superiority of the 5FU/LV+ pmab arm vs. 5FU/LV alone with a hazard ratio (HR) of 0.75, power of 80% and a significance level of 10%. Secondary endpoints included overall survival (OS), objective response to induction- and maintenance therapy as well as quality of life. The trial is registered with ClinicalTrials.gov, NCT01991873. **Results:** The full analysis set consists of 248 pts (125 pts 5FU/LV + pmab and 123 pts 5FU/LV) who were randomized and received maintenance therapy. Median age was 66 vs. 65 years, male patients were 69.6% vs. 63.4%, ECOG 0 was 56.8% vs. 60.2% in the respective trial arms (5FU/LV+ pmab vs. 5FU/LV). At data cut-off, with 218 events, PFS of maintenance therapy was improved with 5FU/LV+ pmab vs. 5FU/LV alone (8.8 (80% CI 7.6-10.2) months vs. 5.7 (80% CI 5.6-6.0) months, HR 0.72 (80%CI 0.60-0.85), p = 0.014). OS (event rate 54.4%) numerically favoured the 5FU/LV+ pmab arm (28.7 (95% CI 25.4-39.1) months) as compared to 5FU/LV alone (25.7 (95% CI 22.2-28.2) months), HR 0.84 (95% CI 0.60-1.18). **Conclusion:** In *RAS* WT mCRC, maintenance therapy with 5FU/LV+ pmab appears to be superior to 5FU/LV alone and should be regarded as standard of care maintenance regimen following induction therapy with FOLFOX plus pmab. Clinical trial information: NCT01991873. Research Sponsor: AMGEN, Arbeitsgemeinschaft Internistische Onkologie (AIO).

3504 **Oral Abstract Session**

Oral maintenance capecitabine versus active monitoring for patients with metastatic colorectal cancer (mCRC) who are stable or responding after 16 weeks of first-line treatment: Results from the randomized FOCUS4-N trial. *First Author: Richard Adams, Cardiff University and Velindre Cancer Centre, Cardiff, United Kingdom*

Background: There is extensive randomised evidence supporting the use of treatment breaks in mCRC, but breaks from treatment are not universally offered to patients despite reductions in toxicity, without detriment to OS. Prior trials have shown that the combination of Cp and bevacizumab extend PFS but not OS. FOCUS4-N explores oral maintenance Cp monotherapy in patients with disease control on first line therapy. **Methods:** FOCUS4 was a molecularly stratified trial programme registering patients with newly diagnosed mCRC from 88 hospitals in the UK. Whilst undergoing 16 wks of first line treatment, a sample of tumour was sent for laboratory testing to stratify their disease into molecular subtypes: MSI, BRAF, PIK3CA, TP53 and RAS mutations. For some molecular groups, a targeted therapy subtrial was available but entry into the FOCUS4-N trial was offered to those in whom a targeted subtrial was unavailable. Patients were randomised 1:1 between maintenance Cp therapy or AM. The primary outcome was PFS assessed using 8-wkly RECIST reported CT scans with quality of life (using EQ5D 8 weekly) and OS as secondary outcomes. Toxicity and tolerability were assessed 4-wkly. On progression, from the nadir, patients recommenced first line treatment. Cox regression was used to assess efficacy by intention-to-treat (ITT) with adjustment for tumour location, WHO status, metastatic burden, first line treatment and biomarker subtype. **Results:** Between March 2014 and March 2020, 254 patients were randomised (127 to Cp and 127 to AM). Baseline characteristics were balanced between groups but event rates were higher than anticipated in the AM group and the final analysis was triggered early as a result of the COVID-19 pandemic halting recruitment. The table presents results for PFS and OS. Compliance with treatment was good with per-protocol analysis results very similar to ITT (PFS HR=0.38 (95% CI 0.28-0.51)). Toxicity from Cp v AM was as expected with G≥2 fatigue (25% v 12%), diarrhoea (23% v 13%) and hand-foot syndrome (26% v 3%). Quality of life showed no statistically significant differences between the two arms. **Conclusions:** Despite strong evidence of prolongation of PFS with maintenance therapy, OS remains unaffected and FOCUS4-N provides additional evidence to support the use of treatment breaks as a safe management alternative for patients who are stable or responding well to first line treatment for mCRC. Cp without bevacizumab may be used to extend PFS, in the interval after 16 weeks of combination therapy. Clinical trial information: ISRCTN#90061546. Research Sponsor: Cancer Research UK, Other Government Agency.

	Cp		AM		
Outcome	Events/N	Median (IQR) survival time (mths)	Events/N	Median (IQR) survival time (mths)	Cox regression adjusted HR (95% CI) p-value
PFS	117/127	3.88 (2.10-7.39)	122/127	1.87 (1.64-3.65)	0.40 (0.21-0.75) <0.0001
OS	99/127	13.9 (9.07-20.4)	90/127	13.3 (7.72-20.0)	0.87 (0.64-1.18) 0.37

3505 **Oral Abstract Session**

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): Final results from a phase 2, multicenter, open-label study (DESTINY-CRC01). *First Author: Takayuki Yoshino, National Cancer Center Hospital East, Kashiwa, Japan*

Background: T-DXd is an antibody–drug conjugate of a humanized anti-HER2 antibody bound to a topoisomerase I inhibitor by a cleavable linker. The primary analysis of DESTINY-CRC01 (DS8201-A-J203; NCT03384940), a phase 2, open-label, multicenter study of T-DXd in pts with HER2-expressing mCRC showed promising antitumor activity and a manageable safety profile (cohort A median follow-up [FU], 27.1 weeks; Siena S, ASCO 2020). We present updated longer-term efficacy and safety data. **Methods:** Pts had centrally confirmed HER2-expressing, *RAS* wild-type mCRC that progressed after ≥2 prior regimens. 6.4 mg/kg of T-DXd was administered every 3 weeks (Q3W) in 3 cohorts (A: HER2 IHC3+ or IHC2+/ISH+; B: IHC2+/ISH−; C: IHC1+). The primary end point was confirmed objective response rate (ORR) by independent central review in cohort A. Secondary end points were disease control rate (DCR; CR + PR + SD), duration of response (DOR), progression-free survival (PFS), and overall survival (OS). **Results:** At data cutoff (Dec 28, 2020), 86 pts (A, 53; B, 15; C, 18) received T-DXd. Median age was 58.5 y (range, 27-79), 53.5% were male, and 90.7% had left colon or rectum cancer. Median prior regimens for metastatic disease was 4 (range, 2-11). All pts had prior irinotecan; 30.2% in cohort A had prior anti-HER2 therapy. Median (m) treatment duration (all pts) was 3.0 mo (95% CI, 2.1-4.1; cohort A, 5.1 mo [95% CI, 3.9-7.6]). In cohort A (median FU, 62.4 weeks), confirmed ORR was 45.3% (24/53 pts; 95% CI, 31.6-59.6), DCR was 83.0% (44/53 pts; 95% CI, 70.2-91.9), mDOR was 7.0 mo (95% CI, 5.8-9.5), mPFS was 6.9 mo (95% CI, 4.1-8.7) with 37 (69.8%) PFS events, and mOS was 15.5 mo (95% CI, 8.8-20.8) with 36 (67.9%) OS events. These results are consistent with the primary analysis. Confirmed ORR was 43.8% (7/16 pts; 95% CI, 19.8-70.1) in pts with prior anti-HER2 therapy, 57.5% (23/40 pts; 95% CI, 40.9-73.0) in pts with IHC3+ status, and 7.7% (1/13 pts; 95% CI, 0.2-36.0) in pts with IHC2+/ISH+ status. In cohorts B and C, mPFS was 2.1 mo (95% CI, 1.4-4.1) and 1.4 mo (95% CI, 1.3-2.1); mOS was 7.3 mo (95% CI, 3.0-NE) and 7.7 mo (95% CI, 2.2-13.9), respectively. Treatment-emergent adverse events (TEAEs) of grade (G) ≥3 occurred in 65.1% of pts (56/86); the most common TEAEs were hematologic and gastrointestinal. TEAEs leading to drug discontinuation occurred in 13 pts (15.1%). 8 pts (9.3%) had interstitial lung disease (ILD) adjudicated by an independent committee as related to T-DXd (4 G2; 1 G3; 3 G5). **Conclusions:** T-DXd at 6.4 mg/kg Q3W showed promising activity and durability with longer-term FU in this pt population. The safety profile was consistent with prior results; ILD continues to be recognized as an important identified risk that requires careful monitoring and intervention as needed. These results support continued exploration of T-DXd in pts with HER2-overexpressing mCRC. Clinical trial information: NCT03384940. Research Sponsor: Daiichi Sankyo, Pharmaceutical/Biotech Company.

3506 **Oral Abstract Session**

Phase II study of anti-EGFR rechallenge therapy with panitumumab driven by circulating tumor DNA molecular selection in metastatic colorectal cancer: The CHRONOS trial. *First Author: Andrea Sartore-Bianchi, Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, University of Milano, Milan, Italy*

Background: Despite advances in molecular segmentation of metastatic colorectal cancer (mCRC), beyond *RAS* status therapeutic actionability remains confined to the limited subgroups of *ERBB2* amplified, *BRAF* mutated and MSI-H patients. Optimization of available treatments is therefore warranted. Rechallenge with anti-EGFR monoclonal antibodies is often empirically used with some benefit as late-line therapy. We previously found that mutant *RAS* and *EGFR* ectodomain clones, which emerge in blood during EGFR blockade, decline upon antibody withdrawal leading to regain drug sensitivity. Based on this rationale, we designed CHRONOS, a multicenter phase II trial of anti-EGFR therapy rechallenge guided by monitoring of the mutational status of *RAS, BRAF* and *EGFR* in circulating tumor DNA (ctDNA). To our knowledge, this is the first interventional clinical trial of liquid biopsy for driving anti-EGFR rechallenge therapy in mCRC. **Methods**: Eligible patients were PS ECOG 0-2 *RAS/BRAF* WT mCRC having first achieved an objective response and then progression in any treatment line with an anti-EGFR antibody containing regimen, displaying *RAS, BRAF* and *EGFR* ectodomain WT status in ctDNA at molecular screening after progression to the last anti-EGFR-free regimen. Clonal evolution in ctDNA was analyzed by ddPCR and next generation sequencing. Panitumumab 6 mg/kg was administered IV every two weeks until progression. The primary endpoint was objective response rate (ORR) by RECIST version 1.1 with independent central review. 27 total patients and 6 responses were required to declare the study positive (power = 85%, type I error = 0.05). **Results**: Between Aug 19, 2019 and Nov 6, 2020 52 patients were screened by liquid biopsy and 36 (69%) were negative in ctDNA for *RAS/BRAF/EGFR* mutations. Of these, 27 patients were enrolled in 4 centers. Median age was 64 years (range: 42-80). PS ECOG was 0/50%, 1/46%, 2/4%. Previous anti-EGFR was administered in 1st line in 63%, 2nd in 15% and $>$ 2nd in 22%. Median number of previous treatments was 3. The primary endpoint was met, with 8/27 partial responses (PR) observed (2 unconfirmed) (ORR = 30%, 95% CI: 12-47%). Stable disease (SD) was obtained in 11/27 (40%, 95% CI: 24-59%), lasting $>$ 4 months in 8/11. Disease control rate (PR plus SD $>$ 4 months) was therefore obtained in 16/27 (59%, 95% CI: 41-78%). Median progression-free survival was 16 weeks. Median duration of response was 17 weeks (1 ongoing). Maximal grade toxicity was G3, limited to dermatological and occurring in 19% of patients. ctDNA dynamics were studied in all patients. **Conclusions**: Liquid biopsy-driven rechallenge with anti-EGFR antibodies leads to further objective responses in one third of patients. Genotyping tumor DNA in the blood to direct therapy can be effectively incorporated in the management of advanced CRCs. Clinical trial information: 2016-002597-12. Research Sponsor: Associazione Italiana per la Ricerca sul Cancro (AIRC), Other Foundation, Amgen provided panitumumab.

3507 **Oral Abstract Session**

The TRUSTY study: A randomized phase 2/3 study of trifluridine/tipiracil plus bevacizumab versus irinotecan and fluoropyrimidine plus bevacizumab as second-line treatment in patients with metastatic colorectal cancer. *First Author: Yasutoshi Kuboki, Department of Experimental Therapeutics, National Cancer Center Hospital East, Kashiwa, Chiba, Japan*

Background: The efficacy of trifluridine/tipiracil (FTD/TPI) plus bevacizumab (BEV) as a later-line treatment for metastatic colorectal cancer (mCRC) has been demonstrated in clinical trials. Therefore, we conducted a randomized phase 2/3 study to determine whether FTD/TPI plus BEV is non-inferior to either FOLFIRI or S-1 and irinotecan plus BEV in terms of overall survival (OS) as second-line treatment in patients with mCRC. **Methods:** Patients with histologically confirmed mCRC who failed first-line doublet chemotherapy including fluoropyrimidine plus oxaliplatin with either BEV or an anti-EGFR antibody (in cases of *RAS* wild-type) were eligible. Patients were randomized to receive either FTD/TPI plus BEV (experimental group, BEV 5.0 mg/kg on days 1 and 15, FTD/TPI 35 mg/m^2 twice daily on days 1–5 and 8–12 of each 28-day cycle) or either FOLFIRI or S-1 and irinotecan plus BEV (control group). The primary endpoint was the OS. The non-inferiority margin of a hazard ratio (HR) of 1.33 was based on the assumption of a median survival time of 19 months for the control (power 0.80, 1-sided alpha 0.025). The secondary endpoints were the progression-free survival (PFS), response rate (RR), disease control rate (DCR), time to treatment failure, time to post-study treatment failure, proportion of patients receiving post-study treatment, quality of life, and safety. **Results:** As a result of the interim analysis for futility, the study was terminated in July 2020, and 397 patients were finally enrolled at 65 institutions from October 2017. The baseline characteristics were similar between the groups. The median OS were 14.8 months in the FTD/TPI plus BEV group and 18.1 months in the control group [HR: 1.38; 95% confidence interval (CI): 0.99–1.93; p = 0.5920 for non-inferiority]; non-inferiority of FTD/TPI plus BEV was not demonstrated. The median PFS were 4.5 months in the FTD/TPI plus BEV group and 6.0 months in the control group (HR: 1.45; 95% CI: 1.14–1.84). The RR and DCR were 3.8% and 61.2% in the FTD/TPI plus BEV group, respectively, and 7.1% and 71.7% in the control group, respectively. The proportions of patients receiving post-study treatment in the FTD/TPI plus BEV and control groups were 59.9% and 52.3%, respectively. The main grade 3 or 4 adverse events in the FTD/TPI plus BEV and control groups were neutropenia (65.8% and 41.6%, respectively), diarrhea (1.5% and 7.1%, respectively), and grade 1 or 2 alopecia (3.6% and 24.9%, respectively). **Conclusions:** FTD/TPI plus BEV did not show non-inferiority to FOLFIRI or S-1 and irinotecan plus BEV as second-line treatment in patients with mCRC. *Post hoc* subgroup analyses are ongoing to investigate patients who likely benefit from FTD/TPI plus BEV. Clinical trial information: jRCTs031180122. Research Sponsor: Taiho Pharmaceutical Co, Ltd.

3508 **Poster Discussion Session**

CCTG CO.28 primary endpoint analysis: Neoadjuvant chemotherapy, excision and observation for early rectal cancer, the NEO trial. *First Author: Hagen Fritz Kennecke, Providence Cancer Institute, Portland, OR*

Background: CO.28 (NCT03259035) is a phase II study designed to determine if patients with cT1-T3a/bN0 rectal cancer can be treated with induction chemotherapy (FOLFOX/CAPOX) and organ-preserving surgery. **Methods:** Patients with MRI staged cT1-3a/bN0 tumors and no pathologic (p) high risk features received 6/4 cycles of FOLFOX/CAPOX, repeat sigmoidoscopy/pelvic MRI and subsequent Transanal Endoscopic Surgery (TES) in the absence of tumor progression. ypT0/T1N0 tumors were treated with observation while ypT2+ or ypN+ stage were recommended Total Mesorectal Excision (TME). The primary endpoint was protocol specified Organ Preservation Rate (psOPR = ypT0/T1N0, no p high risk features) and actual Organ Preservation Rate (aOPR = ypT0/T1N0 stage plus higher yp stage patients who declined TME surgery). The study would be considered negative with an psOPR of 50% or lower (H0) and as promising if it is 65% or higher (H1). **Results:** Between 08/2017 to 05/2020, 58 eligible patients were accrued in Canada and the United States, median age was 67 years, 71% male. All had well-moderately differentiated, non-mucinous rectal adenocarcinoma and median tumor height was 6 cm (range 0-18). Median follow-up was 15.4 months. Chemotherapy with FOLFOX (32) or CAPOX (26) was administered, 90% completed all planned cycles. A total of 56/58 (97%) proceeded to TES, while one patient was ineligible due to tumor progression (1.7%) and one declined. In the intention to treat analysis, the psOPR was 57% (95% CI 43-70%) while the aOPR was 79% (95% CI 67% to 89%) due to 13/23 declining recommended TME surgery. Of 10 patients who proceeded to recommended TME, a complete R0 TME was performed in 9/10, and no p residual carcinoma was found in 7/10. Crude loco-regional (LR) and distant recurrence rates were 3.5% (95% CI 0.4 to 12%) and 0%, respectively. A recurrence occurred in 1/13 patients who initially declined TME surgery. **Conclusions:** In select patients with early stage rectal cancer, three months of induction CAPOX/FOLFOX followed by TES resulted in a high OPR without the use of pelvic irradiation. The observed high rate of pathologic downstaging may point to high chemo-responsiveness in early rectal adenocarcinoma with no p high risk features. Further trials to evaluate this approach are justified and updated results will be presented. Clinical trial information: NCT03259035. Research Sponsor: CCTG (Canadian Cancer Trials Group), Other Foundation.

Eligible patients		N = 58	100%
Gender	Female/Male	17/41	29/71%
Race	White/Indigenous/Asian	48/6/4	83/10/7%
Age	Median	67 y (Range 31-83)	
cT	T1/T2/T3a/b	8/37/13	14/64/22%
cN	N0	58	100%
Transanal Endoscopic Surgery (TES)	TEMS/TAMIS/Excision	26/27/3	45/47/5%
TES Margin status	R0/R1/R2	52/2/2	93/3.5/3.5%
TES ypT	T0/T1/T2/T3	20/14/20/2	36/25/36/3%
TES ypN	NX/N0	56	100%

3509 **Poster Discussion Session**

Survival and organ preservation according to clinical response after total neoadjuvant therapy in locally advanced rectal cancer patients: A secondary analysis from the organ preservation in rectal adenocarcinoma (OPRA) trial. *First Author: Hannah Thompson, Colorectal Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY*

Background: Clinical response following neoadjuvant therapy is paramount to identifying locally advanced rectal cancer (LARC) patients suitable for Watch and Wait (WW). A 3-tier schema was devised to stratify clinical response. Patients with a complete clinical response (cCR) are considered for WW, while those with an incomplete clinical response (iCR) are recommended for total mesorectal excision (TME). A near complete response (nCR) tier captures patients with significant, but not complete, response to be considered for WW. This schema's efficacy has yet to be validated. We investigated survival and organ preservation (OP) rates based on this 3-tier clinical response assessment in patients with LARC who underwent total neoadjuvant therapy (TNT) in a prospective, multi-center clinical trial. **Methods:** Patients with MRI stage II and III rectal adenocarcinoma were randomized to either induction chemotherapy (FOLFOX or CAPEOX) followed by chemoradiation or chemoradiation followed by consolidation chemotherapy (FOLFOX or CAPEOX). At 8+/-4 weeks following TNT, response on digital rectal and endoscopic examinations was evaluated by the 3-tier schema. The date of this restaging clinical response assessment was used as time zero. The endpoints of rate of OP, disease-free survival (DFS), TME-free DFS, and overall survival (OS) were evaluated using the Kaplan-Meier method with differences analyzed by the log-rank test. **Results:** Clinical response assessments were available for 294 patients. The median time to assessment after neoadjuvant therapy was 7.9 weeks. Based on the 3-tier schema, 124 patients were categorized as cCR, 113 as nCR, and 57 as iCR. Baseline age, sex, average distance from the anal verge, clinical T classification, and clinical N classification were similar between the response groups. The table shows the 3-year rates of OP, DFS, TME-free DFS, and OS. The median follow-up was 2.36 years. Of the patients with a nCR, the 3-year TME rate was 48% compared with 21% in the cCR group. **Conclusions:** The 3-tier clinical response assessment has prognostic implications for OP and DFS in patients with LARC who underwent TNT. In patients with a nCR, more than half achieved OP at 3 years. This information should be utilized to counsel patients regarding their expected outcomes. Clinical trial information: NCT02008656. Research Sponsor: U.S. National Institutes of Health.

3-year rates by 3-tier clinical response assessment.

	cCR (n=124)		nCR (=113)		iCR (n=57)		
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI	*p*-value
Organ Preservation	79%	72-87%	52%	42-63%	9%	4-21%	<0.0001
Disease-Free Survival	84%	77-92%	76%	67-86%	52%	37-72%	<0.0001
TME-Free Disease-Free Survival	72%	64-81%	44%	35-55%	4%	1-14%	<0.0001
Overall Survival	97%	93-100%	93%	87-99%	90%	79-100%	0.11

CI=Confidence Interval.

3510 **Poster Discussion Session**

A multicenter, randomized, phase III trial of short-term radiotherapy plus chemotherapy versus long-term chemoradiotherapy in locally advanced rectal cancer (STELLAR): The final reports. *First Author: Jing Jin, Department of Radiation Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: It's presented the results of a phase III trial of short-term radiotherapy (SCRT) combined with chemotherapy versus long-term chemoradiotherapy (LCRT) in patients with locally advanced rectal cancer (LARC). **Methods:** Patients with distal or middle third, T3-T4 and/or N+ rectal adenocarcinomas diagnosed by MRI, were randomly assigned to experimental group or control group. In experimental group, patients received SCRT (25 Gy / 5 fractions / 5 days), followed by four courses of CAPOX. In control group, patients received LCRT (50 Gy / 25 fractions / 35 days with concurrent capecitabine). Surgery was recommended in both groups and performed 6-8 weeks after preoperative treatment. Two or six courses of CAPOX was prescribed as the postoperative chemotherapy in experimental group and control group, respectively. This trial was a multicenter, open-label, randomized, noninferior, phase III study, and all the patients were from 16 hospitals of China. The primary endpoint for this study was 3-year disease-free survival (DFS). **Results:** From Aug 30, 2015 to Aug 27, 2018, 599 patients were enrolled and entered random. Finally, 591 intention-to-treat (ITT) populations were included in the analysis, 298 patients assigned to SCRT followed by chemotherapy and 293 to CRT. For the experimental group and control group, cT3 and cT4 accounted for 82.3% vs. 84.6% and 15.4% vs. 12.3%, respectively, and approximately 85% were mrN positive (85.6% vs. 84.0%). As a whole, the completion and full-dose completion rates of preoperative treatment were 82.6% vs. 95.2% ($p < 0.001$) and 74.8% vs 93.2% ($p < 0.001$) in the experimental and control groups, respectively. Among the 465 patients who received surgery, 16.6% and 11.8% of them achieved pCR (p=0.134), respectively. Accounting for cCR after preoperative treatment, the total rate of pCR+cCR in experimental group was 22.5% and significantly higher than control group (12.6%, p=0.001). With median follow-up 35.0 months, the HR between experimental and control of DFS was 0.883, with 1-sided noninferiority p-value <0.001, so the noninferiority hypothesis was confirmed. The probability of DFS and OS at 3 years was 64.5% and 86.5% in the experimental group compared with 62.3% and 75.1% in control group. It's observed the OS rate of the experimental group was significantly higher than that of the control group (p=0.036) and no significant difference in metastasis-free survival or loco-regional recurrence was observed. **Conclusions:** For LARC with high risk factors, SCRT combined with sequential chemotherapy was noninferior to CRT and could be used as an alternative to LCRT. Meanwhile, SCRT combined with chemotherapy presented a higher cCR+pCR and 3-year overall survival rates as compared with CRT. However, the long term results need to be further followed up. (ClinicalTrails No.: NCT02533271). Clinical trial information: NCT00833131. Research Sponsor: Collaborative Innovation Center for Cancer Medicine.

3511 **Poster Discussion Session**

Phase II study of preoperative (PREOP) chemoradiotherapy (CTRT) plus avelumab (AVE) in patients (PTS) with locally advanced rectal cancer (LARC): The AVANA study. *First Author: Lisa Salvatore, Oncologia Medica, Comprehensive Cancer Center, Fondazione Policlinico Universitario Agostino Gemelli–IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*

Background: Preop CTRT is considered the standard of care in the management of LARC. RT can induce antigen release from a low neoantigen-burden tumor (such as a mismatch repair proficient colorectal cancer) and activate dendritic cells leading to a CD8+ T lymphocyte-mediated anticancer immune response. In LARC patients, neoadjuvant CTRT increases PD-L1 expression in tumor cells, strongly suggesting a neoadjuvant combinatory strategy with RT and PD-1/PD-L1 pathway blockade. Based on such considerations, we have designed the AVANA study to investigate the role of Ave in combination with preop CTRT in LARC. **Methods:** This is an Italian multi-center, phase II study. Pts with resectable LARC, defined by the presence of at least one of the following features: cN+, cT4, high risk cT3, received standard preop CTRT (capecitabine 825 mg/sqm/bid 5 days/week+ 50.4 Gy in 28 fractions over 5.5 weeks) plus 6 cycles of Ave 10 mg/Kg every 2 weeks. Surgery with total mesorectal excision was performed at 8-10 weeks after the end of CTRT. The primary end-point was the pCR rate, defined as complete histological regression with no available tumor cells ypTONO. Secondary end-points were R0 resection rate, tumor downstaging, local recurrence, sphincter preservation rate, progression-free survival, overall survival, safety profile, and the evaluation of exploratory predictive and/or prognostic biomarkers. Assuming as null hypothesis p0 a pCR rate of 15%, a significance level of 5% (one-side), and a power of 80%, a sample size of 101 pts was needed to detect an absolute increment of 10% in pCR rate (from 15% to 25%). The experimental regimen is considered for further studies if, in at least 22 pts, we observe a pCR. **Results:** From April 2019 to November 2020, a total of 101 resectable LARC pts were enrolled in 10 Italian Centers. The median age was 63 years (23-82), 62 (61.4%) pts were male, 93 (92%) had ECOG PS 0. At baseline, 94 (93%) and 16 (16%) pts had cN+ and cT4 LARC, respectively. All pts completed the induction phase. Out of 96 pts evaluable for pathological response, 22 (23%) pts achieved a pCR and 59 (61.5%) pts a major pathological response (a central review is ongoing). At this time, microsatellite status is available only in 39 pts, of which only one was instable. The rate of grade 3-4 non-immune and immune-related adverse events was 8% and 4%, respectively. Avelumab was early interrupted in 9 pts out 101, mainly due to toxicity. **Conclusions:** The combination of preop CTRT plus Ave showed a promising activity and a feasible safety profile. According to our statistical considerations, the experimental regimen will be considered for further studies. Updated results will be presented during the Congress. Sponsored by GONO and partially supported by Merck. EUDRACT 2017-003582-10. Clinical trial information: NCT03854799. Research Sponsor: Gruppo Oncologico del Nord Ovest (GONO Group), Pharmaceutical/Biotech Company.

3512 **Poster Discussion Session**

Phase II trial of neoadjuvant mFOLFOX 6 with panitumumab (P) in T3 rectal cancer with clear mesorectal fascia (MRF) and *KRAS*, *NRAS*, *BRAF*, *PI3KCA* wild type (4WT). GEMCAD 1601 PIER trial. *First Author: Carlos Fernandez-Martos, Hospital Quironsalud, Valencia, Spain*

Background: Patients with advanced colorectal cancer with 4WT tumors achieve increased response rates with chemotherapy and anti-EGFR therapy as compared with chemotherapy alone. In clinically staged (c) T3 rectal cancer neoadjuvant oxaliplatin/fluoropyrimidine combination has shown to induce encouraging pathological complete response (pCR). We hypothesize that combining FOLFOX and P could improve outcomes in 4WT tumors. **Methods:** PIER was an investigator-initiated phase II, single-arm, multicentre clinical trial to evaluate the safety and efficacy of neoadjuvant mFOLFOX6 with P in pts < 75-y, with 4WT rectal cancer of the middle third staged as T3 by centrally-reviewed magnetic resonance imaging (MRI) and clear MRF, who were candidate for a R0 resection with sphincter preservation surgery. Pts received 6 cycles and underwent re-staging with MRI and sigmoidoscopy. Pts without progression underwent total mesorectal excision 4 weeks after the last cycle. Patients with progression were treated with pre-op chemoradiotherapy. The primary endpoint was pCR. The study followed a 2-Stage Simon's MiniMax design (P0 of 16%, P1 of 35%, alpha and beta of 0.1). The target sample size was 35 patients and if 9 or more achieved a pCR, the results would be compatible with efficacy. We present primary and early secondary endpoints. **Results:** Between 9/2017 and 6/2020, 90 patients were screened (56 excluded; 42 were excluded due to mutations, 12 were excluded due to discrepancies with central review of radiology) of whom 34 were enrolled. In the ITT population a pCR was observed in 11 pts (32.3%; [95% CI 17.39-50.53]) and a near-complete pathological response (Mandard 1+2) was observed 17 pts (52.9%). Clinical complete or near complete response was achieved in 50% and there were no progressions. R0 resection rate and pathological circumferential resection margin neg- were 100%. Full compliance with induction was 88%. Neoadjuvant G3/4 toxicity occurred in 54% and was consistent with FOLFOX/P safety profile. G3/4 postoperative related toxicity was 19% with one reoperation. **Conclusions:** The study met the threshold for efficacy. mFOLFOX6 with P as neoadjuvant therapy can be effective and safe without unexpected toxicities in mrT3, clear MRF and 4WT rectal cancer and resulted in a higher rate of pCR compared with our previous series (GEMCAD 0801; The Oncologist 2014) in a similar molecular-unselected population. This study was funded by Amgen S.A. Clinical trial information: NCT03000374. Research Sponsor: AMGEN.

3513 **Poster Discussion Session**

Molecular correlates of clinical benefit in previously treated patients (pts) with *BRAF* V600E-mutant metastatic colorectal cancer (mCRC) from the BEACON study. *First Author: Scott Kopetz, MD Anderson Cancer Center, Houston, TX*

Background: Encorafenib + binimetinib + cetuximab (enco/bini/cetux; triplet) and enco + cetux (doublet) regimens improved overall survival and objective response rate vs standard of care in pts with previously treated *BRAF* V600E-mutant mCRC in the randomized phase 3 BEACON study. To identify molecular correlates of clinical outcome, we performed molecular profiling in tumors from pts in the study. **Methods:** Baseline tumor samples were retrospectively analyzed by whole-exome sequencing (WES) and whole transcriptome sequencing (WTS) using ImmunoID NeXT (Personalis, Menlo Park, CA, USA). *BRAF*-mutant (BM) and consensus molecular subtypes (CMS) were determined using published classifiers. Pathway activities were evaluated with gene set variation analysis. Objective tumor response was evaluated according to each subtype. Additional association and interaction analyses between molecular features and clinical outcomes by treatments are ongoing and will be presented. **Results:** Baseline tumor samples were analyzed by WES and/or WTS from 527 of 665 (79.2%) randomized pts. The biomarker analyses set is representative of the total pt population and had similar clinical outcomes. Of the 460 pts analyzed by WTS (165/224 [73.7%] in the triplet arm, 146/220 [66.4%] in the doublet arm, and 149/221 [67.4%] in the control arm), 84.6% were classified as either CMS1 (n = 225) or CMS4 (n = 164). The proportion of pts classified as BM1 was 32.2% (n = 148) and the majority (84.5%) of these were CMS4, whereas many of those classified as BM2 (67.8%, n = 312) were CMS1 (64.7%). In the BM1 and CMS4 tumors, expression of inflammatory response and epithelial mesenchymal transition genes were elevated, and expression of cell cycle genes was reduced. The response rate in pts with CMS4 and/or BM1 tumors was higher in the triplet arm (CMS4: 33.3% [95% CI: 21.7–46.7]; BM1: 33.3% [95% CI: 21.4–47.1]) compared with the doublet arm (CMS4: 19.2% [95% CI: 9.6–32.5]; BM1: 14.9% [95% CI: 6.2–28.3]). **Conclusions:** Molecular characteristics and biological properties observed in *BRAF* V600E-mutant mCRC suggest that a subset of pts with specific molecular features may derive greater clinical benefit from triplet than doublet therapy. Additionally, these findings support the utility of gaining further understanding of the biological landscape in *BRAF*-mutant mCRC to enable potential hypotheses for pt selection to improve clinical outcome in future studies. Clinical trial information: NCT02928224. Research Sponsor: Pfizer.

3514 **Poster Discussion Session**

Rarity of acquired mutations (MTs) after first-line therapy with anti-EGFR therapy (EGFRi). *First Author: Christine Megerdichian Parseghian, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Colorectal cancers (CRC) lacking *RAS* MTs treated with EGFRi are thought to evolve by a repetitive process of genetic diversification and clonal evolution. Acquired MTs in *KRAS, NRAS, BRAF, MAP2K1*, and *EGFR* are known mechanisms of acquired resistance in the EGFRi refractory population. However, the prevalence of MTs in the first line (1L) setting is not well established as most experience with EGFRi has been beyond the 1L setting. **Methods:** We analyzed paired plasma samples from *RAS/BRAF/EGFR*^{WT} mCRC patients (pts) enrolled in 3 large randomized phase 3 trials who had been treated with EGFRi and in whom paired baseline (BL) and time of progression (PRO) plasma samples had been collected for sequencing of ctDNA on a platform optimized for very low allele frequencies (Plasma*Select*-R™ and Resolution Bio™). Prevalence of MTs at BL and PRO from a 1L study ('203; FOLFOX ± panitumumab) were compared with 2 studies in the third line setting (3L; '007; panitumumab + best supportive care [BSC] vs BSC; and 3L; '763; panitumumab vs. cetuximab), to assess the frequency of acquired resistance mutations via ctDNA analysis. **Results:** For pts with available paired plasma samples (n = 112 for '203; n = 89 for '007; n = 274 for '763), acquisition of at least one *KRAS, NRAS, BRAF, MAP2K1*, or *EGFR* MT was significantly less common in post-progression samples in the EGFR containing arms of the 1L '203 study compared to the 3L '763 and '007 studies (6.8% vs 50.4% vs 39.6%, respectively; p < 0.001). In the non EGFR containing arms of the '203 and '007 study, the rate of acquired MTs was 7.5% and 0%, respectively (p = 1). While this difference in the rate of acquired MTs between the EGFR and non EGFR containing arms was statistically significant for the 3L study (p < 0.001) it was not significant for the 1L study. Further, pts on both 3L studies treated with EGFRi who experienced CR, PR or SD acquired more MTs than those who had PD as best response (53.6% vs 33.3%, respectively; p < 0.001). This relationship was not significant in the 1L setting (7.7% vs 0%; p = 1). Subclonal MTs (rMAF < 25%) in *KRAS, NRAS, EGFR, BRAF* and *MAP2K1* were present at BL in 129 pts (27%). Based on the hypothesis that EGFRi is selecting for rare existing mutated cells in the tumor, we would expect expansion of any preexisting subclones in the BL samples. However, in contrast to expectations, these subclones rarely expanded to become clonal at the time of progression (12.4%). **Conclusions:** In contrast to expectations, acquired *KRAS, NRAS, BRAF, EGFR*, or *MAP2K1* MTs rarely develop after 1L therapy. While selective pressure appears to increase the frequency of acquired MTs in the 3L setting, preexisting subclonal MTs do not appear to be the dominant source of acquired MTs at progression, implying that there may also be a transient mutational process driving resistance rather than expansion of preexisting clones. These findings have significant implications for ongoing and planned EGFRi rechallenge studies. Research Sponsor: Amgen inc.

3515 **Poster Discussion Session**

Immune signatures to affect overall survival (OS) and response to bevacizumab (Bev) or cetuximab (Cet) in patients (pts) with metastatic colorectal cancer (mCRC) of CALGB/SWOG 80405 (Alliance). *First Author: Federico Innocenti, University of North Carolina at Chapel Hill, Chapel Hill, NC*

Background: CALGB/SWOG 80405 was a randomized phase III trial in first-line mCRC patients treated with Bev, Cet, or both, plus chemotherapy. No difference in OS was found between Bev and Cet. We tested the effect of immune signatures on OS in all the three arms of the study and analyzed differences in OS between the Cet and Bev arms. **Methods:** 578 primary tumors were profiled by RNAseq. Immune signatures of TGF-β, cytotoxic T cells, wound healing, macrophages, lymphocytes, and INF-γ, as well as relative frequencies of CD8+ T-cells, memory resting CD4+ T cells, memory activated CD4+ T cells, macrophages M1 and M2, and activated mast cells were measured. Multivariate Cox proportional hazard models were applied using elastic-net penalization with covariates (age, race, gender, all *RAS* and *BRAF* V600E mutations). For relevant signatures, optimal cut-offs for OS were calculated. **Results:** In all the three arms of the study, high expression of macrophages M2 (HR 6.81, 95% CI 3.56-30.16) and TGF-β (HR 1.37, 95% CI 1.03-2.10) conferred reduced OS compared to low expression; high expression of plasma cells (HR 0.52, 95% CI 0.27-0.83) and memory-activated CD4+ T cells (HR 0.34, 95% CI 0.10-0.65) conferred increased OS compared to low expression. Using optimal cut-offs from these 4 signatures, pts have been categorized as to whether they had either 4, 3, 2, 1, or 0 beneficial signatures associated with increased OS. In all arms of the study (N = 469, after accounting for covariates), the median (95% CI) OS decreased from 42.5 (35.8-47.8; N = 79), to 31.0 (28.8-34.4; N = 177), 25.2 (20.6-27.9; N = 144), and 17.0 (13.5-20.4; N = 69) months when the number of beneficial signatures decreased from 4, to 3, 2, and 0-1 (combined due to a low number of pts), respectively (p = 3.48e-11). In the Bev arm (N = 205), high expression of macrophages M2 conferred reduced OS compared to low expression (HR 6.6, 95% CI 2.7-67.1). In the Cet arm (N = 165), high expression of macrophages M2 conferred reduced OS compared to low expression (HR 4.3, 95% CI 2.1-79.8); high expression of plasma cells (HR 0.36, 95% CI 0.06-0.55) and memory activated CD4+ T cells (HR 0.37, 95% CI 0.03-0.98) conferred increased OS compared to low expression of either signatures. The plasma cell signature interacted with Bev and Cet on the OS of pts (interaction p = 0.009). **Conclusions:** Tumor immune signatures in mCRC pts are determinants of survival. In pts treated with Bev- and Cet-combination therapies that are standard of care, immune signatures affect response to therapy. These results, provide new markers for treatment selection and for the development of novel active combinations including immune checkpoint inhibitors. Support: U10CA180821, U10CA180882, U24CA196171; https://acknowledgments.alliancefound.org Research Sponsor: U.S. National Institutes of Health.

3516 **Poster Discussion Session**

Examination of the tumor immune microenvironment (TIME) with multispectral immunofluorescence (m-IF): Association of markers with prognosis and bevacizumab (bev) benefit in NRG Oncology/NSABP C-08. *First Author: Katherine L. Pogue-Geile, NSABP/NRG Oncology, Pittsburgh, PA*

Background: The purpose of this study was to quantify different molecules of TIME including T cells, macrophages, and immune checkpoint proteins (ICPs), and determine their association with clinical outcomes and treatment benefit in pts enrolled in C-08, which tested the efficacy of adding bev to 5-fluoruracil+leucovorin+oxaliplatin. Our prespecified, NCTN-CCSC approved primary objective hypothesized that pts with more CD8 cells would have a better prognosis and receive benefit from bev. **Methods:** Tissue microarrays were used to assess TIME of 1,509 C-08 pts using m-IF and the Vectra Pathology System. Three m-IF panels were used to quantitatively assess T cells (CD3, CD8, CD45RO, FOXP3), macrophages (CD68, CD163), and ICPs (PD-1, PD-L1, CTLA4, TIM3, LAG3, OX40) in stromal and tumor (panCK) regions. The primary objective was to determine the association between overall survival (OS) and high (top 3rd) *v* low CD8 expression in both stromal and tumor regions. All markers were tested for associations with OS and recurrence-free interval (RFI) and with bev prediction using Cox models and median cut points. **Results:** Based on our pre-specified analysis, pts with high CD8 cells had better OS, HR=0.66 (95%CI: 0.49-0.88), p=0.005 but pts with high CD8 cells did not receive bev benefit. All T cells and double stained CD8/PD-1 were associated with better RFI. CD3, CD8, CD68, PD-1, PD-L1, and LAG3 cells were associated with better OS. PD-1 and CD8/PD-1 were associated with RFI in pts with deficient mismatch repair (dMMR) and proficient (p)MMR but TIM3, CD3/CD45RO and CD163 were only associated with RFI in dMMR. Association of CD8 cells with bev benefit (RFI) was seen in dMMR pts, HR 0.27 (95% CI: 0.1-0.73), p=.01 and OS, HR=0.27, (95% CI: 0.12-0.64), p=0.0028 but there was no significant interaction. Single staining CD8, PD-1, and double staining CD8/PD-1 cells were associated with bev benefit in dMMR pts but with bev harm in pMMR pts. However, pts with tumors having >1% of PD-1 and PD-L1 cells (n=197 including 76 dMMR, 100 pMMR, and 21 unknown), received significant bev benefit (int p=.0056). **Conclusions:** CD8 cells were associated with better OS but were not associated with bev benefit. All T cells and PD-1, PD-L1, and LAG3 cells, were associated with better prognosis in the entire cohort but when pts were stratified for MMR status differences in their association with prognosis and bev benefit emerged. PD-1, CD8, and CD8/PD-1 cells were associated with bev harm in pMMR but bev benefit in dMMR. A significant interaction for the association of high % PD-1 and PD-L1 with bev benefit regardless of MMR status may be a chance finding. However, VEGF has immunosuppressive effects and bev may block these effects in tumors with high PD-L1 and PD-1, regardless of MMR status. NCT: 00096278 PA DOH, U10CA-180868, -180822, -196067, Genentech, Sanofi; NSABP. Clinical trial information: 00096278. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency, Pharmaceutical/Biotech Company.

3517 **Poster Discussion Session**

Early-onset stage II/III colorectal adenocarcinoma in the IDEA database: Treatment adherence, toxicities, and outcomes from adjuvant fluoropyrimidine and oxaliplatin. *First Author: Elisa Fontana, Sarah Cannon Research Institute, United Kingdom, London, United Kingdom*

Background: Incidence of early-onset colorectal cancer (eoCRC, age < 50) is steadily increasing. Decisions on adjuvant treatment (adjTx) regimen and duration should consider tx adherence, toxicity (tox) and expected outcomes in a population with life-expectancy longer than late onset CRC (loCRC, age ≥ 50). **Methods:** Individual patient data from stage II/III patients (pts) from 6 randomised trials in the IDEA database were used to compare characteristics, tx adherence, and adverse events of eoCRC to loCRC. To reduce the confounder of non-cancer-related deaths due to age/co-morbidities, time-to-recurrence (TTR) and cancer-specific survival (CSS) were compared by stratified Gay k-sample test. 5-year cancer-specific mortality (CSM) rate were estimated by adjusted cumulative incidence function. 3-year relapse-free survival (RFS) rate were compared by stratified and adjusted COX models. **Results:** Out of 16,349 pts included, 1564 (9.6%) were eoCRC. Compared to loCRC, eoCRC had lower percent of male pts (51% vs 57%, p < 0.01) better performance status (PS0 86% vs 80%, p < 0.01), similar T stage distribution (% T1-3/T4: 76/24 vs 77/23, p = 0.97), higher rate of N2 disease (24% vs 22%, p < 0.01), more likely to complete pre-planned duration of adjTx (83.2% vs 78.2%, p < 0.01) and received a higher tx intensity especially with 6 month tx (mean oxaliplatin dose intensity 75% vs 72%, p < 0.01; capecitabine 85% vs 78%, p < 0.01; 5FU 85% vs 82% p < 0.01). Gastrointestinal tox was more common in eoCRC (any grade nausea 58% vs 45%, p < 0.01; any grade vomiting 22% vs 16%, p < 0.01); haematological tox was more frequent in loCRC (62% vs, 69%, p = < 0.01); any grade neuropathy rate was similar (75%). Significant interaction was found between age and T stage for TTR (p = 0.04). Clinical outcome estimates and comparisons are shown in Table. Notably, high risk stage III (T4/N2) eoCRC had significantly lower 3-y RFS rate (54% vs 64%, HR_{adj} 0.74, p < 0.01). **Conclusions:** eoCRC have better tx adherence than loCRC, as expected. While in high risk stage II and low risk stage III, cancer-specific outcomes are not different, in high risk stage III young age is negatively prognostic and associated with significantly higher relapse rate and risk of CRC death; this is despite a higher administered adjTx-intensity, suggesting a more aggressive disease biology. Clinical trial information: NCT00749450 (SCOT); NCT00646607 (TOSCA); NCT01150045 (CALGB/SWOG 80702); NCT00958737 (IDEA France); Research Sponsor: EORTC GI Group supported the pooled analyses, ACHIEVE supported by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) and funded by Yakult Honsha Co, Ltd; CALGB/SWOG 80702 was supported by grants (U10CA180821, U10CA180835, UG1C).

		eoCRC	loCRC	Adjusted Hazard Ratio (95% Confidence Interval)	p-value
3-y RFS, %	High risk Stage II	87.6 (84.1-91.3)	88.0 (86.8-89.2)	0.98 (0.72-1.34)	0.91
	Stage III T1-3 N1	81.6 (78.0-85.3)	84.0 (83.0-84.9)	0.99 (0.80-1.22)	0.90
	Stage III T4 or N2	54.5 (49.7-59.9)	64.5 (63.1-65.9)	0.74 (0.64-0.87)	**0.0003**
5-y CSM %	High risk Stage II	4.8 (2.9-7.8)	7.6 (6.6-8.7)	1.38 (0.84-2.27)	0.21
	Stage III T1-3 N1	7.1 (5.1-9.8)	6.9 (6.3-7.5)	0.96 (0.70-1.30)	0.78
	Stage III T4 or N2	23.9 (20.0-28.6)	20.7 (19.5-21.9)	0.81 (0.67-0.99)	**0.040**

3518 **Poster Discussion Session**

Prevalence of fertility discussions between young adult colorectal cancer survivors and their providers. *First Author: Julia Stal, University of Southern California, Los Angeles, CA*

Background: Clinical guidelines indicate that oncologists should discuss potential treatment-induced infertility with patients with reproductive potential. Due to tumor location and use of multimodal therapies, young adults with colorectal cancer (CRC) are at heightened risk for treatment-related infertility. **Methods:** An online, cross-sectional survey was administered in collaboration with a national patient advocacy organization for young adult CRC survivors (currently under age 50). Survivors were asked to indicate if a doctor had ever talked to them about potential problems with their ability to have children after treatment and if they banked eggs/embryos (females) or sperm (males) prior to their cancer therapy. Those who reported that they did not preserve fertility were asked to indicate why (*not sure; I chose not to; I did not know this was an option; I wanted to, but could not afford it;* and *I wanted to, but my treatment would not allow it*). **Results:** A total of 234 colon (N=86) or rectal (N=148) cancer survivors were included in the study (male [61.9%] and White [77.9%; table]). Most respondents were diagnosed with stage 2 cancer (55.8% colon, 61.6% rectal). Over half of male and female survivors reported that their doctor did not talk to them about problems with their ability to have children after treatment, and 75% did not bank eggs/embryos or sperm prior to their cancer therapy. Of those, over 20% endorsed 'I wanted to, but could not afford it' and over 20% endorsed 'I did not know this was an option'. **Conclusions:** Most CRC survivors in this study reported never having a fertility discussion with their provider, suggesting that survivors are not receiving, or cannot recall, comprehensive and guideline-concordant cancer care. In addition, one-fifth were not aware of preservation options, suggesting potential healthcare and/or provider-level barriers to appropriate fertility counseling. Fertility preservation cost is another barrier to the appropriate delivery of care. Providers must ensure that patients receive timely fertility discussions covering options to preserve fertility to mitigate this late effect of cancer treatment to ensure optimal quality of life for CRC patients with reproductive potential. Research Sponsor: The Aflac Archie Bleyer Young Investigator Award in Adolescent and Young Adult Oncology from the Children's Oncology Group. Additional support was provided by the NCI Cancer Center Support Grant from the USC Norris Comprehensive Cancer Center.

Fertility preservation frequencies (N=234).

	Gender	
	Male	**Female**
Has a doctor ever talked to you about problems with your ability to have children after your treatment?		
Yes	60 (41.38)	35 (41.18)
No	81 (55.86)	49 (57.65)
Not Sure	4 (2.76)	1 (1.18)
Did you bank eggs/embryos (female; sperm, male) prior to your cancer therapy?		
Yes	30 (20.98)	19 (22.35)
No	107 (74.83)	64 (75.29)
Not Sure	6 (4.20)	2 (2.35)
If no (did not bank eggs/embryos or sperm), I decided not to because...		
I wanted to, but my treatment would not allow it	9 (6.38)	4 (4.82)
I wanted to, but could not afford it	31 (21.99)	19 (22.89)
I did not know this was an option	33 (23.40)	18 (21.69)
I chose not to	58 (41.13)	38 (45.78)
Not sure	10 (7.09)	4 (4.82)

3519 **Poster Discussion Session**

Microbiome signature, global methylation and immune landscape in early onset colorectal cancer. *First Author: Ning Jin, Univ of Wisconsin, Madison, WI*

Background: The incidence of colorectal cancer (CRC) in young adults (< 50 years old) has been rapidly increasing by 2% per year since early 1990. Approximately 20% of early-onset (EO) CRC cases are due to germline gene mutations. However, the etiology of sporadic EO CRC remains poorly understood. Research suggests that environmental factors such as the Western diet (high in fat and low in fiber) may be associated with an increased incidence of sporadic EO CRC. The gut microbiota decompose and ferment dietary fibers to produce microbial metabolites, which play pivotal roles in maintaining the integrity of intestinal epithelium as well as the immune cell homeostasis. Also, these microbial metabolites may influence the host epigenome by altering either the activity of epigenetic enzymes or by modifying the availability of cofactors needed for epigenetic modifications. The aim of our research is to associate intratumoral microbiota with methylation pattern and immune cell composition in EO CRC. **Methods:** A total of 358 CRC cases, including 54 cases of EO CRC (age < 50 years) and 304 cases of late onset (LO) CRC (age ≥ 50 years), with matched methylation array (Infinium HM450), RNA-sequencing (Illumina HiSeq) from colon adenocarcinomas (COAD) and rectal adenocarcinomas (READ), and clinicopathological information of each patient, were extracted from the Cancer Genome Atlas (TCGA). We characterized and compared the intra-tumoral microbiota composition, tumor-infiltrating lymphocytes (TILs), and methylation profile between EO and LO CRC. **Results:** We found that there is a distinct microbial distribution, gene expression and methylation pattern in the EO CRC when compared with LO CRC. Non-human sequences from several kingdoms including bacteria, fungi and viruses were found and the incidences were consistent with reported values by other methods, e.g. *Fusobacterium* incidence. The EO CRC cases showed global hypomethylation, even though hypermethylation pattern is expected in the young chronological age group (known as Horvath's clock). Pathway overrepresentation analysis of differentially expressed genes showed significant activation of p53 and pentose phosphate pathways and *de novo* nucleotide synthesis in EO CRC. Integration across datasets showed positive correlations between microbes and inflammasome pathway, positive correlation with regulatory T cells (Tregs), and negative correlations with CD4 memory T cells. **Conclusions:** These data suggest a mechanism by which the colorectal cancer-associated microbiota may be associated with epigenetic regulation and host immune response. Research Sponsor: Internal grant (Division of Internal Medicine Seed Grant) at OSU.

3520 **Poster Session**

HPV-mediated anal squamous cell carcinoma and precancerous lesions in HIV positive patients. *First Author: Omar Bushara, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: Anal cancer affects over 8,000 patients per year in the United States and the incidence is increasing. A significant risk factor for anal cancer and precancerous lesions is human papilloma virus (HPV), with up to 90% of cases being associated with HPV infection. Another emerging risk factor is HIV co-infection. In the present study, we further address if CD4 count is a significant factor for driving higher-grade HPV-mediated anal squamous lesions in HIV/HPV co-infection patients with a single institution large cohort. **Methods:** A retrospective cohort of HPV-positive patients with anal biopsies was obtained from 2002-2020. Information on the grade of their anal lesion, HIV status, and CD4 count (cells/mm^3) were collected. In patients with HIV, the most recent CD4 count up to one year prior to or one month after their biopsy was utilized in our analysis. Lesions were grouped into low grade squamous intraepithelial lesions (LSIL) and higher grade squamous intraepithelial lesions (HSIL), carcinoma in situ (CIS), or squamous cell carcinoma (SCC). The Center for Disease Control CD4 count levels to define HIV status were utilized in our sub-analyses. The distribution of lesion grades was compared between HIV-negative and -positive patients, and between HIV-negative and three subgroups of HIV-positive patients using the Fisher's exact test. **Results:** Our cohort comprised of 3,354 total HPV-positive patients. 2,036 of these patients were HIV-negative and 1318 were HIV-positive. The proportion of higher grade lesions was significantly higher in HIV/HPV co-infected patients regardless of CD4 count (Table). The full cohort of HIV-positive patients had lower rates of LSIL (60.8% vs. 74.0%) and higher rates of higher-grade lesions (39.2% vs. 26.0%) ($p<0.001$) compared to HIV-negative patients. The distribution of lesion grades was also significantly different between HIV-negative patients and all HIV-positive patient subgroups, with all subgroups having higher rates of higher-grade lesions than HIV-negative patients (all $p<0.001$). **Conclusions:** Our data show that HIV-HPV co-infection is a risk factor for higher grade anal lesions, regardless of CD4 status. This suggests that CD4 count is not the only factor responsible for the increased risk of higher-grade anal lesions, as the groups of HIV-positive patients with CD4 counts between 200-499 and above 499 still had a higher rate of higher-grade lesions than HIV-negative patients. Further research into other HIV-related immunologic changes that increase risk for higher-grade HPV-driven anal lesions is warranted. Research Sponsor: None.

Distribution of anal lesions by HIV and CD4 status.

		LSIL		HSIL/CIS/SCC		
	Total N	N	%	N	%	P Value
Full Cohort	3354	2309	68.8%	1045	31.2%	
HIV Negative	2036	1507	74.0%	529	26.0%	
HIV Positive	1318	802	60.8%	516	39.2%	<0.001
CD4 < 200	*170*	*79*	*46.5%*	91	53.5%	*<0.001*
CD4 200-499	*492*	*296*	*60.2%*	196	39.8%	*<0.001*
CD4 > 499	*656*	*427*	*65.1%*	229	34.9%	*<0.001*

3521 **Poster Session**

Final analysis of dose-finding and single-arm confirmatory study (phase I/II study) of definitive chemoradiotherapy (dCRT) with S-1/mitomycin-C (MMC) in patients (pts) with clinical (c) Stage II/III squamous cell carcinoma of the anal canal (SCCA): JCOG0903. *First Author: Yoshinori Ito, Department of Radiation Oncology, Showa University School of Medicine, Tokyo, Japan*

Background: dCRT with 5-FU/MMC is a standard treatment for cStage II/III SCCA. S-1 is an oral fluoropyrimidine and has a greater effect on radiosensitivity. We conducted this trial of dCRT with S-1/MMC to determine the recommended dose (RD) of S-1 in dose-finding (phase I) part and to evaluate the efficacy and safety in confirmatory (phase II) part for cStage II/III SCCA. We reported the RD of S-1 and the 3-year survival at 2019 Gastrointestinal Cancers Symposium. We report the final data after 5-year follow-up. **Methods:** Eligibility criteria included histologically proven SCCA, cStage II/III (UICC 6th), PS 0-1, and age 20-80 years. dCRT consisted of MMC (10 mg/m^2 on days 1, 29) and S-1 (60 mg/m^2/d in level 0 and 80 mg/m^2/d in level 1 on days 1-14, 29-42) with concurrent radiotherapy of 59.4 Gy/33fr. The dose-finding part adopted the 3+3 cohort design. The primary endpoint of confirmatory part was 3-year event-free survival (EFS). The sample size was 65 in the confirmatory part, with one-sided alpha of 5% and power of 80%, threshold and expected 3-year EFS as 60% and 75%. Key secondary endpoints were overall survival (OS) and progression-free survival (PFS) and colostomy-free survival (CFS), and adverse events. Final analysis was planned after 5-year follow-up for all pts. **Results:** From Feb/2010 to Mar/2015, 69 pts (3 in level 0 and 66 [7 in phase I and 59 in phase II] in level 1) were enrolled. Pts characteristics for level 1 were as follows: M/F, 12/54; Age, median 64 (range 33-80); cStage II/IIIA/IIIB, 29/9/28. Three in level 1 were ineligible and 63 eligible assigned to level 1 were included in efficacy analysis. In the dose-finding part, RD of S-1 was determined as 80 mg/m^2/d. The complete response rate was 81% (95% CI, 69.1-90.0%) on central review. With a median follow-up of 5.4 years, 3- and 5-year EFS was 65.0% (90% CI 54.1-73.9%) and 63.4% (95% CI 50.2-73.9%). 5-year OS, PFS, and CFS were 84.1% (95% CI 72.5-91.1%), 84.1% (95% CI 72.4-91.1%), and 73.0% (95% CI 60.2-82.3%), respectively. In a univariable analysis, male sex ($p = 0.045$) prognosticated for poor OS and cT3 or T4 ($p = 0.001$), male sex ($p = 0.019$) and, PS 1 ($p = 0.048$) prognosticated for poor CFS. Nine (14.3%) of 63 pts at a dose level 1 developed recurrence or disease progression. Locoregional recurrence only and distant metastasis were observed in 1 pts (1.6%) and 8 pts (12.7%) respectively. Among all treated 65 pts, only 5 pts (7.7%) showed grade 3 late toxicities including jejunum obstruction, jejunum ulcer, proctitis, lower gastrointestinal hemorrhage, anal pain, radiation dermatitis, and ureteral stenosis. No Grade 4 or 5 late toxicities were observed. **Conclusions:** dCRT with S-1/MMC showed acceptable toxicities and favorable 5-year survival and could be a possible treatment option for pts with locally advanced SCCA. Clinical trial information: jRCTs031180002. Research Sponsor: 26-A-4, 29-A-3, 2020-J-3, Grants-in-Aid for Clinical Cancer Research (H23Gann-012) from the Ministry of Health.

3522 **Poster Session**

Association between cancer stem cell marker ALDH1 and clinical and morphological factors of colorectal cancer prognosis. *First Author: Elena A. Nikipelova, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Cancer stem cells (CSCs) capable of self-sustaining and multipotent differentiation are considered among the most important factors limiting treatment effectiveness. ALDH1 is a marker of colorectal cancer (CRC) CSCs; it is involved in cell differentiation and proliferation, determines resistance to alkylating chemotherapeutic agents, and also induces epithelial-mesenchymal transition (EMT), which increases the invasive and metastatic potential of tumors. The purpose of the study was to assess the association between the expression of the ALDH1 CSC marker in tissues of CRC of different stages and clinical and morphological factors of the disease prognosis. **Methods:** The study included 299 patients (aged 42-86 years, mean age 64.2±1.7) with stage II-IV CRC T1-4N0-2M0-1; histologically verified G1-G3 adenocarcinoma in all patients. Tissues of surgically removed tumors were studied with IHC analysis using mouse monoclonal anti-ALDH1 antibodies (clone B-5, Santa Cruz Biotechnology) diluted 1:1800 and the Reveal Polyvalent HRP-DAB Detection System. The percentage of cells positively stained for ALDH1 among all tumor cells was assessed. Statistical analysis was performed using the STATISTICA 13.0 program (StatSoftInc., USA). **Results:** Positive ALDH1+ expression was registered in 52.5% of all patients, negative expression – in 47.5%. Statistically significant association was observed between the ALDH1 expression and the CRC stage, since the ALDH1+ expression increased from stage II to stage IV ($p = 0.003$). The ALDH1 expression was statistically significantly associated with the depth of tumor invasion ($p = 0.018$) and the presence of distant metastases ($p < 0.001$). No significant relationship was observed between the ALDH1 expression and regional lymph node metastasis ($p = 0.788$). Statistically significant association was registered between the ALDH1 expression and the tumor grade ($p < 0.001$), perineural invasion ($p = 0.010$) and lymphocytic infiltration ($p < 0.001$). No significant relationship was observed between the tumor histological structure ($p = 0.979$), lymphovascular invasion ($p = 0.772$) and ALDH1 expression. Tumor site was not statistically significantly associated with ALDH1 expression ($p = 0.349$). **Conclusions:** The study demonstrated statistically significant association between the ALDH1 expression and clinical and morphological characteristics of CRC, determining invasive and metastatic potential of the tumor, and ALDH1 may be an independent prognostic factor and a new therapeutic target for the regulation of the progression process. Research Sponsor: None.

3523 **Poster Session**

Circulating tumor DNA-based genomic profiling of small bowel adenocarcinoma. *First Author: Pat Gulhati, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Small bowel adenocarcinoma (SBA) is a rare malignancy, with lower incidence, later stage at diagnosis, and worse overall survival compared to other intestinal cancers, such as colorectal cancer (CRC). Since the majority of small bowel tumors are not accessible to endoscopic biopsy, comprehensive genomic profiling using circulating tumor DNA (ctDNA) may enable non-invasive detection of targetable genomic alterations (GA) in SBA patients. In this study, we characterize the ctDNA GA landscape in SBA. **Methods:** Analysis of 299 ctDNA samples prospectively collected from 265 SBA patients between 2017 to 2020 was performed using a 73 gene next generation sequencing panel (Guardant360). A subset of patients underwent longitudinal analysis of changes in GA associated with systemic therapy. **Results:** Of the 265 patients, 160 (60.3%) were male; the median age was 66 (range: 21-93 years). The most common GA identified in SBA patients included TP53 [58%], KRAS [44%], and APC [40%]. MSI was detected in 3.4% of SBA patients. When stratified by primary tumor location, APC, KRAS, TP53, PIK3CA, and ARID1A were the most common GA identified in both duodenal and jejunal adenocarcinomas. ERBB2, BRCA2 and CDK6 alterations were enriched in duodenal adenocarcinoma, while NOTCH and BRAF alterations were enriched in jejunal adenocarcinoma. The most common currently-targetable GA identified were ATM [18%], PIK3CA [17%], EGFR [15%], CDK4/6 [11%], BRAF [10%], and ERBB2 [10%]. Unique differences in GA between SBA and CRC were identified: i) the majority of ERBB2 alterations are mutations (89%) in the extracellular domain and kinase domain, not amplifications (11%); ii) the majority of BRAF alterations are non V600E mutations (69%) and amplifications (28%); iii) there is a significantly lower rate of APC mutations (40%). Alterations in DNA damage response pathway proteins, including ATM and BRCA 1/2, were identified in 30% of SBA patients. ATM alterations were more common in patients ^{3}65 years old. The most common mutations predicted to be related to clonal hematopoiesis of indeterminate potential were TP53, KRAS and GNAS. Longitudinal ctDNA analysis in 4 SBA patients revealed loss of mutations associated with therapeutic response (TP53 R342*, MAPK3 R189Q) and acquired mutations associated with therapeutic resistance (NF1 R1968*, MET S170N, RAF1 L613V). **Conclusions:** This study represents the first large-scale blood-based ctDNA genomic profiling of SBA. SBA represents a unique molecular entity with differences in frequency and types of GA compared to CRC. Variations in GA were noted based on anatomic origin within the small intestine. Longitudinal ctDNA monitoring revealed novel GA associated with therapeutic resistance. Identification of multiple targetable GA may facilitate clinical decision making and improve patient outcomes in SBA, especially when a tissue biopsy is not feasible or sufficient for comprehensive genomic profiling. Research Sponsor: None.

3524 **Poster Session**

Association of HER2 expression with pathologic features and prognosis in stage II and III colon cancer. *First Author: Zehua Wu, Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: We examined the frequency, tumor characteristics, and prognostic impact of HER2 protein expression in stage II and III colon cancer after curative resection. **Methods:** Paraffin-embedded tumors from consecutive primary stage II and III colon cancer patients were analyzed for HER2 protein expression by immunohistochemistry between April, 2013 and May, 2020. HER2 determination of immunohistochemistry scores (0/1+/2+/3+) was according to HERACLES diagnostic criteria. **Results:** A total of 2088 stage II and III colon cancer patients were included (53.8% stage II, 46.3% stage III). HER2 scored positive (3+) was detected in 48(2.3%) tumors, and was correlated with younger age ($P < 0.001$), well/moderate differentiation ($P = 0.026$), proficient mismatch repair (pMMR) ($P = 0.045$) and KRAS wild-type ($P < 0.001$). HER2 scored positive (3+) was not significantly associated with disease-free survival (DFS) compared with HER2 scored negative (0/1+), neither in stage III patients (multivariable HR, 0.86; 95CI, 0.38 to 1.94; $P = 0.717$), nor in stage II patients (multivariable HR, 1.68; 95CI, 0.74 to 3.84; $P = 0.218$). In a separate analysis involving stage II patients without any high-risk factor ($n = 741$), those with HER2 scored positive (3+) tumors ($n = 16$) showed significantly reduced DFS (multivariable HR, 2.91; 95CI, 1.04 to 8.81; $P = 0.041$) compared with patients with HER2 scored negative (0/1+) tumors, independent of sex, age and MMR status. **Conclusions:** HER2 scored positive (3+) was independently associated with poor DFS in stage II colon cancer patients without high-risk factors. HER2 expression determination may help to judge the prognosis of those patients and guide adjuvant chemotherapy. Research Sponsor: None.

3525 **Poster Session**

Clinical utility of stool-based *SDC2* methylation test for the detection and screening of colorectal cancer in a Chinese population. *First Author: Yanmei Liu, The Qingyuan People's Hospital, Qingyuan, China*

Background: In 2020, colorectal cancer (CRC) ranks second in incidence and third in mortality among all types of cancers in China based on data from GLOBOCAN. Moreover, the rates of incidence and mortality have been continuously rising over the past several decades. In addition to conventional methods for detection and screening of CRC such as gFOBT, FIT, and colonoscopy, a stool-based methylation test of human *SDC2* gene was recently approved by National Medical Product Association (NMPA) of China. We hereby report the performance of this newly approved test in a hospital-based cohort of more than 10,000 patients in the real world of daily clinical practice. **Methods:** The methylation target, human *SDC2* gene, was extracted from stool and purified via sequence-specific capture technology. The isolated DNA was further treated with bisulfite before it was subsequently amplified by quantitative methylation-specific polymerase chain reaction (qMSP) to analyze the fecal level of *SDC2* methylation. Subjects were further examined by colonoscopy or CT imaging. Pathological examination would also be performed in cases deemed necessary. **Results:** A total of 11,284 individuals were tested using the novel *SDC2* methylation test. Among them, 858 and 10,426 were tested positive and negative, respectively. Follow-up visits, treatment, and medical information were complete for 429 positive and 780 negative patients who were included in this final analysis. Positive predictive value (PPV) of CRC and adenomas was 36.4% (156/429) and 24.5% (105/429), respectively. Stratified analysis implies that *SDC2* methylation level in CRC was significantly higher than those in adenoma and normal groups. In CRC, no significant correlation was observed between *SDC2* methylation and clinicopathological features including gender and grade of dysplasia. In < 65 and ≥ 65 age groups, the CRC detection rate in males was higher than that in females-almost two times higher in ≥ 65 age group. **Conclusions:** The stool-based *SDC2* methylation test demonstrated high accuracy in the detection of CRC and advanced adenomas. It is a sensitive and valid modality expected to play a significant role to aid diagnosis and screening of CRC and precancerous lesions in order to reduce the morbidity and mortality of this malignant disease. Research Sponsor: None.

3526 **Poster Session**

Patient-reported quality of life data from patients with pre-treated metastatic colorectal cancer receiving trifluridine/tipiracil: Interim results of the TALLISUR study. *First Author: Meinolf Karthaus, Klinikum Neuperlach/Harlaching, Munich, Germany*

Background: Compared to placebo, trifluridine/tipiracil (FTD/TPI) significantly improved overall and progression-free survival in patients (pts) with pre-treated metastatic colorectal cancer (mCRC) in the phase III RECOURSE trial. Although time to deterioration of ECOG performance status (PS) from 0/1 to ≥ 2 was significantly longer in pts treated with FTD/TPI, health-related quality of life (HRQoL) was not formally assessed by direct means. Therefore, a two-arm trial with best supportive care (BSC) as appropriate comparative treatment was designed to specifically address the effect of FTD/TPI on HRQoL. **Methods:** In this prospective, multi-center, German, open-label, phase IV study, pts with pre-treated mCRC could choose between BSC or oral FTD/TPI (35 mg/m^2 *bid* on days 1-5 and 8-12 of each 28-day cycle). EORTC QLQ-C30 and EQ-5D-5L questionnaires were employed to assess HRQoL. Primary endpoint was the rate of responders with stabilized (> -10 and < 10 scores) or improved (≥ 10 scores) response (RR). Response was calculated as the mean score of the EORTC QLQ-C30 global health status/QoL scale from the 2nd cycle until the end of treatment/ observation compared to the baseline score. **Results:** Of 194 eligible pts, 185 pts chose treatment with FTD/TPI (median 3 cycles), while 9 pts decided to receive BSC only. Questionnaires from 109 pts receiving FTD/TPI and from 6 pts with BSC were evaluable for RR. The primary endpoint (RR) was 59.6% (95% CI 49.8 – 68.9) in FTD/TPI-treated pts and 50.0% (95% CI 11.8 – 88.2) in pts receiving BSC. Analysis of the extended follow-up period, demonstrated that RR was 67.0% (95% CI 57.3 – 75.7) in FTD/TPI-treated pts. In the FTD/TPI-group, median time to deterioration of HRQoL was 121 days ($n = 61$; 95% CI 87 – 151) according to EORTC QLQ-C30 and 119 days ($n = 63$; 95% CI 85 – 138) according to EQ-5D-5L. **Conclusions:** If pts can choose between treatment and BSC in late-stage CRC, the vast majority opts for treatment. According to the present results, FTD/TPI-treatment induced prolonged stabilization of HRQoL, a highly desired attribute of therapies for pts with late-stage cancer. Clinical trial information: No 2017-000292-83. Research Sponsor: Servier Pharma Germany.

3527 **Poster Session**

Globo H expression in metastatic colorectal cancer (CRC). *First Author: Priya Jayachandran, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Globo H is a carbohydrate antigen that is highly expressed on the cell surface of epithelial cancers but not in normal tissue, and has been reported to correlate with poor prognosis. An attractive therapeutic target, Globo H-targeted agents are being tested in early clinical trials (e.g., OBI-833, a Globo H antigen conjugated to a mutated diphtheria toxin with potential antineoplastic activities, and OBI-999, an antibody-drug conjugate (ADC) consisting of a Globo H monoclonal antibody with a synthetic antineoplastic agent). We aim to describe the molecular features associated with Globo H expression in CRC. **Methods:** A total of 7,604 CRC tumors were tested by Caris Life Sciences (Phoenix, AZ) by NextGen DNA and RNA sequencing. The expression of β3GalT5, FUT-1 and FUT-2 were evaluated as surrogates for Globo H expression as they are the key enzymes in its biosynthesis. An average z-score of the 3 genes (GloboH) and of β3GalT5 (B3) alone were calculated; tumors with top quartile z-scores were considered expression-high (Q4) and bottom quartile, expression-low (Q1). QuantiSEQ was used to assess immune cell infiltration in the tumor microenvironment (TME). Statistical significance was determined using chi-square/Fisher-Exact and adjusted for multiple comparisons ($q<0.05$). Consensus molecular subtype (CMS) was developed using RNA seq data. **Results:** When the 3 genes were considered, GloboH-H tumors showed higher prevalence of CMS1 and CMS4 (23.8% vs. 12%; 38.7% vs. 29.4%) and lower prevalence of CMS2 (40% vs. 18.7%) compared to GloboH-L. Similar patterns of CMS distribution were seen for B3 alone. B3-H tumors were significantly more frequently TMB-H ($>=10$) (11.4% vs. 8.3%), PD-L1 positive (5.7% vs. 3.4%) and MSI-H/dMMR (8.3% vs. 5.5%). Strong positive associations were seen with mutations in *BRAF*, *KRAS*, *RSPO3* fusion, and *cMYC* amplification with B3 alone and GloboH (all $q<0.05$). Anti-tumor CD4+ T cells and NK cells were increased in the TME with increased expression of GloboH and B3 ($q<0.05$). However, immune suppressive neutrophils and Tregs were also increased. Dendritic cells were negatively associated with B3 expression while endothelial cells and fibroblasts showed a positive association with GloboH and B3. **Conclusions:** The association with TMB-H, MSI-H, and PD-L1 status suggests that in some tumors Globo H may be a promising target for combination therapy with immune checkpoint inhibition. The association with different cell populations suggests manipulating the cellular balance in the TME as an approach to improve the efficacy of treatment. NK cell checkpoint inhibitors are in clinical trials and might be utilized in high Globo H cancers; treatments inducing DCs in tumors have been shown to enhance responses to *BRAF* and PD-L1 blockade and might be applicable in the context of Globo H immunotherapy to overcome Treg immune suppression. Anti-Globo H vaccines and ADCs might be particularly effective in *BRAF* and *KRAS*-mutant CRC patients. Research Sponsor: None.

3528 **Poster Session**

Use of circulating tumor DNA in colorectal cancer patients to assess tumor burden and response to therapy: An observational study. *First Author: Erin L Symonds, Flinders University, Adelaide, SA, Australia*

Background: Residual disease after treatment for colorectal cancer (CRC) poses a risk for recurrence but imaging and CEA are limited in their capacity to detect residual disease. A simple test is needed for assessing treatment response. This study determined whether levels of methylated *BCAT1/IKZF1* DNA in blood correlate with tumor burden and whether post-treatment levels inform efficacy of different treatments for CRC. **Methods:** Patients with primary CRC had blood collected prior to treatment (n = 282, 59.9% males, median age 68.5y). Cell free DNA (cfDNA) was extracted from plasma and assayed for methylation in *BCAT1* and *IKZF1*. Detection of methylation in either gene deemed a sample positive; levels were expressed as %methylation (average methylation/average cfDNA). Positive patients had additional samples collected post-treatment for early stage CRC (surgery, n = 31), advanced/metastatic CRC (surgery + adjuvant chemotherapy, n = 15), and rectal cancer (neoadjuvant therapy, surgery +/- chemotherapy, n = 6), or following mid-therapy suspension of treatment in advanced CRC (n = 24). Tumor size was expressed as the maximum diameter of the primary (assessed surgically or by MRI). **Results:** Pretreatment results increased with CRC stage. Positivity by stage was: I, 23.7% (14/59); II, 62.1% (54/87); III, 68.6% (70/102); IV, 85.3% (29/34). Level by stage: I, 0.0%; II, 0.06%; III, 0.07%; IV, 4.07%, $p < 0.001$). Pretreatment levels correlated significantly with tumor size ($r = 0.372$, $p < 0.001$). Post-treatment blood was collected a median 2.4mo (IQR 1.7-3.9) after therapy completion. Positivity decreased after completing treatment (Table), with 88.4% of cases (46/52) becoming ctDNA negative. All cases with complete treatment had a reduction in biomarker levels, whereas in those with incomplete therapy, 54.5% (12/22) remained positive and the pre- and post-treatment levels were not significantly different. Of those positive after treatment, 13 had a further blood sample: 8 had become ctDNA negative and all but one remained disease free. Five remained positive and all had further suspected or confirmed disease. **Conclusions:** Levels of methylated *BCAT1* and *IKZF1* DNA in blood correlated with tumor burden; levels became undetectable in the majority of patients following completion of planned curative intent treatment. The methylated ctDNA blood test aids monitoring of responses to therapy and identification of those cases with residual cancer who might benefit from ongoing therapy. Research Sponsor: Clinical Genomics, NHMRC Australia.

	Post-treatment results	
Treatment	**No. positive (%)**	**No. that decreased in ctDNA level (%)**
Surgery (n = 31)	3/31 (9.7%)	31/31 (100%)
Surgery and complete adjuvant chemotherapy (n = 15)	3/15 (20.0%)	15/15 (100%)
Total neoadjuvant radiotherapy, plus surgery (+/- complete adjuvant chemotherapy) (n = 6)	1/6 (16.7%)	6/6 (100%)
Surgery, but incomplete or no adjuvant chemotherapy (n = 22)	12/22 (54.5%)	18/22 (81.8%)

3529 **Poster Session**

Profiling plasma angiogenesis factors after use of biologics in metastatic colorectal cancer (mCRC): Update results from GI-SCREEN CRC Ukit study. *First Author: Yu Sunakawa, Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan*

Background: No predictive biomarkers have been validated to determine which patients (pts) with metastatic colorectal cancer (mCRC) benefit the most from angiogenesis inhibitors. Recent studies suggest that plasma angiogenesis factors and their dynamics may have some prognostic or predictive value. **Methods:** In this prospective longitudinal study, serial plasma sample collections were done at the time points of pre- and post-treatments in mCRC pts receiving biologics in either first- or second-line chemotherapy (chemo). Comprehensive measurements of 17 factors were performed by the multiplex assay with Luminex technology. Statistical analyses were conducted by using the Brunner-Munzel and Jonckheere-Terpstra test. **Results:** From Sep 2017 to Dec 2020, 789 plasma samples were collected from 498 enrolled pts [first-line chemo plus bevacizumab (BEV, n=102), first-line chemo plus anti-EGFR antibody (aEGFR, n=100), second-line chemo plus BEV (n=100), second-line FOLFIRI plus ramucirumab (RAM, n=99), second-line FOLFIRI plus aflibercept (AFL, n=85) and other treatment (n=7)]. 789 samples were evaluable for this analysis. In the analysis of first-line, level of VEGF-D was significantly higher in both post-BEV and post-aEGFR comparing with pre-first-line [pre-first-line; 264 pg/ml, post-first-line BEV; 354 pg/ml ($p<0.001$), post-first-line aEGFR; 380.5 pg/ml ($p<0.001$)], while PlGF was significantly higher only in post-BEV [pre-first-line; 6.7 pg/ml, post-first-line BEV; 23.4 pg/ml ($p<0.001$), post-first-line EGFR; 7.4 pg/ml ($p=0.650$)]. These dynamics were also observed in pts with paired samples (Table). In pts with paired samples who received second-line treatment, level of VEGF-A was significantly decreased in post-BEV, while it significantly increased in post-RAM and AFL. A significant elevation of VEGF-D level was observed in only post-RAM. PlGF level significantly increased in post all second-line angiogenesis inhibitors. In the distribution analysis of angiogenesis factors, there were no or weak correlations between VEGF-D and PlGF at the time points of all post-treatments ($r = 0.09$-0.26). **Conclusions:** Plasma levels of VEGF-D, VEGF-A and PlGF were independently changed by angiogenesis inhibitors as well as anti-EGFR therapy, suggesting the possibility of usefulness for selecting better biologics by measuring baseline angiogenesis-related factors in first- and second-line chemo. Clinical trial information: UMIN000028616. Research Sponsor: Japan Agency for Medical Research and Development.

First line	**Chemo plus BEV (n=46)**			**Chemo plus aEGFR (n=34)**		
Median, pg/mL	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**
VEGF-D	263.5	361.0	0.054	341.0	447.0	0.037
PlGF	7.5	21.5	<0.001	8.8	5.9	0.121
VEGF-A	95.1	30.0	<0.001	224.5	107.0	0.009

Second line	**Chemo plus BEV (n=70)**			**FOLFIRI plus RAM (n=51)**			**FOLFIRI plus AFL (n=45)**		
Median, pg/mL	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**	**Pre**	**Post**	**p**
VEGF-D	327.5	342.5	0.362	301.0	732.0	<0.001	342.0	365.0	0.397
PlGF	17.6	21.6	0.006	24.1	158.0	<0.001	18.0	259.0	<0.001
VEGF-A	40.0	30.0	<0.001	30.7	804.0	<0.001	40.0	99.1	0.001

3530 **Poster Session**

The role of *HPSE* in *BRAF* V600E-mutant colorectal cancer. *First Author: Mengling Liu, Department of Medical Oncology, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: *BRAF* mutations occur in about 10% of colorectal cancer (CRC), more than 90% of which are *BRAF* V600E mutation. Patients (pts) with *BRAF* V600E mutation present poor prognosis. Complex molecular biological mechanisms in this population have not been well annotated. *HPSE* plays a multifunctional role in cell proliferation, invasion and angiogenesis in cancer. Here we identified differentially expressed genes (DEGs) between pts with and without *BRAF* V600E mutation, and then focused on the function of *HPSE,* one of top DEGs, in *BRAF* V600E-mutant CRC. **Methods:** Clinical and transcriptional data of pts with CRC from The Cancer Genome Atlas (TCGA, n = 525) database and GSE39582 dataset (n = 510) were analyzed to explore the top overlapped DEGs between *BRAF* V600E mutant and wild-type pts. Records and tumor samples of 172 pts with *BRAF* V600E-mutant CRC diagnosed at Zhongshan Hospital Fudan University between 6/2015-12/2018 were collected. The HPSE protein expression status of tumor samples was evaluated by immunohistochemistry staining. Moderate or strong staining in > 25% of tumor cells was interpreted as HPSE positive. Overall survival (OS) was analyzed using Kaplan-Meier Curves with Log-rank test and multivariable Cox regression. Next, lentiviral shRNA-based silencing of *HPSE* was performed in two *BRAF* V600E-mutant CRC cell lines (HT-29, RKO). The effect of *HPSE* on tumor growth was investigated through colony formation assays, cell cycle assays and subcutaneous xenograft models. **Results:** The top overlapped genes of the DEGs list included *HPSE, TFF2, AXIN2, MLH1, RNF43, EPM2AIP1.* Among them, *HPSE* had significantly high expression in *BRAF* V600E-mutant group. Of 172 pts with *BRAF* V600E mutation, 83 were identified as HPSE positive and 89 were negative. Two groups were generally well balanced on age ($p = 0.096$), gender ($p = 1.000$), location ($p = 0.658$), stage ($p = 0.249$) and MMR status ($p = 0.129$). HPSE positive pts had a significantly worse OS in comparison to HPSE negative pts ($p = 0.037$, median OS not reached). The multivariate analysis showed that HPSE positive was independently associated with inferior OS [HR 1.97 (95%CI: 1.02 – 3.80), $p = 0.044$). Silencing *HPSE* gene impaired colony formation activity significantly and arrested more cells in G0/G1 phase of *BRAF* V600E-mutant CRC cell lines. Tumor growth was inhibited apparently in *HPSE*-silencing xenograft models. **Conclusions:** Pts with *BRAF* V600E-mutant CRC had a high *HPSE* expression level, while HPSE protein expression was an independent prognostic factor for this population. The silencing of *HPSE* expression in *BRAF* V600E-mutant CRC cell lines inhibited cell proliferation and tumor growth in vitro and in vivo. HPSE may contribute to the poor prognosis of *BRAF* V600E-mutant CRC and might be a promising therapeutic target for this subtype of CRC. Research Sponsor: National Nature Science Foundation of China (81772511, 81602038).

3531 **Poster Session**

The impact of colorectal cancer screening on incidence and stage IV disease in the Netherlands. *First Author: Myrtle F Krul, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Population-based screening for colorectal cancer (CRC) aims to decrease incidence and mortality due to precancerous polyp removal, early detection and early treatment of CRC. In the Netherlands, phased introduction of a biennial fecal immunochemical hemoglobin test started in 2014 for individuals aged 55-75. This evaluation of the national data focuses on the initial effect of CRC screening on incidence and stage distribution and the impact on stage IV disease. **Methods:** All CRC patients diagnosed in the Netherlands between 2009 and 2018 were selected from the Netherlands Cancer Registry (NCR). Patients were linked to the Dutch national pathology registry (PALGA) to identify screen-detected tumors. **Results:** The NCR identified 137,717 CRC patients between 2009 and 2018. The incidence within screening age (55-75 yr) of all CRC stages showed an initial peak after introduction of screening in 2014, followed by a continuous decrease for all stages. CRC incidence outside the screening age did not show these explicit changes between 2009 and 2018. In 2018, the incidence of stage IV CRC within screening age was lower than the level at the start of the screening program. Stage distribution within screening age shifted towards earlier stages in the screening period (2014-2018) compared to the period before screening (2009-2012) (stage I: 31% vs. 18%, stage II: 22% vs. 26%, stage III: 29% vs. 31%, Stage IV: 18% vs. 25%, respectively). In the period 2014-2018 and within screening age, the ratio of screen-detected and symptom-detected tumors was highest in stage I (47%:53%) and lowest in stage IV (9%:91%). Screen-detected compared to symptom-detected stage IV patients diagnosed in the period 2014-2018 and within screening age had more frequently single organ metastases (74.5% vs 57.4%, $p < 0.001$), higher resection rate of the primary tumor (57.5% vs. 41.3%; $p < 0.001$) and higher local treatment rate of metastases (40.0% vs. 23.4% $p < 0.001$). The median overall survival of screen-detected stage IV patients was significantly longer than that of symptom-detected stage IV patients (31.0 months (95% CI: 27.7 – 34.3) vs. 15.0 months (95% CI: 14.5 – 15.5), $p < 0.001$). **Conclusions:** The initial results of the introduction of CRC screening in the Netherlands showed a favorable trend on CRC incidence and stage distribution. Screen-detected patients with stage IV disease had less extensive disease, resulting in better treatment options and improved survival. Research Sponsor: None.

3532 **Poster Session**

Resectability, conversion and resections rates, and outcomes in *RAS*&*BRAF* wildtype (wt), *RAS* mutant (mt) and *BRAF*mt metastatic colorectal cancer (mCRC) subgroups in the prospective Finnish RAXO-study. *First Author: Pia J. Osterlund, Tampere University Hospital and University of Tampere, Department of Oncology, Tampere, Finland*

Background: Outcomes of metastasectomy varies with *RAS* and *BRAF*-status, but the effect on resectability, conversion and resection rates has not been extensively studied. **Methods:** The prospective Finnish RAXO study (NCT01531621) included 1086 patients 2011-2018 (Osterlund et al TLRHE 2021, Isoniemi et al BJS 2021) of which 906 were included in this secondary endpoint analysis. Excluded had missing *KRAS*/*NRAS*/*BRAF*-V600E test, were untreatable or had an atypical *BRAF* mutation. We studied repeated centralized resectability assessment, conversion and resectability rates in mCRC, and overall survival (OS) after resection and/or local ablative therapy (LAT) and systemic therapy. **Results:** Included were 289 *RAS*&*BRAF*wt, 529 *RAS*mt (overrepresented) and 88 *BRAF*mt, with median age 65.8/66.1/66.9 years. Demographics per *RAS*&*BRAF*wt, *RAS*mt and *BRAF*mt showed significant differences in male proportion (68/61/39%), ECOG PS 2-3 groups (16/14/25%), primary tumour location (right colon 16/30/69%, left colon 47/34/17%, rectum 38/36/14%), but not for Charlson comorbidity index, BMI, resection of primary, synchronous presentation or adjuvant therapy (Bonferroni corrected Chi-square). Metastatic profile was different for liver (78/74/61% per *RAS*&*BRAF*wt, *RAS*mt and *BRAF*mt), lung (24/35/28%) and peritoneal (15/15/32%) metastases, but not for lymph nodes or other sites, nor for number of metastatic sites (1 in 53/54/52%). Upfront resectability rates were different with 32/29/15% for *RAS*&*BRAF*wt, *RAS*mt and *BRAF*mt, respectively, as were conversion rates with 16/13/7%, and resection/LAT rates with 45/37/17%, respectively. Kaplan-Meier median OS estimate in R0/1/2-resected and/or LAT group (n = 342) was 83/69/30 months for *RAS*&*BRAF*wt, *RAS*mt and *BRAF*mt groups, respectively and 5-year OS-rates 67/60/24%, with Cox HR ref/1.53 (95% CI 1.04-2.25)/3.11 (1.49-6.49). In the "systemic therapy only" (n = 564) OS was 29/21/15 months and 5-year OS-rates 11/6/2% respectively, with HR ref/1.43 (1.15-1.76)/2.34 (1.73-3.17). Resection/LAT patients had improved OS over "systemic therapy only" patients in all subgroups, HR 5.74 (3.90-8.44)/5.06 (3.92-6.55)/2.89 (1.43-5.86). **Conclusions:** There were significant differences in resectability, conversion and resection/LAT rates according to *RAS*&*BRAF*wt, *RAS*mt and *BRAF*mt status. OS was also significantly longer for *RAS*&*BRAF*wt versus either mutant. Resected/LAT had better OS than "systemic therapy alone" patients in all subgroups. Clinical trial information: NCT01531621. Research Sponsor: The Finnish Cancer Foundation, Finska Lakaresallskapet, Competitive state research Helsinki, Tampere, Turku, Oulu, Kuopio and Satakunta hospitals, Research funds at Tampere and Helsinki University Hospitals, Pharmaceutical/Biotech Company.

3533 **Poster Session**

A model combing an immune-related genes signature and an extracellular matrix-related genes signature in predicting prognosis of left- and right-sided colon cancer. *First Author: Min-Er Zhong, Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Primary tumor sidedness has been found to be prognostic in colorectal cancer (CRC), with right-sided colon cancer (RCC) having a worse survival than left-sided tumors (LCC), even after controlling for known negative prognostic factors. Our previous proteomic study identified differences in protein profiles between LCC and RCC. Immune-related proteins were found to be up-regulated in LCC while the differentially expressed proteins in RCC were mainly enriched in extracellular matrix-related proteins. Herein we aim to construct a prognostic prediction model for LCC and RCC patients by using immune-related genes (IRGs) and extracellular matrix-related genes (ECMGs). **Methods:** A total of 1,868 CRC patients with complete follow-up data from 1 training cohort (n = 562) and 3 independent validation cohorts (n = 622, n = 403, n = 281, respectively) were enrolled in our study. Tumors located in the splenic flexure, descending colon, sigmoid colon, and rectum are defined as LCC. In contrast, tumors located in the region from the hepatic flexure to the cecum are defined as RCC. The Least Absolute Shrinkage and Selection Operator (LASSO) algorithm was used to construct the multi-gene signatures. Univariate and multivariate analyses were used to test the prognostic value of these models. **Results:** Our biomarker discovery effort identified a 9-gene IRGs signature that significantly associated with poor DFS for LCC (HR = 3.46, 95%CI = 2.38-5.01, $P < 0.001$) and a 21-gene ECMGs signature associated with prognosis for RCC (HR = 4.53, 95%CI = 2.84-7.22, $P < 0.001$). For LCC, the IRGs signature was significantly correlated with worse prognosis in three independent validation cohort (Validation-1 cohort: HR = 2.08, 95%CI = 1.41-3.09, $P < 0.001$; Validation-2 cohort: HR = 2.19, 95%CI = 1.26-3.81, P = 0.004; Validation-3 cohort: HR = 2.94, 95%CI = 1.53-5.63, $P < 0.001$). Similarly, the ECMGs signature also robustly predicted survival for RCC in three independent validation (Validation-1 cohort: HR = 1.86, 95%CI = 1.22-2.83, P = 0.003; Validation-2 cohort: HR = 1.96, 95%CI = 1.18-3.26, P = 0.008; Validation-3 cohort: HR = 2.8, 95%CI = 1.27-6.17, P = 0.007). When compared with Oncotype DX, we found IRGs achieved an improved survival correlation in LCC (C-index, validation-3 cohort: 0.75 vs 0.64) and ECMGs got a better survival correlation in RCC (C-index, validation-3 cohort: 0.74 vs 0.58). **Conclusions:** Combing a 9-gene IRGs signature for LCC and a 21-gene ECMGs signature for RCC, we established a prognostic model that can robustly stratify CRC patients into high- and low- risk groups of tumor recurrence and predict prognosis. Research Sponsor: National Natural Science Foundation of China (82002221, FG), Other Foundation.

3534 **Poster Session**

Automated computed tomography (CT)-derived skeletal muscle mass determination as a significant prognostic factor in colorectal cancer patients using deep neural network model. *First Author: Dongjin Seo, Yonsei University College of Medicine, Seoul, South Korea*

Background: Although recent evidence suggests skeletal muscle depletion predicts the survival of patients with cancer, the retrieval and manual measurement of the computed tomography (CT) images hinder clinical application in routine clinical practice. The advent of recent deep learning applications enables highly accurate noninvasive longitudinal evaluation of skeletal muscle mass (SMM) changes. Here, we evaluated the prognostic impact of DNN-measured skeletal muscle changes in colorectal cancer (CRC) patients. **Methods:** A total of 6,196 newly diagnosed CRC patients were analyzed in the Yonsei Cancer Registry Database between Jan 1, 2010, and Sep 30, 2020. SMM is measured by the Skeletal muscle index (SMI). The formula used was: L3 skeletal muscle cross-sectional area (cm^2)/height^2 (m^2). Patients' SMI patterns were grouped by difference ratio of initial and last SMI. Patients were also classified by BMI pattern with the result of K-means clustering. Association of baseline SMI, baseline body mass index (BMI), SMI changes, BMI changes, and demographic factors with overall survival (OS) were evaluated. Univariate and multivariate analyses were conducted. Concordance (c) statistics were used to test the predictive accuracy of survival models. **Results:** Fully automated UNet architecture-based deep learning algorithms were applied for the third lumbar transverse CT detection, skeletal muscle segmentation, and skeletal muscle area quantification in CRC patients undergoing abdominal CT between at the time of diagnosis and one year after the diagnosis. Baseline BMI distribution was 28% obese, 26% overweight, 42% normal weight, and 4% underweight. Patients in all SMI categories varied widely in BMI. Changes in SMI were categorized into three groups: SMI increase (33%), steady (45%), and decrease (22%) group. Similarly, BMI changes were categorized into three groups: BMI increase (24%), BMI stable (57%), and BMI decrease (19%) group. Low baseline SMI, low baseline BMI, SMI decrease, and BMI decrease were independently prognostic of survival. Intriguingly, BMI and SMI changes had a different prognostic impact in men and women. For women, the SMI increase group (hazard ratio [HR], 0.4; 95% CI, 0.3-0.7; $P = 0.001$) was associated with longer OS, while the SMI decrease group (HR, 1.2; 95% CI, 0.6-2.2; $P = 0.619$) was not associated with shorter OS, both compared with SMI steady group. **Conclusions:** Automated CT-derived SMM depletion had a negative prognostic impact independent of BMI and age in CRC patients. A noninvasive automatic deep learning algorithm provides a unique opportunity to apply to routine clinical practice and understand how and when cachexia impacts cancer prognosis. Research Sponsor: A grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Korea.

3535 **Poster Session**

Genetic variants involved in the cGAS-STING pathway to predict outcome in patients (pts) with metastatic colorectal cancer (mCRC): Data from FIRE-3 and TRIBE trials. *First Author: Jingyuan Wang, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: The intracellular DNA sensor stimulator of interferon genes (STING) plays a vital role in anti-tumor immune responses by recognition of self-DNA from tumors and by-products of genomic instability. Activation of STING was reported to enhance cetuximab mediated natural killer cell activation and dendritic cell maturation. Previous reports suggested that polymorphisms of cGAS-STING can affect innate immune response. Therefore, we hypothesized that genetic variants in the cGAS-STING pathway may predict first-line treatment outcome in mCRC pts treated with bevacizumab/cetuximab-based chemotherapy. **Methods:** Genomic DNA from blood samples of pts enrolled in two independent randomized trials, FIRE-3 (cetuximab arm, n = 129; bevacizumab arm, n = 107) and TRIBE (bevacizumab arm, n = 215), was genotyped through the OncoArray, a customized array manufactured by Illumina including approximately 530K SNP markers. The impact on outcome of 7 selected SNPs in 3 genes involved in the STING pathway (cGAS, STING, IFNB1) was analyzed. **Results:** In the Cetuximab cohort, pts with STING rs1131769 any T allele (N = 29) showed significantly shorter overall survival (36.3 vs 56.07 months) compared to carriers of C/C (N = 95) in both univariate (hazard ratio [HR] = 2.08; 95% confidence interval [CI]: 1.06-4.07; p = 0.003) and multivariate (HR = 2.98; 95%CI 1.35-6.6; p = 0.00848) analysis; Pts carrying IFNB1 rs1051922 any A allele (N = 68) showed significant shorter progression-free survival (10.23 vs 14.1 months) than carriers of G/G (n = 59) in both univariate (HR = 1.87; 95%CI 1.26-2.78; p = 0.00163) and multivariate (HR = 2.03; 95%CI 1.25-3.3; p = 0.004) analysis. No association were observed in the bevacizumab cohort of TRIBE and FIRE-3. **Conclusions:** Our study demonstrates for the first time that STING and IFNB1 polymorphisms could predict outcomes of Cetuximab-based treatment in mCRC patients; These finding may provide insight for the combination of STING agonist and anti-EGFR treatment in mCRC patients. Research Sponsor: National Cancer Institute (grant number P30CA014089), The Gloria Borges WunderGlo Foundation-The Wunder Project, Dhont Family Foundation, San Pedro Peninsula Cancer Guild, Daniel Butler Research Fund and Call to Cure Fund.

3536 **Poster Session**

Multimodal circulating tumor DNA (ctDNA) colorectal neoplasia detection assay for asymptomatic and early-stage colorectal cancer (CRC). *First Author: Jeeyun Lee, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: To improve average risk CRC screening compliance, additional options are needed, especially options that address patient and provider reported barriers such as time and convenience. LUNAR-2 is a multimodal blood-based colorectal neoplasia detection assay incorporating ctDNA assessment of somatic mutations and tumor derived methylation and fragmentomic patterns, aimed to maximize sensitivity for early stage CRC detection. We evaluated this test in a large patient cohort with newly diagnosed CRC. **Methods:** Individuals diagnosed with CRC between 2013-2016 consented to provide blood samples prior to surgical resection. Those treated with neoadjuvant chemotherapy were excluded. Isolated plasma samples (median 3mL from EDTA) from 434 individuals were analyzed with LUNAR-2 (Guardant Health, USA) and included in the analysis. Median age at CRC diagnosis was 63 years (range 28 - 89) and 41% were female. Control samples were from 271 age-matched cancer free individuals. "ctDNA detected" and "ctDNA not detected" results were generated by a model trained on a separate sample set (N=614) from both cancer free individuals and those with CRC. Calling threshold was determined based on this held-out set to target 90% specificity. ctDNA results and clinical characteristics were correlated. **Results:** Overall CRC sensitivity was 91% (393/434), with high sensitivity across all stages; 88% Stage I/II, 93% Stage III (Table). Specificity was 94% (255/271). There was no difference in sensitivity when excluding those with early (<45 years) or late (>84 years) onset CRC (90% sensitivity; 388/429; p=0.95; 88% Stage I/II, 93% Stage III). There were no differences in sensitivity for asymptomatic CRC (88%) compared to symptomatic CRC (91%; p=0.4; Table). However, higher cell-free DNA tumor fractions were observed in the symptomatic cohort. Sensitivity for detection of right-sided and left-sided CRC was similar (93% vs. 90%; p=0.5; Table). **Conclusions:** In this large early-stage CRC cohort, multimodal ctDNA assessment has high sensitivity for CRC detection with high specificity. Equivalent sensitivity in the asymptomatic cohort suggests this test will have clinically meaningful performance in an average risk screening population. A prospective registrational study is ongoing to evaluate the test in an average risk CRC screening cohort. Research Sponsor: Guardant Health.

Cohort demographics.

		Overall Cohort (N = 434)	ctDNA Detected Cohort (N = 393) (N; %)
Stage	I / II	239	211; 88%
	III	195	182; 93%
Presentation at CRC diagnosis	Asymptomatic	139	123; 88%
	Symptomatic	233	212; 91%
	Unknown	62	58; 94%
Location of Primary Tumor	Right-Sided	83	77; 93%
	Left-Sided	334	302; 90%
	Transverse	17	14; 82%

3537 **Poster Session**

Comprehensive characterization of neurotransmitters and neuronal signaling (NT) pathway alterations in colorectal cancer (CRC). *First Author: Francesca Battaglin, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Aberrant NT signaling has been shown to activate uncontrolled proliferation and dissemination in several gastrointestinal cancer types. Neurotransmitters have been shown to affect endothelial cells and immune cells in the tumor microenvironment to promote tumor progression. We previously showed that single nucleotide polymorphisms in the dopamine and GABA pathways are associated with outcome in patients with metastatic CRC receiving first-line treatment. Here we further evaluated the distribution and molecular context of NT pathway alterations in CRC. **Methods:** A total of 7,595 CRC tumors tested at Caris Life Sciences (Phoenix, AZ) with NextGen Sequencing on DNA (Next Seq, 592 genes or NovaSeq, WES) and RNA (NovaSeq, WTS) were analyzed. ssGSEA (single-sample gene set enrichment analysis) was used to calculate pathway enrichment scores (ES) of 7 NT gene sets (GABA, nicotinic, muscarinic, dopamine (DA), reelin, glial cell line-derived neurotrophic factor and neurotrophins). X2/Fisher-Exact was used for comparison and significance was determined as p-value adjusted for multiple comparison of (q) < 0.05. **Results:** ES based on sample sites showed a substantial heterogeneity in NT enrichment. Notably, when compared to primary tumors, all 7 gene sets were significantly enriched in brain metastases (mets; ES ratio 1.14-1.55), while abdomen, liver, and peritoneal mets displayed significant decreases in most NT gene sets. DA was enriched in ovarian and lung mets (ES ratio: 1.18 and 1.09, respectively), the latter also showing increased neurotrophins ES (1.06) (all $q < 0.05$). When investigating primary tumors grouped according to overall ES by unsupervised clustering, right-sided and CMS4 CRCs were more prevalent in the high ES cluster compared to the low ES cluster (32 vs 29%, $P = 0.02$ and 46 vs 30%, $P < 0.001$, respectively). In addition, tumors in the high ES cluster showed lower prevalence of TMB-H (≥ 10mt/MB) (7 vs 10%), MSI-H (6 vs 10%) and PD-L1 (2 vs 6%), while higher CNA rates were noted in 9 genes (all $q < 0.05$). High ES tumors showed significant positive associations with microenvironment infiltration of B cells, T cells (NK, CD4+ and CD8+ T cells, but not Treg), M2 Macrophages, Myeloid Dendritic Cell, Neutrophils, and an inverse association with M1 Macrophages, regardless of MSI status ($q < 0.05$). **Conclusions:** This is the first and most extensive molecular profiling study to investigate NT signaling pathway alterations in CRC. Our data show a distinct distribution of pathway enrichment according to metastatic site, distinct molecular features in high vs low ES clusters in primary tumors (including CMS subtypes, TMB, MSI and PD-L1 rates), and differential immune cell infiltration. These findings support the role of NT signaling in the metastatic spread of CRC and modulation of tumor immune microenvironment. Research Sponsor: NCI P30CA014089, Gloria Borges WunderGlo Foundation, Dhont Family Foundation, Victoria and Philip Wilson Research Fund, San Pedro Peninsula Cancer Guild, Daniel Butler Research Fund.

3538 **Poster Session**

KMT2C as a positive predictor for treatment of immune checkpoint inhibitor and correlation with immune infiltrates in colorectal cancer (CRC). *First Author: Ling Zhang, The First Affiliated Hospital of Nanchang University, Nanchang, China*

Background: Lysine Methyltransferase 2C (KMT2C), a member of the myeloid/lymphoid or mixed-lineage leukemia (MLL) family, possesses histone methylation activity and is involved in transcriptional co-activation. Present study has shown that KMT2C is positive correlated with better efficacy of Immune checkpoint inhibitor (ICI) in NSCLC. However, the role of KMT2C in treatment of ICI on colorectal cancer (CRC) is still unknown. **Methods:** NGS (Next Generation Sequencing) was performed on 1628 CRC patients. TMB of these patients were analyzed. A public accessible cohort (Samstein2018) with data from 130 CRC patients were used to investigate the correlation between KMT2C mutation and efficacy of ICI. WES and survival data of TCGA database (1099 CRC) was used to analyze prognostic effect of KMT2C mutation. Furthermore, CIBERSORT was used to analyze the tumor-infiltrating immune cells present in COAD (colon adenocarcinoma, 404 patients) from TCGA database. **Results:** Among 1628 CRC patient, 230(14.1%) had KMT2C mutation. TMB was positive correlated with KMT2C mutation (Mut vs. WT, 30.75 vs. 7.26 mut/Mb, $p < 0.0001$). The Samstein2018 cohort showed that KMT2C mutations (15.4%, 20/130) were significantly associated with better OS (Mut vs. WT, 11.5 vs. 7.5 month, HR = 0.29; 95% CI, 0.1-0.81; P = 0.012), and a higher TMB was also observed in KMT2C-Mut group (p = 1.98e-08). In TCGA, no association between KMT2C mutation and OS was observed (P = 0.23), suggesting that was not prognostic factor. Moreover, we analyzed the relationship between KMT2C mutation and immune cell infiltration through CRC TCGA database. The results showed, in COAD, KMT2C mutation was positively correlated with the abundance of CD8+ T cells (P = 0.0014), B cells (P = 0.014), M1 macrophages (P = 0.015), neutrophil (P = 0.0019) and NK cells (P = 0.043), and negatively correlated with Treg cells (p = 0.0063). **Conclusions:** KMT2C has an impact on the immune microenvironment and may be used as a potential positive predictor for treatment of ICI on CRC patients. The role of KMT2C in immunotherapy warrant further studies. Research Sponsor: None.

3539 **Poster Session**

Multi-omics analysis to reveal the role of gut microbiome–associated serum metabolites in the detection of colorectal cancer and adenoma. *First Author: Feng Chen, State Key Laboratory of Molecular Oncology, Department of Clinical Laboratory, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Gut microbiome and their metabolites have been revealed to be associated with the initiation and progression of colorectal cancer (CRC), and gut microbiome produced or associated metabolites could enter the circulation system. **Methods:** Integrated analysis of untargeted serum metabolomics by liquid chromatography–mass spectrometry (LS-MS) and metagenome sequencing of fecal samples derived from matched individuals were used to profile serum metabolites that are both significantly affected by CRC and co-related with the gut microbiome. Targeted LC-MS was further used to test the ability of these metabolites for discriminating CRC and adenoma from healthy individuals. **Results:** More than 300 gut microbiome–associated serum metabolites with significantly altered abundance in both colorectal carcinoma (CRC) and adenoma patients have been identified. A panel of eight gut microbiome–associated serum metabolites (GMSM panel) was established and accurately discriminated CRC and adenoma from normal population. The GMSM panel–based CRC and colorectal adenoma prediction model yielded an area under the curve (AUC) of 0.94 (95% confidence interval: 0.90–0.99) and AUC of 0.91 (sensitivity 82%, specificity 91%) in the training and validation set respectively. This GMSM model shows significantly superior performance to the clinical marker carcinoembryonic antigen (CEA) (AUC 0.72), and more importantly, it suggests promising diagnostic potential in detecting adenoma (AUC = 0.81) and early-stage CRC (AUC = 0.91). **Conclusions:** Our results indicate that gut microbiome reprogramming in CRC patients is associated with the alterations of the serum metabolome, and these gut microbiome–associated serum metabolites has potential application for the detection of earlier CRC and adenoma. Research Sponsor: CAMS Innovation Fund for Medical Sciences (CIFMS), Other Foundation, Pharmaceutical/Biotech Company.

3540 **Poster Session**

Serial circulating tumor DNA analysis to assess recurrence risk, benefit of adjuvant therapy, growth rate and early relapse detection in stage III colorectal cancer patients. *First Author: Tenna V Vesterman Henriksen, Department of Molecular Medicine, Aarhus University Hospital, Aarhus, Denmark*

Background: Challenges in the postoperative management of stage III colorectal cancer include: 1) selection of high-risk patients for adjuvant chemotherapy (ACT), 2) lack of markers to assess ACT efficacy, 3) assessment of recurrence risk after ACT, and 4) lack of markers to guide treatment decisions for high-risk patients e.g. additional therapy or intensified surveillance. Circulating tumor DNA (ctDNA) is a promising marker with potential to mitigate the challenges. Here we used serial ctDNA measurements to assess the correlation between recurrence and ctDNA detection: postoperative, during and after ACT, and during surveillance; and to assess growth rates of metachronous metastases. Uniquely, we also used concurrent CT scans and ctDNA measurements to compare the sensitivity for detecting recurrence. **Methods:** Stage III CRC patients treated with curative intent at Danish and Spanish hospitals in 2014-2019 were recruited (n = 166). Blood samples (n = 1227) were collected prior to and immediately after surgery, and every third month for up to 36 months. Per patient 16 personal mutations were used to quantify plasma ctDNA (Signatera, bespoke mPCR NGS assay). **Results:** Detection of ctDNA was a strong recurrence predictor, both postoperatively (HR 7.2, 95% CI 3.8-13.8, $P< 0.001$), directly after ACT (HR = 18.2, 95% CI 7.1-46, $P < 0.001$), and when measured serially after end of treatment (HR = 41, 95% CI 16-100, $P < 0.001$). The recurrence rate of postoperative ctDNA positive patients treated with ACT was 80% (16/20). Patients who stayed ctDNA positive during ACT all recurred. Serial post-treatment ctDNA measurements revealed exponential growth for all recurrence patients following either a SLOW (26%-increase/month) or a FAST (126%-increase/month) pattern ($P < 0.001$). From ctDNA detection to radiologic recurrence, ctDNA levels of FAST patients increased by a median 117-fold, and up to 554-fold. The 3-year overall survival was 43% for FAST patients and 100% for SLOW and non-recurrence patients (HR = 41.3, 95% CI 7.5-228, $P < 0.001$). Coinciding CT scans and ctDNA measurements (n = 113 patients, 235 coinciding events, median 2 per patient) showed a high agreement (92%) and ctDNA either detected residual disease before the CT scan (n = 7 patients) or at the same time (n = 14 patients). The median lead-time was 7.5 months. **Conclusions:** The study confirmed the prognostic power of serial postoperative ctDNA analysis. Moreover, it provided novel analyses demonstrating that ctDNA is more sensitive for recurrence detection than CT scans and can be used for tumor growth rate assessments. The difference between FAST and SLOW growing tumors suggest that growth rates could guide whom to start on systemic therapy rapidly and whom to send for diagnostic imaging. Altogether, the study highlights many potential utilities of ctDNA in guiding clinical decision-making. Research Sponsor: Danish Cancer Society, Other Foundation, Pharmaceutical/Biotech Company.

3541 **Poster Session**

The effect of primary tumor location on second- or later-line treatment with anti-EGFR antibodies in patients with metastatic colorectal cancer: A single-center cohort study. *First Author: Anita Archwamety, Division of Medical Oncology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand*

Background: The guideline recommends anti-EGFR monoclonal antibodies (anti-EGFR Ab) as first-line treatment only for patients with left-sided *RAS* wild type *(RASwt*) metastatic colorectal cancer (mCRC). However, there are no recommendations on tumor sidedness in subsequent lines. This study aimed to evaluate the effect of primary tumor location on second- or later-line treatment outcomes in patients with *KRASwt* mCRC. **Methods:** Medical records of patients diagnosed with mCRC at Siriraj Hospital between 2008 and 2019 were retrospectively reviewed. Patients with *KRAS*wt who received anti-EGFR Ab in second- or later-line treatment were included. The impact of tumor sidedness on progression-free survival (PFS) was determined using the Kaplan-Meier method and compared using the log-rank test. **Results:** Of 671 patients who had data on *KRAS* analysis, 396 patients (59%) had *KRASwt*. Of these, 210 patients received anti-EGFR Ab in second- or later-line treatment. Twenty-nine percent of patients (60 out of 210) had extended *RAS* analysis. Thirty patients (14%) had right-sided tumors, while 180 patients (86%) had left-sided tumors. Sixty-nine percent of patients (146 of 210) were treated in the third line, while 19% and 12% were treated in the second and the fourth line, respectively. Single-agent irinotecan was the most commonly used chemotherapy backbone (92%). Patients with right-sided tumors had non-significantly inferior PFS compared with patients with left-sided tumors (median PFS was 4.7 months, 95% CI 0.8–8.7 vs. 6 months, 95% CI 4.6–7.3; p = 0.55). Subgroup analysis on the impact of primary tumor location showed no difference in PFS when stratified by treatment lines. **Conclusions:** This study demonstrated that tumor sidedness has no impact on treatment outcomes in patients treated with anti-EGFR Ab in second- or later-line treatment. Therefore, there is not enough evidence to use tumor sidedness for treatment selection in these settings. A multi-center retrospective study is ongoing. Research Sponsor: None.

3542 **Poster Session**

Multi-omics characterization of left-right colorectal cancer. *First Author: John Marshall, Georgetown University, Washington, DC*

Background: Right (R) vs left (L) sided colorectal cancers are clinically distinguishable based on prognosis and response to certain therapies, but as of yet, limited data have emerged to explain these differences. The science of molecular testing has evolved rapidly. Enabled by improved technologies and computing power, it is now feasible to obtain to systematic multi-omic datasets covering DNA, RNA, proteins, phospho-proteins and metabolomics on large numbers of patients. Multi-omic analysis can further define disease specific subgroups but pre-analytic quality of the tissues (ischemia time) and comparison to normal tissue controls is paramount to optimize results. **Methods:** Following informed consent, 450 colorectal cancer primary tumors and paired normal tissues were collected following an SOP to minimize ischemia time, and were analyzed using comprehensive genomics, transcriptomics, proteomics, phosphoproteomics, morphology and annual clinical information. Right (C18.0,2,3) and left (C18.6,7) CRC tumors, normal tissue were compared using machine learning tools to unravel the molecular mechanisms that underpin these clinically distinguishable phenotypes as well as correlating with known genomic metrics such MSI and KRAS mutation status. **Results:** Through leveraging the tumor and paired normal patient samples, systematic differences between left and right tumor samples were observed including specific molecular events associated with these anatomical differences. The detailed results will be presented at the meeting. **Conclusions:** Progress in precision medicine requires the inclusion of multi-omics which in turn requires changes to our current SOPs of tissue collection. The ability to define molecular distinctions such as between R and L colon cancer will permit the rapid discovery of clinically useful prognostic and predictive markers, dramatically adding to our fundamental understanding to colon cancer biology. Future work will focus on the discovery of novel targets and signatures, creating innovative tools that depict multi-omic results for clinicians. Research Sponsor: Indivumed GmbH.

3543 **Poster Session**

Genome-wide analysis indicating cancer associated fibroblast (CAF) impacts on colorectal cancer (CRC) prognosis via immunosuppression. *First Author: Yu-feng Chen, Department of Colorectal Surgery, The Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, China*

Background: Cancer associated fibroblast (CAF) in tumor microenvironment is associated with poor prognosis and chemo-resistance in multiple solid tumors, however, there is lack of universal measure of CAF in colorectal cancer (CRC). The aim of this study was to assess fibroblast-signature for predicting outcome and analyze relevant mechanism. **Methods:** A dataset including 316 CRC patients without adjuvant chemotherapy was used as the discovery cohort for the identification of prognostic fibroblast-related genes (FRGs). A total of 1,352 CRC patients were then divided into one training cohort (n = 461) and two validation cohorts (n = 338, n = 553, respectively) for the construction of fibroblast-related gene signature (FRGS) and the verification of its prognostic value in stage II/III CRC patients. Functional annotation and analysis were performed to reveal the relevant mechanism. **Results:** A 11-gene signature was derived, which was prognostic for stage II/III CRC patients in two validation cohort (Validation-1 cohort: HR = 1.90, 95%CI = 1.16-3.12, $P< 0.01$; Validation-2 cohort: HR = 1.95, 95%CI = 1.39-2.73, $P< 0.001$). High CAF risk was correlated with worse prognosis in CRC patients without adjuvant chemotherapy (HR = 3.63, 95%CI = 2.24-5.88, $P< 0.001$), but not in patients who received adjuvant chemotherapy ($P= 0.154$). Similar trends were found in Validation-1 cohort. After integrated with clinical characteristics, FRGS was confirmed as an independent prognostic factor after adjusted for TNM stage of tumor in multivariate analysis (Training cohort: HR = 3.19, 95%CI = 1.88-5.41, $P< 0.001$; Validation-1 cohort: HR = 5.00, 95%CI = 1.58-15.85, $P= 0.007$; Validation-2 cohort: HR = 2.99, 95%CI = 1.44-6.21, $P= 0.003$). Furthermore, enrichment analysis found that anti-tumor immune response was suppressed in the high CAF risk group. **Conclusions:** The 11-gene FRGS had independent prognostic value for CRC patients, as well as in prediction of benefit from chemotherapy. CAF in tumor microenvironment might impact on the prognosis of CRC patients via inhibiting immune response. Research Sponsor: National Natural Science Foundation of China (NSFC) (No. 82003197).

3544 **Poster Session**

***NTRK* fusion positive colorectal cancer as a unique subset of CRC with high tumor mutation burden and microsatellite instability.** *First Author: Hui WANG, Department of Medical Oncology, Beijing Hospital, National Center of Gerontology; Institute of Geriatric Medicine, Chinese Academy of Medical Sciences, Beijing, China*

Background: Neurotrophin receptor tyrosine kinase (*NTRK*) gene fusions are rare but actionable oncogenic drivers that are present in a wide variety of solid tumors. This study aims to identify the frequency and the clinicopathologic and genetic features of *NTRK*-driven colorectal cancers (CRC). **Methods:** Colonic and rectal tumor DNA specimen from colorectal cancer patients submitted for molecular profiling at a CLIA-certified genomics laboratory in China that performed *NTRK1/2/3* fusion detection by hybridization-based targeted next generation sequencing (NGS) were retrospectively reviewed. Patients' demographic, clinical characteristics, and treatment history were retrieved from the database for further evaluation. **Results:** A total of 2,519 unique Chinese colorectal cancer cases were profiled from April 2016 to May 2020, and 17 *NTRK+* fusion events were identified (0.7%, 17/2,519) consisting of 14 cases of *NTRK1+* and 3 cases of *NTRK3+* fusions. Furthermore, thirteen out of 17 *NTRK+* CRC tumors (76%) were microsatellite instability-high (MSI-H) tumors, a much higher rate than that of the molecularly unselected CRC population (8%) or *NTRK+* non-CRC tumors ($<$ 1%). *NTRK+* CRC patients also had increased tumor mutation burden (median TMB = 65 mut/MB) compared to that of non-*NTRK+* CRC (median TMB = 7.7 mut/MB) or *NTRK+* non-CRC tumors (median TMB = 4 mut/MB). *POLE/POLD1* mutations were also enriched in *NTRK+* CRC (8/17, 47%) relative to molecularly unstratified CRC patients (8%) with over half carrying concurrent *POLE* and *POLD1* mutations. *TPM3* was the most common fusion partner of *NTRK1* (78%, *N* = 14), followed by *LMNA* and *TRP*. Three *NTRK3+* CRC were identified *(ETV6-NTRK3, RUNX1-NTRK3, CSNK1G1-NTRK3). RNF43* (71%) was the most frequently mutated gene and the aberrations of *RNF43* and *ARID1* were significantly enriched in MSI-positive *NTRK+* tumors as compared to the MSS *NTRK+* subgroup. *TP53* (53%) and *APC* (35%) aberrations frequently co-occurred with *NTRK* fusions, whereas the majority of the *NTRK+* cohort were *RAS/BRAFwild-type*, except in one case that an oncogenic *KRAS* Q61R variant co-occurred with *RUNX1-NTRK3*. **Conclusions:** *NTRK+* colorectal cancer is rare. In addition to the absence of canonical driver mutations, *NTRK+* tumors demonstrated increased tumor mutation burden, higher frequency of microsatellite instability, and an enrichment of *POLE/POLD1* mutations relative to molecularly unselected CRC population. Research Sponsor: None.

3545 **Poster Session**

A panel of DNA methylation markers for the classification of consensus molecular subtypes 2 and 3 in patients with colorectal cancer. *First Author: Inge van Den Berg, Erasmus MC, Rotterdam, Netherlands*

Background: Consensus molecular subtypes (CMSs) can guide precision treatment of colorectal cancer (CRC). Currently available assays can identify CMS1 and CMS4 cases well, while a dedicated test to distinguish CMS2 and 3 is lacking. This study aimed to identify a panel of methylation markers to distinguish between CMS2 and 3 in patients with CRC. **Methods:** Fresh-frozen tumor tissue of 239 patients with stage I-III CRC was included. CMS classification was performed on RNA-seq data using the single-sample-prediction parameter from the "CMSclassifier" package. Methylation profiles were obtained using the Infinium HumanMethylation450 BeadChip. We performed adaptive group-regularised logistic ridge-regression with post-hoc group-weighted elastic net marker selection to build prediction models for classification of CMS2 and CMS3 based on 15, 10 or 5 markers. Data from TCGAwas used for validation. **Results:** Overall methylation profiles differed between CMS2 and CMS3. Group-regularisation of the probes was done based on their location either relative to a CpG island or relative to a gene present in the CMS classifier resulting in two different prediction models and subsequently different marker panels. For both panels, even when using only 5 markers, sensitivity, specificity, and accuracy were $>$ 90%. Validation showed comparable performances. **Conclusions:** Our highly sensitive and specific methylation marker panel can be used to distinguish CMS2 and 3. This enables development of a qPCR DNA methylation assay in patients with CRC to provide a specific and non-invasive classification tool. Research Sponsor: None.

3546 **Poster Session**

Clinical performance of methylation-based liquid biopsy test COLVERA after optimization of test interpretation rules. *First Author: Zivjena Vucetic, Clinical Genomics, Bridgewater, NJ*

Background: Clinical guidelines recommend surveillance for patients who complete primary treatment for colorectal cancer (CRC) with the aim of detecting recurrence when amenable to curative intent treatment. Currently recommended surveillance protocols, including imaging and CEA have limitations both in sensitivity and specificity, thus novel methods that detect circulating tumor DNA (ctDNA) have been introduced into clinical practice. COLVERA is a laboratory-developed, real-time PCR test that detects DNA methylation of BCAT1 and IKZF1 genes. These two genes are hypermethylated in 95% of CRC tissue and COLVERA showed improved sensitivity for detection of recurrent disease in comparison to CEA in several clinical populations. The current study evaluated the impact of optimizing the assay's qualitative reporting method on actionability and clinical performance for recurrence detection in CRC surveillance setting. **Methods:** Two previously described cohorts of CRC patients (N=322 and N=144) who completed primary treatment and were undergoing surveillance were evaluated. Imaging and blood collections were performed at, or adjacent to, a standard of care visit. cfDNA was extracted from whole blood, bisulphite-treated and assayed in triplicates for BCAT1/IKZF methylation. Previously, any positive replicate of either target gene was reported as COLVERA "detected". In the current study, COLVERA is "detected" when at least one replicate of IKZF1 or multiple replicates of either IKZF1 and/or BCAT1 are present. Sensitivity, specificity, and diagnostic odds ratio (DOR) for CRC recurrence detection from a single time-point blood sample was determined using radiological imaging as clinical reference standard. **Results:** In the first cohort (N=322), overall COLVERA test positivity was 6.5% (21/322) with a sensitivity of 59.3% (95% CI: 38.8 - 77.6) and specificity of 98.3% (96.1 - 99.5) for detecting recurrence at a time-point adjacent to imaging, representing improved specificity, from 91.5% (87.7 - 94.4%), with minimal decrease in sensitivity, from 63.0% (42.4 – 80.6). Similarly, in the second cohort (N=144) sensitivity was 62% (47.2 -75.4), compared to 66.0% (57.1 – 69.3) under the prior interpretation method, while specificity was 92.6% (85.3-97), compared to 90.4% (84.7 - 94.7). A high DOR of 84 (26 - 272) (previously 18 (7.6 – 44.4)) indicates that the revised COLVERA interpretation method is clinically more informative and differentiates with greater accuracy patients with and without the disease. **Conclusions:** This change in the COLVERA interpretation rule resulted in optimized clinical specificity with minimal impact on sensitivity. For an assay intended to aid in surveillance and early recurrence detection, improved accuracy allows the physician to have increased confidence in making actionable decisions based on test result, including further imaging or treatment. Research Sponsor: Clinical Genomics Pathology, Inc.

3547 **Poster Session**

Effect of Medicaid expansion on incidence of early-onset colorectal cancer incidence among Hispanics. *First Author: Shafia Rahman, Albert Einstein College of Medicine/Montefiore Medical Center, New York, NY*

Background: Early onset colorectal cancer (EO-CRC, age $<$ 50 years) is an emerging public health crisis; especially in Hispanics. Access to healthcare is critical for timely detection and is tied to medical insurance. In 2010, the Affordable Care Act allowed for expansion of Medicaid eligibility across the country, however, states were permitted to opt out by the US Supreme Court ruling of 2012, which created an unintended experiment in the healthcare market. We evaluated the effects of Medicaid expansion on the incidence of EO-CRC among Hispanics with the hypothesis that it would lead to an increase in incidence and early detection EO-CRC. **Methods:** The National Cancer Data Base was used to collect data on newly diagnosed Hispanics with EO-CRC (40-49 years), across all stages, from 2010-2017. Data for 21 expansion states (ES) that expanded Medicaid in 2014, and 16 non expansion (NES) states was analyzed. The yearly state-wise Hispanic population was collected from U.S Census Bureau for 2010-17. Incidence was computed as number of new cases of CRC divided by size of the state's Hispanic population. Segmented Poisson generalized linear mixed effects model was used to analyze rate of change in yearly incidence of EOCRC before and after 2014, in ES and NES. **Results:** Average annual incidence (AI) of EO-CRC in Hispanics was 6/100,000 and 8/100,000 pre and post expansion, in ES, and 8/100,000 and 9/100,000 pre and post 2014 in the NES, respectively. Increase in AI of EO-CRC was 3.6% per year (2010-14) (95% CI: -0.1% to 7.4%), and 9.8% (2014-17) (95% CI: 5.2% to 14.7%) for ES states; and 6.4% (2010-14) (95% CI: 2.1% to 10.8%), and 1% (2014-17) (95% CI: -3.8% to 6.1%) in NES. ES showed greater change in EO-CRC incidence post expansion (2014) vs. pre-expansion, as compared to NES (p=0.078) table. There was no difference in stage at diagnosis between pre- and pos- expansion periods between ES and NES. **Conclusions:** Increase in incidence of EO-CRC in ES is likely due to greater access to health care due to Medicaid coverage as compared to NES. Other potential factor is migration of Medicaid eligible persons from NES to ES. However we need data past 2017 to confirm the current trend. Research Sponsor: None.

Rate of change in yearly incidence of early onset colorectal cancer.

	Pre- 2014	Post 2014	p=0.078
Non-expansion states	6.4% per year (95% CI: 2.1% to 10.8%)	1% per year (95% CI: -3.8% to 6.1%)	
Expansion states	3.6% per year (95% CI: -0.1% to 7.4%)	9.8% per year (95% CI: 5.2% to 14.7%)	

3548 **Poster Session**

PMC: A more precise classifier of POLE mutations to identify candidates for immune therapy. *First Author: Fadl Zeineddine, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Specific somatic mutations in DNA polymerase epsilon (*POLE*) can cause a hypermutant phenotype with tumor mutation burden (TMB) in excess of 100 mutations per megabase. It has been reported that *POLE* mutant tumors are enriched in response to immune therapy and this association is being tested in multiple active clinical trials. However, most *POLE* mutations are passenger mutations and have no pathogenic role. Current methods to classify *POLE* mutations are limited in both accuracy and completeness, which could lead to inappropriate use of immune agents in tumor such as MSS CRC, where response rate is 5% or less. Here we present a new classifier, *POLE* Mutation Classifier or PMC, based on the unique trinucleotide mutation signature caused by selective loss of the proofreading function (LOP) of POLE. **Methods:** cBioPortal was queried to identify all tumors with *POLE* mutation. TMB was calculated for each, additionally, trinucleotide mutation signatures were obtained for all *POLE* mutant tumors in TCGA. Using OncoKB to identify a gold standard of 12 functional *POLE* mutations (n = 98 tumors) a *POLE* mutational signature was created. A combination of mutational signature, amino acid location, and TMB was used to classify each POLE variant. **Results:** Among all 48035 unique tumors the overall frequency of *POLE* mutations was 2.5% (n = 1184), however only 9.2% (n = 110) were determined to cause the selective LOP. The incidence of LOP *POLE* mutation was highest in uterine carcinoma and CRC, these tumors also had the highest ratio of LOP to passenger mutations. In a pan-cancer analysis the overall survival of LOP *POLE* patients was significantly better than those with passenger mutations (not-yet-reached vs. 51 mo, HR = 4.4, $p < 0.0001$). A similar analysis performed using the polyphen-2 classifier to identify functional *POLE* mutations did not show a difference in overall survival (HR = 1.0, p-value = 0.57). To further validate the improved specificity of the PMC classifier TMB was used as a surrogate marker, using the PMC classifier 98% of tumors with LOP showed hypermutation (TMB $>$ 20mut/Mb), vs. 53% called functional by polyphen-2. A retrospective analysis of MD Anderson CRC patients identified 25 patients with LOP *POLE* mutation, who had improved OS relative to 267 CRC patients with passenger *POLE* mutation (not-yet-reached vs. 70 mo, HR:4.2, p = 0.028). Four metastatic CRC patients with LOP *POLE* mutation were treated with immune therapy (nivolumab, or ipilimumab/nivolumab) in 2nd or 3rd line, all four achieved objective response and remain on therapy (mean time on treatment 15 mo). **Conclusions:** The PMC classifier specifically identifies mutations in *POLE* that cause loss of the proofreading function, outperforming both manually curated databases and machine learning-based methods. Clinical trials that use *POLE* mutation as a selection criteria for immune therapy should be restricted to just those *POLE* mutations that cause LOP. Research Sponsor: U.S. National Institutes of Health, Other Government Agency, U.S. National Institutes of Health.

3549 **Poster Session**

Are current family-history based colorectal cancer screening guidelines adequate for early detection and potential prevention of young-onset cases? *First Author: Y. Nancy You, Department of Colon and Rectal Surgery, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Strategies to detect and prevent young-onset colorectal cancer (YOCRC, diagnosed under age 50) are critical. Established high-risk screening guidelines (SGs) aim to detect/prevent YOCRCs arising from hereditary syndromes. For non-hereditary YOCRCs, average-risk screening is being considered at an earlier age, but family history (FH)-based increased-risk screening has been poorly studied. We aimed to define the proportion of non-hereditary YOCRC with a FH, and to determine whether existing SGs could have detected/prevented these cases. **Methods:** 394 consecutive YOCRC patients presenting for surgical resection were reviewed for tumor MMR status, pedigree and genetic testing. Those with known/suspected hereditary syndrome (by phenotype, MMR status, and/or germline mutation) were excluded (N = 65). Pedigrees (N = 329) were analyzed for first- or second-degree relatives (FDR, SDR) with CRC and the ages of diagnosis. The gap between the recommended age for FH-based CRC screening and the age of YOCRC diagnosis was calculated. **Results:** 89 (27%) non-hereditary YOCRC patients had a FH of CRC. The median age of diagnosis was 45; the tumors were mostly from the distal colon (22%) and rectum (60%), and stage III (48%) and IV (27%). Twenty-one (24%) patients had 22 FDRs with CRCs diagnosed at age 64 (median); and 71 (80%) patients had 92 SDRs with CRCs diagnosed at age 65 (median). Thirteen (15%) had a FH of YOCRC. The existing SGs consider 39 patients (44%) at increased-risk, and the remaining, average-risk (Table). Screening would have begun prior to the YOCRC diagnoses in 28 (31% [or 46, 52%]) patients. But YOCRC diagnosis preceded the recommended screening age in the remaining 61(69% [or 43, 48%]) patients by a median of 5.3 [or 3.9] years (Table). **Conclusions:** FH is found in 27% of the non-hereditary YOCRC patients; 15% has a FH of YOCRC. In nearly half of the patients, YOCRC was diagnosed several years earlier than the recommended age for FH-based screening, even assuming perfect SG adoption and starting average risk screening at age 45. Refining existing FH-based SGs can potentially be impactful. Research Sponsor: University of MD Anderson Cancer Center Clinical Innovator Award.

FH-based Screening Recommendation	Criteria (Age at Diagnosis)	Endorsed by	YOCRCs Meeting Criteria (N; % of 89)	YOCRCs Diagnosed AFTER Recommended Screening Age (N; Median Gap)	YOCRC diagnosed PRECEDING/AT Recommended Screening age (N; median gap)
Increased-risk		At least 1	39 (44%)	26 8.4 years	13 - 3.5 years
Start at age 40 y or 10 y before earliest CRC	FDR at $<$ 60 or $>$2 SDR at any age	NCCN MSTF ACS ACG	20 (22%)	16	
Start at age 40 y	FDR at $>$60	MSTF ACS	16 (18%)	12	
Start at age 50 y	SDR at $<$ 50	NCCN	3 (4%)	0	
Average-risk		NCCN	50 (56%)	2	48
Start at age 50 y (or 45y)		MSTF ACS ACG		0.6 years [or 20 2.8 years]	-5.9 years [or 30 -4.1 years]

y = years; NCCN = National Comprehensive Cancer Network; MSTK = Multi-society Task Force on CRC; ACS = American Cancer Society; ACG = American College of Gastroenterology.

3550 **Poster Session**

A nationwide analysis of outcomes and healthcare utilization in HIV versus non-HIV patients with colon cancer. *First Author: Syed Ali Amir Sherazi, Department of Internal Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, IL*

Background: The incidence and mortality of Colon cancer (CC) is reportedly similar in HIV and non-HIV populations with same screening guidelines. The pathogenesis of HIV-CC may be multifactorial; related to chronic inflammation from AIDS colopathy, 2-fold increase in risk of polyps, smoking, elevation in proinflammatory cytokines, decrease in adiponectin, activation of b-catenin signaling pathway all of which may promote neoplastic growth of colonic mucosa. With increasing survival in HIV due to effective antiretroviral therapy, non-AIDS defining cancers are rising as population ages. We attempted to compare demographics and outcomes of HIV and non-HIV-CC patients in a national database. **Methods:** Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS) was queried to identify all HIV and non-HIV-CC admissions. The groups were compared for socio-demographic differences, medical comorbidities, inpatient mortality, length of stay (LOS) and hospital charges (THC). Secondary outcomes studied included rates of sepsis, septic shock (SS), Anemia, transfusions, GI bleeding, colostomy rates, Acute Kidney Injury (AKI) and protein energy malnutrition (PEM). Statistics were performed using t-test, univariate and multinomial logistic regression. **Results:** A total 895 HIV-CC and 514,840 non-HIV-CC admissions were identified. HIV-CC were younger (mean age 56.3 vs 67.3 years, $p < 0.001$) with 76% $<$ 65 years old compared to 40% in non-HIV-CC. HIV-CC were more likely male (75.4% vs 50.5%, $p < 0.001$), African Americans (AA) (43% vs 14%, $p < 0.001$) and Hispanic (19% vs 9%, $p < 0.001$), were more likely from lowest income quartile zip codes (44% vs 28%, $p < 0.001$) from the Northeast region of US (27% vs 19%, $p < 0.001$) and on Medicaid (30% vs 10%, $p < 0.001$). HIV-CC had significantly lower rates of medical comorbidities (hypertension, diabetes, obesity, dyslipidemia, heart failure, all $p < 0.05$) compared to non-HIV-CC. The odds of adjusted inpatient mortality were significantly lower in HIV-CC (aOR = 0.46 CI = 0.24-0.87, p = 0.018), however HIV-CC had longer mean LOS (8.17 vs 6.66 days, $p < 0.01$) and higher mean THC ($88,305 vs $76,317, p = 0.051). Cancer pain and PEM were significantly higher in the HIV-CC group, but other secondary outcomes were similar. **Conclusions:** HIV-CC patients were significantly younger and minorities with significantly lower all-cause mortality compared to non-HIV-CC. The lower mortality may be explained by younger age, treatment of teaching hospitals for HIV-CC and lower incidence of medical comorbidities which may be driving mortality higher in non-HIV-CC. However, healthcare utilization of HIV-CC was higher with over $10 million in extra charges in 3 years compared to non-HIV-CC. The young age of HIV-CC compared to non-HIV suggests a need for studies to evaluate the role of starting colon-cancer screening at a younger age in the HIV population. Research Sponsor: None.

3551 **Poster Session**

Investigating intra-tumor microbes, blood microbes, and CEA for development of non-invasive biomarkers in colorectal cancer. *First Author: Pannaga G. Malalur, The Ohio State University/Wexner Medical Center, Columbus, OH*

Background: The development of non-invasive biomarkers has the potential to revolutionize clinical care for colorectal cancer (CRC) patients. The presence of bacteria in CRC tumor biopsies has been shown to contribute to CRC development. In a previous study, our group showed some intra-tumor microbes in CRC tumor biopsies correlated with overall survival in CRC patients. However, the correlations between microbes in tumor vs blood, and between non-invasive serum marker carcinoembryonic antigen (CEA) and microbes are unknown. We hypothesize that tumor microbes will also be found in blood, and that CEA will correlate with certain microbes. **Methods:** We obtained RNA-seq data from CRC tumor biopsies from patients treated at The Ohio State University Comprehensive Cancer Center as part of the Oncology Research Information Exchange Network (ORIEN). Reads were aligned to human and exogenous genomes using TopHat2 and Kraken2/Bracken, respectively. RNA-seq from CRC tumor biopsies as well as peripheral blood at the Cancer Genome Atlas (TCGA) consortium were processed by the same method. **Results:** The analyzed ORIEN cohort included 93 CRC patients with an age range from 30-83 years, 60.2% male, 87.1% adenocarcinoma, and 47.3% with metastatic CRC. The TGCA cohort included 495 CRC patients with an age range from 31-90 years, 53.3% male, 85.1% adenocarcinoma, and 15.5% with metastatic CRC. Over fifteen exogenous phyla (including bacteria, viruses, fungi) were observed in both ORIEN and TCGA cohorts. Several of the samples were dominated by viral sequences while others by bacteria, suggesting considerable tumor microbiome heterogeneity. Evaluation of the fraction of microbes in tumor and blood showed that nearly all the microbes found in blood (97.6%) were also observable in tumor in the TCGA cohort. Microbial abundances of various taxa, including *Fusobacterium*, significantly correlated between blood and tumor. Several bacteria including members of the genera *Bacillus* and *Staphylococcus* were positively associated with tumor stage (metastatic vs non-metastatic), but microbial relative abundances were not correlated with the location of tumor in colon (right, left, transverse colon). Certain microbial species from the ORIEN cohort were found to positively correlate with CEA, (including from the genera *Fusobacterium, Lactobacillus, Pseudomonas, Vibrio, Clostridium)* and these associations remained when adjusted for alcohol and smoking by multivariate analysis. **Conclusions:** Nearly all the microbes found in blood were found in tumor and abundances of various taxa were significantly correlated, suggesting that blood-based cancer microbiome analysis has great potential. Serum CEA has a low diagnostic ability when used alone, but combining this with blood microbiome could improve diagnostic/prognostic utility as a non-invasive biomarker. Research Sponsor: Award Number UL1TR002733.

3552 **Poster Session**

Consensus molecular subtypes and *RAS* status as biomarker of treatment intensity with fluoropyrimidine, bevacizumab, and irinotecan in metastatic colorectal cancer (XELAVIRI, AIO KRK 0110). *First Author: Arndt Stahler, Medical Department, Division of Hematology, Oncology and Tumor Immunology (CCM), Charité Universitaetsmedizin Berlin, Berlin, Germany*

Background: Prognostic biomarkers beside *RAS/BRAF* status are necessary to identify metastatic colorectal cancer (mCRC) patients who benefit from combined (COMB) versus sequential (SEQ) treatment with fluoropyrimidine, bevacizumab and irinotecan (randomized phase III XELAVIRI trial). **Methods:** mRNA was extracted from formalin-fixed paraffin embedded (FFPE) tumor tissue of 337 patients, gene expression was measured by the Nanostring PanCancer Progression Panel. Consensus molecular subtypes (CMS) classification was re-derived using a multinomial regression model. Data of Guinney et al. (Nat. Med. 2015. 21:1350-6) and FIRE-3 served as training and validation set. *RAS/BRAF* MUT were assessed by pyrosequencing. Median overall (OS) and progression free survival (PFS), hazard ratios (HR) and 95% confidence interval (CI) were estimated by Kaplan-Meier method and univariate Cox regression. **Results:** The multinomial regression model employed in the present analysis correctly predicted CMS labels in 98.3 % of the original Guinney- and 100.0 % of FIRE-3 population. In XELAVIRI, CMS subgroups were predicted as follows: CMS1: n = 62 (18.4 %); CMS2: n = 174 (51.6 %); CMS3: n = 9 (2.7 %); CMS4: n = 92 (27.3 %). A general prognostic impact of CMS was not observed when all patients were analysed. In *RAS/BRAF* WT mCRC patients, substantial benefit of COMB versus SEQ treatment was shown for OS and PFS in CMS2 and CMS4, but not in CMS1. Conversely, OS was significantly longer for COMB treatment in patients with *RAS* MUT and CMS1 mCRC, while SEQ treatment was not inferior in *RAS* MUT and CMS2 or CMS4 subgroups (see TABLE). Additional data for overall response rates, early tumor shrinkage and sidedness might be presented at the meeting. **Conclusions:** This retrospective analysis of XELAVIRI suggests that CMS may serve as biomarker that predicts response to initially combined versus less intensive sequential chemotherapy in patients with *RAS/BRAF* WT mCRC. Research Sponsor: Roche.

Outcome of XELAVIRI patients according to molecular subtype (CMS) and stratification for *RAS* status.

	CMS1 n = 56				CMS2 n = 161				CMS3* n = 8				CMS4 n = 87			
	*RAS/BRAF*WT n = 26		*RAS* MUT n = 30		*RAS/BRAF*WT n = 74		*RAS* MUT n = 87		*RAS/BRAF*WT n = 5		*RAS* MUT n = 3		*RAS/BRAF*WT n = 37		*RAS* MUT n = 50	
Outcome	COMB n = 13	SEQ n = 13	COMB n = 12	SEQ n = 18	COMB n = 41	SEQ n = 33	COMB n = 42	SEQ n = 45	COMB n = 2	SEQ n = 3	COMB n = 1	SEQ n = 2	COMB n = 17	SEQ n = 20	COMB n = 26	SEQ n = 24
OS, median	31.4	31.4	21.0	14.1	29.9	27.3	25.3	21.3	n/a				28.5	18.7	19.8	23.5
HR	1.18		0.43		0.56		0.95						0.53		1.24	
(95% CI)	(0.45 – 3.11)		(0.20 – 0.95)		(0.33 – 0.96)		(0.61 – 1.50)						(0.26 – 1.08)		(0.66 – 2.33)	
p	0.74		**0.038**		**0.036**		0.84						**0.079**		0.50	
PFS, median	12.7	8.5	9.4	6.5	13.4	7.8	10.4	10.3					13.0	8.5	10.6	6.2
HR	0.71		0.54		0.48		1.15						0.54		0.84	
(95% CI)	(0.31 – 1.65)		(0.24 – 1.22)		(0.29 – 0.79)		(0.74 – 1.78)						(0.27 – 1.07)		(0.46 – 1.56)	
p	0.43		0.14		**0.004**		0.53						**0.078**		0.59	

* Outcome not estimated owing to the limited sample size.

3553 **Poster Session**

FOLFOX plus panitumumab or FOLFOX alone as additive therapy following R0/1 resection of RAS wild-type colorectal cancer liver metastases: The PARLIM trial (AIO KRK 0314). *First Author: Dominik Paul Modest, Department of Medicine III, University Hospital, LMU Munich, Munich, Germany*

Background: This trial investigates the addition of panitumumab to chemotherapy with fluorouracil/ folinic acid and oxaliplatin (FOLFOX) in a 2:1 randomized, controlled, open label, phase II trial in *RAS* wild-type colorectal cancer patients with R0/1-resected liver metastases. **Methods:** The primary endpoint was progression-free survival (PFS) two years after randomisation. The experimental arm (12 wks of biweekly mFOLFOX6 plus panitumumab followed by 12 wks of panitumumab alone) was considered active if the 2-year-PFS rate was ≥65%. Based on historical data, a 2-year-PFS rate of 50% was estimated in the control arm (12 wks of biweekly FOLFOX). The trial was performed with a power of 80% and an alpha of 0.05. Secondary endpoints included overall survival (OS) and toxicity. The trial is registered with ClinicalTrials.gov, NCT01384994. **Results:** The full analysis set consists of 70 patients (pts) in the experimental arm and 36 pts in the control arm. The 2-year-PFS rate was 34.3% with FOLFOX plus panitumumab and failed to meet the primary endpoint. The 2-year-PFS rate in the control arm was 25%. In the experimental arm, a more favourable outcome was observed with regard to PFS (HR: 0.72, 95%CI 0.45-1.17; P = 0.18) and OS (HR: 0.76 (95% CI 0.34-1.71, P = 0.51) which did, however, not reach the level of significance. Updated data including toxicity and subgroup analyses might be presented at the meeting **Conclusions:** The PARLIM trial clearly failed to demonstrate a PFS rate of 65% after resection of colorectal liver metastases 2 years after randomisation, potentially indicating that the generally high frequency of recurrence and the choice of primary endpoint did not correspond in this study population. However, a trend for improved PFS and OS by the addition of panitumumab to 12 wks of FOLFOX followed by 12 wks panitumumab maintenance therapy may support future trials with ant-EGFR antibodies in this specific treatment setting. Clinical trial information: NCT01384994. Research Sponsor: AMGEN, University of Munich (LMU).

3554 **Poster Session**

Impact of a metastatic site on circulating tumor DNA (ctDNA) analysis in patients (pts) with metastatic colorectal cancer (mCRC). *First Author: Hideaki Bando, Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Japan*

Background: ctDNA genotyping has been used as an alternative to tissue genotyping for precision oncology. In mCRC, although low plasma *RAS* variant allelic frequencies (VAFs) and low concordance with tissue *RAS* tests have been reported in pts with lung-only metastasis (mets) (Kagawa Y. et al., Clin Cancer Res 2021), the association of ctDNA identified using the next-generation sequencing method with metastatic sites is still unknown. **Methods:** We investigated the association between metastatic site and ctDNA detection by using the Guardant360 (G360), a ctDNA assay which detects 74 gene alterations including mutations with the 95% of limit of detection of 0.2%, in mCRC pts with single organ mets in pts who had not received anti-EGFR therapy in the SCRUM-Japan GOZILA study. We also evaluated the correlations between the size/number of mets by CT and detected VAFs. **Results:** Of 1187 mCRC pts enrolled in GOZILA, 138 pts (49 with liver-only, 15 with lymph node-only, 27 with peritoneum-only, and 47 with lung-only mets) were eligible for this study. The concordance of *RAS*/*BRAF* status between G360 and tissue in-vitro diagnostic tests were 93.9% in liver-only, 80.0% in lymph node-only, 56.0% in peritoneum-only, and 65.9% in lung-only mets. The median maximum VAF (maxVAF) corresponding to the highest ctDNA fraction and the median numbers of detected variants were 23.1% and 5 in liver-only, 6.0% and 5 in lymph node-only, 0.4% and 3 in peritoneum-only, and 0.4% and 3 in lung-only (all $P<0.001$, Kruskal-Wallis test). A few pts with liver-only (2.0%) and lymph node-only mets (13.3%) had a maxVAF of <0.2%, but maxVAF was more frequently <0.2% in pts with lung-only (27.7%) or peritoneum-only mets (29.6%), especially in those with lung-only mets <20 mm as the longest diameter and <20 lesions (69.2%) or with peritoneum-only mets <20 mm as the longest diameter (87.5%). **Conclusions:** Lung-only and peritoneum-only mets had significantly lower maxVAF and lower numbers of detected variants, suggesting lower detections of subclonal variants. To ensure the sufficient clinical performance in G360 assay, inclusion of pts with lung-only mets ≥20 mm of longest diameter and/or ≥20 lesions, and ≥20 mm of the longest diameter in pts with peritoneum-only mets may be required. Research Sponsor: None.

	Liver-only (N=49)	Lymph node-only (N=15)	Peritoneum-only (N=27)	Lung-only (N=47)
maxVAF (%) (median, (range))	23.1 (0.04, 80.4)	6.0 (0, 45.5)	0.4 (0, 31.6)	0.4 (0, 10.9)
***RAS*/*BRAF* VAF (%) (median, (range))**	10.4 (0.06, 44.3)	9.1 (1.0, 36.8)	0.6 (0.09, 31.6)	0.4 (0.08, 7.6)
maxVAF< 0.2 (%)	2.0 (1/49)	13.3 (2/15)	29.6 (8/27)	27.7 (13/47)
Number of detected variants (median, (range))	5 (0, 52)	5 (0, 23)	3 (0, 32)	3 (0, 7)
Longest diameter (median, (range))	41.0 (11.5, 149.8)	25.2 (12.0, 53.0)	18.3 (4.9, 67.6)	19.2 (7.5, 56.0)
Lesion numbers (median, (range))	5 (1, 82)	3 (1, 35)	2 (1, 16)	7 (1,100<)

3555 **Poster Session**

Pertuzumab plus trastuzumab and real-world standard of care (SOC) for patients (pts) with treatment refractory metastatic colorectal cancer (mCRC) with *HER2* (*ERBB2*) amplification (amp) confirmed by tumor tissue or ctDNA analysis (TRIUMPH, EPOC1602). *First Author: Wataru Okamoto, Cancer Treatment Center, Hiroshima University Hospital, Hiroshima, Japan*

Background: *HER2* amp occurs in 1-4% of mCRC pts. Two single arm phase 2 studies, HERACLES and MyPathway, showed efficacy for dual HER2-targeted therapy in pts with *RAS* wild type (*RAS* wt) mCRC with *HER2* amp detected in tumor tissue; however, efficacy for pts prospectively enrolled with *HER2* amp identified in ctDNA is unknown. Furthermore, the efficacy of real-world non-HER2-targeted SOC for *HER2* amplified *RAS*wt mCRC pts is not clear. **Methods:** We conducted a phase 2 trial to evaluate the efficacy of pertuzumab (P) plus trastuzumab (T) in *RAS*wt mCRC pts with *HER2* amp centrally confirmed by tissue (IHC and/or FISH) and/or ctDNA (Guardant360) who had progressed on SOC including EGFR blockade. Pts received intravenous P (840 mg loading dose followed by 420 mg) and T (8 mg/kg loading dose followed by 6 mg/kg) every 3 weeks. The primary endpoint was confirmed objective response rate (ORR) by investigator assessment, analyzed for two primary populations: pts with *HER2* amp in tissue (tissue$^+$) or in ctDNA (ctDNA$^+$). Efficacy of real-world non-HER2-targeted SOC for *HER2* amplified *RAS*wt mCRC pts was prospectively assessed in a concurrent registry: the SCRUM-Japan registry. **Results:** Among 75 pts screened, concordance of *HER2* amp between tissue and ctDNA was 83%. The primary endpoint was met in each cohort of TRIUMPH, with confirmed ORR of 30% (95% CI 14-50%) in 27 tissue$^+$ pts and 28% (12-49%) in 25 ctDNA$^+$ pts. In contrast, ORR in first salvage SOC after EGFR blockade was 0% (0.0-24.7%) in the real-world cohort. Median progression free and overall survival were 4.0 months (1.4-5.6) and 10.1 months (4.5-16.5) in the tissue$^+$ pts and 3.1 months (1.4-5.6) and 8.8 months (4.3-12.9) in the ctDNA$^+$ pts. One pt withdrew due to an adverse event (grade 3 decreased ejection fraction), but no treatment related deaths occurred. In exploratory analyses, pts without ctDNA mutations of *RAS*/*BRAF*V600/*PIK3CA*/*HER2* were more likely to respond to P+T than those with a ctDNA mutation in at least one of these genes (ORR 44% vs. 0% in tissue$^+$ and 37% vs. 0% in ctDNA$^+$). Decreased ctDNA fraction and *HER2* plasma copy number at 3 weeks after treatment initiation corresponded to P+T response. At least one actionable alteration emerged after progression in 16 (62%) of 26 pts with ctDNA results at both baseline and progression. Among 5 pts who achieved response and had ctDNA results at both time points, 4 pts acquired actionable alteration at progression. **Conclusions:** We demonstrate promising efficacy and safety of P+T for *RAS*wt mCRC pts with *HER2* amp in either tumor tissue or ctDNA. Our results show that complete ctDNA genotyping identifies pts most likely to benefit from dual HER2 blockade and can be used to monitor response and detect actionable resistance biomarkers. Clinical trial information: UMIN000027887 and UMIN000028058. Research Sponsor: Japan Agency for Medical Research and Development.

3556 **Poster Session**

Repeat sequential oxaliplatin-based chemotherapy (FLOX) and nivolumab versus FLOX alone as first-line treatment of microsatellite-stable (MSS) metastatic colorectal cancer (mCRC): Initial results from the randomized METIMMOX study. *First Author: Anne Hansen Ree, Akershus University Hospital, Lorenskog, Norway*

Background: Immune checkpoint blockade (ICB) has revolutionized patient outcome for the small mCRC subgroup with highly immunogenic disease. The majority of mCRC cases, however, are MSS without innate ICB susceptibility. In our ongoing METIMMOX study, we hypothesize that MSS mCRC can be transformed into an immunogenic condition by short-course oxaliplatin-based therapy (FLOX), enabling patients with unresectable, previously untreated metastases to obtain durable disease control when adding ICB therapy. Here we present the protocol-planned interim analysis. **Methods:** Eligibility criteria include infradiaphragmatic metastasis and C-reactive protein < 60 mg/L. At analysis 15 January 2021, 54 patients stratified according to primary tumor sidedness and mutational status and evaluable for the primary end point (progression-free survival; PFS) had been randomly assigned to a standard-of-care schedule of 8 FLOX cycles Q2W (control arm) or repeat sequential 2 FLOX cycles and 2 nivolumab cycles (240 mg Q2W) to a total of 8 cycles (experimental arm), for both arms before treatment break until disease progression and reintroduction of a new treatment sequence. Radiologic response assessment is every 8 weeks. Safety, tolerability, objective response rate, and duration of response are among secondary end points. **Results:** At median follow-up of 6.4 (range, 0.5-20) months, patients were well balanced between the treatment arms with regard to the predefined strata and single-organ or multiple-organ metastases. Median PFS for the entire groups of control and experimental arm patients was 5.6 (range, 0.5-15; $n = 26$) and 6.6 (range, 0.5-20; $n = 28$) months, respectively. The number of FLOX-related CTCAE grade 3 or higher adverse events, including 2 deaths after initial FLOX administration, was comparable in the two arms. Twelve immune-related grade 3-4 adverse events (no new safety signals) were recorded. In the experimental arm, 4 (16%) patients, all *RAS/BRAF*-mutant cases, had experienced complete response and 9 (32%) patients had ongoing objective response at 8 months. The control arm cases had 0 with complete response and 6 (23%) with ongoing objective response at 8 months, 1 of whom had proceeded to curative-intent liver surgery. **Conclusions:** MSS mCRC patients may hold the opportunity of ICB responsiveness evoked by short-course oxaliplatin-based chemotherapy. The search for predictive biomarkers of ICB responsiveness is ongoing in the specifically designed METIMMOX correlative study program. Clinical trial information: NCT03388190. Research Sponsor: Norwegian Cancer Society Grant 182496, Pharmaceutical/Biotech Company.

3557 **Poster Session**

Impact of BRAF mutations on prognosis and immunotherapy response in microsatellite instability/mismatch repair deficient metastatic colorectal cancer: A systematic review and meta-analysis. *First Author: Robin Park, MetroWest Medical Center, Framingham, MA*

Background: Mismatch repair deficient/microsatellite instability high (dMMR/MSI-H) colorectal cancer (CRC) defines a molecular subtype with distinct clinicopathologic characteristics including an excellent response to immunotherapy. Although *BRAF* mutations are established as a negative prognostic marker in CRC, whether they retain their negative prognostic impact in or alter the response to immunotherapy in dMMR/MSI-H CRC remains unknown. Herein, we present a systematic review and meta-analysis of the impact of *BRAF* mutations on the overall survival (OS) and immune checkpoint inhibitor (ICI) response in dMMR/MSI-H CRC. **Methods:** Studies published from inception to 26 January 2021 were searched in PubMed, Embase, and major conference proceedings (AACR, ASCO, and ESMO). Eligible studies included the following: 1) observational studies reporting outcomes based on *BRAF* mutation status in dMMR/MSI-H CRC patients and 2) experimental studies of ICI reporting outcomes based on *BRAF* mutation status in dMMR/MSI-H CRC patients. A summary hazard ratio (HR) was calculated for OS in *BRAF* mutated (*BRAF*mut) vs. *BRAF* wild type (*BRAF*wt) patients (pts) with the random effects meta-analysis (REM). A summary odds ratio (OR) was calculated for objective response rate (ORR) in *BRAF*mut vs. *BRAF*wt pts treated with ICI with the REM. **Results:** Database search conducted according to PRISMA guidelines found 4221 studies in total. Initial screening identified 30 studies and after full-text review, 9 studies (N = 4158 pts) were included for the meta-analysis of prognosis (analysis A) and 3 studies (N = 178 pts) were included for the meta-analysis of ICI response (analysis B). The outcome measures are summarized in the table below. Analysis A showed that in stage I-IV dMMR/MSI-H CRC pts, *BRAF*mut was associated with worse OS than *BRAF*wt (HR 1.57, 1.23-1.99). The heterogeneity was low ($I^2 = 21\%$). Subgroup analysis showed no significant difference in the prognostic impact of *BRAF* mutation status between stage IV only and stage I-IV CRC pts. Analysis B showed no difference in ORR (OR 1.04, 0.48-2.25) between *BRAF*mut vs. *BRAF*wt dMMR/MSI-H pts who received ICI. The heterogeneity was low ($I^2 = 0\%$). **Conclusions:** *BRAF* mutations retain their negative prognostic impact in dMMR/MSI-H stage I-IV and stage IV CRC but are not associated with differential ICI response. Limitations include the following: analysis A was based on retrospective studies; also, the impact of *BRAF* status on the survival outcome of ICI could not be assessed due to limited number of studies. Research Sponsor: None.

***BRAF* mutated vs. *BRAF* wild type**	**Number of Studies (Pts)**	**Outcome**
Overall Survival (I-IV)	9 (N = 4158)	HR 1.57 [1.23-1.99]*
Overall Survival (IV only)	3 (N = 3247)	HR 2.02 [1.20-3.42]
Objective Response Rate to ICI	3 (N = 178)	OR 1.04 [0.48-2.25]**

**Lower HR favors BRAFmut **Higher OR favors BRAFmut.*

3558 **Poster Session**

Phase II study of panitumumab monotherapy in chemotherapy-naïve frail or elderly patients with unresectable, *RAS* wild type colorectal cancer: OGSG 1602, survival update data. *First Author: Shingo Noura, Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Japan*

Background: We previously reported the result of the phase II OGSG1602 study in which single agent of panitumumab (Pmab) demonstrated 76.5% and 50% of disease control rate (DCR), primary endpoint, and response rate (RR), respectively, in chemotherapy-naïve frail or elderly patietns (pts) with wild-type (wt) *RAS* unresectable colorectal cancer (CRC). Here, we reports the survival analysis including overall survival (OS) and progression free survival (PFS) in terms of sidedness and early tumor shrinkage (ETS). **Methods:** Thirty-six pts aged ≥76 years, or ≥65 considered unsuitable for intensive chemotherapy were enrolled and received Pmab 6 mg/kg intravenously every 2 weeks. Primary tumors located in the cecum to transverse colon were coded as right-sided tumors (RST), while tumors located from the splenic flexure to rectum were considered left-sided tumors (LST). Early tumor shrinkage (ETS) was determined as tumor reduction of 20% at week 8 compared to baseline. **Results:** Of total of 36 enrolled pts, 34 pts were included in the efficacy analysis, with pts with LST vs. RST being 26 vs. 8 cases, while pts who achieved ETS (ETS+) vs. those who did not achieve ETS (ETS-) being 15 vs. 19 cases. Among the evaluable 34 pts, the median PFS (mPFS) and median OS (mOS) were 6.0 months (95% Confidence Interval [CI]: 5.4-10.0) and 17.5 months (95%CI, 13.8-24.3), respectively, with the median follow-up of 17.0 months. For PFS, there were no significant differences between pts with LST vs. RST [6.6 months (95%CI, 5.4-11.5) vs. 4.9 months (95%CI, 1.9-NA), p = 0.120] but between pts with ETS+ vs. ETS- [10.4 months (95%CI, 7.4-NA) vs. months (95%CI, 2.1-7.9), p = 0.001]. Furthermore, OS was significantly different either in pts with LST vs. RST [19.3 months (95%CI, 14.2-NA) vs. 12.3 (95%CI, 9.9-NA), p = 0.043] or in pts with ETS+ vs. ETS- [months (n = 15, 95%CI, 19.6-NA) vs. 10.1 months (n = 19, 95%CI, 6.8-21.8), p < 0.001]. **Conclusions:** Pmab monotherapy showed the favolable OS in the frail or elderly pts with *RAS* wt, unresectable CRC. Our data also confirmed the prognostic value of sidedness as well as predictive value of ETS in this setting. Clinical trial information: UMIN000024528. Research Sponsor: OGSG and Takeda Pharmaceutical Company Limited.

PFS and OS in subgroup analysis.

	n	**mPFS (months)**	**mOS (months)**
All patients	34	6.0 95% CI (5.4-10.0)	17.5 95% CI (13.8-24.3)
LST vs. RST	26 vs. 8	6.6 vs 4.9 p = 0.120 (HR 0.518)	19.3 vs 12.3 p = 0.043 (HR 0.413)
ETS+ vs. ETS-	15 vs. 19	10.4 vs 3.6 p = 0.001 (HR 0.282)	34.8 vs 10.1 p < 0.001 (HR 0.184)

HR; hazard ratio.

3559 **Poster Session**

Phase Ib/II open-label, randomized evaluation of atezolizumab (atezo) + Imprime PGG (Imprime) + bevacizumab (bev) vs regorafenib (rego) in MORPHEUS: Microsatellite-stable (MSS) metastatic colorectal cancer (mCRC). *First Author: Marwan Fakih, City of Hope Comprehensive Medical Center, Duarte, CA*

Background: The MORPHEUS platform consists of multiple, global, open-label, randomized Phase Ib/II trials designed to identify early efficacy and safety signals of treatment (tx) combinations across cancers. Here, atezo (anti-PD-L1) was tested with Imprime and bev (anti-VEGF) for MSS mCRC, a poorly immunogenic cancer generally resistant to checkpoint inhibitors. Imprime acts as a pathogen-associated molecular pattern that, when bound to anti-β glucan antibodies (ABA), activates the innate immune system with the potential to 1) promote priming and expansion of tumor-specific T cells, 2) promote M2-M1 macrophage polarization and 3) enhance the immunomodulatory effects of atezo and bev. Therefore, we hypothesized that atezo + Imprime + bev would induce an antitumor response beyond that of rego, a standard-of-care multikinase inhibitor, in patients (pts) with MSS mCRC. **Methods:** Pts with MSS mCRC unselected for the Imprime-specific biomarker (ABA) and refractory to 1-2 prior lines of standard therapy received atezo (1200 mg IV every 3 weeks [q3w]) + Imprime (4 mg/kg IV on Days 1, 8, 15) + bev (7.5 mg/kg IV q3w) or control tx with rego (160 mg orally days 1-21; dose escalation to 160 mg during Cycle 1 allowed per institutional guidelines). The primary endpoint was objective response rate (ORR; investigator-assessed RECIST 1.1); secondary endpoints included disease control rate (DCR; response or stable disease ≥ 12 weeks), progression-free survival (PFS), overall survival (OS) and safety. **Results:** Pts were followed-up for ≥18 wk. 15 pts received atezo + Imprime + bev and 13 received rego. Grade (Gr) 3/4 tx-related adverse events (TRAEs) were seen in 13% of atezo + Imprime + bev and 62% of rego pts. No Gr 5 AEs occurred in atezo + Imprime + bev pts and 1 (8%) was reported in a rego pt. One pt in each arm (7% vs 8%, respectively) withdrew from tx due to a TRAE. No radiological responses were seen in either arm. Five pts (33%) receiving atezo + Imprime + bev and 8 (62%) receiving rego had stable disease as best response. DCR was 13% with atezo + Imprime + bev and 23% with rego. Median PFS was 1.5 mo (95% CI: 1.4, 2.8) and 2.8 mo (95% CI: 1.6, 3.1), and median OS was 5.7 mo (95% CI: 4.4, 10.5) and 10.2 mo (95% CI: 4.8, NE) with atezo + Imprime + bev and rego, respectively. There was no apparent correlation between baseline PD-L1 expression or CD8+ lymphocyte tumor infiltration and clinical benefit. Further, the systemic exposure of atezo, Imprime and bev and immunogenicity of atezo and bev are in line with previous clinical experience. Additional biomarker, pharmacokinetics and anti-drug antibody data will be shown. **Conclusions:** Atezo + Imprime + bev was well tolerated; toxicities were consistent with the safety profiles of the individual agents. No efficacy signal was identified with atezo + Imprime + bev in pts with MSS refractory mCRC. Clinical trial information: NCT03555149. Research Sponsor: F. Hoffmann-La Roche, Ltd.

3560 **Poster Session**

Single-arm, phase 2 study of regorafenib plus nivolumab in patients with mismatch repair-proficient (pMMR)/microsatellite stable (MSS) colorectal cancer (CRC). *First Author: Marwan Fakih, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: The role of immunotherapy in the treatment of pMMR/MSS metastatic CRC is not established. A Japanese phase 1b trial in this setting showed the combination of regorafenib (multikinase inhibitor with immunomodulatory activity) plus nivolumab (anti PD-1) had encouraging activity and manageable safety (Fukuoka, 2020). This study further assessed the safety and efficacy of this combination. **Methods:** Patients (pts) from the US aged ≥18 years who progressed on/were intolerant to standard chemotherapy were enrolled. Regorafenib was given orally, once daily in 28-day (D) cycles (21D on/7D off) plus IV nivolumab 480 mg on D1. Regorafenib starting dose was 80 mg; if well tolerated, it could be escalated to 120 mg in Cycle 2. Primary endpoint was overall response rate (ORR; RECIST 1.1); secondary aims included disease control rate (DCR), overall survival (OS), progression-free survival (PFS), and safety (NCI-CTCAE v5.0 grade). Biomarker analysis was exploratory. **Results:** 70 pts (59% male) started treatment. At baseline, median age was 57 years (range 34–85), ECOG PS 0/1 was 51%/49%, 67% had liver metastases (mets), and the primary tumor site was right-sided colon in 36% and rectum in 17%. Median number of cycles was 3.0 (range 1–13); 41% of pts escalated regorafenib to 120 mg. Five pts (7.1%) had a partial response (PR) lasting ≥16 weeks (wks) and 22 (31.4%) had stable disease (SD); pts without liver mets had a higher ORR (21.7%). In pts with tumor samples (n = 40), higher baseline expression (IHC) of cytotoxic T cells (CD3+/CD8+/GranzymeB+), Tregs (FoxP3+), and macrophages (CD68+) trended with clinical benefit (PR/SD ≥16 wks/PFS); pts with liver mets had lower expression. Lower plasma levels of biomarkers of vascular biology (e.g. VEGF-D, Ang-2, VWF) trended with longer PFS. Grade (Gr) 3 treatment-emergent adverse events (TEAEs) occurred in 53% of pts and Gr 4 in 10%. Three pts had a Gr 5 TEAE: n = 1 related to the combination (sepsis); n = 1 related to nivolumab only by investigator (sepsis); n = 1 unrelated to treatment (respiratory failure). Most common Gr 3/4 TEAEs: maculopapular rash (14%), fatigue (7%), pneumonia (6%), increased bilirubin (6%). **Conclusions:** Combination treatment with regorafenib (up to 120 mg/day) and nivolumab (480 mg every 28D) has manageable safety. Efficacy of this combination in the North American population did not emulate results in the Japanese population. Absence of liver mets and expression of specific biomarkers indicate a better response and may warrant further analysis. Clinical trial information: NCT04126733. Research Sponsor: Bayer, Bristol Myers-Squibb, Ono.

	No liver mets n = 23	Liver mets n = 47	All patients N = 70
ORR, n (%)	5 (21.7)	0	5 (7.1)
PR, n (%)	5 (21.7)	0	5 (7.1)
SD, n (%)	8 (34.8)	14 (29.8)	22 (31.4)
Progressive disease, n (%)	9 (39.1)	27 (57.4)	36 (51.4)
Not evaluable, n (%)	1 (4.3)	6 (12.8)	7 (10.0)
DCR at 40 wks, n (%)	13 (56.5)	14 (29.8)	27 (38.6)
Median duration of SD, wks	30	21	30
Median PFS, wks	15	8	8
Median OS, wks	52	47	52

3561 **Poster Session**

Concurrent BRAFV600E and BRCA mutations in microsatellite stable (MSS) metastatic colorectal cancer (mCRC): Prevalence and case series of mCRC (pts) with prolonged overall survival (OS). *First Author: Timothy Lewis Cannon, Inova Schar Cancer Institute, Fairfax, VA*

Background: *BRAF* V600E+, MSS mCRC patients comprise up to 10% of advanced CRC. They have a poor prognosis with median survivals typically <1 year. Despite use of multi-agent first-line chemotherapy regimens and combination targeted therapies, outcomes are still poor. In our Institutional Molecular Tumor Board database, we identified 3 consecutive mCRC pts with MSS/*BRAF* V600E who also had a *BRCA1* or *BRCA2* co-mutation and had prolonged overall survival. Prior studies suggested that *BRCA* mutations are uncommon in CRC and we queried the Foundation Medicine (FM) genomic database to evaluate the prevalence of these cases as well as those with co-mutations in other homologous recombination genes. **Methods:** 36,966 CRC pts were sequenced by FMI using hybrid capture comprehensive genomic profiling (CGP) to evaluate all classes of genomic alterations (GA) for pathogenic *BRAF* mutations and/or a mutation in BRCA1/2 or a co-mutation in other homologous recombination (HR) genes (*BARD1, CDK12, FANCL, PALB2, ATM, RAD54L, CHEK2, BRAF, BRIP1, RAD51D, RAD51C, RAD51B, CHEK1*). Selected cohort analysis were *BRAF* V600E co-mutated with *BRCA1* and *BRCA2,* separated into MSI-H and MSS cohorts. The clinicopathological features and genomic loss of heterozygosity (gLOH) of those with a *BRAF* V600E and a *BRCA1/BRCA2* mutation are described along with 3 consecutive cases of CRC patients, identified through the Inova Schar Cancer Institute (ISCI) molecular tumor board (MTB) registry, whom had prolonged OS. **Results:** Of 36,966 colorectal cancer pts, 6.6% were *BRAF* V600E+ and 1.5% had any co-occurring HR gene mutation(s) with 0.6% having co-mutations of BRAF V600E and *BRCA1/2.BRCA* co-mutations were higher in MSI-High *BRAF* V600E, however 24.1% of these occurred in MSS *BRAF* V600E. *BRCA1* co-mutated was more commonly associated with MSS BRAF V600E and was associated with a higher gLOH than MSI-H *BRAF* V600E (18.7% vs 2.8%; p <0.001). In our institutional MTB database, (3/241;1.2%) CRC patients were MSS, *BRAF* V600E+ with *BRCA1 or BRCA2* co-mutations, one confirmed germline and 2 somatic in origin, and had average gLOH of 21.4% with overall survivals of 72+(alive), 17+(alive), and 30 months, respectively. **Conclusions:** Co-existence of *BRAF* V600E/*BRCA1/2* may represent a unique subset of advanced MSS CRC that may have a better prognosis and represent an opportunity to test novel targeted therapies. Larger prospective clinical validation trials in this subset is warranted. Research Sponsor: None.

Summary of colorectal cancer with comutation of BRAFV600E and HR variants.

All CRC Cases (N= 36,966)	MSI-High (N=707)	MSS (N=32141)	MSI-unknown (N= 3172)
# any BRAF mutation	707	2431	255
# of *BRAF* V600E	663	1610	175
***BRAF* V600E + any HR gene mut**	384	158	21
BRAF* V600E + *BRCA1* or *BRCA2	165	55	8
BRCA1	22	27	2
BRCA2	126	28	2
BRCA1 and BRCA2	17	0	1
	2.80	18.7	NR
Average gLOH *BRCA2*	2.02	9.5	NR
Average gLOH *BRCA1/2*	2.84	NR	NR

3563 **Poster Session**

Increased neutrophil infiltration and lower prevalence of tumor mutation burden and microsatellite instability are hallmarks of RAS mutant colorectal cancers. *First Author: Emil Lou, University of Minnesota School of Medicine, Minneapolis, MN*

Background: The tumor microenvironment (TME) of colorectal cancers (CRC) is modulated by oncogenic drivers such as KRAS. The TME comprises a broad landscape of immune infiltration. How tumor genomics associates with the immune cell landscape is less known. We aim to characterize immune cell types in RAS wild-type (WT) and mutant (MT) CRC, and to examine the prevalence of immuno-oncologic (IO) biomarkers (e.g. tumor mutation burden (TMB), PD-L1, MSI-H/dMMR) in these tumors. We performed genomic and transcriptomic analysis to confirm associations of mutant RAS with immune infiltration of the TME conducive to metastasis vs. potential response to immunotherapies. **Methods:** A total of 7,801 CRC were analyzed using next-generation sequencing on DNA (NextSeq, 592 Genes and WES, NovaSEQ), RNA (NovaSeq, whole transcriptome equencing) and IHC (Caris Life Sciences, Phoenix, AZ). MSI/MMR was tested by FA, IHC and NGS. TMB-H was based on a cut-off of > 10 mutations per MB). Immune cell fraction was calculated by QuantiSeq (Finotello 2019, Genome Medicine). Significance was determined by X^2 and Fisher-Exact and p adjusted for multiple comparisons (q) was <0.05. **Results:** Mutant KRAS was seen in 48% of mCRC tumors; NRAS in 3.7%, HRAS in 0.1%. The distribution was similar in patients < or >= than 50 yrs. In MSS tumors, there was a significantly higher neutrophil infiltration in KRAS MT (median cell fraction 6.6% vs. 5.9%) and NRAS MT (6.9%) overall and also when individual codons were studied. B cells, M2 macrophages, CD8+ T cells, dendritic cells and fibroblasts were lower in KRAS mutant tumors; B cells and M1 macrophages are lower in NRAS (q<0.05). dMMR/MSI-H was significantly more prevalent in RAS WT (9.1%) than in KRAS (2.9%) or NRAS MT (1.8%) tumors, and highest in HRAS MT tumors (60%, q<0.05).TMB-H was more prevalent in RAS WT (11%) than KRAS (5.8%) or NRAS (5.1%) MT, and highest in HRAS MT tumors (70%, all q<0.05). In MSS tumors, KRAS MT tumors showed more TMB-H than WT (3.1% vs. 2.1%, q<0.05), especially in KRAS non 12/13/61 mutations (5.5%, vs. 2.1%, q<0.05) and G12C (4.4%, p<0.05). PD-L1 expression was studied: in MSS tumors, KRAS-G12D (10.4%) and G13 MT (11.8%) showed higher mutation rates than RAS WT tumors (q<0.05). **Conclusions:** KRAS & NRAS mutations are associated with increased neutrophil abundance, with codon specific differences, while HRAS shows no difference. Overall CD8+ T cells and B cells are less abundant in KRAS & NRAS mutants; substantial variability was seen amongst different protein changes. RAS mutations were more prevalent overall than generally reported, but did not vary by age. These results demonstrate significant differences in the TME of RAS mutant CRC that identify variable susceptibilities to immuno-oncologic agents, and provide further detailed characterization of heterogeneity between RAS variants, at the molecular as well as immunogenic levels. Research Sponsor: None.

3564 **Poster Session**

LEAP-005: A phase 2 multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—Results from the colorectal cancer cohort. *First Author: Carlos A. Gomez-Roca, Institut Claudius Regaud, Toulouse, France*

Background: Pembrolizumab (pembro), an anti-PD-1 antibody, is approved for the treatment of patients (pts) with unresectable or metastatic microsatellite instability-high (MSI-H) or mismatch repair (MMR) deficient colorectal cancer, both as first-line treatment and after progression following treatment with fluoropyrimidine, oxaliplatin, and irinotecan. The combination of lenvatinib, a multiple receptor tyrosine kinase inhibitor, and anti-PD-1 treatment showed synergistic antitumor activity in preclinical models. LEAP-005 (NCT03797326) is evaluating the efficacy and safety of lenvatinib plus pembro in pts with previously treated advanced solid tumors. We present findings from the colorectal cancer cohort. **Methods:** In this nonrandomized, open-label, phase 2 study, adult pts (aged ≥18 y) with histologically/cytologically documented metastatic and/or unresectable colorectal cancer, non–MSI-H/pMMR tumor per local determination, previous treatment with oxaliplatin and irinotecan in separate lines of therapy, measurable disease per RECIST v1.1, ECOG PS of 0–1, and a tissue sample evaluable for PD-L1 expression were eligible. Pts received lenvatinib 20 mg QD plus pembro 200 mg Q3W for up to 35 cycles of pembro (~2 y) or until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Treatment with lenvatinib could continue beyond 2 y in pts with clinical benefit. Primary endpoints were ORR (per RECIST v1.1 by blinded independent central review) and safety. Secondary endpoints included disease control rate (DCR), duration of response (DOR), PFS, and OS. Tumor imaging was performed Q9W from treatment initiation for 54 wks, then Q12W to week 102, and Q24W thereafter. **Results:** 32 pts with colorectal cancer received treatment with lenvatinib plus pembro (median age, 56 y [range, 36-77]; male, 81%; 3L, 91%); median time from first dose to data cutoff (April 10, 2020) was 10.6 mo (range, 5.9-13.1). ORR was 22% (95% CI, 9–40; table). Grade 3–5 treatment-related AEs occurred in 16 (50%) pts. Treatment-related AEs led to treatment discontinuation in 3 pts (grade 2 ischemic stroke [n = 1], grade 3 increased liver transaminases [n = 1], grade 5 intestinal perforation [n = 1]). **Conclusions:** In pts with previously treated advanced non–MSI-H/pMMR colorectal cancer, lenvatinib plus pembro demonstrated promising antitumor activity and a manageable safety profile. Enrollment in the colorectal cohort was expanded to 100 pts. Clinical trial information: NCT03797326. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Efficacy results.

Outcome	N = 32
ORR (CR+PR), % (95% CI)	22 (9–40)
DCR (CR+PR+SD[a]), % (95% CI)	47 (29–65)
DOR, median (range), mos	NR (2.1+–10.4+)
PFS, median (95% CI), mos	2.3 (2.0–5.2)
OS, median (95% CI), mos	7.5 (3.9–NR)

NR, not reached.
[a]Confirmation was not required for best overall response of SD, but a final visit response of SD or better must have occurred ≥6 wks after starting study treatment.

3565 **Poster Session**

Circulating tumor derived cell-free DNA (ctDNA) to predict recurrence of metastatic colorectal cancer (mCRC) following curative intent surgery or radiation. *First Author: Bryant Chee, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Over half of patients (pts) with oligometastatic CRC treated with curative intent surgery or radiotherapy experience cancer recurrence with or without adjuvant chemotherapy. ctDNA detection post-definitive treatment could identify high risk pts for additional intervention to eliminate molecular residual disease. Here we report results of a prospective observational study aiming to determine ctDNA detection rates using a sensitive liquid biopsy and to correlate post-procedure ctDNA detection (post-ctDNA (+)) with radiographic mCRC recurrence. **Methods:** Pts with mCRC intending to undergo a curative intent procedure were prospectively recruited at two US sites. ctDNA was collected pre-procedure, 3 weeks post-procedure, and at multiple structured follow-up timepoints. The presence of ctDNA was evaluated using a plasma-only integrated genomic and epigenomic assay (Guardant Reveal, Guardant Health). A bioinformatic classifier was applied to differentiate tumor derived versus non-tumor derived cell-free DNA. **Results:** Among 52 enrolled pts, post-ctDNA data is available for 45 pts (87%), with a median of 4 (range 1-10) timepoints per pt. The sample analysis failure rate was 1% (2/217). As of 1/1/2021, the radiographic recurrence rate was 60% with a median follow-up time of 50 (range 4-192) weeks. 23 of 25 pts with post-ctDNA(+) have had recurrence (Positive Predictive Value [PPV], 92%). On average, ctDNA was detected 28 weeks before radiographic recurrence (mean 12 vs. 40 weeks, respectively). The two pts with post-ctDNA(+) but no recurrence have $>$ 3 years follow-up; one pt received adjuvant chemotherapy and cleared ctDNA. With a median event-free follow-up time of 97 (range 4-192) weeks, 4 of 20 pts with no post-ctDNA detection (-) have recurred (Negative Predictive Value, 80%). 3 of 4 pts with recurrence despite post-ctDNA(-) also were pre-ctDNA(-). We observed a sensitivity of 85% and a specificity of 89% for the ctDNA assay. The median time to radiographic recurrence was 36 wks for ctDNA(+) vs. not reached for ctDNA(-) (Hazard Ratio, 7.7; 95% CI, 2.6-22.5; $P < .001$). **Conclusions:** In mCRC pts undergoing curative intent surgery or radiotherapy, detection of ctDNA post-procedure had a high PPV for cancer recurrence, with a median lead time of 6 months compared to surveillance imaging. Thus, ctDNA holds promise as a biomarker for pt enrollment on clinical trials and as an endpoint for monitoring of response to experimental therapies in this oligometastatic CRC population. Research Sponsor: Guardant Health.

3566 **Poster Session**

RAMucirumab in combination with TAS102 versus TAS102 monotherapy in metastatic colorectal cancer: Safety results from the phase IIb part of the RAMTAS phase II/III trial of the German AIO (AIO-KRK-0316). *First Author: Stefan Kasper, University Hospital Essen, West German Cancer Center, Essen, Germany*

Background: Patients (pts) with mCRC progressing on standard chemotherapy have limited therapeutic options. Trifluridine/tipiracil (TAS102) significantly improved survival in patients with refractory mCRC. Ramucirumab (ram) is approved in combination with FOLFIRI for second-line treatment. There is a strong rationale to evaluate the efficacy and safety of ram in combination with TAS102 in pts with refractory mCRC. **Methods:** This is a randomized, open-label, multicenter, starting as phase IIb and extended to a phase III study in pts with advanced mCRC. Eligible pts were randomized to receive either ram (8 mg/kg on d1+15, q4w) and TAS102 (35 mg/m^2 on d1-5 and d8-12, q4w, arm A) or TAS102 alone (arm B). The primary endpoint is overall survival. A total of 145 pts were enrolled into phase IIb. Here, we present the data from an interim safety analysis comprising the first 80 treated pts. The trial was extended to phase III including a total of 426 pts. Enrolment of additional 281 pts started in Dec 2020. The trial endpoints remained unchanged. **Results:** Pts (40 arm A, 40 arm B) received a median of 2.5 treatment cycles in arm A and 2 cycles in arm B; 31 pts in treatment arm A and 32 pts in arm B discontinued participation prematurely, mainly due to cancer progression. Most patients developed adverse events (AEs): grade 3 AEs were observed in 28 pts (70%) in arm A (24 treatment-related) and 27 pts (67%, 17 treatment-related) in arm B. More grade 4 AEs were seen in arm A (13 pts, 32.5%) than in arm B (5 pts, 12.5%). In total, 46 Serious AEs (SAEs) occurred, 27 in arm A (10 treatment-related) and 19 in Arm B (2 treatment-related). Five SAEs (3 in arm A, 2 in arm B) had a fatal outcome (one in arm A treatment-related). Within the analyzed population, no SUSAR occurred. **Conclusions:** This safety analysis demonstrates a minor increase in AEs in the experimental arm but no unexpected events. There were no excessive toxicity or unacceptable risks. In summary, a favorable risk-benefit-profile was confirmed. Based on these safety results and the ongoing need for efficient treatment in the tested population, the trial was extended to phase III. Clinical trial information: NCT03520946. Research Sponsor: Lilly.

3567 **Poster Session**

Neoadjuvant chemotherapy to improve colon cancer survival in resectable metastatic colon cancer: A real world NCDB data analysis. *First Author: Saurabh Parasramka, University of Kentucky, Lexington, KY*

Background: According to the SEER database, approximately 21% of colon cancer patients have synchronous metastatic disease at presentation with a five-year survival of only 14%. Liver is by far the most common site of metastasis. For resectable and borderline resectable metastatic lesions after conversion to surgical resection, five-year survival ranges between 40-70% in different series. Survival advantage of neoadjuvant chemotherapy is not clear. We present here an updated analysis of effect of different variables on survival of 3,247 patients from the National Cancer Database (NCDB) treated from 2010-2015. **Methods:** Adults 20 years or older with primary colon cancer and single organ metastatic disease either in the liver and/or lung at diagnosis were identified. All patients had received surgery to the primary site, resection of the distant site and chemotherapy within 1 year of diagnosis. Patients were categorized into 2 cohorts based on whether they received chemotherapy in the pre-operative/peri-operative setting (neoadjuvant chemotherapy –NAC) or post-operative setting (adjuvant chemotherapy AC). Descriptive analysis, Kaplan-Meier plots, Log-Rank tests and Cox regression models for multivariate survival analyses were performed. To assess uncertainty of estimates, a sensitive analysis was also performed based on the intention to treat principle by including additional surgery only and chemotherapy only cases. **Results:** A total of 3,247 patients with colon cancer with liver or lung metastases were identified. A large majority 2,527 patients (77.8%) received AC. 54.5% were males and 45.5% females. On multivariate analysis, patients who received NAC had overall survival (OS) advantage with hazard ratio (HR) 0.86 (0.75-0.98). Clinical factors associated with worse survival included age $>$ 75 HR 1.31; positive margin status with R1 HR 1.49 or R2 HR 2.33; Comorbidity index $\geq$ 2 HR 1.68; positive KRAS status HR 1.20; N2 disease HR1.95; ; having liver metastasis compared to lung HR 1.65 ;. Factors associated with improved survival were CEA less than 30 ng/ml at diagnosis and left sided tumor with HR of 0.64 (0.56-0.72) and 0.75(0.67-0.84) respectively. **Conclusions:** Metastatic colon cancer with single organ liver or lung lesions benefit from neoadjuvant chemotherapy based on our analysis of the real-world data. The survival advantage in this setting has not been shown before. Research Sponsor: None.

3568 **Poster Session**

Influence of dietary insulin scores on survival in patients with metastatic colorectal cancer (mCRC): Findings from CALGB (Alliance) 80405. *First Author: Katherine DiNardo, Brigham and Women's Hospital, Boston, MA*

Background: Diets inducing an elevated insulin response have been associated with increased recurrence and mortality in patients with non-metastatic colorectal cancer, but it remains unknown if postprandial hyperinsulinemia also affects progression and mortality in mCRC patients. The goal of this study was to assess the influence of dietary insulin load (DIL) and dietary insulin index (DII) on survival of mCRC patients. **Methods:** This was a prospective cohort study of 1,177 patients with previously untreated mCRC enrolled in a phase III trial of systemic chemotherapy plus biologics who reported dietary intake within one month after chemotherapy initiation. DIL was calculated as a function of food insulin index and the energy content of individual foods reported on a food frequency questionnaire. DII was calculated by dividing DIL by total energy intake. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and treatment-related adverse events (TRAEs). The primary statistical test was a test for trend, which was performed using the median value for each quintile of dietary insulin score as a continuous variable. Cox proportional hazards regression was used to adjust for potential confounders including assigned treatment arm, known prognostic factors, comorbidities, body mass index, and physical activity. **Results:** Higher DIL was significantly associated with worse OS (p_{trend} = 0.04); patients in the highest quintile survived 34.1 months, compared to 27.7 months in the lowest quintile (Cox hazard ratio [HR] 1.22, 95% confidence interval [CI] 0.99 - 1.51). Higher DII was non-significantly associated with worse OS (HR 1.18, 95% CI 0.94 - 1.48, p_{trend} = 0.09). There was no significant association between dietary insulin scores and PFS. The influence of dietary insulin scores on survival did not differ significantly by various molecular markers involved in the insulin signaling pathway, including C-peptide, adiponectin, IGF-1, IGFBP-3, and IGFBP-7. Higher dietary insulin scores were significantly associated with greater risk of any TRAE. Those with a DIL greater than the median had a 75.4% rate of any TRAE, compared to 70.8% in those with a DIL less than or equal to the median (HR 1.19, 95% CI 1.03 - 1.38, p=0.02); the most significant associations were with neutropenia (HR 1.30, 95% CI 1.05 - 1.61, p=0.01) and diarrhea (HR 1.43, 95% CI 1.00 - 2.06, p=0.05). **Conclusions:** Higher DIL was significantly associated with worse OS, and both higher DIL and DII were significantly associated with increased TRAEs, in patients with previously untreated mCRC. These findings may inform future dietary recommendations for patients with mCRC. Further investigation into the molecular mechanisms underlying these associations is warranted. Clinical trial information: NCT00265850. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3570 **Poster Session**

Exploratory biomarker findings from cohort 2 of MODUL: An adaptable, phase 2, signal-seeking trial of fluoropyrimidine + bevacizumab ± atezolizumab maintenance therapy for BRAF^{wt} metastatic colorectal cancer. *First Author: Josep Tabernero, Vall d'Hebron University Hospital and Institute of Oncology (VHIO), IOB-Quiron, UVic-UCC, Barcelona, Spain*

Background: MODUL is an adaptable, phase 2, signal-seeking trial testing novel agents as first-line therapy for predefined subgroups of patients with metastatic colorectal cancer (mCRC). Previously reported findings demonstrated that adding atezolizumab to fluoropyrimidine (FP)/bevacizumab as first-line maintenance treatment after induction with FOLFOX + bevacizumab did not improve efficacy outcomes in BRAF^{wt} mCRC. Given these efficacy results, exploratory assessments on tumour samples were conducted to provide insights into factors that might affect efficacy of maintenance treatment and provide guidance on appropriate therapeutic strategies for BRAF^{wt} mCRC. **Methods:** In patients with BRAF^{wt} tumours (Cohort 2), experimental treatment was FP/bevacizumab + atezolizumab. Primary efficacy endpoint: progression-free survival (PFS). Overall survival (OS) was a secondary endpoint. Archival tissue samples from 104 patients were analysed by immunohistochemistry (IHC) at HistoGeneX (PD-L1; CD8/GrB/FoxP3). SP142 antibody was used for PD-L1 IHC analysis, which evaluated PD-L1^{low} (IC 0–1) vs PD-L1^{high} (IC $>$ 1) in correlation with PFS and OS in the control and experimental arms. CD8/GrB/FoxP3 triplex staining was also performed to evaluate potential correlations with efficacy. **Results:** 445 patients with BRAF^{wt} mCRC were randomised (2:1 ratio) to maintenance treatment in Cohort 2. Archival samples from 104 patients were analysed: FP/bevacizumab + atezolizumab (n = 82); FP/bevacizumab (n = 22). The biomarker evaluable population (BEP) for PD-L1 was n = 81 for FP/bevacizumab + atezolizumab [PD-L1^{low} n = 35 (43%); PD-L1^{high} n = 46 (57%)] and n = 22 for FP/bevacizumab [PD-L1^{low} n = 16 (72%); PD-L1^{high} n = 6 (28%)]. The BEP for CD8/GrB was n = 50 for FP/bevacizumab + atezolizumab and n = 16 for FP/bevacizumab. No difference in PFS or OS was observed in the FP/bevacizumab + atezolizumab vs FP/bevacizumab arms for PD-L1^{high} [PFS: HR = 1.5 (95% CI 0.45−4.8), p = 0.51; OS: HR = 1.3 (95% CI 0.38−4.1), p = 0.71] or PD-L1^{low} [PFS: HR = 0.92 (95% CI 0.47−1.8), p = 0.81; OS: HR = 0.78 (95% CI 0.4−1.5), p = 0.48]. Similar results were observed with CD8/GrB^{high} [PFS: HR = 0.73 (95% CI 0.27−2.0), p = 0.55; OS: HR = 0.66 (95% CI 0.24−1.8), p = 0.44], CD8/GrB^{low} [PFS: HR = 1.0 (95% CI 0.42–2.5), p = 0.96; OS: HR = 0.73 (95% CI 0.3–1.8), p = 0.5], FoxP3^{high} [PFS: HR = 0.97 (95% CI 0.37−2.5), p = 0.95; OS: HR = 0.95 (95% CI 0.36−2.5), p = 0.91] and FoxP3^{low} [PFS: HR = 0.73 (95% CI 0.29−1.9), p = 0.53; OS: HR = 0.5 (95% CI 0.19−1.3), p = 0.18]. **Conclusions:** These findings suggest that PD-L1, CD8/GrB and FoxP3 might not be predictive biomarkers in BRAF^{wt} mCRC. Further analyses are needed to further evaluate potential predictive and prognostic factors of response in this setting. Clinical trial information: NCT02291289. Research Sponsor: F. Hoffmann-La Roche Ltd.

3571 **Poster Session**

Treatment responses and disease dynamics in patients with untreated metastatic colorectal cancer receiving bevacizumab-based sequential versus combination chemotherapy: Analysis of a phase 3 trial (AIO KRK0110, XELAVIRI study). *First Author: Annika Kurreck, Charité University Medicine Berlin, Berlin, Germany*

Background: Early response parameters such as early tumor shrinkage (ETS), depth of response (DpR), and time to DpR represent exploratory endpoints that may serve as early efficacy endpoints and potential predictors of long-term outcome. We analyzed the association of these endpoints with bevacizumab-based sequential (initial fluoropyrimidines) versus combination (initial fluoropyrimidines plus irinotecan) chemotherapy within a randomized phase III trial. **Methods:** DpR (change from baseline to smallest tumor diameter), ETS (≥20% reduction in tumor diameter at first reassessment), and time to DpR (study randomization to DpR-image) were analyzed in the XELAVIRI-trial. Moreover, progression-free survival (PFS) and overall survival (OS) were evaluated with ETS as stratification parameter (ETS vs. no ETS) according to treatment arm, molecular subgroup, and sex. **Results:** 370 patients were available for analysis of early treatment response parameters. A higher rate of ETS (60.9% vs. 43.5%; p = 0.001) and significantly greater DpR (-40.0% vs. -24.7%; p $<$ 0.001) were observed in the initial combination compared to the sequential therapy arm, respectively. The improvement of ETS and DpR was pronounced in the subpopulation of *RAS*/*BRAF* wildtype patients. Male in contrast to female patients significantly benefitted from initial combination treatment in terms of median DpR (male: -40.0% vs. -22.2%; p $<$ 0.001; female: -34.0% vs. -24.4%; p = 0.13) and rate of ETS (male: 64.8% vs. 40.2%; p $<$ 0.001; female: 52.5% vs. 49.3%; p = 0.73). Achievement of ETS correlated with improved survival irrespective of treatment arm (PFS: p $<$ 0.001; OS: p = 0.012) and molecular subgroup (PFS: p $<$ 0.001; OS: p $<$ 0.001). Whereas the survival benefit in male patients achieving ETS was statistically significant (PFS: p $<$ 0.001, HR 0.532 (0.409-0.692); OS: p $<$ 0.001, HR 0.574 (0.437-0.756)), there were no significant differences in PFS (p = 0.107) and OS (p = 0.965) of female patients depending on ETS. **Conclusions:** In the XELAVIRI trial, initial irinotecan-based combination therapy with bevacizumab improves ETS and DpR in mCRC patients. Improvement in early response parameters appears pronounced in patients with *RAS*/*BRAF* wildtype tumors suggesting a high sensitivity to irinotecan-based treatment. ETS was predictive of PFS and OS regardless of treatment arm. This finding was rather driven by male than female patients, potentially indicating that ETS might be less predictive of long-term outcome in an elderly, female population. Research Sponsor: Arbeitsgemeinschaft Internistische Onkologie.

3572 **Poster Session**

Serial circulating tumor DNA (ctDNA) monitoring in metastatic colorectal cancer (mCRC) reveals dynamic profile of actionable alterations. *First Author: Jonathan M. Loree, BC Cancer, Vancouver, BC, Canada*

Background: Serial ctDNA can measure dynamic changes in disease burden over time, however utility of serial profiling to detect changes in actionable alterations remains unclear. **Methods:** We evaluated 501 patients with ≥3 serial Guardant360 assays performed between 09/2016 and 11/2020 and compared MSI, fusion, amplification and single nucleotide variant (SNV) detection over time. This comprised 2147 assays with a median of 4 assays per patient (min 3, max 18) occurring an average of 163 days apart (+/- SD of 147 days). Maximum detected variant allele frequency in samples (maxVAF) was assessed for relation to changes in detected alterations as a surrogate for tumor volume. **Results:** Among 406 patients with assays assessable for MSI-status, 17 (4.2%) had MSI detected. New MSI detection on a subsequent assay always occurred with a rising maxVAF (3/3) that was also ≥0.7%, while loss of detectable MSI between assays always associated with falling maxVAFs (7/7) with 6/7 occurring when maxVAF fell below 0.4%. Fusions were noted in 9/501 (2%) patients. Among 3 patients who lost a detectable fusion, maxVAF decreased in 1 patient and changed ≤0.2% between assays in 2, while 2/3 patients with new fusions had rising maxVAFs and 1 patient had a falling maxVAF. Amplifications were detected in 242/501 patients (48%). While most genes had highly variable amplification detection between assays (9% serially detected), ERBB2 amplifications were more consistent and serially detected in 39% of detected cases (P $<$ 0.0001). New detection of amplifications occurred more commonly in cases with rising maxVAF (OR 11.70, 95% CI 7.61-18.00, P $<$ 0.0001) and loss of detectable amplifications occurred more between samples with falling maxVAF (OR 12.37, 95% CI 8.35-18.66, P $<$ 0.0001). Change in maxVAF correlated with change in number of detected amplifications (r = 0.62, P $<$ 0.0001), but only partially explained changes seen (R^2= 0.39). Between serial assays, SNVs changed a median of 0 variants (IQR -1 to 1), however some patients had significant changes (max gain 21/max loss 18). Among 1646 serial time points, 454 (28%) had no change in SNVs, 674 (41%) gained SNVs, and 518 (31%) lost SNVs on subsequent assays. Gains were more common in samples with rising maxVAF (OR 7.76, 95% CI 6.18-9.73, P $<$ 0.0001) while losses were more common when maxVAF fell (OR 6.90, 95% CI 5.47-8.66, P $<$ 0.0001). The correlation between maxVAF change and SNV change was significant (r = 0.29, P $<$ 0.0001), but minimally explained SNV changes (R^2= 0.086) and was a much weaker association than noted for amplification changes. **Conclusions:** We noted significant differences in detection of actionable alterations across serial ctDNA assays. Increased ctDNA volume (higher maxVAF) due to tumor progression may explain some variation over time, but variability also occurs outside these changes, likely reflecting clonal evolution following therapy. Research Sponsor: None.

3573 **Poster Session**

Efficacy and safety of vactosertib and pembrolizumab combination in patients with previously treated microsatellite stable metastatic colorectal cancer. *First Author: Tae Won Kim, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: Microsatellite stable metastatic colorectal cancer (MSS mCRC) represents a high unmet need since there are currently no approved immunotherapy options. Since the inhibition of the transforming growth factor-β (TGF-β) pathway is known to contribute to the enhancement of immunotherapy efficacy, here, we report the results of vactosertib, a potent and selective TGF-β receptor I kinase inhibitor, combined with pembrolizumab in patients with MSS mCRC. **Methods:** In this phase 2, open label trial, patients have received vactosertib (300 mg BID, 5 days on / 2 days off) and pembrolizumab (200 mg, every 3 weeks) until confirmed progressive disease (PD), unacceptable toxicity or consent withdrawal. Patients with histologically confirmed mCRC who had disease progression after treatment with all available therapies including fluoropyrimidine and oxaliplatin or irinotecan were enrolled. Eligible patients were ≥19 years old, had ECOG status ≤1, and had no prior exposure to immunotherapy. The objectives were to evaluate the safety and efficacy (objective response rate (ORR) per RECIST v1.1). **Results:** Thirty-three patients with MSS mCRC were enrolled. Median age was 60 (range 33-72), 55% were male, median number of previous lines of chemotherapy was 3 (range 1-7), and 82% were consensus molecular subtype (CMS) 4. The ORR was 15.2% including 5 partial responses (PRs), 7 stable diseases, and 17 PDs as best overall responses; 12 patients remain on treatment. Among 5 patients with PR, 3 patients had confirmed PR and median duration of response was not reached yet. As of 04 Jan 2021, the most common treatment related adverse events (AEs) were increased amylase (21.2%), pruritus (21.2%), rash (21.2%), and increased lipase (18.2%). There were 3 treatment-related SAEs reported; drug induced pneumonitis (3%), nausea (3%), and vomiting (3%). **Conclusions:** The combination treatment with vactosertib and pembrolizumab showed favorable safety profile with promising efficacy in patients with MSS mCRC. Updated data including pharmacodynamic markers will be presented at the meeting. Clinical trial information: NCT03724851. Research Sponsor: MedPacto.

3574 **Poster Session**

Safety and pharmacokinetic analysis of *UGT1A1* genotype-guided dosing of irinotecan. *First Author: Emma C Hulshof, Department of Clinical Pharmacy, Catharina Hospital, Eindhoven, Netherlands*

Background: Irinotecan is commonly used in the treatment of advanced colorectal and pancreatic cancer. The polymorphisms *UGT1A1*28* (7 TA repeats) and *UGT1A1*93* (SNP -3156G > A) are significantly associated with increased systemic exposure of irinotecan's active metabolite SN-38 and subsequently severe irinotecan-associated adverse-events (AEs) including (febrile) neutropenia and diarrhea. Severe AEs may lead to hospitalization, loss of quality of life, treatment delay and/or treatment discontinuation. Nonetheless, prospective genetic screening is not yet routinely performed. The aim of this study was to determine the safety and pharmacokinetics of *UGT1A1* genotype-guided dosing of irinotecan in UGT1A1 poor metabolizers (PMs), i.e. *UGT1A1 *28/*28* and/or *UGT1A1*93/*93* individuals, in order to reduce the incidence of severe irinotecan-associated AEs. **Methods:** A prospective, multi-center, non-randomized study was conducted in patients intended to be treated with irinotecan at a dose of $\geq$ 180 mg/m^2 or 450-600 mg flat dose. All patients were pre-therapeutically genotyped for *UGT1A1*28* and *UGT1A1*93*. In UGT1A1 PMs, an initial 30% dose reduction in the first cycle was applied followed by further individual dose titration based on neutrophil count and clinical tolerability. The primary endpoint was the incidence of febrile neutropenia in the first 2 cycles of irinotecan treatment. UGT1A1 PMs were compared to 1] historical control patients, i.e. homozygous polymorphic patients treated with full dose therapy identified from systematic literature review and to 2] UGT1A1 non-PMs treated with standard dose therapy. In addition, systemic SN-38 exposure ($AUC_{0\text{-}500h}$) of reduced dosing in the UGT1A1 PM cohort was compared to a standard dosed irinotecan patient cohort [doi: 10.1200/JCO.2000.18.1.195] by an independent T-test. **Results:** A total of 349 patients were pre-therapeutically genotyped and included for analysis. Thirty-one (8.9%) patients were UGT1A1 PM, in whom an initial median 30% dose reduction was applied. The incidence of febrile neutropenia in this group was 6.5% compared to 24% in historical controls (n = 50) (p = 0.042) and comparable with the incidence (4.1%; p = 0.632) in UGT1A1 non-PMs treated with full dose therapy. The systemic exposure of SN-38 of reduced dosing in UGT1A1 PMs (n = 17) was comparable to the systemic exposure of the standard dosed irinotecan patient cohort (n = 46) with a relative difference of +24% (p = 0.054) with a geometric mean (CV) of SN-38 $AUC_{0\text{-}500h}$ of 391 (43.7%) versus 298 (75.3%) ng*h/mL, respectively. **Conclusions:** *UGT1A1* genotype-guided dosing significantly reduces the incidence of febrile neutropenia in UGT1A1 PM patients treated with irinotecan. In addition, systemic drug exposure remained adequate, despite the 30% dose reduction. Therefore, *UGT1A1* genotype-guided dosing of irinotecan should be considered standard of care in order to improve the individual patient safety. Clinical trial information: Trial NL6270 (NTR6612). Research Sponsor: Catharina Research Foundation.

3575 **Poster Session**

Characteristics of patients (pts) and prognostic factors across treatment lines (TL) in metastatic colorectal cancer (mCRC): An analysis from the Analysis and Research in Cancers of the Digestive System (ARCAD) database. *First Author: Jean-Baptiste Bachet, Pitié-Salpêtrière Hospital, Paris, France*

Background: Pts with mCRC frequently receive $\geq$1 sequential treatment TL. Approximately 50%-60% of pts receive second-line (L2) and 20%-30% third-line (L3) regimens in routine practice. We investigated the pts clinical/tumor characteristics and their prognostic impact across TL. **Methods:** Data from 37,560 pts enrolled in 48 randomized trials (34 in first (L1), 9 in L2, and 5 in L3) were analyzed. Candidate variables (VAR) measured at enrollment were sex, age, body mass index, performance status (PS), bilirubin, hemoglobin (Hb), platelets (Pl), derived white blood cells-to-absolute neutrophil counts ratio (WBC/ANC), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), primary tumor location, and number and location of metastatic sites (MS). Missing data were imputed. VAR with significant value at all TL were selected to construct a prognostic score of overall survival (OS) in training set (TS, n=30,050; 80%). For each TL, the score was calculated as the sum on the estimations of the VAR' coefficients from the common multivariate model; Cox's model was used to define risk groups. The discrimination capability was assessed using the Harrell's C-index. External validation was done in the validation set (VS, n=7,510; 20%). **Results:** A total of 26,974 pts in L1, 7,693 pts in L2 and 2,893 pts in L3 were analyzed. The following characteristics increased continuously over TL: $\geq$2 MS (57%, 72%, 82%), lung metastases (50%, 74%, 91%), lymph nodes metastases (51%, 61%, 80%), *KRAS* mutation (37%, 47%, 51%) and elevated ALP (46%, 52%, 61%). *BRAF* mutation decreased (9%, 7%, 5%). In L1 vs L3 trials, 70% vs 89% of patients had primary tumor resection, 10% vs 80% had at least one metastasectomy and 31% vs 78% had a late metachronous (>12 months) metastasis. 7 independent VAR were retained in the prognostic score (PS, Hb, Pl, WBC/ANC, LDH, ALP, and the number of MS); four pt groups with significantly different prognoses were defined (table). This score remained valid when excluding pts with PS 2. Third-line oral drugs (vs placebo) and subsequent line (L2/L1 or L3/L2) were effective in all prognostic groups. **Conclusions:** Clinical/tumor pt characteristics significantly varied over subsequent TL in patients included in randomized trials. The same prognostic model using practical clinical and biological variables can be used in all TL. Research Sponsor: ARCAD.

	L1*		L2*		L3*	
Score class	**TS**	**VS**	**TS**	**VS**	**TS**	**VS**
1	25.7 [25.3–26.3]	27.0 [26.0–27.7]	17.1 [16.5–17.7]	17.4 [16.1–18.6]	10.1 [9.7–11.1]	10.2 [8.9–12.5]
2	18.8 [18.4–19.3]	18.4 [17.6–19.4]	11.4 [10.8–11.8]	12.0 [11.2–13.0]	6.0 [5.6–6.3]	5.6 [4.9–6.2]
3	13.8 [13.4–14.3]	14.1 [13.2–15.0]	8.2 [7.7–8.7]	8.3 [7.7–9.2]	4.2 [3.8–4.6]	3.9 [3.3–4.9]
4	10.3 [9.8–10.7]	11.0 [10.3–12.0]	5.2 [4.7–5.7]	5.0 [4.3–6.1]	2.7 [2.4–3.2]	3.1 [2.7–4.2]
1-yr OS C-index	0.65	0.65	0.66	0.66	0.69	0.68

*median OS [95% CI], months.

3577 **Poster Session**

Liquid biopsy-driven anti-EGFR rechallenge in patients with metastatic colorectal cancer. *First Author: Stefano Mariani, University of Cagliari, Cagliari, Italy*

Background: The rechallenge with EGFR inhibitors represents an emerging strategy for anti-EGFR pre-treated patients with RAS wild type colorectal cancer (CRC). Unfortunately definitive selection criteria for anti-EGFR rechallenge in this setting are lacking. Very recently RAS wild type status on circulating tumor DNA (ct-DNA) at the time of rechallenge along with already known clinical criteria emerged as a potential watershed for this strategy. In the present study we explored liquid biopsy-driven anti-EGFR rechallenge strategy in the clinical practice for patients with metastatic colorectal cancer. **Methods:** Ct-DNA from RAS and BRAF wild type metastatic CRC patients previously treated with an anti-EGFR containing therapy was analyzed for RAS/BRAF mutations with the aim to evaluate the rechallenge strategy with anti-EGFR. The ct-DNA was analyzed for RAS-BRAF mutations using pyro-sequencing (PyroMark Q24 MDx Workstation) and nucleotide sequencing (Genetic Analyzer ABI3130) assays. Real-time PCR (Idylla) and droplet digital PCR (QX200 System) were performed to confirm the RAS-BRAF mutation status. Several clinical variables including previous response to anti EGFR containing therapy, tumor sidedness and anti-EGFR free interval were evaluated in relation to outcome. Tumor response evaluation was performed according to RECIST 1.1. Differences between categorical variables were evaluated using the Fisher's exact test. Survival probability over time was estimated by the Kaplan–Meier method. Significant differences in the probability of survival between the strata were evaluated by log-rank test. **Results:** Twenty patients were included in the study. All patients were tested for RAS-BRAF mutations in ct-DNA. Fourteen patients (70%) showed a RAS-BRAF WT molecular profile, six patients (30%) showed a KRAS mutation. All the patients with ct-DNA RAS-BRAF WT profile underwent rechallenge with anti-EGFR. In details 11 patients (78.6%) underwent irinotecan+ cetuximab treatment, whereas 3 patients (21.4%) underwent panitumumab monotherapy. As for the outcome results to the rechallenge strategy, the median OS was 7 months (95% CI 5.0 to 13.0), the median PFS was 3 months (95% CI 2.0 to 6.0), the ORR was 27.3% with a DCR of 54.5%. Among the clinical variables evaluated as putative predictive/prognostic factors, previous response to anti-EGFR treatment was related to a not statistically significant improved OS (12 months vs 5 months HR:0.19 p: 0.06) and to a statistically significant improved ORR (75% vs 0% p:0.03). **Conclusions:** The rechallenge strategy with anti-EGFR confirmed to be feasible in clinical practice. The clinical outcome resulted consistent with the literature data. In addition to the molecular selection through the analysis of ct-DNA for RAS, previous response to anti EGFR treatment is confirmed as a prospective selection criteria for this therapeutic option. Research Sponsor: None.

3578 **Poster Session**

Final results from the CAVE (cetuximab rechallenge plus avelumab) mCRC phase II trial: Skin toxicity as a predictor of clinical activity. *First Author: Giulia Martini, Medical Oncology, Università degli Studi della Campania "Luigi Vanvitelli", Naples, Italy*

Background: Promising antitumor activity of so called rechallenge treatment with anti-epidermal growth factor receptor (EGFR) drugs in patients with RAS wild type (RAS WT) metastatic colorectal cancer (mCRC) has been recently reported. Beside the absence of resistance mutations at plasma circulating tumor DNA (ctDNA) analysis, no biomarkers of response to anti-EGFR rechallenge strategy have been identified. **Methods:** We conducted the single arm phase II CAVE mCRC trial to evaluate the combination of cetuximab as rechallenge plus avelumab treatment in 77 RAS WT mCRC patients, with complete (CR) or partial response (PR) to first line chemotherapy plus anti-EGFR drugs, who developed acquired resistance and received a subsequent line of therapy. A post-hoc baseline analysis of circulating tumor DNA (ctDNA) for KRAS, NRAS, BRAF and EGFR-S492R mutations was performed for 67/77 (87%) patients. The correlation of skin toxicity (ST) and other clinical variables with OS, PFS and response rate (RR) was assessed. **Results:** Cetuximab plus avelumab provided in the intention to treat population (ITT) median overall survival (mOS) of 11.6 months [95% Confidence Interval (CI), 8.4-14.8] and median PFS (mPFS) of 3.6 months (95% CI, 3.2-4.1) with a manageable toxicity profile. Thirty-three (42.9%) patients experienced grade 2-3 ST with mOS of 17.8 months (CI 95% 14.9-20.7), whereas 44 (57.1%) patients with grade 0-1 ST exhibited mOS of 8.2 months (CI 95% 5.6-11), (HR 0.51, CI 95% 0.29-0.89, P = 0.019). mPFS was 4.6 months (CI 95% 3.5-5.8) in patients with grade 2-3 ST, compared to 3.4 months (CI 95% 2.8-4.1) in patients with grade 0-1 ST (HR 0.49, CI 95% 0.3-0.8, P = 0.004). Grade 2-3 ST and baseline RAS/BRAF/EGFR WT ctDNA were the only variables with statistically significant effect on OS both at univariate and multivariate analyses. ST, number of metastatic sites $\leq$2, surgery of primary tumor and RAS/BRAF/EGFR WT ctDNA were associated with an improvement in PFS only at univariate analysis. In the 33 patients with grade 2-3 ST, 1 (3%) CR, 2 (6.1%) PR and 24 (72.7%) stable disease (SD) were observed, with disease control rate (DCR) of 81.8%. In the 44 patients with grade 0-1 ST 0 CR, 3 (6.8%) PR, 20 (45.5%) SD, with 52.3% DCR were reported. **Conclusions:** Cetuximab plus avelumab is effective and well tolerated as rechallenge treatment in mCRC. ST is a clinical biomarker for the identification of RAS/BRAF mCRC patients that could benefit from anti-EGFR rechallenge. Clinical trial information: NCT04561336. Research Sponsor: Regione Campania I-Cure Research Project.

3579 **Poster Session**

Circulating tumor DNA and circumferential resection margin as key prognostic indicators for survival in rectal cancer. *First Author: Mia Shepherdson, Flinders University, Adelaide, SA, Australia*

Background: Recurrence of colorectal cancer has been linked to the presence of epigenetic circulating tumour DNA (ctDNA) in patient plasma after surgery. The prognostic significance of ctDNA prior to treatment remains unknown. This study investigated the correlation between pre-treatment ctDNA and current radiological (MRI) prognostic markers in patients with rectal cancer. **Methods:** Forty-two patients with rectal cancer were enrolled, with all having staging MRI prior to treatment. Plasma was taken for ctDNA at diagnosis. The presence of either methylated branched-chain amino acid transaminase 1 (BCAT1) or Ikaros family zinc finger (IKZF1) in cell-free DNA from plasma was deemed a positive ctDNA result. Correlation of MRI prognostic indicators and ctDNA results was assessed with chi-square tests. Univariable and multivariable cox regression analyses were performed to determine variables associated with overall survival (OS). **Results:** Mean age was 64.4 years (SD 12.5) and majority were male (30/42, 71.4%). 11, 13, 9 & 9 patients had stages I, II, III, IV respectively. Patients had a minimum follow-up of 36 months. Thirty-three (78.6%) patients received neoadjuvant chemoradiotherapy. 29 (69.0%) patients underwent surgical resection. 3-year survival rate was 64% in the overall group. 67% (n=28/42) of patients were positive for the methylated ctDNA at diagnosis. 11 out of 12 patients with a positive circumferential resection margin (CRM +) were ctDNA positive (p=0.03). Univariable analysis showed that prognostic indicators for OS were presence of extramural venous invasion (EMVI) (HR 3.0, 95% CI 1.1-8.4), CRM+ (HR 12.2, 95%CI 3.9-37.6), metastatic disease (HR 7.32, 95% CI 2.63-20.37) and ctDNA% methylation (HR 1.1, 95% CI 1.04-1.13) (Table 1). The presence of CRM+ and a positive ctDNA had a HR of 20.5 (95% CI 5.1-82.3). With multivariable analysis, including adjustment for age and EMVI, only CRM+/ctDNA+ variable was an independent predictor for poor survival (HR 20.2, 95% CI 4.5-90.9). **Conclusions:** In rectal cancer, almost all patients with CRM involvement have ctDNA, and these patients had the worst prognosis. Future studies with longitudinal ctDNA assessment pre and post treatment could potentially inform prognosis and help tailor patients' treatment. Research Sponsor: Clinical Genomics and Cancer Australia.

Univariable analysis for overall survival.

Variable	Hazard ratio (95% CI)	P value
Age	0.99 (0.96-1.03)	0.78
Lower rectal (vs mid and upper)	1.79 (0.65-4.96)	0.26
T4 (vs T1, T2, T3)	2.49 (0.78-7.91)	0.12
EMVI (vs absent)	3.00 (1.07-8.38)	0.04
N1/2 (vs N0) (excluding tumour deposits/N1c)	1.10 (0.38-3.23)	0.86
Tumour deposits / N1c (vs no tumour deposits)	0.83 (0.20-3.52)	0.80
M1 (vs M0)	7.32 (2.63-20.37)	<0.01
CRM involved (vs not involved)	12.16 (3.93-37.63)	<0.01
ctDNA % methylation	1.09 (1.04-1.13)	<0.01
ctDNA+/CRM+ (vs both negative or only 1 positive)	20.51 (5.11-82.34)	<0.01

3580 **Poster Session**

Parameters associated with outcomes in pretreated MSI/dMMR metastatic colorectal cancer (mCRC) treated with immune checkpoint inhibitors (ICI): Subgroup analysis of a prospective cohort. *First Author: Raphael Colle, Sorbonne Université, Department of Medical Oncology, Saint-Antoine Hospital, AP-HP, Paris, France*

Background: Immune checkpoint inhibitors (ICI) have demonstrated efficacy in patients (pts) with MSI/dMMR mCRC . We aimed to evaluate clinical, pathological and molecular factors associated with progression-free survival (PFS) and overall survival (OS) in ICI-treated pretreated mCRC patients (pts). **Methods:** Pts are drawn from a prospective cohort of all patients treated with ICI for MSI/dMMR mCRC at Saint-Antoine Hospital, Paris, France. All MSI/dMMR mCRC pts with disease progression after $\geq$ 1 prior systemic treatment (fluoropyrimidine and oxaliplatin or irinotecan ± targeted therapy) were included. MSI/dMMR status was centrally reviewed. Lynch syndrome or sporadic status was determined according to MMR gene germline mutational testing, *MLH1* methylation status and $BRAF^{V600E}$ mutation. PFS and objective response rate (ORR) were assessed using iRECIST criteria. The impact of Lynch syndrome on PFS was analyzed apart from the multivariate analysis due to the interaction with the $BRAF^{V600E}$ mutation status. **Results:** Of 130 included pts, 66 received anti-PD1 alone, 1 anti-PDL1 alone and 63 anti-PD1 plus anti-CTLA4. 71% have had at least 2 prior lines of treatment. 33 patients (25%) have $BRAF^{V600E}$mutation (mt) and 49 (38%) RASmt. The ORR for the whole population was 62.8 % IC95% [53.8; 71.1]. Median follow-up was 21.0 months, median PFS and OS were not reached. Results of PFS unadjusted and adjusted analysis are displayed in the table. $BRAF^{V600E}$ and RAS mutation were not associated with PFS and OS in multivariate analyses. After adjustment for the treatment type, Hazard Ratio (HR) for PFS between patients with proven Lynch syndrome (N=44) and patients with proven sporadic tumors (n= 44) was 0.57 (95%IC 0.26 -1.26). **Conclusions:** In this cohort, main known clinical, pathological and molecular factors do not influence the efficacy of ICI in pre-treated MSI/dMMR mCRC. Research Sponsor: None.

	PFS Unadjusted HR [IC95%]				
Sexe Female vs. Male	**N=125**	**1.41 [0.74; 2.67]**	**p=0.29**	**Adjusted HR [IC95%]**	
Age at first injection (years)	125	1.02 [1.00; 1.05]	0.07		
KRAS/NRAS-mutated versus wild-type	125	0.63 [0.31; 1.28]	0.20	0.61 [0.26; 1.47]	0.27
BRAFV600E-mutated vs. wild-type	125	1.98 [1.02; 3.84]	**0.0422**	1.20 [0.52; 2.76]	0.67
Mucinous Yes vs. No	125	1.83 [0.97; 3.45]	0.06	1.90 [0.96; 3.76]	0.07
Localization Left vs. Right	125	0.83 [0.41; 1.68]	0.61		
Treatment type Bitherapy vs. Monotherapy	125	0.35 [0.17; 0.68]	**0.0023**	0.40 [0.20; 0.80]	**0.0097**
Number of prior treatment lines >=2 vs. 1	125	0.51 [0.27; 0.98]	**0.0425**	0.57 [0.28; 1.15]	0.12
ECOG performance score >=1 vs. 0	125	1.72 [0.87; 3.40]	0.12		

3581 **Poster Session**

The role of PP2A variants to predict outcome in patients (pts) with metastatic colorectal cancer (mCRC): Data from FIRE-3 and TRIBE trials. *First Author: Jingyuan Wang, Division of Medical Oncology, USC Norris Comprehensive Cancer Center, Keck School of Medicine, Los Angeles, CA*

Background: Protein phosphatase 2A (PP2A) is a serine/threonine phosphatase with functions that counter-balance kinase-mediated phosphorylation throughout cell signaling networks. PP2A was reported to upregulate the angiogenesis, while negatively regulate the pathways downstream of receptor tyrosine kinases at multiple nodes. Previous studies showed PP2A variants were associated with the increased risk of cancer. Therefore, we hypothesized that PP2A variants may predict first-line treatment outcome in mCRC pts treated with bevacizumab (bev)/cetuximab (cet)-based chemotherapy. **Methods:** Genomic DNA from blood samples of pts enrolled in two independent randomized trials, TRIBE (bev arm, n=215, as discovery cohort) and FIRE-3 (bev arm, n=107, as validation cohort; cet arm, n=129, as control cohort), was genotyped through the OncoArray, a customized array manufactured by Illumina including approximately 530K SNP markers. The impact on outcome of 17 selected SNPs in 3 main PP2A core subunits (PPP2CA, PPP2R1B, PPP2R1A), one phosphatase activator (PPP2R4) and 2 endogenous inhibitors (TIPRL, CIP2A) was analyzed. **Results:** In the discovery cohort, pts with PPP2R4 rs2541164 A/A (N=16) showed significantly shorter overall survival (15.3 vs 27.3 months) compared to carriers of any G allele (N=198) in both univariate (hazard ratio [HR]=1.8; 95% confidence interval [CI]: 1.1-3.1; *p=0.02*) and multivariate (HR=2.4; 95%CI: 1.4-4.4; *p=0.006*) analysis. These data were validated in the FIRE-3 bev cohort in both univariate (A/A vs. Any G: 17.3 vs 39.9 months, HR=2.8, 95%CI: 1.4-5.9, *p=0.004*) and multivariate (HR=4.3, 95%CI: 1.5-12.2, *p=0.0095*) analysis. Conversely, pts carrying CIP2A rs13069780 C/C (N=24) only showed significantly longer progression-free survival (17.7 vs 12.3 months) than carriers of any T allele (n=105) in the FIRE-3 cet cohort in both univariate (HR=0.6; 95%CI 0.4-0.99; p=0.04) and multivariate (HR=0.5; 95%CI 0.3-0.94; p=0.02) analysis, but no association were observed in the bev cohort of TRIBE and FIRE-3. **Conclusions:** Our study demonstrated for the first time that PPP2R4 polymorphisms could predict outcomes of bev-based treatment in mCRC patients; Meanwhile CIP2A polymorphism could predict outcomes of cet-based treatment in mCRC patients. These findings support a possible role of the PP2A variants in contributing to resistance to anti-VEGF/EGFR treatment. Research Sponsor: National Cancer Institute (grant number P30CA014089), The Gloria Borges WunderGlo Foundation-The Wunder Project, Dhont Family Foundation, San Pedro Peninsula Cancer Guild, Daniel Butler Research Fund and Call to Cure Fund.

3582 **Poster Session**

The prognostic impact of *RAS* and *TP53* mutation according to primary tumor location in colorectal liver metastases. *First Author: Yongjun Cha, National Cancer Center, Goyang, South Korea*

Background: Somatic gene mutations have been suggested to impact survival following resection of colorectal liver metastases (CRLM). However, most studies included a selected population with known mutation data and did not employ homogeneous methods. This study aimed to determine the prognostic impact of somatic gene mutations and microsatellite instability (MSI) in CRLM using a standardized protocol and assess their survival effects according to primary tumor location. **Methods:** A total of 568 patients who underwent resection of CRLM during 2001-2014 were identified from a prospectively maintained registry of the National Cancer Center. MassARRAY based mutation profiling of cancer-related genes (*KRAS*, *NRAS*, *HRAS*, *BRAF*, *PIK3CA*, *MET*, *PTEN*, *APC*, *TP53*)/MSI analysis was made in primary tumors from 538 (94.7%)/526 (92.6%) patients. **Results:** Primary tumor locations were: right colon for 51 (9.0%); transverse colon for 42 (7.4%); left colon for 238 (34.5%); rectum for 279 (49.1%) patients. Right sided tumors were associated shorter overall survival (OS) after liver resection compared to left colon primary tumors (5-year OS, 31.4% vs. 54.0% [P = 0.011]). Mutation frequencies were: 45.9% for *RAS* ; 2.4% for *BRAF* ; 8.4% for *PIK3CA* ; 0.2% for *PTEN* ; 0.4% for *MET* ; 12.1% for *APC* ; 24.3% for *TP53*. *RAS* (5-year OS, 40.8% vs. 55.7% [P = 0.001], *PIK3CA* (5-year OS, 31.1% vs. 50.5% [P = 0.027]), and *TP53* mutation (5-year OS, 42.7% vs. 50.8% [P = 0.035]) were associated with worse OS after liver resection. On multivariable analyses, *RAS* (hazard rato [HR] 1.27; P = 0.033) and *TP53* mutation (HR 1.35; P = 0.014) were significantly associated with poor OS after adjustment for covariates. Co-mutation in *RAS*/*TP53* (12.4%) was associated with the worst oncologic outcome (HR 1.81; $P < .001$). Notably, while the negative prognostic impact of *RAS* mutation did not differ significantly according to primary tumor location, the adverse effect of *TP53* mutation was limited to rectal cancer (interaction P = 0.002). In this study, MSI-high (2.3%) was not associated with survival. **Conclusions:** Both *RAS* and *TP53* mutation are associated with worse survival following CRLM resection. In contrast to *RAS* mutation, the negative prognostic impact of *TP53* mutation appears to be limited to CRLM from the rectal origin. Research Sponsor: NCC-1910210.

3583 **Poster Session**

Overall survival (OS) with encorafenib (enco) + cetuximab (cetux) in BEACON CRC: Effect of prior therapy for *BRAF* V600E-mutant metastatic colorectal cancer (mCRC). *First Author: Scott Kopetz, MD Anderson Cancer Center, Houston, TX*

Background: Enco + cetux (doublet) has been approved in the US, EU, and Japan for the treatment of *BRAF* V600E-mutant mCRC after progression on 1–2 prior regimens. In the BEACON CRC study (NCT02928224), median OS (95% CI) with the doublet was 9.3 months (8.0–11.3) compared with 5.9 months (5.1–7.1) with cetux + irinotecan or FOLFIRI (control) in patients (pts) with *BRAF* V600E-mutant mCRC (HR 0.61 [95% CI: 0.5–0.8]). This *post-hoc* analysis investigates OS by prior therapies to the doublet treatment in pts with *BRAF* V600E-mutant mCRC from the BEACON CRC study. **Methods:** OS of pts treated with the doublet or control were compared according to prior treatment with bevacizumab, oxaliplatin, or FOLFOXIRI and duration of prior anticancer therapy (ACT). **Results:** The proportion of pts in the doublet and control arms who received prior bevacizumab were 64% and 55%, respectively. Of pts who had one prior therapy, 95% and 88% received prior oxaliplatin and 20% and 14% received prior FOLFOXIRI, respectively. OS by prior treatment in the doublet and control arms is shown in the table. In the doublet arm, pts who had bevacizumab < 4 months before start of study treatment had a median OS of 8.3 months (95% CI: 6.2–11.2); those who had bevacizumab ≥4 months prior had a median OS of 10.7 (95% CI: 7.5–17.7). Within each treatment arm, OS was similar regardless of prior treatment with oxaliplatin or FOLFOXIRI. The duration of prior ACT was similar across study arms, ranging from 5.6–5.8 months for the first line of ACT. **Conclusions:** In the BEACON CRC study, pts treated with the doublet for *BRAF* V600E-mutant mCRC demonstrated similar OS regardless of prior therapies or duration of prior therapy use. This exploratory *post-hoc* analysis provides data that reflect the prior treatment landscape clinicians may face when deciding subsequent treatment regimens for pts with *BRAF* V600E-mutant mCRC. Clinical trial information: NCT02928224. Research Sponsor: Pfizer.

	Doublet		Control		
Prior treatment	**Events/subjects (%)**	**Median OS (95% CI), mos**	**Events/subjects (%)**	**Median OS (95% CI), mos**	**HR (95% CI)**
Prior bevacizumab	67/111 (60)	8.3 (6.2–11.2)	78/103 (76)	5.1 (4.0–6.4)	0.53 (0.4–0.7)
< 4 months	16/29 (55)	10.7 (7.5–17.7)	15/19 (79)	4.4 (2.0–11.6)	0.47 (0.2–1.0)
≥4 months	45/80 (56)	9.4 (7.6–16.5)	64/99 (65)	7.4 (5.6–9.5)	0.71 (0.5–1.1)
No prior					
Prior oxaliplatin*					
Yes	81/138 (59)	9.7 (8.3–12.3)	88/128 (69)	6.4 (5.2–8.0)	0.60 (0.4–0.8)
No	3/8 (38)	8.4 (3.6–NR)	10/17 (59)	6.5 (3.2–NR)	0.73 (0.2–2.7)
Prior FOLFOXIRI*					
Yes	18/29 (62)	9.4 (5.3–17.7)	13/21 (62)	4.6 (2.1–NR)	0.63 (0.3–1.3)
No	66/117 (56)	10.7 (8.3–12.6)	85/124 (68)	6.5 (5.6–8.8)	0.59 (0.4–0.8)
Duration of prior ACT*					
≤6 months	46/72 (64)	8.8 (7.6–10.7)	55/78 (71)	5.8 (4.8–7.3)	0.61 (0.4–0.9)
> 6 months	38/74 (51)	11.3 (8.4–17.7)	43/67 (64)	6.5 (4.8–11.3)	0.61 (0.4–0.9)

*Based on pts with only 1 line of prior ACT.
NR, not reached.

3584 **Poster Session**

A phase 1 first-in-human study of the anti-LAG-3 antibody MK4280 (favezelimab) plus pembrolizumab in previously treated, advanced microsatellite stable colorectal cancer. *First Author: Elena Garralda, Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain*

Background: Patients (pts) with microsatellite stable (MSS) metastatic colorectal cancer (mCRC) that progressed on ≥2 prior therapies have limited treatment options, with median OS ranging from 6-9 months (mo). In the dose-escalation phase of this first-in-human multicohort study (NCT02720068), the anti-lymphocyte activation gene (LAG)-3 antibody favezelimab (fave) was well tolerated alone and with pembrolizumab (pembro) across all dose levels (Lakhani, SITC, 2018, abstract O26). Here, we evaluate the safety and efficacy of fave alone or in combination with pembro in pts with advanced MSS CRC from the dose confirmation phase. **Methods:** Eligible pts with MSS PD-1/PD-L1-treatment-naïve mCRC that progressed on prior standard-of-care (3L+) were enrolled (cohort A) to receive the RP2D of 800 mg fave alone (Arm 1), 800 mg fave + 200 mg pembro (Arm 2C), or 800 mg fave + 200 mg pembro (MK-4280A) co-formulation (Arm 5), all Q3W. Treatment continued for 35 cycles or until progression, unacceptable toxicity, or investigator/pt decision. Pts with confirmed progression per irRECIST v1.1 on fave alone could crossover to 800 mg fave + pembro. Safety was assessed in all treated pts; efficacy in the full analysis set (FAS) of all treated pts with baseline scan. Objectives included safety (primary), ORR (RECIST v1.1 by investigator [secondary]), and DOR, PFS, and OS (exploratory). Interim analysis data cut-off was: Oct. 23, 2020. **Results:** A total of 20 pts received fave (Arm 1); 89 pts (including 9 crossover) received fave + pembro (Arms 2C+5); 12 pts (Arm 1) and 36 pts (Arms 2C+5), had PD-L1 CPS ≥1 tumors. At data cut-off, median follow-up was 5.8 months (mo) in Arm 1 and 6.2 mo in Arms 2C+5. Treatment-related adverse events (TRAEs) were 65% with fave (Arm 1) and 65.2% with fave + pembro (Arms 2C+5). Grade ≥3 TRAEs were 15% (Arm 1), and 20% [Arms 2C+5]). No grade 5 TRAEs were reported. Common TRAEs (≥15%) included fatigue (20.0%), nausea (15%) with fave, and fatigue (16.9%) with fave + pembro. Confirmed ORR was 6.3% (4PR, 1CR) with fave + pembro (Arms 2C+5). No pt receiving fave alone responded. In Arms 2C+5, median DOR was 10.6 mo (range, 5.6-12.7). ORR, OS and PFS by PD-L1 status are reported in the Table. **Conclusions:** Favezelimab alone or in combination with pembrolizumab had a manageable safety profile, with no treatment-related deaths. Promising antitumor activity was observed with combination therapy, including with MK-4280A, compared with monotherapy most notably in pts with PD-L1 CPS ≥1 tumors. Clinical trial information: NCT02720068. Research Sponsor: Merck & Co., Inc.

Fave + pembro[a,b]	**Total N = 80[c]**	**CPS ≥1 N = 36**	**CPS < 1 N = 35**
ORR, n (%)	5 (6.3)	4 (11.1)	1 (2.9)
OS, median, mo (95% CI)	8.3 (5.5-12.9)	12.7 (4.5-NR)	6.7 (3.8-11.0)
12-mo OS rate, %	40.8	50.6	29.5
PFS, median, mo (95% CI)	2.1 (1.9-2.2)	2.2 (1.8-4.2)	2.0 (1.9-2.1)
6-mo PFS rate, %	16.2	25.4	9.1

[a]Includes MK-4280A; [b]Missing PD-L1 status (n = 9); [c]FAS; NR, not reached.

3585 **Poster Session**

Differential impact of different TP53 gain-of-function mutations on overall survival of patients with metastatic colorectal cancer: Results from a large integrated healthcare system. *First Author: Minggui Pan, Kaiser Permanente, Dept of Medical Oncology, Santa Clara, CA*

Background: TP53 mutation is present in approximately 50% of metastatic colorectal cancer (CRC). The spectrum of the TP53 mutations is extremely broad including approximately 80% missense mutations. Several missense mutations have been found to possess gain-of-function (GOF) properties in cell line and animal studies, however, confirmation of the concept of GOF in human malignancies is still lacking. **Methods:** We investigated the impact of TP53 GOF mutations in patients with metastatic CRC using the NGS data within Kaiser Permanente Northern California (KPNC), a large integrated healthcare system. **Results:** From November 2017 to January 2021, genomic profiling by StrataNGS was performed on 8658 patients, with 1056 patients being metastatic CRC, among whom 740 patients harbored a TP53 mutation (TP53mut) and 316 patients had wild-type TP53 (TP53wt). Ras (KRAS and NRAS) and BRAF mutation appropriately discriminated the overall survival (OS) of patient populations with either TP53wt or TP53mut, confirming the validity of our dataset. We identified seven GOF TP53 mutations (R175H, R248W, R248Q, R249S, R273H, R273L, R282W) in these CRC patients. We show that different GOF mutation differentially impacts the OS. Patients whose CRC harbored TP53mut R248W, R249S, and R282W (poor prognostic TP53mut, N = 47) had significantly worse OS versus patients whose CRC harbored TP53mut R248Q, R175H, R273H and R273L (N = 160, median OS 29.4 vs 44.2 months, HR 0.47, p = 0.007). The OS of the poor prognostic TP53mut patients was also significantly inferior compared to patients whose CRC harbored all other TP53 mutations (N = 1099, median OS 50.1 months, HR 0.55, p = 0.01) or TP53wt (N = 316, median OS 47,5 months, HR 0.54, p = 0.01). The demographics and the percent of Ras, BRAF, and PI3KCA mutations were similar except that the patients with the poor prognostic TP53mut had significantly higher percent of Ras mutation compared to the rest of the GOF TP53mut patients (p = 0.035). When compared to R248Q alone, R248W confers worse OS (median OS 36.3 vs 63.2 months, p = 0.05). **Conclusions:** Our data suggest that different TP53 GOF mutations are associated with very different clinical outcomes. Additional studies identifying specific TP53 GOF mutations that impact outcomes may provide further insight for drug development and clinical trial design. Research Sponsor: None.

3586 **Poster Session**

Mucinous colorectal cancer: Disease characteristics, treatment outcomes and the impact of metastasectomy. *First Author: Darren Cowzer, Mater Misericordiae University Hospital, Dublin, Ireland*

Background: Mucinous colorectal cancer (CRC) differs from adenocarcinoma with regard to clinical and histological features and is reported to have inferior outcomes when compared to non-mucinous CRC. This study aims to evaluate the clinical features and outcomes of patients with mucinous CRC at our institution. **Methods:** Medical records of patients with CRC that were referred to medical oncology between September 1999 and September 2018 were retrospectively reviewed. Mucinous histology was defined as those containing > 50% mucin identified on histology specimens. Statistical analysis was performed using Prism V9.0. **Results:** We identified 1,115 patients with CRC that were referred to medical oncology during this period. The tumours of 81 (7.3%) patients were classified as mucinous. Median age was 65 (28-94 years) and 45 (55.5%) were male. Forty-one patients (51%) had right sided tumours, 27 (33%) had left sided tumours and 13 (16%) had rectal tumours. Twenty-three (28.4%) had *de novo* metastatic disease. Eleven of 24 patients (46%) with stage II disease relapsed and 18 of 33 (55%) of those with stage III disease relapsed. Radiological surveillance identified 20/29 (69%) of relapsed disease, 5 (17%) were symptomatic and 4 (14%) had a rise in CEA. Median follow up for patients with stage II disease was 53 months and 3 year and 5-year disease free survival (DFS) was equal in both groups at 60.9%. For stage III disease 3- and 5-year DFS was 58.1% and 48.4% respectively with a median follow up of 43 months. In the metastatic setting, we observed no significant difference in overall survival (OS) between left and right sided tumours (*p = 0.550*). Median OS for pts with stage IV mucinous CRC who received any treatment was 25 months. Metastasectomy was performed in 25/52 (48%) patients and was associated with a significant improvement in OS, 23 vs 51 months (*p < 0.005, HR 0.4*). **Conclusions:** Mucinous CRC has been associated with inferior responses to treatment and worse overall outcomes compared to non-mucinous histologies. Survival in advanced-stage disease in our cohort is higher than what has been reported in the literature. With an effective multi-disciplinary approach and the increasing use of metastasectomy as a treatment option, survival in the advanced disease setting may be comparable to non-mucinous CRC. Research Sponsor: None.

3587 **Poster Session**

Young-onset colorectal cancer treatment side effects: Infertility, sexual dysfunction, and quality-of-life outcomes. *First Author: Laura Diane Porter, Colorectal Cancer Alliance, Washington, DC*

Background: Colorectal cancer is the third-most commonly diagnosed cancer and the second-leading cause of cancer death in men and women combined in the United States. Young-onset colorectal cancer refers to individuals diagnosed under the age of 50. In recent years, the incidence has increased by 2.2% annually in individuals younger than 50 years and 1% in individuals 50-64, in contrast to a 3.3% decrease in adults 65 years and older. Young-onset (YO) CRC patients and survivors face unique clinical challenges with fertility and sexual dysfunctions, but this risk is not well quantified. There is limited data and public discussion on the long-term effects of colorectal cancer treatments on fertility and sexual dysfunction and the long-term impact on the quality of life. **Methods:** To explore the unique challenges and unmet needs of the young-adult patient population, a cross-sectional study was conducted. Colorectal cancer patients and survivors (N = 884) diagnosed between the ages of 20 to 50 years old (median age 42 ± 7.0) completed an online questionnaire based on established instruments EORTC-QOL-30, EORTC-CR-29, and EORTC-SHC-22. **Results:** Thirty-one percent of respondents stated that a medical professional spoke to them about fertility preservation at the time of diagnosis and during treatment. Only 31% were referred to a reproductive endocrinologist, even though 37% of women and 16% of men reported that treatment left them infertile or sterile. Among survey respondents, 12% of women had an egg retrieval procedure, and 36% of men had their sperm preserved prior to the start of treatment. Fifty-three percent of women reported treatment led to premature menopause. Sixty-five percent of respondents suffer from some level of sexual dysfunction due to treatment. In patients who received radiation therapy, women were 12% less likely than men to have discussed sexual side effects with the provider before treatment. Patients who have an ostomy reported more severe sexual dysfunction (17.8%). Rectal cancer patients were 2.5 times more likely than those with colon cancer to report severe dysfunction after their treatment. More than 25% of the respondents said they would have considered alternative treatment if they would have known the risks of sexual dysfunction. **Conclusions:** Our survey demonstrates inadequate communications between patients and providers about the irreversible fertility and sexual effects of colorectal cancer treatments. Younger patients and survivors face unique long-term challenges and require further information about fertility preservation options and emotional support regarding their sexuality post-treatment. Other studies are needed to assess the physical and psychological side effects endured by young-onset CRC patients and survivors. Research Sponsor: None.

3588 **Poster Session**

Dietary fat in relation to overall and progression-free survival among patients (pts) with advanced or metastatic colorectal cancer (CRC): Data from CALGB 80405 (Alliance). *First Author: Erin Van Blarigan, University of California San Francisco, San Francisco, CA*

Background: Growing data suggest dietary factors are associated with survival among pts with non-metastatic CRC. However, data on diet and survival among pts with advanced or metastatic disease are very limited. **Methods:** We prospectively examined dietary fat intake assessed at initiation of treatment for advanced or metastatic CRC in relation to OS and PFS. This analysis was conducted among 1,149 pts in the CALGB 80405 randomized controlled trial who completed a validated food frequency questionnaire. We examined intakes of saturated, monounsaturated, and polyunsaturated (total n-3, long-chain n-3, and total n-6) fats as well as animal and vegetable fats. Based on data from non-metastatic CRC and other cancers, we hypothesized that higher intakes of long-chain n-3 fatty acids and vegetable fats would be associated with longer OS and PFS and higher intakes of saturated fat and animal fat would be associated with shorter OS and PFS. We used Cox proportional hazards regression to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI). **Results:** Over a median follow-up of 6.1 years [y; interquartile range (IQR): 5.3, 7.2 y], we observed 974 deaths and 103 events of progression without death during follow-up. Participants in this analysis had a median age of 59 y (IQR: 51 to 67 y); 41% were female and 86% identified as white. We observed no statistically significant associations between any type of dietary fat and OS. However, vegetable fat was non-linearly associated with longer PFS (HR comparing 4th to 1st quartile: 0.78; 95% CI: 0.64, 0.96; *p*-trend: 0.10). We also observed a linear association between continuous saturated fat and PFS (HR per 5% kcal/d: 1.21; 95% CI: 1.03, 1.42; *p*-value: 0.02), perhaps driven by pts with high saturated fat intake. **Conclusions:** We observed no statistically significant associations between types of dietary fat and OS among pts with advanced or metastatic CRC. However, a healthy diet that includes vegetable fat and is modest in saturated fat may be associated with longer PFS. Future studies to replicate these findings and examine diet in relation to cancer survival in racially/ethnically diverse populations are needed. Support: K07CA197077, U10CA180821, U10CA180882, https://acknowledgments.alliancefound.org. Clinical trial information: NCT00265850. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

3589 **Poster Session**

Assessment of HER2 (*ERBB2*) amplification (HER2amp) using blood-based circulating tumor DNA (ctDNA) next generation sequencing (NGS) and correlation with tissue-based testing in metastatic colorectal cancer (mCRC). *First Author: Kanwal Pratap Singh Raghav, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: HER2 amplified mCRC has emerged as a unique clinical subset, characterized by resistance to anti-EGFR therapy and response to anti-HER2 strategies. Accurate identification and quantification of HER2amp has predictive value for efficacy of anti-HER2 therapies and appropriate patient selection. Despite availability and use of various tumor tissue-based and blood-based assays for detecting HER2amp, data on cross-performance of these platforms are lacking. **Methods:** Leveraging a multicenter international consortium (Italy, Japan and USA), we generated a large cohort (N = 353) of mCRC patients (pts), tested for HER2amp using both tissue and blood. Tissue testing was done using immunohistochemistry (IHC), in-situ hybridization (ISH) and (NGS). ctDNA NGS was performed using CLIA-certified Guardant360 ctDNA assay, capable of detecting HER2 copy number (CN) variations. The primary endpoint was to correlate HER2 gene CNs in tissue (tCN) and plasma (pCN). Descriptive statistics, spearman correlation (r) and Fisher's exact test were used. **Results:** Baseline tumors characteristics included right-sided primary in 234 (23%), proficient mismatch repair in 264 (98%) and *RAS/BRAF* wild type (WT) genotype in 194 (67%) pts. Tissue testing was done by IHC, ISH and NGS in 76%, 64% and 74% pts, respectively. A total of 177 pts had HER2amp detected by at least one test: 116 (66%), 157 (89%) and 96 (54%) of which had tissue +, ctDNA +, and both tissue and ctDNA + disease, respectively. Discordant cases consisted of 20 (6%) with positivity in tumor only and 61 (17%) in ctDNA only. Sensitivity, specificity, positive and negative predictive values of ctDNA assay (vis-à-vis tissue) were 83%, 74%, 61% and 90% respectively. Among HER2amp pts, median (range) HER2/CEP17 (ISH) ratio, tCN and pCN were 5.2 (2–12), 11.6 (2–700) and 3.5 (2–122), respectively. The pCN showed strong correlation with ISH ratio (r = 0.69) and tCN (r = 0.68) ($P < 0.001$). Median pCN differed significantly between pts with HER2 IHC 3+ (12.0), 2+ (2.2) and 0/1+ (2.0) tumors ($P < 0.001$). High HER2amp (pCN > 4.0) appeared to be enriched with tissue + cases (69% vs 8% [OR 24.6, $P < 0.001$]), tumor tissue HER2 + status (IHC3+ [75%] vs IHC2+ISH+ [50%] vs IHC2+/ISH- or IHC0/1+ [12%], $P < 0.001$), HER2 tCN > 6 (79% vs 31% [OR 8.7, $P < 0.001$]) and *RAS/BRAF* WT tumors (41% vs 17% [OR 3.5, P = 0.064) but not left sidedness (41% vs 38%; OR 1.1; P = 0.82). **Conclusions:** In this large diverse cohort of mCRC, we demonstrated correlation of HER2 tCN and pCN obtained by tissue-based and blood-based ctDNA assay. Further prospective efforts are needed to standardize this cross-platform quantification of HER2amp to facilitate robust clinical application of HER2 therapies. This effort shows the value of strategic international partnership in furthering research for rare cancer subsets. Research Sponsor: None.

3590 **Poster Session**

XELOX or mFOLFOX6 chemotherapy combined with resection of primary lesion versus chemotherapy alone for colon cancer with unresectable metastases: A randomized clinical trial. *First Author: Weijian Guo, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*

Background: It is still controversial for colon cancer patients with unresectable metastases whether to resect the primary tumor when there are no symptoms of primary lesion. **Methods:** This is an open-label, single-center, prospective, randomized, controlled phase II trial. Colon cancer patients aged 18-80 years with unresectable metastases at enrollment will be randomly allocated to either resection group (group A) or chemotherapy group (group B), and stratified by tumor response and number of organ metastases, after receiving induction chemotherapy with 4 cycles of XELOX or 6 cycles of mFOLFOX6, excluding those with disease progression, lesions radically resectable, or primary lesion unresectable. Patients in group A received resection of primary lesion and then continued chemotherapy, and patients in group B just continued chemotherapy, both up to 4 cycles of XELOX or 6 cycles of mFOLFOX6, and capecitabine maintenance afterwards. If progression occurs 3 months after discontinuation of oxaliplatin and toxicity has recovered to grade I, the original regimen can be applied again. The primary endpoint was TFS (time to failure of strategy, defined as the time from randomization to secondary progression in patients received re-introduce of the induction chemotherapy regimen, or to first progression in patients without re-introduce of the original regimen). The secondary endpoints included progression-free survival (PFS, the time from randomization to first progression), overall survival (OS, the time from enrollment to death), and adverse events (AEs). Efficacy data were analyzed on an intention-to-treat (ITT) basis. This study is registered with ClinicalTrials.gov, number NCT02291744. **Results:** Between April, 2015, and July, 2020, 140 patients were enrolled, and 54 patients withdrew due to colon obstruction (16), perforation (1), disease progression (22), death (1), radical resection (3), or other reasons (11). Finally, 86 patients were randomized into group A (n = 42) or group B (n = 44). The median TFS was 143 days (95%CI: 104.9-181.1) in group A, and 196 days (95%CI: 96.5-295.5) in group B (HR:0.930 95%CI:0.589-1.468, p = 0.755). The median PFS was 147 days (95%CI: 105.7-188.3) in group A, and 206 days(95%CI:180.9-231.1) in group B (HR:0.831, 95%CI:0.522-1.323, p = 0.436). The median OS was 530 days (95%CI: 308.9-751.1) in group A, and 779 days (95%CI:626.3-931.7) in group B (HR:0.948 95%CI:0.554-1.622, p = 0.845). The incidence of treatment-related AEs was similar between two groups. **Conclusions:** Resection of primary tumor after induction chemotherapy could not bring survival benefits. It's not recommended for patients without symptoms of primary lesion to receive primary tumor resection, but it also requires individualized treatment as colon obstruction or perforation occurred in some patients. Clinical trial information: NCT02291744. Research Sponsor: Foundation from Fudan University Shanghai Cancer Center.

3591 **Poster Session**

Association of plasma adiponectin with tumor infiltrating lymphocytes and survival in patients with stage III colon cancer (NCCTG N0147; Alliance). *First Author: Frank A. Sinicrope, Mayo Clinic, Rochester, MN*

Background: Adiponectin is a peptide hormone exclusively secreted by adipocytes that plays a role in immune regulation and in the host inflammatory response to cancer. We examined postsurgical adiponectin levels in relationship to tumor infiltrating lymphocytes (TILs), clinicopathological features, vitamin D status, and patient survival in participants in a phase 3 trial of adjuvant chemotherapy. **Methods:** Plasma adiponectin and 25-hydroxyvitamin D [25(OH)D] were analyzed by radioimmunoassay in 600 patients with stage III colon carcinoma who received adjuvant FOLFOX +/- cetuximab. TIL densities were determined at light microscopy in routine histopathological sections. The associations between adiponectin and 25(OH)D, TILs, other factors were evaluated by Fisher's Exact, Chi-squared, t-test, and Kruskal-Wallis tests where appropriate. The association between adiponectin or 25(OH)D with disease-free survival (DFS), time to recurrence (TTR) and overall survival (OS) were evaluated by multivariable Cox regression, adjusting for body mass index (BMI), race, T, N stage, performance status, tumor location, TILs, *BRAF/KRAS*, and mismatch repair status. **Results:** A statistically significant and inverse association between adiponectin level and BMI was observed with lower levels found with obesity (BMI > 30 kg/m^2) [$p < 0.001$]. The level of adiponectin was significantly lower in men vs women ($p < 0.001$), in blacks vs whites or Asians ($p < 0.032$), and in patients with fewer regional lymph node metastases (N1 vs N2 stage, $p = 0.011$). A significantly lower level of adiponectin was found in patients whose tumors had high vs low TIL densities ($p = 0.040$), but was unrelated to 25(OH)D. Insufficiency of 25(OH)D (< 30 ng/ml) was detected in 291 (49%) of patients and was not associated with TILs. By multivariable analysis, adiponectin was not associated significantly with patient DFS (HR_{adj}= 0.98, 95% CI 0.74-1.29, p_{adj}= 0.88) nor with OS nor time-to-recurrence (TTR). TIL densities were significantly prognostic, but 25(OH)D was not (DFS: HR_{adj}= 1.12, 95% CI 0.85-1.47, p_{adj}= 0.44). No significant interaction was observed for adiponectin with TILs for the association with DFS. **Conclusions:** Lower adiponectin levels were associated with significantly increased TIL densities in colon cancers, indicating an enhanced anti-tumor immune response. In contrast to TILs, adiponectin was not independently associated with patient outcome. Nearly one-half of stage III patients were vitamin D insufficient, although 25(OH)D was not prognostic. Research Sponsor: U.S. National Institutes of Health.

3592 **Poster Session**

Young-onset colorectal: Emotional and psychosocial effects on patients, survivors, and caregivers. *First Author: Laura Diane Porter, Colorectal Cancer Alliance, Washington, DC*

Background: Colorectal cancer is the third-most commonly diagnosed cancer and the second-leading cause of cancer death in men and women combined in the United States. Young-onset colorectal cancer refers to individuals diagnosed under the age of 50. In recent years, the incidence has increased by 2.2% annually in individuals younger than 50 years, and 1% in individuals 50-64, in contrast to a 3.3% decrease in adults 65 years and older. The Colorectal Cancer Alliance launched the Never Too Young Survey and the Caregiver Survey to assess and better understand the unmet needs of the young-onset population and their caregivers. **Methods:** A cross-sectional study, conducted in the form of an online survey, was launched to better understand the experiences around YO-CRC patients and caregivers. YO-CRC patients and survivors (N = 885) and caregivers (N = 204) completed an online questionnaire that was based on established instruments including PROMIS, EORTC-QOL-30, and EORTC-CR-29. The final survey instrument and study plan were reviewed and approved by the Aspire Inc. Institutional Review Board. **Results:** Nearly 75% of patients/survivors shared that they have been concerned about their mental health, and 64% responded that they have needed help for their depression. Further, 67% of caregivers surveyed responded that they were also concerned about their mental health, and 68% responded that they needed help with their depression. Seventy-one percent of caregivers often felt sadness, and 30% indicated that they had lost hope. Emotional exhaustion was reported by 77% of caregivers, whether they were providing round-the-clock care or caregiving from a distance. The effect was more pronounced in the patient/survivor cohort, with 95% indicating that emotional exhaustion impacted their lives. As a result, 71% of caregivers and 29% of patients/survivors indicated that they had withdrawn from other people. These results indicate the emotional toll that colorectal cancer has on patients/survivors and caregivers and their need for further resources. **Conclusions:** The Colorectal Cancer Alliance is committed to meeting these needs and providing resources that support patients, survivors and caregivers. Information and services may assist the caregiver in helping the patient make decisions, including shifting roles and routines in response to changing demands of YO-CRC. Further studies should investigate psychological well-being and support strategies. Research Sponsor: None.

3593 **Poster Session**

Doublet (FOLFOX or FOLFIRI) versus triplet (FOLFOXIRI) backbone chemotherapy regimen as first-line treatment of metastatic colorectal cancer: A meta-analysis and systematic review. *First Author: Vishal Jindal, Beaumont Health, Department of Hematology and Oncology, Oakland University William Beaumont School of Medicine, Royal Oak, MI*

Background: Doublet chemotherapy FOLFOX and FOLFIRI are standard for first-line treatment of metastatic colorectal cancer (mCRC). Recently, use of triplet chemotherapy FOLFOXIRI has shown an increased anti-cancer activity but still there is uncertainty regarding first line backbone chemotherapy. Therefore, we conducted this metanalysis to determine the efficacy, safety and outcome of triplet vs doublet chemotherapy. **Methods:** The study protocol was published at PROSPERO (CRD42020166745) and prepared as per PRISMA guidelines. Total 10 studies were included, with sample size of 1536 participants in triplet arm and 1535 participants in doublet arm. The primary outcome is Response rate (RR) and secondary outcomes are Progression-free survival (PFS), Overall survival (OS), post chemotherapy radical (R0) surgical resection rate of metastases. Quantitative synthesis was performed using "R" statistical package. Dichotomous outcomes were summarized using odds ratio (OR) and time to event data was summarized using hazard ratio (HR). **Results:** A total of 678 articles were retrieved. The Medline article search gave a result of 271 article, Embase 296, the Cochrane Library 100 and Clinical tral.gov 11, when searched through April 2020. Total 10 studies were included. All the studies were randomized, open-label, multicenter study. Out of the 10 trials 5 each were phase II and phase III studies. The pooled odds ratio for RR was 1.66 (95% CI 1.42 to 1.93) and PFS was (HR, 0.70; 95% CI, 0.63–0.78) in favor of triplet chemotherapy. There was significant improvement in radical resection (R0) of metastases (OR 1.59; 95% CI, 1.27–1.98) in triplet arm. Triplet arm was also associated with increased toxicity especially neurological events 2.51(0.88-7.16), diarrhea 2.40(1.74-3.31), neutropenia, 2.23(1.71-2.90) and thrombocytopenia 1.94(1.05-3.59). **Conclusions:** Findings in this meta-analysis showed that FOLFOXIRI significantly improves the PFS, RR, OS, and R0 resection rate of overall metastases over the doublet chemotherapy. The incidence of fatal adverse events was found to be more in triplet chemotherapy compared to doublet therapy. Therefore, we concluded that with moderate evidence FOLFOXIRI provide clinically meaningful efficacy benefit at cost of increased toxicity. Research Sponsor: None.

Outcome	Odds ratio (OR)/Hazard ratio(HR) (95% Confidence interval)	Number of studies	Number of participants	I^2 Value (%)
OS	HR - 0.81(0.73-0.89)	7	2235	0
PFS	HR - 0.70(0.63-0.78)	8	2568	19
RR	OR -1.66 (1.42-1.93)	10	2815	0
RO Resection Rate	OR- 1.59 (1.27-1.98)	10	2834	0
Neurological events	OR- 2.51(0.88-7.16)	9	2578	44
Diarrhea	OR- 2.40(1.74-3.31)	9	2578	54
Neutropenia	OR- 2.23(1.71-2.90)	9	2578	0
Thrombocytopenia	OR- 1.94(1.05-3.59)	7	2149	69
Mucositis	OR- 1.68(1.35-2.10)	9	2498	91

3594 **Poster Session**

A novel clinical tool to estimate risk of false negative KRAS mutation in circulating tumor DNA testing. *First Author: Stefania Napolitano, Università Degli Studi Della Campania, "Luigi Vanvitelli", Naples, Italy*

Background: Recently, in metastatic colorectal cancer (mCRC), the detection of RAS mutations by circulating tumor (ct) DNA has recently emerged as a valid and non-invasive alternative approach, overall showing a high concordance with the standard tissue genotyping, giving information on response to EGFRi treatment and resistant mechanisms. However, RAS mutations may be missed due to low levels of any ctDNA in the blood (false-negative), and it has been difficult to distinguish this from patients without a RAS mutation in the tumor (true-negative). We propose a methodology that can be applied to multi-gene ctDNA testing panels to accurately distinguish true- and false-negative tests. **Methods:** 357 subjects with tissue and multi-panel ctDNA testing from MD Anderson (MDACC) were used as a training dataset and 295 subjects from Massachusetts General Hospital (MGH) dataset as the testing dataset. CtDNA panels contained between 65 and 70 genes, allowing evaluation of tumor ctDNA shedding from variant allele fraction (VAF) levels in the plasma from other genes (such as APC and TP53). Based on the relationship between KRAS and the VAFs of other gene, we established a Bayesian model providing a posterior probability of false negative in the ctDNA test, using thresholds of $< 5\%$ (low), 5-15% (medium), and $> 15\%$ (high). This model was validated on the MGH database. **Results:** Across both cohorts, 431 patients were ctDNA wild type for KRAS. Of those, 29 had tissue documenting a KRAS mutation for a false negative rate of 8%. The model provides the posterior probability that a KRAS mutation is indeed present in the tissue given the observed values of allele frequencies for other mutated genes in the plasma. In the validation cohort, a predicted low false negative had no false negatives (0/62, 95% CI 0%-5.8%), while a predicted medium false negative rate was associated with 3% false negative (1/32, 95% CI 0%-16%). In contrast, a high predicted false negative rate was associated with 5% false negative (5/100, 95% CI 1.6%-11%). The results demonstrate the ability of our tool to discriminate between subjects with true negative and false negatives, as a higher proportion of false negatives are observed at higher posterior probabilities. **Conclusions:** In conclusion, our approach provides increased confidence in KRAS ctDNA mutation testing in clinical practice, thereby facilitating the identification patients who will benefit from EGFR inhibition while reducing the risk of false negative tests. Extension of this methodology to NRAS and BRAF is possible, with clinical application enabled by a freely available online tool. Research Sponsor: None.

3595 **Poster Session**

Impact of time to treatment initiation on real-world (RW) outcomes in metastatic colorectal cancer (mCRC) in the United States. *First Author: Olumide B. Gbolahan, Indiana University School of Medicine, Indianapolis, IN*

Background: The COVID-19 pandemic caused disruptions in cancer care delivery and forced oncologists to make recommendations about safely delaying initiation of therapy. Compared to the adjuvant setting, information about the impact of time to treatment initiation on outcomes in the palliative setting for CRCis scarce. We sought to determine the median time to initiation of systemic therapy (TIT) in mCRC in the US pre-pandemic, and to assess the impact of TIT on survival outcomes. **Methods:** We retrospectively analyzed de-identified data of patients (pnts) with mCRC in the Flatiron Health nationwide EHR-derived database (metastatic diagnosis dates 01/2013 - 04/202000. Demographics, treatments (tx), and outcomes were collected. TIT, the period between diagnosis and initiation of first-line systemic therapy was split into 3 categories (I: < 2 weeks, II: 2- < 4 weeks, and III: 4-8 weeks). Overall survival (OS) was defined from time of diagnosis to time of death. Post-chemotherapy survival (PCS) was time from initiation of first-line therapy to death. Adjusted and unadjusted multinomial logistic regression were used to evaluate the association of demographics and clinical factors with TIT. PCS and OS were estimated using Kaplan-Meier curves. Adjusted (demographics and clinical factors) Cox proportional hazard models were used to estimate the effect of TIT groups on PCS and OS. Category II was control group. **Results:** 7,108 pnts with mCRC who received at least one line of tx were identified. 16% (N = 1132), 34% (N = 2406), and 50% (N = 3570) were in TIT categories I-III. The mean age at diagnosis was 63.4 years, with no significant difference in age (P = 0.6) among categories. Median TIT was 28 days. Multinomial logistic regression showed that compared to TIT II, Hispanic pnts were more likely than Whites to receive chemotherapy in 4-8 weeks (OR 1.4, 95% CI 1.12- 1.7, P= 0.0022). Females were more likely to receive treatment in 4-8 weeks (OR 1.14, 95% CI 1.03- 1.27, P= 0.01). Pnts without documented KRAS testing were more likely to receive tx within 2 weeks (OR 1.3, 95% CI 1.05- 1.48, P= 0.01). Median RW OS favored group III (I: 18.1, II: 22.6, III: 26.9, P< 0.0001). Adjusted Cox regression analysis suggested that Blacks had a higher hazard of death compared to Whites, (HR, 1.14. 95% CI 1.03 -1.27, P = 0.01) Also, compared to TIT of 2-4 weeks, TIT < 2 weeks was associated with lower RW PCS (HR, 1.22, 95% CI 1.11-1.33, P= 0.0001), and RW OS (HR, 1.25, 95% CI 1.14- 1.37, P= <0.0001). In contrast, TIT 4-8 weeks was associated with higher RW PCS (HR, 0.81, 95% CI 0.75- 0.87, P= 0.0001) and RW OS (HR, 0.78, 95% CI 0.72- 0.83 P= <0.0001. **Conclusions:** This RW analysis suggests that pre-pandemic, 50% of patients with mCRC who receive first-line therapy were treated within 4 weeks of diagnosis. We observed disparities in TIT. Paradoxically, RW survival increased with TIT, with the best outcomes reported in those treated in 4-8 weeks. Research Sponsor: None.

3596 **Poster Session**

Real-world survival outcomes associated with completion of adjuvant chemotherapy for stage III colon cancer. *First Author: Jemma Megan Boyle, London School of Hygiene and Tropical Medicine, London, United Kingdom*

Background: The optimal duration of adjuvant combination chemotherapy administered to patients with stage III colon cancer is debated. Our study assessed the effect of completed chemotherapy cycles on 3-year colon cancer-specific mortality, as well as the effect of dose reduction and early discontinuation of oxaliplatin in patients with 100% completion, within a real-world population. **Methods:** 4,147 patients undergoing major resection between 01 June 2014 and 30 April 2017 with pathological stage III colon cancer in the English National Health Service were identified. Chemotherapy data were obtained from linked administrative hospital records and a national chemotherapy dataset. Patients were stratified according to completion of < 50% (< 6 FOLFOX cycles or < 4 CAPOX cycles), 50-92% (6-11 FOLFOX cycles or 4-7 CAPOX cycles) or 100% of cycles (12 FOLFOX cycles or 8 CAPOX cycles). Competing-risk regression analysis for 3-year colon cancer-specific death was performed with adjustment for patient, tumour and hospital-level characteristics to estimate subdistribution hazard ratios (sHR) as a measure of relative risk. **Results:** Patients included within our study were less fit and had increased rates of high-risk disease (T4 and/or N2 pathological staging) compared to the IDEA study. For FOLFOX, the 3-year cumulative incidence of colon cancer-specific death in patients completing 100% of cycles was 15.1% (95% CI, 12.8% to 17.6%), 18.2% (95% CI, 15.3% to 21.3%) for 50-92% of cycles and 26.4% (95% CI, 20.6% to 32.5%) for < 50% of cycles. For CAPOX, this was 12.0% (95% CI, 10.2% to 14.0%) for 100% completion of cycles, 18.2% (95% CI, 15.6% to 21.0%) for 50-92% of cycles, and 19.8% (95% CI, 15.8% to 24.1%) for < 50% cycles. Compared to 100% completion of FOLFOX cycles, colon cancer-specific death was higher in patients recorded as completing < 50% (sHR 2.17; 95% CI, 1.56 to 3.03; $P = < 0.001$) and 50-92% of FOLFOX cycles (sHR 1.40; 95% CI, 1.09 to 1.78; $P = 0.007$). Compared to 100% completion of CAPOX cycles, colon cancer-specific death was higher in patients recorded as completing < 50% (sHR 2.02; 95% CI 1.53 to 2.67; $P< 0.001$) and 50-92% of CAPOX cycles (sHR 1.63; 95% CI 1.27 to 2.10; $P< 0.001$). Dose reduction and early discontinuation of oxaliplatin did not have a statistically significant effect on mortality. **Conclusions:** Patients within the real world setting were more likely to have poor prognostic factors. Those who completed adjuvant chemotherapy for stage III colon cancer had improved survival rates regardless of dose reduction or early discontinuation of oxaliplatin. Research Sponsor: None.

3597 **Poster Session**

Clinicopathological and molecular characteristics of early-onset stage III colon adenocarcinoma: An analysis of 25 studies with 35,713 patients in the Adjuvant Colon Cancer End Points (ACCENT) database. *First Author: Zhaohui Jin, Division of Medical Oncology, Mayo Clinic, Rochester, MN*

Background: Colon cancer (CC) incidence and mortality have decreased since the 1970s, but the incidence in young adults (20-49 years) is increasing. There are limited data suggesting that, as a group, patients with early onset CRC (eoCC) may have different phenotypic characteristics compared to those with late onset CRC (loCC, age ≥ 50 years). **Methods:** Individual patient data on 35,713 subjects with stage III CC from 25 randomized studies (recruiting between 1987 and 2009) in the ACCENT database were pooled. The distributions of demographics, clinicopathological features, biomarkers, and outcome data were summarized by age group. Overall survival (OS), disease-free survival (DFS), recurrence free rate (RFR), and survival after recurrence (SAR) were assessed by Kaplan-Meier curves and Cox models stratified by treatment arms within studies, adjusting for gender, race, body mass index, performance status, disease stage, grade, risk group, number of lymph nodes examined, disease sidedness and molecular markers. **Results:** Using a 5% difference between age groups as the clinically meaningful cutoff, patients with stage III eoCC (n = 6246) had similar distributions according to gender, race, PS, risk group, tumor sidedness and T/N stage compared to those with loCC (n = 29467). Patients with eoCC were significantly less likely to be overweight (30.2% vs 36.2%) but more commonly had ≥ 12 lymph nodes resected (69.5% vs 58.7%). The eoCC tumors were more frequently mismatch repair deficient (16.4% vs 11.5%), and less likely to have $BRAF^{V600E}$ (5.6% vs 14.0%), suggesting a higher frequency of Lynch syndrome in eoCC. In univariate analysis, patients with stage III eoCC had significantly better OS, DFS, and SAR; the difference between 3-year DFS and RFR strongly suggests the OS/DFS difference between these the eoCC and loCC may be due to increased competing risks and comorbidities in patients with loCC. In multivariate analysis, age at onset lost its prognostic value when outcome was adjusted for molecular markers. The clear relation between age of onset and KRAS/BRAF status was confirmed in the interaction analysis. **Conclusions:** Tumor biology was an important determinant of prognosis regardless of patient age. In multivariate analysis age of onset was not a statistically significant determinant of outcome. Research Sponsor: None.

			Univariate Analysis		Multivariate analysis with molecular markers	
	eoCC	loCC	Hazard Ratio	95% CI	Adjusted Hazard Ratio	95% CI
5-y OS,%	76.0	71.6	0.80	0.76-0.85**	0.92	0.80-1.05
3-y DFS, %	69.4	68.2	0.89	0.85-0.93**	0.94	0.83-1.06
3-y RFR, %	70.2	70.4	1.00	0.95-1.05	1.07	0.95-1.22
median SAR, months	20.4	17.5	0.85	0.80-0.90**	1.01	0.89-1.16

**p < 0.001.

3598 **Poster Session**

Clinical efficacy and safety of early adjuvant chemotherapy for stage III colon cancer: Short-term outcomes of a multicenter, randomized, open-label, phase 3 trial. *First Author: Jun Seok Park, Colorectal Cancer Center, Kyungpook National University Medical Center, Daegu, South Korea*

Background: Adjuvant chemotherapy (AC) is recommended to commence within 8 weeks since after surgical resection of stage II or III colon cancer. Results of many retrospective studies showed inferior survival outcomes following delay of AC delay. Moreover, preclinical studies showed that the progression of disseminated cancer cells is profound during the postoperative period. This study is the first prospective trial to evaluate early (≤ 14 days postoperative) AC for patients (pts) with stage III colon cancer. **Methods:** This study is a prospective, multicenter, randomized phase III trial. Pts with pathological stage III colon cancer were enrolled and randomized 1:1 to early AC (starting AC ≤ 14 days after surgery) or conventional AC (starting AC > 14 days after surgery). Pts were recommended to receive 12 cycles of FOLFOX-6 for AC. The primary endpoint was disease-free survival. The secondary endpoints were overall survival, adverse events, surgical complication during AC, and patient-reported outcomes (quality of life) during 1 year after surgery. Herein, safety data, chemotherapy delivery, and quality of life are presented. **Results:** This study randomized 443 pts either early AC arm (221pts) or early AC arm (222 pts) to the during September 2011 to March 2020. 380 pts who received at least one cycle of FOLFOX-6 were included in the safety analysis (192 and 188 in the early and conventional AC arms, respectively). The baseline characteristics of the two groups were well-balanced except for the interval from the surgery to the initial AC. The early and conventional AC arms started their first chemotherapy at median of 13 (4-43 days) and 29 (17-53 days) after surgery ($p < 0.001$), respectively. No significant differences were seen in the median chemotherapy cycles, AC completion, and relative oxaliplatin dose intensity between groups. AC Completion without any change of dose or schedule delay was seen in 18% and 20% in early and conventional AC arms respectively, while dose reduction or delay was 65% and 61%, respectively. Toxicities of grade 3 or more were seen in 28% in both groups. One patient in the early AC arm underwent an emergent operation for anastomotic leakage on the second day of 5-fluorouracil infusion (postoperative day 14). However, the surgical complication was not seen in any other patient. The scores of the European Organization for Research and Treatment of Cancer Quality of Life core 30 questionnaire were similar in both arms at baseline (before starting AC), and 1 month, 3 months, 6 months, and 12 months after surgery. **Conclusions:** Early AC was safe and did not increase either chemotherapy-related adverse events or surgery-related complications during treatment. Moreover early AC did not reduce the quality of life of the pts during 1 year after surgery. This study continues to follow-up the patients for survival outcomes. Clinical trial information: NCT01460589. Research Sponsor: None.

3599 **Poster Session**

Patient-specific meta-analysis of 3 validation studies of the 12-gene colon cancer recurrence score assay for recurrence risk assessment after surgery with or without 5FU and oxaliplatin. *First Author: Greg Yothers, NSABP, NRG Oncology and the University of Pittsburgh, Pittsburgh, PA*

Background: The 12-gene Oncotype DX Colon Recurrence Score assay is a clinically validated genomic assay that evaluates recurrence risks in stage II and stage III colon cancer patients independent of clinical-pathologic features. Improved colon cancer care has reduced recurrence rates since the late 1990's. **Methods:** Pre-specified patient-specific meta-analysis methods were used to estimate 1-, 3- and 5-year recurrence risk combining the 12-gene colon recurrence score (RS) validation studies CALGB 9581, NSABP C-07 and SUNRISE. Cox models had effects for RS result, number of nodes examined (<12 or ≥ 12), T-stage, MMR status, and stage (II, IIIAB or IIIC). Baseline cumulative hazard estimates used the latest two studies to reflect current medical practice. Estimates for surgery, surgery+5FU and surgery+5FU+oxaliplatin treatment were provided by integrating stage-specific 5FU hazard ratios from a meta-analysis of the QUASAR study (2007) and a pooled analysis of NSABP studies (Wilkinson 2010), and oxaliplatin treatment effect estimates from NSABP C-07. Recurrence risk with 5FU alone was not estimated for MMR-deficient patients due to expected lack of 5FU efficacy in these patients (Sargent 2010). **Results:** In the overall population of 2,179 patients, 55%, 32% and 13% were Stage II, IIIA/B and IIIC, 63% had $\geq$12 nodes examined, 90% were T3, and 88% were MMR proficient. Median RS result was 31 (IQR 23–39). RS result and each clinical-pathologic factor contributed independent prognostic information (meta-analysis Wald tests, all $p<.001$). Risk estimates are generally lower than previous RS report risk estimates. For patients with pathological stage II, T3, MMR-proficient tumors with $\geq$12 nodes examined, approximately 40% are expected to have 5-year recurrence risk $\leq$10% with surgery alone based on the distribution of RS results. The table shows example 5-year recurrence risk estimates for specific RS results and clinical-pathologic characteristics. **Conclusions:** The new recurrence risk estimates provide more patient-specific information reflecting more current medical practice than previous reports using RS result, allowing better, more individualized treatment decisions. Research Sponsor: None.

Example 5-year recurrence risk estimates (95% confidence intervals).

T-stage	Nodes ex.	MMR status	Stage	RS result	Surgery alone	Surgery+5FU	Surgery+5FU+oxali
T3	$\geq$ 12	Proficient	II	10	7% (5%, 9%)	5% (4%, 7%)	4% (3%, 6%)
				30	10% (8%, 13%)	8% (6%, 10%)	7% (5%, 9%)
				55	17% (13%, 22%)	13% (10%, 18%)	11% (7%, 15%)
		Proficient	IIIAB	10	15% (11%, 20%)	9% (7%, 13%)	8% (5%, 11%)
				30	22% (17%, 29%)	15% (11%, 19%)	12% (8%, 17%)
				55	34% (26%, 44%)	23% (17%, 31%)	19% (13%, 27%)
		Deficient	IIIAB	10	9% (5%, 13%)	–	4% (3%, 8%)
				30	13% (8%, 20%)	–	7% (4%, 11%)
				55	20% (13%, 31%)	–	11% (6%, 18%)

56% of patients in the meta-analysis population were T3 with $\geq$12 nodes examined.

3600 **Poster Session**

Prognostic value of baseline and early changes of circulating-free (cf) and circulating tumor (ct) DNA in the neoadjuvant (NA) setting of early stage colon cancer (CC). *First Author: Giacomo Bregni, Institut Jules Bordet-Université Libre de Bruxelles (ULB), Brussels, Belgium*

Background: ctDNA is an indicator of minimal residual disease and negative prognostic factor in stage II-III CC treated with surgery +/- adjuvant chemotherapy (CT). No study, however, has ever analysed the prognostic value of this biomarker in CC patients (pts) treated with NACT. We sought to evaluate the prognostic value of baseline and early changes of cf/ctDNA in stage II-III CC pts who were treated with one cycle of NA FOLFOX CT followed by surgery +/- adjuvant FOLFOX CT in the PePiTA trial. **Methods:** PePiTA was a multicentre, single-arm, prospective phase II trial testing *in vivo* tumour chemosensitivity of early stage CC (as assessed by ^{18}F-FDG PET/CT-based metabolic response to one cycle of NA FOLFOX) and its association with long-term outcome (NCT00994864). Plasma samples were prospectively collected at baseline, 2 weeks after one cycle of NA FOLFOX CT, and before surgery. NPY and WIF1 were selected as universal methylation markers for ctDNA and analysed with digital droplet (dd)PCR technology. Data from ddPCR were processed with the QuantaSoft v1.6 software (Bio-Rad). Survival outcome measures were 5-year disease-free survival (DFS) and 6-year overall survival (OS). ROC curve analyses, Kaplan-Meier method, cox proportional hazards models and log-rank tests were used. Statistical analyses were carried out with SPSS v25.0 (SPSS Inc.). **Results:** 80 pts were included (44 ypStage I-II and 36 ypStage III). After a median follow-up of 52.5 months, 5-year DFS and 6-year OS were 68% (95%CI 52-84) and 84% (95%CI 74-94), respectively. Pts with high ($\geq$1600 ng/ml) baseline cfDNA had worse 6-year OS (HR 6.45, 95%CI 1.61-25.84; p = 0.008). Early changes of cfDNA after one cycle of NA FOLFOX CT failed to predict survival (HR DFS 0.96, 95%CI 0.38-2.43; p = 0.92; HR OS 0.62, 95%CI 0.16-2.50; p = 0.50). At baseline, 25 out of 60 (42%) ctDNA-assessable patients were positive. Detectable ctDNA at baseline (HR DFS 2.06, 95%CI 0.65-6.49; p = 0.22; HR OS 3.11, 95%CI 0.57-16.99; p = 0.19) or at any timepoint before surgery (HR DFS 1.65, 95%CI 0.54-5.04; p = 0.38; HR OS 2.80, 95%CI 0.54-14.44; p = 0.22) was not significantly associated with survival. A trend toward a significant association between ctDNA increase at surgery and 5-year DFS was found (HR 3.66, 95%CI 0.81-16.44; p = 0.09). Data on the correlation between early changes of cf/ctDNA and ^{18}F-FDG PET/CT-based metabolic response will be presented at the meeting. **Conclusions:** For the first time, we have shown that baseline cfDNA may predict survival outcome in early stage CC pts treated with NACT. Pending confirmation in larger series, testing for cfDNA at baseline could help select high-risk pts who may benefit from FOxTROT-like, NACT treatment strategies. While analysis of ctDNA in this setting did not appear useful to predict prognosis, these results might be secondary to the small sample size. Research Sponsor: Fondation Les Amis de Bordet.

3601 **Poster Session**

Association of suboptimal lymph node yield with inferior survival in resected stage 1 colon cancer patients. *First Author: Alexander C. Chacon, University of Rochester Medical Center, Rochester, NY*

Background: A minimum of 12 lymph nodes are required during colectomy to accurately stage colon cancer. Prior studies in stage II colon cancer patients demonstrate association of inadequate lymph node examination (LNE) with worse overall survival (OS). No large-scale analogous studies related to LNE have been completed in stage I colon cancer patients. We evaluated patients with stage I colon cancer to determine the association between lymph node yield and OS. **Methods:** We reviewed the National Cancer Database between 2004-2015 to identify patients with pathologic stage I colon cancer (pT1N0 or pT2N0) who underwent definitive surgical resection. Patients who received radiation therapy or had missing values were excluded. Clinical and demographic characteristics were analyzed. Based on LNE, patients were stratified into 4 cohorts (LNE, 0-5, 6-11, 12-19, 20+) and 2 cohorts (0-11, 12+). Univariable and multivariable analyses were performed to identify variables associated with OS. Kaplan-Meier survival curves were computed to compare the cohorts. **Results:** We included 81,909 patients for analyses. Median age at diagnosis was 69. A majority were female (51.1%), white (83.8%), received care in a community cancer program (59.5%), and had a Charlson-Deyo score of 0 (66.6%). Only 0.7% of patients had a margin positive resection with a 2.5cm median tumor size. Patients were similarly split between pT1 and pT2. Suboptimal LNE was noted in 27.8% of patients. Patients with LNE were distributed - 10.7% (0-5), 17.1% (6-11), 43.4% (12-19) and 28.9% (20+). Postoperative 30-day mortality was 1.9%. 521 (0.7%) received systemic therapy. Ten-year survival in patients with 0-5 LNE was 52.8% compared to 60.1% with 20+ LNE. On multivariable analyses, patients aged $\geq$ 69, male sex, increasing tumor size (quartile), pT2 staging and a higher Charlson-Deyo score independently predicted worse OS ($p < 0.001$). LNE categories were significantly associated with OS ($p < 0.001$) (Table). On regrouping into 0-11 and 12+ LNE groups, 0-11 LNE group predicted worse OS (HR 1.22, $p < 0.001$). On multivariable analysis, the above variables continued to show similar association with OS ($p < 0.001$). **Conclusions:** Our study demonstrates that lymph node yield is associated with overall survival in patients with stage 1 colon cancer undergoing surgical resection. Furthermore, patients with suboptimal lymph node yield are associated with an inferior overall survival compared to those with optimal lymph node yield. Moreover, this study finds that a large number of patients ($>$ 25%) continue to have suboptimal lymph node yields. Future efforts should focus on improving the lymph node yield with optimal efforts by the surgeon and pathologist. Future studies should examine the role of systemic therapy in patients with inadequate lymph node yield. Research Sponsor: None.

LNE	HR (95% CI)	P-value
0-5	1.50 (1.43-1.58)	**< .001**
6-11	1.25 (1.20-1.30)	**< .001**
12-19	1.15 (1.11-1.19)	**< .001**
20+	-	-

3602 **Poster Session**

Phase I study of transarterial chemoembolization of lung metastases. *First Author: Franz Edward Boas, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Lung chemoembolization (via the bronchial or pulmonary artery) is a new treatment option for unresectable and unablatable lung metastases. **Methods**: 10 patients with unresectable and unablatable lung, endobronchial, or mediastinal metastases, who failed systemic chemotherapy, were enrolled in this single center, single arm, phase I trial. Pulmonary and bronchial angiography was performed in all patients, to determine the blood supply to the lung metastases. Based on the angiographic findings, bronchial or pulmonary artery chemoembolization was performed, using a lipiodol / mitomycin emulsion, followed by spherical particles. Technical success, safety, efficacy, and pharmacokinetics were evaluated. Wilcoxon signed-rank test was used to compare change in size of treated versus untreated tumors. **Results**: On angiography, all patients had lung metastases that were hypervascular compared to normal lung. 90% of patients had lung metastases supplied by the bronchial artery, and 10% were supplied by the pulmonary artery. Technical success rate of intra-tumoral drug delivery was 100% (95% CI: 76-100%). There were no severe adverse events, and all patients met criteria for discharge 4 hours post procedure. Response rate of treated lesions was 10% by RECIST and 40% by PERCIST. Treated tumors were mostly stable to decreased in size after chemoembolization (median change in size: 0%; IQR: -11% to 2%; mean: -4%), and untreated tumors were mostly increased in size (median change in size: 10%; IQR: 0% to 17%; mean 9%; p= 0.02). Intra-tumoral lipiodol retention at 4-6 weeks was correlated with decreased tumor size and metabolic activity. Pharmacokinetics showed that 45% of the mitomycin dose underwent burst release in 2 minutes, and 55% of the dose was retained intratumorally with a half-life $>$ 5 hours. Initial tumor-to-plasma ratio of mitomycin concentration was 380. Half-life of intratumoral lipiodol retention was 16 days. *In vitro* experiments showed 50% emulsion separation in 6.2 days, and 50% drug release in 7.1 hours. **Conclusions**: Lung chemoembolization can safely treat lung, mediastinal, and endobronchial metastases, with minimal systemic toxicity. High intratumoral drug concentrations after chemoembolization can overcome chemoresistance. Clinical trial information: NCT04200417. Research Sponsor: Brockman Medical Research Foundation, Society of Interventional Oncology.

3603 **Poster Session**

Long-term outcome of a phase III trial on neoadjuvant chemoradiation with capecitabine and irinotecan in patients with locally advanced rectal cancer: Updated results of the CinClare trial. *First Author: Ji Zhu, Fudan University Cancer Center, Shanghai, China*

Background: Adding UGT1A1-guided irinotecan to capecitabine-based neoadjuvant chemoradiotherapy (CRT) significantly increased the pathological complete response (pCR) rate nearly doubling [J Clin Oncol. 2020 Dec 20;38(36):4231-4239]. Here, results of long-term outcome are reported. **Methods:** Eligible patients with clinical stage II/III rectal adenocarcinoma, UGT1A1 genotype *1*1 or *1*28 were randomized to the control group: pelvic radiation of 50 Gy/25 fractions with concurrent capecitabine, followed by a cycle of oxaliplatin and capecitabine; or the experimental group: radiation with capecitabine combined with weekly irinotecan 80 mg/m2 for patients with *1*1 or 65 mg/m2 for patients with *1*28, followed by a cycle of irinotecan and capecitabine. Surgery was scheduled for 8 weeks after completion of CRT. Five cycles of adjuvant XELOX chemotherapy were administered regardless of the pathologic result. Patients were stratified by UGT1A1 genotype (*1*1 vs. *1*28) clinical T stage (cT3 vs. cT4) and tumor distance from the anal verge ($\leq$5 cm vs. $>$ 5 cm). The primary end point of pCR was reached. Survival time was calculated from the date of randomization to the date of event or the last follow-up. Secondary endpoints were defined as local failure for local control (LC), tumor recurrence or death from any cause for disease-free survival (DFS), and death from any cause for overall survival (OS). **Results:** Of the 360 patients initially enrolled, 356 were evaluated as the modified intention-to-treat population (n = 178 in both groups). A total of 311 patients underwent surgery and pCR was achieved in 80 patients, another 10 patients undergo a watch-and-wait approach after achieving cCR. With a median follow-up time of 48 months (Q25-Q75, 41-55 months), 57 deaths (33 and 24), 17 local failures (11 and 6) and 69 distant metastases (37 and 32) were observed, respectively. Overall, the 4y LC rate were 93% and 96% in control and experimental groups, with estimated LC HR of 0.53 (95% confidence interval [CI], 0.20-1.43), the 4y DFS rates were 69% and 74% (HR = 0.74, 95% CI 0.49-1.10), and the 4y OS were 80% and 85%, (HR = 0.70, 95% CI 0.42-1.19), respectively. In the subgroup analysis, irinotecan showed a significant improvement in DFS (HR = 0.77, 95% CI 0.61-0.98) and OS (HR = 0.71, 95% CI 0.51-0.98) in UGT1A1 *1*1 patients. **Conclusions:** The addition of irinotecan to standard capecitabine-based CRT had a tendency towards improving LC, DFS, and OS, but without reaching statistical significance. UGT1A1 *1*1 patients seem to benefit the most from irinotecan. Molecular studies and subsequent therapies should be considered. Clinical trial information: NCT02605265. Research Sponsor: National Natural Science Foundation of China, Natural Science Foundation of Shanghai.

3604 **Poster Session**

Impact of radiotherapy for local control in T3 N0 rectal cancer managed with total mesorectal excision: A systematic review and meta-analysis. *First Author: Jesus C. Fabregas, Billings Clinic Cancer Center, Billings, MT*

Background: Total mesorectal excision (TME) significantly improved rectal cancer outcomes. Radiotherapy (RT) is recommended for T3N0 rectal cancers, though benefit has not been demonstrated in combination with TME for this specific population. This meta-analysis could provide evidence to ameliorate toxicities from treatment. **Methods:** Randomized clinical trials and observational studies published until October 18, 2020 were identified via PubMed and Embase. *Objective:* To determine whether RT decreased the risk of local recurrence (LR) in T3N0 rectal cancer managed with TME. *Study Selection and Extraction:* Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were observed for literature search, extraction, and screening. Studies with LR data specific to T3N0M0 rectal cancer, treated with and without RT, were included. Reviews, non-English articles, and non-TME studies were excluded. Newcastle Ottawa Scale (NOS) evaluated quality. Meta-analysis was done with a random-effects model. *Main outcome:* Meta-analysis of the relative risk of LR was conducted. **Results:** 7,246 studies were screened, 134 full-text studies assessed for eligibility, 5 studies were included in the final analysis. No randomized data reported results specific to our study population. Five retrospective cohort studies involving 932 participants reported LR outcomes. The median follow-up ranged from 38.4 months up to 71 months. Four studies took place in Asia (797 participants) and one in North America (135 participants) (Table). Quality according to NOS ranged from 7–9. The estimated average relative risk for LR at 5 years was 0.63 (95% CI 0.31–1.29; I^2=41.8%) when RT was used. **Conclusions:** This meta-analysis' supports that there is no clear benefit to LR with the addition of RT in T3N0 patients with rectal adenocarcinoma undergoing TME. As meta-analysis was limited to retrospective cohort studies, there is concern for bias. Registration Prospero number CRD42020216058. Research Sponsor: None.

Characteristics of included studies.

Trial	Country	Accrual Time	Design	N Participants	Population	Intervention	Comparator	Median Follow-up (m)	Outcomes
Delaney et al. 2002	USA	1980-2001	Retrospective Cohort	135	pT3NXM0 adenoca, <8cm from AV	Neoadj RT + TME	TME	41	5yr LR 5yr OS
Kim et al. 2010	South Korea	1996-2004	Retrospective Cohort	151	pT3N0 adenoca	TME + Adj RT + Adj Ctx	TME + Adj Ctx	78	5yr LR 5yr OS
Lin et al. 2019	China	2010-2014	Retrospective Cohort	272	cT3N0M0 adenoca	Neoadj RT + TME + Adj Ctx	TME ± Adj CRT + Ctx	*38.4–46.3*	2yr LR 3yr OS
Peng et al. 2019	China	2005-2015	Retrospective Cohort	121	pT3N0M0 adenoca, <7cm from AV	TME + Adj CRT ± Adj Ctx	TME + Adj Ctx	*56.4–57.1*	3yr 5yr LR
Baek et al. 2020	Korea	2003-2012	Retrospective Cohort	365	pT3N0M0 adenoca, negative margins	TME + Adj CRT	TME ± Adj Ctx	71	3yr 5yr OS 5yr LR 5yr OS

AAdj Ctx: Adjuvant Chemotherapy. CRT: chemoradiation.

3605 **Poster Session**

H101 treatment of hepatic metastasis of colorectal cancer with recombinant human adenovirus 5 injection: A phase I clinical trial-TROJAN 021. *First Author: Yang He, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China*

Background: Recombinant human adenovirus serotype 5 injection (H101), obtained through genetic engineering to delete the E1B domain and part of the E3 domain and then selectively replicated in tumor cells, has been approved in 2005 for the local treatment of nasopharyngeal carcinoma and head and neck cancers. This trial aimed to evaluate the safety and the preliminary treatment efficacy of H101 combined with standard treatments in patients with liver metastases from colorectal cancer. **Methods:** In this phase 1, dose-escalation trial (ChiCTR1900027922), 17-75 years old colorectal cancer patients with unresectable liver metastases that failed to first-line therapy were included at The Tenth People's Hospital Affiliated to Tongji University between 2018.9 and 2020.12. All patients received H101 combined with standard therapy (bevacizumab + mFOLFOX6/FOLFIRI). Ultrasound-guided injection of H101 into the liver metastases was performed for all patients, with one of the following doses: 5×10^{11} vp/injection for the low, 1×10^{12} vp/injection for the moderate, 2×10^{12} vp/injection for the moderate-high, and 3×10^{12} vp/injection for the high dose groups. Intravenous infusion of bevacizumab (5 mg/kg) and administration of standard-dose mFOLFOX6 or FOLFIRI within 48 h after the intratumor injection was performed. The primary endpoint of the trial was the maximum tolerated dose (MTD). The secondary endpoints included safety, tumor responses, and tumor marker CEA. The adverse events (AEs) were monitored according to the NCI Common Terminology Criteria for Adverse Events (CTCAE, Version 3.0) and evaluated within 1 week after injection. Imaging examinations were performed for all patients to evaluate the tumor responses, according to the irRECIST. **Results:** Finally, 8 patients were included; the numbers of patients in the 4 groups were 1, 3, 3, and 1, respectively. MTD was not observed in this study. No grade $>$4 AEs were observed. The major AE included fatigue (5/8), fever (4/8), shiver (3/8), abdominal pain (3/8), and night sweat (3/8). The tumor responses included partial response in one patient (moderate dose group), stable disease in 6 patients (1, 1, 3, and 1 in the low, moderate, moderate-high, and high dose groups, respectively), and progressive disease in 1 patient (moderate group). No dose-effect response was found. The tumor marker CEA was reduced in 6 of the 8 patients, including 1 (1/1), 3 (3/3), 2 (2/3), and 0 patients in the low, moderate, moderate-high, and high-dose groups, respectively. **Conclusions:** The safety of H101 combined with standard therapy for liver metastases from colorectal cancer is acceptable, which also shows certain preliminary efficacy. The phase 2 trial is now ongoing. Clinical trial information: ChiCTR1900027922. Research Sponsor: Shanghai Science and Technology Commission Industry-University-Research Medical Project (No: 18DZ1910102).

DLT.

DLT	Low dose (n=1)	Moderate dose (n=3)	Moderate-high dose (n=3)	High dose (n=1)	Total (n=8)
Fatigue	0	3	1	1	5
Fever	0	2	1	1	4
Shiver	0	2	0	1	3
Abdominal pain	0	0	2	1	3
Night sweat	0	1	1	1	3

3606 **Poster Session**

Accurate early-stage colorectal cancer detection through analysis of cell-free circulating tumor DNA (ctDNA) methylation patterns. *First Author: James M. Kinross, Section of Biosurgery & Surgical Technology, Department of Surgery & Cancer, Imperial College London, London, United Kingdom*

Background: Colorectal cancer (CRC) screening programs suffer from poor uptake and biomarkers have limited diagnostic accuracy. The measurement of the methylation status of tumor-derived cell-free DNA in plasma may address these challenges. We used a targeted methylation panel, tumor-derived signal deduction and machine learning algorithm to refine a blood test for the detection of early-stage CRC. **Methods:** This was a prospective, international multicenter observational cohort study. Plasma samples were collected either prior to a scheduled colonoscopy as part of standard colorectal cancer screening or prior to colonic surgery for primary CRC. Differentially methylated regions (DMRs) were initially selected by analyzing CRC and control tissue samples with whole genome bisulfite sequencing. A targeted sequencing assay was designed to capture these DMRs in plasma ctDNA. Individual sequencing reads were evaluated for cancer-specific methylation signal and scores calculated for each DMR in a sample. A panel of methylation scores originating from 203 DMRs was used in a prediction model building and validated in a test cohort of patients. **Results:** Calculated scores were used to train a machine learning model on 68 ctDNA samples from 18 early stage (I-II) and 16 late-stage (III-IV) CRC patients and 34 age, BMI, gender and country of origin matched neoplasia-free controls (median age 63 [50-74], mean BMI 27 [19.5-37], female 50%, Spanish and Ukrainian population, distal cancers 50%). This model was then applied to an independent set of subjects from Spanish, Ukraine and Germany, including 36 stage I-IV cancer patients (median age 61.5 [55-82], BMI 28 [16-39], female 47%, 42% of the tumors were distal) and 159 age and sex matched controls. 87 of the control patients had a negative colonoscopy finding (cNEG), 19 had hyperplastic polyps (HP), 37 had small non-advanced adenomas (NAA) and 16 were diagnosed with other benign gastrointestinal diseases (GID). The model correctly classified 92% (33/36) of CRC patients. Sensitivity per cancer stage ranged from 83% (5/6) for stage I, 92% (11/12) for stage II, 92% (12/13) for stage III to 100% (5/5) for stage IV. Specificity of the model was 97% (154/159), with 100% (37/37) NAA, 94% (15/16) GID, 95% (18/19) HP and 97% cNEG patients correctly identified. Lesion location, gender, BMI, age and country of origin were not significantly correlated to prediction outcome. **Conclusions:** Methylation sequencing data analyzed using read-wise scoring approach combined with a machine-learning algorithm is highly diagnostic for early-stage (I-II) CRCs (89% sensitivity at 97% specificity). This method could serve as the basis for a highly accurate and minimally invasive blood-based CRC screening test with significant implications for the clinical utility of ctDNA in early-stage cancer detection. Research Sponsor: Universal Diagnostics S.L.

3607 **Poster Session**

A phase II study of capecitabine plus concomitant radiation therapy followed by durvalumab (MEDI4736) as preoperative treatment in rectal cancer: PANDORA study first-stage.

First Author: Stefano Tamberi, Ospedale per Gli Infermi, Faenza, Italy

Background: The combination of capecitabine plus long course radiotherapy (RT) is the standard preoperative therapy in cT3-4 cN+ rectal cancer. Pathologic Complete remission (pCR) can be considered as surrogate end point of efficacy of treatment in terms of disease free survival (DFS). Preclinical data points heavily toward a strong synergy between RT and immune treatments. **Methods:** This is a prospective phase II, open label, single arm, multi-centre study, conducted with support from AstraZeneca, in patient with locally advanced rectal cancer who receive concomitant CT/RT therapy (825 mg/m2 twice daily capecitabine every day and 5040 cGy radiotherapy for 5 days per week for 5 weeks) followed by durvalumab (1500 mg Q4W for 3 administrations). Surgery is performed after 10-12 weeks from neoadjuvant therapy. The primary endpoint is pCR rate after at least 1 cycle of durvalumab. The sample size has been estimated by using the optimal Simon's two-stage design. If more than 4 complete responses are observed in the first 19 enrolled patients, 36 additional patients will be accrued for a total of 55 evaluable patients. **Results:** Between November 2019 and July 2020, 20 patients were accrued and 19 were evaluable for study objectives, concluding the first stage of the trial. Baseline characteristics of the first 19 evaluable patients enrolled are listed in the table. All patients received 3 infusions of durvalumab; 18 patients underwent surgery after a median of 13 weeks from CHT/RT end. Five complete pathological responses (ypTON0) were observed, allowing to proceed to the second stage. About toxicity, four patients had Grade 3-4 adverse events (AE); the most frequent G3-4 AE related to the neoadjuvant therapy were anemia (n=1), diarrhea (n=2) and neutrophenia (n=2). No grade 3 and 4 adverse events related to Durvalumab treatment were observed. Eight patients had G1-2 AE related to durvalumab, the most common being asthenia (n=2) and nausea (n=2). **Conclusions:** At the end of study's first stage the preoperative treatment with radiotherapy plus capecitabine followed by durvalumab showed a safe toxicity profile and promising activity in terms of pCR rate. The second part of the trial is ongoing, and the accrual is under completion (44 patients enrolled as of 10 February 2021). Clinical trial information: NCT04083365. Research Sponsor: None.

Characteristic		n (%)
Gender	Female	13 (68.4)
	Male	6 (31.6)
Age	Median	63 years
	Range	35–81 years
ECOG PS	0	14 (73.7)
DRE result	1	5 (26.3)
	Palpable	10 (66.7)
	Not palbable	5 (33.3)
Clinical T stage	Not evaluable	4 (21)
	cTx	1 (5.3)
	cT3	13 (68.4)
Clinical N stage	cT4	5 (26.3)
	cN0	4 (21.0)
	cN1	11 (57.9)
EMVI	cN2	4 (21.1)
	Positive	5 (27.8)
	Negative	13 (72.2)
	Not evaluable	1 (5.3)

ECOG PS: Eastern Cooperative Oncology Group performance status; DRE: digital rectal exploration; cT: clinical tumor; cN: clinical node; T stage: tumor stage; N stage: nodal stage; EMVI: extramural vascular invasion.

3608 **Poster Session**

Minimal residual disease by circulating tumor DNA analysis for colorectal cancer patients receiving radical surgery: An initial report from CIRCULATE-Japan.

First Author: Hiroki Yukami, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Background: Circulating tumor DNA (ctDNA) analysis can be used to predict the risk of recurrence by detecting molecular residual disease (MRD) in patients with colorectal cancer (CRC). We are conducting a prospective observational study to monitor MRD status in patients with clinical stage II–IV or relapsed CRC amenable to radical surgical resection (GALAXY study), as part of the CIRCULATE-Japan, a nationwide ctDNA-guided precision adjuvant therapy project. **Methods:** Analysis of ctDNA is being performed at pre- and post-surgery timepoints and will continue periodically for up to 2 years using Signatera, a personalized, tumor-informed ctDNA assay that is designed to track 16 patient-specific somatic variants based on whole-exome sequencing of tumor tissue. The association of peri-operative ctDNA status with clinicopathological characteristics was investigated. **Results:** As of January 13, 2021, 941 patients have been enrolled in the GALAXY study, of which 400 patients had their pre-operative ctDNA status evaluated. Of the 400 patients, baseline ctDNA was detected in 92% (367/400) of the patients: consisting of 35 patients with pathological stage (pStage) I, 135 with pStage II, 152 with pStage III, and 78 with pStage IV or relapsed disease (pStage IV/R). Patient-specific Signatera assays targeting 16 variants were designed for 100% of the patients. Out of the 6400 designed variants 99.3% passed quality control in the plasma analysis and produced the final results. Among 4425 genes selected for 400 patients, 3330 genes were selected for only one patient, while *TP53* was the most commonly selected in 113 patients (28%). Median ctDNA levels, measured in mean tumor molecules per mL of plasma and ctDNA detection rate, stratified by stage are presented in table. Positive ctDNA status post-surgery was significantly associated with advanced pStage, pT and pN, and lymphovascular invasion. Of the 13 patients with recurrence, 10 were detected with a positive ctDNA at 4-weeks post-surgery, before confirmation of recurrence by the radiological imaging. **Conclusions:** Preoperative ctDNA detection rates were observed to be in >90% in patients with pStage II–III by personalized ctDNA assay based on unique somatic variants, specific to each patient. ctDNA- based MRD detected post-surgery (4W) was significantly associated with certain known clinicopathological factors for recurrence with ctDNA positivity associated with a very short-term of recurrence. Clinical trial information: 000039205. Research Sponsor: Japan Agency for Medical Research and Development.

ctDNA levels and detection rates pre- and post-surgery (4 weeks).

	Pre-surgery		Post-surgery (4 weeks)	
pStage	**Median ctDNA (MTM/mL)**	**ctDNA detection rate**	**Median ctDNA (MTM/mL)**	**ctDNA detection rate**
Stage I	0.73	80%	0.92	6%
Stage II	3.66	96%	0.72	6%
Stage III	4.54	94%	0.46	25%
Stage IV/R	27.07	86%	1.81	32%

3609 **Poster Session**

Pharmacologic ascorbate enhances the therapeutic index of ATM-inhibitor based chemoradiation for colorectal cancer.

First Author: Cameron Callaghan, University of Iowa Hospitals and Clinics, Iowa City, IA

Background: Ataxia telangectasia mutated protein (ATM) is one of the key sensors of DNA damage and specific inhibitors of ATM are potent radiosensitizers. However, their clinical utility with radiation (RT) is limited because they lack tissue specificity and increase normal tissue injury. Pharmacologic (high dose) ascorbate ($P\text{-}AscH^-$) selectively increases oxidative stress in tumors while functioning as a donor antioxidant and reducing RT damage in normal tissues. We hypothesized that $P\text{-}AscH^-$ could enhance the therapeutic index of ATM-inhibitor based chemoradiation (CRT) for colorectal cancer (CRC) by simultaneously enhancing efficacy and reducing RT bowel injury. **Methods:** Human HCT116, SW480, and HT29 and murine CT26 and MC38 CRC models were used. Clonogenic survival was assessed following single-fraction RT (2-8 Gy) +/- $P\text{-}AscH^-$ (5 pM/cell) +/- veliparib (PARP), VE821 (ATR), or KU60019 (ATM). Catalase expression was induced using HCT116 cells expressing a doxycycline inducible catalase transgene. DNA double strand breaks (DSBs) were quantified using neutral comet assays 0-24 hours post RT. Cell cycle phases were assessed using flow cytometry. ATM and pATM localization were assessed using IF. Jejunal toxicity was assessed using IHC in fixed tissues following single fraction (10 Gy) whole abdominal RT in c57blj/6 mice. Tumor growth delay was assessed following RT (5 Gy x 3) +/- drug treatment in unilateral flank tumors. **Results:** Veliparib, VE821, and KU60019 were potent radiosensitizers in HCT116, SW480, HT29, MC38, and CT26 CRC tumor models and $P\text{-}AscH^-$ further reduced clonogenic survival with DRIs in all lines except for HT29. In contrast, $P\text{-}AscH^-$ enhanced survival of cultured HUVEC and FHs-74 cells exposed to RT. Enhanced cell kill with $P\text{-}AscH^-$ is H_2O_2 mediated as it is completely attenuated by inducible catalase expression. $P\text{-}AscH^-$ significantly increased the number of DNA DSBs in tumors after RT *in vitro*. Despite the increase in DNA DSBs, $P\text{-}AscH^-$significantly decreased nuclear localization of activated P-ATM after RT and significantly decreased the fraction of cells in G2/M phases of the cell cycle. *In vivo,* RT + $P\text{-}AscH^-$ + KU60019 induced more tumor growth delay/clearance than all other combinations in unilateral MC38 or HCT116 flank tumors. Finally, $P\text{-}AscH^-$ significantly reduced loss of jejunal crypt cell density, epithelial architecture, and markers of lipid and protein oxidation following whole abdominal RT. **Conclusions:** $P\text{-}AscH^-$ selectively enhances the efficacy of ATM-based CRT in CRC tumor models while simultaneously decreasing RT-mediated small bowel toxicity. In tumors, $P\text{-}AscH^-$ enhances DNA DSBs by stimulating an H_2O_2 flux and prevents activation of DNA repair pathways and cell cycle checkpoints by inhibiting RT-induced activation of ATM. Selective radioprotectors like $P\text{-}AscH^-$ could facilitate the clinical translation ATM inhibitors as radiosensitizers. Research Sponsor: RSNA Resident seed grant #RR1914.

3610 **Poster Session**

Evaluating longitudinal toxicity of cetuximab in patients with metastatic colorectal cancer (mCRC): A pooled analysis from 1,302 patients in the ARCAD database.

First Author: Guilherme Lopes, Mayo Clinic, Rochester, MN

Background: Chronic lower grade adverse events (AE) can negatively affect a patient's quality of life but it is difficult to capture using a traditional toxicity reporting approach. A novel AE reporting method was recently developed to describe, summarize, and present longitudinal AE profiles(Lopes et al, 2021). We leveraged this method to describe and compare the AE profiles of doublet chemotherapy (DC) + Cetuximab and DC alone in mCRC patients. **Methods**: This AE reporting method utilizes two additional AE metrics to complement the maximum (max) toxicity grade usually reported in clinical trials. Onset time indicates the time period in which max grade for an AE occurred for the first time, defined here as "early" (i.e. within first 42 days) and "late" (i.e. after the 42^{nd} day). AE Load (AEL) indicates the overall severity of an AE in the entire treatment. AEL varies from 0 to 1. Higher AEL indicates a worse overall severity of that AE over time. AEL is the key metric for describing chronic AE. We included patients receiving DC + cetuximab (n = 738) and DC alone (n = 564 [ref group]) from two randomized first-line trials in the ARCAD database. Diarrhea, rash, hand-foot syndrome (HFS), fatigue, anorexia, and mucositis were examined and adjusted for backbone (FOLFOX vs. FOLFIRI), ECOG PS, sex, site location, dose reduction, and treatment length. **Results**: For rash, DC + cetuximab had a higher risk of G3+ (21% vs. 0.5%; odds ratio {OR} [95% confidence interval {CI}] = 50 [16,157], $p < 0.001$), increased overall severity over the entire treatment (AEL = 0.257 vs. 0.069; Adjusted difference in means–M_{diff} [95% CI] = 0.22 [0.21,0.23] , $p < 0.001$), and increased risk of early onset (67% vs. 33%; OR [95% CI] = 4.3 [2.7,6.7] , $p < 0.001$). DC + cetuximab also had higher AEL for rash across max grades ($p < 0.001$ within G1, G2, and G3+). For HFS, DC + cetuximab had a higher risk of G3+ (OR [95% CI] = 6.0 [2.5,14], $p < 0.001$), increased overall severity (AEL = 0.139 vs. 0.087; M_{diff} [95% CI] = 0.03 [0.03,0.04], $p < 0.001$), and slightly earlier onset (12.4 vs. 13.9 weeks; M_{diff}, weeks [95% CI] = -4.9 [-0.80,-9.0], p = 0.021). Within each max grade, DC + cetuximab did not have higher AEL of HFS. No associations were found for diarrhea, fatigue, anorexia, or mucositis. **Conclusions**: The addition of cetuximab is associated with higher grade, more persistent, and more immediate rash. The higher severity in HFS with the addition of cetuximab appears to be related to higher grade but not chronic HFS. This method may be useful to describe different strategies, e.g. intermittent cetuximab. It provided a comprehensive view of acute and chronic toxicity profiles supporting its potential interest as new metrics in clinical trials. Lopes GS, Tournigand C, Olswold CL, et al. Adverse event load, onset, and maximum grade: A novel method of reporting adverse events in cancer clinical trials. Clinical Trials. 2021;18(1):51-60 Research Sponsor: None.

3611 **Poster Session**

Influence of preoperative chemoradiation on tumor-infiltrating lymphocytes in locally advanced rectal cancer: The STAR-01 cohort. *First Author: Francesca Negri, University Hospital of Parma, Parma, Italy*

Background: Preoperative chemoradiotherapy may increase antitumor immunity through enhancing T-cell activation and tumor infiltration. These effects could possibly sensitize tumors to immunotherapies, including checkpoint inhibitors. We explored whether preoperative chemoradiation for locally advanced rectal cancer induces immunologic changes and if the post-operative biological parameters are associated with tumor regression grade (TRG sec. Ryan –AJCC Eight ed.). **Methods:** The multicenter STAR-01 study compared a standard preoperative chemoradiotherapy regimen (50.4 Gy in 28 daily fractions with concomitant infused fluorouracil at the dose of 225 mg/m^2/d) with the same regimen plus oxaliplatin given weekly at the dose of 60 mg/m^2 in patients with locally advanced rectal cancers. Paired pre- and post-operative specimens were available for 58 patients from this trial and were analyzed by immunohistochemistry. The immunoistochemical analysis was performed with a panel of immune cells and associated factors as CD3, CD20, CD4/CD8, PD1. The pattern of tumor infiltrating lymphocytes (TILs) and related infiltrating lymphocytes (RILs) was also evaluated. Response to pre-operative chemoradiotherapy was assessed according to TRG. **Results:** After therapy we observed a decreased CD4/CD8 ratio ($p < 0.001$) and reduced expression level of CD20 ($p < 0.001$). The expression level of CD3+ and PD-1+ cells after therapy did not change significantly. The relative increase of lymphocytes CD8+ inside CD4/CD8 ratio evaluated on post-operative samples was significantly associated with TRG 0 ($p < 0.001$). **Conclusions:** Our data suggest that chemoradiation may induce an enrichment of CD8+ T lymphocytes and this translates in better response to chemoradiation. The new frontier of best treatment could be the use of specific immune cells (T lymphocytes) to trigger the system's immune response against disease. Research Sponsor: SNUPI Onlus.

3612 **Poster Session**

Impact of the COVID-19 pandemic in treating gastrointestinal (GI) cancer patients receiving systemic anticancer treatment (SACT): The Guy's Cancer Centre experience. *First Author: Jose Roca, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom*

Background: The COVID-19 pandemic has hugely affected the spectrum of cancer care. Worldwide healthcare systems have rapidly reorganized cancer services to ensure patients continue to receive essential care whilst optimizing the use of systemic anti-cancer treatments (SACT) and minimizing exposure to SARS-CoV-2 infection. Our study aimed to identify the outcome of patients with gastrointestinal (GI) cancers in our Cancer Centre during the pandemic compared to the same period in 2019. **Methods:** Retrospective analysis of all GI patients receiving any SACT at Guy's Cancer Centre from the 1 March-31 May 2020 and 2019. Demographic data (age, ethnicity, socio-economic status (SES), Performance status, cancer and SACT characteristics (type, intent and treatment-line) were collected during both periods. Also we collated the number of COVID-19 infections confirmed by PCR and severity defined by the WHO classification. Patients with clinical or radiological diagnosis were excluded. **Results:** 567 patients received SACT in 2019 and 417 patients in 2020 (26.4% less). No differences were observed in the demographic or tumour type characteristics. Commonest cancers in both periods were similar: colorectal (47.1, 47%), oesophago-gastric (29, 27.6%), pancreatic-biliary and NET tumours (23.8, 25.4%). However, there were a higher proportion of patients with advanced disease treated in 2020 (70.3% versus 55.2%). Treatment intent was similar in both years: radical (3.5 vs 3.8%), adjuvant (18.2% vs 17.3%), neoadjuvant (15.3% vs 12.7%) and palliative (63% vs 66.2%). There was an increase in the proportion of patients treated in the palliative first line setting (63.8% in 2020 vs 47.6% in 2019) and a reduction in the proportion of third or more treatment (8.7% versus 16.2%) mainly in the colorectal patients. Of 417 GI patients receiving SACT, 14 (3.35%) were diagnosed with COVID-19 infection. Of these, 64.3% were male, 92.9% were low SES and 35.7% were of Caucasian ethnicity. Colorectal cancer was the commonest (57.1%) tumour-type in the COVID-positive group and 57.1% had advanced disease. All the patients that died from COVID-19 were male. 13 patients were on chemotherapy and 1 was on targeted/biological treatment. None was in immunotherapy (n=4). Only one patient was neutropenic (grade 1). 8 patients (57.1%) had severe infection and there were 3 (21.4%) COVID-related deaths. **Conclusions:** Our study shows the delivery of SACT through the COVID-19 pandemic is relatively safe with low COVID-related mortality rate. It also reflects how we tailored the delivery of anti-cancer treatments to reduce the possible detrimental myelo-suppressive toxicities that could potentially put GI patients at higher risk of severe SARS-CoV-2 infection. This is crucial data that can inform anti-cancer treatment decision making during the protracted COVID-19 pandemic. Research Sponsor: None.

3613 **Poster Session**

Multi-omics longitudinal analyses in stages I to III CRC patients: Surveillance liquid biopsy test to predict early recurrence and enable risk-stratified postoperative CRC management. *First Author: Xuanhui Liu, Guangdong Provincial Key Laboratory of Colorectal and Pelvic Floor Diseases, The Sixth Affiliated Hospital of Sun Yat-sen University, Guangzhou, China*

Background: One-third of colorectal cancer (CRC) recurs following curative surgery and chemotherapy. Accordingly, novel methods are needed to predict recurrence to enable clinical course mitigating strategies. Serial monitoring of plasma by mass spectrometry (MS) and multi-omics modeling (MMO) of CRC relapse chronology provide the framework for liquid biopsy test development to supersede existing imaging modalities such as CT scans according to relapse related pathologies. We hypothesized that plasma MS and MMO analysis of relapse related pathologies can deconvolute high risk stratification for CRC recurrence within the cancer continuum of care pre/post-surgery and/or pre/post adjuvant chemotherapy (ACT). **Methods:** 189 CRC patients (Stage I-III) underwent one of three treatment modalities: Modality 1 (Surgery followed by ACT), Modality 2 (Surgery only), Modality 3 (Neoadjuvant chemotherapy followed by surgery and ACT). Plasma samples (n = 441) were collected from patients before surgery, 30 days post-op, and every 3 months until death or month 24 whichever came first. The MMO approach was used to analyze biological features encompassing native peptides, proteins, metabolites, lipids, and ceramides. MMO panels were developed comprising the significantly perturbed features as per the treatment modalities. These panels were used to predict relapse from plasma collected pre-op, 30-day post-op or after adjuvant chemotherapy. CEA levels were monitored in parallel. **Results:** Follow-up data was available for 135 patients (Stage I-III) and 25/135 had evidence of radiological recurrence. Irrespective of the treatment modality, longitudinal follow-up using the MMO panel was able to predict disease recurrence greater than 7 months before clinical progression was confirmed by CT scan. There was no significant correlation between longitudinal CEA levels and recurrence status, hence CEA levels alone did not provide any lead time advantage over the MMO panel or radiological surveillance. Kaplan-Meier (KM) survival analysis revealed that patients that were MMO panel positive had a poor survival irrespective of treatment modalities used: Modality 1 (HR = 6.2, p value = 0.003, test immediately post-surgery and immediately before ACT; HR = 31.6, p value = 0.01, test immediately after ACT); Modality 2 (HR = 11.2; p value = 0.01, test immediately after-surgery); Modality 3 (HR $>$ 40, p value = 0.08, test immediately after neo-ACT and before-surgery; HR $>$ 40, p value = 0.004, test immediately after-surgery). **Conclusions:** The MMO panel predicts CRC recurrence several months prior to detection by conventional CT scans, thus providing opportunity for alternative therapeutic strategies much earlier in the disease course. Research Sponsor: National Natural Science Foundation of China (No.81972212), Guangdong Natural Science Foundation of China (No. 2019A1515010063).

TPS3614 **Poster Session**

A randomized phase III study of immune checkpoint inhibition with chemotherapy in treatment-naive metastatic anal cancer patients: A trial of the ECOG-ACRIN cancer research group (EA2176). *First Author: Marc Thomas Roth, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: Anal cancer is growing in annual incidence globally and human papillomavirus (HPV) remains the predominant risk factor underlying its development. Due to its relative rarity, clinical trials in anal cancer have historically been difficult to conduct and treatment options for metastatic disease remain limited. Carboplatin/paclitaxel (CP) was compared to cisplatin/5-fluorouracil (historical standard of care) in a recent randomized phase II clinical trial (InterAACT; EA2133) in treatment-naïve metastatic anal cancer, finding that response rates were equivocal, but that overall survival (OS) was significantly longer in the CP arm (20 months vs 12.3 months, p = 0.014). Additionally, reduced grade 3/4 toxicities were seen in the CP arm. NCI9673, a single-arm phase II study, established safety and efficacy of nivolumab in previously-treated metastatic anal cancer. Progression-free survival (PFS) was 4.1 months (95% CI 3.0-7.9) and OS was 11.5 months (95% CI 7.1-not estimable). Multiple randomized trials in lung cancer have demonstrated efficacy of platinum-based chemotherapy combined with checkpoint inhibitors. Together these studies form the rationale behind combining CP and nivolumab in treatment-naïve metastatic anal cancer. **Methods:** EA2176 (NCT04444921) is the first NCTN phase III randomized clinical trial in treatment-naïve metastatic anal cancer. Stratification factors include HIV status and history of chemoradiation for curative intent. Patients will be randomized to carboplatin (AUC = 5, Day 1) plus paclitaxel (80mg/m2, Days 1, 8, 15) +/- nivolumab 240mg IV (Cycle 1 = Days 1, 15; Cycle $\geq$2 = Day 1, 480mg) q 28-days until disease progression or treatment intolerance. CP will be given for up to 6 cycles, while nivolumab will be continued as maintenance for up to 2 years. The primary endpoint is PFS. Secondary objectives include OS, response rate, and toxicity. Goal enrollment is 205 patients and the study continues accrual. This sample size will provide 80% power at a two-sided α of 0.05 to detect a 4.8-month improvement in PFS assuming 8 months in the control arm. Novel correlative studies include sequential quantitative tumor-derived cell-free HPV ctDNA levels (serotypes 16 and 18; Sysmex-Inostics SafeSEQ NGS assay). Correlative funding provided in part by the Farrah Fawcett Foundation and Sysmex Inostics, Inc. Clinical trial information: NCT04444921. Research Sponsor: NCI/CTEP, Other Foundation, Pharmaceutical/Biotech Company.

TPS3615 **Poster Session**

Total neoadjuvant treatment versus standard chemoradiation to increase the sphincter preservation rate for distal locally advanced rectal cancer (TESS). *First Author: Weiwei Xiao, Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China*

Background: Standard treatment of rectal cancer is neoadjuvant capecitabine chemotherapy with radiotherapy, followed by total mesorectal excision (TME). Total neoadjuvant treatment (TNT), a new concept, suggests organ preservation as an alternative to rectal excision in good responders after neoadjuvant chemoradiotherapy to decrease surgical morbidity and increase quality of life. RAPIDO and PRODIGE-23 trials showed that TNT strategy could improve the pathological complete response (pCR) rateand reduce the risk of distant metastasis. The objective of this trial is to increase the proportion of sphincter preservation rate for distal rectal cancer patients by optimizing tumor response, by using TNT regimen as compared to conventional chemoradiotherapy. TESS (clinicalTrials.gov, NCT03840239), a prospective, open label, multicenter, randomized phase 2 study, is underway. **Methods:** Main inclusion criteria include: cT3-4aNany or cTanyN+ rectal adenocarcinoma aged 18-70y; ECOG performance 0-1; distance≤5cm from anal verge. 168 patients will be randomized 1:1. Patients in the TNT group will receive 2 cycles of neoadjuvant chemotherapy Capeox (capecitabine + oxaliplation) before, during and after radiotherapy 50Gy/25 fractions, before TME (or other treatment decisions, such as watch and wait) and adjuvant chemotherapy capecitabine 2 cycles. Patients in the standard treatment group will receive neoadjuvant radiotherapy 50Gy/25 fractions combined with capecitabine 5 weeks before TME (or other treatment decisions, such as watch and wait), and adjuvant chemotherapy Capeox 6 cycles. Primary endpoint is the rate of sphincter preservation rate (absence of stoma). Secondary endpoints include: Ratio of sphincter preservation strategy; pathological complete response rate and tumor regression grade distribution; acute toxicity; surgical complications; long-term anal function; late toxicity; ECOG standard score; disease-free survival; overall survival. First site opened in January 24, 2019. Clinical trial information: NCT03840239. Research Sponsor: the 5010 Clinical Research Foundation of Sun Yat-sen University.

TPS3616 **Poster Session**

PERSPECTIVE: Tepotinib + cetuximab in patients (pts) with *RAS*/*BRAF* wild-type left-sided metastatic colorectal cancer (mCRC) and acquired resistance to anti-EGFR antibody therapy due to *MET* amplification (*MET*amp). *First Author: Tanios S. Bekaii-Saab, Mayo Clinic, Phoenix, AZ*

Background: *MET*amp is a secondary, or co-driving, genetic change in pts with mCRC and acquired resistance to anti-EGFR therapy, which can contribute to disease progression. In EGFR-resistant pts with mCRC and *MET*amp, MET inhibition + an anti-EGFR agent may achieve disease control by targeting emerging MET pathway activation and maintaining EGFR pathway inhibition. Tepotinib is an oral, once-daily, highly selective, potent MET tyrosine kinase inhibitor (TKI), recently approved in the US for NSCLC harboring *MET* exon 14 skipping. Tepotinib + gefitinib demonstrated improved outcomes in pts with *EGFR*-mutant *MET*amp NSCLC and acquired EGFR TKI resistance vs chemotherapy (INSIGHT: NCT01982955). In these pts, progression-free survival (PFS) was 16.6 vs 4.2 months (HR = 0.13; 90% CI: 0.04, 0.43) and overall survival (OS) was 37.3 vs 13.1 months (HR = 0.08; 90% CI: 0.01, 0.51). In pts with mCRC and acquired resistance to anti-EGFR antibody therapy due to *MET*amp, tepotinib + anti-EGFR antibody cetuximab may be active and provide an effective therapeutic option. **Methods:** This Phase II, multicenter, single-arm, open-label study will assess preliminary safety and tolerability, antitumor activity, and explore pharmacokinetic (PK) profiles of tepotinib + cetuximab in pts with *RAS/BRAF* wild-type left-sided mCRC and acquired resistance to anti-EGFR antibody-targeted therapy due to *MET*amp (NCT04515394). A safety run-in (6–12 pts) will evaluate the recommended Phase II dose of tepotinib to be used in combination with cetuximab (endpoint: dose-limiting toxicities). Enrollment is based on a confirmed advanced left-sided CRC diagnosis (*RAS/BRAF* wild-type), documented previous anti-EGFR therapy and acquired resistance on most recent anti-EGFR antibody and *MET*amp confirmed by liquid and/or tissue biopsy. Pts must be ≥18 years old, have ECOG PS of 0/1 and normal organ function. The study will screen sufficient pts to account for setting-specific heterogenecity in reported *MET*amp incidence. Approximately 42 pts are planned to receive study treatment: ~22 in Cohort A (second-line, outside US) and 20 in Cohort B (≥third-line, US only). Primary endpoint: investigator-assessed objective response (RECIST 1.1). Secondary endpoints are investigator-assessed duration of response (DoR), PFS (RECIST 1.1) and OS, tolerability and safety (NCI-CTCAE v5.0), and cetuximab immunogenicity (measured by antidrug antibody assays at the start and end of treatment). Additional endpoints include assessment of tepotinib and cetuximab PK profiles, and expression of biomarkers of resistance (from blood and/or tissue samples). Retrospective assessment of best overall response, DoR and PFS by an independent review committee may be conducted. No formal statistical hypothesis will be tested in this exploratory study. Clinical trial information: NCT04515394. Research Sponsor: Merck KGaA, Darmstadt, Germany.

TPS3618 **Poster Session**

Colorectal Cancer Metastatic dMMR Immuno-Therapy (COMMIT) Study: A randomized phase III study of atezolizumab (atezo) monotherapy versus mFOLFOX6/bevacizumab/atezo in the first-line treatment of patients (pts) with deficient DNA mismatch repair (dMMR) or microsatellite instability high (MSI-H) metastatic colorectal cancer (mCRC)—NRG-GI004/SWOG-S1610. *First Author: Michael J. Overman, University of Texas MD Anderson Cancer Center, and SWOG, Houston, TX*

Background: The superiority of inhibition of programmed cell death-1 (PD-1) pathway in dMMR/MSI-H over chemotherapy with either anti-vascular endothelial growth factor receptor (VEGFr) or anti- epithelial growth factor receptor (EGFr) antibodies in mCRC has been demonstrated in a phase III trial (N Engl J Med 2020; 383:2207). However, more patients had progressive disease as the best response in the anti-PD1 monotherapy arm (29.4% vs. 12.3%) with mean progression-free survival (PFS) of 13.7 months. Preclinical models have demonstrated synergistic interactions between FOLFOX, anti-VEGF, and anti-PD-1. We hypothesize that the dMMR/MSI-H mCRC patients may be more effectively treated by the combination of PD-1 pathway blockade and mFOLFOX6/bevacizumab (bev) rather than with anti-PD-L1 therapy (atezo) alone. **Methods:** Initially a three-arm study, the mFOLFOX6/bev arm was closed to new enrollment on 6-4-20 due to emerging data; the redesigned COMMIT trial was reactivated on 1/29/2021 as a prospective phase III open-label trial that randomizes (1:1) mCRC dMMR/MSI-H pts (N=211) to either atezo monotherapy or mFOLFOX6/bev+atezo combination. Stratification factors include BRAFV600E status, metastatic site, and prior adjuvant CRC therapy. Primary endpoint is PFS as assessed by site investigator. Secondary endpoints include overall survival (OS), objective response rate (RECIST v1.1), safety profile, disease control rate, duration of response, and centrally-reviewed PFS. Health-related quality of life is an exploratory objective. Archived tumor tissue and blood samples will be collected for correlative studies. Key inclusion criteria are: mCRC without prior chemotherapy for advanced disease; dMMR tumor determined by local CLIA-certified IHC assay (MLH1/MSH2/MSH6/PMS2) or MSI-H by local CLIA-certified PCR or NGS panel; and measurable disease per RECIST. Clinical trial: NCT02997228. Support: U10CA180868, -180822, -180888, -180819, UG1CA189867, U24CA196067; Genentech, Inc. Clinical trial information: NCT02997228. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS3619 **Poster Session**

BREAKWATER: Randomized phase 3 study of encorafenib (enco) + cetuximab (cetux) ± chemotherapy for first-line (1L) treatment (tx) of *BRAF* V600E-mutant (*BRAF*^{V600E}) metastatic colorectal cancer (mCRC). *First Author: Scott Kopetz, MD Anderson Cancer Center, Houston, TX*

Background: Approximately 10% of patients (pts) with mCRC have *BRAF* mutations (mostly V600E). 1L tx options for *BRAF*^{V600E} mCRC are limited to cytotoxic chemotherapy ± anti-VEGF or anti-EGFR, or immune checkpoint inhibitors in pts with MSI-H tumors. In Europe, Japan, and USA, the combination of BRAF inhibitor enco + EGFR inhibitor cetux is approved for tx of *BRAF*^{V600E} mCRC after prior therapy. In BEACON CRC, enco + cetux resulted in a median overall survival (OS) of 9.3 months (95% confidence interval [CI]: 8.0–11.3) and an objective response rate (ORR) of 19.5% (95% CI: 14.5%–25.4%) in previously treated pts with *BRAF*^{V600E} mCRC (median follow-up: 12.8 months); 57.4% of pts had grade 3/4 adverse events (AEs); 9% discontinued due to AEs. Given the poor prognosis of pts with *BRAF*^{V600E} mCRC and based on the efficacy and tolerability of enco + cetux from BEACON CRC, BREAKWATER will evaluate efficacy and safety of enco + cetux ± chemotherapy in tx-naive pts with *BRAF*^{V600E} mCRC. **Methods:** BREAKWATER is an open-label, global, multicenter, randomized, phase 3 study with a safety lead-in (SLI). Approximately 60 and 870 pts will be enrolled in the SLI and phase 3 parts of the study, respectively. Pts must have *BRAF*^{V600E} mCRC (determined using tumor tissue or blood); ECOG performance status 0/1; and adequate bone marrow, hepatic, and renal function. Pts in the SLI must have evaluable disease (RECIST v1.1) and have received ≤ 1 prior tx regimen; those previously treated with a BRAF or EGFR inhibitor, or both oxaliplatin and irinotecan, will be excluded. Pts in the phase 3 study must have measurable disease and be tx naive for metastatic disease. Study tx and endpoints are shown in the table. Enrollment began on 6 January 2021. Clinical trial information: NCT04607421. Research Sponsor: Pfizer.

	SLI	Phase 3
Tx*	Enco 300 mg QD + cetux 500 mg/m^{2†} + mFOLFOX6† or Enco 300 mg QD + cetux 500 mg/m^{2†} + FOLFIRI†	Arm A Enco 300 mg QD + cetux 500 mg/m^{2†} Arm B Enco 300 mg QD + cetux 500 mg/m^{2†} + mFOLFOX6† or FOLFIRI† (depending on SLI) Control (± bevacizumab) mFOLFOX6† or FOLFOXIRI† or FOLFIRI† or CAPOX (21-day cycle; oxaliplatin, Q3W; capecitabine, BID Days 1–14)
Endpoints		
Primary	Incidence of dose-limiting toxicities	Progression-free survival (PFS; by blinded independent central review [BICR]) (arm A vs control; arm B vs control)
Secondary	Incidence/severity of AEs, ORR, duration of response (DOR), PFS, time to response (TTR), OS, pharmacokinetic (PK) parameters, drug–drug interaction of enco with irinotecan/oxaliplatin	**Key:** OS (arm A vs control; arm B vs control) **Other**: ORR, DOR, PFS (arm A vs arm B by BICR; arm A vs control; arm B vs control; arm A vs arm B by investigator), OS (arm A vs arm B), TTR, progression after next tx line, incidence/severity of AEs, pt-reported outcomes, PK parameters, MSI status, *BRAF* V600E variant allele fraction

*All 28-day cycles except CAPOX; † Q2W.

TPS3620 **Poster Session**

Trastuzumab deruxtecan in patients with HER2-overexpressing locally advanced, unresectable, or metastatic colorectal cancer (mCRC): A randomized, multicenter, phase 2 study (DESTINY-CRC02). *First Author: Kanwal Pratap Singh Raghav, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Trastuzumab deruxtecan (T-DXd) is an antibody–drug conjugate consisting of an anti-HER2 antibody (trastuzumab) linked to a potent topoisomerase I inhibitor (DXd). T-DXd has been approved to treat HER2-positive metastatic breast cancer (United States, Japan, Europe) and advanced gastric cancer (United States, Japan). It is currently being evaluated in other solid tumor types including colorectal cancer. The phase 2 DESTINY-CRC01 study included patients with *RAS* wild-type mCRC, with median 4 (range, 2-11) prior lines of therapy. Preliminary results in patients with HER2-overexpressing (IHC 3+ or IHC 2+/ISH+) mCRC showed T-DXd treatment (6.4 mg/kg intravenously [IV] every 3 weeks [Q3W]) resulted in a confirmed objective response rate (ORR) of 45.3% (24/53; 95% CI, 31.6%-59.6%) and a median progression-free survival (PFS) of 6.9 months (95% CI, 4.1 months-not evaluable; Siena *J Clin Oncol.* 2020;38[15]:4000). Activity was also seen in patients treated with prior anti-HER2 therapy. Although 5.4-mg/kg and 6.4-mg/kg doses of T-DXd have shown clinical efficacy in multiple cancer indications, the lower dose has not yet been tested in patients with HER2-overexpressing mCRC. Preliminary data also suggest T-DXd may be active in *RAS* mutant mCRC, unlike other anti-HER2 therapies. The DESTINY-CRC02 study aims to determine efficacy and safety of T-DXd in patients with HER2-overexpressing, *RAS* wild-type or mutant mCRC at 5.4-mg/kg and 6.4-mg/kg doses. **Methods:** DESTINY-CRC02 (NCT04744831) is a multicenter, randomized, double-blind, 2-arm, parallel phase 2 study that will be conducted in 2 stages. Eligible patients (≥18 years; ≥20 years in Japan, Taiwan, and Korea) will have HER2-overexpressing (IHC 3+ or IHC 2+/ISH+) locally advanced, unresectable or metastatic CRC and have previously received chemotherapy, anti-EGFR therapy, anti-VEGF treatment, and/or anti–PD-1/PD-L1 therapy, as clinically indicated. Prior anti-HER2 therapy will be allowed. In stage 1, patients will be randomly assigned 1:1 to receive T-DXd IV Q3W at a dose of 5.4 mg/kg (n = 40; arm 1) or 6.4 mg/kg (n = 40; arm 2). Randomization will be stratified by ECOG PS (0 or 1), HER2 status (IHC 3+ or IHC 2+/ISH+), and *RAS* status (wild-type or mutant). After stage 1 enrollment is complete, eligible patients in stage 2 (n = 40) will receive T-DXd 5.4 mg/kg until disease progression or other treatment discontinuation criteria are met. The study is actively enrolling and aims to enroll 120 patients across 60 sites. The primary objective is to assess efficacy of T-DXd at the 5.4-mg/kg and 6.4-mg/kg doses, with a primary end point of confirmed ORR by blinded independent central review. Secondary end points include investigator-assessed ORR, PFS, duration of response, disease control rate, clinical benefit rate, overall survival, pharmacokinetics, and safety. Clinical trial information: NCT04744831. Research Sponsor: Daiichi Sankyo, Inc, Pharmaceutical/Biotech Company.

TPS3621 **Poster Session**

JCOG1805 (PanDRa-BD study): A randomized controlled study of adjuvant chemotherapy for stage II colorectal cancer patients at high-risk of developing recurrence according to T-stage and three selected pathological factors (Pn, DR, and BD). *First Author: Megumi Ishiguro, Department of Chemotherapy and Oncosurgery, Tokyo Medical and Dental University, Tokyo, Japan*

Background: Adjuvant chemotherapy for stage II colorectal cancer (CRC) still remains controversial. Although the NCCN and ESMO guidelines recommend adjuvant chemotherapy for patients with "high-risk features," the survival benefit has not been confirmed. We reviewed the evidence levels for prognostic values of risk factors, because lack of their robustness is a major source of uncertainty regarding the optimal indication of adjuvant chemotherapy. Consequently, on top of the T-stage, three pathological factors—perineural invasion (Pn), tumor budding (BD), and desmoplastic reaction (DR)—were selected as robust risk factors of recurrence. Among the conventional factors, the prognostic value of Pn had been well validated in a multicenter study conducted by the Japanese Society for Cancer of the Colon and Rectum (JSCCR; Am J Surg Path 2013), but others were deemed suboptimal in terms of the prognostic value. BD and DR are novel tumor- and stroma-factors, respectively, associated with cancer microenvironment at the tumor front. According to the JSCCR and ITBCC 2016 criteria, tumors are graded as BD1, BD2, or BD3. The DR heterogeneity is categorized into Mature, Intermediate, and Immature patterns based on site-specific products of cancer-associated fibroblasts—keloid-like collagen and myxoid stroma. According to a recent prospective multicenter study, BD and DR characterization represent a higher level of prognostic value than other conventional factors (SACURA trial; J Clin Oncol 2019, Br J Cancer 2021). Based on the four selected risk factors, we can exclude the patient group with favorable prognosis (i.e., > 90% of 5-year RFS), which accounts for approximately 40% of the total population, resulting in enabling us to identify the concentrated population of high risk of developing recurrence. **Methods:** The Japan Clinical Oncology Group (JCOG) launched a randomized controlled phase III trial to evaluate the superiority of adjuvant chemotherapy in terms of relapse-free survival (RFS) over observation only in stage II CRC patients aged 20–80 years having one or more of the following risk factors: pathological T4, Pn, BD3, and non-Mature DR. Patients are randomised, in a 1:1:1 ratio, to [A] observation, [B] capecitabine monotherapy for 6 months, or [C] capecitabine and oxaliplatin (CAPOX) for 3 months. A total of 1680 patients will be accrued from 54 Japanese institutions assuming 3-year RFS with [A] to be 82% and expected 5% increase in 3-year RFS for [B] and [C] with one-sided alpha of 2.5% and power of 80% for each pair comparison. Patient enrollment was started in January 2020 and 170 patients have been enrolled until January 2021. This trial has been registered at Japan Registry of Clinical Trials as jRCTs031190186. Clinical trial information: jRCTs031190186. Research Sponsor: Japan Agency for Medical Research and Development.

TPS3622 **Poster Session**

Phase II/III study of Circulating tumOr DNA as a predictive BiomaRker in Adjuvant chemotherapy in patients with stage II colon cancer: NRG-GI005 (COBRA). *First Author: Van K. Morris, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: There are currently no validated predictive biomarkers for stage II resected colon cancer (CC) after adjuvant chemotherapy. However, circulating tumor DNA (ctDNA) that is shed into the bloodstream represents a highly specific and sensitive approach for identifying microscopic or residual tumor cells. For patients (pts) with CC, the detection of ctDNA is associated with persistent disease after resection and may outperform traditional clinical and pathological features as a prognostic factor to assess risk for recurrence. We hypothesize that for pts whose stage II colon cancer has been resected and who have no traditional high-risk features, a positive ctDNA status may identify those who will benefit from adjuvant chemotherapy. **Methods:** In this prospective phase II/III clinical trial, pts (N = 1,408) with resected stage II CC without traditional high-risk features and whom the evaluating oncologist deems suitable for no adjuvant chemotherapy will be randomized 1:1 into 2 arms: standard-of-care/observation (Arm A), or prospective testing for ctDNA (Arm B). Postoperative blood will be analyzed for ctDNA with the GuardantHealth LUNAR panel, covering CC-relevant mutations and CC-specific methylation profiling. Pts in Arm B with ctDNA detected will be treated with 6 months of adjuvant (FOLFOX) chemotherapy. For all pts in Arm A, ctDNA status will be analyzed retrospectively at the time of endpoint analysis. The primary endpoints are clearance of ctDNA with adjuvant chemotherapy (phase II) and recurrence-free survival (RFS) for "ctDNA-detected" pts treated with or without adjuvant chemotherapy (phase III). Secondary endpoints will include time-to-event outcomes (OS, RFS, TTR) by ctDNA marker status and treatment, prevalence of detectable ctDNA in stage II CC, and rates of compliance with assigned intervention. Archived normal and matched tumor and blood samples will be collected for exploratory correlative research. The trial is actively accruing towards the phase II endpoint in North America. NCT#: 04068103. Support: U10-CA-180868, -180822; UG1CA-189867; GuardantHealth. Clinical trial information: NCT04068103. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS3623 **Poster Session**

Neoadjuvant chemoradiotherapy with sequential ipilimumab and nivolumab in rectal cancer (CHINOREC): A prospective randomized, open-label, multicenter, phase II clinical trial. *First Author: Johannes Laengle, Division of Visceral Surgery, Department of General Surgery, Comprehensive Cancer Center Vienna, Medical University of Vienna, Vienna, Austria*

Background: Immune checkpoint inhibitors (ICI), such as ipilimumab (anti-cytotoxic T-lymphocyte-associated protein 4) or nivolumab (anti-programmed cell death protein 1) have been proven to be an effective strategy in solid cancers. However, ICI seem not to be effective in microsatellite stable (MSS) cancers. As they might lack an immunogenic priming, radiotherapy (RT) is capable to induce an immunogenic cell death (ICD) and subsequently an immunogenic tumor immune microenvironment (TIME). Thus, RT might restore the susceptibility of MSS tumors to ICI and consequently leading to an effective anti-tumor immune response. **Methods:** This is a prospective, randomized, open-label, multicenter, phase II investigator-initiated clinical trial (IIT), including patients with locally advanced rectal cancer (LARC). Patients receive either neoadjuvant chemoradiotherapy (CRT) alone (50 Gy in 2 Gy fractions over 25 working days + capecitabine 1650 mg/m^2/d PO) or in combination with ipilimumab (1 mg/kg IV on day 7) and nivolumab (3 mg/kg IV on day 14, 28 and 42). Patients will undergo surgery within 10-12 weeks post CRT. The primary endpoint is incidence of treatment-emergent adverse events (AEs) assessed by the Clavien-Dindo classification of surgical complications and the common terminology criteria of adverse events (CTCAE). Secondary objectives are radiographic and pathological therapy response. Serial liquid (plasma, serum and peripheral blood mononuclear cells) and tissue biopsies will be taken before, during and after neoadjuvant treatment. Genomic, transcriptomic, epigenomic and proteomic pattern of liquid and tissue biopsies, as well as the immune cell infiltrate of resected specimen, will be correlated with therapy response and clinical outcome. Currently 8 of planned 80 patients have been enrolled. Registration numbers: NCT no. NCT04124601, EudraCT no. 2019-003865-17. Clinical trial information: NCT04124601. Research Sponsor: This is an investigator-initiated trial (IIT), which received a research grant and the study medications from Bristol-Myers Squibb (BMS).

4000 **Oral Abstract Session**

ESCORT-1st: A randomized, double-blind, placebo-controlled, phase 3 trial of camrelizumab plus chemotherapy versus chemotherapy in patients with untreated advanced or metastatic esophageal squamous cell carcinoma (ESCC).

First Author: Rui-hua Xu, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China

Background: The current standard first-line therapy for advanced or metastatic ESCC is doublet chemotherapy, and prognosis remains poor. Camrelizumab, a humanized anti-PD-1 monoclonal antibody, has shown promising antitumor activity in previously treated advanced or metastatic ESCC (Huang et al. *Lancet Oncol* 2019). Immunotherapy may work synergistically with chemotherapy, but lacking clinical evidences in ESCC. Here, we report the findings of the phase 3 ESCORT-1st study which evaluated the efficacy and safety of camrelizumab plus chemotherapy vs chemotherapy in patients with untreated advanced or metastatic ESCC. **Methods:** Eligible patients were randomized 1:1 to receive camrelizumab 200 mg or placebo, both combined with up to 6 cycles of paclitaxel (175 mg/m^2) and cisplatin (75 mg/m^2). All were given intravenously Q3W. Tumor response was assessed every 6 weeks according to RECIST v1.1. Co-primary endpoints were OS and independent review committee (IRC)-assessed PFS. Efficacy was assessed in all randomized patients and safety was assessed in all treated patients. Data cutoff date for the prespecified interim OS and final PFS analysis was Oct 30, 2020. **Results:** From Dec 3, 2018 to May 12, 2020, 596 patients were randomized. 298 patients were treated with camrelizumb-chemotherapy and 297 patients with placebo-chemotherapy. With a median follow-up of 10.8 months, camrelizumab plus chemotherapy significantly improved OS compared with placebo plus chemotherapy (median, 15.3 month [95% CI 12.8-17.3] vs 12.0 months [11.0-13.3]; HR, 0.70 [95% CI, 0.56-0.88]; one-sided P = 0.0010). Camrelizumab plus chemotherapy was also superior for PFS (per IRC) vs placebo plus chemotherapy (median, 6.9 months [95% CI, 5.8-7.4] vs 5.6 months [95% CI, 5.5-5.7]; HR, 0.56 [95% CI, 0.46-0.68]; one-sided P $<$ 0.0001). ORR per investigator was 72.1% in camrelizumab-chemotherapy group vs 62.1% in placebo-chemotherapy group, and median DoR was 7.0 vs 4.6 months. Incidences of grade $\geq$3 treatment-related AEs were comparable between the two groups (63.4% vs 67.7%), with decreased neutrophil count (39.9% vs 43.4%) as the most common one. Serious treatment-related AEs occurred in 30.2% vs 23.2% of patients, and treatment-related deaths occurred in 3.0% vs 3.7% of patients, respectively. **Conclusions:** Addition of camrelizumab to chemotherapy provided superior OS and PFS vs placebo plus chemotherapy, with a manageable safety profile. Camrelizumab in combination with paclitaxel and cisplatin has the potential to become a new standard first-line therapy in patients with advanced or metastatic ESCC. Based on this trial, we are submitting NDA to seek the approval from China National Medical Products Administration for camrelizumab plus chemotherapy in the treatment of untreated advanced or metastatic ESCC. Clinical trial information: NCT03691090. Research Sponsor: Jiangsu Hengrui Medicine.

LBA4001 **Oral Abstract Session**

Nivolumab (NIVO) plus ipilimumab (IPI) or NIVO plus chemotherapy (chemo) versus chemo as first-line (1L) treatment for advanced esophageal squamous cell carcinoma (ESCC): First results of the CheckMate 648 study.

First Author: Ian Chau, Royal Marsden Hospital, Sutton, United Kingdom

The full, final text of this abstract will be available at abstracts.asco.org at 5:00 PM ET on Thursday, June 3, 2021.

4002 **Oral Abstract Session**

First-line (1L) nivolumab (NIVO) plus chemotherapy (chemo) versus chemo in advanced gastric cancer/gastroesophageal junction cancer/esophageal adenocarcinoma (GC/GEJC/EAC): Expanded efficacy and safety data from CheckMate 649.

First Author: Markus H. Moehler, Johannes-Gutenberg University Clinic, Mainz, Germany

Background: CheckMate 649 is the largest randomized, global phase 3 study of 1L programmed death (PD)-1 inhibitor–based therapy in GC/GEJC/EAC. 1L NIVO + chemo demonstrated superior overall survival (OS) vs chemo, with progression-free survival (PFS) benefit and an acceptable safety profile in pts whose tumors expressed PD-ligand (L)1 at combined positive score (CPS) $\geq$ 5 and $\geq$ 1, and in all randomized pts (Moehler et al. *Ann Oncol* 2020). We report additional data for all randomized pts. **Methods:** Eligible pts had previously untreated, unresectable advanced or metastatic GC/GEJC/EAC. Known HER2-positive pts were excluded. Pts were randomized to receive NIVO (360 mg Q3W or 240 mg Q2W) + chemo (XELOX Q3W or FOLFOX Q2W), NIVO + ipilimumab, or chemo. Dual primary endpoints for NIVO + chemo vs chemo were OS and PFS by blinded central review in PD-L1 CPS $\geq$ 5 pts. Hierarchically tested secondary endpoints were OS in PD-L1 CPS $\geq$ 1 and all randomized pts. **Results:** At 12-month minimum follow-up for 1581 randomized pts, NIVO + chemo had a statistically significant OS benefit vs chemo (HR 0.80 [99.3% CI 0.68–0.94; P = 0.0002]) in all randomized pts; PFS benefit was also seen (HR 0.77 [95% CI 0.68–0.87]). OS benefit was observed in multiple prespecified subgroups, consistent with the primary population. Grade 3–4 treatment-related adverse events (TRAEs) were reported in 59% (NIVO + chemo) and 44% (chemo) of pts. TRAEs with potential immunologic etiology (select TRAEs; sTRAEs) are shown in the table. Pts in the NIVO + chemo arm had decreased risk of symptom deterioration on treatment vs those in the chemo arm (HR 0.77 [95% CI 0.63–0.95; P = 0.0129]). Tolerability as measured by the FACT-Ga GP5 item was similar in both treatment groups. **Conclusions:** The addition of NIVO to chemo demonstrated improved OS and PFS benefit in all randomized pts, along with an acceptable safety profile and maintained tolerability as well as QoL, providing further support for NIVO + chemo as a standard 1L treatment for advanced GC/GEJC/EAC. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.

sTRAEs (NIVO + chemo, N = 782).

	Pts with sTRAEs, n (%)		Median time to onset (range), weeks	Median time to resolution (range),[b] weeks	Pts with resolution of sTRAEs,[b] n (%)
	Any grade	Grade 3–4[a]			
Endocrine	107 (14)	5 (< 1)	15.0 (2.0–124.3)	72.1 (0.4–139.1+)	46 (43)
GI	262 (34)	43 (5)	4.3 (0.1–93.6)	1.6 (0.1–117.6+)	228 (87)
Hepatic	203 (26)	29 (4)	7.9 (0.1–61.3)	10.1 (0.4–150.6+)	156 (78)
Pulmonary	40 (5)	14 (2)	23.9 (1.6–96.9)	10.1 (0.3+ to 121.3+)	28 (70)
Renal	26 (3)	6 (< 1)	12.4 (1.7–59.4)	3.1 (0.1–42.4+)	19 (73)
Skin	214 (27)	26 (3)	9.6 (0.1–97.4)	23.4 (0.1–153.6+)	124 (58)

[a]There were no grade 5 events; [b]Events without a stop date or where stop date was death date were considered unresolved. Events without worsening from baseline were excluded.

4003 **Oral Abstract Session**

Adjuvant nivolumab (NIVO) in resected esophageal or gastroesophageal junction cancer (EC/GEJC) following neoadjuvant chemoradiotherapy (CRT): Expanded efficacy and safety analyses from CheckMate 577.

First Author: Ronan Joseph Kelly, The Charles A. Sammons Cancer Center, Baylor University Medical Center, Dallas, TX

Background: In CheckMate 577 (NCT02743494), NIVO demonstrated a significant and clinically meaningful improvement in disease-free survival (DFS; primary endpoint) vs placebo (PBO) and was well tolerated in patients (pts) with resected (R0) stage II/III EC/GEJC who received neoadjuvant CRT and had residual pathologic disease. Median DFS doubled with NIVO vs PBO (22.4 vs 11.0 months; HR 0.69; 96.4% CI 0.56–0.86; P = 0.0003). Serious treatment-related adverse events (TRAEs) and TRAEs leading to discontinuation were reported for $<$ 10% of pts with NIVO and 3% with PBO. **Methods:** Pts were randomized 2:1 to NIVO 240 mg or PBO Q2W for 16 weeks, followed by NIVO 480 mg or PBO Q4W. Here, we present additional efficacy, safety, and quality-of-life (QoL) data from CheckMate 577. **Results:** 794 pts were randomized (NIVO, 532; PBO, 262). Distant recurrence was reported for 29% vs 39% and locoregional recurrence for 12% vs 17% of pts in the NIVO vs PBO groups, respectively. Median distant metastasis-free survival was 28.3 vs 17.6 months with NIVO vs PBO (HR 0.74; 95% CI 0.60–0.92). Median progression-free survival 2 (PFS2; time from randomization to progression after subsequent systemic therapy, initiation of second subsequent systemic therapy, or death, whichever is earlier) was not reached with NIVO vs 32.1 months with PBO (HR 0.77; 95% CI 0.60–0.99). TRAEs with potential immunologic etiology (select TRAEs; sTRAEs) reported for NIVO are presented in the table. Results for the FACT-ECS and FACT-G7 showed similar trends for QoL improvement from baseline for NIVO and PBO during treatment and maintained benefit post-treatment. **Conclusions:** Adjuvant NIVO demonstrated clinically meaningful efficacy, an acceptable safety profile, and maintained QoL, providing further support for its use as a new standard of care for pts with resected EC/GEJC who received neoadjuvant CRT with residual pathologic disease. Clinical trial information: NCT02743494. Research Sponsor: Bristol Myers Squibb.

TRAEs with potential immunologic etiology in the NIVO group (n = 532).

	Pts with any grade sTRAEs,[a] n (%)	Median time to onset (range), weeks	Median time to resolution (range),[b] weeks	Pts receiving immune-modulating medication, n (%)	Pts with resolution of sTRAEs,[b] n (%)
Endocrine	93 (17)	9.7 (1.7–52.4)	21.1 (2.0–150.0+)	10 (11)	62 (67)
Gastrointestinal	91 (17)	7.4 (0.1–49.3)	3.5 (0.1–84.1+)	9 (10)	83 (94)
Hepatic	49 (9)	6.1 (1.1–49.3)	7.6 (0.4+ to 126.4+)	7 (14)	37 (80)
Pulmonary	23 (4)	12.7 (4.0–47.9)	5.9 (0.7–65.0)	17 (74)	17 (74)
Renal	7 (1)	12.1 (1.9–37.1)	2.6 (0.7–17.0)	2 (29)	6 (100)
Skin	130 (24)	6.1 (0.1–49.0)	17.9 (0.1–163.1+)	50 (38)	85 (65)

[a]Most sTRAEs were grade 1 or 2. Grade 3–4 sTRAEs occurred in $\leq$ 1% of pts and there were no grade 5 sTRAEs. [b]Events without a stop date or where stop date was death date were considered unresolved; events without worsening from baseline were excluded.

4004 **Oral Abstract Session**

Neo-AEGIS (Neoadjuvant trial in Adenocarcinoma of the Esophagus and Esophago-Gastric Junction International Study): Preliminary results of phase III RCT of CROSS versus perioperative chemotherapy (Modified MAGIC or FLOT protocol). (NCT01726452). *First Author: John V Reynolds, Cancer Trials Ireland and St James's Hospital, Dublin, Ireland*

Background: The optimum combination curative approach to locally advanced adenocarcinoma of the esophagus and esophago-gastric junction (AEG) is unknown. A key question is whether neoadjuvant multimodal therapy, specifically CROSS (carboplatin/paclitaxel, 41.4Gy radiation therapy), is superior to optimum peri-operative chemotherapeutic regimens including modified MAGIC (epirubicin, cisplatin (oxaliplatin), 5-FU (capecitabine)) and more latterly FLOT (docetaxel, 5-FU, leucovorin, oxaliplatin). Neo-AEGIS was designed as the first randomised controlled trial to address this question. **Methods:** 377 patients with $cT_{2\text{-}3}N_{0\text{-}3}M_0$ AEG were randomly assigned to CROSS or peri-operative chemotherapy (ECF/ECX/EOF/EOX pre-2018, FLOT option 2019/20) at 24 sites (Ireland, UK, Denmark, France, Sweden). The primary outcome was overall survival. The initial power calculation was based on CROSS superiority of 10%. This was modified after the first futility analysis (70 events) to a non-inferiority margin of 5%. Secondary end points included toxicity, pathologic measures of response, and postoperative complications as per the Esophageal Complications Consensus Group (ECCG) definitions and Clavien-Dindo severity grade. **Results:** Of 362 evaluable patients, 178 CROSS, 184 MAGIC/FLOT (157/27), 90% were male, median (range) age 64 (35-83), 84% were cT3, and 58% cN1. At a median (range) follow up of 24.5 (1-92) months, at the second futility analysis (60% of planned events), there were 143 deaths, 70 CROSS and 73 MAGIC/FLOT arm, with 3-year estimated survival probability of 56% (95% CI 47,64) and 57% (95% CI 48,65), respectively [(HR 1.02 (95%CI. 0.74-1.42))]. Based on the absence of futility evidenced in this data the DSMB recommended closure of recruitment in December 2020. **Conclusions:** This RCT reveals no evidence that peri-operative chemotherapy is unacceptably inferior to multimodal therapy, notwithstanding greater proxy markers of local tumour response in the CROSS arm. Oncologic and operative outcomes were consistent with optimum modern benchmarks. These data strongly suggest non-inferiority and support equipoise in decision making in modern practice. Clinical trial information: NCT01726452. Research Sponsor: Health Research Board Ireland, Cancer Research UK (C49462/A18483), Irish Cancer Society, Oesophageal Cancer Fund Ireland.

	Arm A (Magic/FLOT)	Arm B CROSS
R0 (negative margins)	82%	95%
ypN0	44.5%	60.1%
Tumor regression grade 1 & 2	12.1%	41.7%
Pathologic complete response	5%	16%
Neutropenia (Gr 3/4)	14.1%	2.8%
Neutropenic sepsis	2.7%	0.6%
Postoperative in-hospital deaths	3%	3%
Postoperative Pneumonia/ARDS	20%/0.6%	16%/4.3%
Anastomotic Leak	12%	11.7%
Clavien-Dindo > III<V	23.6%	22%

4005 **Oral Abstract Session**

Multicenter, randomized phase II study of neoadjuvant pembrolizumab plus chemotherapy and chemoradiotherapy in esophageal adenocarcinoma (EAC). *First Author: Manish A. Shah, Weill Cornell Medicine, New York, NY*

Background: Recent transformative studies in the treatment of EAC support adjuvant nivolumab for patients with residual disease following neoadjuvant chemoradiotherapy (CRT) (Checkmate 577) and pembrolizumab (P) with chemotherapy in untreated metastatic disease (Keynote 590). We hypothesized that pre-operative P combined with CRT can further improve outcomes in patients with locally advanced EAC. **Methods:** Patients with cT3-4Nx or T2N1 M0 EAC or gastroesophageal junction (GEJ) adenocarcinoma eligible for curative surgery were randomized (1:1) to receive either full-dose paclitaxel (T)/ carboplatin (C) or T/C + P induction therapy. All patients then received CRT with weekly T/C, RT 41.4Gy in 23 fractions, and P every 3 weeks. Following resection, patients received P for one year. The primary endpoint is rate of major pathologic response (MPR), defined as pathologic complete response or near complete response ($<$ 10% residual cancer), with 80% power and 0.1 one-sided significance level to detect the difference between a MPR proportion of 30% (historical control) and an alternative hypothesis of 47% (with preoperative P). Tissue was collected for tumor immune microenvironment (TIME) analysis including bulk and single cell RNA(scRNA) expression analysis, DNA sequencing, and flow cytometry. **Results:** From 8/4/17 to 10/26/20, 40 patients were enrolled: median age 68 [38-81], male 32, esophagus/GEJ type I (n = 16), GEJ II/III (n = 24). CRT was well tolerated, with no grade 3-4 adverse events attributed to P. Notable toxicity included grade 3-4 pneumonitis (13%), anastomotic leak (13%), infection (35%). In 31 evaluable patients to date, the MPR rate was 50.0% (95% CI, 32.7%-67.3%). 1-yr disease free survival was 100% for patients with MPR vs. 31.8% without MPR, p = 0.002. Esophageal/GEJ type I cancers had a significantly higher MPR rate when compared with GEJ type II/III (76.9% vs 37.5%, p = 0.03). scRNA seq on $>$ 100,000 tumor cells revealed EAC/GEJ type I had higher infiltration of activated dendritic cells (p = 0.12), whereas GEJ tumors have significantly higher infiltration of activated B cells (p = 0.02). **Conclusions:** The addition of P to preoperative CRT for EAC is safe and associated with a significantly higher MPR rate compared to historical data. We found MPR to be significantly enriched in EAC/GEJ type I tumors compared with GEJ II/III, associated with important differences in the baseline tumor immune microenvironment. Clinical trial information: NCT02998268. Research Sponsor: Merck Inc, GI Oncology Translational Research Fund - Weill Cornell Medicine.

4006 **Oral Abstract Session**

Liposomal irinotecan (nal-IRI) in combination with fluorouracil (5-FU) and leucovorin (LV) for patients with metastatic biliary tract cancer (BTC) after progression on gemcitabine plus cisplatin (GemCis): Multicenter comparative randomized phase 2b study (NIFTY). *First Author: Changhoon Yoo, Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea*

Background: There is no globally established second-line therapy after progression on GemCis in BTC. Although ABC-06 trial showed the clinical benefit of mFOLFOX compared to active symptom control, further investigation is needed. **Methods:** NIFTY is an investigator-initiated, multicenter, open-label, randomized, phase 2b study. Pts with $>$ 19 years, ECOG PS 0/1, histologically confirmed metastatic BTC, and disease progression on first-line GemCis were eligible. Pts were randomized 1:1 to nal-IRI (70 mg/m2, 90 min) plus 5-FU (2400 mg/m2, 46 hours)/LV (400 mg/m2, 30 min), every 2 weeks or 5-FU/LV, every 2 weeks until disease progression per investigator review or intolerable toxicities (stratification: primary tumor site, prior surgery and institution). Tumor response was evaluated per RECIST v1.1, every 6 weeks (fixed schedule). Primary endpoint is progression-free survival (PFS) per blinded independent central review (BICR). Secondary endpoints were PFS per investigator review, overall survival (OS) overall response rates (ORR), and safety. This study was designed to improve median PFS from 2 months (P0) to 3.3 months (P1; HR 0.6) with 2-sided alpha of 0.05, power of 80% and follow-up loss rates of 10%; a total of 174 pts were required. **Results:** A total of 178 patients were enrolled between SEP 2018 and FEB 2020; with exclusion of 4 pts who did not receive any study treatment, 174 pts (88 for nal-IRI plus 5-FU/LV group and 86 for 5-FU/LV group) were included in the Full Analysis Set. Median age was 64 yrs (range 37-84); 99/75 pts were male/female; 74/47/53 pts had intrahepatic/extrahepatic/gallbladder cancers. Pts characteristics were well balanced between two arms. With median follow-up duration of 6.1 mo (IQR 3.5-11.2), median PFS per BICR in nal-IRI plus 5-FU/LV group and 5-FU/LV group was 7.1 mo (95% CI, 3.6-8.8) and 1.4 mo (1.2-1.5), respectively (HR=0.56 [0.39-0.81], p=0.0019); median PFS per investigator review was 3.9 mo (2.7-5.2) and 1.6 mo (1.3-2.2), respectively (HR=0.48 [0.34-0.69], p$<$0.0001). Median OS was 8.6 mo (5.4-10.5) and 5.5 mo (4.7-7.2), respectively (HR=0.68 [0.48-0.98], p=0.0349). ORR was 14.8% and 5.8% per BICR, respectively (p=0.0684) and 19.3% and 2.3% per investigator review, respectively (p=0.0002). Grade $\geq$3 adverse events (AEs) were reported in 68 pts (77.3%) of nal-IRI plus 5-FU/LV group and 27 pts (31.4%) of 5-FU/LV group. Most common grade $\geq$3 AEs in nal-IRI plus 5-FU/LV group were neutropenia (n=21, 23.9%), fatigue (7, 8.0%), and nausea (5, 5.7%). **Conclusion**: Nal-IRI plus 5-FU/LV significantly improved PFS and OS compared to 5-FU/LV in BTC pts who progressed on prior GemCis. Nal-IRI plus 5-FU/LV should be considered as standard second-line therapy for advanced BTC. ClinicalTrials.gov identifier: NCT03524508 Clinical trial information: NCT03524508. Research Sponsor: Servier.

4007 **Oral Abstract Session**

Hepatic arterial infusion chemotherapy of oxaliplatin plus fluorouracil versus sorafenib in advanced hepatocellular carcinoma: A biomolecular exploratory, randomized, phase 3 trial (The FOHAIC-1 study). *First Author: Ning Lyu, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Advanced hepatocellular carcinoma (HCC) with mega liver masses and macrovascular invasion were commonly observed at the first diagnosis, while with less extrahepatic metastases (77.5% vs. 37.9%). However, in clinical trials IMbrave150, SHARP, and Asia-Pacific SHARP, the percentage of extrahepatic metastases reached 63%, 53%, and 68.7%, respectively, while macrovascular invasion only accounted for 38%, 36%, and 36%. Unlike the previous and ongoing phase 3 clinical trials exploring the optimal systemic medication in the first-line treatment of advanced HCC, this study mainly focused on a population with a heavy intrahepatic tumor burden. **Methods:** In this open-label, phase 3 trial, patients were randomly assigned in a 1:1 ratio to undergo hepatic arterial infusion chemotherapy (HAIC) of FOLFOX regimens (HAIC-FO) or sorafenib treatment. Patients in the HAIC-FO group were recommended to receive tumor and normal tissue biopsy to search for the potential genomic biomarkers in predicting the response to treatment. **Results:** Between May 2017 and May 2020, 551 patients were recruited. Two hundred sixty eligible patients were randomly assigned to receive HAIC-FO (n = 130) or sorafenib (n = 132) and were included in the intention-to-treatment population. Macrovascular invasion with or without extrahepatic metastasis was present in 82.8% of patients (84.6% and 81.1%; P = 0.446). The median tumor diameter was 11.7 cm (IQR 8.3-14.0) of the HAIC-FO group and 10.8 cm (8.7-13.6) of the sorafenib group (P = 0.439). The percentage of patients with $>$ 50% tumor volume involvement of the liver was 41.5% and 39.4%, respectively (P = 0.724). At the time of data cutoff (Oct 31, 2020, at 190 deaths [79 of HAIC-FO and 111 of sorafenib]), patients receiving HAIC-FO had a median overall survival of 13.9 months (95%CI 10.6-17.2), compared with 8.2 months (7.5-9.0) for those receiving sorafenib (HR 0.408 [95%CI 0.301-0.552], P $<$ 0.001). Tumor downstaging occurred in 16 (12.3% of 130) patients of the HAIC-FO group, including 15 (93.8%) receiving curative surgery or ablation and finally achieving a median overall survival (progression-free survival) of 20.8 (16.4) months (95%CI 9.1-32.5 [7.5-25.3]) with a 1-year rate of 93.8% (68.8%). Analyses of predictive biomarkers based on the whole genome sequencing were ongoing in the HAIC-FO group. **Conclusions:** This randomized phase 3 study proved that HAIC-FO had superior efficacy and survival outcome than sorafenib in the first-line treatment of primary diagnostic, advanced HCC, indicating that patients with heavy intrahepatic tumor burden, HAIC-FO monotherapy might be a better strategy than sorafenib. Clinical trial information: NCT03164382. Research Sponsor: The clinical trial was supported by the Sun Yat-sen University Clinical Research 5010 Program of China (No. 2018013).

4008 **Oral Abstract Session**

Neoadjuvant transarterial infusion chemotherapy with FOLFOX could improve outcomes of resectable BCLC stage A/B hepatocellular carcinoma patients beyond Milan criteria: An interim analysis of a multi-center, phase 3, randomized, controlled clinical trial. *First Author: Shaohua Li, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: The efficacy of operation, as the only radical option for resectable BCLC stage A/B hepatocellular carcinoma (HCC) patients beyond Milan criteria, is still unsatisfactory. This study aimed to investigate to efficacy and safety of preoperative neoadjuvant transarterial infusion chemotherapy (TAI) with FOLFOX regimen for these patients. **Methods:** In this multi-center, prospective, phase 3, randomized, open-labeled, controlled clinical trial, resectable BCLC stage A/B HCC patients beyond Milan criteria were randomly assigned (1:1) before hepatectomy to receive either neoadjuvant TAI (NT group) or operation directly without any neoadjuvant treatment (OP group). The primary endpoint was overall survival (OS), the secondary endpoints are progression-free survival (PFS), recurrence free survival (RFS), and safety. **Results:** Between March, 2016 and July, 2020, 208 patients enrolled from five Chinese hospitals were randomly assigned to NT group (n=104) or OP group (n=104) with 99 patients in NT group and 100 patients in OP group included in the efficacy and safety analysis. Clinicopathological characteristics were balanced between the two groups. The 1-, 2-, and 3-year OS rates for NT group were 92.9%, 78.6%, and 63.5%, and were 79.5%, 62.0%, and 46.3% for OP group, respectively. The 6-, 12-, and 18-month PFS rates for NT group were 77.6%, 50.4%, and 47.4%, and were 52.7%, 42.8%, and 34.8% for OP group, respectively. The OS and PFS were significantly better in NT group than in OP group (p=0.016 and 0.017, respectively). The 6-, 12-, and 18-month RFS rates for NT group were 63.8%, 47.3%, and 47.3%, and were 52.7%, 42.8%, and 34.8% for OP group, respectively. The RFS between the two group had no difference (p=0.385). No patients in NT group experienced grade 3 or more severe TAI related adverse events. The operation related adverse events were similar between two groups (p=0.300). **Conclusions:** Neoadjuvant TAI before hepatectomy may bring survival benefits for resectable BCLC stage A/B HCC patients beyond Milan criteria. Trial number: NCT03851913. Clinical trial information: NCT03851913. Research Sponsor: None.

4009 **Clinical Science Symposium**

***IDH1* and *IDH2* Driven Intrahepatic Cholangiocarcinoma (IHCC): A comprehensive genomic and immune profiling study.** *First Author: Shalini Makawita, MD Anderson Cancer Center, Houston, TX*

Background: *IDH1/2* genetic aberrations (GA) occur in 20% of IHCC cases and may be specifically targeted by IDH inhibitors. The genomic and immunologic profile of IHCC with *IDH1/2* GA remains undefined. *IDH1* mutations impair DNA damage repair (DDR), loss of heterozygosity (LOH) and may represent a biomarker for DDR in these patients. **Methods:** Comprehensive genomic profiling (CGP) was performed in 3,067 cases of advanced stage IHCC using a hybrid capture-based FDA-approved assay. Tumor mutational burden (TMB) was determined on 0.8 Mbp of sequenced DNA and microsatellite instability (MSI) was determined on 95 loci. PD-L1 expression in tumor cells (Dako 22C3) was measured by immunohistochemistry (IHC). Genomic LOH (gLOH) was assessed for samples meeting quality criteria. Densities of tumor associated immune cells and immune-checkpoint markers expressed in epithelial malignant cells and in the tumor microenvironment of 100 surgical samples from 96 patients were evaluated by IHC using digital image analysis of 14 markers (CD3, CD4, CD8, CD68, PD1,PD-L1, B7-H4, B7-H3, IDO1, ICOS, VISTA, OX40, TIM3, LAG3). Tissue microarrays were generated for multiplex immune panel analysis. A p value < 0.05 was considered statistically significant. **Results:** 426 (14%) of IHCC were *IDH1+* and 125 (4%) were *IDH2+* (Table) and were mutually exclusive. All *IDH1* GA occurred at the R132 locus and included R132C (69%) and R132L/G/S/H/F (16%/7%/4%/3%/ $< 1\%$) and 119Q ($< 1\%$) and *IDH2* GA at R172 (94.4%) and R140 (6.6%). *IDH1+* and *IDH2+* IHCC had fewer co-occurring targetable GA than *IDH1/2* wildtype (WT, *IDH*wt) cases including *FGFR2* rearrangements (RE) ($P < .0001$), *ERBB2* ($P = .0009$) and *BRAF* ($P = .04$). Median gLOH were not significantly different between *IDH1+IDH2+* IHCC vs. *IDH*wt IHCC ($p = 0.37$). Potential biomarkers of immune checkpoint inhibition (ICI) response including MSI High, TMB > 10 mut/Mb, and PD-L1 positivity were more frequent in *IDH*wt IHCC than *IDH1+* IHCC. 29/96 (30%) surgical patients were positive for *IDH1/2* mutation though mutational status did not confer a statistically significant difference in the 14 immune biomarker panel expression. **Conclusions:** CGP reveals significant differences in GA between *IDH1+*, *IDH2+* and *IDH*wt IHCC consistent with IDH1 and IDH2 being driver oncogenes for IHCC. Immune biomarker expression and gLOH did not differ significantly between *IDH* mutated and WT cases. Research Sponsor: None.

	IDH1+ IHCC (N = 426)	*IDH2+* IHCC (N = 125)	*IDHwt* IHCC (N = 2516)	P Value
TP53	12%	9%	39%	$< .0001$
CDKN2A/CDKN2B	20%/16%	12%/9%	33%/23%	$< .0001$
MTAP	8%	6%	17%	$< .0001$
FGFR2 RE	1%	1%	10%	$< .0001$
***ERBB2 short variants*/amplifications**	$< 1\%$/2%	2%/1%	1%/4%	0.0009
BRAF	4%	2%	5%	0.04
MSI-High	$< 1\%$	0%	1%	0.009
TMB > 10 mut/Mb	$< 1\%$	0%	5%	$< .0001$
gLOH	10.37	10.55	10.21	0.37

4010 **Clinical Science Symposium**

FIGHT: A randomized, double-blind, placebo-controlled, phase II study of bemarituzumab (bema) combined with modified FOLFOX6 in 1L FGFR2b+ advanced gastric/gastroesophageal junction adenocarcinoma (GC). *First Author: Daniel V.T. Catenacci, Gastrointestinal Oncology Program, University of Chicago, Chicago, IL*

Background: Bema is a first-in-class humanized IgG1 monoclonal antibody selective for fibroblast growth factor receptor 2b (FGFR2b). Results from the FIGHT study showed an improvement in progression-free survival (PFS), overall survival (OS), and overall response rate with the addition of bema to mFOLFOX6 in FGFR2b+, non HER2+ GC. This report provides updated analyses of patient (pt) subgroups, additional data on ocular adverse events (AEs), and the median OS result for the bema+mFOLFOX6 combination. **Methods:** Pts were treated with mFOLFOX6 and randomized 1:1 to bema (15 mg/kg) or placebo (pbo) every 2 weeks (wks) with an additional 7.5 mg/kg bema/pbo dose on cycle 1 day 8. Eligible pts had unresectable locally advanced or metastatic GC not known to be HER2+, and had FGFR2b overexpression (any 2+/3+ staining) by centrally performed immunohistochemistry (IHC+) or *FGFR2* amplification by circulating tumor DNA (ctDNA+). **Results:** Of the 155 pts who were randomized, 149 (96%) were FGFR2b+ by IHC, 26 (17%) by ctDNA, and 20 (13%) by both. 96 pts (62%) had tumors with FGFR2b IHC 2+/3+ in $\geq$10% of tumor cells. The proportion of pts with ctDNA+ or with $\geq$5% or $\geq$10% tumor cells FGFR2b+ by IHC was similar across geographic regions. Bema showed a benefit vs pbo across pre-specified subgroups including age, gender, geographic region, and prior adjuvant therapy. Patients with FGFR2b overexpression irrespective of ctDNA gene amplification benefited from bema: IHC+/ctDNA- PFS hazard ratio (HR) 0.63 (95% CI 0.4, 0.99), OS HR 0.66 (95% CI 0.39, 1.12); IHC+/ctDNA+ PFS HR 0.15 (95% CI 0.02, 1.18), OS HR 0.10 (95% CI 0.01, 0.83). Frequency and severity of ocular AEs were similar for the overall enrolled population and for pts with $\geq$5% or $\geq$10% FGFR2b+ by IHC. Corneal AEs in the bema arm increased in frequency and severity over time; 10.5% (0% G3) wk 1-8 vs 44.1% (15.3% G3) wk $\geq$25. Following discontinuation of study treatment, subsequent anti-cancer therapy was balanced in the 2 arms (bema 53%; pbo 49%). With a median follow-up of 12.5 months (mo), the bema arm had a median OS of 19.2 mo (95%CI: 13.6, not reached) vs 13.5 mo (95%CI: 9.3, 15.9) for placebo (HR:0.60 95%CI: 0.38, 0.94) for the intent-to-treat population; for the subset of pts with $\geq$10% FGFR2b+ by IHC, the median OS for bema was 25.4 mo (95%CI: 13.8, not reached) vs 11.1 mo (95% CI: 8.4, 13.8) for placebo (HR: 0.41 95%CI: 0.23, 0.74). **Conclusions:** The addition of bema to mFOLFOX6 improved the OS of 1L FGFR2b + GC pts vs mFOLFOX6 alone. Outcomes favored bema across pre-specified subgroups. Pts with overexpression of FGFR2b even without ctDNA amplification demonstrated a benefit from the addition of bema to mFOLFOX6, supporting further evaluation of bema in tumors with FGFR2b overexpression without the requirement for gene amplification. Clinical trial information: NCT03694522. Research Sponsor: Five Prime Therapeutics, Inc.

4011 **Clinical Science Symposium**

hENT1 gene expression as a predictor of response to gemcitabine and nab-paclitaxel in advanced pancreatic cancer. *First Author: Sheron Perera, Princess Margaret Cancer Centre/University Health Network/University of Toronto, Toronto, ON, Canada*

Background: Human equilibrative nucleoside transporter 1 (hENT1) belongs to a family of nucleoside transporters critical to entry of gemcitabine into cells. The prognostic and predictive characteristics of this biomarker in pancreatic ductal adenocarcinoma (PDAC) have primarily been evaluated by immunohistochemistry, with conflicting results. We explored the impact of hENT1 gene expression in the Comprehensive Molecular Characterization of Advanced Ductal Pancreas Adenocarcinoma for Better Treatment Selection (COMPASS) trial. **Methods:** Patients were enrolled on COMPASS from December 2015 to June 2020 and underwent a biopsy for whole genome sequencing (WGS) and RNA sequencing prior to first chemotherapy in the advanced setting. Biopsies underwent laser capture microdissection to enrich for tumour epithelium. Chemotherapy regimen was determined based on clinician preference. The cut-off thresholds for hENT1 expression were determined using the maximal chi-squared statistic. Response rates and overall survival (OS) were computed based on hENT1 expression and chemotherapy regimen. **Results:** 254 patients were included in the analyses with a median follow-up time of 18 months. 146 patients were treated with modified FOLFIRINOX (FFX), 104 with gemcitabine and nab-paclitaxel (GnP), and 16 received no systemic therapy. Based on gene expression levels, 133 patients were classified as hENT1 ^{high} and 121 as hENT1 ^{low}. hENT1 expression was significantly associated with the modified Moffitt classifier with higher expression seen in classical tumours ($p < 0.001$). In the entire cohort, median OS was 10.0 months in hENT1 ^{high} vs. 8.3 months in hENT1 ^{low} (adjusted HR 0.78, 95% confidence interval 0.59 - 1.03, $p = 0.08$). In patients receiving modified FFX, there was no difference in response rates (32% vs. 31%, $p = 1.00$) or OS (10.6 vs. 10.6 months, $p = 0.94$) between the hENT1 ^{high} and hENT1 ^{low} groups, respectively. However, in patient treated with GnP, response rates were significantly higher in hENT1 ^{high} patients compared to those with hENT1 ^{low} tumors (45% vs. 21%, $p = 0.035$). Median OS in this GnP treated cohort was 9.8 months in hENT1 ^{high} vs. 6.1 months hENT1 ^{low} ($p = 0.003$). In an interaction analysis, hENT was predictive of treatment response to GnP ($p = 0.0002$). **Conclusions:** Biomarkers predictive of response to GnP and FFX are urgently needed. Here we demonstrate that hENT1 gene expression is a predictor of response to GnP in advanced PDAC. Research Sponsor: This study was conducted with the support of the Ontario Institute for Cancer Research (PanCuRx Translational Research Initiative) through funding provided by the Government of Ontario, the Wallace McCain Centre for Pancreatic Cancer supported by the Prin.

4012 **Poster Discussion Session**

RATIONALE 302: Randomized, phase 3 study of tislelizumab versus chemotherapy as second-line treatment for advanced unresectable/metastatic esophageal squamous cell carcinoma. *First Author: Lin Shen, Department of Gastrointestinal Oncology, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Peking University Cancer Hospital & Institute, Beijing, China*

Background: Tislelizumab (tisle) monotherapy or plus chemotherapy demonstrated antitumor activity in patients (pts) with solid tumors, including esophageal squamous cell carcinoma (ESCC) (NCT03469557 and CTR20160872). **Methods:** In this global phase 3 study (NCT03430843), adults with histologically confirmed advanced/unresectable or metastatic ESCC whose disease progressed following prior systemic therapy with ≥1 evaluable lesion per RECIST v1.1 and an Eastern Cooperative Oncology Group performance score (ECOG PS) of ≤1 were included. Pts were randomized (1:1) to receive tisle 200 mg intravenously every 3 weeks or investigator-chosen standard chemotherapy ([ICC]; paclitaxel, docetaxel, or irinotecan) and treated until disease progression, unacceptable toxicity, or withdrawal. Stratification factors included ICC option, region, and ECOG PS. The primary endpoint was overall survival (OS) in the intent-to-treat (ITT) population. The key secondary endpoint was OS in the programmed death-ligand 1 (PD-L1)+ population (visually-estimated combined positive score [vCPS] ≥10%, by VENTANA PD-L1 SP263 assay). Other secondary endpoints included (by RECIST v1.1) progression-free survival, overall response rate (ORR), duration of response (DoR), and safety. **Results:** Overall, 512 pts (median age: 62 years; range 35-86 years) from 132 sites in 10 countries in Asia (404 pts [79%]), Europe, and North America (108 pts [21%]) were randomized to tisle (n=256) or ICC (n=256) (ITT population). Of these, 157 pts (tisle [n=89], ICC [n=68]) had vCPS ≥10% (PD-L1+ population). On 1 Dec 2020 (data cut-off), median follow-up was 8.5 months (m) with tisle and 5.8 m with ICC. The study met its primary endpoint: tisle clinically and significantly improved OS vs ICC in the ITT population (median OS: 8.6 vs 6.3 m; HR 0.70, 95% CI 0.57-0.85, p=0.0001). Tisle also demonstrated significant improvement in OS vs ICC in the PD-L1+ population (median OS: 10.3 vs 6.8 m; HR 0.54, 95% CI: 0.36-0.79, p=0.0006). Survival benefit was consistently observed across pre-defined subgroups, including baseline PD-L1 status and region. Treatment with tisle was also associated with a higher ORR (20.3% vs 9.8%) and more durable response (median DoR: 7.1 vs 4.0 m; HR 0.42, 95% CI 0.23-0.75) than ICC in the ITT population. Fewer pts had ≥Grade 3 (46% vs 68%) treatment-emergent adverse events with tisle vs ICC. Of these, fewer ≥Grade 3 AEs were treatment-related (TR) with tisle vs ICC (19% vs 56%). Fewer pts discontinued tisle vs ICC (7% vs 14%) due to a TRAE. **Conclusion:** Tisle demonstrated statistically significant and clinically meaningful improvement in OS vs ICC in pts with advanced or metastatic ESCC who had disease progression during or after first-line systemic therapy. Tisle showed a higher and longer response vs ICC. The safety profile of tisle was more favorable than ICC. Clinical trial information: NCT03430843. Research Sponsor: This study is sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Yasmin Issop, PhD, and Kirsty Millar, MSc, of Ashfield MedComms, an Ashfield Health company, and was funded by BeiGene, Ltd.

4013 **Poster Discussion Session**

Pembrolizumab plus trastuzumab and chemotherapy for HER2+ metastatic gastric or gastroesophageal junction (G/GEJ) cancer: Initial findings of the global phase 3 KEYNOTE-811 study. *First Author: Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Trastuzumab (tras) plus chemotherapy (chemo) is standard-of-care (SOC) 1L therapy for HER2+ metastatic G/GEJ cancer. In two phase 2 studies, tras, chemo, and pembrolizumab (pembro) in combination showed promising efficacy and manageable safety. The ongoing global, randomized, double-blind, placebo-controlled phase 3 KEYNOTE-811 study is assessing whether adding pembro to SOC improves efficacy vs SOC alone for HER2+ metastatic G/GEJ cancer (NCT03615326). **Methods:** Eligible patients (pts) with previously untreated, unresectable or metastatic HER2+ G/GEJ cancer and ECOG PS 0 or 1 are randomized 1:1 to pembro 200 mg IV Q3W or placebo IV Q3W. All pts receive tras and investigator's choice of 5-fluorouracil and cisplatin (FP) or capecitabine and oxaliplatin (CAPOX). Treatment is given up to 2 y or until intolerable toxicity or PD. Dual primary end points are PFS per RECIST v1.1 by blinded, independent central review (BICR) and OS. Secondary end points are ORR and DOR per RECIST v1.1 by BICR and safety. Planned enrollment in the global cohort is 692 pts; accrual is almost complete. The protocol-specified first interim analysis (IA1) was to occur when the first 260 pts enrolled had ≥8.5 mo of follow-up and tested whether pembro + SOC significantly improved ORR; the superiority boundary was $P = 0.002$. The ORR difference was calculated using the Miettinen and Nurminen method stratified by the randomization stratification factors of geographic region, PD-L1 status, and chemo choice. Efficacy is presented for the first 264 pts enrolled. Safety is presented for all treated pts enrolled as of Jun 17, 2020. **Results:** Among the first 264 pts enrolled, 133 were randomized to pembro + SOC, 131 to placebo + SOC; 0.8% had MSI-H tumors, CAPOX was chosen for 87.1%, and median study follow-up was 12.0 mo (range, 8.5-19.4). Confirmed ORR (95% CI) was 74.4% (66.2-81.6) for pembro + SOC vs 51.9% (43.0-60.7) for placebo + SOC (difference, 22.7 percentage points [95% CI, 11.2-33.7], $P = 0.00006$); CR rate was 11.3% vs 3.1% and DCR (95% CI) was 96.2% (91.4-98.8) vs 89.3 (82.7-94.0). Median (range) DOR was 10.6 mo (1.1+ to 16.5+) for pembro + SOC vs 9.5 mo (1.4+ to 15.4+) for placebo + SOC; KM estimates of DOR ≥6 mo and ≥9 mo were 70.3% vs 61.4% and 58.4% vs 51.1%. As of data cutoff, 433/434 enrolled pts were treated (217/217 pembro + SOC, 216/217 placebo + SOC). AEs were grade 3-5 in 57.1% of pts with pembro + SOC vs 57.4% with placebo + SOC, led to death in 3.2% vs 4.6%, and led to discontinuation of any drug in 24.4% vs 25.9%. **Conclusions:** Adding pembro to tras and chemo resulted in a substantial, statistically significant increase in ORR versus trastuzumab and chemo alone as 1L therapy for HER2+ metastatic G/GEJ cancer; responses were durable and safety was manageable. These initial data support pembro plus tras and chemo as a potential new treatment option for this population. Clinical trial information: NCT03615326. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4014 **Poster Discussion Session**

Phase III trial comparing XELOX regimen (oxaliplatin plus capecitabine) versus EOX regimen (epirubicin, oxaliplatin and capecitabine) as first-line treatment for advanced gastric cancer: EXELOX trial. *First Author: Weijian Guo, Department of Medical Oncology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, China*

Background: At present, there is no standard chemotherapy regimen for advanced gastric cancer (AGC), and there is no consensus whether the three-drug combination is better than two-drug combination in first-line treatment. Both of XELOX regimen and EOX regimen are widely recommended as firs-line chemotherapy regimens for AGC. In this EXELOX trial, we aimed to compare the efficacy and safety of EOX and XELOX regimens. **Methods:** EXELOX is an open-label, multicenter, prospective, randomized phase III trial that enrolled 448 previously untreated patients with histologically confirmed advanced gastric adenocarcinoma from 7 hospitals in China. Patients were randomly assigned (1:1) to receive XELOX regimen (oxaliplatin 130mg/m^2 d1; xeloda 1000mg/m^2 bid d1-14) or EOX regimen (epirubicin 50mg/m^2 d1; oxaliplatin 130mg/m^2 d1; xeloda 1000mg/m^2 bid d1-14) in this study. Treatment was repeated every 3 weeks until disease progression, intolerable toxicity, patient death, withdrawal of informed consent, or up to eight cycles, followed by xeloda single-agent maintenance. We stratified randomization by Eastern Cooperative Oncology Group status, extent of disease(locally advanced/metastatic) and clinical trial center. Patients and clinicians were not masked to the allocated treatment. The primary endpoint was progression-free survival (PFS) on an intention-to-treat basis with a non-inferiority upper margin of 1.3 for the hazard ratio (HR). The clinical trial was a non-inferiority study that was registered with ClinicalTrials.gov, Number NCT02395640. The study is ongoing, but no longer recruit new participants. **Results:** Between Apr 10,2015 and Aug 20,2020, a total of 448 AGC patients were randomized to receive XELOX (n = 222) or EOX (n = 226). In ITT basis, the median PFS was 5.0 months (95%CI 4.5-6.0) in XELOX group and 5.5 months (95%CI 5.0-6.0) in EOX group (HR 0.989, 95%CI 0.812-1.203; $P_{\text{non-inferiority}} = 0.0032$). In Per-protocol population (n = 428), the median PFS was 5.0 months (95%CI 5.0-6.0) in XELOX group and 5.5 months (95%CI 5.0-6.0) in EOX group (HR 0.983, 95%CI 0.807-1.198; $P_{\text{non-inferiority}} = 0.0028$). The incidence of grade 3-4 adverse events (AEs) was 42.2% (90/213) in XELOX group and 72.5(156/215) in EOX group ($p = 0.001$). The most common grade 3-4 AEs were neutropenia (affecting 13.1% (28/213) in XELOX group and 48.4% (104/215) in EOX group ($p = 0.000$). The incidence of chemotherapy dose reduction was 35% (75/213) in XELOX group and 55% (120/215) in EOX group($p = 0.009$). One treatment-related death (lung infection) was observed in EOX group, and none in XELOX group. **Conclusions:** XELOX regimen is noninferior to EOX regimen in PFS with a better safety profile as first-line treatment for AGC patients, therefore XELOX is a more favorable choice and might be one of the standard first-line chemotherapy regimens. Clinical trial information: NCT02395640. Research Sponsor: This study was funded by The National Key Research and Development Program of China (grant no. 2017YFC1308900), Other Foundation.

4015 **Poster Discussion Session**

Maintenance durvalumab after first-line platinum-based chemotherapy in advanced oesophago-gastric (OG) adenocarcinoma: Results from the PLATFORM trial. *First Author: Caroline Fong, The Royal Marsden NHS Foundation Trust, London and Sutton, United Kingdom*

Background: PLATFORM is a prospective, open-label, multicentre, adaptive phase II trial assessing maintenance therapy in patients (pts) with OG adenocarcinoma after platinum-based first-line induction chemotherapy. HER2 negative pts were initially randomised 1:1:1:1:1 to surveillance (A1), capecitabine (A2), durvalumab (A3), with rucaparib (A4) and capecitabine + ramucirumab (A5) added later as per adaptive design. Here we report the primary analysis of durvalumab maintenance vs. surveillance. **Methods:** Pts were randomised upon achieving response or stable disease following 18 weeks of platinum-based chemotherapy and were stratified by region, disease extent and performance status. A1 pts had 4 weekly surveillance visits and A3 pts received 10mg/kg durvalumab iv Q2W. Target accrual was 154 pts/arm; however, A3 was closed prematurely after cessation of industry support. The primary endpoint was progression-free survival (PFS) from randomisation post induction chemotherapy to disease progression according to RECIST 1.1 criteria, or death. Secondary endpoints were time to treatment failure (TTF), objective response rate (ORR), overall survival (OS) and toxicity. Survival analyses according to PD-L1 using the combined positive score (CPS, Ventana SP263 assay) was conducted. **Results:** A total of 205 pts were concurrently randomised into A1 (n = 100) and A3 (n = 105). At data cut-off (02 Feb 2021), median follow up was 24.2 months [95% confidence interval (CI) 21.6-36.8]. There was no significant difference in PFS between A1 and A3 [median PFS: 3.2 vs. 4.7 months (hazard ratio (HR) 0.79 (95% CI 0.59-1.06, p = 0.122) respectively]. Median OS was 11.4 vs. 11.3 months (HR 0.92, 95% CI 0.66-1.27, p = 0.60) in A1 and A3 respectively and no significant difference in TTF was detected between both arms (median TTF: 3.2 vs. 3.5 months (HR 0.92, 95% CI 0.69-1.23, p = 0.558)]. ORR was 6% in A3 (n = 2 complete and n = 4 partial responses) whereas no radiological responses were seen in A1. PD-L1 results were available for 76 pts in A1 and 77 pts in A3. PFS was comparable between subgroups using the PD-L1 CPS thresholds of ≥1, ≥5 and ≥10. The safety population consisted of 199 pts (A1: 98 pts and A3: 101 pts). Grade ≥3 treatment-related adverse events were reported in 18% of A3 pts and no new safety signals were identified. **Conclusions:** Although a survival advantage was not seen with maintenance durvalumab compared to surveillance, a subset of patients who received durvalumab demonstrated incremental radiological responses. Exploratory analysis of PD-L1 expression was not associated with improved survival outcomes. Clinical trial information: NCT02678182. Research Sponsor: The Royal Marsden NHS Foundation Trust, Pharmaceutical/Biotech Company.

4016 **Poster Discussion Session**

Preoperative chemoradiotherapy to improve overall survival in pancreatic cancer: Long-term results of the multicenter randomized phase III PREOPANC trial. *First Author: Casper H.J. Van Eijck, Department of Surgery, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands*

Background: Preoperative chemoradiotherapy (CRT) may improve overall survival in resectable pancreatic cancer (RPC) and borderline resectable pancreatic cancer (BRPC). Long term results are presented. **Methods:** In this multicenter phase III trial, patients with RPC or BRPC were randomized between preoperative CRT, (gemcitabine 1000 mg/m^2 weekly for 7 of 10 weeks, and 15x2.4 Gy radiotherapy in week 4 to 6), followed by surgery and four cycles of adjuvant gemcitabine (1000 mg/m^2 weekly for 3 of 4 weeks), or immediate surgery followed by 6 cycles of adjuvant gemcitabine (1000 mg/m^2 weekly for 3 of 4 weeks). Primary endpoint was overall survival by intention-to-treat (ITT). **Results**: From April 2013 to July 2017, 246 eligible patients were accrued by 16 Dutch centers and randomized, 119 to preoperative CRT and 127 to immediate surgery. After a median follow up of 56 months (35.3-92.0 months), 210 patients have died, 93 (78%) in the preoperative CRT arm and 117 (92%) in the immediate surgery arm. Three- and five-year overall survival ITT was 27.7% and 20.5% after preoperative CRT versus 16.5% and 6.5% after immediate surgery (HR 0.73; 95% CI 0.56 to 0.96; p = 0.025). In addition, disease-free survival (HR 0.70; p = 0.009) locoregional failure-free interval (HR 0.57; p = 0.004) and distant metastases free interval (HR 0.74; p = 0.071) improved after preoperative CRT. Also in the stratified subsets RPC and BRPC, preoperative CRT improved OS: RPC (n = 133, HR 0.79; 95% CI 0.54 to 1.16; P = 0.23). BRPC (n = 113, HR 0.67; 95% CI 0.45 to 0.99; p = 0.045). We could not demonstrate a difference in treatment effect between these subsets (interaction test p = 0.56). **Conclusions:** Preoperative gemcitabine-based CRT for RPC or BRPC improves long term overall survival compared to immediate surgery with adjuvant gemcitabine. Clinical trial information: NTR3709. Research Sponsor: Dutch Cancer Foumdation (KWF).

4017 **Poster Discussion Session**

Randomized phase II study of modified FOLFIRINOX versus gemcitabine plus nab-paclitaxel combination therapy for locally advanced pancreatic cancer (JCOG1407). *First Author: Masato Ozaka, Department of Gastroenterology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: FOLFIRINOX, consisting of leucovorin (LV), fluorouracil (FU), irinotecan (IRI) and oxaliplatin (L-OHP), and GnP, consisting of gemcitabine (GEM) plus nab-paclitaxel (nPTX), have shown superior efficacy over GEM in patients (pts) with metastatic pancreatic cancer. Although several studies have reported the efficacy of FOLFIRINOX or GnP for pts with locally advanced pancreatic cancer (LAPC), no randomized controlled trial to compare the two regimens has been conducted in those pts. To select the most promising chemotherapy for LAPC, a randomized phase II selection design trial (JCOG1407) was conducted to compare between modified FOLFIRINOX (FOLFIRINOX with dose reduction of IRI and without bolus FU; Arm A) and GnP (Arm B) for pts with LAPC. **Methods:** In Arm A, 85 mg/m^2 of L-OHP, 200 mg/m^2 of l-LV, 150 mg/m^2 of IRI, followed by 2,400 mg/m^2 of continuous FU over 46 hours are infused every 2 weeks. In Arm B, 125 mg/m^2 of nPTX followed by 1,000 mg/m^2 of GEM are infused on days 1, 8, and 15 every 4 weeks. The primary endpoint was overall survival (the proportion of 1-year OS), and secondary endpoints included progression-free survival (PFS), distant metastasis-free survival (MFS) and response rate in pts with target lesions. The planned sample size was 124 pts to select more effective regimen in 1-year OS with a probability of at least 0.85 and to test the null hypothesis of 53% in 1-year OS with a one-sided alpha of 5% and 80% **Results:** From 2015 to 2019, a total of 126 pts was enrolled from 29 Japanese institutions, and were allocated to Arm A (n = 62) or Arm B (n = 64). The median (range) age was 66 (44-75) years and 58.7% were male. At the analysis, after a median (range) follow-up of 1.52 (0.55-3.99) years, 75 (59.5%) pts died. The proportion of 1-year OS was better in Arm B, 77.4% [95% CI 64.9–86.0] vs. 82.5% [95% CI 70.7–89.9], but 2-year OS was better in Arm A, 48.2% [95% CI 33.3–61.7] vs. 39.7% [95% CI 28.6–52.5]. Median OS was 2.0 years [95% CI 1.6-2.7] in Arm A and 1.8 years [95% CI 1.5-2.0] in Arm B. 1-year PFS for Arm A/B was 47.5 % [95% CI 34.5-59.4]/40.2% [95% CI 27.8-52.3], and 1-year MFS was 64.2 % [95% CI 50.9-74.8]/57.3% [95% CI 43.9-68.6]. Arm A was better OS in pts with CA19-9 $<$1000 U/mL and the opposite trend was observed in pts with CA19-9$>$1000 U/mL. Response rate was 30.9% [95% CI 19.1-44.8] in Arm A, and 41.4% [95% CI 28.6-55.1]) in Arm B. Incidences of grade 3-4 non-hematological toxicities for Arm A and Arm B were 66.1% and 67.2%, respectively. There was no treatment-related death. **Conclusions:** This study was the first randomized trial comparing the two regimens. The 1-year OS of the primary endpoint in GnP was better than mFOLFIRINOX, but mFOLFIRINOX achieved longer survival in 2-year OS. It is required to confirm longer OS and safety profiles which regimen should be selected as a standard regimen in LAPC. Clinical trial information: jRCTs031180085. Research Sponsor: Japan Agency for Medical Research and Development.

4018 **Poster Discussion Session**

Masitinib plus gemcitabine as first-line treatment of pancreatic cancer with pain: Results from phase 3 study AB12005. *First Author: Joel Ezenfis, Centre Hospitalier Sud Francilien, Corbeil-Essonnes, France*

Background: Masitinib (MAS) is a small molecule drug targeting mast cell and macrophage activity, innate immune cells that are critical components of the tumor microenvironment. Proof of concept that MAS in combination with gemcitabine (GEM) improved overall survival (OS) in pancreatic cancer (PC) patients (pts) with pain, was previously shown [doi 10.1093/annonc/mdv133]. The presence of pain in PC is thought to identify pts whose disease is driven in part by a pro-tumoral immune response. **Methods:** AB12005 was a prospective, placebo (PBO) controlled, double blind, randomized (2:1 MAS:PBO, stratified by disease stage, ECOG and geographic region) phase 3 trial, evaluating oral MAS (6.0 mg/kg/d) in combination with GEM (1000 mg/m^2) against PBO plus GEM for the treatment of unresectable locally advanced PC (LAPC) and/or metastatic PC (mPC) pts with pain criteria; i.e. baseline visual analog scale of pain intensity (VAS) $>$ 20 and/or pt treated with an opioid analgesics dose $\geq$1 mg/kg/d at baseline. Eligible pts were chemo-nave with histologically or cytologically confirmed inoperable LAPC or mPC and an ECOG status $\leq$2. The estimated sample size was ~330 pts to detect an OS hazard ratio (HR) of 0.68 (80% power, 2-sided α = 0.025) after 310 deaths. The study was successful if improvement in median OS (primary endpoint) relative to control reached a 2.5% level of statistical significance for either a targeted subgroup of LAPC with pain criteria, or the overall study cohort. **Results:** A total of 384 pts were enrolled (safety population n = 383; mITT n = 379; target subgroup n = 92). In the predefined subgroup of unresectable LAPC with pain, MAS-GEM (n = 62) showed significant benefit over PBO-GEM (n = 30) with median OS of 13.0 months (97.5% CI [11.0;18.0]) vs 11.2 months (97.5% CI [7.4;13.0]); p = 0.007. The HR was 0.46 (97.5% CI [0.2;0.9], p = 0.0047), corresponding to a significant 54% reduction in risk of death for MAS-GEM pts relative to control. Secondary analyses in the same subgroup were convergent with this primary outcome. Median PFS showed a 1.8 month between group difference in favor of MAS-GEM (p = 0.039), with a HR of 0.47 (97.5% CI [0.3;0.9], p = 0.014). The 12-month and 18-month OS rates showed a 1.3 fold and 3.4 fold improvement, respectively, in favor of MAS-GEM (53.2% and 33.9% for MAS-GEM vs 40.0% and 10% for PBO-GEM, respectively). In the overall population, comprising LAPC and mPC pts with pain, no survival benefit was observed; median OS for MAS-GEM (n = 244) was 6.9 months vs 8.0 months for PBO-GEM (n = 135); p = 0.461. The MAS-GEM combination was well tolerated with no sign of add-on toxicity. The proportion of patients presenting at least one adverse event (AE) or serious AE was respectively, 96.3% and 19.1% for MAS-GEM (n = 246) vs 99.3% and 21.3% for PBO-GEM (n = 136). **Conclusions:** The combination MAS (6.0 mg/kg/d) plus GEM may provide a new first line treatment option for unresectable LAPC pts with associated pain. Clinical trial information: NCT03766295. Research Sponsor: AB Science.

4019 **Poster Discussion Session**

Gemcitabine (Gem) and nab-paclitaxel (NP) ± nivolumab (nivo) ± CD40 agonistic monoclonal antibody APX005M (sotigalimab), in patients (Pts) with untreated metastatic pancreatic adenocarcinoma (mPDAC): Phase (Ph) 2 final results. *First Author: Mark H. O'Hara, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: Results from a ph1b trial evaluating gem/NP with CD40 agonistic monoclonal antibody APX005M ± nivo demonstrated promising clinical activity in pts with untreated mPDAC (O'Hara 2021). Herein, we report results from the follow-on, randomized (rand) ph2 trial evaluating gem/NP ± nivo ± APX005M. **Methods:** Pts with untreated mPDAC were rand to 1 of 3 open-label arms: gem/NP/nivo (A), gem/NP/APX005M (B), gem/NP/nivo/APX005M (C). All pts were treated with 1000 mg/m^2 gem and 125 mg/m^2 NP. Patients received 240 mg nivo in arms A and C and 0.3 mg/kg APX005M (RP2D) IV in arms B and C. Ph1b pts were included in ph2 analyses. 1° endpoint: 1-year OS rate of each arm, compared to a 35% historical OS rate for gem/NP (Von Hoff 2013). Key 2° endpoints: ORR, DCR, DOR, PFS and safety. Tumor and blood were collected for biomarker analysis. Planned enrollment of 35 pts/arm provided 81% power for testing the alternative of 58% OS rate vs 35%, using a 1-sided, 1-sample Z test with 5% type I error. Trial was not powered for cross-arm comparison. **Results:** 93 pts were rand in ph2 (N = 34, 30, 29 to A, B, C); when ph1b pts included, a total of 105 pts (34, 36, 35) were analyzed for efficacy and 108 pts (36, 37, 35) for safety. Min follow-up was 14 months (mos). Baseline characteristics were balanced across arms, inclusive of tumor burden, presence of liver metastases and stage at initial diagnosis (stage 1-3 vs 4). 1-year OS rate was 57% (1-sided p = 0.007 vs 35% historical rate, 95% lower CI bound = 41%) for A, 51% (p = 0.029, 95% bound = 36%) for B and 41% (p = 0.236, 95% bound = 27%) for C. Median OS and secondary endpoints are listed in Table. TRAE rates were similar across arms and to ph1b. 8 (7%) pts experienced an AE leading to tx discontinuation (6, 1, 1 in A, B, C), 40 (37%) pts experienced a serious TRAE (14, 15, 11 in A, B, C) and 2 pts died due to TRAEs; 1 each in B (acute hepatic failure) and C (intracranial hemorrhage). **Conclusions:** In this ongoing, seamless ph1b/2 trial of gem/NP ± nivo ± APX005M in pts with mPDAC, antitumor activity was observed in all arms. 1° endpoint of 1-year OS $>$ 35% was met when combining gem/NP with either nivo or APX005M; however, not the combination. Safety was manageable; consistent with ph1b. Detailed multiomic immune and tumor biomarker analyses are underway to elucidate mechanisms of action and inform pt subsets that benefit most from these combinations. Clinical trial information: NCT03214250. Research Sponsor: Parker Institute for Cancer Immunotherapy, Other Foundation, Pharmaceutical/Biotech Company.

% (n) [95% CI]	A (n = 34)	B (n = 36)	C (n = 35)
ORR*	50 (17) [32–68]	33 (12) [19–51]	31 (11) [17–49]
ORR (confirmed)*	35 (12) [20–54]	33 (12) [19–51]	26 (9) [13–43]
DCR	74 (25) [56–87]	78 (28) [61–90]	69 (24) [51–83]
Median DOR, mos	4.8 [2.5–NE]	5.5 [3.7–7.6]	6.6 [1.9–NE]
Median PFS, mos	6.3 [5.2–8.8]	7.2 [5.3–9.2]	6.7 [4.1–9.8]
Median OS, mos	16.7 [9.8–20.4]	14.5 [7.2–20.1]	10.1 [7.9–13.2]
1-year OS, % [p]	57 [0.007]	51 [0.029]	41 [0.236]

*1 CR observed in A; NE = Not estimable.

4020 **Poster Discussion Session**

KG 4/2015: A randomized, controlled, multicenter, open-label phase III clinical trial of GV1001 with gemcitabine/capecitabine in previous untreated, eotaxin-high patients with advanced pancreatic ductal adenocarcinoma. *First Author: Jung Hyun Jo, Yonsei University Severance Hospital, Seoul, South Korea*

Background: In the TeloVac study, GV1001 with Gemcitabine/capecitabine (G/C) did not show increased overall survival (OS) than G/C in patients (pts) with advanced pancreatic ductal adenocarcinoma (PDA). But cytokine examination suggested high serum eotaxin level may predict improved survivals in pts received GV1001 with G/C. This phase III trial was designed to assess the efficacy of GV1001 with G/C for previous untreated eotaxin-high Korean pts with advanced PDA. **Methods:** Eligible pts with histologically proven locally advanced and metastatic PDA (except peritoneal carcinomatosis), age > 18 years, and ECOG PS 0–2 were recruited. Pts were randomly assigned (1:1) to receive either G/C or G/C with GV1001 (G/C/GV). All pts receiving G/C/GV were with high serum eotaxin level (≥81.02 ng/mL), and the pts receiving G/C were randomly assigned again (1:1) to eotaxin-high and eotaxin-low pts. Study was designed according to Korean MFDS guidance for approval of clinical trial. G/C treatment included G (1000 mg/m^2, 30 min IVF, D 1, 8, & 15) and C (830 mg/m^2 BID for 21 days per month (m). G/C/GV treatment included an intradermal injection of GM-CSF (75 μg) and GV1001 (0.56 mg; D 1, 3, & 5, once on week 2–4, & 6, then monthly thereafter) from the start of G/C. The primary endpoint was OS. The secondary endpoints included time to progression (TTP), objective response rate, and safety. Survival data was analyzed using the copula graphic estimate method under dependent censoring. The response was independently assessed per RECIST v1.1. Under the one-sided significance level of 2.5% and to achieve the power of 80% of the statistical significance with the median OS difference from 7.9 to 14.9 m (HR = 0.53), 85 events and 118 registrations needed. Considering 20% drop-outs, 148 registrations were required. **Results:** Between Nov 2015 and Apr 2020, of 511 pts screened in 16 centers, eotaxin-high pts were identified as 34.7% (174 / 502 pts). 148 pts randomly assigned to G/C/GV (n = 75; all eotaxine-high) and G/C (n = 73; 37 eotaxine-high, 36 eotaxine-low). Median OS was significantly improved in the G/C/GV group with 11.3m [95% CI 8.6-14.0] than G/C group with 7.5 m [95% CI 5.1-10.0] (p = 0.021). Also, median TTP was significantly improved in the G/C/GV group (7.3 m [95% CI 5.0-9.7]) than in the G/C group (4.5 m [95% CI 3.2-5.8], p = 0.021). In other secondary endpoints, no statistical significance was confirmed between the two groups. Grade 3-4 treatment-emergent adverse events were reported in 49 pts (73.13%) vs. 58 pts (77.33%) in the G/C and G/C/GV group, without significant differences (p = 0.562). **Conclusions:** G/C/GV treatments significantly extend OS and TTP in advanced PDA than G/C, and specific safety-related issues had not been found. GV1001 should be considered as one of the options in PDA pts with high serum eotaxin levels. Clinical trial information: NCT02854072. Research Sponsor: SAMSUNG PHARM CO., LTD.

4021 **Poster Discussion Session**

High CXCR4 expression in pancreatic ductal adenocarcinoma as characterized by an inflammatory tumor phenotype with potential implications for an immunotherapeutic approach. *First Author: Andreas Seeber, Department of Internal Medicine V (Hematology and Oncology), Medical University of Innsbruck, Comprehensive Cancer Center Innsbruck, Innsbruck, Austria*

Background: Immunotherapy is considered ineffective in the majority of patients with pancreatic ductal adenocarcinoma (PDAC), a consequence of a highly immunosuppressive tumor microenvironment (TME). However, treatment induced inhibition of CXC chemokine receptor 4 (CXCR4) and programmed cell death protein-1 (PD-1) in the COMBAT trial caused T cell infiltration and tumor regression in a subset of PDAC patients. Elucidating a phenotype that predicts response is clinically relevant. We performed a comprehensive molecular landscape study in PDAC evaluating CXCR4 RNA expression. **Methods:** 3,647 PDAC specimens were centrally analysed. NextGen DNA sequencing (NextSeq, 592 gene panel or NovaSeq, whole-exome sequencing), whole-transcriptome RNA sequencing (NovaSeq) and immunohistochemistry (Caris Life Sciences, Phoenix, AZ) were performed. Gene expression is reported as TPM (Transcripts per million). Pathway gene enrichment analyses were done using GSEA (Subramaniam 2015, PNAS). Immune cell fraction was calculated by QuantiSeq (Finotello 2019, Genome Medicine). The cohort was stratified in quartiles according to CXCR4 RNA expression status. **Results:** Overall, CXCR4 expression was higher in primary tumors compared to distant metastasis (38 vs. 28 TPM, p < 0.0001). CXCR4-high (top quartile: > 59 TPMs), when compared to CXCR4-low (bottom quartile: < 17 TPM) PDACs, were characterized by a high prevalence of mutations in signal transduction pathway genes (e.g. *GNAS*: 3.6 vs. 0.5%), an increased infiltration of immune cells (e.g. $CD8^+$ T cells, M1 macrophages), and a higher expression of HLA-DRA and HLA-E (all p < 0.0001). We detected an upregulation of CXCL9, CXCL10, CXCL12, CCL5, IDO1 and LAG3 in CXCR4-high compared to CXCR4-low tumors. In contrast, lower PD-L1 expression (17.4 vs. 13.1%, p = 0.02), genomic loss of heterozygosity (17.4 vs. 10.8%), and a lower frequency of gene amplifications in *ERBB2* (2.1 vs. 0.1%), *TNFRSF14* (2.0 vs. 0.1%), and *TP53* (82 vs. 73%, all p < 0.0001) were observed. Moreover, CXCR4-high expression was associated with a better survival (HR: 1.417, 95% CI [1.168-1.72], p < 0.001). **Conclusions:** This is the first study comprehensively investigating the molecular landscape of PDACs according to CXCR4 RNA expression. High CXCR4 expression is associated with an improved survival and a pro-inflammatory phenotype that may identify a subset of tumors with greater responsiveness to immunotherapeutic approaches. Research Sponsor: None.

4022 **Poster Discussion Session**

Identification and prognostic impact of *PBRM1* mutations in biliary tract cancers: Results of a comprehensive molecular profiling study. *First Author: Kai Zimmer, Department of Internal Medicine V (Hematology and Oncology), Medical University of Innsbruck, Comprehensive Cancer Center Innsbruck, Innsbruck, Austria*

Background: The prognosis of biliary tract cancers (BTC) remains dismal and novel treatment strategies are needed to improve survival. Polybromo-1 (*PBRM1*) is a subunit of the PBF chromatin-remodeling complex and preclinical studies suggest induction of synthetic lethality by PARP inhibitors in *PBRM1*-mutated cancers. Therefore, we aimed to describe the molecular landscape in BTC harboring *PBRM1* mutations. **Methods:** 1,848 BTC samples were included in this study. Specimens were analyzed using NextGen DNA sequencing (NextSeq, 592 gene panel or NovaSeq, whole-exome sequencing), whole-transcriptome RNA sequencing (NovaSeq) and immunohistochemistry (Caris Life Sciences, Phoenix, AZ). Pathway gene enrichment analyses were done using GSEA (Subramaniam 2015, PNAS). Immune cell fraction was calculated by QuantiSeq (Finotello 2019, Genome Medicine). Survival was calculated from time of tissue collection to last contact using Kaplan-Meier estimates. **Results:** *PBRM1* mutations were identified in 8.1% (n = 150) of BTC tumors and were more prevalent in intrahepatic BTC (9.9%) than in gallbladder cancer (6%, p = 0.0141) and in extrahepatic BTC (4.5%, p = 0.008). In *PBRM1*-mutated tumors, we found a higher rate of MSI-H/dMMR (8.7% vs. 2.1%, p < 0.0001) and a higher median TMB (4 vs. 3 mt/MB, p < 0.0001). When compared to *PBRM1*-wildtype cancers higher rates of co-mutations in chromatin-remodeling genes (e.g. *ARID1A,* 31% vs. 16%, p < 0.0001) and DNA damage repair pathway (e.g. *ATRX,* 4.4% vs. 0.3%, p < 0.0001) were detected. Within *PBRM1*-mutated tumors, a significant higher frequency of infiltrating M1 macrophages was observed (p < 0.0001). Gene set enrichment analysis revealed that genes associated with tumor inflammation (e.g. *HLA-DRA*, *HLA-DRB1*, *IFNGR1*) were enriched in *PBRM1*-mutated tumors (NES = 2.02, FDR = 1.3%, p < 0.0001). Overall survival analysis showed that *PBRM1* mutations were associated with a favorable outcome (HR 1.502, 95% CI [1.013-2.227], p = 0.041). This relationship was also present in MSS subgroup (HR: 1.667, [1.026-2.71], p = 0.037). **Conclusions:** This is the largest and most extensive molecular profiling study focusing on *PBRM1*-mutated BTC. Co-mutations in chromatin-remodelling and DNA damage repair genes might set the stage for clinical testing of PARP inhibitors in *PBRM1*-mutated BTC. Moreover, a distinct tumor microenvironment characterized by high M1 macrophages infiltration and an enrichment of inflammatory genes suggest a potential benefit of immunotherapy. Research Sponsor: None.

4023 **Poster Discussion Session**

Multimodal profiling of biliary tract cancers to detect potentially actionable biomarkers and differences in immune signatures between subtypes. *First Author: Kabir Mody, Mayo Clinic, Jacksonville, FL*

Background: Biliary tract cancers (BTC) are increasingly subtyped by molecular alterations, but little is known about the relationship between gain-of-function mutations and the RNA transcript expression of immune-related pathways. **Methods:** A sample of retrospective, clinicogenomic and transcriptomic data from de-identified records of patients with BTC in the Tempus database was selected. We then investigated the relationship between the mutational landscape and immune-related RNA signatures of different anatomic and genomic BTC subtypes. **Results:** The cohort included 455 samples of intrahepatic bile duct (IH) (n=267), gallbladder (GB) (n=153), and extrahepatic bile duct (EH) (n=35) cancer subtypes. Across all subtypes, we detected alterations in *TP53* (43.8%), *ARID1A* (19.8%), *KMT2C* (18.2%), *BAP1* (14.6%), *KRAS* (12.7%), *TERT* (12.0%), *IDH1* (11.4%), *KMT2D* (11.0%), *LRP1B* (11.0%), and *PBRM1* (10.7%), along with *FGFR2* fusions (2.6%). Potentially actionable biomarkers (*FGFR2* and *NTRK1-3* fusions, *IDH1* and $BRAF^{V600E}$ mutations, tumor mutational burden [TMB]>10, HER2 expression, and/or microsatellite instability) were identified in 21.1% of all BTC and 28.6% of IH samples. Mutually exclusive alterations observed between subtypes were *TP53* & *BAP1*, *KRAS* & *BAP1*, *TP53* & *IDH1*, *KRAS* & *IDH1*, and *SMAD4* & *BAP1* ($P < 0.001$ for all). GB was more inflamed based on RNA signatures and classical immune biomarkers, including PD-L1 and TMB. RNA signature analyses revealed a higher expression of immune-related pathways in GB than IH ($P = 0.001$) with no differences in comparison with EH. PD-L1 expression and continuous TMB were elevated in GB versus the other anatomical subtypes. Significant associations were noted between particular genetic mutations and immune profiling features (table). **Conclusions:** BTC subtypes are diverse in DNA alterations, RNA inflammatory signatures, and immune markers. Notably, potentially actionable biomarkers were identified in a sizable portion of the cohort and varied significantly between subtypes. These results provide guidance for targeted therapy development and support the use of multimodal immune profiling for BTC. For example, GB-specific clinical trials may be considered due to the relative increase in immune-related biomarkers observed in GB and the historically limited success of BTC trials. Research Sponsor: None.

Biomarker associations.

Gene	Biomarker	Mean Biomarker Value in Mutated Samples	Mean Biomarker Value in Wild-Type Samples	Log2 fold-change	Adjusted *P*
ARID1A	TMB	4.82	2.28	0.82	0.0026
BRCA1	TMB	3.81	2.73	0.94	0.049
BAP1	PD-L1 expression	0.73	0.96	-0.59	4.43E-05
BAP1	GEP score	-0.66	-0.47	0.49	0.0026
BAP1	BMS score	1.71	1.83	-0.10	0.0129
BAP1	NRS score	1.87	2.01	-0.11	0.0193
NRAS	PD-L1 expression	0.69	0.94	-0.57	0.027
NRAS	CD8	0.011	0.063	-2.833	0.027
TP53	TMB	3.37	2.32	0.75	0.00044
TP53	NRS score	2.03	1.96	0.0496	0.021

4024 **Poster Session**

The prognostic value of tumor markers in patients (pts) with resectable gastric cancer (GC) receiving perioperative therapy in the CRITICS trial. *First Author: Astrid E. Slagter, Antoni van Leeuwenhoek/Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 are well-known tumor markers. Most studies on CEA and CA 19-9 in pts with GC were performed in Asia, and/or in the metastatic setting. The aim of this study was to investigate the prognostic value of blood derived laboratory parameters in a cohort of European pts with resectable non-metastatic GC. **Methods:** In the CRITICS trial, 788 pts with resectable GC underwent perioperative therapy (preoperative chemotherapy plus either postoperative chemotherapy or postoperative chemoradiotherapy). Blood levels of CEA, CA 19-9, alkaline phosphatase (AP), creatinine, neutrophils, hemoglobin (Hb) and lactate dehydrogenase (LDH) were determined prior to treatment. Data for these variables were available for at least 89% of the pts. Factors significant on univariable cox regression analysis were further explored in multivariable analysis. Probabilities to undergo potentially curative surgery was investigated for factors significant on multivariable analysis. The relationship between tumor markers and the presence of circulating tumor DNA (ctDNA) was explored in 50 pts with available ctDNA data. **Results:** CEA and CA 19-9 were identified as independent prognostic factors for survival (Table). Probabilities to undergo potentially curative surgery were 86%, 77% and 60% for pts with no elevated tumor makers *versus* those with elevated CEA or elevated CA 19-9 *versus* those with both tumor markers elevated, respectively ($p<0.001$). No relationship was found between elevated tumor marker(s) and the presence of ctDNA neither pretreatment nor preoperatively. **Conclusions:** Pretreatment blood levels of CEA and CA 19-9 were identified as prognostic factors for overall survival in a large cohort of European GC pts with potentially curable disease. These factors may guide treatment choices at an early phase and should be included in future trials to determine their role in clinical decision making. Research Sponsor: Dutch Cancer Society, Dutch Colorectal Cancer Groupp, Hoffman La Roche.

Uni-/multivariable analysis on overall survival.

	Factor[1]	Hazard ratio	95% CI	p value
Univariable analysis[2]	CEA	1.45	1.15-1.84	0.002
	CA 19-9	1.75	1.42-2.16	<0.001
	CEA + CA 19-9			
	Both ≤ULN	*		
	CEA or CA 19-9 >ULN	1.46		
	Both >ULN	2.45	1.17-1.81	0.001
			1.77-1.39	<0.001
	AP	1.14	0.78-1.66	0.488
	Creatinine	0.60	0.39-1.07	0.082
	Neutrophils	0.89	0.64-1.22	0.450
	Hb	1.09	0.91-1.30	0.372
	LDH	1.08	0.81-1.43	0.594
Multivariable analysis[3]	CEA + CA 19-9			
	Both ≤ULN	*	1.24-2.00	<0.001
	CEA or CA 19-9 >ULN	1.57	1.86-3.76	<0.001
	Both >ULN	2.65		

[1]All factors were tested categorically (cut-off according to local reference). The lower category was used as reference. [2]Additional included factors of which the data is not shown are age, sex, performance status (PS), Lauren classification, tumor localization and body mass index (BMI); [3]Additional included factors of which the data is not shown are Lauren classification, PS and BMI. *reference.

4025 **Poster Session**

Phase 1 study of the liposomal formulation of eribulin (E7389-LF): Results from the advanced gastric cancer expansion cohort. *First Author: Kensei Yamaguchi, Department of Gastroenterological Chemotherapy, The Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan*

Background: Eribulin has proven efficacy in previously treated metastatic breast cancer and liposarcoma. E7389-LF is a new formulation that uses liposomes to encapsulate eribulin, which is anticipated to improve eribulin concentration in tumor tissues. In the dose-expansion part of a phase 1 study of E7389-LF, the safety profile was acceptable and 2 patients (pts) out of 10 with gastric cancer (GC) had an objective response. Thus, the GC cohort was expanded for further evaluation. Here, we report efficacy and safety data from the phase 1 expansion cohort of pts with advanced GC who were treated with E7389-LF. **Methods:** Eligible pts were those with GC who had no alternative standard or effective therapy options after ≥2 prior chemotherapy regimens. Target total enrollment was 32 pts (10 pts in the initial GC cohort plus an additional 22 pts in the expanded cohort). E7389-LF 2.0 mg/m^2 was administered intravenously once every 3 weeks. Tumor responses were assessed every 6 weeks (± 1 week) by RECIST v1.1. **Results:** At data cutoff (Oct 16, 2020), 34 pts with GC were enrolled (10 pts in the initial GC cohort; 24 pts in the expanded GC cohort) with a median of 5 prior therapies (range, 2–11). Previous immune checkpoint inhibitor (ICI) therapy was reported for 26 (76.5%) pts. All pts were evaluable for objective response rate (ORR) and progression-free survival (PFS), and 30 pts were evaluable for overall survival (OS). Among all pts with GC, the ORR was 17.6% (95% CI 6.8–34.5) and the disease control rate was 79.4% (95% CI 62.1–91.3). Median PFS was 3.7 months (95% CI 2.7–4.3) and median OS was 7.6 months (95% CI 6.7–15.4). The ORRs were 19.2% (95% CI 6.6–39.4) in ICI-pretreated pts and 12.5% (95% CI 0.3–52.7) in pts without prior ICI therapy. Median PFS was similar regardless of prior treatment with ICIs (3.7 months [95% CI 2.7–5.6] in ICI-pretreated pts vs 3.4 months [95% CI 1.0–4.3] in pts without prior ICI therapy); however, the PFS rate at 6 months in ICI-pretreated pts was higher vs the rate in pts without prior ICI therapy (35.9% [95% CI 17.2–55.1] vs 0%, respectively). Median OS was also longer in ICI-pretreated pts (evaluable pts, n = 23) vs pts without prior ICI therapy (evaluable pts, n = 7) (10.0 months [95% CI 6.7–not estimable] vs 6.7 months [95% CI 3.1–8.5], respectively). Common grade ≥3 adverse events included neutropenia (41.2%), leukopenia (29.4%), and anemia (26.5%). In cycle 1, there were no cases of febrile neutropenia among the 22 pts treated with prophylactic peg-GCSF; among pts who did not receive prophylactic peg-GCSF, 16.7% of pts had febrile neutropenia. **Conclusions:** E7389-LF had a manageable safety profile and encouraging activity in pts with heavily treated GC. In pts with GC, prior treatment with ICIs might enhance the potential efficacy of E7389-LF. These results support further development of E7389-LF for advanced GC. Clinical trial information: NCT03207672. Research Sponsor: Eisai Co., Ltd., Tokyo, Japan.

4026 **Poster Session**

Neoadjuvant nivolumab monotherapy in patients with resectable gastric cancer: Preliminary results from a multicenter study. *First Author: Shuji Takiguchi, Nagoya City University, Nagoya, Japan*

Background: In recent years, several studies suggest that neoadjuvant treatment improve outcomes of patients with resectable advanced gastric cancer (GC). In addition, nivolumab has demonstrated clinical efficacy in multiple types of advanced cancer, and the efficacy of neoadjuvant nivolumab monotherapy has been suggested in a past clinical trial in patients with resectable non-small cell lung cancer (NSCLC). Therefore, this phase I study was planned to evaluate the safety and efficacy of neoadjuvant nivolumab monotherapy in patients with resectable GC or NSCLC. Here we report preliminary results from GC patients. **Methods:** This study is a phase I, multicenter, open-label, single arm study to evaluate the safety and efficacy of neoadjuvant nivolumab monotherapy in patients with resectable GC (stage I or II [cT2 or more advanced for both], or stage III) before standard surgery. Nivolumab 240 mg was administered twice every two weeks. The primary endpoint is safety. Efficacy endpoints include major pathological response (MPR) defined as residual disease < 10% and the response of primary lesion, and surgical endpoints include proportion of patients undergoing surgery with curative intent and R0 resection rate. Biomarkers such as PD-L1 expression and MSI status are also evaluated. **Results:** From November 2018 to December 2019, 31 GC patients were enrolled into this study. The median age was 69 years (range, 44-84) and 21 patients (67.7%) were men. According to UICC 8th, clinical stage was stage I in 7 patients (22.6%), stage IIA in 0 patients (0%), stage IIB in 14 patients (45.2%), and stage III in 10 patients (32.3%). MSI status was high in 7 patients (22.6%), low in 4 patients (12.9%), and stable in 20 patients (64.5%). Treatment-related adverse events (TRAEs) occurred in 7 patients (22.6%). The most frequent TRAE was rash which occurred in 2 patients (6.5%); the other TRAEs occurred in 1 patient each. Asymptomatic lipase increased was the only grade 3 TRAE; the other TRAEs were all grade 1 or 2 with no new safety signal. All enrolled patients completed 2 doses of nivolumab. Five patients (16.1%) had MPRs, of whom 1 patient had pathological complete response (pCR). Four of 5 MPRs, 1 pCR included, was observed in 7 MSI-H patients (57.1%) and the remaining case of MPR was observed among 20 MSS patients (5%), whereas no MPRs was achieved in 4 MSI-L patients. Among the 31 patients, 30 patients underwent surgery. The remaining 1 patient discontinued the study before surgery due to disease progression. A total of 27 patients (90%) had R0 resection. **Conclusions:** Neoadjuvant nivolumab monotherapy showed acceptable safety profile and antitumor activity in patients with resectable GC. Recurrence free survival and overall survival in these patients are under follow-up. Clinical trial information: JapicCTI-183895. Clinical trial information: JapicCTI-183895. Research Sponsor: ONO Pharmaceutical CO., LTD, Pharmaceutical/Biotech Company.

4027 **Poster Session**

A phase II study of chemoselection with docetaxel, cisplatin, and 5–fluorouracil as a strategy for organ preservation in patients with resectable esophageal cancer (CROC trial). *First Author: Chikatoshi Katada, Department of Gastroenterology, Kitasato University School of Medicine, Sagamihara, Japan*

Background: In patients with resectable esophageal squamous cell carcinoma (SCC), the outcomes of chemoradiotherapy (CRT) for good responders after three courses of induction chemotherapy (IC) with docetaxel, cisplatin, and 5–fluorouracil (DCF chemotherapy) were unclear. **Methods:** Patients with clinical stage IB–III (UICC 7th) resectable esophageal SCC were eligible. IC included docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1, and 5–fluorouracil 750 mg/m^2 on days 1–5, repeated every 3 weeks for 3 cycles. The response was evaluated after 2 and 3 courses of IC. Patients were considered to have a remarkable response (RR) if an endoscopic examination with a central review showed shrinking of the primary lesion equivalent to T1 and the short axis of the metastatic lymph nodes were all < 1 cm on computed tomography—in other words, down staging to T1N0M0 stage IA. Patients were considered to have a poor response (POR) if they had progressive disease or no signs of reduction. Patients who did not achieve RR or POR were deemed to have limited partial response (LPR). CRT was administered to patients who achieved RR, and surgery was performed in patients who achieved LPR or POR. CRT included cisplatin 75 mg/m^2 on day 1 and 5–fluorouracil 1000 mg/m^2 on days 1–4, repeated every 4 weeks for 2 cycles. Radiotherapy was administered as 50.4 Gy in 28 fractions. The primary endpoint was a 1–year progression free survival (PFS) for RR followed by CRT. **Results:** A total of 92 patients were enrolled. Two patients with non–SCC (n = 1) and distant metastasis (n = 1) were excluded. Therefore, 90 patients were included in the analysis group. Although 1 patient could not continue IC due to renal failure, the remaining 89 patients completed 3 courses of IC. The response after IC were RR in 58.4% (52/89), LPR in 41.6% (37/89), and POR in 0.0% (0/89). Three patients who achieved RR underwent surgery owing to renal dysfunction (n = 1), curative irradiation difficulty due to intestinal malrotation (n = 1), and CRT refusal (n = 1). Six patients who achieved LPR underwent CRT owing to surgery refusal (n = 3), unresectable tumors (n = 2), and respiratory dysfunction due to emphysema (n = 1). The complete response rate for RR followed by CRT was 89.8%. During the median follow–up period of 33 months (range: 1–85), the 1 and 3–years overall survival (OS) for the analysis group were 96.6% and 74.1%, respectively. The 1 and 3–years organ preservation survival for the analysis group were 56.8% and 45.3%, respectively. The 1 and 3–years OS for RR followed by CRT (n = 49) vs. LPR followed by surgery (n = 31) were 100% vs. 93.1% and 83.7% vs. 62.8%, respectively (p = 0.06). The 1 and 3–years PFS for RR followed by CRT were 89.8% and 70.0%, respectively. **Conclusions:** Three courses of DCF chemotherapy followed by CRT is an effective treatment for patients with resectable esophageal SCC who respond to the IC regimen. Clinical trial information: 8086. Research Sponsor: Yakult Honsha Co., Ltd.

4028 **Poster Session**

Camrelizumab plus chemotherapy as neoadjuvant therapy for resectable, locally advanced esophageal squamous cell carcinoma (NIC-ESCC2019): A multicenter, open-label, single-arm, phase 2 study. *First Author: Jingpei Li, Department of Thoracic Surgery/Esophageal Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*

Background: Despite multidisciplinary therapies, prognosis of pts with resectable esophageal squamous cell carcinoma (ESCC) remains poor. Combining PD-1 blockade to neoadjuvant chemotherapy might be a feasible and effective strategy. Camrelizumab (an anti-PD-1 antibody) was approved for advanced or metastatic ESCC in the second-line setting and showed improved anti-tumor activity and survival benefit when combined with chemotherapy in multiple advanced tumors. **Methods:** In this NIC-ESCC2019 phase 2 study, histologically or cytologically confirmed ESCC pts (stage II-IVA) were enrolled to receive two cycles of neoadjuvant chemoimmunotherapy (NIC) with camrelizumab (200 mg on day 1) plus nab-paclitaxel (260 mg/m^2 in total on day 1 and day 8) and cisplatin (75 mg/m^2 in total on days 1-3) of each 21-day cycle, followed by esophagectomy. The primary endpoint was complete pathologic response (CPR) rate in the primary tumor. Besides, we also explored the relationship between the tumor genomic profile or primary-tumor microenvironment and the pathological response. **Results:** Between Jan 17, 2020 and Dec 8, 2020, 56 pts were enrolled. 51 pts underwent surgical resection, and all had complete tumor resection. CPR was achieved in 18 (35.3%; 95% CI, 21.7%-48.9%) pts; 12 (23.5%) pts had major pathologic response (MPR), and 21 (41.2%) had incomplete pathological response (IPR). Of note, 16 (31.4%) pts achieved CPR in both primary tumor and lymph nodes. The objective response rate was 66.7% (95% CI, 40.0-70.4). No in-hospital mortality occurred. The most common treatment-related adverse events (TRAEs) were decreased WBC (20 [36%] of 56 pts), vomiting (19 [34%]), and alopecia (18 [32%]). Grade 3 TRAEs only occurred in 6 (11%) pts, and there were no grade 4 or 5 TRAEs. The most common immune-related AEs included grade 1-2 rash maculo-papular (7 [13%]) and reactive cutaneous capillary endothelial proliferation (5 [9%]). Presence of mutations in CREBBP and KMT2D at treatment-nave time-point was correlated with non-response group (IPR and stable disease) (CREBBP, p = 0.046; KMT2D, p = 0.047). Among the immune populations, CD8+, CD8+PD-1+ and CD8+PD-L1+ T cells increased significantly after two doses of NIC, especially in the CPR+MPR group (CD8+, p = 0.013; CD8+PD-1+, p < 0.001; CD8+PD-L1+, p = 0.068). **Conclusions:** The addition of camrelizumab to neoadjuvant chemotherapy in ESCC demonstrated promising efficacy with acceptable toxicity, supporting the further investigation in a randomized phase 3 clinical trial. Clinical trial information: NCT04225364. Research Sponsor: Jiangsu Hengrui Medicine and BGI Genomics.

Correlation analysis of present of mutations in significantly mutant genes and response to PD-1 blockade.

	Non-response (n=10)	Response (n=41)	p value assessed by Pearson's Chi-squared test
CREBBP			0.046
Mut.	3 (30.0%)	3 (7.3%)	
Wild	7 (70.0%)	38 (92.7%)	
KMT2D			0.047
Mut.	5 (50.0%)	8 (19.5%)	
Wild	5 (50.0%)	33 (80.5%)	

4029 **Poster Session**

Nivolumab and ipilimumab for second-line therapy in elderly patients with advanced esophageal squamous cell cancer: Safety interim analysis of the RAMONA trial. *First Author: Nicolai Hartel, Heidelberg University, Mannheim, Germany*

Background: Advanced esophageal squamous cell cancer (ESCC) is frequently diagnosed in elderly patients (pts) with additional comorbidities. Limited treatment options are available. We report the safety interim analysis of a phase II clinical trial evaluating nivolumab and ipilimumab as second-line therapy for advanced ESCC in elderly pts. **Methods:** RAMONA is a multicenter open-label phase II trial assessing nivolumab/ipilimumab combination therapy in elderly pts (≥65 years). The geriatric status of the pts was assessed using the G8 screening tool and the Deficit Accumulation Frailty Index (DAFI). After a run-in phase of 3 cycles nivolumab (240mg Q2W), cohort assignment was based on a safety assessment. Pts with toxicities grade ≤2 were considered eligible for escalation to nivolumab (240mg Q2W)/ipilimumab (1mg/kg Q6W) combination therapy (cohort B). Other pts remained on nivolumab monotherapy (cohort A). Primary endpoint is overall survival (OS). Key secondary endpoint is time to Quality of Life deterioration defined as a loss of ≥ 10 points in the EORTC QLQ-C30 compared to baseline. Adverse events were assessed according to NCI-CTCAE version 4.03. **Results:** From February 2018 until February 2020, 69 pts entered the study. 61 pts were eligible for safety interim analysis. Median age of the pts was 71.9 yrs (± 5.4), median KPS score was 80% (50-100%). In 73.8% of the pts, metastases were detected at the time of study inclusion. Most pts received the IO therapy in ≥ 2nd line (91.8%). The mean G8-score at screening was 11.9 points (46 pts ≤ 14 points, 75.4%) (mean DAFI: 0.19). Based on safety assessment, 42 pts were escalated to nivolumab/ipilimumab, while 9 pts remained on nivolumab monotherapy. 10 pts were not allocated at the time of analysis. Median numbers of cumulative doses were 3.0 [1.0 - 3.0] for the run-in phase (nivolumab), 6.0 [1.0 – 48.0] for nivolumab therapy (cohort A/B) and 2.5 [1.0 – 16.0] for ipilimumab (cohort B). Median treatment duration was 144.5 days (56-781 days) in cohort A and 231 days (85-484 days) in cohort B. Frailty indices remained stable after 3 cycles of nivolumab with limited toxicity at the time of the safety assessment. Drug-related treatment emergent adverse events (AEs) were observed in 42 pts (68.9%); 29/42 in cohort A, 8/9 in cohort B, and 5/10 pts not allocated at the time of analysis. Grade ≥3 AEs were detected in 9 pts of 42 in cohort A and 4 of 9 pts in cohort B. Drug-related treatment emergent serious adverse events (SAEs) were detected in 12 pts (19.7%); 8/42 in cohort A, 2/9 pts in cohort B, and 2/10 pts not yet allocated. **Conclusions:** Combined nivolumab/ipilimumab is a safe and feasible second-line therapy for elderly pts with advanced ESCC. Most pts could be escalated to nivolumab/ipilimumab. Treatment duration was exceptional long for a subset of pts. Clinical trial information: NCT03416244. Research Sponsor: Bristol-Meyers-Squibb.

4030 **Poster Session**

LEAP-005: A phase 2 multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—Results from the gastric cancer cohort. *First Author: Hyun Cheol Cheol Chung, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Lenvatinib, an anti-angiogenic multiple receptor tyrosine kinase inhibitor, in combination with the anti–PD-1 antibody pembrolizumab, has demonstrated promising antitumor activity with manageable safety in the first- or second-line in a phase 2 trial of patients with advanced gastric cancer. LEAP-005 (NCT03797326) is a phase 2, multicohort, nonrandomized, open-label study evaluating efficacy and safety of lenvatinib plus pembrolizumab in patients with previously treated advanced solid tumors; here, we present findings from the gastric cancer cohort of LEAP-005. **Methods:** Eligible patients were aged ≥18 years with histologically or cytologically confirmed metastatic and/or unresectable gastric cancer, received at least 2 prior lines of therapy, had measurable disease per RECIST v1.1, ECOG PS of 0–1, and provided a tissue sample evaluable for PD-L1 expression. Patients received lenvatinib 20 mg once daily plus pembrolizumab 200 mg Q3W for up to 35 cycles of pembrolizumab (approximately 2 years) or until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Treatment with lenvatinib could continue beyond 2 years in patients experiencing clinical benefit. Primary endpoints were ORR (per RECIST v1.1 by blinded independent central review) and safety. Secondary endpoints included disease control rate (DCR; comprising CR, PR, and SD), duration of response (DOR), PFS, and OS. Tumor imaging was performed Q9W from treatment initiation for 54 weeks, then Q12W to week 102, and Q24W thereafter. **Results:** 31 patients were enrolled in the gastric cancer cohort; 87% were male, 58% were aged < 65 years, and 71% had PD-L1 combined positive score (CPS) ≥1. Median time from first dose to data cutoff (April 10, 2020) was 7.0 months (range, 1.9–11.9); 19 patients (61%) had discontinued treatment. ORR was 10% (95% CI, 2–26); 1 patient had CR (3%), and 2 had a PR (6%). 12 patients (39%) had SD. Median DOR was not reached (range, 2.1+ to 2.3+ months). DCR was 48% (95% CI, 30–67). Median PFS was 2.5 months (95% CI, 1.8–4.2). Median OS was 5.9 months (95% CI, 2.6–8.7). 28 patients (90%) had treatment-related AEs, including 13 patients (42%) with grade 3–5 AEs. 1 patient had a treatment-related AE that led to death (hemorrhage). 8 patients (26%) had immune-mediated AEs: hypothyroidism (n = 5), hyperthyroidism (n = 2), and pneumonitis (n = 1). There were no infusion-related reactions. **Conclusions:** In patients with advanced gastric cancer who received 2 prior lines of therapy, lenvatinib plus pembrolizumab demonstrated promising antitumor activity and a manageable safety profile. Based on these data, enrollment in the gastric cancer cohort has been expanded to 100 patients. Clinical trial information: NCT03797326. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4031 **Poster Session**

Frequency of homologous recombination-related (HRR) genes mutations in gastric cancer. *First Author: Wei Wang, Guangdong Provincial Hospital of Chinese Medicine, Guangzhou, China*

Background: Homologous recombination deficiency (HRD) might contribute to predict response of immunotherapy and Chemotherapy response and PARP inhibitor (PARPi) therapy. The HRD phenotype has been defined as the presence of a non-silent somatic mutation in homologous recombination-related (HRR) genes. We aimed to analyze the mutational pattern of HRR genes and the relationship between HRR-related genes and clinical outcomes in gastric cancer. **Methods:** We prospectively sequenced 386 Chinese patients with gastric cancer using next-generation sequencing techniques with 808 cancer-related genes. 440 patients with WES data from the TCGA project were included. The 15 HRR genes were selected on clinical evidence of sensitivity to PARP inhibitors and immunotherapy. Correlations between HRR genes and clinical outcomes were identified via bioinformatic analysis using TCGA datasets. **Results:** In the Chinese cohort, 10.4% (40/386) patients exhibited genomic alterations in HRR genes. The frequently mutated genes were BRCA2 (2.3%), ATM (1.8%), CDK12 (1.8%), BRCA1 (1.0%), CHEK2(1.0%), PALB2(0.8%), BARD1 (0.5%), RAD51B (0.5%), and RAD54L (0.3%). 8.3% patients had at least one somatic HRR genes mutation. Pathogenic germline variants were identified in 2.1% (8/386) patients. No participants carried both germline and somatic HRR gene mutations. In TCGA cohort, 19.1% (841/440) patients had at least one somatic mutation in an HRR gene. The frequently mutated genes were BRCA2 (6.4%), ATM (6.4%), CDK12 (3.2%), BRCA1 (3.2%), BARD1 (2.3%), PALB2 (2.3%), HEK2 (1.6%), CHEK1 (1.4%), BROP1 (1.1%), RAD54L (1.1%), FANCL (0.9%), RAD51D (0.9%), RAD51C (0.7%), PPP2R2A (0.5%), and RAD51B (0.5%). Chinese cohort had lower frequently somatic mutation of HRR genes compared to that in TCGA cohort (8.3% vs 19.1%, p < 0.001). Interestingly, in the TCGA cohort, patients with HRR-mut had significantly elevated tumor mutational burden, microsatellite instability status and enhanced immune activity than patients with HRR-wt. In the MSK-IMPACT cohort comprising 49 patients treated with ICIs, patients with HRR-mut had significantly better overall survival compared to those in patients with HRR-wt (p = 0.027). **Conclusions:** Our data suggest that patients with altered HRR genes may be rational candidates for precision oncology treatment and provide new opportunities to predict the tumor response to multiple treatments, such as immunotherapeutic combine PARP inhibitor (PARPi) therapy. Exploring other biomarkers of HRD to predict the response to PARPi and immunotherapeutic in GC is necessary. Research Sponsor: None.

4032 **Poster Session**

ENSURE: An international multicenter study exploring whether surveillance after esophageal cancer surgery impacts oncological and quality-of-life outcomes. *First Author: Jessie A Elliott, St. James's Hospital, Dublin, Ireland*

Background: Although established and emerging therapies for recurrent esophageal cancer (EC) may impact on survival and health related quality of life (HRQL), surveillance protocols after the primary curative treatment of EC are varied and inconsistent, reflecting a limited evidence-base to guide an optimum approach. Specifically, whether advantages exist for an intensive surveillance protocol is unknown and was the focus of this study. **Methods:** European iNvestigation of SUrveillance after Resection for Esophageal cancer (ENSURE) is an international multicenter retrospective observational study of consecutive patients undergoing surgery with curative intent for esophageal and gastroesophageal junction cancers (2009 – 2015) across 20 European and North American cancer centers (NCT03461341). Intensive surveillance (IS) was defined as routine annual CT/PET-CT along with clinical assessment during the first three postoperative years, and compared with standard surveillance (SS) with investigation as clinically indicated. The primary outcome measure was overall survival (OS), secondary outcomes included treatment administered, disease-specific survival (DSS), disease-free survival (DFS), recurrence pattern, and HRQL. Multivariable linear, logistic and Cox proportional hazards regression analyses were performed to determine the independent impact of surveillance on oncologic outcomes and HRQL. **Results:** 4,682 patients were studied (72.6% adenocarcinoma, 69.1% neoadjuvant therapy). 45.5% underwent IS. At a median follow-up of 60 months, 47.5% developed disease recurrence. Oligometastatic recurrence occurred in 39% of cases, with 31% receiving best supportive care, 60% chemotherapy and/or radiation, and 8% surgical resection. IS was associated with reduced symptomatic recurrence (odds ratio [OR] 0.17 [0.12–0.25]), increased tumor-directed therapy (OR 2.09 [1.58–2.77]), and improved OS (HR 0.90 [0.82–0.98], 5-year OS 47.9±1.2% versus 43.2±1.1%). After adjusting for confounders, significantly improved overall survival with IS was maintained for patients who underwent surgery alone as initial therapy (HR 0.60 [0.47–0.78]) and in those with lower pathological (y)pT stages (Tis-2, HR 0.72 [0.58–0.89]). IS was associated with greater anxiety (P= 0.016), but similar overall HRQL. **Conclusions:** These data suggest that IS may improve oncologic outcomes, particularly in patients with early stage disease at presentation or with a favorable pathological stage post induction therapy. This may be relevant to guideline development and provide a framework and rationale for RCTs. It may also inform shared decision-making with patients at a time where therapeutic options for recurrence are expanding. Research Sponsor: Supported by a fellowship award from the Health Research Board, Ireland, to Jessie A Elliott (HPF 2015-1013) and a grant award from the Surgical Research Society, United Kingdom and Ireland.

4033 **Poster Session**

Circulating tumor DNA (ctDNA) analysis by low-coverage whole genome sequencing (lcWGS) of resectable esophageal adenocarcinoma (rEAC) patients. *First Author: Tom van den Ende, Amsterdam UMC, University of Amsterdam, Department of Medical Oncology, Cancer Center Amsterdam, Meibergdreef 9, Amsterdam, Netherlands*

Background: ctDNA is becoming an established marker to assess tumor burden, relapse after surgery, and to identify responders in immunotherapy studies. In the phase II PERFECT trial rEAC patients were treated with neoadjuvant chemoradiotherapy (nCRT) and a PD-L1 inhibitor (van den Ende et al. CCR. 2021). Here we evaluated the potential of cell-free DNA (cfDNA) to predict pathological complete response (pCR) and recurrence. **Methods:** The cohort consisted of 40 patients and 145 plasma samples. EDTA blood samples were drawn at baseline (B, N = 40), in week 5 of nCRT (W5, N = 40), before surgery (OR, N = 33) and 3 months after surgery (FU, N = 32). cfDNA was isolated by affinity columns (CNAkit, QIAgen) quantified by spectrofluorometer (BioAnalyzer, Agilent), sequencing libraries were prepared for lcWGS (< 5-fold coverage, Tag-seq, Takara) and sequenced on a NovaSeq (S4, PE150). Sequencing data were processed with an in-house pipeline. Copy number aberrations (CNA) and the tumor fraction were estimated using the ichorCNA tool. Insert sizes were recovered and we determined a Tumor Enriched Fragment Fraction (TEFF), calculated by doing the ratio of fragments between 90-150 bp and 250-320 bp (enriched in tumor signal) and fragments between 150-250 bp and 320-360 bp (poor in tumor signal). ichorCNA and TEFF were used to quantify the ctDNA fraction in plasma samples. pCR was defined as ypT0N0. Residual tumor, progression or death before surgery were considered non-pCR. Relapse-free survival (RFS) was defined as the time after surgery until recurrence. **Results:** The pCR rate was 25% (10/40). The median fold change TEFF between B and W5 was -0.15 (range -0.67 to 0.44) in the pCR group and 0.16 (range -1.40 to 0.76) in the non-pCR group (Mann–Whitney U; p = 0.047). Of the 17 patients in whom ctDNA was detected (TEFF≥0.3 and/or ichorCNA≥0.03) in the FU sample, 13 (76%) showed a recurrence. Of the 15 patients with no ctDNA detected 5 (33%) showed a recurrence. Patients with ctDNA detected at FU had worse RFS, HR = 2.72 (95%CI 0.96-7.71; p = 0.050). Recurrences were detected earlier by FU ctDNA than by imaging due to physical complaints with a median of 312 days (163-798 days). **Conclusions:** lcWGS appears to be a useful tool to predict pCR and recurrence in resectable esophageal cancer. These lcWGS results will be further combined with fragmentomics analysis and targeted mutational data (Ion Torrent next-generation sequencing) in order to assess response to immunotherapy. Clinical trial information: NCT03087864. Research Sponsor: MLDS fund, Pharmaceutical/Biotech Company.

4034 **Poster Session**

DNA and RNA sequencing analysis revealed alterations of *ANK3*, *PKHD1* and olfactory transduction as potential biomarker of three-year survival in gastric cancer. *First Author: Jian Wang, Department of Oncology, The First Affiliated Hospital of Nanjing Medical University, Nanjinng, China*

Background: Gastric cancer is the third leading cause of cancer related death worldwide. Although targeted and immune therapy have brought new benefit for patients, it still faces challenges of limited effective group and survival. Here we investigate the association of overall survival with DNA and RNA alterations to explore potential biomarkers of prognosis in gastric cancer. **Methods:** Whole-exome sequencing, RNA sequencing and clinical data of 442 patients with stomach cancer were downloaded from TCGA. Clinical factors and mutational landscape (insertion/ deletion/ single nucleotide variant) were compared between group of OS3+ (overall survival > 3 years) and OS3- (OS < 3 years). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analyses were performed based on differentially expressed RNAs between the two groups. **Results:** 415 of 442 patients with stage information were included. The corresponding rates of OS3+ for patients in stage of I/II/III/IV was 15.5% (9/58), 10.8% (9/58), 10.9% (9/58), 13.6% (9/58), respectively. When comparing the 49 patients with OS3+ to others with OS3-, no difference of stage or sex distribution was discovered, except that OS3+ group had lower median age at diagnosis than OS3- group (63 vs. 71 years, *P = 0.029*). Tumor mutation burden was comparable between groups. Mutational landscape showed that the two groups shared 70% of top 20 mutations. Among the 20 hot genes, mutations of *ANK3(P = 0.006), PKHD1(P = 0.008)* were more frequent in OS3+ group, Studies in breast and prostate cancer inferred that, *ANK3* was involved in activity of androgen receptor signaling and cyclins, increased expression of ANK3 in cancer was probably associated with better survival. *PKHD1* was involved in calcium ion binding and actin binding and was identified as a protective factor for colorectal cancer. OS3- group tend to have higher mutation frequency of *HMCN1(P = 0.062)*. Previous reports showed that mutation of *HMCN1* was enriched in peritoneal metastasis of gastric cancer, it might contribute to progression in gastric cancer. Enrichment analysis revealed difference between the two groups in olfactory transduction ($P < 0.01$, KEGG analysis), neuroactive ligand-receptor interaction ($P < 0.05$, KEGG analysis) and detection of chemical stimulus in sensory perception of smell ($P < 0.01$, GO analysis). Numbers of discussions have inferred that genes involved in olfactory transduction may also participate in tumor cell proliferation, migration, and invasion. **Conclusions:** Patients with OS3+ was enriched with mutations of *ANK3* and *PKHD1* and present significant functional difference in olfactory transduction. These are potential biomarkers of better survival in gastric cancer. Further studies are needed to figure out their roles in tumor activity and provide insight for novel antitumor treatment development. Research Sponsor: None.

4035 **Poster Session**

The prognosis of gastric adenocarcinoma depends on the crosstalk between immune profiles and tumor genomic alterations. *First Author: Deqiang Wang, Department of Medical Oncology, Cancer Therapy Center, Affiliated Hospital of Jiangsu University, Zhenjiang, China*

Background: Gastric adenocarcinoma (GAC) is with a complex microenvironment of tumor cells. A better understanding of the immune landscape of GACs may lead to the improved treatment strategies with ICIs. **Methods:** To determine whether the molecular characteristics can serve in prognostic stratification of GACs, tumor tissue and blood samples were collected from 231 GAC patients. The median follow-up time was 34 months. The TCR profile was determined by TCR-β CDR3 sequencing while mutation and gene expression profiles were determined by whole exon and whole transcriptome sequencing, respectively. Tumour-infiltrating immune cells were characterized using immunofluorescence (IF) staining. **Results:** The results showed the OS of patients with high levels of TCR clonality (TCR clonal expansion) was significantly improved compared with patients with low levels (HR = 1.80 and 2.22, p = 0.022 and 0.008, respectively**)** in the whole group and in the subgroup of patients with stages IB to III disease. Furthermore, low local clonality was an independent risk factor for OS (adjusted-HR = 1.68 and 1.95, p = 0.049 and 0.029, respectively). Thus, TCR clonal expansion in tumour tissue had a strong prognostic value for GAC patients, independent of clinicopathological factors. Based on whole exon and whole transcriptome sequencing, RNF43/FBXW7/ARID2 mutations and local TCR clonality jointly impacted prognosis ($p < 0.001$), and functional changes in corresponding Wnt pathway/Notch pathway/SWI/SNF complex characterized a GAC subset with enhanced tumour immunogenicity and TCR clonal expansion. TCR CDR3 sequence similarity comparisons yielded clusters of TCR clones of likely similar functions. The most expansive TCR clusters negatively correlated with the percentage of subclonal mutations (Pearson r = -0.8183, $p < 0.001$), indicating that tumors with less genomic heterogeneity might induce a greater immune response. By IF staining and mutual correlation analysis, only M1 macrophages showed a significant positive correlation with local TCR clonality for epithelia, stroma, and total cell counts. Tumors were categorized according to the density of M1 macrophages, M1 macrophage infiltrated subtype was associated with favorable OS (p = 0.040 and 0.043) and its combination with the local TCR clonality improved prognosis stratification ($p < 0.001$). Finally, the scoring by local TCR clonality, RNF43/FBXW7/ARID2 mutations and M1 infiltration determined the best prognosis ($p < 0.001$). **Conclusions:** TCR profiles were associated with genomic alterations and may serve as a prognostic biomarker for GACs. A multi-omic model including TCR profiles might produce an improved stratification for treatments and outcomes. Research Sponsor: None.

4036 **Poster Session**

Camrelizumab combined with FLOFOX as neoadjuvant therapy for resectable locally advanced gastric and gastroesophageal junction adenocarcinoma: Updated results of efficacy and safety. *First Author: Ying Liu, Department of Medical Oncology, Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China*

Background: Although anti-PD-1 antibody in combination with chemotherapy has shown promising antitumor activity in advanced gastric or gastroesophageal junction adenocarcinoma (GC/GEJC), the evidence of neoadjuvant therapy for locally advanced GC/GEJC is limited. Camrelizumab combined FOLFOX as neoadjuvant therapy for resectable locally advanced GC/GEJC was a prospective, single-arm, phase 2 study we conducted. Here, we updated the results of efficacy and safety of this study. **Methods:** Patients confirmed by endoscopic ultrasonography (EUS) and imaging with clinical stage≥T2 and/or positive lymph nodes were enrolled. They received 4 cycles of camrelizumab (200mg ivgtt on day1, q2w) plus FOLFOX (oxaliplatin 85mg/m^2 ivgtt, LV 200mg/m^2 ivgtt, 5-Fu 400mg/m^2 iv followed by 2.4mg/m^2 CIV 46 hours on day 1, q2w) as neoadjuvant therapy. Then patients without disease progression evaluated by imaging underwent gastrectomy of D2 lymph node dissection. The primary endpoint was pCR, the secondary endpoints were R0 resection rate and safety. **Results:** Between Jul 24 2019 and Nov 30 2020, 49 patients were enrolled. The median age was 57 years (29-72 years). All patients completed 4 cycles treatment. Unfortunately, 2 of them were confirmed PD by imaging. In addition, two patients refused gastrectomy and withdrew from the study. Eventually, 45 patients underwent gastrectomy, of which 3 patients had intraperitoneal metastases during the operation. A total of 42 patients were evaluable, all of them gained R0 resection (100%), 4 patients (10%) achieved pCR and 10 patients (24%) reached TRG1. Among the patients experienced pCR, one of them was Her-2 positive, one was MSI-H, the rest two of them were PD-L1-positive (CPS≥10). The most common ≥grade 3 adverse events (AEs) were neutropenia (35%) and leukopenia (16%). Only 1 patient (2%) experienced grade 3 immune-related AEs of alanine aminotransferase and aspartate aminotransferase increase. No serious AEs resulted in termination of treatment or death. **Conclusions:** Camrelizumab combined with FOLFOX was an effective and safe neoadjuvant therapy strategy for patients with resectable locally advanced GC/GEJC. Furthermore, the analysis of biomarkers with clinical benefits is undergoing. Clinical trial information: NCT03939962. Research Sponsor: None.

Patients characteristics (N=49).

Characteristics	N	%
Sex		
Male	35	71
Female	14	29
ECOG (PS)		
0	31	63
1	18	37
Clinical stage		
T≥3	47	96
N≥1	49	100

4037 **Poster Session**

Randomized phase II study comparing docetaxel versus paclitaxel in patients with esophageal squamous cell carcinoma who are refractory to fluoropyrimidine and platinum-based chemotherapy: OGSG1201. *First Author: Takayuki Kii, Department of Cancer Chemotherapy Center, Osaka Medical College Hospital, Osaka, Japan*

Background: Fluoropyrimidine and platinum-based chemotherapy are considered first-line therapy options for patients with unresectable advanced or recurrent metastatic esophageal squamous cell carcinoma(ESCC). After fluoropyrimidine and platinum-based chemotherapy is failed, taxanes (docetaxel(DTX) and paclitaxel(PTX)) was mainly used as a second-line treatment for ESCC. Therefore, we conducted a trial to compare DTX and PTX in patients with unresectable advanced or recurrent ESCC who were failed to previous fluoropyrimidine and platinum-based chemotherapy. **Methods:** We did a randomized, an open-labeled and multicentre phase 2 study. Inclusion criteria included age 20 to 80 years with unresectable advanced or recurrent ESCC, Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1. Patients who were refractory to fluoropyrimidine and platinum-based chemotherapy. Treatment consisted of DTX 70 mg/m2 repeated every 21 days or PTX 100 mg/m2 once weekly on days 1, 8, 15, 22, 29, and 36 of a 49-day cycle. **Results:** 80 patients were enrolled between May 2012 and April 2019. 41 patients received DTX and 39 patients received PTX. After assessment of eligibility, two patients proved uneligible (one for double cancer, one for contraindication to DTX) and were excluded from the analysis. But, 80 patients were evaluable for the toxicity analyses. A median follow-up time was 32 months. Overall survival was significantly longer in the PTX group than in the DTX group (median, 8.8 months vs. 7.3 months; hazard ratio, 0.62; 95% CI, 0.38 to 0.9998; P = 0.047). The median progression-free survival was significantly longer in the PTX group than in the DTX group (median, 4.4 months vs. 2.1 months; hazard ratio, 0.49; 95% CI, 0.30 to 0.78; P = 0.002). The median time to treatment failure was significantly longer in the PTX group than in the DTX group (median, 3.8 months vs. 2.1 months; hazard ratio, 0.45; 95% CI, 0.28 to 0.73; P 0.001). The most common adverse events of grade 3 or higher were a decreased neutrophil count (in 28% of the PTX group and in 80% of the DTX group). Febrile neutropenia was also more frequent in the DTX group than the PTX group (46 vs. 0%). There was one death from sudden death in which treatment-related mortality could not be ruled out. **Conclusions:** Secound-line treatment with PTX, as compared with DTX, reduced the risk of ESCC. Clinical trial information: UMIN000007940. Research Sponsor: None.

4039 **Poster Session**

Real-world data (RWD) reveals benefit for adjuvant chemotherapy with docetaxel, oxaliplatin and fluorouracil/leucovorin (FLOT) is limited to those with tumour regression grade (TRG) ≥3 in oesophago-gastric cancer (OGC). *First Author: Brindley Sonal Hapuarachi, Weston Park Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom*

Background: Despite potentially curative surgery, long-term survival from OGC remains poor due to high relapse rate. Neoadjuvant (naFLOT) and adjuvant (aFLOT) FLOT is currently standard treatment for resectable OGC based on data from the FLOT-4 trial. We explored whether TRG was associated with FLOT-outcome using RWD. **Methods:** Pts with OGC treated with naFLOT +/- aFLOT at a tertiary UK centre were identified following institutional board approval. Clinical and laboratory data were extracted from the patient record. TRG was evaluated by a histopathologist. Median overall survival (OS) and median progression-free survival (PFS) were evaluated using Kaplan-Meier and Log-rank tests; time taken from start of naFLOT, and associations between factors with Fisher's exact (FE) test. **Results:** 171 pts were identified, median FU 30 mths. 144 (84%) male; median age 66 (32-84); oesophagus 66 (38%), junctional (GOJ) 73 (43%), gastric 32 (19%); stage IB 3 (2%), stage IIB 26 (15%), stage III 91 (53%), stage IVA 47 (28%) and unknown 4 (2%). Pts had median of 2 comorbidities (range 0-6); performance status (PS) 0: 95 (56%), PS 1: 71 (41%), PS 2: 3 (2%) and PS unknown 2 (1%). 132/171 pts completed 4 cycles of naFLOT and this was significantly associated with undergoing surgery (p = 0.02). Those who had surgery (140/171) had significantly improved PFS (not reached (NR) vs. 6 mths; 95% CI 2-10; p < 0.001) and OS (NR vs. 12 mths; 95% CI 6-18; p < 0.001). TRG was reported for 126/140 patients who underwent surgery. TRG 1/2 (42/126) vs. TRG ≥3 was significantly associated with improved PFS (NR vs. 35 mths; 95% CI NR; p < 0.001) and OS (median NR either group; p < 0.001). Pts with TRG 1/2 who commenced aFLOT (≥1 cycle; n = 31/42) or completed 4 cycles of aFLOT (17/31) did not have improved PFS or OS vs. those who did not. Those with TRG ≥3 who commenced aFLOT (≥1 cycle; n = 62/85) had improved PFS (median NR vs. 22 mths; 95% CI 13-31 p = 0.006) and OS (median NR vs. 25 mths; 95% CI 18-32 p = 0.019). Those with TRG ≥3 who completed 4 cycles of aFLOT (n = 38/62) had significantly improved PFS (median NR vs. 25 mths; 95% CI 14-36 p = 0.016) and OS (median NR vs. 36 mths; 95% CI 16-55 p = 0.012). There was no difference in PFS or OS in pts with TRG ≥3 who had a dose reduction at any time during aFLOT. **Conclusions:** TRG is a predictor of outcome following naFLOT + surgery with superior outcomes in those with TRG 1/2. Our analyses suggest that only pts with TRG >3 following naFLOT + surgery benefit from adjuvant FLOT. Prospective randomised studies are required to confirm whether pts with TRG 1/2 require treatment with aFLOT. Research Sponsor: None.

4040 **Poster Session**

SHARED: Efficacy and safety of sintilimab in combination with concurrent chemoradiotherapy (cCRT) in patients with locally advanced gastric (G) or gastroesophageal junction (GEJ) adenocarcinoma. *First Author: Jia Wei, The Comprehensive Cancer Centre of Drum Tower Hospital, Medical School of Nanjing University & Clinical Cancer Institute of Nanjing University, Nanjing, China*

Background: PD-1 inhibitor and chemotherapy have shown significant clinical benefits in 1L-treatment of G/GEJ. While it is not clear for locally advanced stage. The aim of this single-arm phase Ib trial is to assess the feasibility of sintilimab (PD-1 inhibitor) in combination with cCRT in locally advanced GC. **Methods:** Patients (pts) with initial histopathologically confirmed G/GEJ adenocarcinoma, diagnosed as locally advanced III-IVA per AJCC 8th and ECOG PS of 0-1 were eligible. Sintilimab (200mg, iv, Q3W) was given with CRT sandwich in sequence of one induction chemotherapy (S-1+Nab-PTX), weekly Nab-PTX(80-100mg/m^2, d1, d8, d15, d22), concurrent radiotherapy (45Gy/1.8Gy*25f), and one consolidation chemotherapy (S-1+Nab-PTX). Pts received three additional combinations of sintilimab and chemotherapy after surgery or investigator's best choice for unresectable pts after planned therapy. The primary endpoint was pCR and a Simon two-stage was employed at first 9 pts. This interim analysis was pre-planned after finishing stage I assessment. Accrual is ongoing with another 25 in next stage. **Results:** In the first stage, 5 out of 9 pts achieved pCR and passed to next stage. As of 7th Feb 2021, 28 pts met inclusion criteria with median age 67 yrs (range 47-81), men 86%, PS 1 25%, cT3/4a/4b 28%/54%/18%, cN1/N2/N3 7%/50%/43% and Borrmann II/III/IV 57%/18%/25% . The location on GEJ and G was 14% and 86%. Of 23 pts completed neoadjuvant, all were evaluated as D2-surgery feasibility. 19 pts had completed gastrectomy (4 pts waiting for surgery) with pCR 42.1% (8/19), MPR (≤10% viable tumor cells) 73.7% (14/19) and R0 resection 94.7% (18/19). Down-staging to pT0 and pN0 were both observed in 42.1%. The median follow-up was 5.8m unavailable for survival evaluation at present. Grade (gr) 3-4 TRAE occurred in 39.3% (11/28) pts with most common events as myelosuppression (39.3%) and increased transaminase (10.7%). IrAEs occurred in 21.4% (6/28) pts with one gr 4 hepatitis and others gr 1-2. Peri-operative complications occurred in 3 pts with gr 1-2 pneumonia, increased transaminase, and ileus. No death or unexpected toxicity observed. **Conclusions:** SHARED interim analysis demonstrated a promising feasibility of sintilimab in combination with cCRT with preliminary impressive pCR & MPR and acceptable toxicity in phase III-IVA G/GEJ cancer. These results warrant further accrual and evaluation. Clinical trial information: ChiCTR1900024428. Research Sponsor: Innovent Biologics.

4041 **Poster Session**

Final survival results from a multicenter, randomized phase II trial of intravenous paclitaxel plus FOLFOX (ivPOF) and/or intraperitoneal paclitaxel plus FOLFOX (ipPOF) versus mFOLFOX6 as first-line treatment of advanced gastric cancer (AGC): SYLT/FNF 004. *First Author: Shen Zhao, Gastrointestinal Medical Oncology, Fujian Cancer Hospital, Fuzhou, China*

Background: Progression-free (PFS) and overall (OS) survival for SYLT/FNF 004 were previously reported in ASCO and ASCO-GI 2019. At that time, PFS was statistically significantly improved with ivPOF or ipPOF compared to mFOLFOX6 as first-line treatment of AGC; however, there were no significant between-treatment differences in OS. Herein, we report final survival results for this trial. **Methods:** Subjects were randomly assigned to one of three treatments: intravenous paclitaxel 135 mg/m^2 + mFOLFOX6 omitting the 5-FU bolus (ivPOF); intraperitoneal paclitaxel 80 mg/m^2 + mFOLFOX6 omitting the 5-FU bolus (ipPOF); or mFOLFOX6 (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2 followed by 5-FU 400 mg/m^2 bolus and 5-FU 2400 mg/m^2 as a 46-hour continuous infusion). Treatment cycles were repeated every 14 days for up to 9 cycles. Thereafter, maintenance treatment with S-1 80 mg/m^2/day for 14 days every 3 weeks until disease progression, unacceptable toxicity, patient refusal, or physician decision. The original study objective was to compare ivPOF or ipPOF vs. mFOLFOX6 for PFS. Due to slow accrual, the protocol was later amended to compare POF (ivPOF and ipPOF) with mFOLFOX6 for PFS. **Results:** Between Nov 2015 and May 2018, 89 subjects (30 ivPOF, 29 ipPOF, 30 mFOLFOX6) were enrolled. As of the data cutoff on Dec 31, 2020, median follow-up was 41 (IQR: 37-43) months. The median number of cycles administered was 7 (IQR: 4-9) for POF; 6 (IQR: 4-9) for ivPOF; 9 (IQR: 4-9) for ipPOF; and 4 (IQR: 3-9) for mFOLFOX6. Median PFS and OS, respectively, were 6.23 (95% CI: 4.90 to 9.07) and 10.17 (95% CI: 8.97 to 16.4) months for POF and 4.55 (95% CI: 2.73 to 6.87) and 6.87 (95% CI: 5.83 to 13.6) months for mFOLFOX6. Both PFS and OS were statistically significantly better with POF, ivPOF or ipPOF versus mFOLFOX6 (Table). Safety was consistent with previous reports. **Conclusions:** POF, ivPOF or ipPOF improved both PFS and OS compared with mFOLFOX6, with similarly manageable adverse effects. Clinical trial information: NCT02845908. Research Sponsor: None.

	POF* (n=59)	ivPOF* (n=30)	ipPOF* (n=29)	mFOLFOX6 (n=30)
Median PFS, mos. (95% CI)	6.23 (4.90 to 9.07)	6.52 (4.13 to 10.27)	5.83 (4.43 to 10.93)	4.55 (2.73 to 6.87)
P-value	0.012	0.026	0.037	
Hazard Ratio (95% CI)	0.56 (0.35 to 0.88)	0.56 (0.33 to 0.94)	0.56 (0.33 to 0.96)	
Median OS, mos. (95% CI)	10.17 (8.97 to 16.4)	9.83 (7.70 to 19.2)	11.03 (9.93 to 21.8)	6.87 (5.83 to 13.6)
P-value	0.014	0.043	0.029	
Hazard Ratio (95% CI)	0.57 (0.36 to 0.90)	0.59 (0.35 to 1.00)	0.54 (0.32 to 0.93)	

Note: *Comparison with mFOLFOX6.

4042 **Poster Session**

Immunogenomic features of pathologic response to neoadjuvant immune checkpoint blockade in esophageal cancer. *First Author: Zineb Belcaid, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Improving immunotherapy efficacy remains an unmet need in esophagogastric cancer and a deeper understanding of tumor and immune system dynamics during therapy may tailor immuno-oncology approaches. **Methods:** We performed whole exome sequencing (WES) and bulk RNA sequencing (RNAseq) of 70 serial tumor samples from 23 patients with stage II/III esophageal/gastroesophageal junction (E/GEJ) cancer treated on a phase 1B clinical trial with neoadjuvant nivolumab with or without relatlimab (anti-LAG-3) and chemoradiation followed by surgery (NCT03044613; CA209-906). Pathologic response was measured by tumor regression at the time of resection. Median follow up was 23 months post-surgery. Serial tumor samples were collected prior to therapy, after 2 cycles of induction immune checkpoint blockade (ICB), and at the time of resection. Twenty-two baseline tumor/normal DNA pairs were analyzed by WES and 48 serial tumor samples were analyzed by RNAseq. WES data was analyzed to identify somatic mutations, generate tumor mutation burden (TMB) estimates and assess the fraction of expressed mutations in conjunction with RNAseq data. Immune cell subset composition was determined by RNAseq data deconvolution by CIBERSORT and gene set enrichment analyses were performed utilizing GSEA. B-cell density was inferred by immunoglobulin rearrangements detected by RNAseq. **Results:** Gene set enrichment expression analyses revealed an upregulation of effector pro-inflammatory cytokines after induction ICB. Interferon-gamma, interferon-alpha and TNF-alpha related genes were significantly upregulated after induction ICB compared to baseline ($p < 0.0001$). In contrast, significant downregulation of E2F targets ($p = 0.002$), G2M checkpoint genes ($p = 0.005$) and DNA damage repair genes ($p = 0.004$) was observed post ICB; enrichment analyses were independent of response to therapy and treatment arm. While TMB was not predictive of pathologic response ($p = 0.22$), patients with tumors harboring a higher number of expressed mutations were more likely to achieve a pathologic complete response (pCR; $p = 0.026$). RNAseq deconvolution analyses revealed a higher B-cell density post ICB induction in tumors with pCR ($p = 0.018$). Furthermore, an increased baseline content of intra-tumoral activated M1 macrophages differentiated tumors from patients achieving a pCR ($p = 0.0034$), which was further exemplified post induction ICB. **Conclusions:** Neoadjuvant immunotherapy induces an inflammatory immune response in the tumor microenvironment that is linked with tumor elimination and pathologic response. Our findings highlight the importance of nuanced multi-omics analyses to understand the wiring of response to immunotherapy and guide therapy for E/GEJ cancer. Research Sponsor: Bristol Myers Squibb.

4043 **Poster Session**

A multicenter phase II study of S-1 plus ramucirumab as first-line treatment in elderly patients with advanced/recurrent gastric cancer (KSCC1701). *First Author: Hiroo Katsuya, Saga University, Saga, Japan*

Background: Elderly patients are often intolerable in the combination with cytotoxic agents. Therapy with S-1 alone is a key option for initial chemotherapy for Japanese elderly patients with unresectable gastric cancer in clinical practice. However, there are some cases in which the antitumor effects with S-1 alone are insufficient. We aimed to investigate the efficacy and safety of S-1 plus ramucirumab therapy to elderly patients with advanced/recurrent gastric cancer. **Methods:** Patients aged 70 years and older with previously untreated unresectable or recurrent gastric cancer patients were included in Japan. They received S-1 therapy (40-60 mg twice daily for 28 days, every 6 weeks) plus ramucirumab therapy (8 mg/kg, every 2 weeks) until disease progression. The primary endpoint was the one-year survival rate and null hypothesis of one-year survival was set as 40%, which is the lower bound of the 95% confidence interval in previously reported studies on S-1 therapy. The secondary endpoints included progression-free survival (PFS), overall survival (OS), response rate (RR), and safety. **Results:** Between September 2017 and November 2019, 48 patients were enrolled in this study. The characteristics of patients were male/female: 34/14, median age: 77.5 years (range: 71-87), and PS (0/1): 20/28. The one-year survival rate was 65.2% (95% confidence interval 49.8-78.6%), which means this trial met the primary endpoint. The median OS and PFS were 16.4 months (95%CI:12.0–20.7) and 5.8 months (95%CI:4.0–7.2), respectively. The best RR (CR+PR) was 60.9%. The frequent grade 3 or grade 4 adverse events were neutropenia (27.7%), anorexia (23.4%), anemia (19.1%), hypertension (14.9%), leucopenia (12.8%) and hypoalbuminemia (12.8%). **Conclusions:** Based on the observed efficacy and safety, S-1 plus ramucirumab is an appropriate first-line treatment for elderly patients with advanced/recurrent gastric cancer. Clinical trial information: UMIN000028309. Research Sponsor: Eli Lilly and Company.

4044 **Poster Session**

Survival analysis by tumor response from real-world data in advanced gastric cancer treated with nivolumab: The DELIVER trial (JACCRO GC-08). *First Author: Yosuke Kito, Department of Medical Oncology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan*

Background: The phase III ATTRACTION-2 trial demonstrated survival benefit of nivolumab (Nivo) as third- or later-line treatment in previously treated advanced gastric or gastroesophageal junction (GEJ) cancer, with response rate (RR) of 11% (Kang YK, et al. *Lancet* 2017). It has been shown that some tumors grow rapidly after Nivo treatment, but the proportion and survival are still uncertain. We therefore prospectively investigated clinical outcomes from real-world data of Nivo treatment in advanced gastric cancer (GC). **Methods:** The DELIVER trial was a prospective, multicenter, observational study which assessed patients (pts) with advanced gastric or GEJ adenocarcinoma treated with Nivo alone and ECOG PS 0-2 (UMIN000030850). The aims were to evaluate the efficacy and safety of Nivo treatment in real world. Primary endpoint was overall survival (OS), secondary endpoints were RR, disease control rate (DCR), progression-free survival (PFS), tumor growth rate (TGR) at 1st evaluation, and safety. The sub-group analyses were performed for survival according to tumor response and clinical factors. The survival data was fixed at the timepoint of 1 year after the last enrollment. **Results:** In 501 pts enrolled from Mar 2018 to Aug 2019, 487 pts were evaluable (median age 70y, 71% male, ECOG PS0/1/2 42/44/14%, no. of prior regimen 1/2/≥3 2/39/59%, 21% HER2-pos, 42% pts with ascites). Median OS was 5.8 months (m) (95%CI 5.3-7.0) with 1y-survival rate of 30%, and median PFS was 1.8 m (95%CI 1.7-2.0), at 454 events for PFS and 389 events for OS. The DCR were 39.4%, and RR was 14.2% in 282 pts with measurable lesions. Median OS and PFS by tumor response (CR/PR/SD/PD) were Not Reached (NR)/NR/11.3/4.1m and NR/11.7/3.8/1.4m, respectively. A sub-group analysis of OS by clinical factors is the following: male/female; 6.5/5.0m (p= 0.002), tub/por/sig; 8.1/5.4/4.1m ($p<$ 0.0001), albumin < 3.5/≥3.5; 4.2/8.9m ($p<$ 0.0001), w/peritoneal mets/w/o; 4.9/8.4m ($p<$ 0.0001), and w/ascites/w/o; 3.7/8.9m ($p<$ 0.0001). These findings were also observed in PFS. In 219 evaluable pts for TGR, 20.5% pts were identified as hyper-progressive disease (HPD). An exploratory approach by logistic regression analysis indicated that level of free-T3 in blood before Nivo treatment was higher in the HPD compared to the non-HPD group (2.5 vs. 2.2 pg/ml, p= 0.005). Survival time was comparable between the HPD group and PD without HPD group. Median period from 1st evaluation to death was 2.8 m for HPD, 5.7 m for non-HPD, and 2.4 m for PD at 1st evaluation without HPD. **Conclusions:** The real-world data of Nivo treatment in advanced GC indicated comparable survival to previous result in a clinical trial. Differences in survival time by tumor response or some clinical factors were observed in Nivo treatment. In addition, our study revealed the rate of HPD and the prognosis in advanced GC pts treated with Nivo. Clinical trial information: UMIN000030850. Research Sponsor: Ono Pharmaceutical and Bristol-Myers Squibb.

4045 **Poster Session**

ERBB2 copy number (CN) as a quantitative biomarker for real-world (RW) outcomes to anti-HER2 therapy in advanced gastroesophageal adenocarcinoma (adv GEA). *First Author: Samuel J Klempner, Massachusetts General Hospital, Boston, MA*

Background: HER2 (*ERBB2*) overexpression or amplification (amp) are biomarkers for approved anti-HER2 therapies. *ERBB2*amp may be a superior predictor of anti-HER2 therapy outcome compared to IHC/ISH, and degree of CN gain may further stratify patients (pts). We investigated the distribution of *ERBB2*amp in adv GEA and hypothesized that increased CN was associated with better outcome to trastuzumab (T). **Methods:** Genomic analysis was performed using the Foundation Medicine (FM) tissue database (DB) of 313,896 pts with solid tumors including 12,749 pts with GEA and 34,629 pts with breast cancer (BC) used for comparison. *ERBB2*amp was defined as predicted CN $\geq$5 with $>$ 80% of exons amplified. Using the nationwide US-based Flatiron Health-FM clinico-genomic DB linking de-identified EHR-derived clinical data to FM genomic data, pts with *ERBB2*amp adv GEA (01/2011 - 12/2020) were selected. RW progression (rwP) was obtained via technology-enabled abstraction of EHR. Multivariable Cox proportional hazard models were used for outcome comparisons. **Results:** *ERBB2*amp was detected in 15% (1,920/12,749) of GEA samples; median CN 22 (IQR 9-73), and 97% of cases had full gene amp. Median *ERBB2* amplicon size was 0.27Mbp (IQR 0.13-0.95). In comparison, *ERBB2*amp was detected in 9.2% (3,193/34,629) of BC samples; median CN 20 (IQR 9-40), median amplicon size 0.32Mbp (IQR 0.13-1.37). In both cancers, smaller amplicons were associated with higher CN ($P < 0.001$), excluding amplicons $<$ 0.1Mbp where less than 100% target amp was common. *ERBB2*amp was additionally seen in 2.7% of other solid tumors, and specifically in 2.3% of NSCLC and 3.1% of CRC. In the RW DB of 183 pts with *ERBB2*amp adv GEA, chemo + T (45%) and chemo alone (17%) were the most common first therapies after genomic report. In 101 evaluable first-line T treated pts *ERBB2* CN was a significant predictor of rwP free survival (rwPFS) as a continuous variable (aHR = 0.74 [95% CI: 0.61 - 0.89], P = 0.002) and a range of cutoffs were similarly predictive. For control, in *ERBB2*amp pts treated with chemo *ERBB2* CN was not predictive of rwPFS (aHR = 0.93, [95% CI: 0.72 – 1.20], P = 0.060). Among T treated pts, co-*PIK3CA* mutation was more common with lower CN (p = 0.03 by Wilcox test); no significant differences were observed for primary tumor location, age, stage at adv diagnosis, co-*KRAS*mut, *EGFR*amp or *FGFR1/2*amp. **Conclusions:** *ERBB2*amp was detected in 15% of GEA tissue samples, with significant diversity in *ERBB2* CN and amplicon focality, but with a similar CN distribution and amplicon focality seen in *ERBB2*amp BC. *ERBB2* CN was predictive of rwPFS as a continuous variable for pts with GEA treated with T in the RW setting. Further studies exploring the clinical utility of quantitative *ERBB2* CN, and extending to ctDNA, particularly in the setting of the evolving anti-HER2 landscape and combination therapies, are warranted. Research Sponsor: Foundation Medicine.

4046 **Poster Session**

Phase II trial of perioperative chemotherapy + avelumab in locally advanced gastroesophageal adenocarcinoma: Preliminary results. *First Author: Thierry Alcindor, McGill University Health Centre, Montréal, QC, Canada*

Background: Perioperative chemotherapy improves cure rate in locally advanced gastroesophageal adenocarcinoma (GEA), and immune checkpoint inhibitors are active at the metastatic stage. This trial tests the hypothesis that the addition of avelumab to perioperative chemotherapy will increase the major pathologic response (MPR) rate in comparison with historical controls. **Methods:** Phase II study of avelumab + chemotherapy (docetaxel, cisplatin and 5-FU or mDCF) given every 2 weeks for 4 cycles before and after surgery. Main inclusion criteria: GEA, cT3 and/or cN+, M0, WHO PS 0-1. Main exclusion criteria: use of immunosuppressants, serious autoimmune disease, daily intake $>$10 mg prednisone. Staging studies: CT, PET-CT, endoscopic ultrasound, diagnostic laparoscopy. Surgical resection: D2 lymphadenectomy, en-bloc esophagectomy for type I/II gastroesophageal junction (GEJ) tumors. Aim of the study: MPR as defined as tumor regression grades 0-1 (modified Ryan scheme); as per hypothesis, this experimental regimen will result in a 20% rate of MPR, compared with 7% with chemotherapy alone. Simon 2-stage design: if less than 2 MPR are seen in the first 16 patients, the study will be closed. The study hypothesis cannot be rejected if at least 6 MPR are seen in the first 50 patients. All adverse effects are prospectively recorded per CTCAE guidelines in patients who have received at least one treatment cycle. Survival rates are calculated with Kaplan-Meier method. Preliminary results are presented since the study has met its primary endpoint. **Results:** Feb 2018-Feb 2020: 28 patients enrolled (25 M/3 F, age 45-78). Location: GEJ (23), stomach (5). Staging: cT3 (25), cT4 (1), cN+ (20). Biomarkers expression: mismatch repair (MMR) protein loss (3/28); PD-L1(clone 73-10) expression in 1% (TPS) or more of tumor cells seen in 12/28 samples, and $>$10% in 6 patients. Grade 3 toxicity: stomatitis (2/28); nausea (2/28); vomiting (1/28); diarrhea (1/28); hypothyroidism (1/28); arthralgia (3/28); neutropenia (1/28). Grade 4 toxicity: pneumonia (1/28); neutropenia (2/28). Postoperative 30-day mortality: 0%. One patient was excluded from efficacy analyses for M1 staging; 27 patients underwent surgery, 26 with R0 (96%). Six cases (22%) show MPR: 3 grade 0 (11%) and 3 grade 1 (11%) tumor regressions. No correlation was seen between MMR proteins or PD-L1 expression and tumor regression. With a median follow-up of 1.5 years (range 0.4-2.5), the disease-free survival rate is projected to be 0.92 (95% CI 0.83-1.00) at 12 months and 0.77 (95% CI 0.58-1.00) at 24 months. **Conclusions:** The combination of mDCF chemotherapy with Avelumab demonstrates a promising safety and activity profile. Ongoing laboratory investigations are underway to correlate our findings with tumor molecular features before exposure to treatment. Clinical trial information: NCT03288350. Research Sponsor: EMD Serono.

4047 **Poster Session**

Neoadjuvant camrelizumab combined with chemotherapy and apatinib for locally advanced thoracic esophageal squamous cell carcinoma (ESCC): A single-arm, open-label, phase Ib study. *First Author: Zhen Wang, Department of Thoracic Surgery, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Neoadjuvant therapy with PD-1 blockade plus chemotherapy has been found to be effective in the first-line treatment of advanced esophageal cancer. However, evidence of PD-1 blockade combined with chemotherapy as neoadjuvant treatment is limited. This study was designed to investigate the safety and efficacy of camrelizumab, a PD-1 blockade combined with chemotherapy and apatinib as neoadjuvant therapy for locally advanced esophageal squamous cell carcinoma (ESCC). **Methods:** A regiment of 2–4 cycles of neoadjuvant camrelizumab (200 mg, intravenous, day 1), nab-paclitaxel (150 mg/m^2, intravenous, day 1), nedaplatin (50 mg/m^2, intravenous, day 1), and apatinib (250 mg, orally, day 2–4) was given to the treatment-naive patients with resectable locally advanced ESCC. The treatments were repeated every 14 days. In this study, six patients were planned to receive two cycles of neoadjuvant therapy as safety assessment, and then 24 patients received four cycles of neoadjuvant therapy, followed by esophagectomy after 4–8 weeks. The primary end points were safety and feasibility. The secondary end points were the rate of major pathologic response (MPR) and pathologic complete response rate (pCR). **Results:** A total of 30 patients were enrolled, among them, five patients received two planned cycles of neoadjuvant therapy, and one patient missed the second cycle of therapy due to grade 3 ALT elevations. Further, all other 24 patients received four planned cycles of neoadjuvant therapy. A total of 11 patients (11/30, 36.7%) experienced grade 3 neoadjuvant treatment-related adverse events (TRAEs). No grade 4 and grade 5 TRAEs were reported. The most frequent grade 3 TRAEs was neutropenia (7/30, 23.3%). Twenty-nine patients underwent minimally invasive esophagectomy (McKeown procedure) after neoadjuvant therapy. The reason for not undergoing surgery was due to bone metastasis. There were five treatment-related surgical delays that were caused by adverse reactions (hyperglycemia, arthritis, anemia, leukopenia, capillary endothelial proliferation in oral mucosa). Among the 29 patients undergoing esophagectomy, 15 patients (15/29, 51.7%) achieved MPR, including 7 patients with pCR (7/29, 24.1%). Among the 24 patients who received four cycles of neoadjuvant treatment, there were 7 patients with pCR (7/24, 29.2%), and 14 patients with MPR (14/24, 58.3%). No surgery related mortality was documented. **Conclusions:** Neoadjuvant camrelizumab combined with chemotherapy plus apatinib is a safe and tolerable treatment for patients with locally advanced ESCC, and the MPR and pCR rate are promising. Clinical trial information: ChiCTR1900023880. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

4048 **Poster Session**

Trastuzumab deruxtecan (T-DXd; DS-8201) in patients with HER2-positive advanced gastric or gastroesophageal junction (GEJ) adenocarcinoma: Final overall survival (OS) results from a randomized, multicenter, open-label, phase 2 study (DESTINY-Gastric01). *First Author: Kensei Yamaguchi, The Cancer Institute Hospital of JFCR, Tokyo, Japan*

Background: T-DXd is an antibody–drug conjugate comprising an anti-HER2 antibody, a cleavable tetrapeptide-based linker, and a topoisomerase I inhibitor. DESTINY-Gastric01 (DS8201-A-J202; ClinicalTrials.gov, NCT03329690) is an open-label, multicenter, randomized, phase 2 trial of T-DXd in patients with HER2-positive advanced gastric cancer (GC) or GEJ adenocarcinoma. In the primary analysis (101 OS events; median survival follow-up, 12.3 mo), T-DXd showed statistically significant benefit vs standard chemotherapy in objective response rate (ORR) and OS (Shitara K, et al. *N Engl J Med.* 2020;382:2419-2430); here, we present the final OS analysis as well as updated efficacy and safety. **Methods:** Patients (pts) with locally advanced or metastatic, centrally confirmed HER2-positive (IHC3+ or IHC2+/ISH+ on archival tissue) GC or GEJ cancer that had progressed after $\geq$2 previous lines of therapy including trastuzumab were randomly assigned 2:1 (T-DXd 6.4 mg/kg Q3W or physician's choice [PC] irinotecan [I] or paclitaxel [P]). Pts were stratified by country, ECOG performance status (0, 1), and HER2 status. Primary end point was ORR by independent central review. Key secondary end points were OS, duration of response (DOR), progression-free survival (PFS), disease control rate (DCR), confirmed ORR, and safety. Final OS analysis was performed at 133 OS events. **Results:** 187 pts received T-DXd (n = 125) or PC (n = 62 [55 I; 7 P]); 79.7% of pts were Japanese and 20.3% were Korean. Pts had a median of 2 prior lines of therapy, and 44.4% had $\geq$3. At data cutoff (June 3, 2020), 8% of T-DXd and 0% of PC pts remained on treatment (median survival follow-up, 18.5 mo). OS was improved with T-DXd vs PC (median OS, 12.5 vs 8.9 mo; hazard ratio [HR], 0.60 [95% CI, 0.42-0.86]); 12-month OS, 52.2% vs 29.7%. ORR was 51.3% (61/119; 11 CR; 50 PR) with T-DXd vs 14.3% (8/56; all PR) with PC ($P < 0.0001$); confirmed ORR, 42.0% (50/119; 10 CR; 40 PR) vs 12.5% (7/56; all PR) ($P = 0.0001$); DCR, 86.6% vs 62.5% ($P = 0.0003$); confirmed median DOR, 12.5 vs 3.9 mo; median PFS, 5.6 vs 3.5 mo (HR, 0.47 [95% CI, 0.31-0.71]; $P = 0.0003$). Grade $\geq$3 AEs occurred in 85.6% of T-DXd pts vs 56.5% with PC; the most common were neutrophil count decreased (49.6%, 22.6%), anemia (38.4%, 22.6%), and white blood cell count decreased (20.8%, 11.3%). 16 pts (12.8%) had T-DXd–related interstitial lung disease (ILD; 13 grade 1/2, 2 grade 3, 1 grade 4, no grade 5) vs 0 with PC. As reported in the primary analysis, there was 1 T-DXd–related death from pneumonia (non-ILD). **Conclusions:** With additional follow-up after the primary analysis, T-DXd continued to demonstrate OS benefit and clinically relevant improvement in ORR compared with standard chemotherapy, and a manageable safety profile, in HER2-positive advanced GC or GEJ adenocarcinoma. Clinical trial information: NCT03329690. Research Sponsor: Daiichi Sankyo, Pharmaceutical/Biotech Company.

4049 **Poster Session**

First-line pembrolizumab plus chemotherapy versus chemotherapy in patients with advanced esophageal cancer: Chinese subgroup analysis of KEYNOTE-590. *First Author: Zhigang Li, Shanghai Chest Hospital, Shanghai, China*

Background: In the randomized, double-blind, placebo-controlled, multicenter, phase 3 KEYNOTE-590 study (NCT03189719), pembrolizumab + chemotherapy provided superior OS, PFS, and ORR versus chemotherapy with a manageable safety profile in patients with untreated locally advanced/unresectable or metastatic adenocarcinoma or esophageal squamous cell carcinoma (ESCC) or Siewert type 1 esophagogastric junction (EGJ) adenocarcinoma. We present results from the subgroup of patients enrolled in China. **Methods:** Eligible patients were randomly assigned 1:1 to pembrolizumab 200 mg or placebo Q3W for ≤35 cycles (~2 years) + chemotherapy (cisplatin 80 mg/m^2 Q3W [d1; 6 doses] + 5-FU 800 mg/m^2 on d1-d5 Q3W). Randomization was stratified by region, histology, and ECOG performance status. Primary end points were OS in patients with ESCC PD-L1 combined positive score (CPS) ≥10 tumors and OS and PFS (RECIST v1.1; by investigator) in ESCC, PD-L1 CPS ≥10, and all patients; ORR (RECIST v1.1; by investigator) in all patients was the key secondary end point. Data cutoff was July 2, 2020. **Results:** Of 749 patients enrolled, 106 (14.2%) enrolled in China (51 in pembrolizumab + chemotherapy arm; 55 in chemotherapy arm); 88.7% were male and 49.1% had PD-L1 CPS ≥10. In Chinese patients, ECOG performance status 1 (81.1% vs 59.8%) and ESCC (98.1% vs 73.2%) were more prevalent than they were in all patients enrolled in the study. Additionally, in Chinese patients (pembrolizumab + chemotherapy vs chemotherapy), median OS was 10.5 months versus 8.0 months (HR, 0.51; 95% CI, 0.32-0.81), median PFS was 6.2 months versus 4.6 months (HR, 0.60; 95% CI, 0.39-0.92), ORR was 37.3% versus 20.0%, and median DOR (range) was 6.4 months (2.2+ to 18.9+) versus 4.0 months (1.5+ to 16.6+). Grade 3 or 4 treatment-related adverse events (TRAEs) were reported in 74.5% of patients in the pembrolizumab + chemotherapy arm and 66.7% in the chemotherapy arm; no grade 5 events were reported. Eight patients (15.7%) in the pembrolizumab + chemotherapy arm and 3 patients (5.6%) in the chemotherapy arm discontinued because of TRAEs. Immune-mediated AEs (defined for the safety profile of pembrolizumab as events with potentially treatment-related immunologic causes) were reported in 21.6% of patients in the pembrolizumab + chemotherapy arm and 13.0% in the chemotherapy arm; most were grade 1 or 2 and were manageable with interruption or discontinuation of study drug or standard medical therapy. **Conclusions:** In Chinese patients with advanced esophageal or EGJ cancer, pembrolizumab + chemotherapy improved OS, PFS, and ORR versus chemotherapy as first-line therapy, and safety was manageable. These findings were consistent with those in the global study population. Clinical trial information: NCT03189719. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4050 **Poster Session**

Phase II study of perioperative toripalimab in combination with FLOT in patients with locally advanced resectable gastric/gastroesophageal junction (GEJ) adenocarcinoma. *First Author: Hongli Li, Department of Gastrointestinal Medical Oncology, Tianjin Medical University Cancer Institute & Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin's Clinical Research Center for Cancer, Tianjin, China*

Background: FLOT is the standard perioperative treatment for resectable gastric /gastroesophageal junction (GEJ) adenocarcinoma. However, patient's outcome is still poor. Toripalimab, a humanized IgG4 monoclonal antibody against programmed cell death receptor-1 (PD-1), has shown remarkable clinical efficacy in various cancers. This trial evaluates the addition of Toripalimab to FLOT for resectable patients. **Methods:** This is a prospective, single-arm, investigator-initiated phase II trial. Patients with histologically confirmed, resectable, gastric and GEJ adenocarcinoma (≥cT2 or cN+) were enrolled to receive 4 pre-and post-operative cycles of toripalimab (240mg, q2w) plus FLOT (docetaxel 50 mg/m2; oxaliplatin 85 mg/m2; leucovorin 200 mg/m2; 5-FU 2600 mg/m2, q2w). The primary endpoint was pathological complete response rate (pCR). The secondary endpoints included major pathological (complete and nearly complete) response (MPR), and R0-resection rate, 3-year disease-free survival rate, overall survival, and adverse events. **Results:** In total, of 36 patients were enrolled from June 2019 through Dec 2020. Male, 66.7%; median age, 60y; cT3 8.3%, T4, 83.3%; cN+ 88.9%; GEJ 47%; MSI-H, 5.6%, Her-2neu-positive, 5.6%, EBER-positive, 5.6%). Two patients refused surgery, six patients have not yet completely neoadjuvant treatment. 100% of patients completed the 4 pre-cycle. Patients who had received gastrectomy after neoadjuvant treatment (n=28) were included in this analysis. 6 (21%) patients had operations involving a thoracic approach (oesophagogastrectomy with two field lymphadenectomy), 21 (75%) gastrectomy with D2 lymphadenectomy. 8 (29%) evaluable patients had Clavien-Dindo grade II post-operative complications and 2 (7%) grade IIIA complications; one patient had an anastomotic leakage that was treated endoscopically. There were no emergency re-operations. All 28 patients achieved R0-resection and were discharged home after a median of 12 days (range:7-63) in hospital. 7 25% patients achieved pCR (TRG1a) and 12 (42.9%) patients achieved major pathologic response (MPR, TRG1a/b). Treatment-related adverse events (TRAEs) to any drug were reported in 30 (94%) patients. Mostly TRAEs were grade 1-2, the grade 3 or 4 TRAEs included neutropenia (34%), neutropenia (25%), lymphopenia (3%), Alanine aminotransferase increased (3%), hypokalemia (3%) and anaemia (3%). **Conclusions:** Perioperative toripalimab in combination with FLOT showed promising efficacy with high pCR and MPR rate and well tolerated safety profile in patients with resectable gastric/GEJ adenocarcinoma. This combination regimen might present a new option for patients with locally advanced, resectable gastric/GEJ adenocarcinoma. Clinical trial information: NCT04354662. Research Sponsor: None.

4051 **Poster Session**

The sequence of chemotherapy and anti-PD-1 antibody influence the efficacy of neoadjuvant immunochemotherapy in locally advanced esophageal squamous cell cancer: A phase II study. *First Author: Lingdi Zhao, Department of Immunology, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou City, China*

Background: PD-1 blockade may result in expansion of tumor-specific T cells. However, traditional immunochemotherapy regimens usually designed to use chemotherapy drugs and anti-PD-1 antibody on the same day, which may make chemotherapy drugs kill activated T cells. The purpose of this study was to investigate the rate of pCR of chemotherapy plus anti-PD-1 therapy and the influence of sequence of chemotherapy and anti-PD-1 therapy on pCR in patients with locally advanced esophageal squamous cell cancer. **Methods:** Thirty esophageal squamous cell cancer patients with T3, T4, or lymph node positive were assigned into experiment group (anti-PD-1 antibody was administrated two days after chemotherapy) and control group (anti-PD-1 antibody and chemotherapy were administrated on the same day) according to the order of enrollment. There were fifteen patients in each group. The chemotherapeutic regimen was paclitaxel and cisplatin, paclitaxel was given at the dose of 150-175mg/m^2 on day 1 and cisplatin was given at the dose of 70-75mg/m^2 on day 1. The anti-PD-1 antibody was toripalimab at the fixed dose of 240mg on day 3 or day 1. Operation was performed four to six weeks after the second cycle of chemotherapy combined with toripalimab. **Results:** From July 2019 to September 2020, a total of 30 patients completed at least one cycle of immunochemotherapy. 11 in the experimental group received operation after two cycles of neoadjuvant chemotherapy plus toripalimab. Thirteen in control groupreceived operation aftertwo cycles of neoadjuvant chemotherapy plus toripalimab. Four patients in experimental group and one in control group got pCR, the rates of pCR in experimental group and control group were 36.4% and 7.7% individually. Although the difference was not significant in statistics, the experimental group had the trend of higher pCR rate(c^2= 3.092, p = 0.079). PD-L1 CPS examination before treatment was performed in fourteen patients, it was found that except one patient with PD-L1 CPS was 10, the left thirteen with PD-L1 CPS were all below one. The patient with PD-L1 CPS 10 was in control group and pCR was got in this patient. Except one patient in the experimental group had grade 3 immune-related enteritis, one patient in the control group died from immune-related myocarditis after operation, there were no more immune-related events more than grade 3. **Conclusions:** Toripalimab was delayed on day 3 when toripalimab plus chemotherapy was taken as neoadjuvant therapy regimen in locally advanced esophageal squamous cell carcinoma might achieve a higher pathological complete response than toripalimab and chemotherapy used on the same day. Clinical trial information: NCT 03985670. Research Sponsor: None.

4052 **Poster Session**

Risk factors for recurrence in each pattern after curative gastrectomy for pStage II/III gastric cancer: An exploratory analysis of a randomized controlled trial (JCOG1001). *First Author: Tetsuro Toriumi, Division of Gastric Surgery, Shizuoka Cancer Center, Shizuoka, Japan*

Background: Peritoneal, lymph node, and hematogenous recurrence are frequently observed as patterns of recurrence after surgery for gastric cancer. However, the clinicopathological characteristics associated with each recurrence have rarely been comprehensively reported in a multicenter study. Understanding the risk factors for each pattern of recurrence would be helpful for the early detection of recurrence and the initiation of optimal treatment. This study investigated the risk factors for the first recurrence in each pattern after curative gastrectomy, using data from a multicenter randomized controlled trial (JCOG1001) that was designed to investigate the efficacy of bursectomy. **Methods:** Patients of 20-80 years of age, with cT3(SS)-T4a(SE) gastric carcinoma according to the 14th Japanese Classification of Gastric Carcinoma, with an ECOG PS of 0-1, and a body mass index of < 30 kg/m^2, and without bulky lymph nodes, Borrmann type 4 or large type 3 carcinoma were eligible for inclusion in JCOG1001. Of the 1204 patients who were enrolled in JCOG1001, 932 pStage II/III patients with a common histological type were included in this study. Risk factors for hematogenous, lymph node, and peritoneal patterns of recurrence were estimated by a multivariable Fine and Grey model considering death or site of recurrence other than the first site of recurrence as competing risks. **Results:** The overall rate of recurrence was 27.1%. Hematogenous recurrence was the most frequent pattern (12.3%), followed by peritoneal (11.2%) and lymph node (7.5%) recurrence. Differentiated type (HR, 1.818; 1.237-2.674; p = 0.0024), pT4 (in comparison to pT1-3, HR, 1.511; 95% CI, 1.011-2.257; p = 0.0440), and pN3 (in comparison to pN0-2, HR, 2.431; 95% CI, 1.635-3.616; p < 0.0001) were associated with an increased incidence of hematogenous recurrence. Conversely, more than D2 lymphadenectomy reduced this pattern of recurrence (in comparison to D1+or D2 lymphadenectomy, HR, 0.575; 95% CI, 0.364-0.907; p = 0.0174). Peritoneal recurrence was significantly associated with large (≥5 cm) tumor (HR, 1.649; 95% CI, 1.034-2.629; p = 0.0356), pT4 (in comparison to pT1-3, HR, 3.222; 95% CI, 2.086-4.976; p < 0.0001), pN3 (in comparison to pN0-2, HR, 1.865; 95% CI, 1.275-2.727; p = 0.0013), and undifferentiated type (HR, 2.674; 95% CI, 1.628-4.394; p = 0.0001). Extended lymph node metastasis (pN3) was the only risk factor (in comparison to pN0-2, HR, 8.030; 95% CI, 4.605-14.002; p < 0.0001) for lymph node recurrence. **Conclusions:** The risk factors for recurrence differed according to the patterns of recurrence. Vigilant follow-up with an understanding of patterns of recurrence is required, especially for high-risk patients. Research Sponsor: Japan Agency for Medical Research, Development and National Cancer Center Research and Development Fund (2020-J-3).

4053 **Poster Session**

Risk factors of metachronous peritoneal carcinomatosis after potentially curative gastric cancer resection in the CRITICS trial. *First Author: Irene A. Caspers, Antoni van Leeuwenhoek/Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Peritoneal carcinomatosis (PC) is accountable for over 50% of metastatic spread in gastric cancer (GC). Little is known about factors contributing to the risk of metachronous PC as a single site of metastases after preoperative chemotherapy and potentially curative resection. An accurate prediction model of risk factors identifying high risk populations may pave the way for new treatment strategies, such as intraperitoneal chemotherapy. In this analysis, risk factors for the development of isolated metachronous PC after preoperative chemotherapy and surgical resection were investigated. **Methods:** In the CRITICS trial, 788 patients with resectable GC were randomized for preoperative chemotherapy and gastrectomy followed by either chemotherapy or chemoradiotherapy. Patients who underwent a potentially curative resection without peritoneal metastases at time of surgery were included in this analysis. Univariate and multivariate analyses were performed using a competing risk model. **Results:** In total, 617 patients met the inclusion criteria. Overall, 97 of 617 (16%) patients developed metachronous PC. The peritoneum was the first site of recurrence in 64 of 617 (10%) patients. Diffuse or mixed type GC, ypT4 stage and ypN3 stage or a lymph node ratio (LNR) with >20% tumor positivity were independent predictors of isolated PC in both univariate and multivariate analyses with hazard ratios (HR) of 2.90, 2.63 and 2.31, respectively (Table). ypT4 and ypN3 stage or a LNR >20% were also independent predictors of distant recurrence or death with HR of 1.46 and 2.34, respectively. Patients in whom all predictors were present had the highest 2 year cumulative incidences of both isolated PC development and other events of 39.6% and 48.8%, respectively. **Conclusions:** Diffuse or mixed tumor type, ypT4 and ypN3 or a LNR >20% were identified as independent risk factors for metachronous PC as a single site of metastases in a large cohort of patients treated with preoperative chemotherapy followed by surgical resection. The combination of these factors might identify a subgroup that could benefit from preventive treatment strategies. Research Sponsor: None.

Uni-/multivariate competing risk analysis on isolated metachronous PC. Other events are competing risk.

Univariate analysis*	Factor	HR	95% CI	p value
Allocated treatment				
Chemoradiotherapy	#			
Chemotherapy	0.98	0.77–1.25	*0.89*	
ypT-stage				
ypT0-pT3	#			
ypT4	1.83	1.38–2.34	*<0.001*	
ypN-stage and lymph node ratio				
ypN3 or pos. LNR>20%	3.09	1.89–5.04	*<0.001*	
Lauren classification				
Intestinal	#			
Diffuse or mixed	3.47	1.95–6.17	*<0.001*	
Multivariate analysis				
ypT-stage				
ypT0-pT3	#			
ypT4	2.63	1.60–4.31	*<0.001*	
ypN-stage and lymph node ratio				
ypN3 or pos. LNR>20%	2.31	1.40–3.82	*0.001*	
Lauren classification				
Intestinal	#			
Diffuse or mixed	2.90	1.48–5.68	*0.002*	

*Data of the additionally included factors age, sex and tumor localization are not shown. #reference.

4054 **Poster Session**

Long-term quality of life and nutritional results after laparoscopic sentinel node navigation surgery versus laparoscopic standard gastrectomy for early gastric cancer: Secondary outcomes of a multicenter, randomized phase 3 trial (SENORITA). *First Author: Bang Wool Eom, National Cancer Center, Goyang-Si, South Korea*

Background: Laparoscopic sentinel node navigation surgery (LSNNS) has been suggested as an alternative to laparoscopic standard gastrectomy (LSG) in early gastric cancer patients to improve long-term quality of life (QOL) and nutritional outcomes. Here, we present 3-year results of patient-reported quality of life (QOL) and nutrition, secondary endpoints of SENORITA trial. **Methods:** SENORITA is a prospective multicenter randomized phase 3 trial. Patients diagnosed with early gastric cancer of 3 cm or less were randomly allocated (1:1) to LSNNS for stomach preservation or LSG. The primary endpoint was 3-year disease-free survival. In this study, we analyzed QOL assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC stomach module (STO22) and nutritional parameters at 3, 12, 24, and 36 months after surgery. Linear mixed model analyses was used to evaluate differences between the two groups. This trial is registered with ClinicalTrials.gov, NCT01804998. **Results:** From March 2013 to March 2017, a total of 580 patients were randomly assigned and 527 patients were included in the modified intention-to-treat analysis population (258 in LSNNS and 269 in LSG group). QOL questionnaires were available for 99.4% of patients at baseline and then for 92.2%, 83.2%, 72.8%, and 66.9% at 3, 12, 24, and 36 months after surgery, respectively. The LSNNS group had higher physical function score than the LSG group at all time points ($p = 0.002$). However, there were no significant differences in other scales of EORTC QLQ-C30. Regarding EORTC QLQ-STO22, pain, eating restriction, anxiety, and taste scores were lower (better QOL) at all time points in the LSNNS group than in the LSG group ($p = 0.002$, < 0.001, < 0.001, and < 0.001, respectively). The summary score of EORTC QLQ-STO22 was also higher in the LSNNS group representing better QOL ($p < 0.001$). Body mass index, hemoglobin and total protein were significantly higher in the LSNNS group compared with the LSG group. **Conclusions:** The LSNNS group had better physical function and less symptoms, including pain, eating restriction, anxiety, and taste change compared with the LSG group. Moreover, the nutritional parameters were better maintained in the LSNNS group than in the LSG group. These findings showed benefits of stomach preserving surgery in LSNNS and can be used to help decision making about treatment for patients with early gastric cancer. Clinical trial information: NCT01804998. Research Sponsor: Grant 1110550, 1410140, 1710160, 2010150-1.

4055 **Poster Session**

Apatinib in combination with docetaxel and S1 chemotherapy in the first-line treatment of metastatic gastric cancer. *First Author: Ling Xia, Department of Radiation and Medical Oncology, Zhongnan Hospital, Wuhan University, Wuhan, China*

Background: First-line chemotherapy in metastatic gastric cancer, either doublet or triplet-regiment, the average OS is less than one year. Anti-VEGF target therapy is proven to be effective both in second and third line settings. As for apatinib, which is the tyrosine kinase inhibitor showed highly affinity for VEGFR2, is permitted by SFDA to be used in the third line treatment of gastric cancer since September 2014. The post-market stage IV clinic trial Ahead-G201 further confirmed it can improve the OS in chemotherapy-refractory gastric cancer. What's more, apatinib could reverse paclitaxel resistance and improve the R0 resection rate in conversion of unresected gastric cancer in neoadjuvant settings. However, the safety and efficacy of apatinib in combination with docetaxel plus S1 in the first line treatment of metastatic gastric cancer is unknown and worthy of investigation. **Methods:** With expectation to improve PFS from 5.3m (the START Study) to 7m, this investigator-initiated, single arm, multi-center, registered phase II prospective study was designed to enroll 48 eligible patients diagnosed with metastatic gastric cancer. Each participant was expected to finish six cycles of chemotherapy plus apatinib (docetaxel 75mg/m2, d1, Q3W; S1 according to BSA: <1.25 40mg po bid; 1.25~1.5 50mg po bid; >1.5 60mg po bid; d1-14, Q3W; apatinib 500mg po qd). The toxicity was determined according to CTCAE 4.0. Efficacy assessed every two cycles (6 weeks) during the study and every 2 months during the follow-up period. The primary endpoint was PFS. The secondary endpoint was OS, ORR, and DCR. The tumor response was determined according to RECIST 1.1 criteria. **Results:** Baseline characteristics (FAS population): From July 2017 to December 2020, 45 patients from 5 centers across Hubei province were enrolled. Among them, 44 are eligible for analysis. There are 15 females and 30 males, median age 55 years old, median metastasis sites is 2, yet 63.6% of them have involved at least 2 organs. Safety: 90.91% patients reported adverse events (AEs). The incidence of grade 3-4 AEs was 47.73%. Main 3-4 AEs were oral ulceration (13.64%), leucopenia (13.64%), neutropenia (13.64%), hand-foot syndrome (6.82%), hypertension (6.82%), and thrombocytopenia (6.82%). Efficacy: By Jan 31th, 2021, 44 patients were evaluable for response and survival, 26 of them achieved partial response (PR), 9 achieved stable disease (SD), and 8 experienced progression disease (PD). The ORR is 60.47%, the DCR is 81.4%. Median PFS is 7.46m, median OS is 12.42m. So we closed the study in advance. **Conclusions:** Adding apatinib to standard DS chemotherapy as the first line treatment would be well tolerant in patients with metastatic gastric cancer, the spectrum of toxicity were not exceeding expectation. This modality also exhibits prolonged PFS, which might provide an alternative therapeutic strategy for metastatic gastric cancer. Clinical trial information: NCT03154983. Research Sponsor: None.

4056 **Poster Session**

Real-world outcomes of second-line ramucirumab plus paclitaxel in patients with advanced gastric or gastroesophageal junction adenocarcinoma: A nationwide retrospective study in Korea (KCSG-ST19-16). *First Author: Dae Young Zang, Division of Hematology-Oncology, Department of Internal Medicine, Hallym University Medical Center, Hallym University College of Medicine, Anyang, South Korea*

Background: Ramucirumab as monotherapy or in combination with paclitaxel is a second-line treatment option recommended for patients with locally advanced unresectable or metastatic gastroesophageal junction (GEJ) or gastric adenocarcinoma. However, real-world data of large samples focused on ramucirumab plus paclitaxel in gastric cancer are limited. We conducted a nationwide retrospective study to evaluate the efficacy, safety, and factors potentially associated with survival in patients with gastric or GEJ adenocarcinoma who received second-line ramucirumab plus paclitaxel in a real-world setting. **Methods:** The study population comprised all patients with gastric or GEJ cancer who received ramucirumab plus paclitaxel in South Korea between May 1, 2018, and December 31, 2018. We included patients with advanced gastric or GEJ adenocarcinoma and disease progression after first-line platinum and fluoropyrimidine-containing combination chemotherapy. **Results:** A total of 1,063 patients with advanced gastric or GEJ adenocarcinoma who received ramucirumab plus paclitaxel were included. The objective response rate and disease control rate were 15.1% and 57.7%, respectively; the median progression-free survival was 4.03 months (95% CI, 3.80–4.27), and the median overall survival was 10.3 months (95% CI, 9.33–10.73). The common treatment-related adverse events (TRAEs) at any grade were neutropenia (44.7%), anemia (41.8%), neuropathy (29.1%), fatigue (25.9%), and anorexia (25.0%). Grade 3 or higher TRAEs with incidences of ≥5% were neutropenia (35.1%) and anemia (10.5%). Adverse events of special interest were infrequent, including hypertension (2.1%) and proteinuria (3.0%). Based on multivariate analysis, overall survival was negatively associated with Eastern Cooperative Oncology Group performance status ≥2, weight loss in the previous 3 months ≥10%, GEJ of primary tumor, poor or unknown histology grade, number of metastatic sites ≥3, presence of peritoneal metastasis, no prior gastrectomy, and time to second-line since first-line treatment < 6 months. **Conclusions:** Our large-scale, nationwide, real-world data analysis of an unselected real-world population added evidence for the efficacy and safety of second-line ramucirumab plus paclitaxel in patients with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma. Clinical trial information: NCT04192734. Research Sponsor: Health Insurance Review & Assessment Service.

4057 **Poster Session**

Quality-adjusted time without symptoms or toxicity (Q-TWiST) of trastuzumab deruxtecan (T-DXd) versus chemotherapy in patients with advanced gastric cancer from the DESTINY-Gastric01 trial. *First Author: David Cella, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL*

Background: DESTINY-Gastric01 (NCT03329690) is a randomized, phase 2 study evaluating trastuzumab deruxtecan (T-DXd) in patients with HER2-positive advanced gastric cancer who progressed after ≥2 regimens. T-DXd significantly improved objective response rate (51% vs. 14%; $P < 0.001$) and overall survival (median OS; 12.5 vs. 8.4 months; $P = 0.01$) relative to chemotherapy (irinotecan or paclitaxel), leading to regulatory approval in USA and Japan. This post hoc analysis evaluated the overall effect of treatment differences on the quality of survival after discounting for time spent with toxicities or disease progression by comparing the Q-TWiST for patients who received T-DXd versus those who received chemotherapy. **Methods:** Patients were randomized 2:1 to receive T-DXd or chemotherapy. For each treatment arm, OS, truncated at 10.1 months (the median OS for the entire analysis population, following Q-TWiST convention), was partitioned into three health states: time with grade ≥3 toxicities before disease progression (TOX), time before disease progression without symptoms of disease progression or toxicity (TWiST), and time following disease progression prior to death or censoring (PROG). Mean duration in each state was weighted by a utility score, determined first in a threshold analysis, using a range of hypothetical utility values to generate quality-adjusted states, and then based on observed EQ-5D-5L scores, for that state; the sum of the utility-weighted durations yielded the Q-TWiST value for the time until the end of 10.1 months' follow-up. In both threshold and observed utility analyses, 95% confidence intervals (CIs) and two-sided P values were calculated using the bootstrap method. **Results:** Relative to patients receiving chemotherapy (n = 62), patients receiving T-DXd (n = 125) had significantly longer unweighted durations of TOX (3.0 vs. 1.6 months; $P < 0.01$) and TWiST (3.1 vs. 2.1 months; $P < 0.05$) and a shorter unweighted duration of PROG (2.4 vs. 3.7 months; $P < 0.01$). Using a matrix of 25 hypothetical utility-weight combinations, with a TWiST utility of 1 and TOX and PROG utilities ranging from 0 to 1, Q-TWiST differences between treatment arms ranged from −0.5 to 2.3 months, favoring T-DXd in 22 combinations, of which 15 were statistically significant. Using observed EQ-5D-5L utility values, Q-TWiST was 0.9 months (95% CI, 0.2-1.5) longer for T-DXd than for chemotherapy (6.6 vs. 5.7 months), significantly favoring T-DXd ($P < 0.05$). **Conclusions:** Over a 10-month follow-up period, treatment with T-DXd was associated with a statistically significant gain in quality-adjusted OS versus chemotherapy among previously treated patients with gastric cancer. An analysis using observed EQ-5D-5L utility scores found a statistically significant advantage in Q-TWiST for T-DXd. Clinical trial information: NCT03329690. Research Sponsor: Daiichi Sankyo.

4058 **Poster Session**

Early predictors of benefit to dual anti-PD1/HER2 inhibition: Biomarker analysis from phase 2 trial of pembrolizumab/trastuzumab in HER2-positive metastatic esophagogastric (mEG) cancer. *First Author: Steven Brad Maron, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Pembrolizumab and trastuzumab (P&T) and chemotherapy demonstrated 27 month mOS, 13 month mPFS, and 91% response rate in first-line HER2-positive mEG cancer irrespective of PD-L1 status (Janjigian Lancet Oncology 2020). Biomarkers including ^{89}Zr-trastuzumab PET, blood, and tumor analysis were correlated with progression-free survival. **Methods:** Twenty-five patients received P&T once 3 weeks prior to addition of chemotherapy to P&T. Pre-treatment tumor biopsies, ^{89}Zr-trastuzumab PET scans, serial plasma ctDNA (Guardant360, Redwood City, CA) and CT scans were performed. Tumor-matched DNA alterations were identified by correlating ctDNA and tissue-NGS variant calls. Pre-, on-, and post-treatment biopsies were analyzed using WES and IHC (HER2, PD-L1). Biomarkers were correlated with mPFS and 6-month PFS, the primary endpoint. **Results:** Of patients with tumor-matched mutations ctDNA at baseline, 12 of 16 had a decline in their maxVAF by week 3, corresponding to a mPFS of 14.7 (11.0-NR) vs 5.9 (95% CI 4.1-NR) months (p=0.009) and a mOS of 29.7 (95% CI 27.2-NR) vs 7.71 (95% CI 6.6-NR) months (p=0.006). 9 of 12 (75%) patients with decline in ctDNA at 3 weeks post-P&T achieved the 6-month PFS primary endpoint while the 4 patients with no decline in ctDNA all progressed in under 6-months. Similarly, 7 of 9 (78%) patients who had a decline in CT-measurements in all disease sites achieved the 6 month PFS primary endpoint, versus 10 of 16 (62.5%) of patients who did not respond in all sites (p=0.66), suggesting that ctDNA is superior to CT as an early predictive biomarker of response. Lack of *ERBB2* amplification (amp) by NGS in ctDNA and/or tumor was associated with lack of response to P&T alone prior to addition of chemotherapy. Interestingly, no lesions from patients lacking *ERBB2* ctDNA amp (n=3) responded to induction P&T by CT, while lesions from 3/9 patients lacking *ERBB2* tissue amp responded to P&T by 3-week CT, suggesting intrapatient HER2 heterogeneity. Eight patients also underwent ^{89}Zr-Trastuzumab PET scans prior to P&T and up to 5 lesions per disease site were measured on serial CT scans. All 15 lesions with intense uptake (SUVmax>10) responded to P&T, but only 9/24 lesions with SUVmax<10. All 4 patients who had at least 1 intense lesion achieved a post-P&T CT response and later 6+ month PFS. All 3 of 3 evaluable patients with intense uptake had baseline ctDNA *ERBB2* amp. **Conclusions:** Patients with a decline in tumor-matched maxVAF after one dose of P&T were more likely to achieve durable PFS. Pre-treatment ctDNA *ERBB2* amp and/or intense ^{89}Zr-trastuzumab PET avidity are non-invasive predictive biomarkers of response to HER2-directed therapy. Evaluation of tumor immune environment digital spatial profiling is underway. Clinical trial information: NCT02954536. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company, MSK Society.

4060 **Poster Session**

A phase II study of neoadjuvant immunotherapy combined with chemotherapy (camrelizumab plus albumin paclitaxel and carboplatin) in resectable thoracic esophageal squamous cell cancer (NICE study): Interim results. *First Author: Zhigang Li, Shanghai Chest Hospital, Shanghai, China*

Background: We conducted a phase II trial of preoperative chemotherapy with albumin paclitaxel and carboplatin combined with camrelizumab (NICE regimen), in patients with locally advanced esophageal squamous cell carcinoma (ESCC) with multiple lymph nodes metastasis. Initial results were analyzed to assess the efficacy and safety of this strategy. **Methods:** This was a prospective, multicenter, open, single arm, phase II trial. Eligible patients were histologically confirmed thoracic ESCC, staged as T1b-4a, N2-3 (≥ 3 stations), and M0 or M1 lymph node metastasis (confined to the supraclavicular lymph nodes) according to the 8th edition of American Joint Committee on Cancer. Patients received neoadjuvant treatment (NICE regimen) with intravenous camrelizumab (200 mg, day 1) plus albumin paclitaxel (100 mg/m2, day 1, 8, 15) and carboplatin (area under curve 5, day 1) of each 21-day cycle, for two cycles before surgery. The primary endpoint is pathological complete response (pCR) rate in the per-protocol population, which included all patients who had tumor resection and received at least one cycle of neoadjuvant treatment. Secondary endpoints include R0 resection rate, adverse events and disease-free survival. Safety was assessed in the modified intention-to-treat population. **Results:** Of the planned 60 patients enrolled, 55 (91.7%) patients have received the full two-cycles NICE regimen successfully, 4 patients didn't receive the complete neoadjuvant therapy due to intolerance (3 patients) and drop out (1 patient), 1 patient died due to pneumonia on the second cycle of neoadjuvant therapy. Grade 3-5 treatment-related adverse events (TRAEs) rate was 53.3% and TRAEs resulting in discontinuation rate was 6.7%. The common grade 3-5 TRAEs included lymphopenia (50%), thrombocytopenia (10%), pneumonia (5%) and thyroid dysfunction (3.3%). At the time of writing, 47 patients underwent surgery within 27-85 days (median 36 days) after NICE treatment, in which 7 patients had delays to surgery due to TRAEs. All patients achieved radical (R0) resection. There was no in-hospital and postoperative 30-day mortality. pCR (ypT0N0) was identified in 20 (42.5%) of 47 patients and 5 (10.6%) patients had complete pathological response of the primary tumor but residual disease in lymph nodes alone (ypTON+). **Conclusions:** Preoperative NICE regimen has achieved satisfatory initial results of disease response in locally advanced thoracic ESCC. A phase III randomized controlled trial is required to demonstarate the possible survival improvement. Trial registration: ChiCTR1900026240 Clinical trial information: ChiCTR1900026240. Research Sponsor: Hengrui Pharmaceutical Co., Ltd.

4061 **Poster Session**

A prospective, phase II, single-arm study of neoadjuvant/conversion therapy with camrelizumab, apatinib, S-1 ± oxaliplatin for locally advanced cT4a/bN + gastric cancer. *First Author: Song Li, Qilu Hospital of Shandong University, Jinan, China*

Background: The prognosis of cT4a/bN+ gastric cancer (GC) is poor due to low R0 resection rate and frequent recurrence. We evaluated the feasibility, safety, and efficacy of a combination of immunotherapy, anti-angiogenesis, and chemotherapy for neoadjuvant/conversion treatment of cT4a/bN+ GC. **Methods:** Patients with T4a/bN+ GC were enrolled to receive camrelizumab (200mg d1), apatinib (250mg d1-14), S-1 (50mg bid d1-10) ± oxaliplatin (85 mg/m^2 d1) for at least 2 cycles, followed by re-evaluation and operation. Peri-treatment samples were collected for whole-exome, transcriptome, and T cell receptor (TCR) sequencing. Pathological response (PR) and its relationship with genomic biomarkers are primary endpoints. **Results:** 25 patients were enrolled, with median age 63 (48-70), 19 male, 11 cT4aN2-3 and 14 cT4bN2-3. The radiological response (RR) rate of the treatments was 33.3% (8/24), and tumor downstaging rate 79.2% (19/24). 24 patients completed re-evaluation, with 3 failed conversion, 2 refused surgery, and 1 postponed surgery for immune-related pneumonia. Among the 18 patients with R0 resection, 3 got complete PR (CPR), 2 major PR (MPR, ≤10% residual cancer cells), and 3 partial PR (11~49% residual cancer cells), with a PR rate of 44.4% and MPR+ (MPR & CPR) rate of 27.8%. 62.5% patients with PR and 83.3% patients with RR overlapped with each other. At a median of 12.5 (3.4-19.5) months of follow-up, 13 of 17 patients (76.5%) with R0 resection were recurrence-free. No ≥3 toxicity was found. Besides high microsatellite instability, tumor mutation/neoantigen burden (TMB/TNB), mutation signatures (DNA damage repair and DNA mismatch repair) and related gene mutations (BRCA2, PRKDC, ATM, POLD1, POLE), several novel driver mutations (SSPO, TRPS1, and DOCK2) and copy number variants (DUSP15 loss, FDFT1 gain, and RBBP8NL loss) were related to MPR+ GC. The combination therapy decreased TMB/TNB, facilitated infiltration of active immune cells (CD4$^+$ memory T, CD8$^+$ T, activated and plasmacytoid dendritic cells, and M1 macrophage), and specifically boosted TCR clonality in MPR+ patients. Besides, numbers of mesenchymal stem cells decreased in MPR+ but increased in MPR- GC after the treatment. **Conclusions:** Combination of camrelizumab, apatinib, S-1 ± oxaliplatin is feasible, safe, and efficient in neoadjuvant/conversion therapy for cT4a/bN+ GC. It may remodel immune microenvironments and induce anti-tumor immune responses. Clinical trial information: NCT03878472. Research Sponsor: None.

	Total (n = 25)	cT4aN+ (n = 11)	cT4bN+ (n = 14)
Mean cycles of treatment(95% CI)	2 (2.07-3.21)	2 (2-2)	3.14 (2.16-4.13)
R0 resection rate	85.7% (18/21)	100% (11/11)	70% (7/10)
PR rate	44.4% (8/18)	54.5% (6/11)	28.6% (2/7)
RR rate	33.3% (8/24)	27.3% (3/11)	38.4% (5/13)
MPR+ rate	27.8% (5/18)	36.4% (4/11)	14.3% (1/7)
Tumor down-staging rate	79.2% (19/24)	81.8% (9/11)	76.9% (10/13)

4062 **Poster Session**

Efficacy and safety of KN046 plus paclitaxel/cisplatin as first-line treatment for unresectable locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC). *First Author: Jianming Xu, Affiliated Hospital Cancer Center, Academy of Military Medical Sciences, Beijing, China*

Background: The prognosis of pts with advanced esophageal squamous cell carcinoma (ESCC) remains dismal clinically. Paclitaxel and cisplatin were used as the standard first-line regimen in ESCC for almost two decades. Recently, the combination of PD-1/PD-L1 pathway blockades with chemotherapy has shown synergistic efficacy in a few clinical trials. KN046 is the world's first dual immune checkpoint inhibitor, which can block PD-1/PD-L1 and CTLA-4 pathways at the same time. The purpose of this ongoing phase II trial (NCT03925870) in China was to evaluate the efficacy and safety of KN046 monotherapy or combined with chemotherapy for unresectable locally advanced, recurrent or metastatic ESCC. **Methods:** This trial included 3 cohorts, one of which enrolled systemic treatment nave pts with histologically or cytologically confirmed unresectable locally advanced, recurrent or metastatic ESCC who have ECOG PS of 0-1. Eligible subjects were given paclitaxel (135-175mg/m^2, iv, d1, q3w) and cisplatin (75mg/m^2, iv, d2-4, q3w) plus KN046 (5mpk, iv, d1, q3w) for 4~6 cycles during initial therapy. For those without progressive disease, maintenance treatment was administrated with KN046 monotherapy (5mpk, iv, q2w) until progression or unacceptable toxicity. Tumour response was assessed according to RECIST 1.1 every 6 weeks. The primary endpoint was investigator-assessed ORR. Secondary endpoints included DCR, safety, PK profile, and immunogenicity. **Results:** As of December 14, 2020, 15 pts were enrolled, all of them were male, 52.3% ≥60 years, 64% ECOG 1, 80% with distant metastasis. Median exposure time to KN046 was 11.4 wks and average KN046 treatment was 2.4 cycles. 12 pts were included in the efficacy analysis and 15 pts in the safety analysis. The overall response rate (ORR) and disease control rate (DCR) were 58.3% and 91.6%, respectively. 7 pts (58.3%) had partial response (PR) including one complete response of target lesion. 4 pts (33.3%) had stable disease (SD) with 3 pts showing more than 20% of tumor burden reduction. The overall incidence of KN046 related adverse events was 80.0%, with 13.3% Gr 3 or above TRAE. Infusion-related adverse events occurred during 7.8% and most were mild. Immune related adverse events irAE were seen in 53.3% and the most common Gr 3 irAE were nausea (n 1, 6.7%) and rash (n 1, 6.7%). **Conclusions:** KN046 plus paclitaxel/cisplatin demonstrated clinical efficacy and acceptable safety as first-line treatment, and might be a favorable option for pts with advanced ESCC. Clinical trial information: NCT03925870. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd. Clinical trial information: NCT03925870. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd.

4063 **Poster Session**

Multicenter phase Ib/II study of second-line trastuzumab, ramucirumab, and paclitaxel in patients with HER2-positive advanced gastric or gastroesophageal junction cancer (HER-RAM study). *First Author: Sun Young Rha, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: We evaluated the safety and efficacy of adding trastuzumab to ramucirumab and paclitaxel (TRP) as a second line treatment in human epidermal growth factor receptor 2 (HER-2)-positive advanced gastric or gastroesophageal junction (G/GEJ) cancer progressed from trastuzumab containing chemotherapy. **Methods:** Patients with HER-2-positive advanced G/GEJ cancer who progressed after first-line chemotherapy with trastuzumab in combination with fluoropyrimidine and platinum were eligible. Trastuzumab (Herzuma[CT-P6], Celltrion Inc.) 4mg/kg on day 1 followed by 2mg/kg on days 8, 15, and 22, ramucirumab 8mg/kg on days 1 and 15, and paclitaxel (dose level 1: 80mg/m^2, dose level -1: 70 mg/m^2) on days 1, 8, and 15 of a 28-day cycle was tested. After safety analysis of lead-in safety cohort (phase 1b), phase 2 part was conducted to evaluate the primary endpoint of progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), disease control rate (DCR), overall survival (OS), and safety. **Results:** At the phase 1b part, as there was no dose limiting toxicity in 3 patients at the dose level 1, dose level 1 with full dose combination was determined as recommended phase 2 dose. At the time of data lock on Jan. 31, 2021, 45 patients among enrolled 50 patients were evaluable for response and safety including 3 patients from phase 1b part. Median age was 59 years old (range 30-82) and most patients were male (37/45). At baseline, 33 patients had tumors with HER-2 3+ by immunohistochemistry (IHC) and 12 had those with HER-2 2+ by IHC with *ERBB2* amplification by in situ hybridization. With median follow-up duration of 11.6 months, median PFS and OS were 7.2 months (95% confidence interval [CI]: 6.0-8.5 months) and 13.6 months (95% CI: 10.3-16.9 months), respectively. ORR was 55.6% (25/45, complete response = 1, partial response = 24) and DCR was 95.6% (43/45), respectively. Most common hematologic adverse event (AE) was neutropenia (all grade: 64.4%, grade 3/4: 51.1%) with 1 case of febrile neutropenia (2.2%). Most common non-hematologic AE was peripheral sensory neuropathy (all grade: 33.3%, grade 3: 2.2%). Gastrointestinal (GI) bleeding occurred in 4 patients (grade 3 upper GI bleeding: 6.7%, grade 1 lower GI bleeding: 2.2%), whereas GI perforation was not observed. Hypertension occurred in 3 patients (all grade: 6.7%, grade 3: 4.4%). No new or unexpected AEs resulting in treatment cessation were observed with this combination regimen. **Conclusions:** The continuous use of trastuzumab beyond progression in combination with ramucirumab and paclitaxel showed promising activity and manageable safety profile in HER2 positive G/GEJ cancer patients who progressed after trastuzumab containing chemotherapy. Updated outcomes for ongoing patients will be presented. Research Sponsor: None.

4064 **Poster Session**

A phase II/III study of perioperative nivolumab and ipilimumab in patients (pts) with locoregional esophageal (E) and gastroesophageal junction (GEJ) adenocarcinoma: Results of a safety run-in—A trial of the ECOG-ACRIN Cancer Research Group (EA2174). *First Author: Jennifer Rachel Eads, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: E/GEJ adenocarcinoma has a high mortality rate despite curative intent therapy. The use of immune checkpoint inhibition is beneficial for treatment of this cancer in the metastatic and adjuvant settings but the role of these agents in the perioperative setting remains unclear. Here we report the results of an initial safety run-in of nivolumab when given in combination with neoadjuvant chemoradiation. **Methods:** Pts with a localized T1N1-3M0 or T2-3N0-2M0 E/GEJ adenocarcinoma with an ECOG PS of 0-1 and whom were deemed surgical candidates for an esophagectomy by a qualified surgeon were eligible. In step 1, pts were randomized to neoadjuvant therapy with carboplatin AUC 2 and paclitaxel 50 mg/m2 intravenously (IV) weekly x 5 along with 41.4-50.4 Gy radiation without (Arm A) or with (Arm B) nivolumab 240 mg IV during weeks 1 and 3 of treatment, followed by esophagectomy. Pts underwent a second randomization (step 2) to adjuvant nivolumab 240 mg IV every 2 weeks x 12 cycles with or without ipilimumab 1 mg/kg IV every 6 weeks during cycles 1, 4, 7 and 10. For the safety run-in, 30 pts were planned for accrual to allow for 12 evaluable pts per arm. Pts were followed for safety during neoadjuvant therapy through surgery and toxicities monitored per CTCAEv5. Pre-specified early stopping rules were defined to allow halting of the trial if deemed unsafe. Planned study accrual is 278 pts. Neoadjuvant primary endpoint is pathologic complete response rate, adjuvant primary endpoint is disease-free survival. **Results:** A total of 31 pts were enrolled to the safety run-in element of the study (Arm A, n = 16; Arm B n = 15). Male, 94%; White, 100%; median age, 62; esophageal adenocarcinoma, 52%; GEJ, 48%. Grade (G) 3 events occurring in more than one pt on Arm A—decreased lymphocytes (n = 5). G4 events occurring on Arm A—decreased lymphocytes (n = 1). G3 events occurring in more than one pt on Arm B—decreased lymphocytes (n = 2); anemia (n = 2); leukopenia (n = 4); hypotension (n = 2). G4 events occurring on Arm B—decreased lymphocytes (n = 3); cardiac tamponade and pericardial effusion (n = 1). Cardiac events were thought to be secondary to tumor location, not neoadjuvant treatment. On Arm B, notable G3 events seen in one pt each included colonic obstruction, wound infection and esophageal anastomotic leak. Of pts who have reached the time for surgery, 12/14 pts on Arm A and 13/13 pts on Arm B have proceeded to surgery. Of pts who have completed step 1, 7/14 pts on Arm A and 8/11 pts on Arm B have registered to step 2. **Conclusions:** The addition of nivolumab to carboplatin, paclitaxel and radiation in the neoadjuvant setting appears to be safe with no disproportionate level of toxicity observed between the two treatment arms. Accrual to the remainder of the trial continues with 43/278 patients accrued. Clinical trial information: NCT03604991. Research Sponsor: U.S. National Institutes of Health.

4065 **Poster Session**

Intraperitoneal aerosolized nanoparticle albumin based paclitaxel (NAB-PTX) for irresectable peritoneal metastases: A first in human phase I study. *First Author: Wim Ceelen, Ghent University Hospital, Department of GI Surgery, Ghent, Belgium*

Background: Pressurized intraperitoneal aerosolized chemotherapy (PIPAC) was recently introduced in the palliative treatment of peritoneal metastases (PM). Results from preclinical experiments suggest that intraperitoneal (IP) Nab-PTX may result in superior efficacy compared to solvent based paclitaxel (PTX). We performed a phase I first-in-human trial of PIPAC using Nab-PTX in patients with PM from upper gastrointestinal, breast, or ovarian cancer. **Methods:** Eligible patients with biopsy-proven PM underwent up to three PIPAC treatments using Nab-PTX with a four-week interval at two university hospitals. Patients underwent laparoscopy with IP nebulization of Nab-PTX over 5 min; the procedure was completed after 30 min. The dose of Nab-PTX was escalated from 35 to 140 mg/m^2 using a Bayesian approach until the maximally tolerated dose (MTD) was reached. Secondary endpoints included surgical morbidity, pharmacokinetics (PK), histological treatment response, and overall survival. Blood and tissue samples were taken after each PIPAC procedure. Population PK analysis was performed using Monolix version 2020R1. Quality of life was measured using the EORTC QLQ-C30 questionnaire and visual analogue pain scales (VAS). **Results:** Twenty-three patients were included. The primary tumor was gastric cancer (55%), ovarian cancer (20%), hepatobiliary or pancreatic cancer (15%), breast cancer (5%), and miscellaneous (5%). No dose limiting toxicity was observed. Grade 3 thrombopenia was observed in one patient allocated to a dose of 90 mg/m^2. One patient allocated to the highest dose experienced grade 3 neutropenia one week after each PIPAC. The most frequent treatment-related toxicities were liver toxicity (grade 1 to 3, 75%) and anemia (grade 1 to 3, 70%). Eight patients (40%) showed surgical site infections including wound infection and wound dehiscence (grade 1 to 3), four of whom required treatment with antibiotics. Treatment was associated with histological response in 35% of patients, while stable disease and progressive disease were found in 35% and 30%, respectively. The absorption of PTX continued long after the end of the procedure (30 min), with the T_{max} reached between 2 and 6 h after initiation of the procedure. Median tumor PTX concentrations suggested accumulation: 9.37 ng/mg, 14.78 ng/mg and 25.75 ng/mg after the first, second and third PIPAC, respectively. EORTC global health, functional, and symptom scores as well as VAS scores remained stable throughout the treatment period. Overall survival after one year was 57%. **Conclusions:** PIPAC with Nab-PTX may be applied safely up to a dose of 140 mg/m^2 and results in a favorable PK profile and promising anticancer activity. At the MTD of 140 mg/m^2, considerable surgical site infections and liver toxicity were observed. Therefore, the recommended dose for future phase II trials is 112.5 mg/m^2. Clinical trial information: NCT03304210. Research Sponsor: Kom op tegen Kanker - Flemish Cancer League.

4066 **Poster Session**

Health-related quality of life (HRQOL) in patients (pts) with advanced gastric cancer/gastroesophageal junction cancer (GC/GEJC) or esophageal adenocarcinoma (EAC): Interim results of nivolumab plus chemotherapy (N +C) versus (C) from CheckMate 649.

First Author: Lucjan Wyrwicz, Klinika Onkologii i Radioterapii, Narodowy Instytut Onkologii, Warsaw, Poland

Background: CheckMate 649 (NCT02872116) is a randomized, open label phase 3 study in first line (1L) GC/GEJC/EAC. Prespecified interim results showed statistically significant improvement in overall survival (OS) and progression-free survival (PFS) for N+C vs C in all randomized pts and pts whose tumors expressed programmed death-ligand 1 combined positive score (CPS) $\geq$ 5. We present interim HRQOL results for CPS $\geq$ 5 pts, included as exploratory in the study. **Methods:** HRQOL was assessed using EQ-5D-3L (EQ-5D) and Functional Assessment of Cancer Therapy–Gastric Cancer (FACT-Ga). Assessments were performed at baseline (BL), every 6 weeks during treatment, and during follow-up. Change from BL EQ-5D Visual Analog Scale (VAS), Utility Index (UI) and FACT-Ga scores were analyzed using mixed models. Time to first symptom deterioration (TTSD), time until definitive deterioration (TuDD), and time to improvement (TTI) were estimated with Kaplan-Meier estimators and stratified Cox models; deterioration/improvement was based on prespecified meaningful change thresholds. **Results:** 1,581 pts were randomized to N+C (n = 789) and C (n = 792); of those, 955 pts had CPS $\geq$ 5 (N+C [n = 473] and C [n = 482]). Among 821 pts with BL and post BL PROs (N+C [n = 421] and C [n = 400]), BL scores for FACT-Ga total were similar for N+C and C. Least-squares mean differences from BL favored N+C at most visits for EQ-5D and FACT-Ga total and GaCS, and were comparable for other FACT subscales (data not shown). TTI largely favored N+C (most hazard ratios (HR) > 1) but was not significantly different between treatments. For TTSD, pts treated with N+C had decreased risk of deterioration (HR < 1) in EQ-5D UI, FACT-Ga total, and GaCS. TuDD showed statistically significant delays in deterioration (HR with confidence intervals [CI] < 1) for all scores. **Conclusions:** Pts with 1L GC/GEJC/EAC experienced better HRQOL with N+C compared with C alone. Change from BL in EQ-5D and FACT-Ga total and GaCS favored N+C at most visits. N+C decreased deterioration risk compared to C with OS and PFS improvement, suggesting favorable benefits in 1L GC/GEJC/EAC pts with CPS $\geq$ 5. Clinical trial information: NCT02872116. Research Sponsor: Bristol Myers Squibb.

Instrument/Scale	TTSD HR (95% CI)	TuDD HR (95% CI)	TTI HR (95% CI)
Physical Well-Being (WB)	0.82 (0.67-1.01)	**0.70 (0.55-0.91)**	1.00 (0.79-1.26)
Social WB	0.85 (0.68-1.05)	**0.68 (0.51-0.90)**	1.13 (0.86-1.49)
Emotional WB	0.99 (0.77-1.26)	**0.65 (0.47-0.90)**	0.95 (0.78-1.17)
Functional WB	0.88 (0.71-1.08)	**0.63 (0.48-0.82)**	1.06 (0.86-1.31)
FACT-G Total	0.81 (0.65-1.01)	**0.62 (0.47-0.82)**	0.87 (0.70-1.09)
GaCS Subscale	**0.64 (0.49-0.83)**	**0.57 (0.41-0.79)**	1.05 (0.86-1.28)
FACT-Ga Total	**0.74 (0.57-0.96)**	**0.56 (0.40-0.78)**	1.04 (0.84-1.29)
EQ-5D U I (UK set)	**0.80 (0.65-0.99)**	**0.65 (0.50-0.83)**	1.16 (0.95-1.43)
EQ-5D VAS	0.85 (0.69-1.04)	**0.68 (0.53-0.87)**	1.13 (0.93-1.38)

4067 **Poster Session**

Individual patient data meta-analysis of neoadjuvant chemotherapy followed by surgery versus upfront surgery in esophageal or gastro-esophageal carcinoma.

First Author: Matthieu Faron, Gustave Roussy Cancer Campus, Villejuif, France

Background: Defining the optimal neoadjuvant treatment for resectable locally advanced esophageal carcinoma remains an open question. The debate is fuelled by the fact that most of the available randomized clinical trials (RCT) accrued two histological subtypes (adenocarcinoma (AC) and squamous cell carcinoma (SCC)) and two anatomical locations (TE and GEJ). The aim of this individual patient data (IPD) meta-analysis was to investigate the effect of preoperative chemotherapy on survival with a specific focus on histological subtypes and anatomical locations. **Methods:** Were eligible published or unpublished RCT closed to accrual before December 2015 and comparing neoadjuvant chemotherapy (CS) to primary surgery (S), identified by electronic database, conference proceedings and clinical trial register. All analyses were conducted on IPD obtained from trial Investigators. The Primary endpoint was overall survival (OS), Secondary endpoints were disease-free survival (DFS) with a 6-months landmark time, local/distant relapse/death without relapse as competing events. Two subgroup analyses were pre-planned one on the histological subtype and another on the anatomical location. A stratified logrank test was used for OS and DFS, and a stratified fine and gray model for competing events. HR, and risk ratios (RR) were combined using a random effect model. **Results:** IPD were obtained from 12 RCT (2601 patients) out of 16 identified (2863 patients) When compared to S, CS was associated with a significantly increased OS, (HR = 0.85[0.78-0.92], $p < 0.0001$), with a 5-year absolute OS benefit of 5.7%. However, the subgroup analysis by histological subtype showed an OS benefit from CS higher for AC (HR = 0.80[0.72-0.91], $p < 0.01$), when compared to SCC (HR = 0.90[0.80-1.01], p = 0.06), but with p for interaction = 0.2. In the subgroup analysis by anatomical location CS benefit was seen across both anatomical location with a trend in favor of GEJ (TE: HR = 0.89[0.81-0.98], p = 0.02 GEJ: HR = 0.71[0.57-0.88]), $p < 0.01$, p for interaction = 0.057). CS also improved DFS (HR = 0.81[0.74-0.88], $p < 0.0001$), with the same trend for the subgroup analyses, with apparent significant benefit for AC HR = 0.80 [0.72-0.91] when compared to SCC HR = 0.90[0.80-1.01], (p for interaction 0.045) and a similar benefit for both location (TE: HR = 0.89[0.81-0.98] $p < 0.01$, GEJ: HR = 0.71[0.57-0.88], p = 0.095, P for interaction 0.11). Local (HR = 0.76[0.63-0.92], p = 0.0045) and distant (HR = 0.87[0.76-0.99], p = 0.04) relapses were also significantly lower in the CS arm, with no significant variation according to histological subtypes or tumor location. **Conclusions:** Neoadjuvant chemotherapy significantly improves OS when added to upfront surgery and was equally effective in AC and SCC. A slightly more pronounced effect was observed for overall survival in the GEJ location vs. the TE. Research Sponsor: French Programme Hospitalier de Recherche Clinique (PHRC).

4068 **Poster Session**

Imaging HER2-positive metastatic esophagogastric cancer with ^{89}Zr-trastuzumab PET and ^{18}F-FDG PET.

First Author: Melissa Amy Lumish, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Variations in HER2 expression between primary tumor and metastases may contribute to drug resistance in HER2-positive mEG cancer. Whole body imaging with ^{89}Zr-trastuzumab PET has a potential advantage over single site biopsies as it can non-invasively assess variations in HER2 expression and target engagement. ^{89}Zr-trastuzumab PK, biodistribution and dosimetry in mEG cancer were previously published by our group (O'Donoghue, *JNM* 2018). We now present lesion level analysis of baseline ^{18}F-FDG-PET and CT in comparison with baseline ^{89}Zr-trastuzumab imaging. **Methods:** Patients with metastatic HER2-positive (IHC 3+, IHC 2+/FISH > 2.0) mEG cancer and RECIST 1.1 measurable disease were consented and imaged with ^{89}Zr-trastuzumab PET, ^{18}F-FDG-PET and CT. All visualized lesions (maximum 5 per organ) were annotated in detail using RECIST 1.1 measurements (CT) and maximum standard uptake values (SUVmax) on ^{89}Zr-trastuzumab and ^{18}F-FDG PET scans. Correlation of visualized disease burden between imaging modalities with clinical and pathologic characteristics was performed. **Results:** 33 patients with mEG adenocarcinoma were imaged with ^{89}Zr-trastuzumab PET, ^{18}F-FDG-PET and CT (12% esophageal, 64% GEJ, 24% gastric). HER2 status (IHC 3+ 70%; IHC2+/FISH+ 27%, NGS 3%) was assessed from biopsy of primary (66.7%) or metastasis (33.3%). Median time from diagnosis to ^{89}Zr-trastuzumab PET was 12.6 months. At the time of ^{89}Zr-trastuzumab PET, 39% were treatment naive, while 61% had received prior therapy including trastuzumab (58%) and afatinib (median lines 2, range 0-6). 82% of patients had the primary tumor in place and all patients had metastatic disease at the time of enrollment with metastases to lymph nodes (70%) peritoneum (24%), liver (58%), lung (33%), and/or bone (9%). Median number of RECIST 1.1 lesions measured on baseline CT was 6 (range 1-15). PET analysis is complete in 18 of 33 patients. Median number of ^{89}Zr-trastuzumab PET positive (SUV > 3) lesions was 5.5 (range 1-11) with 5 patients having at least 1 (max 3) very intense lesion (SUV > 15). Median number of ^{18}F-FDG-PET-positive lesions was 8 (range 1-14). Three patients had at least 1 lesion positive on ^{89}Zr-trastuzumab-PET and negative on ^{8}F-FDG-PET (range 0-5), and 8 patients had at least 1 lesion positive on ^{18}F-FDG-PET and negative on ^{89}Zr-trastuzumab-PET (range 0-7). Of the total lesions identified on ^{89}Zr-PET but not CT, 40% were in bone. Of those identified on ^{89}Zr but not ^{8}F-FDG-PET, 40% were in bone, and of those on ^{18}F-FDG- but not ^{89}Zr-PET, 6% were in bone. **Conclusions:** ^{89}Zr-trastuzumab PET effectively identifies heterogeneity of HER2 expression and allows assessment of lesions throughout the whole body. Bone lesions were better identified and appeared earlier on ^{89}Zr-trastuzumab PET compared with CT. Additional analyses including correlation of baseline HER2 heterogeneity with overall and disease-free survival will be presented. Clinical trial information: NCT02023996. Research Sponsor: Department of Defense.

4069 **Poster Session**

Final results from ClarIDHy, a global, phase 3, randomized, double-blind study of ivosidenib (IVO) versus placebo (PBO) in patients (pts) with previously treated cholangiocarcinoma (CCA) and an isocitrate dehydrogenase 1 (*IDH1*) mutation.

First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center & Weill Medical College at Cornell University, New York, NY

Background: CCA is a rare cancer for which there are limited effective therapies. *IDH1* mutations occur in ~20% of intrahepatic CCAs, resulting in production of the oncometabolite D-2-hydroxyglutarate, which promotes oncogenesis. IVO (AG-120) is a first-in-class, oral, small-molecule inhibitor of mutant IDH1 (mIDH1). ClarIDHy aimed to demonstrate the efficacy of IVO vs PBO in pts with unresectable or metastatic m*IDH1* CCA. The primary endpoint was met with significant improvement in progression-free survival (PFS) by independent radiology center (IRC) with IVO vs PBO (hazard ratio [HR] = 0.37, $p < 0.0001$). Objective response rate (ORR) and stable disease for IVO were 2.4% (3 partial responses) and 50.8% (n = 63) vs 0% and 27.9% (n = 17) for PBO. IVO pts experienced significantly less decline in physical and emotional functioning domains of quality of life at cycle 2 day 1 vs PBO pts (nominal $p < 0.05$). **Methods:** Pts with m*IDH1* CCA were randomized 2:1 to IVO (500 mg PO QD) or matched PBO and stratified by prior systemic therapies (1 or 2). Key eligibility: unresectable or metastatic m*IDH1* CCA based on central testing; ECOG PS 0–1; measurable disease (RECIST v1.1). Crossover from PBO to IVO was permitted at radiographic progression. Primary endpoint: PFS by IRC. Secondary endpoints included overall survival (OS; by intent-to-treat), ORR, PFS (by investigator), safety, and quality of life. The planned crossover-adjusted OS was derived using the rank-preserving structural failure time (RPSFT) model. **Results:** As of 31 May 2020, ~780 pts were prescreened for an *IDH1* mutation and 187 were randomized to IVO (n = 126) or PBO (n = 61); 13 remain on IVO. Median age 62 y; M/F 68/119; 91% intrahepatic CCA; 93% metastatic disease; 47% had 2 prior therapies. 70% of PBO pts crossed over to IVO. OS data were mature, with 79% OS events in IVO arm and 82% in PBO. Median OS (mOS) was 10.3 months for IVO and 7.5 months for PBO (HR = 0.79; 95% CI 0.56–1.12; one-sided p = 0.093). The RPSFT-adjusted mOS was 5.1 months for PBO (HR = 0.49; 95% CI 0.34–0.70; $p < 0.0001$). Common all-grade treatment emergent adverse events (TEAEs, $\geq$ 15%) in the IVO arm: nausea 41%, diarrhea 35%, fatigue 31%, cough 25%, abdominal pain 24%, decreased appetite 24%, ascites 23%, vomiting 23%, anemia 18%, and constipation 15%. Grade $\geq$ 3 TEAEs were reported in 50% of IVO pts vs 37% of PBO pts, with grade $\geq$ 3 treatment-related AEs in 7% of IVO pts vs 0% in PBO. 7% of IVO pts experienced an AE leading to treatment discontinuation vs 9% of PBO pts. There were no treatment-related deaths. **Conclusions:** IVO was well tolerated and resulted in a favorable OS trend vs PBO despite a high rate of crossover. These data – coupled with statistical improvement in PFS, supportive quality of life data, and favorable safety profile – demonstrate the clinical benefit of IVO in advanced m*IDH1* CCA. Clinical trial information: NCT02989857. Research Sponsor: Agios Pharmaceuticals, Inc.

4070 **Poster Session**

Adjuvant nivolumab for hepatocellular carcinoma (HCC) after surgical resection (SR) or radiofrequency ablation (RFA) (NIVOLVE): A phase 2 prospective multicenter single-arm trial and exploratory biomarker analysis.

First Author: Masatoshi Kudo, Department of Gastroenterology and Hepatology, Kindai University Faculty of Medicine, Osaka, Japan

Background: The NIVOLVE trial was designed to assess the efficacy and safety of nivolumab as an adjuvant therapy for HCC, and to identify biomarkers predictive of recurrence in patients after SR or RFA (Registration # UMIN 000026648). **Methods**: The trial involved 11 sites and was conducted in patients with HCC who showed a complete response after SR (n = 33) or RFA (n = 22) (ITT). Overall, 53 of 55 patients with Child-Pugh A received nivolumab (240 mg/body every 2 weeks (8 cycles)), followed by nivolumab (480 mg/body every 4 weeks (8 cycles)) within 6 weeks after SR or RFA. The primary endpoint was the 1 year recurrence-free survival rate (RFSR). The key secondary endpoint was RFS. Exploratory biomarker analysis included mutations, copy number alterations, and tumor mutation burden in tumor tissues. Techniques included next generation sequencing, immunohistochemical staining (IHC) of formalin-fixed paraffin-embedded tissues (n = 31, 13 with recurrence and 18 without) for CD8, PD-1, PD-L1, Foxp3, and β-catenin, and ctDNA analysis using pre-nivolumab whole blood by deep sequencing (CAPP-seq; Avenio). **Results**: The 1-year RFSR and median RFS were 76.7% and 26.0 months (95% confidence interval (CI), 23.9–28.1), respectively, with no difference between SR and RFA. Copy number gains (CNGs) in WNT/β-catenin related genes (*APC, CTNNB1, TCF7L1, TCF7L2*) (n = 8) correlated with shorter RFS (positive: 11.8 months *vs.* negative: not reached [NR]; p = 0.0003). IHC revealed that negative staining for PD-1 ($p < 0.0001$), a low combined positive score for PD-L1 (p = 0.0113), a low number of CD8+ tumor infiltrating lymphocytes (TILs) (p = 0.0130), and positivity for Foxp3+ cells (p = 0.0076) correlated with recurrence. Treatment-related adverse events (AEs) (n = 53) were as follows: all grades, 68%; grades 3–4 (18.9%); and immune related AEs, 25%. HCC cases with low numbers of CD8+ TILs or cases positive for Foxp3+ cells (n = 16) showed a significantly shorter RFS (16.8 months [95% CI, 8.7–25.1]) than those with high numbers of CD8+ TILs and those positive for PD-1/PD-L1 expression (n = 15) (NR [95% CI,26.2months–NR]) ($p < 0.0001$). HCC cases with activation of the WNT/β-catenin pathway assessed by IHC (n = 9) showed shorter RFS (17.0 months [95% CI,1.1–26.2]) than those without activation (n = 22) (NR [95% CI,24.7 months–NR]) (p = 0.0191). Patients positive for ctDNA (n = 10) before nivolumab tended to have shorter RFS than those without ctDNA (n = 30) (26.2 vs. NR). There was no correlation between TMB and RFS. **Conclusions**: The 1 year RFSR and RFS in the NIVOLVE trial were 76.6% and 26.0 months, respectively. No new safety signal was observed. CNG in WNT/β-catenin-related genes, activation of the WNT/β-catenin pathway, the presence of Foxp3+ cells, and low numbers of CD8+ TILs may predict recurrence after SR or RFA with adjuvant nivolumab. Clinical trial information: 000026648. Research Sponsor: Ono Pharmaceutical Company.

4071 **Poster Session**

IMbrave150: Exploratory analysis to examine the association between treatment response and overall survival (OS) in patients (pts) with unresectable hepatocellular carcinoma (HCC) treated with atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor).

First Author: Michel Ducreux, Gustave Roussy Cancer Center, Villejuif, France

Background: Based on IMbrave150 (NCT03434379) results, atezo + bev has been approved in > 60 countries for pts with unresectable HCC who have not received prior systemic therapy (Finn RS, NEJM 2020). OS and objective response rate (ORR) improvements with atezo + bev vs sor were maintained with an additional 12 mo of follow up since primary analysis. Updated median OS was 19.2 mo with atezo + bev vs 13.4 mo with sor (stratified HR, 0.66; 95% CI: 0.52, 0.85). Updated ORR was 30% with atezo + bev vs 11% with sor by independently-assessed (IRF) RECIST 1.1 (Finn RS, ASCO GI 2021). Here, we report an exploratory analysis examining the association of response by RECIST 1.1 with OS and independent predictors of survival. **Methods:** Pts in this Ph III study were systemic treatment–naive with unresectable HCC, ≥1 measurable untreated lesion (RECIST 1.1), Child-Pugh class A liver function and ECOG PS 0/1. Pts were randomized 2:1 to atezo 1200 mg IV q3w + bev 15 mg/kg IV q3w or sor 400 mg bid until unacceptable toxicity or loss of clinical benefit per investigator. ORR was determined by IRF RECIST 1.1. Kaplan-Meier analyses of OS by response status were conducted without landmark and with 4- and 6-mo landmarks. Multivariate analysis was conducted using Cox modeling with time-dependent covariate (responder [yes/no]) with backwards elimination. These analyses only included pts treated with atezo + bev. **Results:** IMbrave150 enrolled 501 pts, including 336 treated with atezo + bev. Median follow-up was 15.6 mo. OS was longer in pts with confirmed response per RECIST 1.1 (responders, CR + PR) vs non-responders by Kaplan-Meier analyses without landmark and with 4- and 6-mo landmarks (Table). By multivariate analysis, in addition to responder (yes/no), 5 of the 10 initially included predictors of OS remained in the final Cox model ($P < 0.10$): ECOG PS (0/1), geographic region (Asia excluding Japan/rest of the world), etiology (hepatitis B/hepatitis C/non-viral), macrovascular invasion and/or extrahepatic spread (yes/no), and baseline alpha-fetoprotein (< 400 ng/mL/ ≥400 ng/mL). **Conclusions:** Atezo + bev is the new standard of care for pts with previously untreated, unresectable HCC. Here we showed that in IMbrave150 pts treated with atezo + bev, response by RECIST 1.1 was associated with OS, suggesting that confirmed response is an independent predictor of OS in these pts. Clinical trial information: NCT03434379. Research Sponsor: F. Hoffmann-La Roche, Ltd.

Kaplan-Meier analyses of the association between confirmed response by RECIST 1.1 and OS.

Analysis	Responders	n	Median OS (95% CI), mo	HR[a] (95% CI)
No landmark	Yes	100	NE (26.2, NE)	0.20 (0.13, 0.32)
	No	222	14.7 (12.5, 17.0)	–
4-mo landmark	Yes	44	NE (NE)	0.23 (0.11, 0.47)
	No	258	15.1 (12.8, 19.6)	–
6-mo landmark	Yes	68	NE (20.2, NE)	0.27 (0.15, 0.47)
	No	208	13.8 (11.1, 17.7)	–

4072 **Poster Session**

Pembrolizumab (pembro) versus placebo (pbo) in patients (pts) with advanced hepatocellular carcinoma (aHCC) previously treated with sorafenib: Updated data from the randomized, phase 3 KEYNOTE-240 study.

First Author: Richard S. Finn, David Geffen School of Medicine at UCLA, Los Angeles, CA

Background: KEYNOTE-240 (NCT02702401) examined the antiPD-1 antibody pembro and showed improvement in OS and PFS vs pbo in pts with aHCC previously treated with sorafenib. The study did not meet prespecified statistical significance criteria for OS and PFS. Median OS (final analysis) was 13.9 mo for pembro vs 10.6 mo for pbo (HR 0.781; 95% CI 0.611-0.998). At the first interim analysis when testing for PFS and ORR was prespecified, median PFS was 3.0 mo for pembro vs 2.8 mo for pbo (HR 0.775; 95% CI 0.609-0.987) and ORR was 16.9% (CR, n = 3) for pembro and 2.2% (CR, n = 0) for pbo. AEs were consistent with the known safety profile of pembro. Longer term data from KEYNOTE-240 after ~1.5 y of additional follow-up are reported. **Methods:** Adults with confirmed aHCC for whom sorafenib therapy failed (progression or intolerance) were randomly assigned 2:1 to receive pembro 200 mg IV Q3W + best supportive care (BSC) or pbo + BSC for ≤35 cycles or until confirmed progression/unacceptable toxicity, pt withdrawal of consent, or investigator decision to withdraw pt. Dual primary end points were OS and PFS, assessed by blinded independent central review (BICR) per RECIST v1.1. Secondary end points included ORR, DOR, DCR, TTP (all assessed by BICR per RECIST v1.1), and safety. **Results:** Of 413 pts, 278 were randomized to receive pembro; 135, to pbo.As of July 13, 2020, median time (range) from randomization to data cutoff was 39.6 mo (31.7-48.8) for pembro and 39.8 mo (31.7-47.8) for pbo. Median OS (95% CI) was 13.9 mo (11.6-16.0) for pembro and 10.6 mo (8.3-13.5) for pbo (HR 0.771; 95% CI 0.617-0.964). Estimated OS rates at 24 and 36 mo for pembro and pbo were 28.8% and 20.4% and 17.7% and 11.7%, respectively. Median PFS (95% CI) was 3.3 mo (2.8-4.1) for pembro and 2.8 mo (1.6-3.0) for pbo (HR 0.703; 95% CI 0.559-0.885). Estimated PFS rate at 24 mo was 11.8% for pembro and 4.8% for pbo. ORR (95% CI) was 18.3% (14.0-23.4) for pembro and 4.4% (1.6-9.4) for pbo. Median time to response (95% CI) was 2.7 mo (1.2-16.9) for pembro and 2.9 mo (1.1-6.9) for pbo. Median DOR (range) was 13.9 mo (1.5+ to 41.9+) for pembro and 15.2 mo (2.8-21.9) for pbo; 53.7% of responders in the pembro arm and 50.0% of responders in the pbo arm had DOR ≥12 mo. DCR was 61.9% for pembro and 53.3% for pbo. Best overall responses were 10 CR, 41 PR, 121 SD, and 85 PD for pembro and 0 CR, 6 PR, 66 SD, and 54 PD for pbo. Median TTP (95% CI) was 4.0 mo (2.8-5.3) for pembro and 2.8 mo (1.6-3.0) for pbo. No new or unexpected AEs occurred. The frequency of sponsor-assessed immune-mediated hepatitis events did not increase with additional follow-up. There continued to be no HBV or HCV viral flare events. **Conclusions:** In previously treated pts with aHCC, improvement in OS and PFS was maintained over time with pembro vs pbo, and the safety profile remained consistent. These data support the benefit:risk profile of pembro. Clinical trial information: NCT02702401. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4073 **Poster Session**

IMbrave150: Exploratory efficacy and safety results of hepatocellular carcinoma (HCC) patients (pts) with main trunk and/or contralateral portal vein invasion (Vp4) treated with atezolizumab (atezo) + bevacizumab (bev) versus sorafenib (sor) in a global Ph III study.

First Author: Valeriy Vladimirovich Breder, N.N. Blokhin Russian Cancer Research Center, Moscow, Russian Federation

Background: Atezo + bev has been approved in >60 countries for pts with unresectable HCC who have not received prior systemic therapy, based on IMbrave150 (NCT03434379; Finn RS *NEJM* 2020). Due to their poor prognosis and the hemodynamic changes from increased portal vein pressure, pts with main portal vein tumor thrombus are often excluded from pivotal HCC trials. Here, we report exploratory efficacy and safety results of pts with Vp4 (presence of a tumor thrombus in the main trunk and/or contralateral portal vein) using updated IMbrave150 data (Finn RS ASCO GI 2021). **Methods:** Pts were randomized 2:1 to atezo 1200 mg IV q3w + bev 15 mg/kg IV q3w or sor 400 mg bid until unacceptable toxicity or loss of clinical benefit per investigator. IMbrave150 enrolled 501 systemic treatment (tx)–naive unresectable HCC pts, ≥1 measurable untreated lesion (RECIST 1.1), Child-Pugh class A liver function and ECOG PS 0/1, including 73 (15%) Vp4 pts. This post hoc exploratory analysis was conducted with a median follow-up of 15.6 mo in ITT pts. **Results:** Of the Vp4 pts, 48 received atezo + bev and 25 received sor. Median OS (mOS) was 7.6 vs 5.5 mo (HR, 0.62; 95% CI: 0.34, 1.11) and median PFS (mPFS) per independent review facility (IRF)–assessed RECIST 1.1 was 5.4 vs 2.8 mo (HR, 0.62; 95% CI: 0.35, 1.09) with atezo + bev and sor, respectively. ORR per IRF RECIST 1.1 was 23% (11/47) with atezo + bev (2 [4%] pts had CR) vs 13% (3/23) with sor (1 [4%] pt had CR). All-grade variceal bleeding was higher with atezo + bev in Vp4 (13.6%) vs rest of ITT pts (2.5%). See table for further efficacy and safety data. **Conclusions:** The benefits of atezo + bev over sor in Vp4 pts are consistent with those in ITT pts across all efficacy endpoints, despite the expected disease-intrinsic increase in variceal bleeding in Vp4 vs rest of ITT pts. The overall positive benefit-risk profile supports the use of atezo + bev in pts with Vp4. Clinical trial information: NCT03434379. Research Sponsor: F. Hoffmann-La Roche, Ltd.

Efficacy and safety in Vp4 and rest of ITT pts.

	Vp4 Atezo + Bev n=48	Vp4 Sor n=25	Rest of ITT Atezo + Bev n=288	Rest of ITT Sor n=140
mOS (95% CI), mo	7.6 (6.0, 13.9)	5.5 (3.4, 6.7)	21.1 (18.0, 24.6)	15.4 (12.6, 18.6)
HR (95% CI)[a]	0.62 (0.34, 1.11)	–	0.67 (0.51, 0.88)	–
mPFS per IRF RECIST 1.1 (95% CI), mo	5.4 (3.6, 6.9)	2.8 (1.5, 5.3)	7.1 (6.1, 9.6)	4.7 (4.2, 6.1)
HR (95% CI)[a]	0.62 (0.35, 1.09)	–	0.64 (0.51, 0.81)	–
AE related to any study tx, n (%)	n=44 37 (84)	n=23 22 (96)	n=285 247 (87)	n=133 126 (95)
Related Gr 3/4 | 5 AE, n (%)	18 (41) | 1 (2)	11 (48) | 0	125 (44) | 5 (2)	61 (46) | 1 (1)
AE leading to withdrawal from any tx, n (%)	11 (25)	2 (9)	61 (21)	16 (12)
AE leading to dose modification/interruption of any tx, n (%)	26 (59)	17 (74)	169 (59)	80 (60)
All-Gr variceal bleeding AE, n (%)[b]	6 (14)	0	7 (2)	2 (2)

[a]Atezo + bev vs sor of each cohort. [b]Preferred terms included: gastric, esophageal hemorrhage and esophageal varices. A pt may be counted >1 time.

4074 **Poster Session**

Pembrolizumab (pembro) monotherapy for previously untreated advanced hepatocellular carcinoma (HCC): Phase 2 KEYNOTE-224 study. *First Author: Jean-Luc Van Laethem, Erasme Hospital, Brussels, Belgium*

Background: Results from cohort 1 of KEYNOTE-224, an open-label, single-arm, multi-country phase 2 trial, demonstrated that pembro monotherapy was efficacious and tolerable in patients (pts) with advanced HCC previously treated with sorafenib. Here, we report results from KEYNOTE-224 cohort 2, which enrolled pts with advanced HCC and no prior systemic therapy. **Methods:** Eligible pts in cohort 2 had radiologically, histologically, or cytologically confirmed, incurable HCC not amenable or refractory to locoregional therapy, Child Pugh A liver disease, measurable disease based on RECIST 1.1 by blinded independent central review (BICR), ECOG PS 0-1, and BCLC stage C or B. Pts received pembro 200 mg IV Q3W for ~2 years or until disease progression, unacceptable toxicity, consent withdrawal, or investigator decision. Primary endpoint was ORR (RECIST 1.1 by BICR). Secondary endpoints included DOR, DCR, TTP, PFS, OS, and safety/tolerability. Response was assessed every 9 weeks. Efficacy and safety were assessed in pts who received ≥1 dose of study treatment. DOR was assessed in responders. The estimate and 95% CI of the ORR and DCR were based on the Clopper-Pearson method. Kaplan-Meier method was used to estimate OS, PFS, and DOR. A sample size of ~50 pts was chosen to provide acceptable precision for the assessment of ORR. **Results:** Cohort 2 enrolled 51 pts. The median time from the first dose to data cutoff (July 31, 2020) was 21 (range, 17-23) mo. The median age of pts was 68 (range, 41-91) years, one pt was HBV+, 80% had alcohol use, 8% were HCV+, 18% had vascular invasion, 35% had extrahepatic disease, 33% had BCLC Stage B disease, and 67% had BCLC Stage C HCC. ORR was 16% (95% CI, 7-29) and was similar across most subgroups. Median DOR was not reached (range, 3-20+ mo); 70% were estimated to have response duration ≥12 mo. Best overall responses were 0 CR, 8 (16%) PRs, 21 (41%) SDs, and 17 (33%) PDs; response was not evaluable or not assessed for 5 (10%) pts. DCR was 57%. The median TTP was 4 (95% CI, 3-8) mo. The median PFS was 4 (95% CI, 2-6) mo, and median OS was 17 (95% CI, 8-NA) mo. PFS rate at 18 mo was 16%, and OS rate at 18 mo was 46%. Treatment-related AEs (TRAEs) occurred in 27 (53%) pts; the most common TRAEs were diarrhea, fatigue, hypothyroidism, and myalgia. Grade ≥3 TRAEs occurred in 7 (14%) pts. TRAEs led to treatment discontinuation in 6% of pts. Immune-mediated AEs and infusion reactions occurred in 11 (22%) pts. One treatment-related death occurred due to myocarditis, with associated immune-related hepatitis. **Conclusions:** In pts with advanced HCC and no prior systemic therapy, pembro monotherapy provided durable anti-tumor activity, promising overall survival, and demonstrated a safety profile consistent with that previously observed for pembro in advanced HCC. These findings support further evaluation of pembro-based regimens for the treatment of HCC in the frontline setting. Clinical trial information: NCT02702414. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4075 **Poster Session**

A phase Ib study of anlotinib plus TQB2450 as second-line therapy for advanced biliary tract adenocarcinoma. *First Author: Yongkun Sun, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Although with modest efficacy, mFOLFOX is recommended as standard second-line chemotherapy for advanced biliary tract adenocarcinoma. Several clinical trials are exploring the combination treatment of anti-angiogenic drugs and immune checkpoint inhibitors. Anlotinib is an oral small molecule inhibitor of receptor tyrosine kinases, with inhibitory effects on tumor angiogenesis and growth. Anlotinib plus TQB2450,an anti-PD-L1 mAb, have shown anti-tumor activity in preclinical study and here we investigate the efficacy and safety of different dosage of this regimen as second-line treatment for advanced biliary tract adenocarcinoma. **Methods:** Patients with advanced biliary tract adenocarcinoma who had progressed after first-line treatment received anlotinib (once daily for 2 weeks on/1 week off) plus TQB2450 (1200mg once) every three weeks. The planned anlotinib dose levels to be explored were 10mg (starting) and 12mg daily. Dose expansion was performed after the determination of the maximum tolerable dose. Response to treatment was evaluated using the RECIST 1.1 criteria, supplemented by iRECIST. The primary endpoints were MTD, ORR, and the secondary endpoints were PFS, OS and safety. **Results:** Both 10mg and 12mg of anlotinib were tolerable after the initial safety observation of different doses from May 2019 to April 2020. 34 patients (8 cases of gallbladder cancer [GBC], 22 of intrahepatic cholangiocarcinoma [ICC] and 4 of extrahepatic cholangiocarcinoma [ECC]) were enrolled, 22 patients in the 10mg dose group and 12 in the 12mg dose group. The median age was 57 (37-72) years and 55.9% (19) of the patients were female. At the analysis cut-off date of 31 December 2020, the median follow-up duration was 14.9 months. Of the 34 patients, 4 patients had partial response (PR, 2 cases in the 10mg group and 2 in the 12mg group), including 2 cases with GBC and 2 with ICC, 17 had stable disease (SD, shrinkage, 12 in the 10mg group and 5 in the 12mg group) and 5 SD (enlargement, 4 in the 10mg group and 1 in the 12mg group), 7 had progression disease (PD, 5 in the 10mg group and 2 in the 12mg group) and 1 patient of ECC could not be evaluated. In the overall population, the median PFS (mPFS) was 5.95 (95%CI: 3.78-11.50) months. The mPFS was 5.29 (95%CI: 3.45-10.32) months in 10mg group and 12.98 (95%CI: 1.38-NR) in 12mg group. The median OS was not reached and the 12-month OS rate was 64.71% (60.87% in the 10mg group and 72.73% in the 12mg group). Grade 3 or higher toxicities were observed in 8 patients, with elevated transaminase (n = 4, 11.8%), elevated bilirubin (n = 3, 8.8%), fatigue (n = 1, 2.9%), hypertension (n = 1, 2.9%) and prolonged QTc (n = 1, 2.9%). **Conclusions:** Anlotinib plus TQB2450 as second-line therapy for advanced biliary tract adenocarcinoma was well tolerated and showed promising efficacy. No unexpected adverse events were observed in both drugs. This regimen is worthy of further exploration. Clinical trial information: NCT03825705. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

4076 **Poster Session**

Update on overall survival (OS) of RESCUE: An open-label, phase 2 trial of camrelizumab (C) in combination with apatinib (A) in patients with advanced hepatocellular carcinoma (HCC). *First Author: Yun Zhang, The Fifth Medical Center, Chinese PLA General Hospital, Beijing, China*

Background: C+A combination therapy displayed high objective response rate, disease control rate, and durable response with a manageable safety profile in patients (pts) with advanced HCC. Here we performed an updated analysis of OS to characterize the OS benefit of C+A in HCC pts. **Methods:** 70 pts in first-line cohort and 120 pts in second-line cohort were enrolled. Median OS and 2-year OS rate were evaluated *via* updated data (data cutoff, 3 January, 2021). Median time from enrollment to data cutoff of the total population (N = 190) was 29.1 months (range, 24.0-33.7). **Results:** OS events had occurred in 58.6% pts in first-line cohort and 60.0% pts in second-line cohort. The median OS was 20.1 months (95% CI, 14.9-NR) and 2-year OS rate was 43.3% (95% CI, 31.3-54.7) in first-line cohort. The median OS was 21.8 months (95% CI, 17.3-26.8) and 2-year OS rate was 44.6% (95% CI, 35.5-53.3) in second-line cohort. **Conclusions:** Long-term follow-up of C+A demonstrated remarkable survival benefit in advanced HCC pts, which further suggested that C+A is a promising combination therapy in advanced HCC pts. Clinical trial information: NCT03463876. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

4077 **Poster Session**

A randomized, double-blinded, phase III study of icaritin versus huachashu as the first-line therapy in biomarker-enriched HBV-related advanced hepatocellular carcinoma with poor conditions: Interim analysis result. *First Author: Yan Sun, Department of Medical Oncology, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China*

Background: Many advanced hepatocellular carcinoma (aHCC) patients (pts) are often with more complicated clinical conditions such as damaged liver or blood function, poor physical conditions. Those aHCC pts are not suitable for molecular target drug like sorafenib or systemic chemotherapy and no standard or generally accepted treatment. Icaritin, a single molecule (> 98% purity) derived from *Epimedii herba* (Traditional Chinese herbal medicine), is a novel immune-modulation anti-tumor agent. Preclinical studies demonstrated that Icaritin induced anti-HCC activities through targeting IL-6/JAK//STAT3 pathways and modulating inflammation-immune systems including Th1 cytokines, and down-regulation of alpha-fetoprotein (AFP). Prior phase II study demonstrated favorable overall survival (OS) improvement in aHCC pts with poor conditions and correlated with the combined serum biomarkers. The current phase III study was designed to confirm above clinical benefits and safety of Icaritin in those patients. **Methods:** An adaptive enrichment design was used in a multicenter randomized, double-blinded study of comparing Icaritin with Huachashu (a TCM formula commonly used in China) as first line therapy for those aHCC pts (NCT03236636). The primary endpoint was overall survival (OS) and secondary endpoints included time-to-progression (TTP), progression-free-survival (PFS), disease control rate (DCR), and safety. The pts were randomized (1:1) to receive either Icaritin at 600mg or Huachashu. Based on prior studies, a composite biomarker score (CBS) of AFP(≥400 ng/mL), TNF-a(< 2.5 pg/mL) and IFN-g(≥7.0 pg/mL) was used for pts selection and a CBS score of 2/3 was predefined positive. Patients with CBS-positive were applied in interim analysis according to the protocol and statistical analysis plan (SAP). **Results:** A total of 283 aHCC pts were enrolled and randomized from Sept. 2017, and 71 enriched pts was CBS-positive with combined risk/poor prognosis factors such as BCLC stage C, HBV infection, and thrombocytopenia etc.. Thirty-three and 38 CBS-positive aHCC pts were treated with Icaritin or Huachashu, respectively. With a median follow-up of 8.1 mo (cutoff date, Dec.30,2020), the treatment outcomes for Icaritin and Huachashu arm showed following, that is mOS, 13.54 vs. 7.06 mo (HR = 0.40, 95%CI 0.21-0.77, p = 0.0046), mTTP, 3.65 vs. 1.84 mo (HR = 0.67, 95%CI, 0.36-1.22), mPFS, 2.79 vs. 1.84 mo (HR = 0.75, 95%CI, 0.43-1.33), and DCR, 48.5% vs. 26.3, respectively. Treatment-related adverse event (AE≥3 grades) observed were 15.2% vs. 31.6%, respectively. **Conclusions:** Small molecule immunomodulation agent Icaritin could significantly improve the overall survival with favorable safety in a prospectively CBS-enriched HBV-related advanced HCC pts with poor conditions. Clinical trial information: NCT03236636. Research Sponsor: Beijing Shenogen Pharma.

4078 **Poster Session**

Updated results of a phase 1b study of regorafenib (REG) 80 mg/day or 120 mg/day plus pembrolizumab (PEMBRO) for first-line treatment of advanced hepatocellular carcinoma (HCC). *First Author: Anthony B. El-Khoueiry, University of Southern California, Los Angeles, CA*

Background: REG, a multikinase inhibitor, and PEMBRO, an anti-PD-1 mAb, are approved as monotherapies in advanced HCC after progression on sorafenib. This phase 1b dose-finding study investigated first-line REG plus PEMBRO in advanced HCC. **Methods:** Patients (pts) in the first cohort received a starting REG dose of 120 mg/day orally for 3 weeks (wks) on/1 wk off, which could be escalated (160 mg) or reduced (80 mg) in later cohorts, plus a fixed dose of PEMBRO 200 mg IV every 3 wks. Due to a high dose modification rate in the REG 120 mg cohort, an exploratory REG 80 mg cohort was introduced. Primary objective was safety and tolerability; secondary aims were to assess the maximum tolerated dose (MTD), recommended phase 2 dose, and anti-tumor activity. **Results:** 35 pts started on REG 120 mg/day and 22 on REG 80 mg/day. Median age was 66 yrs (range 29–81), 84% of pts were male, 70%/30% had ECOG PS 0/1, 26%/74% were BCLC stage B/C, 100% were C–P A, 46% had extrahepatic spread, and 32% had macrovascular invasion. MTD of REG was 120 mg/day. Grade (Gr) 3/4 treatment-emergent adverse events (TEAE) occurred in 86% of pts on REG 120 mg and 50% on REG 80 mg (Table). Most common Gr 3/4 TEAE for REG 120 mg/80 mg were AST increased (23%/9%), lipase increased (20%/5%), ALT increased (17%/9%), and hypertension (17%/9%). TEAE led to REG/PEMBRO dose reductions or interruptions in 71%/57% of pts on REG 120 mg and 59%/45% on REG 80 mg. Median treatment duration (range) was 3.0 months (mo; 0.2–20.5) for REG 120 mg and 3.5 mo (0.03–24.4) for PEMBRO, and 3.5 mo (0.7–10.8) for REG 80 mg and 3.5 mo (0.8–11.3) for PEMBRO. Of 32 evaluable pts on REG 120 mg, 10 (31%) had a partial response (PR) and 18 (56%) had stable disease (SD); disease control rate (DCR) was 88% (RECIST v1.1). Of 22 pts on REG 80 mg, 4 (18%) had a PR and 16 (73%) had SD; DCR was 91%. As of 17 Dec 2020, 16 pts remain on treatment (REG 120 mg n = 5; REG 80 mg n = 11); median follow up was 11.7 mo and 6.9 mo, respectively. REG pharmacokinetic exposure was as expected for 80 mg and 120 mg doses. Flow cytometry analysis of sequential peripheral blood showed changes in subsets of T-cells and monocytes, which may contribute to clinical benefit. **Conclusions:** First-line REG plus PEMBRO in advanced HCC showed no new safety signals and encouraging anti-tumor activity (DCR ~90%). The REG 80 mg cohort appeared to have lower rates of dose reductions and interruptions due to TEAE vs REG 120 mg. Efficacy data for the REG 80 mg cohort are preliminary due to short follow-up. Clinical trial information: NCT03347292. Research Sponsor: Bayer.

	REG 120 mg/day + PEMBRO (n = 35)			REG 80 mg/day + PEMBRO (n = 22)		
TEAE, n (%)	Regardless of relation to study drug	REG related	PEMBRO related	Regardless of relation to study drug	REG related	PEMBRO related
Any Gr	35 (100)	35 (100)	29 (83)	22 (100)	21 (95)	17 (77)
Gr 3	24 (69)	23 (66)	13 (37)	11 (50)	8 (36)	5 (23)
Gr 4	6 (17)	2 (6)	5 (14)	0	0	0
Gr 5	2 (6)	1 (3)*	0	1 (5)	0	0

*Cerebrovascular accident.
MedDRA v23.1 term; NCI-CTCAE v4.03 Gr.

4079 **Poster Session**

Association of cell-free DNA dominant clone allele frequency with poor outcomes in advanced biliary cancers treated with platinum-based chemotherapy. *First Author: Umair Majeed, Mayo Clinic, Jacksonville, FL*

Background: Cell-free circulating tumor DNA (ctDNA) holds significant promise and is being used for clinical decision making in multiple tumors. This study aimed to evaluate the prognostic value of pre-treatment ctDNA in metastatic biliary tract cancers (BTC) treated with platinum based first-line chemotherapy treatment. **Methods:** We performed a retrospective analysis of 67 patients who underwent ctDNA testing before platinum-based chemotherapy for first-line treatment for metastatic BTC. For analysis we considered the detected gene with highest variant allele frequency (VAF). Results of ctDNA analysis were correlated with patients' demographics, progression-free survival (PFS) and overall survival (OS). **Results:** The median age of patients was 67 y/o (27-90). 54 (80.6%) of 67 patients evaluated had intrahepatic cholangiocarcinoma; seven had extrahepatic cholangiocarcinoma and six gallbladder cancer. 46 (68.6%) of the patients were treated with cisplatin plus gemcitabine, 14 (21%) patients received gemcitabine and other platinum (carboplatin or oxaliplatin) combinations while 7 (10.4%) patients were treated on a clinical trial with gemcitabine and cisplatin plus additional targeted agents (CX4945 or PEGPH20). TP53, KRAS, APC, FGFR2 and IDH1 were the genes with highest frequency as dominant clone. The median dominant clone allele frequency (DCAF) was 3% (0-97%). DCAF >3% was associated with statistically significant worse PFS (median PFS: 4.05 vs. 7.70 months, p=0.046) and OS (median OS: 10.8 vs. 18.8 months, p=0.056). Each 1% increase in DCAF is associated with a hazard ratio of 26.21 in OS when adjusting for subtypes, age, treatment type, and CA19-9 [Table]. **Conclusions:** Patients with metastatic BTC with DCAF > 3% at diagnosis have worse PFS and OS compared to patients with low ctDNA when treated with upfront platinum-based chemotherapy. Research Sponsor: None.

Overall survival adjusted for tumor type.

	Hazard Ratio	95%CI	P value
Extra-hepatic cholangiocarcinoma vs. Gall bladder	1.11	[0.1 , 11.94]	0.932186
Intra-hepatic cholangiocarcinoma vs. Gall bladder	1.57	[0.18 , 13.63]	0.684756
Age at diagnosis	1.09	[0.76 , 1.57]	0.625468
Targeted therapy (combined with platinum)	0.96	[0.27 , 3.46]	0.953097
Pre-Treatment CA19-9 Level (>=100)	1.73	[0.8 , 3.75]	0.165673
DCAF (%)	26.21	[3.02 , 227.31]	0.003042

4080 **Poster Session**

Lenvatinib plus pembrolizumab for patients with previously treated biliary tract cancers in the multicohort phase 2 LEAP-005 study. *First Author: Luis Villanueva, Fundación Arturo López Pérez, Providencia, Santiago, Chile*

Background: Second-line treatment options for patients with biliary tract cancers (BTC) are limited. Lenvatinib, an anti-angiogenic multikinase inhibitor, in combination with the programmed death-1 immune checkpoint inhibitor pembrolizumab, has demonstrated promising antitumor activity with a manageable safety profile in patients with select advanced solid tumors. LEAP-005 (NCT03797326) is evaluating the efficacy and safety of lenvatinib plus pembrolizumab in patients with previously treated advanced solid tumors; here we present results from the BTC cohort of LEAP-005. **Methods:** In this nonrandomized, open-label, phase 2 study, eligible patients were aged ≥18 years with histologically or cytologically documented advanced (metastatic and/or unresectable) BTC with disease progression after 1 prior line of therapy, measurable disease per RECIST v1.1, ECOG PS of 0–1, and tissue sample evaluable for PD-L1 expression. Patients received lenvatinib 20 mg once daily plus pembrolizumab 200 mg Q3W for up to 35 cycles (approximately 2 years) or until confirmed disease progression, unacceptable toxicity, or withdrawal of consent. Treatment with lenvatinib could continue beyond 2 years in patients experiencing clinical benefit. Primary endpoints were ORR (per RECIST v1.1 by blinded independent central review) and safety. Secondary endpoints were the disease control rate (DCR; comprising CR, PR, and SD), duration of response (DOR), PFS, and OS. Tumor imaging was performed Q9W from treatment initiation for 54 weeks, then Q12W to week 102, and Q24W thereafter. **Results:** 31 patients were enrolled in the BTC cohort (ECOG PS 1, 55%; 84% ex-US). As of April 10, 2020, median time from first dose to data cutoff (DCO) was 9.5 months (range, 3.1–11.9), with 8 patients on treatment at DCO. There were 3 (10%) PRs and 18 (58%) SDs. ORR was 10% (95% CI, 2–26), and DCR was 68% (95% CI, 49–83). Median DOR was 5.3 months (range, 2.1+ to 6.2). Median PFS was 6.1 months (95% CI, 2.1–6.4). Median OS was 8.6 months (95% CI, 5.6 to NR). Treatment-related AEs occurred in 30 patients (97%), including 15 (48%) who had grade 3 AEs; there were no grade 4 or 5 treatment-related AEs. 2 (6%) discontinued treatment due to treatment-related AEs (myocarditis, pyrexia; n = 1 each). The most frequent treatment-related AEs were hypertension (42%), dysphonia (39%), diarrhea (32%), fatigue (32%), and nausea (32%). 14 patients (45%) had immune-mediated AEs and 1 patient (3%) had an infusion-related reaction. **Conclusions:** Lenvatinib plus pembrolizumab demonstrated encouraging efficacy and manageable toxicity in patients with advanced BTC who had received 1 line of prior therapy. Based on these data, enrollment in the BTC cohort has been expanded to 100 patients. Clinical trial information: NCT03797326. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4081 **Poster Session**

Preliminary results of molecular screening for *FGFR* alterations (alts) in the RAGNAR histology-agnostic study with the *FGFR*-inhibitor (FGFRi) erdafitinib. *First Author: Christophe Massard, Gustave Roussy-Department of Therapeutic Innovation and Early Trials (DITEP), Paris, France*

Background: *FGFR* alts (mutations and fusions) have been reported in multiple advanced solid tumors at varying frequencies. These alts may function as oncogenic drivers of disease independent of the underlying tumor type. RAGNAR is an ongoing phase 2, histology-agnostic trial investigating the efficacy and safety of erdafitinib, a selective pan-FGFRi, in patients (pts) with advanced solid tumors and *FGFR* alts. Little is known about the incidence, diversity or predominant *FGFR* alts across solid tumors in the clinical setting. Here, we provide an update on molecular screening and enrollment in the primary analysis population. **Methods:** Pts with advanced solid tumors were molecularly screened for eligible *FGFR* alts via central next generation sequencing (NGS) or review of local NGS reports. Underlying tumor type, *FGFR* alts, demographics and key disease characteristics were collected at baseline. **Results:** From Nov 2019 to Jan 2021, 5758 pts were molecularly screened (central or local) in 15 countries. 191 pts (3.3%) fulfilled primary analysis molecular eligibility criteria; 110 pts were enrolled. Among pts enrolled, 14 (12.7%) had central screening and 96 (87.3%) had local NGS reports. Eligible *FGFR* alts were identified in 19 tumor types, including rare cancers and ones (eg, pancreatic) with a very low prevalence of *FGFR* alts in genomic databases (Table). Median age was 57 y, and 19 pts (17.3%) were < 40 y. Gender distribution was even. **Conclusions:** Findings from molecular screening in the RAGNAR study indicate a wide range of *FGFR*-altered tumor types, including a notable number of cancers where eligible *FGFR* alts were considered exceedingly rare (eg, pancreatic). These results demonstrate the feasibility of conducting clinical trials on pts with rare genetic alts by adopting a histology-agnostic design and using both central testing and local NGS reports for molecular screening. This approach also helps investigate rare tumors, where histology-specific trials are challenging. Efficacy and safety results from the RAGNAR study will help define the benefit of erdafitinib in *FGFR*-altered advanced solid tumors. Clinical trial information: NCT04083976. Research Sponsor: Janssen Research & Development, LLC.

Cancer	n (%) (N=110)	Predominant Eligible *FGFR* Alt	Cancer	n (%) (N=110)	Predominant Eligible *FGFR* Alt
Cholangiocarcinoma	30 (27)	*FGFR2* fusion	Cancer of unknown primary	4 (4)	*FGFR2* fusion
High-grade glioma	21 (19)	*FGFR3* fusion	Cervical	3 (3)	*FGFR3* mutation
Pancreatic	9 (8)	*FGFR2* fusion	Squamous cell head and neck	3 (3)	*FGFR3* fusion
NSCLC	8 (7)	*FGFR3* fusion	Esophageal	2 (2)	*FGFR3* mutation and fusion
Breast	5 (5)	*FGFR2* mutation and fusion	Low-grade glioma	2 (2)	*FGFR1* mutation
Colorectal	5 (5)	*FGFR3* mutation and fusion	Prostate	2 (2)	*FGFR3* mutation and fusion
Endometrial	4 (4)	*FGFR2* mutation	Salivary gland	2 (2)	*FGFR2* mutation
Gastric	4 (4)	*FGFR3* mutation	Basal cell	1 (1)	*FGFR2* mutation
Ovarian	4 (4)	*FGFR2* fusion	Thymic	1 (1)	*FGFR1* fusion

4082 **Poster Session**

Preliminary efficacy and safety of perioperative treatment of camrelizumab combined with apatinib in resectable hepatocellular carcinoma (HCC): A prospective phase II study. *First Author: Yongxiang Xia, Hepatobiliary Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China*

Background: Although there is no standard perioperative treatment for resectable HCC characterized with high recurrence rate, the strategy of immunotherapy combined with targeted agents is promising in neoadjuvant/adjuvant therapy in various tumors. **Methods:** In this perspective, single-arm, exploratory phase II trial (NCT04297202), eligible patients (pts) were systemic treatment-naive resectable HCC in intermediate/advanced stage. Preoperative combined treatment of anti-PD-1 antibody camrelizumab (200 mg q2w for 3 cycles) and VEGFR-2 inhibitor apatinib (250 mg qd for 21 days) was started on day 1 cycle 1. On the 7th day after the 3 cycles, radiological imaging was assessed to confirm whether to conduct the hepatectomy. Four weeks after the surgery, combined treatment (camrelizumab 200 mg q3w, apatinib 250 mg qd, 3 weeks per cycle) was resumed for the postoperative 8 cycles. The primary endpoint was major pathologic response (MPR) defined as 50%-99% tumor necrosis in resected tissue. Gene expression profiles (GEPs) using immune-related RNA with pre-treatment specimens were analyzed. The association between immune signatures and pathological response (responders (R) vs. non-responders (NR)) was assessed. **Results:** A total of 20 pts were enrolled between Dec 5, 2019 and Jan 27, 2021, with a median follow-up of 5.7 months (range 0.7-9.0). All pts were ECOG PS 0-1 and Child-Pugh class A. There were 85% pts with hepatitis B and 10% with hepatitis C, and 55% in BCLC stage B, 35% in stage C and 10% in stage A. In preoperative phase, with 2 withdraw of informed consent form, partial response was reached in 3/18 (16.7%) and 8/18 (44.4%) pts per RECIST 1.1 and mRECIST, respectively, while disease progression was found in 1/18 (5.6%) pts impossible for hepatectomy, which made the resection rate 17/18 (94.4%). After the surgery, one was found to be combined hepatocellular-cholangiocarcinoma by histopathological examination and failed to proceed the postoperative study. The rates of MPR and pathological complete response (pCR) were 5/17 (29.4%) and 1/17 (5.9%), respectively. The preliminary analysis of GEPs (R:NR = 3:4) revealed higher levels of chemokines (*CXCL10* and *CXCL11*) in responders and higher *MS4A4A* (marker gene of macrophages) in non-responders. The most common TEAEs included hypertension (95%), proteinuria (40%), AST elevation (40%), and platelet count decrease (45%). Grade 3 TEAEs were hypertension (20%), rash (10%), and platelet count decrease (10%). No grade 4/5 TEAEs was observed. The most common surgical complications were ALT and AST increase each with the incidence of 70% (all grades) and 45% (grade $\geq$ 3). **Conclusions:** This study preliminarily demonstrated that the perioperative treatment of camrelizumab combined with apatinib improved the MPR and pCR with managable safety in intermediate/advanced resectable HCC. Clinical trial information: NCT04297202. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

4083 **Poster Session**

A phase II trial of lenvatinib plus toripalimab and hepatic arterial infusion chemotherapy as a first-line treatment for advanced hepatocellular carcinoma (LTHAIC study). *First Author: MinKe He, Department of Hepatobiliary Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, China*

Background: Combining systemic and locoregional therapies represents a promising treatment strategy for patients with advanced hepatocellular carcinoma (HCC). We investigated the efficacy and safety of combined lenvatinib and toripalimab (recombinant, humanized programmed cell death receptor-1 monoclonal antibody) plus hepatic arterial infusion chemotherapy (HAIC) as a first-line treatment in this patient population. **Methods:** This single-arm, phase II study included treatment-naive adult ($\geq$18 years) patients with advanced HCC, Eastern Cooperative Oncology Group performance status 0–2, and Child-Pugh Class A liver function (NCT04044313). Patients initiated lenvatinib (8 mg for bodyweight $<$ 60 kg or 12 mg for bodyweight $\geq$60 kg, orally once daily) 3-7 days prior to initial HAIC to confirm tolerability, and then received 21-day treatment cycles of lenvatinib (day 1 to day 21), toripalimab (240 mg by IV infusion, on day 1), and HAIC (day 1 to day 2) with the FOLFOX regimen (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-fluorouracil bolus 400 mg/m^2 on day 1, and 5-fluorouracil infusion 2400 mg/m^2 for 24 hours) until disease progression or intolerable toxicity. The primary endpoint was progression-free survival (PFS) at six months, evaluated using RECIST 1.1. Secondary endpoints were median PFS and overall survival (OS), objective response rate (ORR) per RECIST 1.1 and mRECIST, and safety. **Results:** Between August 2019 and May 2020, 36 patients (33 men and 3 women; median age, 49 years) were enrolled. The median tumor size was 11.2 cm, 86.1% of patients had portal vein invasion, and 27.8% had extrahepatic metastasis. The primary endpoint showed a 6-month PFS rate of 80.6%. After a median follow up of 11.2 months, the median PFS was 10.5 months (95% CI, 6.21−14.79), and the median OS was not reached. The ORR per RECIST was 63.9% (95% CI, 40.9−73.0), and per mRECIST was 66.7% (95% CI, 43.3−75.1) including five (13.9%) patients who achieved a complete radiological response. The median duration of response was 12.1 months (95% CI, 4.52−19.69). Furthermore, eight patients achieved sufficient downstaging to be converted to resectable disease. Among them, one patient received liver transplantation, and four received curative surgical resection. One of them achieved pathological complete response. Grade 3-4 treatment-related adverse events (AEs) occurred in 72.2% of patients, and the most common were thrombocytopenia (13.9%), elevated aspartate aminotransferase (13.9%), and hypertension (11.1%). All AEs were expected and manageable, and no treatment-related deaths were reported. **Conclusions:** Combination treatment with lenvatinib and toripalimab plus HAIC showed promising antitumor activity and manageable toxicity in patients with advanced HCC. Further randomized, controlled trials are warranted to validate our findings. Clinical trial information: NCT04044313. Research Sponsor: None.

4084 **Poster Session**

Exploratory circulating biomarker analyses: lenvatinib + pembrolizumab (L + P) in a phase 1b trial in unresectable hepatocellular carcinoma (uHCC). *First Author: Andrew X. Zhu, Massachusetts General Hospital Cancer Center and Jiahui International Cancer Center, Boston, MA*

Background: In a phase 1b trial (NCT03006926), L + P had promising antitumor activity as first-line (1L) therapy in uHCC. We present exploratory biomarker analyses of circulating angiogenic factors and cytokines/chemokines related to the mechanism of action of L + P (ie, pharmacodynamic [PD] biomarkers), as well as biomarker correlations with clinical outcomes in patients (pts) with uHCC, from this trial. **Methods**: Pts received lenvatinib 12 mg/d (bodyweight [BW] $>$60 kg) or 8 mg/d (BW $<$ 60 kg) PO + pembrolizumab 200 mg IV Q3W. Tumors were assessed using mRECIST or RECIST v1.1 per independent imaging review. Peripheral blood samples were collected before administration of study drug at baseline, cycle (C) 2, day (D) 1, C3D1, C4D1, and off-treatment. 43 Biomarkers were assayed in serum from 100 1L uHCC pts (excluding 4 pts from the dose-limiting toxicity part of the trial with prior sorafenib). Of these 43, 31 biomarkers (for which $\leq$20% of samples had measurements above/below the quantification limit of the assay) were included in the analyses. Changes in biomarker levels from baseline were evaluated via 1-sample Wilcoxon signed-rank test. Associations were explored between changes in biomarker levels and maximum tumor shrinkage (MTS) via the Spearman's rank correlation test, objective response (OR; complete response + partial response) via the Wilcoxon rank sum test, and PFS via Cox regression analysis and log rank test. Data cutoff date for clinical endpoints was 7 August 2020. **Results**: Levels of PD biomarkers related to angiogenic signaling (VEGF increase/ANG2 decrease), FGF signaling (increase in FGF23/FGF19), and IFNγ signaling (increase in IFNγ, CXCL9/10/11) were changed significantly (adjusted $P<$ 0.05) with L + P (C2D1–C4D1; except for FGF19 at C3D1). Significant decreases of TIMP1 and increases of MCP1 were observed at C4D1 during treatment; these were associated with greater MTS. Greater decreases in TIMP1 and greater increases in MCP1 were observed in pts with OR vs others. Changes in levels of the PD biomarkers ANG2, IL10, and VEGFR2 were found to be associated with PFS by dichotomized analysis. With tertile 2 cutoff, median PFS for pts in the group with greater decreases of ANG2 was 13.9 months vs 9.6 months for pts in the group with lesser decreases of ANG2 (unadjusted P= 0.002; HR 2.65, 95% CI 1.39–5.08). **Conclusions**: These are the first exploratory biomarker analyses for the single-arm study of L + P in pts with uHCC. Changes in serum biomarkers associated with angiogenic-, FGF-, and IFNγ-signaling pathways indicated target engagement of L + P. Decreases in TIMP1 and increases in MCP1 were associated with MTS and OR. Associations were found between longer PFS and a greater decrease in levels of ANG2. Angiogenesis inhibition and modulation of cancer immune response were observed with L + P. Further validation from independent studies is warranted. Clinical trial information: NCT03006926. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4085 **Poster Session**

Treatment-related toxicity and improved outcomes with immune checkpoint inhibitors in patients with hepatocellular carcinoma. *First Author: Alessio Cortellini, Department of Surgery and Cancer, Imperial College London, London, United Kingdom*

Background: The development of treatment-related adverse events (trAE) correlates favorably with clinical outcomes in multiple studies of patients receiving immune checkpoint inhibitors (ICI), however, this relationship is undefined in patients with hepatocellular carcinoma (HCC). This retrospective multi-center study aimed to examine whether trAEs are prognostic in HCC. **Methods:** We established an international consortium of 10 tertiary-care referral centers located in Europe (n = 67), United States (US, n = 248) and Asia (n = 42) to test whether the development of clinically significant trAE (i.e. graded $>$2, trAE2) predicted for improved overall (OS), progression-free survival (PFS), and overall response rates (ORR) following ICI, and subsequently validated this association in a separate cohort of 406 HCC patients receiving ICI therapy as part of international clinical trials submitted to the US Food and Drug Administration (FDA) in support of marketing applications. **Results:** In a multi-institutional cohort of 357 patients, 274 (77%) with Barcelona Clinic Liver Cancer (BCLC) stage C HCC mostly treated with ICI monotherapy (n = 304, 85%), trAE were reported in 146 patients (41%). Development of trAE2 were associated with longer OS (23.3 versus 12.2 months) and PFS (8.6 months versus 3.7 months). After adjusting for viral aetiology, gender, presence of cirrhosis, Child-Pugh class, BCLC stage, AFP levels, ECOG-PS, ICI regimen (mono/combination therapy) and receipt of corticosteroid therapy, trAE2 were confirmed predictors of improved OS (HR 0.55; 95% CI:0.34-0.88) and PFS (HR 0.51; 95%CI: 0.35-0.74). TrAE2 were associated with higher ORR (27% versus 16%) from ICI. The association between trAE2 and patients' OS (HR 0.49; 95%CI:0.34-0.70) and PFS (HR 0.43; 95%CI:0.32-0.59) was also observed in the FDA dataset. After a 6-weeks landmark selection, trAE2 were confirmed to be associated with improved PFS (HR 0.59; 95% CI:0.39-0.87); the additional analysis adjusted for tumour response and duration of treatment within the FDA cohort further confirmed the association with longer PFS (HR 0.67; 95%CI: 0.47-0.94). **Conclusions:** Development of trAE2 may correlate with response and survival in patients with HCC receiving ICI, a clinical setting where the lack of biomarkers still represents an unmet need. Prospective studies aimed at understanding the underlying immunologic foundations of such relationship are warranted to identify predictive biomarkers of toxicity and response. Research Sponsor: None.

4086 **Poster Session**

Pemigatinib for previously treated locally advanced/metastatic cholangiocarcinoma (CCA): Update of FIGHT-202. *First Author: Ghassan K. Abou-Alfa, Memorial Sloan Kettering Cancer Center, Weill Medical College at Cornell University, New York, NY*

Background: Pemigatinib (PEMI), a potent, selective, oral FGFR1-3 inhibitor, has shown efficacy and safety in patients (pts) with CCA and *FGFR2* rearrangements/fusions in FIGHT-202 (NCT02924376; objective response rate [ORR], 35.5%; duration of response [DOR], 7.2 months [mo]). Overall survival (OS: 21.1 mo) was not mature in the primary report (Abou-Alfa. *Lancet Oncol* 2020; cutoff: Mar 22, 2019); herein we report matured efficacy and safety data from FIGHT-202 (cutoff: Apr 7, 2020). **Methods:** Pts (≥18 y) with known *FGF/FGFR* alterations and progression after ≥1 prior therapy had *FGFR2* rearrangements/fusions (cohort A), other *FGF/FGFR* alterations (B), or no *FGF/FGFR* alterations (C). Pts received PEMI 13.5 mg QD (21-d cycle; 2 wks on, 1 wk off) until progression or toxicity. Primary endpoint: independent, centrally confirmed ORR (cohort A); secondary endpoints: ORR (cohorts B, C; cohorts A and B combined); DOR, disease control rate (DCR), progression free survival (PFS), OS, and safety. A *post-hoc* analysis in cohort A evaluated mOS in responders (pts with complete response [CR] or partial response [PR]) vs non-responders (pts with progressive disease [PD] or stable disease (SD]). **Results:** At cutoff, 147 pts were enrolled (cohort A, n=108; B, n=20; C, n=17; *FGF/FGFR* status undetermined, n=2); median follow-up was 30.4 (range, 4.9–38.7) mo and median treatment duration was 5.9 (0.2–36.5) mo. In cohort A, 9.3% of pts remained on therapy at cutoff; in cohorts B and C, all pts had discontinued. Pts discontinued mainly for PD (67.6%, 75%, and 64.7% in cohorts A, B, and C respectively). Independent, centrally confirmed ORR was 37.0%; mOS was 17.5 mo (95% CI, 14.4-22.9) in cohort A (Table 1). mOS for responders (n=40) vs non-responders (n=68) was 30.1 (95% CI, 21.5-NE) mo vs 13.7 (9.6-16.1) mo. Overall, most common all-cause treatment-emergent adverse events (TEAEs) were hyperphosphatemia (58.5%; grade ≥3, 0%), alopecia (49.7%; 0%), diarrhea (46.9%; 3.4%), fatigue (43.5%; 5.4%), nausea (41.5%; 2%), and dysgeusia (40.8%; 0%); 10.2%, 13.6% and 42.2% of pts discontinued, had dose reduction, and treatment interruption due to TEAEs, respectively. **Conclusions:** These results reinforce the primary data, showing continued, durable responses and sustained tolerability in pts receiving PEMI for CCA harboring *FGFR2* rearrangements/fusions. Notably, the matured OS is longer than historical data; OS for responders was more than twice as long vs for non-responders. Clinical trial information: NCT02924376. Research Sponsor: Incyte Corporation.

Efficacy.

	Cohort		
	A (n=108)	B (n=20)	C (n=17)
Best ORR	37.0 (27.9–46.9)	0.0 (0.0–16.8)	0.0 (0.0–19.5)
CR	4 (3.7)	0	0
PR	36 (33.3)	0	0
SD	49 (45.4)	8 (40.0)	3 (17.6)
PD	16 (14.8)	7 (35.0)	11 (64.7)
NE	3 (2.8)	5 (25.0)	3 (17.6)
mDOR	8.1 (5.7–13.1)	NE	NE
DCR	82.4 (73.9–89.1)	40.0 (19.1–63.9)	17.6 (3.8–43.4)
mPFS	7.0 (6.1–10.5)	2.1 (1.2–4.9)	1.5 (1.4–1.8)
mOS	17.5 (14.4–22.9)	6.7 (2.1–10.5)	4.0 (2.0–4.6)

NE, not evaluable; Data are % (95% CI), n (%), or months (95% CI).

4087 **Poster Session**

T-cell receptor pharmacodynamics associated with survival and response to tremelimumab (T) in combination with durvalumab (D) in patients (pts) with unresectable hepatocellular carcinoma (uHCC). *First Author: Patricia McCoon, Translational Medicine, AstraZeneca, Waltham, MA*

Background: Study 22, a phase 2 clinical study (NCT02519348) evaluating T (anti-CTLA-4) and D (anti-PD-L1) as monotherapies and in combination indicated the best efficacy-safety profile with a novel combination regimen containing a single, priming dose of T (T300+D). Additionally, an expansion of proliferative CD8+ lymphocytes at Day 15 was observed with T300+D that was associated with improved response. Here, an exploratory molecular analysis of peripheral blood T cell receptors is presented. **Methods:** Immune-checkpoint inhibitor-nave pts were randomized to 1 of 2 T+D combinations: T300+D (T 300 mg [1 dose] + D 1500 mg, then D every 4 weeks [Q4W]) or T75+D (T 75 mg Q4W + D 1500 mg Q4W [4 doses], then D Q4W); or single agent D (1500 mg Q4W) or T (750 mg Q4W [7 doses] then Q12W). DNA was isolated from PAXgene-preserved whole blood collected at baseline and on Day 29 during the first cycle of Q4W dosing, and then underwent CDR3 sequencing of T-cell receptor β using the immunoSEQ Assay (Adaptive Biotechnologies, Seattle, WA). Associations with objective response rate (ORR) and overall survival (OS) were evaluated. **Results:** The number of evaluable pts, samples, and overall ORR and OS are provided (Table). Immunosequencing analysis did not reveal significant differences in baseline T-cell clonality across arms. Increased T-cell clonal expansion at Day 29 appeared to be T dose dependent (Table), with no significant difference in the median expansion between the D and T75+D arms**.** Across all arms, responders had a larger median number of expanded T-cell clones on Day 29 than nonresponders (77.5 vs 40), and this greater expansion trended with longer OS (Table). Further evaluation by arm demonstrated an increase in T-cell clonal expansion in responders vs nonresponders in the T300+D arm. Pts with T-cell expansion above the median in the T300+D and T75+D arms also exhibited longer OS. Both newly expanded and total expanded clones on Day 29 vs Day 1 were associated with improved OS. **Conclusions:** The observed T dose-dependent increase in T-cell clonal expansion trended with improved ORR and longer OS, with the greatest overall benefit seen with T300+D vs T75+D, D and T. This is consistent with the previously reported observation that T300+D led to the highest median proliferating CD8+ T-cell counts and radiographic response. Further work is needed to differentiate the relative contributions of CD4 and CD8 clonal expansion to increased efficacy. T300+D and D are being evaluated in the phase 3 HIMALAYA study (NCT03298451) in uHCC vs sorafenib. Funding: AstraZeneca. Clinical trial information: NCT02519348. Research Sponsor: AstraZeneca.

	T300+D (n=75)	D (n=104)	T (n=69)	T75+D (n=84)
immunoSeq paired samples, n	30	31	17	26
Dose of T before Day 29, mg	300	0	750	75
Median expanded T cell clones at Day 29, n	56	32	100	36
ORR, %	24.0	10.6	7.2	9.5
Median (95% CI) OS, mo	18.7 (10.8–27.3)	13.6 (8.7–17.6)	15.1 (11.3–20.5)	11.3 (8.4–15.0)

4088 **Poster Session**

Phase I trial of fourth-generation chimeric antigen receptor T-cells targeting glypican-3 for advanced hepatocellular carcinoma. *First Author: Weijia Fang, Department of Medical Oncology, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China*

Background: GPC3 is highly expressed in hepatocellular carcinoma (HCC) and is a promising target for HCC immunotherapy. Earlier phase I trial results demonstrated that second-generation GPC3-specific chimeric antigen receptor (CAR-GPC3) T cells were well tolerated in advanced HCC patients and showed clinical benefits (Shi D, Clin Can Res, 2020). Further preclinical studies showed that CAR-GPC3 T cells combined with multi-tyrosine kinase inhibitors (TKIs) were more effective in killing $GPC3^+$ HCC xenografts (Wu X, Mol Ther, 2019), and fourth-generation (4G) CAR-GPC3 T cells co-expressing a transcription factor more effectively killed $GPC3^+$ HCC xenografts. **Methods:** In this single-arm, open-label, first-in-human phase I trial (NCT03980288), we investigated the safety and antitumor activity of autologous 4G-CAR-GPC3 T cells for $GPC3^+$ heavily pretreated advanced HCC patients. Patients received 4G-CAR-GPC3 T cell infusion(s) after lymphodepletion pretreatment and 67% patients combined with TKIs. Adverse events (AEs) were graded by CTCAE 5.0. Cytokine release syndrome (CRS) was graded by American Society for Transplantation and Cellular Therapy criteria (2019). Tumor response was assessed by RECISTv1.1. **Results:** As of January 30th, 2021, 6 subjects with HBV-related metastatic HCC were enrolled. All had progressed on ≥ 2 lines of systemic therapy, with at least one TKI combined with anti-PD-1/PD-L1 immunotherapy or FOLFOX4 chemotherapy. After lymphodepletion, patients were treated with 1-2 cycles (totaling $2.5–5\times10^8$ CAR^+ cells) of 4G-CAR-GPC3 T cell therapy. Among them, 1 patient received half dose of sorafenib and 3 patients received half dose of regorafenib along with cell infusion. No dose limiting toxicity (DLT) occurred. The maximum tolerated dose (MTD) was not observed. No patient withdrew from the trial due to AE. No treatment-related death or neurotoxicity occurred. The most common ≥ grade 3 AEs were hematological toxicity, mainly due to lymphodepletion, and patients recovered within 2 weeks after therapy. All patients developed CRS including 3 at grade 2 and 3 at grade 3. Patients recovered from CRS after tocilizumab therapy with corticosteroid (4 patients) or without. One patient achieved partial response and continued after 18 weeks. The objective response rate (ORR) and disease control rate (DCR) were 16.7% and 50%, respectively. The median progression free survival (mPFS) was 4.2 months. The median peak CAR-GPC3 copies were 5067 copies/ug gDNA, and CAR-GPC3 copies were detectable on day 28 ranging 113–2071 copies/ug gDNA. **Conclusions:** Our study is the first to report that 4G-CAR-GPC3 T cell therapy in combination with TKIs has a manageable safety profile while demonstrating potential antitumor activity for heavily pretreated advanced HCC patients; however, CRS should be diligently managed. Clinical trial information: NCT03980288. Research Sponsor: Carsgen.

4089 **Poster Session**

Natural history of patients (pts) with advanced cholangiocarcinoma (CCA) with *FGFR2* gene fusion/rearrangement or wild-type (WT) *FGFR2*. *First Author: Rachna T. Shroff, University of Arizona Cancer Center, Tucson, AZ*

Background: CCA is a rare, heterogeneous malignancy with poor prognosis due to late onset of symptoms and relative resistance to available therapies. *FGFR2* fusions are common, occurring in 10–16% of intrahepatic CCA (iCCA). There is increasing awareness of the importance of molecular profiling to inform treatment choices, although real-world data (RWD) are lacking on the natural history of pts with CCA and *FGFR2* fusions/rearrangements receiving therapies for advanced disease. This retrospective, observational, natural history study used a nationwide (US-based) de-identified clinico-genomic database (CGDB) to compare overall survival (OS) in pts with advanced CCA and *FGFR2* fusions/rearrangements vs. those with wild-type (WT) *FGFR2*. **Methods:** This study used the nationwide (US-based) de-identified Flatiron Health-Foundation Medicine CCA CGDB (FH-FMI-CGDB). The data originated from approximately 280 US cancer clinics (~800 sites of care). Pts were ≥18y of age, had chart-confirmed advanced CCA, comprehensive genomic profiling, and ≥2 visits within the Flatiron Health network since Jan 1, 2011. Primary objective: evaluate OS in pts with *FGFR2* fusions/rearrangements and WT *FGFR2* from the index date (date of diagnosis of advanced CCA) to date of death from any cause. A key secondary objective was to evaluate the influence of *FGFR* status on OS after adjusting for potential prognostic variables. Risk-set adjustment was used to account for left truncation for all time-to-event analyses. **Results:** As of May 2020, 571 pts from the CCA FH-FMI-CGDB met the inclusion criteria; 75 pts with *FGFR2* fusions/rearrangements (median age 63y; 64% female; 95% iCCA; 68% stage IV at initial diagnosis), and 496 pts *FGFR2* WT (median age 65y; 48% female; 74% iCCA; 55% stage IV at initial diagnosis). Median OS was numerically higher, but not statistically different, for pts with *FGFR2* fusions/rearrangements vs *FGFR2* WT (12.1m [95% CI 8.5−17.1] vs 7.1m [95% CI 5.7−8.8]; log rank p = 0.184). Median OS was also numerically higher, but not statistically different, for *FGFR2* fusions/rearrangements vs *FGFR* WT in the subset of 437 pts with iCCA (12.1m [95% CI 8.4−17.1] vs 7.8m [95% CI 6.1−10.0]; log rank p = 0.375). *FGFR2* status was not a significant factor contributing to OS in univariate, bivariate, or multivariate models after adjusting for potential prognostic covariates. **Conclusions:** This analysis of RWD did not demonstrate a clear survival advantage for pts with *FGFR2* fusions/rearrangements vs *FGFR2* WT CCA receiving therapies for advanced disease, although a non-significant trend towards longer OS was observed in pts with *FGFR2* fusions/rearrangements. *FGFR2* status was not a significant predictor of OS after adjusting for potential prognostic covariates. An additional sub-analysis is ongoing to determine OS from time of initiation of second-line therapy in pts with *FGFR2* fusions/rearrangements. Research Sponsor: QED Therapeutics Inc.

4090 **Poster Session**

Phase I study of H3B-6527 in hepatocellular carcinoma (HCC) or intrahepatic cholangiocarcinoma (ICC). *First Author: Teresa Macarulla, Hospital Universitario Vall d'Hebron, Barcelona, Spain*

Background: Evidence suggests that hyperactivated fibroblast growth factor 4 (FGFR4) signaling pathway leads to enhanced tumor growth. Targeting FGFR4 may have therapeutic benefit in tumors with altered FGF19 signaling. A phase I study (NCT02834780) was undertaken to assess H3B-6527, a highly selective covalent FGFR4 inhibitor, in patients with HCC/ICC. **Methods:** Adults with advanced HCC/ICC, ECOG PS 0-1, well compensated liver function, who progressed after > one prior therapy, received H3B-6527 po daily (QD) or twice-daily (bid) on a 21-day cycle following a 3+3 design. Doses ranged from 300-2000mg QD or 500-700mg BID. Patients in dose escalation were treated regardless of FGF19 status. Patients in expansion had FGF19+ tumors by mRNA testing. Adverse events (AEs), and pharmacokinetics (PK) were assessed. Response was determined by RECIST 1.1/mRECIST imaging every 6 weeks. **Results:** Study enrollment is complete at 128 patients. Ninety HCC patients were treated (QD = 48, bid = 42). ICC enrollment was suspended after 38 patients due to limited efficacy. No dose-limiting toxicities were seen and no grade 4-5 treatment related AEs have been observed. Recommended Phase II dose for H3B-6527 is 1000mg QD based upon safety, efficacy, and PK data. Grade 3 TEAEs have occurred in 12.5% of patients on QD dosing. Treatment related TEAEs were seen in 62.5% of patients on the QD schedule, with diarrhea (45.8%), fatigue (12.5%), and nausea (12.5%) most frequent. Drug discontinuation due to AEs for QD dosing was 8.3%. Interim data analysis shows that, for HCC patients with >2 prior lines of therapy treated on QD schedule, overall survival was 10.6m, progression-free survival 4.1m, overall response rate 16.7% (all partial responses), and clinical benefit rate 45.8% (responders + durable stable disease >17 weeks). H3B-6527 Cmax and AUC were lower at 300 mg dose but then similar across 500–2000 mg doses. Following oral administration of 1000 mg fasted, H3B-6527 plasma concentration reached peak at a Tmax of ~2-3 hours and then decayed exponentially, with terminal half-life of ~4-5 hours. There was no accumulation following QD dose. Dosing with food did not meaningfully change H3B-6527 plasma exposure. **Conclusions:** H3B-6527 was well tolerated and demonstrated a favorable toxicity and safety profile and encouraging clinical activity in heavily pretreated HCC patients. Final trial results will be presented at conference. Clinical trial information: NCT02834780. Research Sponsor: H3 Biomedicine.

4091 **Poster Session**

Relationship between *Helicobacter pylori* and development of hepatocellular carcinoma: A systematic review and meta-analysis. *First Author: Samragnyi Madala, Northwell Health, Staten Island, NY*

Background: The relationship between *Helicobacter pylori (H.pylori)* and hepatocellular carcinoma (HCC) was first proposed in 1994. Since then, several studies have been performed to explore the association. The role of Hepatitis C (HCV) viruses coexisting with *H.pylori* in causing HCC was also studied. With the emergence of data in this regard, a causal relationship has been postulated, but not confirmed, and hence the relationship remains controversial. Our meta-analysis aims to summarize the research on this topic and investigate if there exists a relationship between *H. pylori* infection and the development of HCC and if the presence of HCV along with H.pylori plays a role in liver carcinogenesis. **Methods:** Following PRISMA guidelines, we performed a systematic review of all relevant studies published in the literature using keywords Helicobacter pylori and Hepatocellular carcinoma on major literature databases, including PubMed, EMBASE, Web of Science, and Cochrane controlled trials register. A total of 656 studies were identified between 1994 to March 2020, out of which 26 studies qualified under our selection criteria. Patients positive for HCC are included as cases and patients that did not have HCC under control group. In both groups, *H.pylori* positive patients and their HCV status, was identified. **Results:** Out of the 26 studies included in the final analysis, the prevalence of *H. pylori* infection was 64.78% (561 of 866) amongst HCC cases and 47.92% (1718 of 3585) in the non-HCC control group. The summary odds ratio for the association of *H. pylori* infection with the risk for HCC using the random-effects model was determined to be 4.75 (95% CI, 3.06-7.37), I^2=63%. Subgroup analysis to determine the odds of developing HCC in the presence of *H.pylori* and HCV coinfection, was 13.97 (95% CI, 3.94-49.61), I^2=81%. Whereas, the odds of developing HCC in the presence of only HCV without *H.pylori* was found to be 2.21 (0.70-6.94), I^2=79. Subgroup analysis by study design showed no significant difference between the study groups (P= 0.5705). **Conclusions:** Our meta-analysis showed a positive association between *H. pylori* infection and the development of HCC. It showed a significantly higher risk of developing HCC in the presence of HCV infection along with *H.pylori*. Further prospective cohort studies are needed to prove the causal relationship, especially in cases of Hepatitis B, C coinfection, and cirrhotic patients. Research Sponsor: None.

Summary of the results.

	HCC positive	HCC negative	Odds ratio [95% CI]
Primary analysis			
Relationship between *H.pylori* and HCC	561/866	1,718/3,585	4.75 [3.06-7.37]
Subgroup analysis			
***H.pylori* and HCV coinfection**	168/422	372/1,275	13.97 [3.94-49.61]
***H.pylori* only without HCV**	36/325	275/719	0.54 [0.11-2.63]
HCV without *H.pylori*	84/262	141/485	2.21 [0.70-6.94]

4092 **Poster Session**

Phase I result of ICP-192 (gunagratinib), a highly selective irreversible FGFR inhibitor, in patients with advanced solid tumors harboring FGFR pathway alterations. *First Author: Ye Guo, Shanghai East Hospital, Shanghai, China*

Background: ICP-192 (gunagratinib), developed by InnoCare Pharma, is a novel pan-FGFR (fibroblast growth factor receptors) inhibitor that potently and selectively inhibits FGFR activities irreversibly by covalent binding. Preclinical data showed that gunagratinib overcomes the acquired resistance to the first-generation reversible FGFR inhibitors, e.g., infigratinib. ICP-CL-00301 is a phase I, first-in-human, clinical study which includes a dose escalation followed by dose expansion. The safety and tolerability as well as pharmacokinetics/pharmacodynamics (PK/PD) of gunagratinib were evaluated in patients with advanced solid tumors, and the preliminary anti-tumor activity was evaluated by RECIST1.1 in patients with FGF/FGFR gene aberrations. **Methods:** In the dose-escalation stage, patients with advanced solid tumors with or without FGF/FGFR alterations were treated with escalating doses (2, 4, 8, 10, 12, 14, 16 mg etc.) of gunagratinib once daily in 21-day cycles until disease progression or unacceptable toxicity. During the dose-expansion stage, patients with cholangiocarcinoma harboring FGFR2 gene fusion/translocation received the treatment of gunagratinib daily at 12 mg continuously. **Results:** As of February 2021, a total of 30 patients had received the treatment of gunagratinib. The median age of the treated patients was 55.0 (range: 28 to 75 years) with 56.7% male and ECOG performance status between 0-1. The maximum tolerated dose (MTD) had not been reached. The most common treatment-related adverse events (TRAEs) (> 20%) included hyperphosphatemia, hypercalcemia, increased ALT or AST, diarrhea and hypertriglyceridemia. Hyperphosphatemia is a commonly reported AE from other trials targeting FGFR and here serves as a PD biomarker of FGFR inhibition. This PD biomarker was observed in 73.3% of the patients treated with gunagratinib at all dose levels and was consistently observed at doses of 8 mg QD and above. Hyperphosphatemia was well managed with oral phosphate binders when necessary. The plasma exposure increased proportionally to the oral dosage levels of gunagratinib. Among the 12 patients with FGF/FGFR gene aberrations who have completed at least one tumor assessment, the overall response rate (ORR) was 33.3%, including 1 patient (8.3%) of cholangiocarcinoma with complete response (CR) and 3 patients (25%) with partial response (PR). The disease control rate (DCR) was 91.7% (11 of 12 patients). **Conclusions:** Gunagratinib is safe and well-tolerated in patients with advanced solid tumors. Anti-tumor activity was demonstrated in patients with FGF/FGFR gene aberrations in multiple tumor types, including cholangiocarcinoma (NCT03758664). Better response is expected with the increase of treatment durations. Clinical trial information: NCT03758664. Research Sponsor: Beijing InnoCare Pharma Tech Co., Ltd.

4093 **Poster Session**

A multicenter randomized controlled trial to evaluate the efficacy of surgery versus radiofrequency ablation for small hepatocellular carcinoma (SURF trial): Analysis of overall survival. *First Author: Masatoshi Kudo, Kindai University Faculty of Medicine, Osaka, Japan*

Background: The initial report of the multicenter SURF trial (surgery vs. radiofrequency ablation [RFA] for small hepatocellular carcinoma [HCC]) showed that recurrence-free survival (RFS) did not differ significantly between patients undergoing surgery and RFA. The focus of the present report was to assess the effect on overall survival (OS). **Methods:** The SURF trial was a multicenter, open-label, randomized, controlled, phase 3 trial conducted in 49 institutions in Japan. Patients (aged between 29 and 79 years) with Child-Pugh scores ≤ 7, largest HCC diameter ≤ 3 cm, and ≤ 3 HCC nodules were considered eligible. Before enrollment, both liver surgeons and hepatologists who perform RFA confirm that all the patients can be treated using both surgery and RFA. Patients were then randomly assigned in a 1:1 ratio to undergo surgery or RFA, stratified by age, hepatitis-C virus infection, numbers of HCC, largest HCC diameter, and institution. The co-primary endpoints were RFS and OS. As per the protocol, RFS was reported previously at 3 years after the last accrual of patients. OS was planned at 5 years after the last accrual. This trial is registered in UMIN000001795. **Results:** During 2009–2015, 308 patients were enrolled. After excluding ineligible patients, the surgery and RFA groups included 150 and 152 patients, respectively. Baseline factors did not differ significantly between the groups. In both groups, 90% of patients had solitary HCC. The median largest HCC diameter was 1.8 cm (interquartile range, 1.5–2.2 cm) in the surgery group and 1.8 cm (interquartile range, 1.5–2.3 cm) in the RFA group. The median (range) follow-up period was 6.4 (0.4–10.8) years in the surgery group and 6.6 (0–10.7) years in the RFA group. OS did not differ significantly between the surgery and RFA groups as the 5-year OS (95% confidence interval [CI]) was 74.6% (66.5%–81.0%) in the surgery group and 70.4% (62.2%–77.3%) in the RFA group (hazard ratio (HR), 0.96; 95% CI, 0.64–1.43; *P*= 0.828). The analysis after long-term follow-up in the current report showed that RFS was not significantly different between the surgery and RFA groups: the 5-year RFS (95% CI), 54.7% (46.0%–62.5%) vs. 50.5% (42.1%–58.3%); HR 0.90; 95% CI 0.67–1.22; *P*= 0.498. **Conclusions:** SURF trial revealed that OS and RFS were not significantly different between patients undergoing surgery and RFA for small HCC (≤ 3 cm and 3 nodules). Clinical trial information: 000001795. Research Sponsor: the Japanese Foundation for Multidisciplinary Treatment of Cancer and the Health and Labor Sciences Research Grant for Clinical Cancer Research (Grant No. H21-015).

4094 **Poster Session**

Gemox chemotherapy in combination with anti-PD1 antibody toripalimab and lenvatinib as first-line treatment for advanced intrahepatic cholangiocarcinoma: A phase 2 clinical trial. *First Author: Zhou Jian, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: The outcome of advanced intrahepatic cholangiocarcinoma (ICC) remains poor with current gemcitabine-based chemotherapy. This study is to evaluate the safety and efficacy of anti-PD1 agent toripalimab, lenvatinib in combination with oxaliplatin and gemcitabine (Gemox) chemotherapy. **Methods:** Locally advanced or metastatic ICC patients (pts) were given 240 mg toripalimab Q3W via intravenous (IV) infusion, 8 mg lenvatinib QD orally, and 1g/m^2 gemcitabine on Day 1 and Day 8, and 85 mg/m^2 oxaliplatin Q3W by IV for 6 cycles. The primary outcome was objective response rate (ORR), which was evaluated according to RECIST v1.1. Secondary outcomes included safety, progression-free survival (PFS) and overall survival (OS). Treatment would be terminated by confirmed disease progression, unacceptable toxicity, or voluntary withdrawal. Whole exome sequencing was performed on available tumor tissues and PD-L1 expression was determined by immunohistochemistry staining. **Results:** From May 2019 to Oct 2019, 30 pathologically-confirmed advanced ICC pts with a mean age of 56.5 (range, 25-73) years, including 11 women (37%), were enrolled at Zhongshan Hospital, Fudan University (one pt withdrawn). At the end of last follow-up (February 1, 2021), the ORR was 80% (24/30; 95% CI: 61.4%-92.3%), and disease control rate (DCR) was 93.3% (28/30; 95% CI:77.9%-99.2%). Median follow-up was 16.6 months. One pt achieved complete response (CR). Three pts with locally advanced disease were down-staged and then underwent resection. They remained disease-free survival at the end of last follow-up. 23 pts experienced disease progression and 12 pts (including one pt withdrawn) have died. The median PFS was 10.0 months and median duration of response (DOR) was 9.8 months. The median OS have not been reached. 12-months OS rate was 73.3% (95% CI: 57.5%-89.2%). No grade 5 adverse event (AE) was observed in present study. Grade 3 or 4 neutropenia and thrombocytopenia observed in 3 (10%) and 1 (3.3%) patient, respectively. Non-hematological toxic effects were jaundice (10 %), rash (6.7 %), proteinuria (6.7 %), increased AST level (3.3%), vomiting (3.3%), upper gastrointestinal hemorrhage (3.3%), sepsis (3.3%), gastrointestinal fistula (3.3%), adrenocortical insufficiency (3.3%), interstitial pneumonia (3.3%), and hyponatremia (3.3%). High ORR was significantly associated with positive PD-L1 expression (p= 0.048) and DNA damage repair (DDR)-related mutations (p= 0.022) in tumor samples. **Conclusions:** Gemox chemotherapy in combination with Anti-PD1 antibody Toripalimab and Lenvatinib provided remarkable efficacy with reasonable tolerability in advanced ICC patients. These findings warrant further validation in a large randomized clinical trial. Clinical trial information: NCT03951597. Research Sponsor: None.

4095 **Poster Session**

An armored GPC3-directed CAR-T for refractory or relapsed hepatocellular carcinoma in China: A phase I trial. *First Author: Zhongwei Zhao, Key Laboratory of Imaging Diagnosis and Minimally Invasive Intervention Research, Affiliated Lishui Hospital of Zhejiang University/the Fifth Affiliated Hospital of Wenzhou Medical University /The Central Hospital of Zhejiang Lishui, Lishui, China*

Background: HCC is a leading cause of cancer-related morbidity and mortality worldwide, of which glypican 3 is a highly specific marker. GPC3-directed CAR-T had shown promising safety but limited efficacy in the treatment of HCC. We developed an armored GPC3-directed CAR-T G3-CAR-ori2 by inserting of a novel and proprietary Ori2 element following the 4-1BB and CD3ζ domains in a second-generation CAR-T. Pre-clinical studies showed a significantly higher memory stem cell ratio and dramatically improved proliferation and persistence, compared with traditional CAR-T, thus offering prolonged efficacy *in vitro* and *in vivo* and potentiality leading to improved activity in the clinical setting (ChiCTR1900028121). **Methods:** This is an open-label, dose-escalation study of G3-CAR-ori2 cell HCC patients in two centers. Eligible patients were aged 18-70 years with histologically confirmed GPC3+ HCC, Child-Pugh score A or B, ECOG≤1, relapsed or refractory to standard therapies. Patients were pre-conditioned with fludarabine (25~30 mg/m2) and cyclophosphamide (200~300 mg/m2) daily for 3 days. G3-CAR-Ori2 was administered as a single infusion via intrahepatic or intravenous route with a total dose of 0.9 to 3x10e8 CAR-T. The objective was to assess the safety, preliminary efficacy, persistence and cytokine profiling of G3-CAR-ori2. Adverse events were graded using the Common Terminology Criteria for Adverse Events (version 5.0). Tumor responses were evaluated per RECIST (version 1.1). CAR-T cell expansion and persistence were measured by qPCR and flow cytometry. **Results:** As of Jan 21, 2021, 10 patients had received single infusion, in which 6 received G3-CAR-ori2 via intravenous route and 4 via intrahepatic route. 7 patients received the highest dose level of 3x10e8. 9 patients reached at least 1 month of follow-up and tolerated the treatment well with no dose-limiting toxicity. All patients experienced transient grade 4 decrease in lymphocyte count resulted from the lymphodepletion regimen. Cytokine release syndrome (CRS) was observed in 8 patients, in which 6 at grade 1 or 2 and 2 at grade 4 notably infused with 3 x10e8 both via intravenous route and reversed within 7 days by administering high-dose steroids and tocilizumab. Other grade 4 hematologic toxicities include thrombocytopenia (2/9) and neutropenia (1/9). No neurotoxicity was observed. Two subjects were not evaluable due to early withdrawal from the trial. Among the 7 evaluable subjects, the best responses achieved are 3 PR, 2 SD, 2 PD. The duration of remission of one patient with PR is more than 4 months, follow up is ongoing. CAR-T gene detected by q-PCR provide preliminary indication that G3-CAR-ori2 is able to expand and persist well in the clinical setting. **Conclusions:** These initial data provide evidence that G3-CAR-ori2 is safe and holds promising antitumor potential, and supports its continuing development in the treatment of r/r GPC3+HCC. Clinical trial information: ChiCTR1900028121. Research Sponsor: Shanghai Origincell Therapeutics Co., Ltd. Shanghai, 201210, China.

4096 **Poster Session**

Regomune: A phase II study of regorafenib + avelumab in solid tumors—Results of the biliary tract cancer (BTC) cohort. *First Author: Sophie Cousin, Medical Oncology, Institute Bergonié, Bordeaux, France*

Background: Regorafenib (R) has shown promising efficacy in patients (pts) with BTC refractory to standard chemotherapy. Anti-PD1/PD-L1 antibodies have only limited clinical activity. Synergy between R and anti–PD-1/PD-L1 antibodies has been shown in pre-clinical solid tumor models. **Methods:** This is a single-arm open-label multicentric phase II trial (Bayesian adaptive design) assessing the efficacy and safety of R (160 mg QD 3weeks/4) + avelumab (A) (10 mg/kg every 2 weeks) combination in BTC pts. The primary endpoint was the objective response rate under treatment, based on central review according to RECIST 1.1. Secondary endpoints included: 1-year progression free survival (PFS), 1-year overall survival (OS), and Safety using NCI-CTCAE v5.0. Correlative studies were planned from pts tumor samples obtained at baseline. **Results:** Between Nov. 2018 and Nov. 2019, 34 BTC pts were enrolled in 4 centers. Median age was 63 (range 36 – 80). Median follow-up was 9.8 months. Median number of previous treatment lines for metastatic or locally advanced disease was: 2 (range 1 – 4). Twenty-nine (85.3%) pts experienced at least 1 dose modification or treatment interruption of R or A due to an adverse event (AE) related to the treatment. The most common grade 3/4 AEs were : Hypertension (17.6%), Fatigue (14.7%), and maculo-papular rash (11.8%). No death was related to the treatment. Among the 29 pts with at least one imaging tumor assessment, 4 (13.8%) achieved a partial response, and 11 (37.9%) demonstrated stable disease including 10 (34.5%) pts with tumor shrinkage. Fourteen pts (48.3%) had progressive disease. The median PFS and OS were 2.5 months (95%CI 1.9 – 5.5) and 11.9 months (95%CI 6.2 – NA) respectively. Baseline tumor samples were available for 27 pts. High IDO and PD-L1 expression at baseline was associated with better outcome. **Conclusions:** The R+A combination is associated with significant anti-tumor activity with promising survival rates in this heavily pre-treated population. Full Biomarkers analyses will be presented at the meeting. Clinical trial information: NCT03475953. Research Sponsor: Bayer, Merck.

4097 **Poster Session**

FOENIX-CCA2 quality of life data for futibatinib-treated intrahepatic cholangiocarcinoma (iCCA) patients with *FGFR2* fusions/rearrangements. *First Author: Juan W. Valle, University of Manchester, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: In FOENIX-CCA2 (NCT02052778), a pivotal phase 2 study among iCCA patients (pts) with *FGFR2* fusions/rearrangements, the highly selective, irreversible FGFR1–4 inhibitor futibatinib demonstrated a confirmed objective response rate of 41.7%, with a 9.7-month median duration of response. Adverse events were manageable with dosing modifications that did not adversely impact on response. We report outcomes for the preplanned analysis of Patient-Reported Outcomes (PROs) during futibatinib treatment as a secondary objective of FOENIX-CCA2. **Methods:** Pts enrolled in FOENIX-CCA2 had locally advanced/metastatic unresectable iCCA with *FGFR2* fusions/rearrangements, ≥1 prior line of therapy (including gemcitabine/cisplatin) and ECOG PS 0-1. Pts received oral futibatinib 20 mg continuous QD dosing per 21-day cycle. PRO measures included EORTC-QLQ-C30 (1 global health, 5 functional, 9 symptom scales), EQ-5D-3L, and EQ visual analogue scale (VAS). PROs were collected at screening, cycles 2 and 4, every 3 cycles thereafter, and end of treatment. PRO data were evaluated up to cycle 13, the last visit before data were missing for >50% of the PRO population (PRO primary assessment time point). **Results:** 92/103 (89.3%) pts enrolled had PRO completion data at baseline and a minimum of 1 follow-up assessment (median age 58 y, 56.5% female), with 48 pts having PRO data at cycle 13. At baseline, mean (SD) EORTC QLQ-C30 global health status score was 70.1 (19.4) and EQ VAS score 71.7 (20.3). Mean EORTC QLQ-C30 global health status scores were maintained from baseline to cycle 13, corresponding to 9.0 months on treatment, with no clinically meaningful (≥10-point) changes in individual functional measures (Table). EORTC QLQ-C30 scores across individual symptom measures were also stable from baseline through cycle 13; only constipation showed an average of 10.0-point worsening at only cycle 4. Mean EQ VAS scores were sustained from baseline to cycle 13 (mean change ranging -1.8 to +4.8 across cycles), with values maintained within the population norm range from across 20 countries. **Conclusions:** Quality of life data from the phase 2 FOENIX-CCA2 trial show that physical, cognitive and emotional functioning, and overall health status were maintained among pts with advanced iCCA receiving futibatinib. Clinical trial information: NCT02052778. Research Sponsor: Taiho Oncology, Inc.

EORTC QLQ-C30 global health status and functional scales, mean (SD) change from baseline.

Functional scale	Cycle 2 n=84	Cycle 4 n=80	Cycle 7 n=66	Cycle 10 n=59	Cycle 13 n=48
Global health	-1.0 (22.0)	+0.4 (20.6)	-0.5 (21.6)	+1.9 (22.8)	+0.9 (21.5)
Physical	-1.1 (17.9)	+0.8 (15.0)	-0.4 (14.1)	-1.4 (15.4)	-2.0 (14.0)
Role	-1.2 (26.0)	-2.3 (24.0)	-0.8 (24.2)	-3.7 (23.6)	-1.4 (25.7)
Cognitive	-3.8 (15.9)	-5.7 (15.1)	-3.3 (12.2)	-4.0 (14.1)	-5.2 (12.5)
Emotional	+3.0 (19.7)	+4.7 (17.6)	+3.7 (16.2)	+2.9 (16.6)	+4.9 (15.6)
Social	+4.4 (27.9)	+0.6 (23.9)	+0.8 (19.9)	+2.9 (23.6)	-0.3 (20.5)

4098 **Poster Session**

The cost effectiveness of lenvatinib versus atezolizumab and bevacizumab or sorafenib in patients with unresectable hepatocellular carcinoma (uHCC) in Canada. *First Author: David Trueman, Source Health Economics, London, United Kingdom*

Background: Hepatocellular carcinoma (HCC) represents 72% of liver cancers in Canada. In the phase III REFLECT trial, lenvatinib met the primary endpoint of non-inferiority in overall survival (OS) versus sorafenib and demonstrated superiority in secondary endpoints of progression free-survival (PFS), time to progression and objective response rate. Based on the REFLECT trial, lenvatinib has become the standard of care in the treatment of Canadian patients with unresectable HCC (uHCC). In the Phase III IMbrave150 trial, the use of the combination of atezolizumab and bevacizumab (atezo+bev) resulted in statistically significant improvement in OS and PFS versus sorafenib for patients with uHCC. The aim of this analysis was to estimate the cost-effectiveness of lenvatinib versus atezo+bev or sorafenib as first-line treatment for patients with uHCC from the perspective of Ministry of Health in Canada. **Methods:** A cost-utility analysis was conducted using a partitioned survival analysis. Health state membership for lenvatinib and sorafenib were estimated based on patient level data and clinical inputs from REFLECT and extrapolated using parametric survival models. Relative efficacy for atezo+bev was estimated from a de novo network meta-analysis. In the base-case analysis, estimates from REFLECT used in the NMA were adjusted for imbalances in baseline characteristics. Sensitivity analyses included the use of alternative approaches to determine relative efficacy. Health state utility values were determined with EQ-5D data collected in REFLECT. Drug acquisition costs were obtained from publicly available sources and medical resource utilization was based on a survey of Canadian clinicians. The time horizon was 10 years. Results of the incremental analysis were calculated sequentially. **Results:** In the base case lenvatinib was associated with cost savings of CAD$4,640 and CAD$120,095 and a QALY difference of 0.15 and -0.28 vs sorafenib and atezo+bev, respectively. The base case deterministic analysis resulted in lenvatinib being dominant over sorafenib and cost-effective vs. atezo+bev (sequential ICER for atezo+bev was CAD$425,754 per QALY). Results of the probabilistic sensitivity analysis (PSA) were consistent with the base case findings with lenvatinib being the optimal treatment strategy in >99% of iterations. **Conclusions:** Results of this analysis demonstrate that lenvatinib represents the optimal use of healthcare resources as a first-line treatment for uHCC in Canada. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4099 **Poster Session**

Lenvatinib plus toripalimab as first-line treatment for advanced intrahepatic cholangiocarcinoma: A single-arm, phase 2 trial. *First Author: Zhou Jian, Department of Liver Surgery and Transplantation, Liver Cancer Institute, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Lenvatinib monotherapy and lenvatinib plus PD-1 antibody have shown some clinical benefit for advanced intrahepatic cholangiocarcinoma (ICC) in the second-line setting. Our study assesses the role of lenvatinib plus toripalimab (PD-1 antibody) for advanced ICC patients as the first line therapy. **Methods:** Patients (pts) with locally advanced or metastatic ICC received 12 mg/day (Body Weight ≥60 kg) or 8 mg/day (Body Weight <60 kg) oral lenvatinib daily plus 240 mg intravenous toripalimab every 3 weeks. The primary endpoint was objective response rate (ORR) and evaluated according to Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST v1.1). Secondary endpoints included safety, progression-free survival (PFS) and overall survival (OS). Treatment continued until confirmed disease progression, unacceptable toxicity, or voluntary withdrawal. This trial is registered with ClinicalTrials.gov (NCT04361331). **Results:** From March 2020 to Sep. 2020, 31 pathologically confirmed advanced ICC pts with a mean age of 58.4 (range, 25-73) years, including 18 women (58.0%), were enrolled at Zhongshan Hospital, Fudan University. At the end of last follow-up (February 10, 2021), the ORR was 32.3% (10/31; 95% CI: 16.7%-51.4%) and the disease control rate (DCR) was 74.2% (23/31; 95% CI: 55.4%-88.1%). Median follow-up was 6.9 months. Two pts with locally advanced disease were down-staged and then underwent resection. They remained disease-free survival at the end of last follow-up. 11 pts exerted disease progression and 7 pts died. The median PFS and OS have not been reached. Median duration of response (DOR) has not been reached and responses were ongoing in 9/10 (90.0%) pts at data cutoff. 6-months OS rate was 87.1%. No grade 5 adverse event (AE) was observed in present study. 32.3% (10/31) of pts experienced Grade 3 or higher AEs and 1 pts discontinued the treatment owing to severe fatigue. **Conclusions:** As the first-line therapy, lenvatinib plus toripalimab provided promising efficacy with reasonable safety profile in advanced ICC patients. It offered an alternative treatment for advanced ICC who cannot tolerate gemcitabine-based chemotherapy. Clinical trial information: NCT04361331. Research Sponsor: None.

4100 **Poster Session**

Molecular markers of response to anti-PD1 therapy in advanced hepatocellular carcinoma. *First Author: Philipp K. Haber, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Checkpoint inhibition with anti-PD1 is able to elicit objective response rates (ORR) of ~ 20% in patients with advanced hepatocellular carcinoma (aHCC) but molecular biomarkers predicting response remain unknown. Here, we define biomarkers of response and primary resistance to anti-PD1 in aHCC by analyzing molecular features prior to systemic therapy. **Methods:** Through an international consortium of 13 referral centers, we gathered 111 fresh and archived tumor samples from patients with advanced HCC treated with single agent anti-PD1 therapy. Genomic analysis was performed with whole genome expression arrays, CTNNB1 exon 3 mutation assessment and histological evaluation. **Results:** Overall, we performed transcriptomic analysis in 83 patients, 28 of which were treated in first-line (ORR: 42.9%) while the remaining 55 patients were treated either in 2nd (41 patients, ORR 29.3%) or 3rd line (14 patients, ORR 7.1%) after prior therapy with tyrosine- kinase inhibitors (TKI) sorafenib or lenvatinib. In patients treated in frontline, response was associated with a significant upregulation in Interferon-γ signaling (IFNγ) and genesets relatedto the antigen presentation machinery (FDR < 0.05). Through differential expression analysis we defined an 11-gene signature that was significantly associated with both major pathways (FDR < 0.01) and was capable of predicting OR as well as progression-free- (PFS) and overall survival (OS) in patients with aHCC. The signature was validated in three independent cohorts of melanoma, lung cancer, and head and neck squamous cell cancer patients were high expression was associated with a significant increase in ORR and longer PFS. In HCC, high expression of the signature was associated with a distinct profile in the immune infiltrate, where an increase in M1 macrophages ($p = 0.003$), CD4 memory T cell ($p < 0.01$) and CD4 nave T cell-infiltration ($p = 0.026$) was observed. Conversely, low expression of the signature was associated with a marked upregulation of regulatory T cells ($p < 0.001$). No association was found, however, between either the overall immune infiltrate or CTNNB1 mutations and response. In patients that were treated with TKIs in frontline before receiving subsequent anti-PD1 therapy, the signature was no longer able to predict either OR or PFS/OS, suggesting that TKIs may reshape the microenvironment in a way that renders previously inflamed tumors no longer amenable to anti-PD1. **Conclusions:** Here, we define an 11-gene signature of response to anti-PD1 in first line aHCC. The signature was validated in patients with other solid cancer types, where it retained its predictive ability. Of note, the signature was not able to identify responders among HCC patients that were treated with TKIs prior to anti-PD1 therapy. The molecular changes induced by different treatment lines would, thus, require fresh biopsies prior to anti-PD1to enable biomarker-driven treatment. Research Sponsor: BAYER.

4101 **Poster Session**

Phase 2 study of AK104 (PD-1/CTLA-4 bispecific antibody) plus lenvatinib as first-line treatment of unresectable hepatocellular carcinoma. *First Author: Li Bai, The General Hospital of the People's Liberation Army, Beijing, China*

Background: Anti–PD-(L)1 plus anti-CTLA-4 therapies (e.g. nivolumab/ipilimumab, tremelimumab/durvalumab) produce durable immune responses in patients (pts) with advanced hepatocellular carcinoma (HCC). More recent data suggests that the combination of immune checkpoint inhibitors (ICIs) with a multi-kinase inhibitor is efficacious against unresectable HCC (uHCC). AK104 is a humanized IgG1 bispecific antibody that simultaneously binds to PD-1 and CTLA-4. Early data suggests that AK104 possesses encouraging anti-tumor activity in selected tumour types and an improved safety profile compared to the co-administration of anti-PD-1 plus anti-CTLA-4 antibodies. Lenvatinib is a multi-kinase inhibitor and approved for first-line treatment of uHCC. Here, we report results from a phase 2 study of AK104 plus lenvatinib in pts with uHCC. **Methods:** In this single-arm, multicenter phase II study (NCT04444167), pts with uHCC, BCLC stage B or C, Child-Pugh class A, who had not previously received systemic treatment received AK104 (6 mg/kg IV q2w or 15 mg/kg IV q3w) and lenvatinib (8 mg [bodyweight < 60 kg] or 12 mg [weight ≥ 60 kg] PO QD). Primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints include disease control rate (DCR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS). **Results:** As of February 1 2021, 30 pts (86.7% male, median age 52.5yrs [31-71], 30% was ECOG 1, 93.3% was HBV+) had received the combination therapy of (AK104 6 mg/kg q2w plus lenvatinib). Of 18 pts evaluable for antitumor activity (defined as pts with the opportunity to be followed for at least 2 scans [≥13 weeks]), ORR per RECIST v1.1 was 44.4% (8/18), DCR was 77.8% (8 PRs and 6 SDs including 2 pts who had 28.4% and 29.2% reduction in tumor size from baseline). Median PFS has not been reached. Treatment-related adverse events (TRAEs) occurred in 83.3% of pts (G3 TRAEs occurred in 26.7% [8/30], and no G4 TRAEs or TRAEs leading to death). Most common TRAEs (≥15%) were increased AST (36.7%) and ALT (36.7%), decreased platelet count (33.3%), decreased neutrophil count (30.0%), and increased blood bilirubin (26.7%), with the vast majority being grades 1 or 2. **Conclusions:** AK104 plus lenvatinib as first-line therapy for uHCC has showed promising antitumor activity and an acceptable safety profile. Toxicities were manageable, with no unexpected safety signals. Enrollment for AK104 15 mg/kg q3w plus lenvatinib is currently ongoing, and longer follow-up is needed to further evaluate the durability of response. Clinical trial information: NCT04444167. Research Sponsor: Akeso Biopharma Inc.

4102 **Poster Session**

Comparative effectiveness of sorafenib, lenvatinib, and nivolumab as first-line systemic therapy for patients with advanced hepatocellular carcinoma and Child-Pugh class B cirrhosis treated at VA Medical Centers. *First Author: William Joseph Chapin, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA*

Background: Up to 90% of cases of hepatocellular carcinoma (HCC) in the U.S. occur in patients with cirrhosis. As prognosis in patients with decompensated cirrhosis may be more related to liver function than tumor stage, patients with Child-Pugh (CP) class B and C cirrhosis are often excluded from randomized trials despite representing up to 30% of patients treated with systemic therapy in clinical practice. While prospective data such as the GIDEON registry and CHECKMATE-040 have demonstrated safety of sorafenib and nivolumab in CP B cirrhosis, studies of comparative effectiveness of sorafenib, lenvatinib, and nivolumab are lacking. **Methods:** We performed a retrospective cohort study of patients with HCC and CP B cirrhosis at U.S. Veterans Affairs Medical Centers who initiated first systemic therapy with sorafenib, lenvatinib, or nivolumab between 9/22/2017 and 2/13/2021. Overall survival (OS) by first systemic therapy was assessed with Kaplan Meier analysis and Cox proportional hazards modeling with prespecified candidate covariates and a backward elimination approach for variable selection. Missing data were imputed by multiple imputation with chained equations. **Results:** Among 401 CP B patients undergoing first systemic therapy, 98% were male, 29% had macrovascular invasion (MVI), 35% had extrahepatic spread (EHS), 57%/29%/13% had CP score 7/8/9, 5% had hepatic encephalopathy, 37% had ascites, 63%/2%/36% had HCV/HBV/non-viral cirrhosis, 63% had prior embolization or ablation, and 35% had ECOG performance status of $>=2$. Of these patients, 320 received sorafenib, 33 received lenvatinib, and 48 received nivolumab. In univariate analysis, median OS was 4.8 months (95% CI 3.8 – 6.0; 1 year OS 21.8%) in the sorafenib cohort, 6.9 months (95% CI 4.4 – 8.4 months; 1 year OS 27.8%) in the lenvatinib cohort, and 7.7 months (95% CI 3.9 – 9.1 months; 1 year OS 31.7%) in the nivolumab cohort. Covariates with at least one category significantly associated with survival that were retained in the multivariate model included CP score, MELD-Na, BMI, log(AFP), time from diagnosis to systemic treatment, ECOG performance status, Cirrhosis Comorbidity index, and VA complexity level (all $p < 0.05$); MVI, EHS, and age were retained in the model as pre-specified despite lack of statistical significance. Compared with sorafenib, nivolumab was associated with significantly lower hazard of death (adjusted HR 0.63; 95% CI 0.43 – 0.91; p = 0.015) while hazard of death for lenvatinib treatment was not significantly different (adjusted HR 0.83; 95% CI 0.54 – 1.28, p = 0.41). **Conclusions:** Among patients with HCC and CP class B cirrhosis undergoing first systemic therapy, nivolumab was associated with significantly lower hazard of death compared to sorafenib after adjusting for important covariates. Research Sponsor: U.S. National Institutes of Health.

4103 **Poster Session**

Tumor-informed assessment of circulating tumor DNA and its incorporation into practice for patients with hepatobiliary cancers. *First Author: Pashtoon Murtaza Kasi, University Of Iowa, Iowa City, IA*

Background: Hepatocellular carcinoma (HCC) and biliary tract cancers [BTC - including cholangiocarcinoma (CCA) and gall bladder cancers (GBC)] represent a heterogeneous group of diseases. Glycoprotein-based tumor markers like alpha-fetoprotein (AFP) or carbohydrate antigen 19-9 (CA-19-9) though part of standard-of-care (SOC), lack sensitivity, and specificity. A fair proportion of these cancers do not produce these glycoproteins. Circulating tumor DNA (ctDNA) testing can fill this void and be used for the assessment of molecular residual disease (MRD), as well as for surveillance purposes in patients with HCC or BTC. Prospective evaluation of this methodology in clinical practice has been limited to date. **Methods:** A personalized and tumor-informed multiplex PCR assay (Signatera bespoke mPCR NGS assay) was used for the detection and quantification of ctDNA. Serial time points were collected on a subset of patients to monitor their ctDNA levels in response to treatment. **Results:** Here we analyzed 200 plasma samples from a total of 90 patients with HCC (n=27) and BTC (n=63), comprising 46 patients with CCA and 17 patients with GBC. Sample-level ctDNA positivity rates, determined using a tumor-informed assay are presented in table. ctDNA detection was significantly associated with the stage of disease (Wilcoxon rank-sum test, $p<0.05$). Serial time point analysis was performed on a subset of patients (n=56) that had 2-7 time points available and correlations between ctDNA levels and clinical response were noted and will be presented. **Conclusions:** Our study is the first to set the benchmark for the utility and feasibility of using a tumor-informed assay in this cohort of hepatobiliary cancers. With adjuvant chemotherapy already a SOC for BTC, and immunotherapy being studied for HCC alongside other novel agents for CCA and GBC, assessment of MRD or ctDNA clearance on therapy would be of value as an additional tool in identifying patients at high risk for recurrence/metastasis. The utility of this study would also lie in incorporation in clinical trials to enrich and study those who are at the highest risk of recurrence i.e. ctDNA positive. Research Sponsor: None.

Sample-level ctDNA positivity rates across biliary tract cancer and hepatocellular carcinoma.

Cancer Type	Baseline	MRD	On treatment and Surveillance
Cholangiocarcinoma (CCA) and Gall Bladder (GBC) , N=138	10/12 (83%)	9/44 (20%)	24/82 (29%)
Liver (HCC), N=62	1/1 (100%)	6/21 (29%)	20/40 (50%)

4104 **Poster Session**

Does adjuvant chemoradiation benefit patients with lymph node-positive biliary tract cancer? A secondary analysis of SWOG S0809. *First Author: Sepideh Gholami, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Biliary tract cancers are rare tumors with a median overall survival (OS) of 16 months for node-positive (N+) and 37 months for node-negative (N0) disease despite resection. Lymph node status is a known strong prognostic factor for local recurrence with an average estimated 2-year disease-free survival (DFS): 65.5% for N0 and 29.7% for N+ tumors. The Phase II Intergroup Trial S0809 showed that adjuvant capecitabine and gemcitabine followed by radiotherapy and concurrent capecitabine improved OS in patients with extrahepatic cholangiocarcinoma (EHCC) and gallbladder cancer (GBC) compared to historical controls. We hypothesized that nodal status is a prognostic factor for local recurrence in this patient population who received adjuvant therapy. **Methods:** This analysis included patients with stage pT2-4, N+ or positive margin EHCC or GBC. Treatment included four cycles of gemcitabine (1,000 mg/m^2 intravenously on days 1 and 8) and capecitabine (1,500 mg/m^2 per day on days 1 to 14) every 21 days followed by concurrent capecitabine (1,330 mg/m^2 per day) and radiotherapy (45 Gy to regional lymphatics; 52.5 to 59.4 Gy to tumor bed). S0809 patients who did not receive radiotherapy were excluded from analysis. Correlations between nodal status, resection margin, and other clinicopathological factors, patterns of recurrence and survival were analyzed, and Cox regression models were used to estimate the prognostic significance of nodal status. A Z-test was used to compare DFS rates between these patients and historical data. **Results:** A total of 69 patients [EHCC n = 46 (66%); GBCA n = 23 (33%)] were evaluated with a median age of 61.7 (26.1-80.6). The majority of N0 patients were female (17/24, 70.8%), whereas most N+ patients were male (25/45, 55.6%; $p < 0.04$). Distribution of R0 (66.7%) and R1 (33.3%) resections was similar in the N0 and N+ groups. Thirty-four patients with EHCC had N+ disease (73.9%) compared with 11 patients with GBCA (47.8%, p = 0.03). Nodal status did not significantly impact OS (HR = 2.03, 95% CI 0.92-4.49, p = 0.08) or DFS (HR = 1.75, 95% CI 0.85-3.59, p = 0.13). Two-year OS was 70.6% for N0 and 60.9% for N+ disease (p = 0.11). Nodal status was not significantly associated with 2-year DFS: 62.5% for N0 and 49.8% for N+ (p = 0.20). N+ vs N0 tumors showed higher rates of distant failure (51.1% vs 25.0%, $p < 0.04$), but similar local recurrence (17.8% vs 12.5%, p = 0.88). The observed 2-year DFS in patients with N+ tumors was significantly longer compared to the historical rate of 29.7% (p = 0.004). **Conclusions:** This combination adjuvant treatment regimen following curative resection for EHCC and GBCA provides favorable outcomes regardless of nodal status. These data suggest that adjuvant chemoradiation may positively impact local control in N+ patients. These findings need to be validated in future clinical trials. Clinical trial information: NCT00789958. Research Sponsor: U. S. National Institutes of Health.

4105 **Poster Session**

ARID1A mutation to predict disease progression during first-line chemotherapy in biliary tract cancer patients. *First Author: Sung Hwan Lee, CHA Bundang Medical Center, CHA University School of Medicine, Seongnam, South Korea*

Background: Biliary tract cancer (BTC) is a retractable disease showing a dismal prognosis with therapeutic resistance. There are clinical unmet needs on predicting therapeutic response and precise strategy for the patient classification according to clinically relevant tumor biology in the patients with BTC. We aimed to identify clinically detectable genomic alteration predicting therapeutic response after first-line chemotherapy in BTC using real-world data. **Methods:** A comprehensive genomic analysis of multi-institutional cohorts of BTC cases was performed using next-generation sequencing (NGS) with targeted DNA panel and patients' clinicopathologic data. **Results:** A total of 200 BTC patients with NGS panel tests from three cancer centers were included in this study. The genomic alteration of TP53 (55.5%), KRAS (23%), ARID1A (10%), and ERBB2 amplification (10%) were the most frequent alteration events in the BTC. Pathologically-proved BTC including extrahepatic (n = 52), ampulla of Vater (n = 4), gallbladder (n = 56), intrahepatic (n = 88) cancers showed a distinct pattern of genomic alterations in terms of ARID1A for extrahepatic BTC and ERBB2 amplification, RB1, ARID2 for GB cancer, and KRAS, IDH1, PBRM1, BAP1 for intrahepatic BTC respectively (chi-square test, $P < 0.05$). The oncologic outcomes for progression-free and overall survival were significantly stratified according to the best response after the first-line chemotherapy (log-rank test, $P < 0.001$). The logistic regression test revealed that ARID1A, BRCA2, and STK11 could significantly predict disease progression during first-line chemotherapy. ARID1A, especially, was the only independent predictive marker in the multivariate regression model in total BTC (OR 3.91, 95%CI 1.25-11.66, P = 0.015) and extrahepatic BTC (OR 5.71, 95%CI 1.23-28.98, P = 0.027). The predictive performance of significant genomic alteration was enhanced with the tumor marker CA19-9 (DeLong's test, Z = 1.933, P = 0.053, AUC 0.73, 95%CI 0.623-0.837). **Conclusions:** Clinically available NGS test showed distinct genomic alterations in terms of different deterioration patterns for oncogenic molecular pathways according to the anatomic locations of BTC. Integrative analysis using the data for genomic alteration and therapeutic response for the first-line chemotherapy uncover that the patients with ARID1A mutation show a significant disease progression rate during initial treatment for BTC, especially in the extrahepatic BTC. Prospective translational studies revealing underlying biology and precision strategy should be followed to improve the therapeutic response of BTC. Research Sponsor: None.

4106 **Poster Session**

Clinical outcomes analysis of TP53-mutated advanced and metastatic biliary tract cancers. *First Author: Sunyoung S. Lee, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Advanced biliary tract cancers (BTC) are lethal cancers with limited treatment options and short survival. Median progression-free survival (mPFS) in the ABC-02 trial was 8.0 months with gemcitabine-cisplatin (GC) and 5.0 m with gemcitabine alone in the front-line setting. The ABC-06 trial showed mPFS of 4.0 m with second-line FOLFOX. TP53 mutation is known to be associated with poor prognosis in other cancers, but its impact on survival in advanced or metastatic BTC has not been detailed. **Methods:** Mutational profiles were obtained from a retrospective database collected via an institutional DNA/RNA sequencing panel, FoundationOne, or Guardant360. Out of 149 patients with TP53 mutations in BTC, 90 had advanced or metastatic BTC treated at a single institution between 2015 and 2021. These patients were not candidates for surgery, radiation, or liver-directed therapy. **Results:** Intrahepatic, hilar, distal, and gallbladder cancer diagnoses were confirmed in 66, 11, 10, and 3 patients. Median age was 63, with a male:female ratio of 1:1. Poorly, moderately, and well-differentiated adenocarcinomas were found in 62, 20, and 1 (not available in 7 patients). The most common TP53 mutations were R175H (n = 5) and R248Q (n = 4). Common co-mutated genes included KRAS (n = 15), ARID1A (n = 15), FGFR2 fusion (n = 14), IDH1 (n = 13), BAP1 (n = 10), CDKN2A (n = 9), and HER2 amplification (n = 8). Microsatellite unstable (MSI-H) tumors were found in 3 patients. The median tumor mutational burden was 2.5/Mb. Patients received front-line GC (n = 54), GC-nab-paclitaxel (GAP, n = 14), FOLFIRINOX (n = 3), and GC with targeted or trial therapy (n = 11, e.g. trastuzumab). mPFS with front-line therapy was 5.0 m (n = 90); it was 4.7 m with GC and 5.1 m with GAP. Patients who had co-mutated IDH1 or FGFR2 fusion had longer mPFS (9.5 and 6.9 m, respectively) than those who did not (n = 63, 3.7 m, $p < 0.05$) from front-line chemotherapy. mPFS after second-line FOLFOX (n = 17) and FOLFIRI (n = 10) was 2.1 and 1.9 m, respectively, and mPFS after third-line FOLFOX/FOLFIRI was 1.8 m (n = 8). The median overall survival (OS) of patients with co-mutated FGFR2, IDH1, or neither was 34.5, 22.0, and 13.1 m, respectively ($p < 0.05$). TP53-mutated BTC with mutations other than FGFR2/IDH1 did not show statistically significant difference in PFS or OS. **Conclusions:** Patients with TP53-mutated advanced BTC have shorter PFS than those without TP53 mutation in front and further-line settings. The presence of co-mutated FGFR2 or IDH1 is associated with improved PFS with chemotherapy (not FGFR/IDH1 inhibitors) and longer OS. Other co-mutations do not appear to have a survival benefit. It is crucial for clinicians to take into account the worse prognosis with TP53 mutation before starting front-line therapy in patients with advanced BTC and consider early clinical trial options. Research Sponsor: None.

4107 **Poster Session**

Impact of cell density in lymphocyte-rich areas in the tumor microenvironment on prognosis and gene expression landscape in hepatocellular carcinoma. *First Author: Jeonghyuk Park, VUNO Inc., Seoul, South Korea*

Background: Cellular and non-cellular components in the tumor microenvironment (TME) impact prognosis and treatment in hepatocellular carcinoma (HCC). We previously reported a deep learning-based model of tissue segmentation in pathology images, showing an impact of stromal and malignant cell distribution with respect to gene expression on survival and molecular subtypes of cancer [1]. **Methods:** Clinical outcomes data, mRNA-seq, and histopathology images of 351 patients (pts) with HCC were obtained from TCGA. We established a combined algorithm of two deep learning models: ResNet-based model for tissue segmentation; YOLO-based model for cell detection, using published data sets [2, 3]. The tissue segmentation model defines six segments having following predominant components: malignant cells, lymphocytes, adipose, stromal, mucinous, and normal liver tissues. The cell detection model calculates density and mapping of cells in the TME. The immune landscape was analyzed via mRNA-seq of 770 genes enriched in TME. This comprehensive analysis defined parameters including the cell density per lymphocyte segmented area (CDpLA), representing the density of lymphocytes on a lymphocyte-rich area in TME. **Results:** Pts were clustered into two groups with high and low CDpLA (212 and 139 pts). High CDpLA was defined as lymphocyte density > 0.5 (13,618 cells/mm^2 lymphocyte area). Pts with high CDpLA showed significantly better median overall survival (OS) than those with low CDpLA (82.9 vs 37.8 month, $p < 0.005$). The hazard ratio of CDpLA in OS was 0.36 (95% CI 0.18-0.72, $p < 0.005$). Among pts with available clinical data, 29 and 21 pts were with hepatitis C (HCV) and hepatitis B (HBV). Out of 29 HCV pts, 23 and 6 pts were with high and low CDpLA; out of 21 HBV pts, 17 and 4 pts were with high and low CDpLA. Fifty three were with alcoholic abuse, and 26 and 27 pts were with high and low CDpLA. Of note, pts with high CDpLA had significantly better OS in HCV pts (61.7 vs 19.9 months, $p < 0.005$). Genomic analysis with mRNA-seq shows that HCV pts with high CDpLA have lower expression of genes related to myeloid-derived suppressor cells (TRANK1, MEGF9, HS3ST2, GPNMB) and higher in genes related to immune activation (PLD4, IL3RA, TNFRSF4). **Conclusions:** A deep learning-assisted model of TME segmentation and cell detection showed an impact on survival from CDpLA, rather than the total number of lymphocytes in the TME. HCV pts are more likely to have higher CDpLA, and CDpLA was a strong prognostic indicator in HCV pts. Pts with high CDpLA are those with elevated expression of genes related to immune activation and decreased expression of immunosuppressive genes. Retrospective and prospective analysis of clinical response to immunotherapy and tyrosine kinase inhibitors is underway. [1] Kim et al. Cancer Res 2020 (80) (16 Supp) 2631 [2] Kather et al. PLoS Med 2019 16(1): e1002730 [3] Gamper et al. arXiv 2020:10778 Research Sponsor: None.

4108 **Poster Session**

Should all pancreatic neuroendocrine tumors (PNET) over 1 cm be resected? *First Author: Diana Hsu, UCSF-East Bay, Oakland, CA*

Background: Pancreatic neuroendocrine tumors (PNET) are a heterogeneous group of tumors that represent 1-2% of all pancreatic neoplasms. Their biologic behaviors are unpredictable with high grade, nodal metastasis, or liver metastasis lending an unfavorable prognosis. Current guidelines recommend resection for functioning tumors and those 2 cm or larger but are less straightforward regarding tumors < 2 cm in size. Previous data show that observation for non-functioning tumors < 2 cm can be safe and feasible; however, a significant portion of these patients may have nodal involvement or metastatic disease. **Methods:** A retrospective review was undertaken to identify patients with pancreatic neuroendocrine tumors treated at Northern California Kaiser Permanente (KP-NCAL) between February 2010 and December 2018. Univariate and multivariate analyses were performed with the log-rank test and Cox regression. Chi-squared test of relevant clinicopathologic factors determined which factors were predictive for overall survival (OS). **Results**: Mean age was 61 years in our cohort of 354 patients, with 29% over the age of 70. Mean tumor size was 3.43 cm; 32% of tumors were 2 cm or smaller. 51% of the patients had localized disease; 32% of the patients presented with metastatic disease. The pancreatic tail was the most common tumor location (38%), followed by the head of the pancreas (24%). On multivariate survival analysis, stage, location of the tumor, and surgical resection were statistically significant in terms of overall survival ($p< .001$). Mean OS for patients with localized and metastatic disease was 93 months versus 37 months ($p< .001$). Surgery was utilized in 8.9% of patients with metastatic disease ($p< .001$). All patients with PNET smaller than 1 cm in our study group had localized disease only. However, in patients with tumor size between 1 and 2 cm, 11% had nodal or metastatic spread. **Conclusions:** PNETs are indolent but have malignant potential at any size. In our retrospective study, all of the patients with tumor size < 1 cm had localized disease. For those with PNETs 1-2 cm in size, 11% had nodal or metastatic spread. Based on our findings, we suggest a more aggressive surgical resection size criteria of 1 cm. Research Sponsor: None.

Tumor size (cm)	Localized disease (%)	Nodal disease (%)	Metastatic disease (%)	Overall survival at 60 months (%)
< 1	100	0	0	90
1-2	89	4	7	80
> 2	35	25	40	54

4109 **Poster Session**

Validation of a clinical score (CS) for patients (pts) with well-differentiated neuroendocrine tumors (WD NETs) under consideration for peptide receptor radionuclide therapy (PRRT) with Lu 177 dotatate. *First Author: Satya Das, Vanderbilt University Medical Center, Nashville, TN*

Background: Questions remain regarding when to sequence PRRT and how to categorize pts being considered for the treatment (tx). We previously developed a CS (comprised of 5 categories: available non-PRRT tx for tumor type, prior systemic tx, pt symptoms, tumor burden in critical organs and peritoneal carcinomatosis presence) at Vanderbilt Ingram Cancer Center (VICC) for pts being considered for PRRT to help answer these questions and demonstrated the score to be associated with progression-free survival (PFS) in pts receiving PRRT. Herein, we present the performance of the CS in a validation cohort (VC) and combined cohort (CC). **Methods:** Our original cohort (OC) included pts with progressive WD NETs (N = 122) under consideration for PRRT between 3/1/2016-3/17/2020 at VICC while our VC included pts under consideration for PRRT (N = 126) between 1/25/2017-11/18/2019 at Ochsner Medical Center (OMC) (N = 51), Markey Cancer Center (MCC) (N = 51) and Rush Medical Center (RMC) (N = 24). All pts in the OC were prospectively scored while pts in the VC were scored retrospectively, with the CS-assigning investigator blinded to patient outcomes. The primary outcome PFS, was estimated by the Kaplan-Meier method; a Cox proportional-hazards model adjusting for primary tumor site, tumor grade and number of PRRT doses administered (0, 1-2 or 3-4) was used to analyze effect of CS. Overall survival (OS) was a key secondary outcome. **Results:** In our VC, on multivariable (MV) analysis, for each 2-point increase in CS, the hazard ratio (HR) for PFS was 2.58 (95% confidence interval (CI) 1.62-4.11). On MV analysis, for each 2-point increase in CS, the HR for OS was 3.89 (95% CI 1.8-4.83). We combined the OC and VC for this analysis in order to increase the predictive power of our originally developed Cox proportional-hazards models. In our CC, of the 248 total pts, median pt age, CS and number of prior tx were 63.3 years, 4 (range 0-8) and 1 (range 0-7), respectively. The most represented primary tumor sites were small intestinal (N = 136), pancreatic (N = 58), unknown primary (N = 26) and lung (N = 14). A total of 140, 82 and 26 pts received 3-4, 0 or 1-2 doses of PRRT, respectively. On MV analysis, for each 2-point increase in CS, the HR for PFS was 2.52 (95% CI 1.90-3.35). On MV analysis, for each 2-point increase in CS, the HR for OS was 3.48 (95% CI 2.33-5.18). No interaction between PRRT doses administered and CS was observed. **Conclusions:** Increases in CS were strongly associated with worsening PFS and OS in our VC and CC, validating findings from our OC. Although we cannot determine whether the CS specifically predicts PRRT response or is prognostic based upon these data, it is the first presented clinical metric which can categorize pts with WD NETs under consideration for PRRT and estimate anticipated benefit from PRRT for pts. Research Sponsor: Neuroendocrine Tumor Research Foundation, U.S. National Institutes of Health.

4110 **Poster Session**

The safety and efficacy of PEN-221 somatostatin analog (SSA)-DM1 conjugate in patients (PTS) with advanced GI mid-gut neuroendocrine tumor (NET): Phase 2 results. *First Author: Daniel M. Halperin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: PEN-221 is a small molecule drug conjugate composed of a SSTR2 binding somatostatin analog linked to the toxin DM1. PEN-221-001 was a study which assessed the safety, tolerability, pharmacokinetics (PK), and preliminary efficacy of PEN-221 in well differentiated neuroendocrine tumors (NETs) and small cell lung cancer. Here we present the efficacy outcomes for patients enrolled in the GI mid-gut cohort and the safety data for the entire study. **Methods:** Pts with advanced, SSTR2+ (by imaging) GI mid-gut NETs were enrolled in this cohort of the study. The primary objective was to determine the safety and efficacy of PEN-221 given intravenously, every (q) 3 weeks in patients with documented radiographic progression within the 6 months prior to enrollment. Patients previously treatment with cytotoxic chemotherapy were excluded. Preliminary efficacy was assessed using RECIST 1.1. A clinically meaningful efficacy result was defined as a Clinical Benefit Rate (CBR) $>$ 75% and a median progression-free survival (mPFS) $>$ 8 months. **Results:** 32 patients (17M/15F) were enrolled between January 2018 to June 2020 and the data cut-off for this report is July 31, 2020. The first nine patients were treated at the phase 1 determined Maximum Tolerated Dose of 18 mg. After review of the safety, tolerability, and PK data from these pts, the regimen was amended to 8.8 mg/m^2 for all subsequent pts to achieve more uniform exposures (AUC) across all pts and reduce toxicity in pts with lower body-surface areas (BSA). The mean number of cycles received by pts in this cohort was 7 (range 1-18), with 5 pts still on treatment at time of data lock. PEN-221 was well tolerated in all pts at the dose of 8.8 mg/m^2. The most frequent ($\geq$20% pts) PEN-221 related adverse events of any grade were fatigue (39%), nausea (38%), diarrhea (35%), decreased appetite (30%), infusion reaction (24%), AST/ALT/Alk Phos increase (24%), and peripheral neuropathy (21%). Only 14 (10%) of these events were grade 3 or greater. Grade 3 PEN-221 related adverse events which were reported in 2 or more pts included fatigue (7.6%), ALT/AST/Alk Phos increase (7.6%), and peripheral neuropathy (3%). PEN-221 plasma median $t_{1/2}$ was ~4.5 h, with exposures uniform using BSA based dosing. Of the 26 pts who were evaluable for response, 23 (88.5%) had stable disease (SD) reported as their best response with a CBR of 88.5%. Target lesion shrinkage was observed in 10 (38%) patients. The median PFS for this cohort was 9 months (CI 5 – 16.5 months). Tumor marker data (Neuron Specific Enolase, Chromogranin A, 5-Hydroxyindoleacetic Acid, and Circulating Tumor Cells) will also be presented. **Conclusions:** PEN-221 appears well tolerated at 8.8 mg/m^2 q 3 weeks and has demonstrated efficacy exceeding its clinical efficacy goals with a CBR of 88.5% and a mPFS of 9 months. A randomized trial of PEN-221 in GI mid-gut NET patients is now in development. Clinical trial information: NCT02936323. Research Sponsor: Tarveda Therapeutics.

4111 **Poster Session**

Subgroup analysis by Ki-67 and baseline CgA of the randomized, placebo-controlled phase 3 study of surufatinib in advanced well-differentiated pancreatic neuroendocrine tumors (SANET-p). *First Author: Xianjun Yu, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: In the phase 3 SANET-p trial (NCT02589821), surufatinib significantly increased progression-free survival (PFS) compared with placebo in patients with progressive, well-differentiated (grade 1 or 2), advanced pancreatic neuroendocrine tumors (NETs). Here we report the relationship of Ki-67 and baseline Chromogranin A (CgA) on efficacy outcomes. **Methods:** A total of 172 patients with advanced pancreatic NETs were randomized to surufatinib or placebo in a 2:1 ratio. Investigator-assessed PFS and objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 were used for the analysis. The *post-hoc* subgroup analyses were performed on Ki-67 subcategory: $<$ 5% (n = 40 vs 21), 5-10% (n = 57 vs 31), $>$ 10% (n = 16 vs 7), and baseline CgA subcategory: $\leq$ 2 times of upper limit of normal (ULN) (n = 59 vs 31), $>$ 2 $\times$ ULN (n = 44 vs 24). **Results:** In the intent-to-treat population, surufatinib was superior to placebo, median PFS (mPFS) of 10.9 vs 3.7 months (mo) (p = 0.0011), with a stratified hazard ratio (HR) of 0.491 (95% confidence interval [CI]: 0.319, 0.755). mPFS was statistically significantly longer in the surufatinib arm versus that in the placebo arm in subgroups of Ki-67 5-10% (11.0 vs 3.7 mo, HR = 0.33, p= 0.0002), Ki-67 $>$ 10% (11.1 vs 2.8 mo, HR = 0.04, p = 0.0003) and CgA $>$ 2 $\times$ ULN (11.0 vs 3.7 mo, HR = 0.36, p = 0.0036). There was numerical PFS improvement with surufatinib compared to placebo in subgroup of Ki-67 $<$ 5% (9.3 vs 5.6 mo, HR = 0.91, p = 0.8015) and CgA $\leq$ 2 $\times$ ULN (9.4 vs 3.7 mo, HR = 0.61, p = 0.0809). ORRs in the subgroups of Ki-67 $<$ 5%, 5-10%, and $>$ 10% with surufatinib were 15.8%, 24.0% and 12.5% respectively. There was only one partial response in the placebo arm (with Ki-67 $<$ 5%). ORRs in the subgroups of CgA $\leq$ 2 $\times$ ULN and $>$ 2 $\times$ ULN with surufatinib were 18.9% and 21.4%, while also only one partial response in the placebo arm with CgA $\leq$ 2 $\times$ ULN. **Conclusions:** Surufatinib showed statistically significant and clinically meaningful improvement in PFS compared to placebo in patients with advanced, progressive, well-differentiated pancreatic NETs. From this exploratory analysis, surufatinib demonstrated benefit irrespective of Ki-67 expression levels or baseline CgA. Clinical trial information: NCT02589821. Research Sponsor: Hutchison MediPharma Limited.

4112 **Poster Session**

Final overall survival in the phase 3 NETTER-1 study of lutetium-177-DOTATATE in patients with midgut neuroendocrine tumors. *First Author: Jonathan R. Strosberg, Moffitt Cancer Center, Tampa, FL*

Background: As demonstrated in the primary analysis of the phase 3 NETTER-1 trial, ^{177}Lu-DOTATATE significantly prolonged progression-free survival (PFS) versus high-dose long-acting octreotide, with a HR of 0.18 (95% CI: 0.11, 0.29; p $<$ 0.0001), in patients with advanced, progressive, well-differentiated, somatostatin receptor-positive midgut neuroendocrine tumors (NETs). Here we report final overall survival (OS) for NETTER-1. **Methods:** In this international open-label trial, eligible patients were randomized to receive either four cycles of ^{177}Lu-DOTATATE 7.4 GBq (200 mCi) every 8 ± 1 weeks plus long-acting octreotide 30 mg or high-dose long-acting octreotide 60 mg every 4 weeks (control arm), both on top of best supportive care. After disease progression on randomized treatment or completion of an 18-month treatment period, patients in both arms entered long-term follow-up and could receive further anti-cancer treatment as recommended by their physicians. The primary endpoint was PFS per RECIST 1.1 and OS was a key secondary endpoint. Primary intention-to-treat analysis of OS was prespecified to take place after 158 deaths or 5 years after the last patient was randomized, whichever occurred first. **Results:** Of 231 randomized patients, 101/117 (86.3%) in the ^{177}Lu-DOTATATE arm and 99/114 (86.8%) in the control arm entered long-term follow-up. Final analysis occurred 5 years after the last patient was randomized, following 142 deaths, with a median follow-up of more than 76 months. During long-term follow-up, 41/114 (36%) of patients in the control arm received subsequent radioligand therapy (cross-over), the majority (22.8%) within 24 months. Median OS was 48.0 months (95% CI: 37.4, 55.2) in the ^{177}Lu-DOTATATE arm and 36.3 months (95% CI: 25.9, 51.7) in the control arm. HR was 0.84 (95% CI: 0.60, 1.17) with p = 0.30 (unstratified 2-sided log-rank test). A total of 2/112 (1.8%) ^{177}Lu-DOTATATE treated patients in the study developed myelodysplastic syndrome (MDS). No new cases of MDS or acute leukemia were reported in the long-term follow-up. Overall, no new safety signals emerged during long-term follow-up. **Conclusions:** Median OS was 48.0 months in the ^{177}Lu-DOTATATE arm of the NETTER-1 trial and 36.3 months in the control arm. This difference was not statistically significant, potentially impacted by a high rate (36%) of cross-over of patients in the control arm to radioligand therapy after progression. In overall conclusion, the NETTER-1 study demonstrated that ^{177}Lu-DOTATATE yielded a clinically and statistically significant improvement in PFS as a primary endpoint (HR: 0.18, p $<$ 0.0001) as well as a clinically meaningful trend towards improvement in median OS of 11.7 months. No new safety signals emerged during the 5-year long-term follow-up. Clinical trial information: NCT01578239. Research Sponsor: Advanced Accelerator Applications, a Novartis Company.

4113 **Poster Session**

Plasma biomarker study of lenvatinib in gastroenteropancreatic neuroendocrine tumors reveals Ang2 and FGF2 as predictors of treatment response: Results from the international phase II TALENT trial (GETNE 1509). *First Author: Jaume Capdevila, Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain*

Background: Predictive biomarkers of response to antiangiogenics currently remain elusive, with several molecules discovered but not fully validated nor clinically applied. TALENT trial is a multicenter prospective phase II study of lenvatinib, a VEGFR1-3 and FGFR1-4 multikinase inhibitor (MKI), in advanced G1/G2 neuroendocrine tumors (NETs) from pancreatic (panNETs) and gastrointestinal (giNETs) origins, which has reported the highest overall response rate (ORR) by central radiology assessment with a MKI in this setting. Here we report the plasma biomarker study. **Methods:** Proangiogenic profiling of plasma samples from patients included in the trial were analyzed by multiplex ELISA (custom made Quantibody Array, RayBiotech). Quantitative determinations of VEGF-A, FGF2, FGF4, Ang2, IL8, PlGF, VEGF-C, VEGF-D and VEGFR2 were obtained from 85 samples of sufficient quality (out of 111 patients included in the study). Association and prediction of response were evaluated for each biomarker and correlated with PFS, OS and ORR in all patients and the different subgroups included in the trial. **Results:** While none of the factors were able to discriminate PFS or OS in the whole population, a significant association of high-Ang2 and low-FGF2 to ORR was observed. Subgroup analysis confirmed this association in the two cohorts of patients, giNETs (p = 0.003) and panNETs (p = 0.024). In the panNET cohort, prior targeted therapy was mandatory. Prior sunitinib exposure was observed in 8 patients. Of the factors studied, Ang2 and VEGFR2 were significantly decreased in plasma from sunitinib-pretreated patients (-73% p = 0.022 and -62% p = 0.042 respectively). Furthermore, in these sunitinib-pretreated patients Ang-2 and VEGFR2 levels associated to ORR (p = 0.029 and p = 0.029 respectively) and were able to discriminate PFS (log rank p = 0.027 and 0.007 respectively). ROC curve analysis defined Ang2 and VEGFR2 plasma levels with optimal predictive power to be 415pg/ml and 1770pg/ml respectively (p = 0.021). **Conclusions:** Plasma proangiogenic profiling of TALENT patient samples unraveled high-Ang2 and low-FGF2 as predictive biomarkers of response to lenvatinib in both cohorts. In antiangiogenic-pretreated patients, Ang2 and VEGFR2 levels significantly predict response to treatment in panNETs. Importantly, current studies with MKIs should confirm the value of these markers for advanced NETs not only to predict response, but also to stablish sequential treatment options for these patients. Research Sponsor: EISAI.

4114 **Poster Session**

Interim analysis results of surufatinib in U.S. patients with neuroendocrine tumors (NETs). *First Author: Andrew Scott Paulson, Texas Oncology/The US Oncology Network, Dallas, TX*

Background: Surufatinib (S) is a targeted inhibitor of tyrosine kinases VEGFR1, 2, and 3; FGFR1; and CSF-1R. A manageable safety profile and statistically significant efficacy of S have previously been demonstrated in patients (pts) with advanced NETs of extrapancreatic (epNET) and pancreatic (pNET) origin in 2 phase 3 randomized trials conducted in China (SANET-ep, NCT02588170; SANET-p, NCT02589821). Pts with epNETs achieved a median progression free survival (PFS) of 9.2 v 3.8 months (mo) (hazard ratio [HR] 0.334; $p < 0.0001$), and pts with pNETs achieved a median PFS of 10.9 v 3.7 mo (HR 0.491; $p = 0.0011$), with S v placebo, respectively. S has recently been approved for the treatment (tx) of pts with epNETs in China. **Methods:** A phase 1, dose escalation (ESC)/expansion (EXP) trial was conducted to evaluate and confirm the efficacy and safety of S in US pts. ESC was completed, and the maximum tolerated dose and recommend phase 2 dose were determined to be 300 mg, same as previous trials. The EXP completed enrollment of the epNET and pNET cohorts, and the primary endpoint was investigator-assessed PFS rate at 11 mo. Secondary objectives included assessment of safety and PK. **Results:** 32 pts with heavily pretreated progressive NETs (16 epNET and pNET each) were enrolled in the dose EXP. The median age was 62.2 years (44-75) and 64.4 years (39-72) for epNET and pNET pts, respectively. 65.6% of pts received ≥3 prior lines of tx (median lines of therapy: epNET: 2 [2-5]; pNET: 4 [1-8]), and all pts previously received everolimus and/or sunitinib. As of the data cutoff of 30-Jun-20, 7 pts remained on tx (4 epNET; 3 pNET). The median number of tx cycles was 8.0 (2, 15) for epNET and 8.5 (2, 23) for pNET pts. The PFS rate at 11 mo was 51.1% (95% confidence interval [CI]: 12.8, 80.3) for pts with epNETs and 57.4% (95% CI: 28.7, 78.2) for pts with pNETs. The observed mPFS was 11.50 mo (95% CI: 6.47, 11.50) and 15.18 mo (95% CI: 5.19, NR) for pts with epNETs and pNETs, respectively. An objective response rate (ORR) of 6.3% was observed for pts with epNETs and 18.8% for pts with pNETs. A disease control rate of 90.6% (95% CI: 75.0, 98.0) was observed for all NET pts (93.8% epNET; 87.5% pNET). The safety profile of S remains consistent with previously completed trials. All pts (n = 32) had reported at least 1 adverse event (AE), and 24 pts (75%) reported AEs ≥grade 3. The most common AEs of any grade reported were fatigue (46.9%), hypertension (43.8%), proteinuria (37.5%), diarrhea (34.4%), vomiting (28.1%), and nausea (25.0%). The most commonly reported AEs ≥grade 3 (> 5%) were hypertension (37.5%); diarrhea (9.4%); and proteinuria, dysphagia, and anemia (6.3% each). AEs leading to tx discontinuation occurred in 21.9% of pts. **Conclusions:** S has demonstrated antitumor activity in heavily pretreated US pts with progressive NETs with a manageable safety profile that is consistent with 2 completed phase 3 studies. S continues to be studied in other ongoing clinical trials globally. Clinical trial information: NCT02549937. Research Sponsor: Hutchison MediPharma Limited.

4115 **Poster Session**

Phase I study of autolytic immunotherapy of metastatic neuroendocrine tumors using intralesional rose bengal disodium. *First Author: Timothy Jay Price, Queen Elizabeth Hospital, University of Adelaide, Adelaide, Australia*

Background: Metastatic neuroendocrine neoplasms (mNEN) originating in the gastrointestinal tract are frequently slow growing yet both symptom and disease control remain important. Treatment options include resection, systemic somatostatin analogues (SSA), and systemic peptide receptor radionuclide therapy (PRRT). Additional options are needed; we have explored intralesional (IL) rose bengal disodium (PV-10), an investigational autolytic immunotherapy that can yield immunogenic cell death and disease-specific functional adaptive immunity. **Methods:** This phase 1 study evaluated safety, tolerability and impact on symptoms and biochemical markers resulting from IL PV-10 administered percutaneously to hepatic lesions in patients (pts) with progressive mNEN not amenable to resection or other potentially curative therapy. Eligible lesion(s) were 1.0 - 3.9 cm in longest diameter with amount of PV-10 administered proportional to size. Cohort 1 (n = 6 pts) received PV-10 to a single lesion per treatment cycle; Cohort 2 (n = 6) could receive injection to multiple lesions per treatment cycle. Pts could receive further PV-10 ≥6 weeks after prior injection. The primary endpoint was safety. Secondary endpoints included objective response rate (ORR) assessed by contrast enhanced CT (RECIST 1.1) and 68Ga-DOTATATE PET, biochemical response (CgA) and patient-reported outcome (EORTC QLQ-C30 and GI. NET21 QOL instruments). **Results:** Twelve pts were enrolled, 50% male, median age 66 yrs (range 47-79). Primary sites: 7 small bowel, 2 pancreas, 1 caecal, 2 unknown; grade: Gd1 = 5, Gd2 = 7. All pts had received SSA and PRRT as part of previous therapy and all had symptomatic, progressive disease. Median CgA was 1585 (range 35-10370). One lesion was injected per cycle for all 12 pts; none were suitable for multiple injections. One pt received 4 sequential PV-10 treatment cycles, 3 received 2 cycles, and 8 received 1 cycle. Toxicity was consistent with experience in other hepatic malignancies: post-procedure pain was reported by most pts; grade 3 photosensitivity reaction occurred in 1 pt; and grade 1 elevation of hepatic enzymes attributed to PV-10 occurred in 2 pts, resolving by day 7. Additionally, carcinoid flare occurred in 1 pt. ORR of injected lesions was 42%; patient-level disease control was 84%. Estimated PFS was 9.2 months; median OS was 22.5 months. CgA remained stable in 10 pts and upregulation of NK and activated CD4+ T lymphocytes was observed post-injection. QOL data at months 1 and 3 showed stable or improved carcinoid symptoms and global health status in 9 pts. **Conclusions:** PV-10 elicited no safety concerns with encouraging evidence of both local and systemic disease and symptom control in a heavily pre-treated population. Multiple cycles were delivered safely in suitable patients. Adaptive immune upregulation is consistent with other solid tumors and supports potential systemic benefit. Clinical trial information: NCT02693067. Research Sponsor: Provectus.

4116 **Poster Session**

Efficacy and safety of ^{177}Lu-DOTATATE in patients (pts) with advanced pancreatic neuroendocrine tumors (pNETs): Data from the NETTER-R international, retrospective registry. *First Author: Dominique Clement, King's College Hospital, London, United Kingdom*

Background: Peptide receptor radionuclide therapy with ^{177}Lu-DOTATATE is indicated in somatostatin receptor (SSTR)-positive gastroenteropancreatic neuroendocrine tumours. The NETTER-R registry builds upon the existing evidence for pts with advanced pNETs, who have limited therapeutic options. **Methods:** NETTER-R is a retrospective registry of pts with unresectable or metastatic, well-differentiated, SSTR-positive, progressive pNETs treated with ^{177}Lu-DOTATATE in the UK, France and Spain. Pts who received ≥1 administration of ^{177}Lu-DOTATATE were included. The primary endpoint was progression-free survival (PFS) based on RECIST v1.1. Secondary endpoints included overall survival (OS), safety and tumour response. **Results:** A total of 110 pts with pNETs were identified. Median age was 58.0 years (range 28–89) and 52.7% were male. At baseline, 96.4% of pts had progressive disease. The Ki-67 index was ≤2% in 23.6%, 3–20% in 66.4% and >20% in 2.7% of pts (7.3% missing). Metastases were present in the liver in 95.5% and bone in 29.1% of pts. Nearly all pts (90.9%) had received at least one prior anticancer therapy (somatostatin analogues: 70.0%, chemotherapy: 61.8%, protein kinase inhibitors: 38.2%). The majority of pts (70.0%) received all four scheduled cycles of ^{177}Lu-DOTATATE. The cumulative activity was 26.6–32.6 GBq in 65.5% of pts (<26.6 GBq: 31.8%, ≥32.6 GBq: 2.7%). 12 pts were re-treated after disease progression and received 1–4 additional cycles of ^{177}Lu-DOTATATE. By RECIST v1.1, evaluable in 62 pts, median PFS was 24.8 months (95% CI 17.5–34.5) and objective response rate was 40.3% (95% CI 28.1–53.6); all responses were partial. The response rate, including radiological, clinical, metabolic and biomarker assessments, evaluable in 100 pts, was 54.0% (95% CI 43.7–64.0), including 2 pts with complete response. Over a median follow-up of 24.5 months (range 2.0–123.4), median OS in 110 pts was 41.4 months (95% CI 28.6–50.2). 71.8% (n=79/110) of pts had at least one treatment-emergent adverse event (TEAE). The most frequent were nausea (28.2%) and fatigue (22.7%), predominantly grade 1/2 in severity. No TEAEs led to treatment discontinuation. Grade 3 anaemia and lymphopenia occurred in 1 (0.9%) and 4 (3.6%) pts, respectively. No grade ≥3 thrombocytopenia or neutropenia were reported. Renal TEAEs occurred in 6 pts (5.5%; grade 1: n=1, grade 2: n=2, grade 3: n=3). Grade 3 renal events were transient (≤24 days) and did not lead to treatment modification. No acute leukaemia or myelodysplastic syndrome were reported within the follow-up. **Conclusions:** In a real-world population of pts with advanced pNETs, ^{177}Lu-DOTATATE was well tolerated with a safety profile consistent with the NETTER-1 trial. With limited follow-up, the OS and PFS compared favourably with cohorts of progressive pNET patients treated with other systemic agents. Research Sponsor: Advanced Accelerator Applications, a Novartis Company.

4117 **Poster Session**

Phase I dose-escalation study of AlphaMedix for targeted-alpha-emitter therapy of PRRT-naive neuroendocrine patients. *First Author: Ebrahim Delpassand, Excel Diagnostics and Nuclear Oncology Center, Houston, TX*

Background: Peptide-receptor-radioligand-therapy (PRRT) has been shown to increase the progression-free-survival (PFS) of neuroendocrine patients, however the objective response rate is rather low. The targeted-alpha-emitter therapy (TAT) of NETs can increase the ORR and induce partial or complete tumor response. In this abstract, we present results of the safety and efficacy of AlphaMedix (^{212}Pb-DOTAMTATE) done in PRRT-nave patients with SSTR-expressing NETs (FDA IND 135150). **Methods:** The phase 1 dose escalation study (IND 135150) was designed according to a 3+3 dose-escalation scheme (30% increase of the dose in each subsequent cohort). We enrolled PRRT nave subjects with biopsy-proven unresectable or metastatic SSTR-expressing NETs from different primary sites (midgut, rectal, pancreas, and lung) with at least one measurable lesion. Response to treatment was measured per RECIST 1.1 criteria and the effect on quality of life was measured with the EORTC-QLQ-C30 QOL questionnaire. **Results:** A total of 20 PRRT nave subjects (10 men and 10 women; median age 60 (range 27-80)) have been treated to date. 10 subjects in MAD4 cohort received at least three cycles of ^{212}Pb-DOTAMTATE at the highest dose level of 67.6 μCi/kg/cycle. Of these, 6/10 subjects (60%) have completed all four-cycles of treatment. Radiographic evaluation of these six-MAD4 patients reveal an ORR in 5 out of 6 subjects (83.3%) per RECIST 1.1 criteria (1CR, 4PR, 1SD) in addition to a 100% response according to ^{68}Ga-DOTATATE-PET/CT-imaging, defined as complete resolution of SSTR-positive lesions (CR) or Partial Response (PR) defined as resolution of most active lesions or substantially decreased SUV (>25%). No progression of disease was noted in the first six subjects enrolled in the MAD4 cohort who have completed treatment. All six-patients have 100% PFS up to 22 months (for the first 3-subjects in MAD4) and up to 19 months (next 3-patients). Except for mild-to-moderate, reversible hair loss, there were no other clinically significant drug related AE, or SAE**.** The most frequent AEs of any grade (> 4 subjects) reported include fatigue (35%), hyperglycemia (30%), lymphopenia (30%) alopecia (30%), and diarrhea (20%). Five grade 3 AEs were reported (back pain, dysarthria, dyspnea, acute kidney injury), no grade 4 AEs, and one grade 5 AE was reported. There was a significant improvement in the quality of life, reduction of pain, shortness of breath in the majority of subjects, with increase of energy. **Conclusions:** This F-I-H clinical study of AlphaMedix shows that PRRT with ^{212}Pb is feasible, well tolerated, and provides substantial reduction in tumor burden to patients with unresectable, metastatic SSTR-expressing NETs. Dramatic improvement in tumor burden and a positive impact on quality of life were seen in all of the PRRT nave subjects who AlphaMedix at the highest dose tested. Clinical trial information: NCT03466216. Research Sponsor: U.S. National Institutes of Health, companies own funds.

4118 **Poster Session**

Clinical impact of pathogenic germline variants in pancreatic cancer: Results from a multicenter prospective universal genetic testing study. *First Author: Pedro Luiz Serrano Uson Junior, Mayo Clinic, Phoenix, Brazil*

Background: Germline variations in cancer susceptibility genes have important implications on treatment and family counseling in pancreatic cancer (PC). We report the prevalence and clinical outcomes of unselected PC patients with pathogenic germline variants (PGV) detected using a universal testing approach. **Methods:** We undertook a prospective multi-site study of germline sequencing using an >80 gene next-generation sequencing platform among 250 PC patients (not selected for age or family cancer history) between April 1, 2018 and March 31, 2020. Demographic, tumor characteristics and clinical outcomes were compared between PGV carriers and non-carriers. **Results:** Of 250 patients, the mean age was 65 years (SD 8.7), 56% were male, 83.6% were white and 65.6% had advanced disease (Stage III and IV). PGV were found in 15.2% (N=38) of patients, two patients had more than one PGV. Variants of uncertain significance were found in 44.4% (N=111). Family history of cancer (OR 2.36, 95% CI: 1.14-5.19, p=0.025) was associated with a higher risk of PGV. In a median follow up of 16.5 months, median overall survival was 16.8 months in PGV carriers compared with 16.5 months in non-carriers (HR 0.51, 95 %CI, 0.25-1.01, p=0.05). Higher levels of CA 19-9 and advanced stages (III and IV) were associated with worse outcomes in both groups. Overall, 68% of PGV carriers had mutations in homologous recombination repair (HRR) genes, including *BRCA1, BRCA2, PALB2, ATM, CHEK2, NBN, RAD51C.* In 65% of HRR gene carrier's systemic therapy with platinum was used. **Conclusions:** Universal multi-gene panel testing in pancreatic cancer reveals that 1 in 6 patients are carriers of PGV and is associated with improved survival. Multi-gene germline testing should be used to aid in treatment selection, prognostication, and familial cancer counseling. Distribution of the 40 PGV by penetrance status. Research Sponsor: Mayo Practice Transformation Grant, Mayo Clinic Center for Individualized Medicine.

	PGV	Total (n=40)
High Penetrance	BRCA1	1 (2.5%)
	BRCA2	9 (22.5%)
	CDKN2A	1 (2.5%)
	MSH6	1 (2.5%)
	PALB2	2 (5.0%)
	SDHA	2 (5.0%)
	TP53	1 (2.5%)
Moderate Penetrance	ATM	7 (17.5%)
	CHEK2	4 (10.0%)
	HOXB13	1 (2.5%)
	NBN	2 (5.0%)
	RAD51C	1 (2.5%)
Low Penetrance	APC (I1307K)	1 (2.5%)
	MUTYH-monoallelic	3 (7.5%)
Recessive	FH	1 (2.5%)
	MSH3	1 (2.5%)
	NTHL1	2 (5.0%)

4119 **Poster Session**

Modified FOLFIRINOX versus S-1 as second-line chemotherapy in patients with gemcitabine-failed metastatic pancreatic cancer: A randomized phase III trial (MPACA-3). *First Author: Se-Il Go, Division of Hematology/Oncology, Department of Internal Medicine, Gyeongsang National University Changwon Hospital, Gyeongsang National University College of Medicine, Changwon, South Korea*

Background: Modified FOLFIRINOX (mFOLFIRINOX) consisting of 5-fluorouracil/leucovorin, irinotecan, and oxaliplatin has been assessed as second-line treatment of patients with advanced pancreatic cancer in retrospective and phase II studies. However, the result was not confirmed by randomized controlled trial. **Methods:** A randomized, open-label, phase III trial was conducted at 9 institutions in Korea. Patients with metastatic pancreatic adenocarcinoma (mPAC) and Eastern Cooperative Oncology Group performance status of 0-1 who failed to first-line gemcitabine-based chemotherapy were randomly assigned to receive mFOLFIRINOX or S-1. The primary endpoint was overall survival. **Results:** A total of 80 patients were enrolled from March 2017 to December 2019. The accrual of patients was early terminated due to clear difference of efficacy in the interim analysis and expectation of poor recruitment due to conflicting adjuvant regimens. Objective response and disease control rates were 15.4% vs. 2.4% (p= 0.041) and 66.7% vs. 36.6% (p= 0.007) in the mFOLFIRINOX and S-1 arms, respectively. The median progression-free survival was 5.2 and 2.2 months in the mFOLFIRINOX and S-1 arms, respectively (p= 0.002). The median overall survival was 9.2 and 4.9 months in the mFOLFIRINOX and S-1 arms, respectively (p= 0.048). The adjusted hazard ratio of the mFOLFIRINOX arm to the S-1 arm for overall survival was 0.402 (95% confidence interval 0.223-0.725, p= 0.002). All grade 3-4 adverse events occurred in 56.5% and 17.1% in the mFOLFIRINOX and S-1 arms, respectively ($p< 0.001$). However, only one patient in each arm prematurely discontinued treatment due to toxicity and there was no treatment-related mortality in both arms. Minimally important differences in the health-related quality of life were not observed in both arms. **Conclusions:** mFOLFIRINOX as second-line treatment in mPAC patients failed to gemcitabine-based chemotherapy demonstrated a survival benefit versus S-1 alone with acceptable toxicities. Clinical trial information: KCT0003534. Research Sponsor: None.

4120 **Poster Session**

A phase I/IIa trial of the RNA oligonucleotide STNM01 by EUS-FNI to investigate the safety and efficacy in patients with first-line refractory, unresectable pancreatic cancer. *First Author: Takayoshi Tsuchiya, Department of Gastroenterology and Hepatology, Tokyo Medical University, Tokyo, Japan*

Background: Carbohydrate sulfotransferase 15 (CHST15) is an enzyme that synthesizes heavily sulfated matrix glycosaminoglycan and shown to promote tumor invasion and correlate with poor prognosis in pancreatic ductal adenocarcinoma (PDAC). To explore the role of CHST15 blockage, we conducted a Phase I/IIa (P I/IIa) study to investigate the safety and efficacy of EUS guided locoregional injection of STNM01, a synthetic RNA oligonucleotide, in patients with unresectable PDAC, refractory to first-line chemotherapy. **Methods:** This was an open-label and dose-escalation study of STNM01 as second-line (2L) therapy in unresectable PDAC patients at 4 centers in Japan. One cycle consists of locoregional injection with STNM01 three times at 2 week-interval in 4 weeks (Days 0, 14 and 28 of dosing) in combination with systemic 2L chemotherapy. A 3+3 dose cohort escalation design initiated with 250 nM (n = 3) followed by 1,000 nM (n = 3), 2,500 nM (n = 3) and 10,000 nM (n = 4) was used for P I part. P IIa part (n = 9) was subsequently conducted with MTD or the highest dose level determined by P I. The primary outcome was incidence of DLT at the end of cycle 1. The secondary outcomes included overall survival (OS), local tumor response, histology and safety. This study was registered with jRCT (jRCT2031190055). **Results:** A total of 22 patients across 4 doses were enrolled in the study of which 21 were evaluable as per protocol population. All patients received S-1 as a systemic 2L chemotherapy and total 3 cycles were repeated at maximum. The most common AEs were abdominal pain and pyrexia. There were 9 grade 3 AEs. No drug-related SAE as well as DLT was observed. Since MTD was not reached in P I, P IIa was conducted with the highest dose, 10,000 nM. The 6-month survival rate in the entire population (n = 21) and in the highest dose population (n = 12; 3 for P I and 9 for P IIa) was 66.7 and 83.3%, respectively. In histological analyses, the % positive area of CHST15 tended to show dose-dependent suppression at the end of cycle 1, especially with 70.0% reduction from baseline in the highest dose population. Increased tumoral infiltrations of $CD3^+$, $CD8^+$ and $CD20^+$ cells were observed during study period in the highest dose population. Local tumor response for the entire population showed 14 patients (66.7%) with stable disease. Notably, one patient showed complete disappearance on the CT image of both primary and metastatic tumors in the regional lymph node. **Conclusions:** Repeated locoregional injection of STNM01 is safe and well tolerated in patients with unresectable PDAC as combined 2L therapy. The 6-month survival rate of 10,000 nM of STNM01 was 83.3%, which is remarkable compared with previously reported data. Unexpected mode of action for tumoral lymphocyte infiltration also suggests the promising potential of locoregional injection of STNM01 as a new therapeutic option for PDAC. Clinical trial information: jRCT2031190055. Research Sponsor: Japan Agency for Medical Research and Development.

4121 **Poster Session**

Genomic profiling of *KRAS* wide-type pancreatic ductal adenocarcinomas identifies targetable genetic alterations. *First Author: Deng Wei, Department of General Surgery, Beijing Friendship Hospital;Capital Medical University;Beijing Key Laboratory of Cancer Invasion and Metastasis Research & National Clinical Research Center for Digestive Diseases, Beijing, China*

Background: Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal cancers and the 5-year survival of PDAC patients is below 10%. The oncogenic *KRAS*mutations account for about 90% of PDAC cases. Unfortunately, there is no FDA-approved targeted therapy for *KRAS* mutations. Therefore, the genomic profiling of *KRAS* wide-type PDACs can provide invaluable sights to the etiology of these patients and offer them the opportunity of precision therapy trials. **Methods:** To characterize actionable targets in 521 Chinese PDAC patients, deep sequencing of a 831-gene panel (OncoPanscan, Genetronhealth) was applied to assess somatic mutations of their tumor tissues including SNV, insertions/deletions, CNV and re-arrangements, as well as possible pathogenic germline variants of paired genomic DNA sample. **Results:** There were 89% (463/521) of patients in our PDAC cohort harbored *KRAS* mutations. Among the remaining 58 patients in *KRAS* wild-type subgroup, 33% (19/58) carried activating mutations in the RTK/Ras/MAPK pathway. Targetable *BRAF* mutations were seen in five (9%) patients: V600E (1/5), G464V (1/5), N486_P490del (2/5) and BRAF fusion (1/5). The frequency of *BRAF* mutations was 9% (5/58) in *KRAS* wild-type PDACs but only 0.4% (2/463) in *KRAS*-mutated PDACs ($P < 0.001$). We found one classic EGFR activing mutation (L747_A750delinsP) and one MAP2K1 activating mutation (F53_Q58delinsL), which can be targeted by EGFR-TKIs and MEK inhibitor trametinib, respectively. An oncogenic *ERBB3* mutation (V104L) was seen in one patient, who was eligible for HER2-targeted therapy clinical trials. We also found *STK11/TSC2* inactivating mutations and a dominant-negative mutation of *PTEN* (R130Q) which could be targeted by mTOR inhibitor everolimus and AKT inhibitor capivasertib, respectively. Additionally, we observed a patient with high level amplification of *MET* and another patient with the *NCOA4-RET* fusion gene which can be targeted by MET inhibitor carbozantinib. Interestingly, we also identified two patients with inactivating mutations in *ELF3* (one frameshift and one in splicing-site), which is a driver gene of ampullary carcinoma. Lastly, two patients carried deleterious germline mutations in *BRCA1* and *PALB2*, which may be targeted with PARP inhibitors. Overall, at least 29% (17/58) *KRAS* wide-type patients harbored potentially actionable genomic alterations to currently used anticancer drugs. **Conclusions:** The mutational landscape of our PDAC cohort provided compelling evidence that targetable driver mutations accounted for a significant portion of *KRAS* wide-type tumors. Our findings demonstrated that genomic profiling of PDAC patients can enable physicians to optimize their clinical management and enroll them into genomically matched clinical trials. Research Sponsor: None.

4122 **Poster Session**

Baseline level and early on-treatment clearance of circulating mutant *KRAS* in metastatic pancreatic ductal adenocarcinoma treated with chemotherapy with or without immunotherapy. *First Author: Jacob E. Till, University of Pennsylvania Abramson Cancer Center, Philadelphia, PA*

Background: Traditional imaging-guided therapeutic decision-making for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC) may lag and, on occasion, be misleading. The concept of liquid biopsy-based molecular response holds promise for proximate and accurate therapy monitoring and assessment of emerging resistance to therapy. Here we investigate the association between baseline (pre-treatment) level and early, on-treatment changes in plasma circulating cell-free DNA (ccfDNA) mutant *KRAS* (ctKRAS) with progression-free survival (PFS) and overall survival (OS) in mPDAC. **Methods:** 189 plasma samples were analyzed from 123 total patients with mPDAC. An initial cohort included 54 patients treated at the University of Pennsylvania who received first-line standard of care (SOC) regimens and had a baseline plasma sample. Of these, 21 also had an on-therapy sample collected at ~8 weeks. We also analyzed an independent cohort of 69 patients enrolled in the PRINCE trial (NCT03214250) who had a baseline sample, of which 45 also had an on-treatment sample at ~8 weeks. PRINCE trial patients received gemcitabine/nab-paclitaxel with immunotherapy (I/O) agents (APX005M and/or nivolumab). ctKRAS variant allele fraction (VAF) was quantified by droplet digital PCR on pre-amplified ccfDNA. Baseline ctKRAS was dichotomized at 5% VAF. ctKRAS clearance was defined as detectable ctKRAS at baseline followed by ctKRAS becoming undetectable in the on-treatment sample. **Results:** Baseline ctKRAS (above/below 5% VAF) and ctKRAS clearance were associated with PFS and OS in both cohorts (Table). Further, in a multivariate cox regression model, ctKRAS clearance associated with improved PFS (HR 3.8, 1.4-10.9 or 3.6, 1.8-7.2) in both the SOC and I/O cohorts, respectively, and OS in the SOC cohort (HR 5.5, 1.5-20.8) after adjusting for baseline VAF. **Conclusions:** Baseline ctKRAS is significantly associated with OS and PFS in mPDAC in both independent cohorts. Further, early on-treatment ctKRAS clearance is strongly associated with improved PFS and OS, independent of baseline ctKRAS VAF. These data strongly support further investigation of ccfDNA as a biomarker of response and resistance to therapy. Research Sponsor: Parker Institute for Cancer Immunotherapy (PICI), Other Foundation, Pharmaceutical/Biotech Company, U.S. National Institutes of Health, Penn Pancreatic Cancer Research Center (PCRC).

Association of baseline and early on-treatment clearance of ctKRAS with PFS and OS. Cox Regression Hazard Ratios (HR) with 95% confidence intervals (CI) and log-rank P-values are presented.

ctKRAS	Cohort	N	PFS HR (CI); Log-rank P-value	OS HR (CI); Log-rank P-value
Baseline	SOC	54	2.5 (1.3-4.6); p=0.004	2.9 (1.5-5.7); p=0.001
Baseline	I/O	69	1.7 (1.0-3.0); p=0.04	2.4 (1.4-4.2); p=0.0002
Clearance	SOC	21	3.4 (1.2-9.4); p=0.01	5.6 (1.5-20.3); p=0.004
Clearance	I/O	45	3.3 (1.6-7.0); p=0.0009	2.2 (1.1-4.6); p=0.03

4123 **Poster Session**

Gemcitabine plus nab-paclitaxel versus gemcitabine alone in elderly patients aged 76 years or older with unresectable pancreatic cancer: A propensity score-matched multicenter prospective observational study. *First Author: Satoshi Kobayashi, Department of Gastroenterology, Hepatobiliary and Pancreatic Medical Oncology Division, Kanagawa Cancer Center, Yokohama, Japan*

Background: Gemcitabine plus nab-paclitaxel (GN) demonstrated a significant improvement of OS over gemcitabine alone (G) in the MPACT trial for metastatic pancreatic cancer. However, since patients aged 75 years or older was less than 10% in the trial, data for the efficacy and safety of GN in that population have been limited. **Methods:** We prospectively enrolled patients who were 76 years or older if they had pathologically proven, clinically unresectable pancreatic cancer and no prior history of chemotherapy. Treatment regimen was based on physicians' choice. The primary endpoint was OS and secondary endpoints included PFS, objective response, and safety. Geriatric assessments including G8, IADL, CCI and Mini-COG were performed at the time of registration and 3 months after. To adjust confounding factors in the comparison of GN and G, propensity score-matched analyses were performed. **Results:** We enrolled 233 eligible patients from 55 centers in Japan between September 2018 and September 2019. GN, G, other therapy, and BSC were administered to 116, 72, 29 and 16 patients, respectively. With propensity scores adjusted for age, sex, clinical stage, ECOG PS, CA19-9, and neutrophil-lymphocyte ratio, 42 patients each in GN and G were compared. Patients characteristics in the matched pair were well-balanced; median age, 79/79 years; ECOG PS 0, 43/36%; stage IV, 69%/64%. With a median follow-up of 14.8 months and 50 observed deaths, OS in GN showed a longer tendency than that in G: 12.2 vs. 9.4 months in median with a hazard ratio (HR) of 0.65 (95% CI, 0.37-1.13; p= 0.120). PFS in GN was significantly longer than that in G: 9.2 vs. 3.7 months in median with a HR of 0.38 (95% CI, 0.23-0.64; p= 0.0002). The objective response rates were 29% and 11% (p= 0.082), and the disease control rates were 81% and 61% (p= 0.088), respectively. Decline of G8 scores at 3 months was observed in 35% and 28% of patients in GN and G, respectively (p= 0.610), and that in IADL scores was observed in 61% and 37%, respectively (p = 0.194). GN had higher incidence of adverse events than G though all were not statistically significant: grade 4 neutropenia (23%/8%); grade 3-4 malaise (13%/8%), fatigue (15 %/10%), peripheral sensory neuropathy (5%/0%). The incidence of the other adverse events was comparable between GN and G: grade 4 leucopenia (3%/5%) and thrombocytopenia (0%/3%); grade 3-4 nausea (3%/5%), vomit (3%/5%) and febrile neutropenia (0%/0%). Treatment discontinuation due to adverse events was more often in GN than G (39%/14%). **Conclusions:** Our data suggests GN is more efficacious than G even in patients aged 76 years or older, although GN have higher incidence of grade 3-4 adverse events and tends to decrease geriatric assessment scores. Clinical trial information: UMIN000034265. Research Sponsor: Pancreas Research Foundation of Japan.

4124 **Poster Session**

Genomic alterations for novel targeted therapies in pancreatobiliary cancers from real-world data. *First Author: Kumiko Umemoto, St. Marianna University School of Medicine, Kawasaki, Japan*

Background: Cancers of the pancreas and biliary tract remain one of the unfavorable malignant tumors with few driver genomic alterations. Tumor-agnostic approaches are promising for cancers with poor prognosis, with some potentially actionable alterations, such as *BRCA1/2* mutations, *ERBB2* amplification, MSI-High, or tumor mutational burden (TMB)-High. However, co-existing alterations, clinical significance of other genomic alterations, or frequency of alterations by clinical and genomic background are unclear. Here we investigated the genomic profile in a large cohort of advanced pancreatobiliary cancers to help refine and discover new targets for improved cancer therapies. **Methods:** Comprehensive genomic profiling was performed at Foundation Medicine, on patients with RWD tested during the course of routine clinical care. Hybrid capture was carried out on up to 395 cancer-related genes and select introns from up to 31 genes frequently rearranged in cancer. 16,913 pancreatic cancer (PC) patients and 3,031 biliary tract cancer (BTC) patients were available for analyses and were stratified by age ($\geq$40/ $<$ 40), MSI status, TMB status (High $\geq$10/Low $<$ 10 Muts/Mb), and select gene alterations. Using a chi-square test with Yate's correction, frequencies of genetic alterations were analyzed according to clinical or genomic background. **Results:** *KRAS* (84.8%), *TP53* (73.3%), *CDKN2A* (51.2%), *CDKN2B* (26.5%), and *SMAD4* (23.2%) were frequently altered in PC patients, versus *TP53* (60.6%), *CDKN2A* (33.5%), *KRAS* (27.1%), *CDKN2B* (20.6%) and *SMAD4* (16.9%) in BTC patients. The frequency of MSI-High and TMB-High in BTC was 1.2% and 5.7%, respectively, while these were lower in PC (0.48% and 2.1%, respectively). In PC patients, the *KRAS* alteration rate was significantly lower in both MSI-High (57.3%, $P<$ 0.001) and TMB-High populations (51.3%, $P<$ 0.001). In BTC patients, the rate of *ERBB2* amplification was 6.4% in TMB-High and 8.6% in TMB-Low population. Interestingly, *CDK12* rearrangement was observed in BTC patients with *ERBB2* amplified tumors but not in those without *ERBB2* amplified tumors. In patients of pediatric/adolescents and young adults ($<$ 40 years old), the mutation rate of *KRAS*/*TP53*/*CDKN2A*/*SMAD4* was lower, and *FGFR2* rearrangement (4%) was observed in PC patients; *GATA6* amplification (11.1%) and rearrangement of *BRAF* (2.8%), *FGFR2* (5.6%) were observed in BTC patients. **Conclusions:** A large real-world dataset showed differences in genomic landscape according to clinical or genomic background, and some potential targets for the development of novel drugs in advanced pancreatobiliary cancers. These findings may lead to the improvement of cancer therapies in PC and BTC patients with poor prognosis. Research Sponsor: None.

4125 **Poster Session**

Alternating gemcitabine/nab-paclitaxel (GA) and 5-FU/leucovorin/irinotecan (FOLFIRI) as first-line treatment for *de novo* metastatic pancreatic cancer (MPC): Safety and effect. *First Author: Brett A Schroeder, Virginia Mason Medical Center, Seattle, WA*

Background: Both gemcitabine and 5FU-based chemotherapy have demonstrated efficacy in MPC. Alternating regimens may 1) reduce toxicity 2) slow resistant cancer biology emergence and 3) provide a broader platform for addition of other therapeutic agents. Alternating GA and FOLFIRI in MPC has been previously reported as part of the SEENA -1 trial ,our own institution , and elsewhere (Picozzi et.al. *GI Cancer Symposium 2017,* Picozzi et.al, *ASCO 2018* Assenat et,al, *ASCO 2018).* An extension of our institutional observations are reported here. **Methods:** Pt eligibility required the following: 1) biopsy proven *de novo* MPC, 2) no prior evidence MPC on CT, 3) ECOG performance status $\leq$ 2, and 4) bi-dimensionally measurable disease. Treatment (Rx) entailed gemcitabine 1000mg/m^2 and nab-paclitaxel 125mg/m^2 1, (8), 15 alternating every 8 wks (2 cycles) with FOLFIRI using standard dosing. Patients were radiographically re-staged every 8 wks. Rx was continued up to 48 wks; Rx thereafter decided by pt/MD. **Results:** 108 pts met eligibility requirements from 10/2015 and 12/2020. Pt characteristics included median age 68 (range 35-81), ECOG PS 0/$\geq$1 54%/46%, # diseases sites 1/$\geq$1 62%/38%, liver /non-liver 76%/24%, biliary obstruction yes/no 40%/60%, C 19.9 NL/ $<$ 59XNL/ $>$ 59X NL 12%/32%/56%; median Ca 19.9 4598 With median f/u of 19.7 mo, 17 pts remain on Rx $<$ 48 wks, 35/91 (38%) completed 48 wks Rx, 56/91 (62%) pts progressed prior to 48 wks. Median # mos on Rx was 8.9. $\geq$ grade 3 heme toxicity included anemia 7%, neutropenia 9%, thrombocytopenia 5%. Neutrophil growth factors were not used in this pt cohort. $\geq$ 3 non-hem toxicity included neuropathy1%, nausea/vomiting 2%, mucositis 2%, diarrhea 1%. Disease control at 16 wks was 81% (35% PR/46% SD/ 16% PD, 95% CI 72-87%). Median OS was 13.7 mo (95% CI 10.9-18.7 mo). 6 /12/18/24 mo OS were 87%/55%/41%/ 20% respectively. Prognostic significance was seen with Rx $>$ vs $<$ 48 wks (21.1 vs 8.0 mo, p $<$ .0001), and ECOG PS 0 vs. $\geq$1 (17.8 vs. 10.9 mo, p = 0.03) Age, # metastatic sites, liver involvement, biliary obstruction and magnitude of CA 19.9 elevation all failed to achieve prognostic significance at the p $<$ .05 level. **Conclusions:** 1) Alternating GA/ FOLFIRI in MPC has a more favorable toxicity profile than standard regimens 2) Med OS appears superior to GA and competitive with FOLFIRINOX ; longer term (18/ 24 mo) OS seemed particularly encouraging 3) $\geq$ 48 wks Rx and ECOG PS 0 were prognostically significant 4) Further investigation using this regimen including a) randomized comparisons, b) incorporation of molecular data and c) addition of additional agents seems indicated Updated survival data will be presented at the meeting Research Sponsor: None.

4126 **Poster Session**

Impact of G-CSF during neoadjuvant therapy on outcomes of operable pancreatic cancer. *First Author: Pranav Murthy, Department of Surgery, University of Pittsburgh, Pittsburgh, PA*

Background: Pancreatic ductal adenocarcinoma (PDAC) is an aggressive disease characterized by chronic inflammation and a tolerogenic immune response. Neutropenia is a common side effect of cytotoxic chemotherapy, managed with administration of recombinant granulocyte-colony stimulating factor (G-CSF, Filgrastim). The interleukin 17 – G-CSF – neutrophil extracellular trap (NET) axis promotes oncogenesis and progression of PDAC, inhibiting adaptive immunity. We evaluated the impact of G-CSF administration during neoadjuvant therapy (NAT) on oncologic outcomes in patients with operable pancreatic cancer. **Methods:** A retrospective review of all patients with localized PDAC treated with NAT prior to pancreatic resection between 2014 – 2020 was completed at a single institution. G-CSF administration, type, and dose were collected from inpatient and outpatient medical records. **Results:** Of 351 patients treated, 138 (39%) received G-CSF during NAT with a median follow-up of 45.8 months. Patients who received G-CSF were younger (64.0 vs 66.7, p = 0.008), had lower BMI (26.5 vs 27.9, p = 0.021), and were more likely to receive 5-FU based chemotherapy (42% vs 28.2%, p < 0.0001), NAT dose reduction (40.6% vs 25.4%, p = 0.003), or experience febrile neutropenia (8.7% vs 3.3%, p = 0.029). No differences were observed in baseline or pathologic tumor staging. In patients who received G-CSF, 130 (94%) received Pegfilgrastim with a median cumulative dose of 12 mg (IQR 6-12). Patients who received G-CSF were more likely to have an elevated post-NAT neutrophil to lymphocyte ratio (45% vs 29.6%, p = 0.004) and systemic immune-inflammation index (39.5% vs 29.6%, p = 0.061). Receiving G-CSF was an independent predictor of perineural invasion (HR 2.4, 95 CI [1.08, 5.5], p = 0.031) and margin positive resection (HR 1.69, 95 CI [1.01, 2.83], p = 0.043). Patients who received G-CSF had decreased overall survival compared to patients who did not receive G-CSF (median OS: 29.2 vs 38.7 months, p = 0.0001). Receiving G-CSF during NAT was an independent negative predictor of progression free (HR 1.38, 95 CI [1.04, 1.83], p = 0.022) and overall survival (HR 2.02, 95 CI [1.45, 2.79], p < 0.0001). In a subset of patients with available pre- and post-NAT serum specimens (n = 28), G-CSF administration resulted in an increased number of citrullinated histone H3 complexes following NAT (+1378±1502 vs -300.7±1147 pg/ml, p = 0.007), indicative of enhanced peripheral NET formation. **Conclusions:** In patients with localized PDAC receiving NAT prior to surgical extirpation, G-CSF administration is associated with worse oncologic outcomes and should be administered with caution. Prospective randomized as well as confirmatory clinical studies are in order. Research Sponsor: None.

4127 **Poster Session**

SBP-101, a polyamine metabolic inhibitor, administered in combination with gemcitabine and nab-paclitaxel, shows signals of efficacy as first-line treatment for subjects with metastatic pancreatic ductal adenocarcinoma. *First Author: Nimit Singhal, Adelaide Cancer Centre, Kurralta Park, SA, Australia*

Background: SBP-101, a polyamine metabolic inhibitor, inhibited growth in 6 human pancreatic ductal adenocarcinoma (PDA) cell lines and 3 murine xenograft tumor models of human PDA. SBP-101 monotherapy in heavily pre-treated PDA patients (> 2 prior regimens) showed a median survival of 5.9 months at the optimal dose level. Purpose: To assess the PK, safety and efficacy of SBP-101 in combination with gemcitabine (G) and nab-paclitaxel (A) in patients with previously untreated metastatic PDA. **Methods:** In a modified 3+3 dose escalation scheme, subcutaneous injections of SBP-101 were dosed at 0.2, 0.4 or 0.6 mg/kg days 1-5 of each 28-day cycle. G (1000 mg/m^2) and A (125 mg/m^2) were administered intravenously on Days 1, 8, and 15 of each cycle. PK was evaluated on day 1 of cycle 1 in cohorts 1-3. Safety was evaluated by clinical and laboratory assessments. Efficacy was assessed by CA19-9 levels, objective response using RECIST criteria, progression-free survival (PFS) and overall survival (OS). A fourth cohort using a modified dosing schedule of 0.4 mg/kg SBP-101 days 1-5 for cycles 1-2 and days 1, 8, and 15 every cycle thereafter was added to mitigate hepatic toxicity, and that dose and schedule were recommended for phase 1b expansion. Interim **Results:** Fifty patients were enrolled (N=25, phase 1a and N=25, phase 1b) and have received up to 12 treatment cycles. SBP-101 plasma C_{max} and $AUC_{0\text{-}t}$ increased in a slightly more than dose proportional manner and were unchanged by the addition of G and A. PK parameters of G and A were unaltered by increasing doses of SBP-101. The most common nonserious adverse events related to SBP-101 (>10%) are fatigue (N=15), LFT/transaminase abnormalities (N=15), vision abnormalities (N=6), injection site pain (N=13), dehydration (N=7), diarrhea (N=7) and nausea (N=6). Serious adverse events related to SBP-101 observed in some subjects include hepatic toxicity (N= 6) and retinal toxicity (N=6) both occurring after prolonged treatment and requiring dose reduction or discontinuation. There is no evidence of SBP-101-related bone marrow suppression or peripheral neuropathy. At the recommended dose and schedule (N=30), CA19-9 levels decreased 60-99% in 19 of 29 evaluable patients, with 12/28 evaluable patients achieving partial responses (43%) and 11/28 achieving stable disease at 8 weeks (39%). Nine subjects are ongoing. PFS was confounded by SBP-101 dosing holds implemented to investigate potential toxicity. Median OS has not been reached. **Conclusions:** Interim results suggest SBP-101 may enhance first-line treatment with G and A in patients with metastatic PDA. Hepatic toxicity can be mitigated with dose reduction or discontinuation. Retinal toxicity that occurred in some subjects is under investigation. Clinical trial information: NCT03412799. Research Sponsor: Panbela Therapeutics, Inc.

4128 **Poster Session**

Randomized multicenter phase Ib/II study of neoadjuvant chemoradiation therapy (CRT) alone or in combination with pembrolizumab in patients with resectable or borderline resectable pancreatic cancer. *First Author: Osama E. Rahma, Dana-Farber Cancer Institute, Boston, MA*

Background: Pancreatic cancer (PC) is a challenging target for immunotherapy due to suppressive immune-microenvironment. Neoadjuvant chemoradiation (CRT) can increase the presence of tumor-infiltrating lymphocytes (TILs). We hypothesized that the combination of CRT and pembrolizumab can lead to further increase in TILs and their activation. **Methods:** Patients with resectable or borderline resectable PC were randomized 2:1 to the investigational treatment (Arm A) of pembrolizumab 200mg IV every 3 weeks concurrently with CRT (capecitabine 825 mg/m2 orally twice daily and radiation 50.4 Gy in 28 fractions over 28 days) or CRT only (Arm B) prior to surgical resection. The primary endpoints were treatment safety and density of TILs with the objective to estimate differences in TILs density between the investigational and the control arms. Immune cell densities were assessed using multiplexed immunofluorescence on resected tumor specimens. Densities of CD8+TILs were measured in 2-10 representative regions containing residual cancer per case and then averaged to obtain overall densities. The study was amended after enrollment of 37 patients to allow FOLFIRINOX prior to CRT, given changes in standard of care. **Results:** 37 patients were enrolled (24 Arm A and 13 Arm B). Post-neoadjuvant therapy, 13 patients had unresectable disease (9 on A and 4 on B), and 24 patients underwent surgery and were evaluable for the TILs primary endpoint (17 arm A and 7 arm B). The mean difference (A-B) in CD8$^+$ cell density was 36 cells/mm^2 (95% CI -85 to 157, stdev 130) (p 0.48). Additional analysis did not show significant differences in CD8$^+$Ki67$^+$ (activated cytotoxic T-cells), CD4$^+$, and CD4$^+$FOXP3$^+$ (regulatory T cells), M1- or M2-like polarized macrophages, or granulocytes. The median recurrence free survival (RFS) was 18.2 months on Arm A and 14.1 on Arm B (p 0.41) and Overall Survival was 27.8 months on Arm A and 24.3 on Arm B (p 0.68) with a median follow up of 2.2 years. The most common grade 3 treatment-related toxicities were lymphopenia reported in 29% on Arm A and 31% on Arm B followed by diarrhea in 8% on Arm A attributed to CRT. There was only 1 DLT of increased ALT attributed to the combination on Arm A that resolved after holding the treatment and receiving steroids. There were no major surgical complications reported within 30 days post-surgery. **Conclusions:** The combination of CRT and pembrolizumab is safe. Preliminary analysis shows that the addition of pembrolizumab to CRT has minimal effects on several immune cell populations including CD8+TILs in the PC microenvironment. The study is currently enrolling 25 more patients who receive FOLFIRINOX prior to randomization to CRT+/- Pembrolizumab, which will help to dissect the immune modulatory effect of chemotherapy followed by CRT. Clinical trial information: NCT02305186. Research Sponsor: Merck.

4129 **Poster Session**

Fecal microbiome composition in pancreatic cancer cachexia and response to nutrition support. *First Author: Natalie Moshayedi, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Pancreatic ductal adenocarcinoma (PDAC) carries a poor prognosis with a 5-year survival rate of 10.0%. Previous studies in stool microbiome indicate that microbiome composition has been associated with therapy response and pathogenesis across multiple cancers, and PDAC patients (pts) with higher bacterial diversity have demonstrated greater long-term survival. The fecal microbiome has not previously been characterized for PDAC pts with cancer cachexia or associated interventions. The study addressed the changes in microbiome over the course of treatment and the association between baseline bacterial composition and outcome in PDAC pts with cachexia. **Methods:** Stool specimens were collected from the PNCX1 trial (NCT02400398), where all pts were given a semi-elemental diet—enzymatically hydrolyzed protein—with enteral tube feeding. Stool samples (n = 29) were collected at time points aligned with enteral feeding and chemotherapy cycles separated by 6 weeks (C1D1, C2D1, and C3D1) and analyzed using 16S v4 sequencing of the microbiome. Microbiome changes from C1D1 to C3D1, weight stability, and overall survival (OS) were measured alongside microbiome characterization. **Results:** Pts with a complete set of stool samples were analyzed (n = 6) for differences in microbiome composition across treatment cycles. C3D1 samples were significantly associated with both an increased population of *Veillonella* and *Actinomyces* and decreased *Bacteroides* and *Butyricicoccus* compared to C1D1. Baseline stool microbiome composition was also evaluated to predict weight stability throughout treatment. In patient stool samples (n = 8) at C1D1, greater abundance of *Veillonella* (p = 0.0006) and reduced *Bifidobacterium* (p = 2.62E-5) were linked to greater weight stability. Microbiome alpha-diversity was also characterized using Shannon and Chao1 indices, where stable weight was related to reduced species richness (Chao1, p = 0.0194) but not evenness (Shannon, p = 0.1716). C1D1 patient stool samples were then analyzed and compared to OS (n = 16). Although no significant differences in global microbiome composition were noted between OS < 180 days and OS > 180 days, *Parasutterella*, *Tyzzerella*, *Phascolarctobacterium*, and *Lachnoclostridium* were identified as more prevalent in OS > 180 days despite their relatively low abundance. **Conclusions:** We are among the first evaluate stool bacteria changes over treatment course in PDAC pts. While *Veillonella* was associated with weight stability in a cohort of advanced PDAC pts all receiving enteral feeding, several genera were found in abundance in pts with prolonged OS, though this needs further validation. The potential impact of the gut microbiome and enteral feeding on weight stability is provocative given that cachexia is a hallmark of PDAC and an effective strategy to mitigate this process would be transformative. Research Sponsor: CTSI grant (UL1TR001881).

4130 **Poster Session**

Circulating cell free tumor DNA detection as a prognostic tool in advanced pancreatic cancer. *First Author: Gehan Botrus, Mayo Clinic Arizona, Phoenix, AZ*

Background: Circulating cell-free tumor DNA (ctDNA) genomic profiling is an emerging tool for pancreatic cancer. The impact of detected genomic alterations in tumor response to systemic treatments and outcomes is under investigation. **Methods:** Patients with advanced pancreatic cancer and ctDNA collected at time of initial diagnosis were retrospectively evaluated. Results of ctDNA analysis were correlated with patients' demographics, systemic treatment response, progression-free survival (PFS) and overall survival (OS). **Results:** A total of 104 patients were included in the analysis. The mean age was 70.5 years (SD: 8.3), 50% were male, 37% with locally advanced disease and 63% with metastatic disease. Somatic alterations were detected in 84.6 % of the patients, no genetic alterations were detected in 15.4%, and were associated more with locally advanced pancreatic cancer as opposed to metastatic, p = 0.025. 60.6 % of the cohort had $\geq$ 2 genomic alterations detected. 28% were treated with FOLFIRINOX and 63% with gemcitabine plus nab-paclitaxel as first-line systemic treatment. Patients with any detectable genomic alterations when compared to patients with no detectable variant had worse median PFS (6.2 versus 15.3 months, p = 0.005) and patients with $\geq$ 2 detectable genomic alterations had worse median PFS (5.6 versus 11.0 months, p $<$ 0.001) and worse median OS (11.5 versus 24.2 months, p = 0.001). KRAS was detected in 62.5% of the patients and was associated with PD to systemic treatments (80.4% vs 19.6%, p = 0.006), worse median PFS (5.8 versus 13.0 months, p $<$ 0.001) and worse median OS (11.5 versus 26.3 months, p = 0.002). TP53 was detected in 60% of patients and was associated with worse median PFS (5.9 versus 10.9 months, p = 0.02) and worse median OS (13.5 versus 24.2 months, p = 0.001). CCND2 was detected in 14% of the patients and was associated with worse median PFS (3.6 versus 8.2 months, p = 0.004). **Conclusions:** Our study showed that initial detection of ctDNA may identify different genomic alterations that help predict disease outcomes, confirmation of these findings in larger studies are warranted. Research Sponsor: None.

4131 **Poster Session**

Body composition measurements and overall survival in patients with resectable pancreatic adenocarcinoma receiving neoadjuvant chemotherapy: Analysis from SWOG S1505. *First Author: Davendra Sohal, University of Cincinnati, Cincinnati, OH*

Background: Sarcopenia and sarcopenic obesity have been associated with overall survival (OS) in patients (pts) with borderline resectable and advanced pancreatic ductal adenocarcinoma (PDA), but little is known about the effect of body composition on OS in pts with resectable PDA. We examined the relationship between skeletal muscle and adipose tissue measurements on baseline computed tomography (CT) and OS of pts with resectable PDA in a secondary analysis of SWOG S1505 (NCT02562716). **Methods:** SWOG S1505 enrolled pts with resectable PDA who were randomized to receive neoadjuvant FOLFIRINOX or gemcitabine-nab paclitaxel, followed by surgical resection. Baseline axial CT images at the L3 level were analyzed with externally validated software and measurements were recorded for skeletal muscle area (SMA), density (SMD) and index (SMI); visceral adipose tissue area (VATA) and density (VATD); and subcutaneous adipose tissue area (SATA) and density (SATD). Sarcopenia was defined as SMI $<$ 52 cm2/m2 for men and $<$ 39 cm2/m2 for women; sarcopenic obesity was defined as sarcopenia and a body mass index (BMI) $>$30 kg/m2. The relationships between CT metrics and OS were analyzed using Cox regression models, with 95% CI. Statistical significance was defined as p $<$ 0.05. **Results:** Of 98 pts with available baseline abdominal CT, 8 were excluded for scan quality, resulting in 90 evaluable cases: 51 men (57%), 39 women (43%); mean age, 63.2 years, SD 8.5; mean BMI, 29.3 kg/m2, SD 6.4; 80 (89%) White, 6 (7%) Black, and 4 (4%) unknown. Sarcopenia was present in 32 (36%) and sarcopenic obesity in 10 (11%) patients. Univariable analyses for the variables of interest indicated VATA (HR 1.24; 0.97-1.60; p = 0.09) and SMD (HR 0.75; 0.57-0.98; p = 0.04) were associated with OS. Analyses adjusted for sex, race, age, BMI, performance score, contrast use, sarcopenia, and sarcopenic obesity showed VATA was associated with OS (HR 1.58; 1.0-2.51; p = 0.05). No significant difference in median OS was observed between pts with vs. without sarcopenia (OS 23.6 [19.3-NA] vs. 27.9 months [18.6-NA], respectively). Pts with vs. without sarcopenic obesity had lower median OS: 18.6 (14.7-NA) vs. 25.1 (10.5-46.0) months, respectively, but this difference was not statistically significant (HR 1.90, 95%CI 0.81-4.47, p = 0.14). **Conclusions:** This is one of the first studies to systematically evaluate body composition parameters in a prospective trial of patients with resectable PDA who received neoadjuvant chemotherapy. We found that visceral fat (VATA) is a prognostic marker in this population, but that sarcopenia may not be predictive in early PDA. Further studies to define the impact of longitudinal changes in body composition on individual outcomes may provide greater precision in predicting OS for subsets of pts with pancreatic cancer. Clinical trial information: NCT02562716. Research Sponsor: U.S. National Institutes of Health.

4132 **Poster Session**

The fear of cancer progression and recurrence in patients with pancreatic cancer. *First Author: Esther N. Pijnappel, Amsterdam UMC Location AMC, Amsterdam, Netherlands*

Background: Patients with pancreatic cancer run a considerable risk of disease progression or, after resection, disease recurrence, ultimately leading to death. Therefore, it is plausible that pancreatic cancer patients experience fear of cancer recurrence or progression (FOP). The aim of this study was to compare FOP in patients with pancreatic cancer treated with surgery, palliative systemic treatment or best supportive care (BSC), and examine the association between quality of life (QoL) and FOP and between FOP and overall survival (OS), respectively. **Methods:** This prospective multicenter cohort study included patients diagnosed with pancreatic cancer between 2015 and 2018, who participated in the Dutch Pancreatic Cancer Project (PACAP). Data on FOP (worry of cancer progression scale [WOPS]) and QoL (EORTC QLQ-C30 summary scale score), were obtained from the PACAP database. Data regarding patient and tumor characteristics were derived from the nationwide Netherlands Cancer Registry. The association between QoL and WOPS was assessed with logistic regression analysis. OS was evaluated using Kaplan Meier curves with log-rank test and multivariable Cox proportional hazard analyses. **Results:** In total, 315 patients were included, of whom 111 patients underwent surgery, 138 received palliative systemic treatment, and 66 BSC. WOPS scores tended to decrease and stabilize over time in all subgroups. Patients who underwent surgery had significantly lower WOPS scores (i.e. less FOP) at initial diagnosis compared to patients in the palliative systemic treatment and BSC group (p = 0.004). Higher QoL scores were independently associated with a lower probability of high WOPS scores in patients receiving BSC only (OR 0.95, P = 0.006). Baseline WOPS score was not independently associated with OS. **Conclusions:** Pancreatic cancer patients reported FOP at diagnosis, which decreased and stabilized over time. Given the distress that FOP evokes, FOP should be explicitly addressed by health care providers when guiding pancreatic cancer patients through their treatment trajectory, especially those receiving palliative treatment or BSC. Research Sponsor: None.

4133 **Poster Session**

Local and systemic recurrence following total neoadjuvant therapy (TNT) and resection for borderline resectable and locally advanced pancreatic adenocarcinoma: Long-term follow up from two phase II studies. *First Author: Grace E. Ryan, Massachusetts General Hospital, Boston, MA*

Background: With the advent of FOLFIRINOX, the management of pancreatic cancer has undergone a profound change. There has been a shift to TNT with FOLFIRINOX followed by radiation and an attempt at surgical resection. Recent trials of TNT have demonstrated an ability to resect locally advanced (LA) and borderline resectable disease. There is a lack of prospective data demonstrating local and systemic recurrence rates after TNT. **Methods:** Two previously reported prospective clinical trials (Murphy JE, et al, JAMA Oncol 2018, 2019) of total neoadjuvant therapy were conducted between 2012 and 2018 for borderline and LA disease (NCT01591733, NCT01821729). Patients received FOLFIRINOX for 8 cycles. Upon restaging, patients with resolution of vascular involvement received short-course chemoradiotherapy (5 Gy x 5 with protons or 3 Gy x 10 w photons) with capecitabine (N=34). Patients with persistent vascular involvement received long-course chemoradiotherapy with capecitabine (N=56). All patients were considered for resection after TNT except for those patients with metastatic or unresectable disease. **Results:** 97 eligible patients were enrolled and started treatment on the borderline resectable (n = 48) and locally advanced (n= 49) study. 90 patients completed therapy. 80 patients were taken to the operating room. 61 patients had R0 resection and 5 patients had R1 resection. The table shows the distribution of local recurrences, local recurrences and metastatic disease, and metastatic disease alone. With a median follow-up of 5.2 years (range: 2.4-6.0), of the 61 R0 patients, 22 patients remained alive and free of disease, 7 patients had a local recurrence, 4 patients had locoregional and metastatic recurrence, and 24 patients had a metastatic recurrence. 3 patients who underwent R0 resection died of unrelated causes. Median survival for patients undergoing R0 resection is 43.8 months. **Conclusions:** Total neoadjuvant therapy for locally advanced and borderline resectable pancreatic cancer is potentially curable and may change the pattern of spread. Research Sponsor: None.

	N	mOS (mos)	LR only	LR+M	M alone	DwD nos	DwoD	NED
All	97	32.3	16	7	40	2	6	26
Unresected*	31	14.5	8	3	14	1	2	3
R0+R1	66	43.8	8	4	26	1	4	23
R0	61	43.8	7	4	24	1	3	22
R1	5	46.0	1	0	2	0	1	1

*Unresected: unresectable and off-study early due to progression, toxicity or withdrawal. mOS: median survival; DwD nos: died of disease, recurrence sites unknown; DwoD: died of unrelated cause; NED: alive free of disease.

4134 **Poster Session**

A phase 2 study of cyclophosphamide (CY), GVAX, pembrolizumab (Pembro), and stereotactic body radiation (SBRT) in patients (pts) with locally advanced pancreas cancer (LAPC). *First Author: Valerie Lee, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins, Baltimore, MD*

Background: Management of locally advanced pancreas cancer (LAPC) standardly involves chemotherapy with consolidative radiation and surgery in selected pts. Checkpoint inhibitors have shown limited benefit alone in pancreas cancer but may be primed by radiation and GM-CSF secreting allogeneic pancreatic cancer vaccine (GVAX). We present data from a phase 2 study for LAPC pts who have not developed metastases after standard of care chemotherapy treated with combination cyclophosphamide (CY), GVAX, pembrolizumab (pembro), and stereotactic body radiation therapy (SBRT). **Methods:** This is a single-arm, single institution, open-label study for pts with LAPC at diagnosis (as per NCCN guidelines, arterial involvement $>$ 180°, or unreconstructible SMV/PV) who remained without metastatic disease after 4-8 28-day cycles FOLFIRINOX or gemcitabine/abraxane based therapy. Pts received CY (200mg/m2 IV) and pembro (200mg IV) on day 1, followed by GVAX (6 intradermal inj) on day 2 q3 wk x 2 cycles, with cycle 2 initiating concurrently with 5 days SBRT. Pts were restaged 4-6 weeks after SBRT, and if non-metastatic, pts underwent surgical resection, irreversible electroporation (IRE), or biopsy (if not undergoing surgical resection). Pts received two cycles of chemotherapy, and if metastasis free, received q3 wk CY/pembro/GVAX x 6 cycles with restaging scans q3 mos. In 5/2017, the protocol was addended to include an extended phase with q3 wk pembro x 9 cycles and q6 mo CY/GVAX x 4. Primary endpoint was distant metastasis free survival (DMFS) defined as C1D1 to distant metastases or death. **Results:** From Jul 2016-Jan 2021, 58 pts with LAPC were enrolled at the Johns Hopkins Hospital, 54 completed 2 cycles CY/pembro/GVAX and SBRT and were evaluable for response (2 dropouts due to thrombocytopenia, 2 due to irAE (DKA and hepatitis)), median followup was 15.8 mos. Demographics: median age 66 (range 42-84), 53% male, 84% White, 12% African American. At first restaging (N = 54), 8 (15%) had metastatic disease, 9 (17%) were unresectable, 37 (69%) were eligible for surgical resection. 35 pts proceeded to the OR (1 died of cholangitis prior to surgery and 1 declined surgery), 24 had tumors resected (44% of evaluable pts, 10 (42%) had grade 1 (marked) pathologic response), 1 IRE, 2 were unresectable, 8 were metastatic. Common related AEs were vaccine site reactions; grade 3 irAE included 1 case each of dermatitis, colitis, DKA, nephritis, and pneumonitis. DMFS was 9.7 mos [95% CI 6.3-19.3 mos]. **Conclusions:** We present data from a ph II study of 54 pts w LAPC treated w CY/GVAX/pembro and SBRT. Primary endpoint of DMFS $>$ 13.6 mos not reached, however 44% of pts underwent surgical resection of whom 42% had grade 1 path response rate. Additional correlative studies are underway. Clinical trial information: NCT02648282. Research Sponsor: Gaitway, Pharmaceutical/Biotech Company.

4135 **Poster Session**

Predictive value of germline *ATM* mutations in the CCTG PA.7 trial: Gemcitabine (GEM) and nab-paclitaxel (Nab-P) versus GEM, nab-P, durvalumab (D) and tremelimumab (T) as first-line therapy in metastatic pancreatic ductal adenocarcinoma (mPDAC). *First Author: Daniel John Renouf, BC Cancer Agency, Vancouver, BC, Canada*

Background: PA.7 evaluated whether combining PD-L1 and CTLA-4 inhibition with GEM and Nab-P increases efficacy. A previous analysis of the PA.7 data demonstrated high plasma based TMB (≥9 mut/Mb) was associated with improved OS in the Gem, Nab-P, D+T arm. DNA repair pathway aberrations beyond mismatch repair have been associated with potential immune sensitivity. We assessed the predictive value of germline *ATM* mutations in the PA.7 trial. **Methods:** This randomized phase II study (ClinicalTrials.gov NCT02879318) assessed the efficacy and safety of GEM, Nab-P, D, and T (arm A) vs. GEM and Nab-P (arm B) in patients (pts) with mPDAC (n = 180). The primary endpoint was overall survival (OS). Pre-treatment plasma was sequenced with the Predicine ATLAS next generation assay (600 gene, 2.4 Mb panel). 2-sided alpha set at 0.1. **Results:** 180 pts were randomized (119 to arm A and 61 to arm B) There was no significant difference in OS (9.8 months in arm A vs. 8.8 months in arm B, p-value 0.72) or PFS (5.5 months and 5.4 months respectively, HR 0.98, p-value 0.91). Plasma analysis was performed on 174/180 pts with available samples. 16/174 (9.2%) pts had germline *ATM* mutations, 12 in arm A and 4 in arm B. GEM, Nab-P, D+T was associated with improved OS in patients with *ATM* mutations (HR 0.10, 90% CI 0.03-0.37; median OS 13.9 months vs. 4.9 months) while no activity was seen in pts with *ATM* Wild Type (HR 0.99, 90% CI 0.73-1.33; median OS 9.79 months vs. 10.2 months); interaction p = 0.014. Germline *ATM* mutation status was independent of plasma TMB levels (Wilcoxon p = 0.76). **Conclusions:** Germline *ATM* mutation appeared predictive of benefit from the addition of dual immune checkpoint inhibitors (D and T) to Gem and Nab-P, with a significant interaction p-value. In addition to previous data from this trial regarding the predictive value of high plasma TMB (≥9 mut/Mb), this data further supports that there may be independent subgroups of PDAC, beyond MSI-H, that may benefit from immunotherapy, and trials evaluating immunotherapy in subgroups of PDAC with these profiles are warranted. Clinical trial information: NCT02879318. Research Sponsor: Canadian Cancer Trials Group (CCTG), Pharmaceutical/Biotech Company.

4136 **Poster Session**

Impact of KRAS alterations in pancreatic ductal adenocarcinoma (PDAC). *First Author: Maahum Mehdi, Medical College of Wisconsin, Wauwatosa, WI*

Background: The genomic alterations which characterize PDAC holds great promise for novel therapeutic interventions. Constitutive signaling via mutated *KRAS* is considered the signature pathognomonic alteration in PDAC, less than 10% of patients (pts) have tumors which are *KRAS* wild type (WT). We retrospectively reviewed our institutional genomic database to characterize PDAC pts with *KRAS* WT tumors. **Methods:** We reviewed electronic medical records of PDAC pts who underwent comprehensive genomic profiling (CPG) utilizing Foundation One CDx (50.6%) or TEMPUS (49.4%) between 2015-2020. Demographic and disease characteristics were compared between cohorts using Wilcoxon rank-sum test or chi-square tests. Left truncation at the time of CGP was used to account for the time of entry into the study cohort. Kaplan-Meier method was used for survival curve estimation, and log-rank test was used for between-group comparison. Cox regression was used to adjust for confounders. **Results:** We identified 235 patients: median age at diagnosis was 65 years and 52% were male. Clinical stages at diagnosis were localized (resectable/borderline resectable), locally advanced, or metastatic in 105 (44.7%), 61 (26.0%), and 69 (29.4%) patients, respectively. *KRAS* status was mutated in 212 (90%) patients: the most common alterations being G12D (48%), G12V (28%) and G12R (14%). *KRAS* WT status was noted in 23 (9.8%) pts, actionable genomic alterations in this subgroup are summarized in the table. Baseline demographic and treatment characteristics were similar between patients with *KRAS* mutated and WT tumors. Of the 23 patients with *KRAS* WT tumors, 16 (69.6%) completed all planned curative intent therapy compared to 121 (57.3%) of the 212 *KRAS* mutated pts (p=0.26). Median Overall Survival of patients with *KRAS* mutated tumors was 18.6 months compared to 44.1 months for WT pts (p=0.03). Adjusting for stage, WT vs. mutated status was associated with a 62% decreased hazard of death (HR 0.38 [0.18-0.83]; p=0.016). **Conclusions:** Patients with *KRAS* WT PDAC appear to have a distinct biology compared to those with *KRAS* mutations, meriting exploration in larger data sets. Further, comprehensive whole genome or transcriptomic characterization of *KRAS* WT tumors is necessary to identify putative driver alterations as well as actionable therapeutic targets. Research Sponsor: None.

Genomic characteristics of KRAS WT.[1]

Most frequent pathologic genomic alterations[2]	N (%)	Strongly actionable alterations	N (%)	Potentially actionable alterations	N (%)
Total	16 (70)	Total	4 (17)	Total	9 (40)
TP53 mutation	7 (30)	BRAF V600E mutation	1 (0.4)	ARID1A mutation	5 (22)
ARID1A mutation	5 (22)	EGFR Exon 19 deletion	1 (0.4)	CHEK2 mutation	2 (9)
CDKN2A mutation/deletion	3 (13)	STK11 mutation	1 (0.4)	ATM mutation	1 (0.4)
SMAD4 mutation	3 (13)	RET fusion	1 (0.4)	BRAF G469S	1 (0.4)

[1]All tumors were microsatellite stable, median TMB was 2.1 [2]Not mutually exclusive.

4137 **Poster Session**

Impact of the COVID-19 pandemic on care delivery and outcomes for patients with metastatic pancreatic ductal adenocarcinoma (mPDAC). *First Author: Ravi Kumar Paluri, Wake Forest Baptist Health, Winston-Salem, NC*

Background: The coronavirus disease 2019 (COVID-19) pandemic has caused abrupt changes to the US health system and disruption in cancer care delivery. Little has been reported on the impact of COVID-19 on patients with mPDAC and the care delivery. Our study aimed to characterize the impact of COVID-19 on healthcare utilization and outcomes for patients with mPDAC in the US in the community oncology setting. **Methods:** We performed a retrospective cohort study of adult patients diagnosed with mPDAC between March – September 2019 and March – September 2020 using the nationwide Flatiron Health EHR database, comprising data from over 280 (largely community based) cancer clinics. Patients were stratified into two cohorts based on the year of diagnosis (2019 vs. 2020). Clinical characteristics were summarized including age at metastatic diagnosis, stage at initial diagnosis, and ECOG performance score (PS). Overall survival (OS) from metastatic diagnosis was estimated using Kaplan-Meier methods. A sensitivity analysis limiting the follow-up time to November of each year was conducted. **Results:** Overall, 1,719 patients were included in the study (2019: n = 923, 2020: n = 796); both cohorts had similar demographic compositions in terms of age and sex (2019: median age = 70 (IQR: 62 – 76), 52.2% male; 2020: median age = 70 [IQR: 62 – 76], 53.5% male). In 2020, the number of newly diagnosed mPDAC patients decreased by 13.8% compared to 2019. A slightly higher proportion of patients were initially diagnosed with stage IV disease in 2020 (69.7%) vs 2019 (62.3%). A similar proportion of patients with ECOG PS 0-1 was observed between the two cohorts (2019: 48.5%; 2020: 47.9%). The number of visits recorded within the first 90 days after metastatic diagnosis was similar between the two cohorts (2019: median 8 [IQR: 3 – 14]; 2020: median 9 [IQR: 4 – 14]). For both cohorts, the proportion of patients who received 1L treatment was similar (2019: 75.8%; 2020: 76.5%), and the most common 1L treatment regimen was gemcitabine plus nab-paclitaxel (2019: 37.6%; 2020: 40.9%). Of the 1L treated populations, 37.6% of patients diagnosed in 2019 received second line (2L) compared to 17.9% of the 2020 cohort; 16.9% of 1L treated patients in 2019 received 2L in the sensitivity analysis. Patients diagnosed in 2020 had a significantly lower median OS of 6.1 months (95% CI: 5.4 – 6.9) compared to patients diagnosed in 2019: 8.4 months (7.5 – 9.0) ($p < 0.001$). **Conclusions:** During the COVID-19 pandemic era, the diagnoses of de novo mPDAC appears to have been impacted, with a higher number of patients diagnosed with advanced stage at presentation. Our analysis suggests that while patients diagnosed in 2020 received a similar level of care as those in 2019, their survival outcomes were adversely affected. Further research is necessary to characterize the impact of the COVID-19 pandemic on cancer care and outcomes. Research Sponsor: Ipsen.

4138 **Poster Session**

Efficacy and safety of KN046 plus nab-paclitaxel/gemcitabine as first-line treatment for unresectable locally advanced or metastatic pancreatic ductal adenocarcinoma (PDAC). *First Author: Gang Jin, Changhai Hospital of Shanghai, Shanghai, China*

Background: Pancreatic ductal adenocarcinoma PDAC is one of the most lethal malignancies worldwide and is characterized by extremely poor prognosis. Nab-paclitaxel plus gemcitabine has been recommended by international guidelines for first-line treatment of advanced PDAC but chemoresistance is difficult to avoid. Combination of immune checkpoint inhibitors (ICIs) and chemotherapy has demonstrated substantial promise for the treatment of several advanced malignancies. A few recent studies have begun to explore the effect of ICIs monotherapy or co in advanced PDAC with few meaningful results. KN046, a novel recombinant humanized bispecific antibody, can simultaneously block PD-1/PD-L1 and CTLA-4 pathways and restore T-cell immune response to tumor. The purpose of this study is to evaluate the efficacy and safety of KN046 plus nab-paclitaxel/gemcitabine as first-line treatment for unresectable locally advanced or metastatic PDAC. **Methods:** This ongoing phase II trial in China enrolled pts with histologically or cytologically confirmed unresectable locally advanced or metastatic PDAC who have ECOG PS of 0-1 and never received systemic anti-tumor therapy for advanced or metastatic diseases. KN046 (5mpk, Q2W) plus nab-paclitaxel (125mg/m^2, D1, 8, 15, Q4W) and gemcitabine (1000mg/m^2, D1, 8, 15, Q4W) were administered 4-6 cycles followed by KN046 (5mpk) maintenance therapy every 2 weeks. Tumour response was assessed according to RECIST 1.1 every 8 weeks. The primary endpoint is investigator-assessed ORR. Secondary endpoints are DCR, DOR, TTP, PFS, OS and safety. **Results:** As of December 15, 2020, 17 pts were enrolled, median (range) age was 56 (36-75) years, 9 pts ECOG 1, and 7 pts had liver metastases. Median KN046 exposure time was 9.5 wks. 9 pts were included in the efficacy analysis and 17 pts in the safety analysis. In best overall response assessment, there were 55.6% PR (5/9) and 33.3% SD (3/9). ORR was 55.6% (95% CI: 21.2~86.3), and DCR was 88.9% (95% CI: 51.8~99.7). The overall incidence of KN046 related treatment-emergent adverse events was 64.7%, with 29.4% were grade 3 TRAE. The most common KN046 related treatment-emergent adverse events (≥10%) were alanine aminotransferase increased (n = 5, 29.4%), nausea (n = 3, 17.6%), rash (n = 3, 17.6%), aspartate aminotransferase increased (n = 2, 11.8%), diarrhoea (n = 2, 11.8%), hyperphosphataemia (n = 2, 11.8%), pyrexia (n = 2, 11.8%), vomiting (n = 2, 11.8%). **Conclusions:** Combining KN046 with nab-paclitaxel and gemcitabine as first-line treatment for unresectable locally advanced or metastatic PDAC patients is safe and feasible, and lays the foundation for subsequent clinical trials. Clinical trial information: NCT04324307. Research Sponsor: Jiangsu Alphamab Biopharmaceuticals Co., Ltd.

4139 **Poster Session**

A phase II trial combining tumor-targeting *TP53* gene therapy with gemcitabine/nab-paclitaxel as a second-line treatment for metastatic pancreatic cancer. *First Author: Chris Poki Leung, SynerGene Therapeutics, Inc., Potomac, MD*

Background: Nearly all stage IV pancreatic adenocarcinoma (PAC) patients progress after first-line treatment, and second-line options are limited. SGT-53 is an investigational product for tumor-targeted *TP53* gene therapy that has completed phase Ia/Ib trials [Senser et al (2013), Mol Ther 21:1096; Pirollo et al (2016) Mol Ther 24:1697]. **Methods:** Here we provide an interim analysis of a Phase II trial (SGT53-02-1; NCT02340117) combining SGT-53 with gemcitabine/nab-paclitaxel (GEM/ABX). Eligible were first-line patients or those who had progressed after FOLFIRINOX (FFX) and/or gemcitabine-based therapy (second-line). In a 7-week treatment cycle, SGT-53 (3.6 mg DNA) was given once or twice weekly with GEM/ABX (1000 mg/m^2/wk and 125 mg/m^2/wk, respectively, for 3 of 4 weeks). Progression-free survival (PFS) and objective response rate (ORR) are primary endpoints.Overall survival (OS) and PFS are estimated by Kaplan-Meier analysis. **Results:** Of all evaluable patients (n=20), best response in 7 patients was determined to be partial response (PR) and 13 had stable disease (SD); none had progressive disease. In the second-line patients (n=11) there were 5 PR and 6 SD after 9 had failed FFX treatment, 3 had failed gemcitabine-based treatment and 1 had failed both. For patients with elevated CA19-9, SGT-53 + GEM/ABX resulted in marked reductions in the tumor marker. Published data for patients with PAC after therapy failure [Mita et al (2019) J Clin Med 8: 761; Portal et al (2015) Br J Cancer 113:989; Wang-Gillam et al (2016) Lancet 387:545] are shown for comparison. Notably, mPFS in our second-line patients was 7.4 months versus 3.1 months for the approved second-line therapy [Wang-Gillam et al (2016)]. This improvement in PFS exceeds the benchmark proposed to predict a clinically meaningful Phase III trial [Rahib et al (2016) Lancet Oncol 2:1209]. **Conclusions:** Our data suggest a clinically meaningful benefit of adding SGT-53 to GEM/ABX particularly for second-line PAC patients, most of whom had failed prior FFX treatment. Clinical trial information: NCT02340117. Research Sponsor: SynerGene Therapeutics, Inc.

	SGT-53-02-01 All patients (n=20)	SGT53-02-01 Second-line patients (n=11)	Mita 2019 Second-line patients	Portal 2015 Second-line patients	Wang-Gillam 2016 Second-line patients
Agents	GEM/ABX + SGT-53	GEM/ABX + SGT-53	GEM/ABX	GEM/ABX	Nanoliposomal Irinotecan + 5-FU/Folinic Acid
Study Type	Phase II trial	Phase II trial	Phase II trial	Prospective Cohort	Phase III trial
mPFS (months)	5.4 (95% CI 4.6-6.1)	7.4 (95% CI 4.2-10.6)	3.8 (95% CI 3.3-4.8)	5.1 (95% CI 3.2-6.2)	3.1 (95% CI 2.7-4.2)
mOS (months)	10.7 (95% CI 9.0-12.4)	13.4 (95% CI 8.9-17.9)	7.6 (95% CI 5.7-8.6)	8.8 (95% CI 6.2-9.7)	6.2 (95% CI 4.8-8.4)
ORR	35%	45%	13.3%		17%
DCR (≥16 weeks)	80%	91%	47%		52%
Elevated CA19-9 Reduced 20%	100% (19/19)	100% (10/10)			40% (38/95)
Elevated CA19-9 Reduced 50%	79% (15/19)	70% (7/10)			28% (27/95)
Elevated CA19-9 Reduced 90%	37% (7/19)	40% (4/10)			

4140 **Poster Session**

Genetic and immune divergence in pancreatic cancer lesions at the time of metastatic relapse compared to primary tumor. *First Author: Bereket Gebregziabher, Abramson Cancer Center at the University of Pennsylvania, Philadelphia, PA*

Background: Relapse of pancreatic ductal adenocarcinoma (PDA) is common even after complete resection and adjuvant therapy. Compared to the resected tumor, the biological characteristics of metastatic tumors at the time of first relapse are poorly understood. **Methods:** Whole-exome sequencing (WES) (250x) and bulk RNA sequencing were performed on samples from 30 patients with PDA. Paired primary tumor samples were obtained after R0 or R1 resection, and metastatic tumor samples were obtained by biopsy at the time of first relapse. 74.1% of patients had received adjuvant chemotherapy and radiation therapy, 7.4% had received adjuvant chemotherapy only, and 3.7% had received adjuvant radiation therapy only. Most common metastatic sites were liver and lung. The cohort was 60% male with a median age at diagnosis of 64 years. The vast majority of patients had stage IIA or IIB disease at diagnosis. Median disease-free survival was 481 days. Analysis used Freebayes (somatic variant calling), Kallisto (transcript quantification), Danaher et al. (cell type deconvolution), and antigen.garnish (neoantigen prediction). **Results:** High-quality WES and/or RNA sequencing were available for 27/30 patients. Among these were 16 pairs of primary and metastatic samples for WES and 15 paired samples for RNA sequencing. Median tumor purity was 32% (primary) and 42% (metastatic). KRAS mutations were present in 43/48 evaluable samples, with conserved KRAS mutations in 14/16 primary-metastatic pairs. Tumors were otherwise highly variable, with 13/16 patients developing oncogenic mutations in metastatic tumors that were undetected in primary tumors (BRCA1 [3/16], AKT3 [3/16], TP53 [2/16], ROS1 [2/16]). Overall, primary and metastatic tumors had similar tumor mutation burden and neoantigen production rate. However, neoantigens were highly variable at the peptide and gene level, with conservation rates of 2.73% and 11.57%, respectively, across primary-metastatic pairs. PDA transcriptomic subtype also differed across primary-metastatic pairs in all cases. Furthermore, metastatic tumors contained lower immune suppressive signal by transcripts and deconvolution (CTLA4: p = 0.0012, FOXP3: p = 0.0026, PDCD11: p = 0.012, regulatory T cells: p = 0.012), while myeloid cells were higher (CD33: p = 0.0067). **Conclusions:** With the exception of KRAS, metastatic PDA tumors at relapse contain new oncogenes, distinct neoantigens, and lower immune-suppressive signal compared to primary PDA tumors. These data suggest a potential clinical utility for tumor biopsies at the time of first metastatic relapse and caution against clinical decisions for relapsed, metastatic patients based solely on sequencing of the originally resected tumor. Research Sponsor: U.S. National Institutes of Health.

4141 **Poster Session**

Identification of pancreatic adenocarcinoma molecular subtypes on histology slides using deep learning models. *First Author: Charlie Saillard, OWKIN, Paris, France*

Background: Pancreatic adenocarcinoma (PAC) is predicted to be the second cause of death by cancer in 2030 and its prognosis has seen little improvement in the last decades. PAC is a very heterogeneous tumor with preeminent stroma and multiple histological aspects. Omic studies confirmed its molecular heterogeneity, possibly one of the main factors explaining the failure of most clinical trials. Two and three transcriptomic subtypes of tumor cells and stroma respectively, were described with major prognostic and predictive implications. The tumor subtypes, Basal-like and Classical, have been shown by several groups to be predictive of the response to first line chemotherapy. As of today, these subtypes can only be defined by RNA profiling which is limited by the quantity and quality of the samples (formalin fixation and low cellularity) as well as by the analytical delay that may restrict its application in routine care. In addition, tumors may harbor a mixture of several subtypes limiting their interpretation using bulk transcriptomic approaches and thereby their clinical use. Here, we propose a multistep approach using deep learning models to predict tumor components and their molecular subtypes on routine histological preparations. **Methods:** 728 whole-slide digitized histological slides corresponding to 350 consecutive resected PAC from four centers with clinical and transcriptomic data were assembled and used as a discovery set. PAC from TCGA (n = 134) was used as a validation set. Tumor regions from slides of the discovery set were annotated to train a multistep deep learning model that first recognizes tumor tissue and then predicts tumor and stroma cells molecular subtypes assessed by the published PurIST algorithm. **Results:** The tumor detection model was very efficient (AUC = 0.98 in the TCGA validation cohort). In the discovery set, the Basal-like/Classical classification performance of the model by cross validation was 0.79 (AUC) and reached 0.86 when restricted to samples with a high-confidence RNA-defined molecular subtype.Subtypes defined by the model were independently associated with overall survival in multivariate analysis (HR = 2.56 [1.87 - 3.49], pval $<$ 0.001), and association was higher relatively to PurIST RNA subtypes (HR = 1.60 [1.17 - 2.19] pval $<$ 0.001). In the validation cohort, the model had an overall AUC of 0.82, and 0.89 in the subset of subtype-pure tumors. In addition to demonstrating the value of histology-based deep learning models for tumor subtyping in PAC, these results also show the limit of molecular-based subtyping in highly heterogeneous samples. **Conclusions:** This study provides the first PAC subtyping tool usable worldwide in clinical practice, finally opening the possibility of patient molecular stratification in routine care and clinical trials. Research Sponsor: Owkin, Other Foundation.

4142 **Poster Session**

Impact of KRAS mutational status on outcomes in patients with pancreatic cancer (PDAC). *First Author: Lucy Xiaolu Ma, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: KRAS mutations (m) (KRASm) are present in over 90% of pancreatic adenocarcinomas (PDAC) with a predominance of G12 substitutions. KRAS wildtype (WT) PDAC relies on alternate oncogenic drivers, and the prognostic impact of these remains unknown. We evaluated alterations in WT PDAC and explored the impact of specific KRASm and WT status on survival. **Methods:** WGS and RNAseq were performed on 570 patients (pts) ascertained through our translational research program from 2012-2021, of which 443 were included for overall survival (OS) analyses. This included 176 pts with resected and 267 pts with advanced PDAC enrolled on the COMPASS trial (NCT02750657). The latter cohort underwent biopsies prior to treatment with first line gemcitabine-nab-paclitaxel or mFOLFIRINOX as per physician choice. The Kaplan-Meier and Cox proportional hazards methods were used to estimate OS. **Results:** KRAS WT PDAC (n = 52) represented 9% of pts, and these cases trended to be younger than pts with KRASm (median age 61 vs 65 years p = 0.1). In resected cases, the most common alterations in WT PDAC (n = 23) included GNASm (n = 6) and BRAFm/fusions (n = 5). In advanced WT PDAC (n = 27), alterations in BRAF (n = 11) and ERBB2/3/4 (n = 6) were most prevalent. Oncogenic fusions (NTRK, NRG1, BRAF/RAF, ROS1, others) were identified in 9 pts. The BRAF in-frame deletion p.486_491del represented the most common single variant in WT PDAC, with organoid profiling revealing sensitivity to both 3rd generation BRAF inhibitors and MEK inhibition. In resected PDAC, multivariable analyses documented higher stage (p = 0.043), lack of adjuvant chemotherapy (p < 0.001), and the KRAS G12D variant (p = 0.004) as poor prognostic variables. In advanced disease, neither WT PDAC nor KRAS specific alleles had an impact on prognosis (median OS WT = 8.5 mths, G12D = 8.2, G12V = 10.0, G12R = 12.0, others = 9.2, p = 0.73); the basal-like RNA subtype conferred inferior OS (p < 0.001). A targeted therapeutic approach following first line chemotherapy was undertaken in 10% of pts with advanced PDAC: MMRd (n = 1), homologous recombination deficiency (HRD) (n = 19), KRASG12C (n = 1), CDK4/6 amplification (n = 3), ERBB family alterations (n = 2), BRAF variants (n = 2). OS in this group was superior (14.7 vs 8.8 mths, p = 0.04), mainly driven by HRD-PDAC where KRASm were present in 89%. **Conclusions:** In our dataset, KRAS G12D is associated with inferior OS in resected PDAC, however KRAS mutational status was not prognostic in advanced disease. This suggests that improved OS in the WT PDAC population can only be achieved if there is accelerated access to targeted drugs for pts. Research Sponsor: This study was conducted with the support of the Ontario Institute for Cancer Research (PanCuRx Translational Research Initiative) through funding provided by the Government of Ontario, the Wallace McCain Centre for Pancreatic Cancer supported by the Prin.

4143 **Poster Session**

TCOG T5217 trial: A phase II randomized study of SLOG versus modified FOLFIRINOX as the first-line treatment in locally advanced or metastatic pancreatic ductal adenocarcinoma. *First Author: Nai-Jung Chiang, National Institute of Cancer Research, National Health Research Institutes, Tainan, Taiwan*

Background: The triplet regimen of S-1, leucovorin, oxaliplatin and gemcitabine (SLOG) has shown promising efficacy for metastatic pancreatic ductal adenocarcinoma (PDAC) in our previous study. Current multicenter randomized, phase II study compared the efficacy and safety of SLOG versus modified FOLFIRINOX (mFOLFIRINOX) in patients with advanced/metastatic PDAC. **Methods:** Patients with chemonave, histologically confirmed advanced/metastatic PDAC, were randomly assigned to either SLOG (gemcitabine 800 mg/m^2, fixed-rate infusion and oxaliplatin 85 mg/m^2 on day 1, plus daily 40/50/60 mg of S-1 based on BSA and 30 mg of oral leucovorin, twice daily, on days 1-7, every 2 weeks) or mFOLFIRINOX (oxaliplatin 85 mg/m^2, irinotecan 150 mg/m^2 and leucovorin 400 mg/m^2 on day 1 plus 5-FU 2400 mg/m^2 for 46 hrs, every 2 weeks). Patients were stratified according to disease extent, ECOG PS and primary tumor location. The primary endpoint was 6-month progression-free survival (PFS) rate. The secondary endpoints were objective response rate (ORR), disease control rate (DCR), PFS, and overall survival (OS) and safety profile. Tumor response was assessed by CT/MRI every 8 weeks according to RECIST v1.1. As an exploratory trial, 130 (65 per arm) patients were estimated to detect a two-sided 15% difference in 6-month PFS (60% in SLOG and 45% in mFOLFIRINOX) with a significant level of $\alpha = 0.1$ and $\beta = 0.25$. **Results:** Between March 2018 and October 2019, 130 patients were accrued. One patient who was assigned to mFOLFIRINOX arm didn't receive assigned treatment. Of them, 62.3% were male, 45.4% were ECOG PS0, 81.5% had metastatic diseases, and 16.9% had prior surgery. The 6-month PFS rate was 55.4% in SLOG arm (n = 65) and 50% in mFOLFIRINOX arm (n = 64) (p = 0.850). The ORR and DCR in the SLOG and the mFOLFIRINOX arms were 40% versus 26.6% (p = 0.135) and 76.2% versus 71.9% (p = 0.550), respectively. The median PFS was 7.5 months in SLOG arm and 6.5 months in mFOLFIRINOX arm (p = 0.395); while the median OS was 12.9 months in SLOG arm and 12.1 months in mFOLFIRINOX arm (p = 0.88). Ten patients underwent conversion surgery, of whom 7 had SLOG and 3 had mFOLFIRINOX. The incidence of grade 3/4 neutropenia was significantly higher in mFOLFIRINOX arm (53.2% vs. 16.9% in SLOG arm, p < 0.0001). **Conclusions:** SLOG could achieve comparable but numerically better ORR, and median PFS and OS as compared to mFOLFIRINOX in patients of advanced PDAC. SLOG can be an alternative first-line regimen for advanced PDAC patients. Clinical trial information: NCT03443492. Research Sponsor: National Health Research Institutes, Pharmaceutical/Biotech Company.

4144 **Poster Session**

Treatment with pembrolizumab in combination with the oncolytic virus pelareorep promotes anti-tumor immunity in patients with advanced pancreatic adenocarcinoma. *First Author: Devalingam Mahalingam, Northwestern University, Chicago, IL*

Background: Pelareorep is an intravenously delivered oncolytic reovirus that can induce a T-cell-inflamed phenotype in pancreatic ductal adenocarcinoma (PDAC). In prior studies, tumor tissue analysis from patients treated with pelareorep shows pelareorep replication, increased T cell infiltration, and upregulation of PD-L1. We hypothesized that pelareorep in combination with pembrolizumab in patients with PDAC would lead to improved responses and anti-tumor immunological changes within peripheral blood and tumor biopsies in responding patients. **Methods:** PDAC patients who progressed after first-line treatment received pelareorep at a dose of $4.5x10^{10}$ $TCID_{50}$ IV on Days 1, 2, 3 & 8 of Cycle (C) 1, and Days 1 & 8 with C2 onwards. Pembrolizumab was administered on Day 1 of each 21-day cycle at 200 mg IV. The primary objective was overall response rate by RECIST v 1.1 criteria. Secondary objectives included evaluating immunological changes within tumor tissue and peripheral blood, performed by multi-plex immunohistochemistry and spectral flow cytometry (Cytek), respectively. **Results:** Thirteen patients were enrolled. Disease control was achieved in 33% of the 12 efficacy-evaluable patients. One patient achieved a partial response (PR). Three additional patients achieved stable disease (SD). On-treatment tumor biopsies, collected during C1, showed pelareorep replication, increased infiltration of CD8 + T cells and PD-L1+ cells, and decreased expression of VDAC1, a mitochondrial gatekeeper for tumor promotion, relative to archival tissue. Reduced infiltration of Foxp3+ regulatory T cells (Treg) was observed in patients showing tumor response. Peripheral blood was collected at day 1 of each cycle and on C1 day 8. Relative to pretreatment samples, the number of CD8+ effector memory T cells and B cells tend to increase while the number of Treg cells declined in C2 onwards in patients with tumor response. Furthermore, these patients had increased expression of the mitochondrial protein TOMM20 in CD8+ T cells and decreased expression of PD-1 and the H3K27me3 epigenetic mark in Treg. Treatment was well tolerated with most treatment-related adverse events, including flu-like symptoms, being grade 1 or 2. **Conclusions:** The combination of pelareorep and pembrolizumab showed a manageable safety profile and modest efficacy in an unselected PDAC population. Additional correlation analyses between treatment efficacy and immunological changes will be presented. The anti-tumor activity of pelareorep and checkpoint blockade therapy is being evaluated further in additional ongoing studies. Clinical trial information: NCT03723915. Research Sponsor: Oncolytics and Merck.

4145 **Poster Session**

Association of total neoadjuvant therapy with major pathologic response and survival in localized pancreatic cancer: A multi-institutional analysis of 504 patients. *First Author: Jashodeep Datta, University of Miami Miller School of Medicine, Miami, FL*

Background: Despite increased utilization of neoadjuvant therapy for pancreatic cancer (PC), a substantial proportion of patients never receive adjuvant therapy. We examined if total neoadjuvant therapy (TNT) would facilitate delivery of all prescribed (≥6 months) non-surgical therapy (NST: chemotherapy ± radiation) to improve oncologic outcomes. **Methods:** Patients receiving neoadjuvant FOLFIRINOX or gemcitabine/nab-paclitaxel ±radiation followed by pancreatectomy at 7 centers were reviewed. Patients receiving TNT (≥6 months NST *pre*-resection) were compared to those receiving < 6 months (< TNT). Primary outcomes were major (complete/near-complete) pathologic response (MPR) and overall survival (OS). **Results:** Of 504 patients, 105 (21%) were selected for TNT. TNT and < TNT patients had similar performance status and rates of borderline resectable/locally advanced disease (82% vs. 80%). TNT patients were significantly more likely to receive ≥6 months NST (100% vs. 31%; p < 0.001) vs. < TNT. While selection of chemotherapy regimen (FOLFIRINOX or gemcitabine/nab-paclitaxel) did not differ between TNT and < TNT cohorts, TNT patients were more likely to receive neoadjuvant radiation (44% vs. 25%, p < 0.001). Rates of vascular resection, postoperative complications, and mortality were similar between groups. TNT was associated with decreased rates of lymphovascular/perineural invasion (p = 0.002) and nodal positivity (p = 0.001), and increased rates of MPR (41% vs. 23%; p = 0.001) and pathologic complete response (13% vs. 6%; p = 0.02). TNT was associated with improved OS compared with < TNT (median 38 vs. 30 months; p = 0.039). Both MPR (median 38 [MPR] vs. 28 [limited response] months; p = 0.002) and ≥6 months NST (TNT or peri-operative) (median 38 [≥6m] vs. 26 [< 6m] months; p = 0.001) were associated with improved OS. Addition of radiation was not associated with MPR or OS. **Conclusions:** The TNT approach allows more patients with localized PC to receive ≥6 months NST and is associated with improved rates of MPR and OS. TNT should be considered for all patients with operable PC when possible. Research Sponsor: None.

4146 **Poster Session**

Prognostic and predictive factors in patients treated with ramucirumab (RAM) with advanced hepatocellular carcinoma (aHCC) and elevated alpha-fetoprotein (AFP): Results from two phase III trials. *First Author: Josep M. Llovet, Mount Sinai Liver Cancer Program, Division of Liver Diseases, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Elevated AFP in patients with aHCC is a poor prognostic factor with distinct molecular features, including high vascular endothelial growth factor (VEGF) signalling and increased angiogenesis. RAM, a human IgG1 monoclonal antibody, VEGF receptor 2 (VEGFR2) inhibitor, demonstrated improved survival vs placebo among patients with elevated AFP in the REACH-2 trial and is accepted as a standard of care for management of aHCC. We analyzed prognostic factors in patients with AFP ≥400 ng/mL and predictors of clinical benefit to RAM in an individual participant data (IPD) meta-analysis of the REACH and REACH-2 Phase III trials. **Methods:** Patients with aHCC, Child-Pugh A, ECOG performance status (PS) ≤1, and prior sorafenib were randomized (REACH 1:1; REACH-2 2:1) to RAM 8 mg/kg or Placebo Q2W. Meta-analysis was conducted in patients with AFP ≥400 ng/mL (n = 542). Univariate (UV) and multivariate (MV) analyses were performed using a Cox proportional hazard regression model. MV used the cut-off p-value < 0.1 from UV, irrespective of treatment arm. Overall survival (OS) was evaluated by Kaplan-Meier estimator and Cox models. To define predictors of RAM benefit, treatment-by-covariate interactions terms were evaluated. **Results:** In terms of prognosis assessed by MV analysis in patients with AFP ≥400 ng/mL, 6 variables among demographic and baseline disease characteristics were associated with poor OS in the RAM cohort (ECOG PS 1, AFP > 1000 ng/mL, Child-Pugh > A5, Extrahepatic site > 1, neutrophil-to-lymphocyte ratio > 3.2 and aspartate aminotransferase > 57 U/L) with an additional 3 factors identified within the whole cohort (macrovascular invasion presence, etiology HCV vs. Other and alkaline phosphatase ≥146). RAM benefit was present across all subgroups, including patients with very aggressive HCCs (AFP > 4000 ng/mL; HR: 0.64; 95% CI: 0.49-0.84) and those with nonalcoholic steatohepatitis /alcohol related aHCC (HR: 0.56; 95% CI: 0.40-0.79). Of note, two treatment-emergent (TE) events were the only factors that were significantly associated with improved RAM-related survival: TE-hypertension (p interaction = 0.0392) and TE-ascites (p interaction = 0.0001). However, these results should be interpreted with caution given that TE events are factors only observed after randomization. **Conclusions:** Several poor prognostic factors for OS were identified in patients with aHCC and elevated AFP. RAM provided an OS benefit irrespective of baseline prognostic covariates, with greater benefit observed in patients with aggressive HCC and those who experienced TE-hypertension or TE-ascites. Clinical trial information: NCT01140347; NCT02435433. Research Sponsor: Eli Lilly and Company.

4147 **Poster Session**

Prognostic impact of pSTAT3 on overall survival (OS) in gastrointestinal (GI) cancers: Data from 3 phase 3, randomized controlled trials (RCTs). *First Author: Emily Brooks, Sumitomo Dainippon Pharma Oncology, Inc., Cambridge, MA*

Background: Retrospective studies of phosphorylated STAT3 (pSTAT3, a regulator of gene expression) in cancer-lineage cells have suggested it is a biomarker of poor prognosis. We analyzed data from 3 phase 3 RCTs (BRIGHTER [T1; NCT02178956], CO.23 [T2; NCT01830621], CanStem111P [T3; NCT02993731]) to evaluate the prognostic impact of pSTAT3 on OS in GI cancer patients (pts). **Methods**: pSTAT3 was evaluated in archival tumor tissue from pts with gastric or gastroesophageal junction adenocarcinoma (T1), colorectal cancer (T2), or pancreatic cancer (T3) who received standard of care in the control arms (CTL) of their respective trials. pSTAT3 positive (+) or negative (−) status was determined by detecting pSTAT3 in both tumor and tumor microenvironment (TME) cells in a laboratory-developed immunohistochemistry (IHC) assay (T1; T2), later developed into the investigational pSTAT3 IHC D3A7 assay (Agilent Technologies, Inc.) (T3). The positivity cutoff requires a sample have both a TME score of 2 and ≥5% of tumor cells staining positively for pSTAT3. Pre-analytical variables (eg, specimen collection, handling, and processing), tumor indication, and slight differences in the assays used for each study may contribute to relative differences in evaluable rates between studies. In an exploratory analysis, OS was compared in pSTAT3+ vs pSTAT3− pts via an unstratified log-rank test. **Results**: In each study, intent-to-treat pts with evaluable pSTAT3 results were considered pSTAT3-evaluable. This abstract includes pSTAT3-evaluable pts randomized to the CTL arms (T1: n/N=248/357, 69.5%; T2: n/N=110/144, 76.4%; T3: n/N=243/569, 42.7%). Baseline characteristics are presented in the table. Median (m) OS was shorter in pts with pSTAT3+ tumors across all studies (T1 hazard ratio [HR]=1.32 [95% confidence interval (CI): 1.00, 1.74]; T2 HR=2.40 [1.50, 3.83]; T3 HR=1.08 [0.77, 1.50]). **Conclusions**: In pSTAT3-evaluable populations from 3 RCTs across GI cancers, CTL pts with pSTAT3+ (vs pSTAT3−) tumors had shorter mOS. These results suggest that pSTAT3 positivity may be a biomarker of poor clinical outcome. Clinical trial information: NCT02178956; NCT01830621; NCT02993731. Research Sponsor: Sumitomo Dainippon Pharma Oncology, Inc.

	T1		T2		T3	
	pSTAT3+ n=126	pSTAT3−n=122	pSTAT3+n=26	pSTAT3−n=84	pSTAT3+n=176	pSTAT3−n=67
Median age, years (range)	64.4(24.1-88.0)	61.3(25.4-79.7)	61.5 (42-78)	64.5 (40-81)	64.5 (27-86)	62.0 (42-85)
Male sex, n (%)	92 (73.0)	79 (64.8)	14 (53.8)	58 (69.0)	89 (50.6)	39 (58.2)
ECOG PS						
0	52 (41.3)	47 (38.5)	7 (26.9)	27 (32.1)	69 (39.2)	38 (56.7)
1	74 (58.7)	75 (61.5)	19 (73.1)	57 (67.9)	107 (60.8)	29 (43.3)
Prior chemotherapy drug class						
< 3	90 (71.4)	78 (63.9)	0	0	176 (100)[a]	67 (100)[a]
≥ 3	36 (28.6)	44 (36.1)	26 (100)	84 (100)	0	0
mOS, months (95% CI)	7.13 (5.55, 8.80)	8.02 (6.47, 9.66)	2.96 (1.71, 4.07)	5.06 (4.60, 6.34)	10.78 (9.40, 12.55)	11.50 (9.46, 14.95)
HR (95% CI)	1.32 (1.00, 1.74)		2.40 (1.50, 3.83)		1.08 (0.77, 1.50)	

[a]First-line metastatic setting.

4148 **Poster Session**

Phase II study of pembrolizumab-based therapy in previously treated extrapulmonary poorly differentiated neuroendocrine carcinomas: Results of Part B (pembrolizumab + chemotherapy). *First Author: Jennifer A. Chan, Dana-Farber Cancer Institute, Boston, MA*

Background: The efficacy of immune checkpoint inhibitor (CPI) therapy has not been established in extrapulmonary poorly differentiated neuroendocrine carcinomas (EP-PDNECs). In small cell lung cancer, CPI therapy is approved for use in the first-line and salvage settings. We investigated the efficacy and safety of pembrolizumab (PEM)-based therapy in biomarker-unselected patients (pts) with EP-PDNECs. PEM alone (Part A, N=14) was inactive (ASCO GI 2019; Abstr#363). We now report the results of Part B (PEM plus chemotherapy). **Methods:** We conducted an open label, multicenter, phase 2 study of PEM-based therapy in pts with EP-PDNECs, excluding Merkel cell carcinoma and well differentiated grade 3 neuroendocrine tumors (NET), with disease progression on first-line systemic therapy. In Part B of this trial, patients were treated with PEM 200 mg IV every 3 week cycle plus dealers' choice chemotherapy (chemo): weekly irinotecan (IRI, 125 mg/m2 day 1,8 of every 21 day cycle) or weekly paclitaxel (PAC, 80 mg/m2). After PEM/IRI safety lead-in (N=6), 16 additional pts (total N=22) were enrolled. This was based on a primary endpoint of objective response rate (ORR) by RECIST 1.1 and a plan to test H_a ORR 31% vs H_0 ORR 10% with 80% power at a type I error rate of 0.05. Secondary endpoints include safety, overall survival (OS), and progression-free survival (PFS). Serial blood samples and baseline tumor biopsies were required in all pts. **Results:** Preliminary data from Part B are available. Of 22 pts enrolled, male/female 15/7; median age 57 years (range 34-75); ECOG PS 0/1: 10/12; 6 large cell, 8 small cell, 8 NOS. Primary sites of disease: GI 73%, GYN 5%, unknown 23%. Ki67 index (available for 18 pts) median 68% (range 30 to >95%). Chemo choice: 17 IRI (77%) and 5 PAC (23%). PEM/IRI was safe based on lead-in. Median number of cycles of therapy administered was 3 (range 0-13). Treatment-related Gr 3 or 4 AE occurred in 7 (32%) of 22 pts overall: 4 (18%) had at least one Gr 3 AE attributed to PEM (1 pt each with pain, ALT increase, or nausea; 2 with fatigue); 7 (32%) had at least one Gr 3/4 AE attributed to chemo (2 with fatigue, 2 with neutropenia; 1 each with pain, ALT increase, hyponatremia, diarrhea, nausea, and/or acute kidney injury). No grade 5 AE. ORR was 9%: PR in 2 pts (9%), SD 3 pts (14%), PD 13 pts (60%); 4 pts (18%) unevaluable (off study before first scheduled scan). Median PFS 2 mo. At last follow-up, 5 pts (23%) were alive with 1 pt still on treatment. Median OS 4 mo. Of 21 pts off treatment, 76% off for PD, 10% off for AE, 14% off for withdrawal of consent/other therapy. **Conclusions:** PEM + chemotherapy was not effective in this pretreated, biomarker-unselected population of EP-PDNECs arising in different organs. Biomarker studies are planned (Parts A/B). Clinical trial information: NCT03136055. Research Sponsor: Merck.

TPS4149 **Poster Session**

Preventive HIPEC in combination with perioperative FLOT versus FLOT alone for resectable diffuse type gastric and gastroesophageal junction type II/III adenocarcinoma: The phase III PREVENT trial of the AIO /CAOGI /ACO. *First Author: Thorsten Oliver Goetze, University Cancer Center Frankfurt, Institut für Klinisch-Onkologische Forschung and Institut für Klinische Krebsforschung IKF GmbH am Krankenhaus Nordwest, Frankfurt, Germany*

Background: The main reason for treatment failure after curative surgical resection of gastric cancer is intra-abdominal spread, with 40- 50% peritoneal seeding as primary localization of recurrence. Peritoneal relapse is seen in 60-70% of tumors of diffuse type, compared to only 20-30% of intestinal type. Hyperthermic IntraPEritoneal Chemoperfusion (HIPEC) is an increasingly used therapy method for patients with peritoneal metastases. The preventive use of HIPEC could represent an elegant approach for patients (pts) before macroscopic peritoneal seeding, since patients with operable disease are fit and may have potential risk of microscopic involvement, thus having a theoretical chance of cure with HIPEC even without the need for cytoreduction. No results from a PCRT from the Western hemisphere have yet been published. **Methods:** This is a multicenter, randomized, controlled, open-label study including a total of 200 pts with localized and locally advanced diffuse and mixed type (Laurens`s classification) adenocarcinoma of the stomach and Type II/III GEJ (i.e. ≥cT3 any N or any T N positive). All enrolled pts will have received 3-6 pre-operative cycles of biweekly FLOT (Docetaxel 50 mg/m^2; Oxaliplatin 85 mg/m^2; Leucovorin 200 mg/m^2; 5-FU 2600 mg/m^2, q2wk). Pts will be randomized 1:1 to receive surgery only and postoperative FLOT (Arm A- Control arm) or surgery + intraoperative HIPEC (cisplatin 75mg/m2 solution administered at a temperature of 42°C for 90 minutes) and postoperative FLOT (Arm B- experimental arm). Surgery is carried out as gastrectomy or transhiatal extended gastrectomy. Primary endpoint is PFS/DFS, major secondary endpoints are OS, R0 resection rate, perioperative morbidity/mortality including VAS pain score and quality of life as assessed by EORTC QLQ C30 questionnaire. The trial starts with a safety run-in phase. After 20 patients had curatively intended resection in Arm B, an interim safety analysis is performed assessing feasibility, safety, and tolerability in Arm B. First patient was randomized on 18JAN2021. Currently one patient is recruited. EudraCT: 2017-003832-35; ClinicalTrials.gov ID: NCT04447352. Clinical trial information: NCT04447352. Research Sponsor: Deutsche Krebshilfe.

TPS4150 **Poster Session**

AdvanTIG-203: A randomized phase 2 study comparing anti-TIGIT ociperlimab plus tislelizumab versus tislelizumab plus placebo as second-line treatment in patients with advanced or recurrent esophageal squamous cell carcinoma (ESCC) expressing programmed death-ligand 1 (PD-L1). *First Author: Rui-hua Xu, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center, Sun Yat-sen University, Guangzhou, China*

Background: The programmed death-1 (PD-1)/PD-L1 pathway plays an important role in tumor induced immunosuppression. PD-L1 overexpression is observed in approximately 30–60% of esophageal cancers and is associated with poor prognosis. Anti-PD-1 agents demonstrate moderate efficacy in PD-L1-positive esophageal cancer in terms of response rate and overall survival, however, long-term outcomes remain poor due to primary and secondary resistance driven by tumor immune escape. The T-cell immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) is upregulated on T-cells and natural killer cells in multiple solid tumors, which can inhibit anticancer immune responses. Ociperlimab (BGB-A1217) is a novel, humanized, monoclonal antibody that binds TIGIT with high specificity and affinity, blocking the interaction with its ligands on tumor cells. Preclinical and clinical studies suggest that dual targeting with anti-TIGIT and anti-PD-1 antibodies produces synergistic immune cell activation and enhanced antitumor activity. **Methods:** AdvanTIG-203 is a phase 2, global, randomized, double-blind, placebo-controlled study (NCT04732494) of patients with unresectable, locally advanced, recurrent or metastatic ESCC, who progressed on or after 1st line systemic therapy and whose tumors express PD-L1 (visually estimated combined positive score $\geq$10%). After stratification by Eastern Cooperative Oncology Group performance status (0 or 1), number of metastatic sites ($\leq$1 or $\geq$2) and region (Asian or non-Asian), 280 patients will be randomized (1:1) to either ociperlimab 900 mg intravenous (IV) plus tislelizumab 200 mg IV every 3 weeks (Q3W), or tislelizumab plus placebo Q3W, until disease progression (per RECIST v1.1), unacceptable toxicity, death or withdrawal of consent. Co-primary endpoints are investigator-assessed overall response rate (ORR) and overall survival (OS) in the intention-to-treat population. A sample size of 280 patients was estimated to provide approximately 94.8% power to detect a 20% difference in ORR at a one-sided significance level of 0.025. With 198 deaths, the study was estimated to provide approximately 86% power to detect a hazard ratio of 0.65 for OS. Secondary endpoints are ORR by independent review, progression-free survival, duration of response, disease control rate, and clinical benefit rate per investigator and independent assessment, cancer-specific health-related quality of life (HRQoL), and safety. Exploratory endpoints include but are not limited to expression of TIGIT, CD226, CD155, CD112, and PD-L1, pharmacokinetics, immunogenicity, and generic HRQoL measures. Clinical trial information: NCT04732494. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Jessica Jones, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

TPS4151 **Poster Session**

MATTERHORN: Efficacy and safety of neoadjuvant-adjuvant durvalumab and FLOT chemotherapy in resectable gastric and gastroesophageal junction cancer—A randomized, double-blind, placebo-controlled, phase 3 study. *First Author: Yelena Y. Janjigian, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Gastric and gastroesophageal junction cancers (GC, GEJC) are the fifth most common cancer types and the third leading cause of cancer-related deaths globally (Globocan 2020). Standard of care for resectable GC/GEJC includes neoadjuvant-adjuvant FLOT chemotherapy (5-fluorouracil + leucovorin + oxaliplatin + docetaxel) combined with surgery and lymph node dissection for some regions of the world. While treatment advances have improved survival, the 5-year recurrence rate remains high and 5-year overall survival (OS) is poor for patients with resectable disease. Evidence suggests cytotoxic chemotherapy can promote antitumor immunity, thus the combination of immune checkpoint inhibitors, such as durvalumab (an anti–PD-L1 antibody), with cytotoxic chemotherapy may result in increased efficacy (Yu et al. *Cancer Lett.* 2019; Li et al. *Mol Cancer.* 2021). MATTERHORN (NCT04592913) is a phase 3, multicenter study evaluating the efficacy and safety of neoadjuvant-adjuvant durvalumab or placebo with FLOT followed by adjuvant durvalumab or placebo in patients with resectable GC/GEJC. **Methods:** Approximately 900 adult patients will be randomized 1:1 to Arm A or Arm B for 2 neoadjuvant and 2 adjuvant cycles (single cycle defined as durvalumab or placebo every 4 weeks [Q4W] + FLOT [Q2W $\times$ 2]); followed by durvalumab or placebo Q4W for 10 cycles. Eligible patients must have histologically confirmed, resectable, stage II or higher GC or GEJC not treated with anticancer therapy, ECOG performance status 0 or 1, and adequate organ function. Complete surgical resection of the primary tumor must be achievable. A tumor tissue sample will be taken at screening or $<$3 months prior to enrollment. Key exclusion criteria are any prior immune-mediated therapy, peritoneal dissemination or distant metastasis, (adeno)squamous cell carcinoma, or gastrointestinal stromal tumor. The primary endpoint is event-free survival (EFS) assessed by blinded independent central radiology review (BICR) and/or local pathology testing. Secondary endpoints include OS and pathological complete response rate (pCR). Safety and tolerability will be evaluated by adverse events, vital signs, laboratory parameters, and electrocardiogram. Enrollment is ongoing. Funding: AstraZeneca. Clinical trial information: NCT04592913. Research Sponsor: AstraZeneca.

TPS4152 **Poster Session**

Phase II trial of docetaxel and ramucirumab combination therapy as second-line treatment in patients with metastatic or advanced gastric cancer (HGCSG1903). *First Author: Rika Saito, Division of Cancer Center, Hokkaido University Hospital, Sapporo, Japan*

Background: Paclitaxel and ramucirumab combination therapy had become a standard regimen in the second-line treatment of advanced gastric cancer, since RAINBOW trial showed paclitaxel and ramucirumab combination therapy increased overall survival compared with paclitaxel monotherapy. However, the incidence of neuropathy in paclitaxel and ramucirumab combination therapy has been reported 70.6% and 38.3% in Japanese and western patients, and the toxicity sometimes disturbs treatment continuation. Whereas docetaxel monotherapy used to be one of standard second-line treatment of advanced gastric cancer as well as paclitaxel monotherapy because the phase III trial, COUGAR-2 showed clinical benefit of docetaxel monotherapy. In addition, the combination therapy of docetaxel and ramucirumab was reported to cause neuropathy at an incidence of 21.3% in patients with lung cancer. Based on these results, we hypothesized that the combination therapy of docetaxel and ramucirumab for patients with gastric cancer could be as effective as the paclitaxel and ramucirumab combination therapy and could reduce the incidence of neuropathy. Therefore, we planned to develop new combination chemotherapy with docetaxel and ramucirumab for advanced gastric cancer. **Methods:** To evaluate efficacy and safety of docetaxel and ramucirumab combination therapy, HGCSG1903 study started as a multicenter, non-randomized, single arm, prospective, phase II study in November 2020. The patients with metastatic gastric adenocarcinoma that were refractory or intolerant to initial chemotherapy are eligible. Docetaxel and ramucirumab combination therapy is administered as follows; an intravenous infusion of docetaxel at 60 mg/m^2 on day 1, an intravenous infusion of ramucirumab at 8 mg/kg on day 1 and day 15 of each 4-week cycle is performed. The therapy is repeated until disease progression, unacceptable toxicity, or patient refusal. The primary endpoint is response rate, and the secondary endpoints are overall survival, progression-free survival, safety, and dose intensity for each drug. The response rate is calculated based on the RECIST version 1.1 criteria. Adverse events are evaluated using the CTCAE v5.0 criteria. A hypothesis test of binary probability was performed, with condition that threshold of response rate was set to 10.7% of docetaxel monotherapy in phase III trial and the expected response rate was set to 27.9% of paclitaxel and ramucirumab combination therapy in RAINBOW trial. A minimum number of cases that achieved a detection power of 80% at a one-sided significance level of 5% was calculated to be 32 cases. In anticipation of dropouts, the total number of registration cases was set to 35. Sixteen institutions are participated, and the registration period is 2 years. This study is registered with Japan Registry of Clinical Trials (jRCTs011200010). Clinical trial information: jRCTs011200010. Research Sponsor: Nipro Corporation.

TPS4153 **Poster Session**

Biomarker-oriented study of durvalumab in combination with olaparib and paclitaxel in gastric cancer: A phase 2 trial-in-progress. *First Author: Tae Yong Kim, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea*

Background: Olaparib (PARP inhibitor) leads to DNA damage and cell death. In phase III study (GOLD), olaparib plus paclitaxel did not improve overall survival (OS) compared with paclitaxel in second-line gastric cancer (GC) patients with statistical significance, even though there was absolute increase of OS (Lancet Oncol 2017). This highlights the importance of biomarker-based patient selection. The changes of tumor microenvironment by paclitaxel/olaparib have not been explored. Besides DNA damage, olaparib induces positive or negative immune modulation by recruiting T cells, promoting type I interferon and upregulating PD-L1, which suggests anti-PD (L1) inhibitor plus olaparib could enhance anti-tumor immunity. Combination of Anti-PD-1 agents with chemotherapy showed a good clinical efficacy in first-line of GC compared with chemotherapy alone (Checkmate 649). Based on these findings, the combination of paclitaxel/olaparib/anti-PD(L1) 1 inhibitor, with different mode of actions, might enhance antitumor activity. This is phase II study of paclitaxel/olaparib/durvalumab combination in second-line GC patients, to find out immune modulation effects by paclitaxel/olaparib combination, and to see the efficacy, safety, optimal biomarkers for this combination. **Methods:** All patients with histologically confirmed unresectable GC have failed to prior one chemotherapy and measurable lesion. Prior exposure to anti-PD(L1)1, PARP inhibitor is excluded. At 1st cycle, paclitaxel (80 mg/m^2) on D1, 8 and 15 and olaparib (150 mg bid) on D1-28 is administered. Pre-treatment biopsy and after first cycle biopsy is done. From second cycle, durvalumab 1500 mg on D1 every 4 weeks is added. At the time of disease progression, tumor biopsy is mandatory. Blood samples for biomarkers should be obtained every cycles. Response evaluation is performed after first 3 cycles and repeated every 2 cycles. Primary endpoint is the disease control rate (the percentage of patients who have achieved complete or partial remission, stable disease based on RECIST v1). Key secondary endpoints are overall response rate, progression-free survival, OS, quality of life and safety. Clinical trial information: NCT03579784. Research Sponsor: AstraZeneca.

TPS4154 **Poster Session**

TGF-β and PD-L1 inhibition combined with definitive chemoradiotherapy in esophageal squamous cell carcinoma: A phase II clinical trial (NCT04595149). *First Author: Linde M. Veen, Department of Medical Oncology, Amsterdam University Medical Centers, location VUMC, Amsterdam, Netherlands*

Background: Esophageal cancer is the 6th leading cause of mortality worldwide, with an overall 5-year survival rate of 10%. This is in part due to more than 50% of patients presenting with irresectable or metastatic disease. With the introduction of definitive chemoradiation, 3-year survival rates of patients with irresectable tumors have risen to up to 40% (Hulshof et al., ASCO GI Oral Presentation, 2020). However, treatment still fails in the majority of patients due to locoregional recurrences or development of metastatic disease. Recently, it has been shown that addition of TGF-β inhibition to chemoradiation may improve treatment efficacy (Steins et al., Int J Cancer, 2019). Additionally, PD-L1 inhibition has emerged as a relevant therapeutic strategy in specific patient subgroups, such as squamous cell carcinoma (Kato et al., The Lancet Oncology, 2019). In this phase II study, we will investigate the feasibility of addition of bintrafusp alfa, a bifunctional fusion protein blocking TGF-β and PD-L1, to definitive chemoradiation in patients with esophageal squamous cell carcinoma. **Methods:** To assess feasibility, 52 patients will receive definitive chemoradiation combined with three doses of bintrafusp alfa at week 1, 4 and 7 (Table). Feasibility is defined as ≥80% of patients completing 2 cycles of bintrafusp alfa and will be tested with a one-sample test for a binomial proportion, comparing the observed percentage to the fixed reference value of unfeasibility (62%). Secondary endpoints are toxicity, progression-free survival, overall survival and quality of life. Additionally, exploratory endpoints include development of biomarkers to predict treatment response. Eligible for inclusion are patients with surgically irresectable (T1-4a N+ M0) squamous cell carcinoma of the esophagus or gastro-esophageal junction, or patients with resectable tumors refraining from radical surgery. Patients with M1 disease solely on the basis of supraclavicular metastasis are eligible. Patients with locoregional recurrences are eligible, provided that full dose of radiation can be safely delivered. Currently, 2 of planned 52 patients have been enrolled. Clinical trial information: NCT04595149. Research Sponsor: Health Holland.

Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7
P	P	P	P	P	P	
C	C	C	C	C	C	
B			B			
RT x5	RT x5	RT x5	RT x5	RT x5	RT x3	B

P = paclitaxel 50 mg/m^2; C = carboplatin AUC = 2; B = bintrafusp alfa 2400 mg; RT = radiotherapy 2.8 Gy.

TPS4155 **Poster Session**

MONEO: A phase II study of avelumab (Av) plus FLOT in the peri-operative treatment for patients (pts) with resectable gastric or gastroesophageal junction cancer (GC). *First Author: Maria Alsina, Vall d'Hebron Institute of Oncology, Barcelona, Spain*

Background: GC represents a worldwide problem; radical surgery remaining the gold standard of curative treatment. In the West, even with peri-operative chemotherapy, 5-year survival rate is approximately 40%. GC is a heterogeneous disease, well characterized by different molecular classifications, all having in common the role of the immune system and a T-cell inflamed phenotype across all subtypes. The anti-PD-L1 Av antibody has demonstrated efficacy in GC with response rates of around 10% in the refractory setting. The addition of other immune checkpoint inhibitors to chemotherapy have demonstrated efficacy in the metastatic setting. The combination of Av to perioperative chemotherapy may increase pathological responses by a synergistic effect, and then improving the survival (OS). **Methods:** The MONEO is an open-label, non-randomized, multicentric, phase II study that explores the combination of Av plus peri-operative FLOT (docetaxel, oxaliplatin, fluorouracil/leucovorin) in resectable GC pts. EudraCT 2019-000782-21; ClinicalTrials NCT03979131. Main inclusion criteria require pts with histologically proven GC, stage Ib (T1N1 only) - IIIC (7th AJCC Ed), available paraffin block from diagnosis and surgery, evaluable disease (RECIST 1.1) amenable to radical surgery. Significant comorbidities and active autoimmune diseases are excluded. Treatment consists of surgery with 4 peri-operatory cycles of FLOT + Av, followed by Av up to one year. The primary objective is the pathological complete response (pCR) rate, compared to historical data. Secondary objectives include OS, disease-free survival, R0 resection rate, tolerability and biomarker analysis. Key point is the comprehensive biomarker analysis from tissue and blood samples (pathological immune response, TCR clonality, immune contexture characterization, immunodynamic monitoring). Statistics for an estimated 33% pCR (historical 16%), 82% power, 0.1 one-side type I error. 37 pts will be recruited from 10 Spanish centers. The sponsor is Vall d'Hebron Institute of Oncology (VHIO), principal investigators Dr. Melero and Dr. Alsina. In compliance with the Helsinki Declaration. At a data cut-off day of 5th of February 2021, 38 patients have been enrolled, 27 of them have had the surgery. Although the difficulties during the COVID19 pandemia, only two patients had been withdrawn from the study. Clinical trial information: NCT03979131. Research Sponsor: Merck.

TPS4156 **Poster Session**

EORTC 1707 VESTIGE: Adjuvant immunotherapy in patients with resected gastric cancer following preoperative chemotherapy with high risk for recurrence (ypN+ and/or R1)—An open-label randomized controlled phase II study. *First Author: Elizabeth Catherine Smyth, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom*

Background: Gastroesophageal adenocarcinoma (GEA) patients with metastatic lymph nodes (ypN+) or a microscopically incomplete surgical resection (R1) following neoadjuvant chemotherapy are at high risk of disease recurrence. Current practice is to continue with the same perioperative chemotherapy used prior to surgery, despite these suboptimal outcomes. Adjuvant immunotherapy with nivolumab has shown efficacy in poor risk GEA patients following chemoradiotherapy and surgery in the CheckMate 577 trial, and nivolumab and ipilimumab have demonstrated activity in advanced GEA. We hypothesise that high risk (ypN+ and/or R1) post resection GEA patients who are treated with nivolumab and ipilimumab will have better disease free survival than patients who continue with standard post-operative chemotherapy. **Methods:** VESTIGE is an ongoing, international, open label randomized phase II study designed to evaluate the efficacy of adjuvant nivolumab plus ipilimumab versus standard post-operative chemotherapy in high risk (ypN+ and/or R1) post resection GEA patients. Eligible patients (n=240) will be randomised 1:1 to receive post-operative adjuvant chemotherapy (identical regimen as pre-operatively) or nivolumab 3mg/kg IV q2w plus ipilimumab 1mg/kg IV q6w x 1 year. Key inclusion criteria include ypN + and/or R1 status following neoadjuvant chemotherapy plus surgery and an adequate pre-specified surgical resection. The primary endpoint of the study is disease free survival, with secondary endpoints of overall survival, safety, toxicity and quality of life. Since start of recruitment in August 2019, the trial has recruited 85 of 240 patients at 18 sites in the Czech Republic, France, Germany, Israel, Italy, Norway, Poland, Spain, and United Kingdom. The VESTIGE translational research programme includes collection of pre-treatment biopsies, post-chemotherapy resection specimens and serial liquid biopsy on treatment to explore biomarkers predictive of immune checkpoint blockade efficacy. Clinical trial information: NCT03443856. Research Sponsor: Bristol-Meyers Squibb.

TPS4157 **Poster Session**

A phase II study of short course FOLFOX chemotherapy with either nivolumab (Nivo) or Nivo plus radiation in the first line treatment of metastatic or unresectable gastroesophageal (GEA) cancers. *First Author: Rutika Mehta, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: GEA remains incurable and novel therapies are needed. Studies have shown that cytotoxic chemotherapy can enhance antigenicity of tumors, leading to the recent practice changing studies that demonstrate checkpoint inhibition therapy combined with chemotherapy in PD-L1 overexpressing patients significantly improves patient survival (Keynote-590 and Checkmate-649). But long-term use can also subsequently dampen the immune response. Moreover, the stop-and-go strategy with chemotherapy can maintain patient survival while minimizing chemotherapy related side effects when compared to the traditional strategy of continuous chemotherapy. These observations prompted the inception of this trial with the hypothesis that a short course of FOFLOX therapy combined with immunotherapy will likely have similar activity to that of continuing FOFLOX until disease progression when combined with immunotherapy. We also will examine the hypothesis that low dose radiotherapy can further augment immunotherapy efficacy. **Methods:** This is a multicenter, randomized phase II study examining Nivo alone vs radiation therapy (RT) with Nivo in subjects who did not have disease progression with 3 months of FOLFOX + Nivo. Subjects with advanced unresectable or metastatic GEA cancer are eligible. All subjects will receive FOLFOX + Nivo therapy. Subjects who demonstrate at least stable disease, on their first imaging assessment at 2 months will receive 1 additional month of FOLFOX + Nivo, and then will be randomly assigned at a 1:1 ratio to receive either Nivo alone or Nivo + RT. After 4 mos of therapy, patients who remain on study will receive Nivo Q4WKly. The primary endpoint is to demonstrate that the addition of fractionated radiation to immunotherapy is associated with an improvement in the 12-month progression-free survival (PFS) proportion from 25% (i.e., historical control estimate; Nivo alone; Arm A) to approximately 50% (i.e., with the fractional radiation and Nivo; Arm B). A key secondary aim is to demonstrate that short course FOLFOX of 3 months + Nivo is similar in efficacy to continuing FOLFOX until disease progression. Another secondary aim of this study is to demonstrate safety of the combination of fractionated RT + Nivo. Target sample size is 74 patients. The study is now open at six sites across the United States. Clinical trial information: NCT04021108. Research Sponsor: Bristol Meyers Squibb.

TPS4158 **Poster Session**

A multicenter, randomized phase 1b/2 study of gemcitabine and cisplatin with or without CPI-613 as first-line therapy for patients with advanced unresectable biliary tract cancer (BilT-04). *First Author: Vaibhav Sahai, University of Michigan, Ann Arbor, MI*

Background: Patients (pts) with advanced biliary tract cancers (BTC) have poor prognosis despite systemic chemotherapy. Gemcitabine and cisplatin is a standard first-line systemic therapy with an overall response rate (ORR) of 26% and a median overall survival of 11.7 months. This investigator-initiated, multi-institutional phase 1b/2 trial is designed to investigate the role of gemcitabine, cisplatin and CPI-613 in pts with advanced BTC. CPI-613 is a stable intermediate of a lipoate analog that inhibits pyruvate dehydrogenase and a-ketoglutarate dehydrogenase enzymes of the tricarboxylic (TCA) cycle preferentially within the mitochondria of cancer cells. **Methods:** Key eligibility criteria include histologically confirmed, metastatic or unresectable BTC (intra- or extra-hepatic and gallbladder) without prior systemic treatment, measurable disease per RECIST v1.1, and ECOG PS 0-1. Primary objective of the phase 1b portion (n = 20 pts; TiTE-CRM methodology) is to determine the recommended phase 2 dose of the combination, and for the phase 2 portion, ORR (n = 48-58 pts; 2:1 randomization). Assuming a null hypothesis ORR of 25% and an alternative hypothesis of 43%, this ongoing trial has at least 80% power with a one-sided alpha of 0.05 to identify treatment efficacy of the study arm. Secondary objectives include evaluation of progression-free survival, overall survival, and safety in this patient population. Exploratory objectives include identification of molecular markers of response and resistance in tumor samples and serially collected blood (pre-, on-, and post-therapy), including whole exome/transcriptomic analysis, and immunohistochemical staining (PDK, PDH, KGDH, SOD2 and CD79a). Gemcitabine 1000 mg/m^2, cisplatin 25 mg/m^2 with or without CPI-613 (dose levels: 500 mg/m^2, 1000 mg/m^2, 1500 mg/m^2, and 2000 mg/m^2) will be given IV on days 1 and 8 every 21 days. In the absence of disease progression, pts may continue therapy for up to 2 years. Total accrual goal is 68-78 evaluable pts. To date, 5 of planned 20 pts enrolled on the phase 1b portion are without dose limiting toxicity. Clinical trial information: NCT04203160. Research Sponsor: Rafael Pharmaceuticals, University of Michigan.

TPS4159 **Poster Session**

The IMMULAB trial: A phase II trial of immunotherapy with pembrolizumab in combination with local ablation for patients with early stage hepatocellular carcinoma (HCC). *First Author: Arndt Vogel, Hannover Medical School, Hannover, Germany*

Background: The investigator-initiated IMMULAB study investigates the clinical activity of peri-interventional treatment with the anti-PD1 antibody pembrolizumab in HCC patients who are candidates for local ablation via either radiofrequency ablation (RFA), microwave ablation (MWA) or brachytherapy, or - as recommended for tumor larger than 3 cm – by combination with TACE. Patients with extrahepatic disease are excluded. Local ablation is known to induce tumor destruction with subsequent antigen release resulting in host adaptive immune responses. However, tumors could quickly overcome the immune responses by upregulating PD-L1/PD-1 expression and inhibiting the function of CD8$^+$ and CD4$^+$ T cells. Thus, combination of local ablation with an anti-PD1 antibody might display interesting effects by activating immune cells and disabling immune inhibitory mechanisms at the same time. **Methods:** This is a prospective investigator initiated single-arm multicenter phase II trial investigating immunotherapy with the PD-1 inhibitor pembrolizumab in combination with local ablation in early stage hepatocellular carcinoma (HCC). Patients with a child-pugh classification score $\leq$ 6, including high risk candidates for local ablation (defined as patients having $\leq$ 5 tumor nodules with diameters $\leq$ 7cm [longest axis] each OR patients with vascular infiltration) receive 200mg pembrolizumab i.v. q3w for 2 cycles. Thereafter, radiologic imaging is followed by local ablation on day 1 of cycle 3. Further pembrolizumab (200mg) is applied 2 days after ablation and thereafter every 3 weeks (q3w) for a total treatment duration of up to 12 months. It is planned to enroll 30 pts. Primary efficacy endpoint is the overall response rate (RECIST 1.1) after 2 cycles of pembrolizumab and before performing local ablation aiming in the conversion / downstaging of borderline candidates by pre-interventional treatment with pembrolizumab. Overall recruitment has started; currently (Feb 2021) 18 of 30 planned patients have been enrolled. Clinical trial information: NCT03753659. Research Sponsor: MSD.

TPS4160 **Poster Session**

Camrelizumab plus apatinib combined with TACE and cryoablation in the first-line treatment of advanced hepatocellular carcinoma. *First Author: Wenge Xing, Department of Interventional Therapy, Tianjin Medical University Cancer Institute and Hospital, Key Laboratory of Cancer Prevention and Therapy, National Clinical Research Center for Cancer, Tianjin, China*

Background: Hepatocellular carcinoma (HCC) is a common cancer in the world, a leading cause of cancer-related death, and especially in China. Most of the HCC patients are diagnosed at an advanced stage and require a multidisciplinary approach. The IMbrave 50 trial has reported the successful efficacy of atezolizumab and bevacizumab combination therapy in advanced hepatocellular carcinoma, which indicate the potential efficacy of combination of immunotherapy and antiangiogenesis therapy in HCC patients. In some studies, the combinatorial approaches with immunotherapy and liver directed therapies such as transarterial chemoembolization (TACE), radiofrequency ablation (RFA), microwave ablation (MWA), and cryoablation are explored. Most combined interventional therapies reveal their enormous advantages as compared with any single therapeutic regimen alone, which may result from the immunologic enhancement effect of the multimodel therapy. In this study, we evaluated the efficacy and safety of combined therapy with camrelizumab plus apatinib mesylate and TACE plus cryoablation in patients with advanced HCC. **Methods:** This study was an open-label, single-arm, single centre, phase 2 trial in patients who were diagnosed with advanced HCC. Patients who meet the following criterias will be enrolled: (1) 18 - 75 years old; (2) Child-Pugh classification A or B($\leq$7);(3) Barcelona Clinic Liver Cancer stage B or C, or China liver cancer staging (CNLC) stage IIb~IIIa; (4) Eastern Cooperative Oncology Group Performance Status (ECOG PS) score of 0–1; (5) no history of previous systematic treatment; (6) expected life expectancy of more than 12 weeks; (7) adequate organs function. The key exclusion criteria were history of active autoimmune disease, or concurrent medical use of immunosuppressive medications or immunosuppressive doses of systemic corticosteroids. Eligible patients received camrelizumab 200 mg intravenously every 2 weeks and apatinib 250 mg orally once per day continuously in a treatment cycle of 4 weeks, treatment continued until 1 year or development of unacceptable toxicity or progression of disease. TACE was administrated at the first treatment cycles on day 1or 2, the chemotherapy regimens included 100-150mg oxaliplatin, 750-1000mg fluorouracil, or 30-50 mg lobaplatin, raltitrexed 2-4mg, and epirubicin 40-80 mg. Two or three weeks after the TACE, percutaneous cryoablation was performed under CT guidance. TACE and cryoablation was given as combination therapy and the periods were assessed by the investigator. The primary endpoint is objective response rate (complete or partial response according to mRECIST) and Progression-Free-Survival (Time ranges from random to the first occurrence of disease progression or death from any cause). This trial is registered with Chinese Clinical Trials Registry, ChiCTR2100043044, and is ongoing. Clinical trial information: ChiCTR2100043044. Research Sponsor: None.

TPS4161 **Poster Session**

A phase II trial of trastuzumab plus modified-FOLFOX for gemcitabine/cisplatin refractory HER2-positive biliary tract cancer (BTC): Multi-institutional study of the Korean Cancer Study Group (KCSG-HB19-14). *First Author: Choong-kun Lee, Yonsei Cancer Center, Division of Medical Oncology, Department of Internal Medicine, Yonsei University College of Medicine, Seoul, South Korea*

Background: Biliary tract cancer (BTC), one of the most fatal cancers with limited treatment options, is generally rare in most high-income countries, but is relatively prevalent in South Korea. Recent genomic profilings have provided druggable molecular targets including HER2 amplification, which accounts for about 15% of total BTC patients. Trastuzumab is a humanized monoclonal antibody against HER2 with known efficacy in patients with HER2-positive breast and gastric cancer, and has not been tested prospectively in patients with HER2-positive BTC. The modified-FOLFOX regimen is currently being tested as a second-line therapy of BTC in phase III ABC-06 trial. This phase II study is investigating the combination of trastuzumab and modified-FOLFOX as second- or third-line treatment in HER2-postivie BTC. **Methods**: This study (KCSG-HB19-14; NCT04722133) is a phase II, multi-institutional, single arm trial to evaluate the efficacy and safety of trastuzumab plus modified-FOLFOX in gemcitabine/cisplatin refractory patients with HER2-positive BTC. The main inclusion criteria are HER2-positive (defined as IHC3+, or IHC2+/ISH+; ISH+ defined as HER2/CEP17 $\geq$2.0, or ERBB2 gene copy number $\geq$ 6.0 by NGS) BTC (intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer and ampulla of vater cancer) patients who progressed on gemcitabine/cisplatin containing chemotherapy (one or two previous cytotoxic chemotherapy lines permitted), ECOG 0 or 1, and adequate organ function. Patients receive trastuzumab-pkrb 4mg/kg (after 6mg/kg load) D1, oxaliplatin 85mg/m^2 D1, leucovorin 200mg/m^2 D1, 5-FU 400mg/m^2 bolus D1, and 5-FU 2400mg/m^2 infusion D1-2 every 2 weeks until unacceptable toxicities or disease progression. The study has a Simon's two-stage design, with objective response rate (ORR) per RECIST v1.1 as primary endpoint. Secondary endpoints included progression-free survival, disease control rate, overall survival, safety, quality of life and correlative biomarker exploration. Additional patients were to be recruited if pre-specified thresholds for ORR are met at the first stage. The study will enroll up to 34 patients and is currently recruiting at eight sites in South Korea. As of February 2021, 16 patients have been enrolled. The pre-specified activity goal for the first stage of accrual was met; second stage accrual began in February 2021. Clinical trial information: NCT04722133. Research Sponsor: Boryung Pharmaceutical, Celltrion, Korean Cancer Study Group.

TPS4162 **Poster Session**

REPLACEMENT trial in progress: Combination therapy with atezolizumab plus bevacizumab for TACE unsuitable patients with beyond up-to-seven criteria in intermediate stage hepatocellular carcinoma: A phase II study. *First Author: Kazuomi Ueshima, Kindai University Faculty of Medicine, Osakasayama, Japan*

Background: Transarterial chemoembolization (TACE) had been developed as a standard of care in patients with intermediate-stage HCC at a time when systemic therapy was not available. This stage includes a certain TACE-unsuitable subpopulation, such as beyond up-to-seven criteria. Recently, the American Association for the Study of Liver Diseases and Asia-Pacific Primary Liver Cancer Expert Meeting have recommended systemic therapy for those patients to achieve overall survival (OS) beyond 2 years without impaired liver function in their consensus guideline. However, there is not enough data on systemic therapy for this population. Atezolizumab (Atezo), anti-PD-L1 antibody, plus Bevacizumab (Bev), anti-VEGF antibody, combination therapy has been shown to significantly improve OS, progression-free survival (PFS), and overall response rate (ORR) against sorafenib, which is a standard of care in unresectable HCC according to a phase III randomized controlled trial, IMbrave150. Therefore, we investigate the efficacy and safety of Atezo+Bev combination therapy in patients with HCC beyond up-to-seven criteria in this trial. **Methods:** REPLACEMENT trial is a multicenter, single-arm phase II study of Atezo+Bev combination therapy. Key eligibility criteria are age ≥20 years, ECOG performance status 0-1, Child-Pugh A, no vascular invasion, no extrahepatic metastasis, beyond up-to-seven criteria, and patients who have received neither systemic therapy nor TACE. Patients will be administrated Atezo 1200 mg/body + Bev 15 mg/kg once every 3 weeks. The primary endpoint is PFS per modified RECIST (mRECIST). The secondary endpoints include PFS, ORR, duration of response (DOR) per mRECIST; PFS, ORR, DOR per RECIST ver.1.1; OS and safety including change of liver function based on albumin-bilirubin (ALBI) score until disease progression. A total of 60 events are necessary to investigate the hypothesis that a target point estimation of PFS rate at 6 months (null population: 55%, alternative population: 73%). The estimated sample size is, therefore, 70 patients. In addition, the results of the Atezo+Bev therapy in this arm will be compared with those in approximately 600 TACE treated consecutive patients with intermediate-stage HCC, using the propensity score matching method, as an exploratory analysis of a possible replacement of TACE by the Atezo +Bev therapy. Patients' enrollment had already started in December 2020, and 12 patients were enrolled as of 16th February '21. Clinical trial information: jRCTs071200051. Research Sponsor: Chugai pharmaceuticals.

TPS4163 **Poster Session**

CaboRISE: A phase II study evaluating reduced starting dose and dose escalation of cabozantinib as second-line therapy for advanced HCC in patients with compensated liver cirrhosis. *First Author: Jorg Trojan, University Hospital, Johann Wolfgang Goethe-University Frankfurt, Frankfurt, Germany*

Background: The multi-targeted tyrosine kinase inhibitor cabozantinib is approved for the treatment of advanced hepatocellular carcinoma (HCC) in adults, who have previously been treated with sorafenib. In the pivotal phase 3 CELESTIAL trial a significant improvement for OS and PFS was shown for cabozantinib in comparison to placebo treated patients (Abou-Alfa GK et al. N Engl J Med 2018; 379:54-63). However, in 62% of patients a dose reduction of cabozantinib was necessary and the median average daily dose was 35.8 mg. The discontinuation rate due to treatment-related adverse events (TRAEs) was 16% and grade 3-4 TRAEs occurred in 68% of patients. For HCC patients treated with sorafenib in first-line, a reduced starting dose of 200 mg BID was not inferior in terms of OS but showed a trend toward a decreased rate of sorafenib discontinuation(Reiss KA et al. J Clin Oncol 2017; 35:3575-3581). The aim of the CaboRISE trial is to study the effect of a reduced starting dose of cabozantinib on tolerability, safety, and efficacy. **Methods:** The CaboRISE trial is an open-label, single arm, multicenter phase II trial, including patients with advanced stage hepatocellular carcinoma (HCC) with compensated liver cirrhosis (Child-Pugh A) in second line treatment, after first line treatment with sorafenib or lenvatinib. Forty evaluable patients will be enrolled in the study to receive a reduced starting dose of 40 mg cabozantinib once-daily for 4 weeks and subsequent dose escalation to 60 mg cabozantinib once-daily to be maintained until disease progression or intolerable toxicities. The objective of the trial is to assess the tolerability of a reduced starting dose of cabozantinib, in order to reduce the treatment discontinuation rates due to treatment-related adverse events below 10%. Primary endpoint is the treatment discontinuation rate due to TRAEs. Secondary endpoints are overall survival, progression free survival at 10 weeks, objective response rate, time on treatment, treatment exposure, toxicity, and quality of life. Study start of the CaboRISE trial was in October 2020. By February 2021, 7 centers across Germany have been initiated and a total of 4 out of 40 planned patients have been enrolled. The study is currently ongoing. This study is financially supported by Ipsen. ClinicalTrials.gov: NCT04522908 EudraCT: 2020-000775-20. Clinical trial information: NCT04522908. Research Sponsor: IPSEN Pharma GmbH.

TPS4164 **Poster Session**

Phase III study of NUC-1031 + cisplatin versus gemcitabine + cisplatin for first-line treatment of patients with advanced biliary tract cancer (NuTide:121). *First Author: Jennifer J. Knox, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada*

Background: Biliary tract cancer (BTC) is an aggressive disease with a poor prognosis. Gemcitabine + cisplatin (GemCis) is the accepted global standard of care (SoC), however key cancer resistance mechanisms associated with the transport, activation and breakdown of gemcitabine are known to limit its clinical activity across a range of tumor types, including BTC. NUC-1031 is a phosphoramidate transformation of gemcitabine designed to overcome these key resistance mechanisms and generate much higher levels of the active anti-cancer metabolite, dFdCTP, in cells. Promising efficacy has been observed with single-agent NUC-1031 in a phase I study in advanced solid tumors and in the phase Ib ABC-08 study of NUC-1031 + cisplatin for first-line treatment of advanced BTC. Of 21 patients enrolled in 2 dose cohorts (NUC-1031 625 mg/m^2 or 725 mg/m^2 + cisplatin 25 mg/m^2 on Days 1 and 8 of 21-day cycle), 16 were considered to be efficacy evaluable. In this population, 1 patient had a CR and 6 patients had PRs, resulting in an ORR of 44% (7/16). This compares favorably to the 26% ORR reported for the SoC regimen. In addition, 6 patients had SD, resulting in a DCR of 81% (13/16). The combination was well tolerated with no unexpected AEs or DLTs. The recommended dose of NUC-1031 with cisplatin was 725 mg/m^2. The tolerability profile, together with encouraging efficacy led to initiation of a global registrational study. **Methods:** NuTide:121 is a phase III, open-label, randomized study of NUC-1031 + cisplatin vs GemCis for first-line treatment of advanced BTC. Patients ≥18 years with histologically- or cytologically-confirmed BTC (including cholangiocarcinoma, gallbladder, or ampullary cancer), who have had no prior systemic chemotherapy for locally advanced/metastatic disease, are eligible. A total of 828 patients are being randomized (1:1) to either 725 mg/m^2 NUC-1031 or 1000 mg/m^2 gemcitabine, both with 25 mg/m^2 cisplatin, administered on Days 1 and 8 of 21-day cycles. Primary endpoints are OS and ORR. Secondary endpoints include PFS, safety, PK and patient-reported quality of life. In addition to the final analysis, three interim analyses are planned. The study has passed an initial safety analysis, with no protocol changes required. NuTide:121 is being conducted at approximately 130 sites across North America, Europe and Asia Pacific. Clinical trial information: NCT04163900. Research Sponsor: NuCana.

TPS4165 **Poster Session**

First-in-human study of highly selective FGFR2 inhibitor, RLY-4008, in patients with intrahepatic cholangiocarcinoma and other advanced solid tumors. *First Author: Alison M. Schram, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Oncogenic activation of FGFR2 via genomic rearrangement, gene amplification, or point mutation in advanced solid tumors provides the opportunity for rapid clinical development of highly selective FGFR2 inhibitors using a precision oncology approach to deliver clinical benefit to genomically-defined patient (pt) populations. Unfortunately, this opportunity remains largely unrealized as current, non-selective small molecule inhibitors (pan-FGFRi) suffer from off-isoform toxicity (FGFR1-hyperphosphatemia; FGFR4-diarrhea) and on-target acquired resistance leading to only modest efficacy primarily limited to FGFR2-fusion+ intrahepatic cholangiocarcinoma (ICC). RLY-4008 is a novel, oral FGFR2 inhibitor designed to overcome the limitations of pan-FGFRi by potently and selectively targeting primary oncogenic FGFR2 alterations and acquired resistance mutations. We initiated a first-in-human (FIH) precision oncology study of RLY-4008 in advanced solid tumor pts with FGFR2 alterations with primary objectives to define the maximum tolerated dose/recommended phase 2 dose (MTD/RP2D) and adverse event (AE) profile of RLY-4008 and key secondary objectives to assess FGFR2 genotype in blood and tumor tissue, pharmacokinetics (PK), and anti-tumor activity. **Methods:** This is a global, multi-center, FIH dose escalation/expansion study of RLY-4008 (NCT04526106) in adult pts who have unresectable or metastatic solid tumors with FGFR2 alteration per local assessment, ECOG performance status 0-2, measurable or evaluable disease per RECIST 1.1, and who are refractory, intolerant, or declined standard therapy including pan-FGFRi. FGFR2 alteration will be confirmed retrospectively by central laboratory assessment. For the dose escalation (N~50), RLY-4008 is administered QD/BID on a continuous schedule with 4-week cycles according to a Bayesian Optimal Interval design that allows accelerated dose titration, additional accrual to dose levels declared tolerable, and exploration of alternative schedules if warranted. The MTD is determined via logistic regression of the dose limiting toxicity rate across all dose levels and an RP2D less than the MTD may be considered based on observed AEs, PK, and anti-tumor activity. Following dose escalation, the dose expansion (N~75) will treat pts with RLY-4008 at the MTD/RP2D and includes 5 groups with any prior therapy (except group 2): 1. FGFR2 fusion+ ICC pts; 2. FGFR2 fusion+ ICC pts with no prior FGFRi; 3. FGFR2 fusion+ pts with other solid tumors; 4. FGFR2-mutation + solid tumor pts and 5. FGFR2-amplified solid tumor pts. The primary endpoints are MTD/RP2D and AE profile; key secondary endpoints are FGFR2 genotype in blood and tumor tissue, PK parameters; overall response rate, and duration of response per RECIST 1.1. US enrollment began SEP2020 and Europe/Asia start-up is underway. Clinical trial information: NCT04526106. Research Sponsor: Relay Therapeutics.

TPS4166 **Poster Session**

DNA-damage response-umbrella study of the combination of ceralasertib and olaparib, or ceralasertib and durvalumab in advanced biliary tract cancer: A phase 2 trial-in-progress. *First Author: Jee Sun Yoon, Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea*

Background: Ceralasertib (AZD6738) is a selective ATR inhibitor that causes stalled replication forks to collapse, leading to accumulation of double-strand DNA breaks, which is expected to have synergistic anti-tumor effects with immune checkpoint inhibitors (ICI) or PARP inhibitors. First, accumulation of DNA damage by ceralasertib induces tumor cell death, leads to the release of tumor-specific antigen, changing the tumor microenvironment to promote antigen presentation and enhances the anti-tumor effect of ICI. Second, by simultaneously inhibiting two DNA-damage response (DDR) pathways downstream of PARP and ATR, cancer cells are unable to repair damaged DNA, leading to cell death. Ceralasertib has demonstrated promising anti-tumor activity and manageable toxicity in combination with durvalumab or olaparib in solid tumors in a phase 1 study (NCT02264678). In preclinical studies, ceralasertib has shown potent anti-tumor effects in biliary tract cancer (BTC) as a monotherapy and in combination with chemotherapy (Nam, et al, 2019). **Methods:** This is an open-label, phase 2 umbrella study assessing the efficacy of ceralasertib in combination with durvalumab or olaparib in patients with advanced BTC. Eligible patients have histologically confirmed BTC (including intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, or ampullary cancer), have failed at least one chemotherapy and have ECOG performance status of 0-1. Patients who have received prior ICI, ATR or PARP inhibitor are excluded. Each cycle consists of 4 weeks. In ceralasertib /durvalumab cohort, 37 patients will receive durvalumab 1.5g on day 1 and ceralasertib 240mg twice daily on days 15-28. In ceralasertib /olaparib cohort, 37 patients receive ceralasertib 160mg once daily on days 1-7 and olaparib 300mg twice daily on days 1-28. The primary endpoint is disease control rate, with key secondary endpoints including overall response rate, progression-free survival, overall survival, and safety. Tissue and blood samples are being collected for translational biomarker studies. Clinical trial information: NCT04298021. Research Sponsor: None.

TPS4167 **Poster Session**

Assessing safety and activity of cabozantinib combined with lanreotide in gastroenteropancreatic (GEP) and thoracic neuroendocrine tumors (NETs): The phase II LOLA trial. *First Author: Francesca Corti, Medical Oncology Department, ENETS Center of Excellence, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Well-differentiated (WD) NETs are a group of rare neoplasms with limited therapeutic options. New combinations of somatostatin analogs (SSAs) and investigational drugs are warranted to improve clinical outcomes. Cabozantinib (CAB) is an orally administered inhibitor of multiple tyrosine kinases, including c-MET and Vascular Endothelial Growth Factor Receptor 2 (VEGFR2), with a pivotal role in NET pathogenesis. The biological rationale of the synergistic effects of CAB plus SSAs lies in the concomitant modulation of the RAS/MAPK and PI3K/Akt/mTOR pathways both at the level of cancer cells and tumor stroma, leading to enhanced anti-proliferative and anti-angiogenic effects. CAB exhibited encouraging activity in a recent phase II trial of patients with progressive carcinoids and pancreatic (p)NETs (Chan JA et al. *JCO* 2017; 35:4_suppl, 228-228). The LOLA trial is the first prospective phase II study aiming to assess the safety and activity of CAB in combination with lanreotide (LAN) in WD NETs of GEP, thoracic and of unknown origin. Clinical trial information: NCT04427787. **Methods:** This is a multicenter, open-label, double-cohort, non comparative, non-randomized, three-stage phase II trial. Eligible patients have to meet the following inclusion criteria: diagnosis of advanced or metastatic, progressive, non-functioning WD thoracic NETs, GEP-NETs or NETs of unknown origin with Ki67 $\geq$10%; positive 68Ga-PET uptake or somatostatin receptor 2 immunohistochemical (IHC) stain; maximum 1 prior systemic regimen for metastatic disease. Two cohorts will be considered: pNETs and carcinoids. In the stage I, the primary objective is to find the optimal dose of CAB in combination with LAN and to evaluate the safety of the combination (defined as the percentage of patients experiencing grade 3-5 toxicities according to NCI-CTCAE v5.0). Starting dose of CAB is 60 mg/day continuously, plus LAN 120 mg every 28 days. In stage II and III, co-primary endpoints are safety and overall response rate (ORR) according to RECIST v1.1. The useful antitumor activity to be detected is fixed in ORR $>$ 20%. Secondary endpoints are progression-free survival and overall survival. Exploratory objectives include the assessment of IHC expression of c-MET, AXL and VEGFR2, with the aim to identify predictive or prognostic tissue biomarkers. Enrolment started in July 2020, with an expected trial duration of 42 months comprehensive of accrual, treatment and follow-up. Considering a drop out rate of 5%, the maximum number of enrolled patients will be 69. Supported by a solid rationale, the trial has the potential to generate milestone data about the synergistic effects of CAB plus LAN in a group of NET patients with relatively aggressive disease and limited therapeutic options, for whom optimal treatment sequencing is not yet defined. Clinical trial information: NCT04427787. Research Sponsor: Ipsen.

TPS4168 **Poster Session**

Biologically optimized schedule of gemcitabine and nab-paclitaxel regimen in metastatic pancreatic adenocarcinoma. *First Author: Laith I. Abushahin, Ohio State University, Comprehensive Cancer Center, Columbus, OH*

Background: Metastatic pancreatic adenocarcinoma has a poor prognosis, and improvements in therapy have been challenging. Alongside efforts in developing novel agents, there is a need to optimize and maximize the benefit of currently approved drugs. Gemcitabine + nab-paclitaxel is a frequently used regimen for pancreatic adenocarcinoma. Nab-paclitaxel is albumin–bound chemotherapy; hence the role of albumin uptake is critical for its effect. Caveolae are small membrane invaginations essential for transendothelial albumin uptake. Cav-1 is the principal structural component of caveolae. Williams and colleagues have published a series of preclinical studies demonstrating that tumor cell-specific Cav-1 expression directly correlates with albumin and albumin-bound chemotherapy uptake and subsequent apoptotic response in tumor cells. In vitro studies showed that exposure of pancreatic cancer cells to Gemcitabine resulted in up-regulation of Cav-1 peaking 48 hours after gemcitabine exposure. This Cav-1 up-regulation correlated with increased temporal albumin cellular uptake. In addition, Williams and colleagues noted that exposure of pancreatic cancer cell lines to Gemcitabine resulted in a time–specific re-entry of cells into the G2/M phase (nab-paclitaxel cytotoxicity phase) between 48-60 hours after gemcitabine treatment. Collectively this data suggest that infusing nab-paclitaxel after 48 hours of gemcitabine infusion would be optimal for both increased uptake as well as increased susceptible tumor cells. We had previously shown this effect on multiple cell lines as well as mouse models. **Methods:** This is a phase II trial; patients will receive a standard of care chemotherapy regimen consisting of FDA-approved Gemcitabine + nab-paclitaxel with modification of the schedule to deliver nab-paclitaxel 48 hours (2 days) after gemcitabine infusions. The primary endpoint is ORR, with a null hypothesis of 20% vs. a target of 35%. Employing a 2-stage design (minimax) and assuming 80% power and a 0.05 significance level, a total of 53 patients will be required. In the first stage, if at least 7/31 patients respond to therapy, an additional 22 patients will be added for a total of 53 patients. The study will be terminated early if $\leq$ six patients respond in the first stage. Observation of response in at least 16/53 patients would be required to warrant further investigation of this infusion schedule of combination therapy. The secondary endpoints include the safety of the regimen schedule, Relative dose intensity, disease control rate, PFS, and OS. The trial opened to enrollment in June 2020 and is accepting patients. Clinical trial information: NCT04115163. Research Sponsor: The Ohio State University Comprehensive Cancer Center.

TPS4169 **Poster Session**

Camrelizumab combined with ablation and chemotherapy for pancreatic cancer with liver metastases: A single-arm, phase II, prospective clinical study. *First Author: Zhiwei Li, The Affiliated Tumor Hospital of Harbin Medical University, Harbin, China*

Background: Pancreatic cancer represents one of the most aggressive tumors and the majority of patients receive a diagnosis of metastatic disease, mainly in the liver, leading to poor prognosis and survival. Currently, chemotherapy has been the treatment of choice for fit patients with pancreatic cancer liver metastases (PCLM), reaching a median survival of about 5 to 7 months. In addition, local ablation of the metastatic tumors, by increasing neoantigen exposure and transforming the immune microenvironment to reduce the progression of liver metastases, might increase the survival benefit of patients. Camrelizumab, an anti-PD-1 monoclonal antibody, has obtained preliminary results in metastatic pancreatic cancer. Therefore, this study aims to explore the effectiveness and safety of camrelizumab combined with ablation and chemotherapy in the treatment of PCLM. **Methods:** In this single-arm, prospective, phase II study, 34 patients with histological or cytological diagnosis of PCLM, ECOG performance score of 0-1, no prior chemotherapy or the interval of adjuvant chemotherapy $\geq$6 months, plan to be enrolled. The enrolled patients first received ablation surgery of liver metastases, then chemotherapy (the standard regimen for advanced pancreatic cancer, determined by the investigator) combined with camrelizumab (200 mg, iv, q3w) is administered 1 week after ablation. If the patient has multiple metastatic tumors, the ablation needs to be performed in stages. The treatment regimens will continue until the disease progression, unacceptable toxicity or withdrawal of consent. The primary endpoint is 6-month progress-free survival (6-month PFS) rate (per RECIST v1.1 by researcher). Secondary endpoints are objective response rate, disease control rate, progression-free survival, overall survival and safety. On the basis of a threshold 6-month PFS rate of 25%, targeting an expected 6-month PFS rate of 44% and assuming 18 months follow-up, 80% power and a one-sided $\alpha = 0.05$, this design requires 34 evaluable patients to be accrued over 2 years. Clinical trial information: NCT04420130. Research Sponsor: None.

TPS4170 **Poster Session**

A phase II, open-label pilot study evaluating the safety and activity of liposomal irinotecan (Nal-IRI) in combination with 5-FU and oxaliplatin (NALIRIFOX) in preoperative treatment of pancreatic adenocarcinoma (NEO-Nal-IRI study) (NCT03483038). *First Author: Sherise C. Rogers, University of Florida/UF Health Cancer Center, Gainesville, FL*

Background: Neoadjuvant treatment for potentially curable pancreatic cancer (PDAC) is increasing in acceptability, but a standard regimen has yet to be established. Multiple studies have demonstrated feasibility and effectiveness of the FOLFIRINOX (5-fluorouracil, leucovorin, oxaliplatin and irinotecan) regimen in the perioperative setting. However, FOLFIRINOX often requires dose modifications, delays and growth factor support due to excessive toxicity which can complicate care delivery when given neoadjuvantly. Liposomal irinotecan injection (Nal-IRI) is FDA approved with a well-tolerated safety profile in relapsed, refractory metastatic PDAC. The current study aims to substitute Nal-IRI for traditional irinotecan in the standard FOLFIRINOX regimen (NALIRIFOX) and to demonstrate safe and effective neoadjuvant delivery. **Methods:** This phase 2, open-label, multicenter single-arm study focuses on patients (pts) with operable PDAC without metastatic disease. Other key eligibility criteria include age ≥18 years, resectability confirmed by multiD GI tumor board (resectable vs. borderline), adequate cardiac, renal, hepatic function and ECOG performance status of 0 to 1. Pts receive NALIRIFOX regimen as per the table every 2 weeks for four months followed by disease reassessment. Pts who remain surgical candidates will undergo surgical resection within 4 to 8 weeks following last dose of therapy. The primary endpoint is to assess safety and feasibility of regimen in perioperative setting. Secondary endpoints include R0 resection rate, clinical, biochemical and radiological response rate and patient-reported quality of life during treatment as measured by the NCI validated FACT-G scale. Enrollment continues to a maximum of 28 evaluable pts to demonstrate a reduction in historical 30 day postoperative complication rate. NCT03483038. NALIRIFOX regimen components given intravenously (IV) every 14 days. Clinical trial information: NCT03483038. Research Sponsor: Ipsen, University of Florida Health Cancer Center.

TPS4171 **Poster Session**

Total neoadjuvant FOLFIRINOX or gemcitabine-based chemoradiotherapy and adjuvant gemcitabine for resectable and borderline resectable pancreatic cancer (PREOPANC-2): A nationwide multicenter randomized controlled trial. *First Author: Quisette Janssen, Erasmus MC Cancer Institute, Rotterdam, Netherlands*

Background: Neoadjuvant therapy has several potential advantages over upfront surgery in patients with localized pancreatic cancer; more patients receive systemic treatment, fewer patients undergo futile surgery, and R0 resection rates are higher, thereby possibly improving overall survival (OS). Two recent randomized trials (including the Dutch PREOPANC trial) have suggested benefit of neoadjuvant chemoradiotherapy over upfront surgery, both including gemcitabine-based chemoradiotherapy regimens. Potentially, the multi-agent FOLFIRINOX regimen (5-fluorouracil with leucovorin, irinotecan, and oxaliplatin) may further improve outcomes in the neoadjuvant setting for localized pancreatic cancer, but randomized studies are needed. The PREOPANC-2 trial investigates whether total neoadjuvant FOLFIRINOX improves OS compared with neoadjuvant gemcitabine-based chemoradiotherapy and adjuvant gemcitabine (i.e. the intervention arm of the PREOPANC trial) in patients with resectable or borderline resectable pancreatic cancer. **Methods:** This nationwide multicenter phase III randomized controlled trial includes patients with pathologically confirmed resectable and borderline resectable pancreatic cancer with a WHO performance score of 0 or 1. Resectable pancreatic cancer is defined as no arterial and ≤90 degrees venous involvement; borderline resectable pancreatic cancer is defined as ≤90 degrees arterial and ≤270 degrees venous involvement without occlusion. Patients receive 8 cycles of neoadjuvant FOLFIRINOX chemotherapy followed by surgery without adjuvant treatment (arm A), or 3 cycles of neoadjuvant gemcitabine with hypofractionated radiotherapy (36 Gy in 15 fractions) added during the second cycle, followed by surgery and 4 cycles of adjuvant gemcitabine (arm B). The primary endpoint is OS by intention-to-treat. Secondary endpoints include progression-free survival, quality of life, resection rate, and R0 resection rate. To detect a hazard ratio of 0.70 with 80% power, 252 events are needed. The number of events is expected to be reached after inclusion of 368 eligible patients, assuming an accrual period of 3 years and 1.5 years follow-up. Between June 2018 and January 2021, 375 patients were enrolled in 20 centers in the Netherlands and accrual is complete. Final analyses are expected at the end of 2022. Netherlands Trial Register: NL7094. Clinical trial information: NL7094. Research Sponsor: Dutch Cancer Society and ZonMW.

TPS4172 **Poster Session**

Australasian Gastro-Intestinal Trials Group (AGITG) MASTERPLAN: Randomized phase II study of modified neoadjuvant FOLFIRINOX alone or in combination with stereotactic radiotherapy (SBRT) for patients with high-risk and locally advanced pancreatic cancer. *First Author: Andrew Oar, Gold Coast University Hospital, Southport, Australia*

Background: Eighty per cent of patients with non-metastatic pancreatic cancer have high-risk, borderline resectable (BRPC) or locally advanced pancreas cancer (LAPC), conferring a 5-year overall survival of only 12%. MASTERPLAN evaluates the safety and activity of stereotactic body radiotherapy (SBRT) added to neoadjuvant chemotherapy in these patient cohorts. **Methods:** MASTERPLAN is an investigator-initiated prospective multi-centre randomized phase II trial. Inclusion criteria include histologically confirmed high-risk, BRPC or LAPC. High risk is defined as tumour > 4cm, extrapancreatic extension or node positive. Randomisation is 2:1 to chemotherapy + SBRT (investigational arm) or chemotherapy (control arm) by minimisation with stratification by operability (potentially operable - high risk; BRPC versus inoperable – LAPC; medically inoperable), planned chemotherapy and institution. Both treatment arms receive 6 x 2 weekly cycles of modified FOLFIRINOX (mFOLFIRINOX). Gemcitabine and *nab*-paclitaxel is permitted if mFOLFIRINOX is unsuitable. The investigational arm receives SBRT (40Gy in 5 fractions) with real time quality assurance. Resectability will be evaluated following initial chemotherapy +/- SBRT. Adjuvant chemotherapy is 6 cycles (12 weeks) of mFOLFIRINOX, or the same duration of gemcitabine and capecitabine (GEMCAP) if neoadjuvant gemcitabine/*nab*-paclitaxel given. SBRT adverse events (AEs) will be recorded until study cessation. The primary endpoint is 12-month locoregional control. Secondary endpoints: safety, surgical morbidity and mortality, radiological response rate, progression free survival, pathological response rate, surgical resection rate, R0 resection rate, quality of life, deterioration free survival and overall survival. Biospecimens are collected for translational research for potential prognostic/predictive biomarkers of clinical endpoints and include serial tumour tissue collection from patients undergoing fiducial marker insertion and/or surgery, biopsy at disease progression, serial blood collection and serial buccal and faecal sample collection. An interim analysis will review locoregional failure, distant metastasis and rate of death on the first 40 patients after completion of 12 months follow up. The sample size is 120 patients (80 intervention:40 control), balanced for BRPC/LAPC (60 in each cohort). The minimum follow up is 12 months. The first site opened in October 2019 and 10 patients have been recruited from five sites at 17 Feb 2021. Overall 15 sites in Australia and New Zealand are planned to open to recruitment. Australian Clinical Trials Registry Number: ACTRN12619000409178. Clinical trial information: ACTRN12619000409178. Research Sponsor: Medical Research Future Fund (MRFF).

TPS4173 **Poster Session**

Phase II study of the anti-TGF-β1 monoclonal antibody (mAb) NIS793 with and without the PD-1 inhibitor spartalizumab in combination with nab-paclitaxel/gemcitabine (NG) versus NG alone in patients (pts) with first-line metastatic pancreatic ductal adenocarcinoma (mPDAC). *First Author: Peter Grell, Masaryk Memorial Cancer Institute, Brno, Czech Republic*

Background: Overall survival remains low for pts with mPDAC despite approved therapies, highlighting the need for further innovative treatment options. Intra-tumoral fibrosis that characterizes PDAC has been associated with a state of immune exclusion and may constitute a mechanical obstacle to the penetration of chemotherapy into the tumor as well as contribute to the lack of efficacy of immunotherapy. TGF-β plays a key role in regulating the tumor microenvironment and emerging evidence points to TGF-β as a pivotal activator of cancer-associated fibroblasts, leading to the development of fibrotic networks. Preclinical data in murine models have shown that TGF-β blockade augmented the benefit of both NG and anti-PD-1 therapy, leading to tumor regression. These data provide the rationale for combining TGF-β-targeting agents with immunotherapy and chemotherapy. NIS793 is a human IgG2 mAb that binds to TGF-β. This study investigates NIS793 with and without spartalizumab combined with NG in treatment nave mPDAC. **Methods:** This is a phase II open-label, randomized, multicenter study (NCT04390763) beginning with a safety run-in period followed by randomization. Eligible pts are adults with previously untreated mPDAC and an ECOG performance status ≤1. Pts are excluded if they have a tumor histology other than adenocarcinoma or microsatellite instability-high tumor. The safety run-in data will be analyzed after ≥6 pts have received NIS793 (intravenously [IV] 2100 mg Q2W) + spartalizumab (IV 400 mg Q4W) + nab-paclitaxel (IV 125 mg/m^2 on Days 1, 8 and 15) + gemcitabine (IV 1000 mg/m^2 on Days 1, 8 and 15) for 1 cycle (28 days) to assess the safety and tolerability of the combination and confirm the dose for the randomized part. Pts will be randomized 1:1:1 to NIS793 + spartalizumab + NG (n=50) or NIS793 + NG (n=50) or NG (n=50). Treatment will continue until unacceptable toxicity, disease progression, discontinuation by investigator's or pt's choice, or withdrawal of consent. The primary objective is to evaluate the progression-free survival of NIS793 + NG ± spartalizumab versus NG alone. Secondary objectives include safety and tolerability, antitumor activity, overall survival, change in CD8 and PD-L1 status, and characterization of immunogenicity and pharmacokinetics. Efficacy will be assessed locally per RECIST v1.1 and iRECIST at screening, every 8 weeks for 1 year and then every 12 weeks until disease progression. Blood and tumor samples will be taken at baseline and during study treatment for pharmacokinetic, immunogenicity and biomarker assessments. This study is ongoing and will enroll pts from 30 sites across 15 countries. The first pt was treated on October 22, 2020. Clinical trial information: NCT04390763. Research Sponsor: Novartis.

TPS4174 **Poster Session**

Trial in progress: Open-label, randomized, comparative phase 2/3 study of combination immunotherapy plus standard-of-care chemotherapy and SBRT versus standard-of-care chemotherapy for the treatment of locally advanced or metastatic pancreatic cancer. *First Author: Tara Elisabeth Seery, Chan Soon Shiong Institute for Medicine, El Segundo, CA*

Background: Pancreatic cancer will claim an estimated 47,050 lives in the USA in 2020, with an expected 5 year survival of 10%. Thus there is an urgent need for novel treatment options in this disease. We hypothesize that effective response against pancreatic cancer requires a coordinated approach that orchestrates both the innate and adaptive immune system. We further hypothesize that by orchestrating the activation of the entire immune system, we could accomplish immunogenic cell death with durable responses in this disease. We describe a novel combination immunotherapy protocol of low-dose chemoradiation, cytokine-induced NK and T cell activation via N-803 (an IL-15 cytokine fusion protein), and off-the-shelf PDL1-targeted high-affinity NK cell (PDL1 t-haNK) infusion. **Methods:** The ongoing QUILT 88 phase II/III, multi-center, three-cohort, open-label, US study (NCT04390399) to evaluate the comparative efficacy and overall safety of standard-of-care chemotherapy versus standard-of-care chemotherapy in combination with aldoxorubicin HCl, N-803, and PD-L1 t-haNK in subjects with locally advanced or metastatic pancreatic cancer. Each treatment setting (ie, first line maintenance, second line, or third line or greater) will be evaluated independently as a separate cohort. Subjects with locally advanced or metastatic pancreatic cancer who have received at least 16 weeks of treatment with gemcitabine plus nab-paclitaxel, and have had either a partial response (PR), CR, or stable disease (SD), will be enrolled into Cohort A to receive first-line maintenance therapy. Subjects who have disease progression on or after receiving first-line treatment with gemcitabine plus nab-paclitaxel or another first-line chemotherapy regimen (eg, FOLFIRINOX), or who have discontinued first-line treatment (eg, due to toxicity or intolerance) will be enrolled into Cohort B to receive second-line therapy randomized to irinotecan-liposome/5FU/LV versus experimental arm. Subjects who have disease progression after receiving at least 2 lines of therapy for pancreatic cancer, will be enrolled into Cohort C to receive third-line or greater treatment. Primary endpoints by cohort are: A) PFS per RECIST V1., B & C) OS. The secondary endpoints include overall response rate, DoR, DCR, OS(cohort A) and QoL by patient-reported outcomes. Clinical trial information: NCT04390399. Research Sponsor: ImmunityBio.

TPS4175 **Poster Session**

GRECO-2: A randomized, phase 2 study of stereotactic body radiation therapy (SBRT) in combination with GC4711 in the treatment of unresectable or borderline resectable nonmetastatic pancreatic cancer (PC). *First Author: Sarah E. Hoffe, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: While systemic treatment of PC has improved, rates of surgical resection - considered optimum treatment - remain low. Patients with un-resectable or borderline PC still have poor outcomes, with both toxicity and disease progression during induction chemotherapy limiting the number eligible for surgery. SBRT practice to enhance margin negative resection or to provide local control, if inoperable after neoadjuvant therapy, has shifted to higher dose delivery (Mellon 2015, Colbert 2018), but timing and appropriate patient selection are under constant debate. SBRT delivery over 50Gy exhibits superior cell killing compared to conventionally fractionated RT but carries potential GI toxicity risk (Zhong 2017). GC4711 is a selective superoxide dismutase mimetic that converts superoxide to hydrogen peroxide. As radiation response modifiers, dismutase mimetics have the potential to increase tumor control without compromising radiation safety (Sishc, AACR 2019). GC4711 consistently augmented tumor control by SBRT in PC experimental xenograft mouse models. In a pilot phase 1/2 trial (GC4419-101), subjects with locally advanced PC were randomized to receive SBRT plus either the selective dismutase mimetic GC4419 or placebo. This pilot trial has demonstrated acceptable safety with SBRT (5×10-11Gy), as well as apparent improvements in survival, surgical resection, locoregional control, and time to distant metastases. Altogether, these data support the hypothesis that GC4711 may improve tumor outcomes and the benefit-risk ratio of 5-fraction SBRT delivering 50Gy by improving efficacy without increasing GI-toxicity. **Methods:** GRECO-2 is a phase 2, multicenter, randomized, double-blind, placebo-controlled study to determine the effect on overall survival of adding GC4711 to SBRT following 4 months of chemotherapy in subjects with un-resectable or borderline non-metastatic PC. Approximately 160 subjects will be enrolled at over 20 sites to receive GC4711 100 mg or placebo IV given as IV infusion over 15 min, prior to each of 5 SBRT fractions of 10Gy). Subjects judged operable will be explored within 8 weeks after SBRT. All subjects will complete 2 additional months of adjuvant chemotherapy. Primary end point is overall survival and secondary endpoints address resection rates, local and distant disease progression, and safety, while exploratory studies include ctDNA, tumor exome/transcriptome sequencing, and immune profiling, patient-reported symptoms (PRO-CTCAE), CA19.9 normalization, and radiomics. Colbert L, Rebueno N, Moningi S et al Advances in Radiation Oncology (2018) 3, 693-700 Mellon EA, Hoffe SE, Springett GM, et al Acta Oncologica, 2015;54:7 Zhong J, Patel K, Switchenko J, et al. Cancer. 2017 Sep 15;123(18):3486-3493. Sishc BJ, Saha D, Story MD. AACR PADC 2019 C52. Clinical trial information: NCT04698915. Research Sponsor: Galera Therapeutics.

TPS4176 **Poster Session**

A phase II open-label study of cpi-613 in combination with modified (m) FOLFIRINOX in patients with locally advanced pancreatic cancer. *First Author: David Lawrence Bajor, University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH*

Background: For patients with locally advanced pancreatic cancer, neoadjuvant trials are the preferred strategy. The goals of neoadjuvant treatment are to diminish the size of the primary tumor to allow for safe surgical resection and to limit the chance of developing metastatic disease. mFOLFIRINOX is the gold-standard for treatment in the adjuvant setting and an acceptable regimen in the neoadjuvant setting with many ongoing neoadjuvant trials using it as a chemotherapeutic backbone. CPI-613 (devimistat) is a small-molecule inhibitor of pyruvate dehydrogenase and alpha-ketogluterate dehydrogenase that has been studied in combination with mFOLFIRINOX in a phase I trial of patients with metastatic pancreas cancer and shown to be safe at the proposed phase II dose. **Methods:** This is a single-center, single-arm phase II trial for patients with locally advanced pancreatic cancer; defined as either borderline resectable or unresectable according to NCCN guidelines and interpreted by the primary investigator. Patients with metastatic disease are excluded. Patients will receive treatment with CPI-613 and mFOLFIRINOX per the table below. The primary endpoint is overall survival. Secondary endpoints are progression free survival and resection rate. At the time of submission this study has completed initial accrual with 37 patients enrolled. Clinical trial information: NCT03699319. Research Sponsor: Rafael Pharmaceuticals Inc.

Drug	Dose	Days given of 14 day cycle
Devimistat/CPI-613	500 mg/m2	Days 1,3
5-Fluorouracil	400 mg/m2 as bolus	Day 1
Leucovorin	400 mg/m2	Day 1
Oxaliplatin	65 mg/m2	Day 1
Irinotecan	140 mg/m2	Day 1
5-Fluorouracil	2400 mg/m2 as continuous infusion	Day 1-3

4500 **Oral Abstract Session**

Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): Results from 42-month follow-up of KEYNOTE-426. *First Author: Brian I. Rini, Vanderbilt-Ingram Cancer Center, Nashville, TN*

Background: In the first interim analysis of the randomized, multicenter, open-label, phase 3 KEYNOTE-426 study (NCT02853331), treatment with pembro + axi significantly improved OS, PFS, and ORR vs sunitinib monotherapy in treatment-naive advanced ccRCC. Extended follow-up (median, 30.6 mo) continued to demonstrate the superior efficacy of pembro + axi vs sunitinib monotherapy in this patient population. Here, we present the results of the prespecified final analysis with 42.8-mo median follow-up. **Methods:** Treatment-naive patients (pts) with advanced ccRCC, KPS ≥70%, and measurable disease (RECIST v1.1) were randomly assigned 1:1 to receive pembro 200 mg IV Q3W for up to 35 doses + axi 5 mg orally BID or sunitinib 50 mg orally QD on a 4-wk on/2-wk off schedule until progression, intolerable toxicity, or withdrawal. Randomization was stratified by IMDC risk (favorable vs intermediate vs poor) and geographic region (North America vs Western Europe vs Rest of World). Dual primary endpoints were OS and PFS. Secondary endpoints were ORR, DOR, and safety. The protocol-specified final analysis was based on a target of 404 OS events. No formal hypothesis testing was performed because all efficacy endpoints were met previously at the first interim analysis; nominal *P* values are reported. **Results:** Overall, 861 pts were randomly assigned to receive pembro + axi (n=432) or sunitinib (n=429). Median duration of follow-up, defined as time from randomization to the database cutoff date, was 42.8 mo (range, 35.6-50.6). At data cutoff, 418 pts had died: 193 (44.7%) of 432 pts in the pembro + axi arm vs 225 (52.4%) of 429 pts in the sunitinib arm. Compared with sunitinib, pembro + axi improved OS (median: 45.7 vs 40.1 mo; HR, 0.73 [95% CI, 0.60-0.88]; $P<0.001$) and PFS (median: 15.7 vs 11.1 mo; HR, 0.68 [95% CI, 0.58-0.80]; $P<0.0001$). The 42-mo OS rate was 57.5% with pembro + axi vs 48.5% with sunitinib; the 42-mo PFS rate was 25.1% with pembro + axi vs 10.6% with sunitinib. For pembro + axi vs sunitinib, ORR was 60.4% vs 39.6% ($P<0.0001$); CR rate was 10.0% vs 3.5%; median DOR was 23.6 mo (range 1.4+ to 43.4+) vs 15.3 mo (range, 2.3-42.8+). Subsequent anticancer therapy was administered to 47.2% of pts in pembro + axi arm vs 65.5% of pts in sunitinib arm. Although a similar proportion of pts in each arm received VEGF/VEGFR inhibitors, only 10.2% of pts in the pembro + axi arm received subsequent treatment with a PD-1/L1 inhibitor compared to 48.7% of pts in the sunitinib arm. No new safety signals were observed. **Conclusions:** With a median follow-up of 42.8 mo, this is the longest follow-up of an anti-PD–1/L1 immunotherapy combined with a VEGF/VEGFR inhibitor for first-line RCC. These results show that pembro + axi continues to demonstrate superior efficacy over sunitinib with respect to OS, PFS, and ORR, with no new safety signals. Clinical trial information: NCT02853331. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4501 **Oral Abstract Session**

CANTATA: Primary analysis of a global, randomized, placebo (Pbo)-controlled, double-blind trial of telaglenastat (CB-839) + cabozantinib versus Pbo + cabozantinib in advanced/metastatic renal cell carcinoma (mRCC) patients (pts) who progressed on immune checkpoint inhibitor (ICI) or anti-angiogenic therapies. *First Author: Nizar M. Tannir, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Dysregulated metabolism is a hallmark of RCC, driven by overexpression of glutaminase (GLS), a key enzyme of glutamine metabolism. Telaglenastat (Tela) is an investigational, first-in-class, selective, oral GLS inhibitor that blocks glutamine utilization and critical downstream pathways. Preclinically, Tela synergized w/ cabozantinib (Cabo), a VEGFR2/MET/AXL inhibitor, against RCC tumors. In a Ph 1 study cohort, Tela+Cabo showed encouraging safety/efficacy as 2L+ therapy for mRCC. This trial compared Tela+Cabo vs Pbo+Cabo in previously treated pts w/ clear-cell mRCC (NCT03428217). **Methods:** Eligible pts had 1-2 prior lines of systemic therapy for mRCC, including ≥1 anti-angiogenic therapy or nivolumab + ipilimumab (nivo/ipi), KPS ≥70%, measurable disease (RECIST 1.1), no prior Cabo or other MET inhibitor. Pts were randomized 1:1 to receive Cabo (60 mg PO QD) with either Tela (800 mg PO BID) or Pbo, until disease progression/unacceptable toxicity, and were stratified by prior PD-(L)1 inhibitor therapy (Y/N) and IMDC prognostic risk group. Primary endpoint was progression-free survival (PFS; RECIST 1.1) by blinded independent radiology review. The study was designed to detect a PFS hazard ratio (HR) of 0.69 w/ alpha 0.05 and 85% power. Data cutoff date: August 31, 2020. **Results:** 444 pts were randomized (221 Tela+Cabo; 223 Pbo+Cabo). Baseline characteristics were balanced between arms. Median follow-up was 11.7 mo; 276 pts received prior ICI, including 128 w/ prior nivo/ipi. Median PFS (mPFS) was 9.2 mo for Tela+Cabo vs 9.3 mo for Pbo+Cabo (HR = 0.94; 95% CI: 0.74, 1.21; stratified log-rank P= 0.65) with overall response rates (ORR; confirmed) of 31% with Tela+Cabo vs 28% Pbo+Cabo, respectively. Overall survival was not mature at data cutoff. In a prespecified subgroup analysis in pts w/ prior ICI, mPFS was numerically longer w/ Tela+Cabo than Pbo+Cabo (11.1 vs 9.2 mo, respectively; unstratified HR = 0.77; 95% CI: 0.56, 1.06). In the Pbo+Cabo arm, mPFS was 9.2 mo for pts w/ prior ICI exposure and 9.5 mo for pts without, and ORR was 32% and 20%, respectively; if ICI included nivo/ipi, ORR was 37%. Rates of adverse events (AEs) were similar between arms.Grade 3-4 AEs occurred in 71% of Tela+Cabo pts and 79% of Pbo+Cabo pts and included hypertension (17% vs 18%) and diarrhea (15% vs 13%). Cabo was discontinued due to AEs in 10% of Tela+Cabo pts and 15% of Pbo+-Cabo pts. **Conclusions:** The addition of Tela did not improve the efficacy of Cabo in mRCC in this study. Tela+Cabo was well tolerated with AEs consistent with known risks of both agents. The study provides valuable insight on efficacy outcomes of a contemporary population of pts w/ mRCC who receive Cabo in the 2/3L setting. Clinical trial information: NCT03428217. Research Sponsor: Calithera Biosciences, Inc.

4502 **Oral Abstract Session**

Health-related quality-of-life (HRQoL) analysis from the phase 3 CLEAR trial of lenvatinib (LEN) plus pembrolizumab (PEMBRO) or everolimus (EVE) versus sunitinib (SUN) for patients (pts) with advanced renal cell carcinoma (aRCC). *First Author: Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: LEN + PEMBRO improved PFS, OS and ORR vs SUN in the first-line treatment of pts with aRCC; LEN + EVE improved PFS and ORR vs SUN (Motzer R et al. *NEJM.* 2021). We report results of a secondary objective of the CLEAR trial comparing the impact of LEN + PEMBRO or EVE vs SUN, on HRQoL. **Methods:** Pts (N=1069) were randomized (1:1:1) to receive LEN 20 mg PO QD + PEMBRO 200 mg IV Q3W; LEN 18 mg + EVE 5 mg PO QD; or SUN 50 mg PO QD (4 wks on/2 wks off). HRQoL was assessed per FKSI-DRS, EORTC QLQ-C30, and EuroQoL EQ-5D-3L, at baseline, on day 1 of subsequent 3 wk cycles starting with cycle 2, and at the off-treatment visit. HRQoL analyses (unless otherwise noted) were based on data from randomized pts with any HRQoL data who received ≥1 dose of study treatment. No adjustments for multiple testing or estimation were used; *P*-values and CIs are nominal and descriptive. **Results:** For comparisons of LEN + PEMBRO vs SUN, overall changes from baseline at mean follow-up (wk 46) favored LEN + PEMBRO with significant differences between treatments for physical functioning (least squares mean difference [LS MD] [95% CI]: 3.0 [0.5, 5.5]) and fatigue (−2.8 [−5.5, −0.1]), dyspnea (−2.8 [−5.3, −0.3]), and constipation (−2.2 [−4.2, −0.2]). LS MD of the FKSI-DRS total score was 0.2 (−0.4, 0.7). For comparisons of LEN + EVE vs SUN, overall changes from baseline at wk 46 favored SUN with significant differences in overall HRQoL (−2.8 [−5.1, −0.5] assessed by the EORTC QLQ-C30 GHS/QoL scale) and pain (2.8 [0.1, 5.5]), appetite loss (4.2 [1.3, 7.1]), and diarrhea (5.3 [2.6, 7.9]). LS MD of the FKSI-DRS total score was −0.4 (−1.0, 0.2). 14 of 18 scales for both LEN + PEMBRO and LEN + EVE vs SUN had no significant differences in LS MD comparisons. The LEN + PEMBRO arm is favored over SUN for the median time to first deterioration (TTD) for physical functioning, dyspnea, appetite loss and EQ-5D VAS (Table). 15 of 19 scales for both LEN + PEMBRO and LEN + EVE vs SUN had no significant differences in TTD comparisons. **Conclusions:** Compared with SUN, pts in LEN + PEMBRO group had similar or better symptoms and HRQoL. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Time to first deterioration.

	Median TTD, wks			HR (95% CI)	
Scale	LEN + PEMBRO	LEN + EVE	SUN	LEN + PEMBRO vs SUN	LEN + EVE vs SUN
FKSI-DRS total score (3-point MID)	9.1	7.9*	12.1	1.1 (0.9, 1.4)	1.2 (1.0, 1.5)
EORTC QLQ-C30: Physical functioning	15.3*	9.4	12.7	0.8 (0.7, 1.0)	1.1 (0.9, 1.3)
Pain	7.1	6.1*	9.9	1.1 (0.9, 1.3)	1.3 (1.1, 1.5)
Dyspnea	39.3*	18.4	21.1	0.8 (0.6, 1.0)	1.1 (0.9, 1.3)
Appetite Loss	18.3*	8.9	9.1	0.8 (0.7, 1.0)	1.2 (1.0, 1.4)
Diarrhea	15.4	9.6*	15.1	0.9 (0.7, 1.1)	1.3 (1.1, 1.6)
EQ-5D Index	9.1	6.3*	15.0	1.1 (0.9, 1.3)	1.3 (1.1 ,1.5)
EQ-5D VAS (7-point MID)	9.4*	6.4	9.1	0.8 (0.7, 1.0)	1.1 (0.9, 1.3)

*Statistically significant log-rank difference of distribution of TTD ($P<0.05$) vs SUN.

4503 **Oral Abstract Session**

Phase 2 trial of gemcitabine, cisplatin, plus nivolumab with selective bladder sparing in patients with muscle- invasive bladder cancer (MIBC): HCRN GU 16-257. *First Author: Matt D. Galsky, Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Transurethral resection of bladder tumor (TURBT) plus systemic therapy has been known for decades to achieve durable bladder-intact survival in a subset of patients with MIBC but efforts to advance this paradigm have been complicated by (a) lack of prospective studies exclusively testing cisplatin-based neoadjuvant chemotherapy, (b) lack of rigorous methods to define clinical complete response (cCR) and its association with long term outcomes and (c) limited understanding of the role of "salvage" cystectomy. **Methods:** Eligible patients were cisplatin-eligible with cT2-T4aN0M0 urothelial bladder cancer. Patients received 4 cycles of gemcitabine, cisplatin, plus nivolumab followed by clinical restaging including urine cytology, MRI/CT of the bladder, cystoscopy and bladder/prostatic urethral biopsies. Patients achieving a cCR (normal cytology, imaging, and cT0/Ta) were eligible to proceed without cystectomy and receive nivolumab q2 weeks x 8 followed by surveillance; otherwise, patients underwent cystectomy. Coprimary endpoints included (1) cCR rate and (2) ability of cCR to predict 2-year metastasis-free survival (MFS). The key secondary endpoint was the impact of genomic alterations in baseline TURBT (TMB, ERCC2, FANCC, RB1, ATM) on performance of cCR for predicting MFS. The cCR rate coprimary endpoint, and interim analysis of 1-year outcomes, are reported. **Results:** Between 8/2018-11/2020, 76 patients were enrolled at 7 sites (male 79%, median age 69; cT2 = 56% , cT3 = 32% , cT4 = 12%) and 64 (84%) have completed post-cycle 4 restaging; 31/64 achieved a cCR (48%; 95% CI 36%, 61%). The median follow-up of cCR patients is 13.7 months (range, 2.5-24 months). One cCR patient opted for immediate cystectomy (pTaN0M0). Outcomes for the entire cohort are summarized in the table below. Local recurrence has occurred in 8/31 cCR patients and 6 underwent cystectomy (pT0N0 = 1, pTaN0 = 1, pTisN0 =1, pT2N0 = 2, pT4N1 = 1). TMB ≥ 10 mut/Mb (p=0.02) or mutant ERCC2 (p=0.02) were associated with cCR or pT0. **Conclusions:** TURBT + gemcitabine, cisplatin, plus nivolumab achieves stringently defined cCR in a large subset of patients with MIBC. 1-year bladder intact survival is possible though the durability of responses, and role of genomic biomarkers in management algorithms, requires longer follow-up. Clinical trial information: NCT03558087. Research Sponsor: BMS, Other Foundation.

% at 1 year	Group	N	Estimate	95% CI
Alive	Overall	76	92.4%	80.9%, 97.1%
	cCR	31	100%	NA
	Non-cCR	33	87.7%	66.2%, 95.8%
Alive, bladder intact	cCR	31	81.2%	60.4%, 91.7%
	Non-cCR	33	11%	2.9%, 25%
Alive, metastasis free	cCR	31	100%	NA
	Non-cCR	33	79.5%	57.4%, 90.9%
Alive, local recurrence free	cCR	31	78%	54.6%, 90.3%

4504 **Oral Abstract Session**

Pembrolizumab (pembro) in combination with gemcitabine (Gem) and concurrent hypofractionated radiation therapy (RT) as bladder sparing treatment for muscle-invasive urothelial cancer of the bladder (MIBC): A multicenter phase 2 trial. *First Author: Arjun Vasant Balar, Perlmutter Cancer Center at NYU Langone Health, New York, NY*

Background: Trimodality bladder preservation therapy (TMT) is a standard treatment option for clinically localized MIBC with curative intent. Pembro has shown activity in MIBC in the neoadjuvant setting and may combine well with TMT to improve outcomes. This trial evaluated the safety and efficacy of pembro added to TMT in MIBC. **Methods:** This multicenter phase 2 trial included pts with cT2 – T4aNOM0 MIBC who declined or were ineligible for cystectomy (RC), ECOG PS 0/1, eGFR > 30 cc/min, and no contraindications to pelvic RT or pembro. No perioperative chemotx for MIBC was permitted. Pts received pembro 200 mg x 1 followed 2-3 weeks by maximal TURBT and then whole bladder RT (52 Gy/20 fx; IMRT preferred) with twice wkly gem 27 mg/m2 and pembro Q3 wks x 3 treatments. 12 wks post-RT, CT/MR AP, TUR of tumor bed and cytology were performed to document response. Up to 6 pts were enrolled to a safety cohort (SC) followed by 48 pts in efficacy cohort (EC). The primary endpt is 2-yr bladder-intact disease-free survival (BIDFS: first of MIBC or regional nodal recurrence, distant metastases, or death) assessed by serial cysto/cytology and CT/MRI. EC had 85% power to detect a 20% absolute improvement in 2-yr BIDFS rate over 60% historical rate (RTOG Pooled analysis; Mak JCO 2014). Key secondary endpts were safety, 12 wks CR rate, metastases-free survival and overall survival. Tumor tissue was collected at study entry, maximal TURBT and post-treatment TUR of tumor bed with serial PBMCs for correlative analyses. **Results:** From 5/2016 to 10/2020, 54 pts (6 SC, 48 EC; 72% M) enrolled at 5 centers; Median age 67 (65-89) for SC and 74 (51-97) for EC. C-stage (74% cT2, 22% cT3, and 4% cT4). 39 (72%) declined RC. All 6 pts in SC and 42/48 (88%) of EC pts completed all study therapy; 1/48 (2%), 2/48 (4%), and 4/48 (8%) discontinued RT/Gem, Gem or Pembro, respectively, most often due to toxicity. As of 1/2021 (median F/U 40.9 mos (38.6-50.8) SC and 11.7 mos (0.6 – 32.2) EC), no recurrences in SC, and 12/48 EC pts had any recurrence (6 NMIBC, 0 MIBC, 2 regional and 4 distant). The estimated 1 yr BIDFS rate is 77% (95% CI: 0.60-0.87). 12 wks CR rate was 100% in SC and 83% for EC (1 PR, 3 NR, 1 Progression, 11 NE; 2 still on active study). In the EC, 35% of pts had a Gr ≥3 TEAE (Gr 3 events included UTI 8%, diarrhea 4%, colitis 4%, bladder pain/obstruction 4%, neutropenia 2%, thrombocytopenia 2%). Notable Pembro Gr ≥3 TRAE included 3 pts (6%) Gr 3 GI toxicity and 1 pt Gr 4 colonic perforation. 1 patient died due to fungemia, unrelated to study therapy. **Conclusions:** Pembro added to hypofractionated RT and twice weekly gem was well-tolerated with promising efficacy in this early analysis. Pembro-related toxicity was consistent with prior monotherapy trials. Selected correlative analyses from serially collected blood and tissue specimens will be presented. Clinical trial information: NCT02621151. Research Sponsor: Merck, U.S. National Institutes of Health.

4505 **Oral Abstract Session**

Phase II trial of durvalumab plus tremelimumab with concurrent radiotherapy (RT) in patients (pts) with localized muscle invasive bladder cancer (MIBC) treated with a selective bladder preservation approach: IMMUNOPRESERVE-SOGUG trial. *First Author: Xavier Garcia del Muro, Medical Oncology. Institut Català d'Oncologia (ICO) L'Hospitalet del Llobregat, Barcelona, Spain*

Background: Bladder-preserving combined-modality therapies constitute an alternative to radical cystectomy for selected pts with MIBC. In preclinical studies, combination of radiation and dual checkpoint blockade appears to activate non-redundant immune mechanisms, potentiating antitumor activity. The purpose of the present study is to explore feasibility, toxicity and activity of this approach in MIBC. **Methods:** Pts with localized MIBC in clinical stages T2-4a N0 M0, ECOG 0-1, without contraindications to immunotherapy, who either wished for bladder preservation or were ineligible for cystectomy, were included in this phase II study. Treatment consisted of initial transurethral resection (TUR) of the tumor, followed by durvalumab 1,500 mg i.v. plus tremelimumab 75 mg i.v., every 4 weeks for 3 doses. Normofractionated external-beam RT was started 2 weeks later, at doses of 46 Gy to minor pelvis and 64-66 Gy to bladder. Pts with either residual or relapsed MIBC were offered salvage cystectomy. The primary endpoint was complete response (CR) defined as absence of MIBC at post-treatment tumor site biopsy. A 2-stage sequential design was used (CR rate P0=5, P1=0.7, α=0.10, β=0.20) requiring at least 6 CR in the first 12 pts to expand to a second cohort of 20 pts. **Results:** From 1/2019 to 8/2020, 32 pts were enrolled at 6 centers. Median age was 71 years (49-91). PS was 0 in 24 pts,1 in 8. 25 were males. Clinical stage was T2 in 28 pts, T3 in 3 and T4a in 1. All pts received at least two immunotherapy cycles. The median dose of RT administered was 64 Gy (60-65). CR at post-treatment biopsy was documented in 26 (81%) pts, 2 pts had residual MIBC and 4 pts were not evaluated due to rejection (1), clinical impairment (1), death from COVID 19 (1) and a suspected treatment-related death from peritonitis (1). After a median follow up of 6.1 months (2.5 - 20.1), 2 pts underwent salvage cystectomy because of MIBC and T1 relapses, respectively. The estimated 6-months rates for disease-free survival (DFS) with bladder intact, DFS and overall survival were 76% (95%CI, 61%-95%), 80% (95%CI, 66%-98%) and 93% (95%CI, 85%-100%), respectively. A total of 31 (97%) pts experienced adverse events related to RT and/or immunotherapy, with diarrhea (41%) and urinary disorders (37.5%) as the most frequent. Grade 3 or 4 adverse events related to therapy were reported in 31% pts, being the most frequent gastrointestinal toxicity (12.5%), acute kidney failure (6%) and hepatitis (6%). **Conclusions:** A combined-modality approach including durvalumab + tremelimumab with concurrent RT is feasible and safe, showing high efficacy in terms of response and eliciting bladder preservation in a large number of pts. Further research on this approach as an alternative to cystectomy is warranted. Clinical trial information: NCT03702179. Research Sponsor: AstraZeneca, Spanish Oncology Genitourinary Group (SOGUG).

4507 **Oral Abstract Session**

A randomized phase II study comparing cisplatin and gemcitabine with or without berzosertib in patients with advanced urothelial carcinoma. *First Author: Sumanta K. Pal, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Cisplatin with gemcitabine (CG) remains the standard upfront chemotherapy regimen for metastatic urothelial cancer (mUC). Preclinical synergy was noted between cisplatin and berzosertib, a selective ATR inhibitor. The current study sought to determine if the combination of berzosertib and CG could improve clinical outcomes in mUC. **Methods:** An open-label, randomized study was conducted across 23 centers in the United States through the Experimental Therapeutics Clinical Trials Network of the National Cancer Institute. Key eligibility criteria included confirmed mUC, no prior cytotoxic therapy for metastatic disease, ≥ 12 months since perioperative therapy and eligibility for cisplatin based on standard criteria. Patients (pts) were randomized to receive either CG alone (control arm) or CG plus berzosertib (experimental arm). In the control arm, 70 mg/m^2 of cisplatin was given on day 1 and gemcitabine at 1000 mg/m^2 on days 1 and 8 of a 21-day cycle. In the experimental arm, 60 mg/m^2 of cisplatin was given on day 1, gemcitabine at 875 mg/m^2 on days 1 and 8 and berzosertib at 90 mg/m^2 on days 2 and 9 of a 21-day cycle. The primary endpoint of the study was progression-free survival (PFS), with secondary endpoints including response rate (RR), overall survival (OS) and toxicity. **Results:** A total of 87 pts (median age 67; M:F 68:19) were randomized; 41 pts received CG alone while 46 received CG with berzosertib. Visceral metastases were present in 49% of pts and 52%, 45% and 3% of pts were Bajorin risk 0, 1 and 2, respectively. Median PFS was 8.0 months for both arms (Bajorin risk adjusted hazard ratio [HR] 1.22, 95% confidence interval [CI] 0.72-2.08). RR was 54%(4 CR, 21 PR) in the CG with berzosertib arm and 63% (4 CR, 22 PR) in CG alone arm (P = 0.66). Median OS was shorter with CG with berzosertib as compared to CG alone (14.4 versus 19.8 months; Bajorin risk adjusted HR 1.42, 95%CI 0.76-2.68). Notably higher rates of grade 3/4 thrombocytopenia (59% vs 39%) and neutropenia (37% vs 27%) were observed with CG plus berzosertib compared to CG alone. Higher rates of toxicity-related discontinuation were seen in the experimental arm (24% vs 15%), and the median cumulative cisplatin dose in the experimental arm was 250 mg/m^2, as compared to 370 mg/m^2 in the control arm (P < 0.001). **Conclusions:** No improvement in PFS was observed with the addition of berzosertib to CG, and a trend towards inferior survival was observed. These results suggest caution in reducing the starting dose of cytotoxic therapy to accommodate addition of a myelosuppressive agent, as in the experimental arm of this study. Clinical trial information: NCT02567409. Research Sponsor: U.S. National Institutes of Health.

4508 **Oral Abstract Session**

First-line pembrolizumab (pembro) in cisplatin-ineligible patients with advanced urothelial cancer (UC): Response and survival results up to five years from the KEYNOTE-052 phase 2 study. *First Author: Peter H. O'Donnell, The University of Chicago, Chicago, IL*

Background: Pembro was approvedfor cisplatin-ineligible patients with untreated advanced UC based on initial results of the phase 2 KEYNOTE-052 study (NCT02335424), which showed an ORR of 29%. Updated results after up to 5 years of follow-up are presented. **Methods:** KEYNOTE-052 is a single-arm, multi-site, open-label trial. Patients had advanced or metastatic UC, were cisplatin ineligible (criteria: ECOG PS 2, CrCl ≥30 to ~60 mL/min, grade ≥2 peripheral neuropathy/hearing loss, NYHA class III heart failure), and had not previously received chemotherapy for advanced/metastatic disease. Patients received pembro 200 mg IV Q3W until progression, unacceptable toxicity, withdrawal, or 24 mo of therapy, whichever occurred first. PD-L1 status was determined by combined positive score (CPS, number of PD-L1–staining cells [tumor cells, lymphocytes, macrophages] divided by the total number of viable tumor cells, multiplied by 100); PD-L1–positive was CPS ≥10. The primary end point was confirmed ORR (RECIST v1.1, independent central review). Key secondary end points were duration of response (DOR), OS, and safety. **Results:** Among 370 enrolled patients, median age was 74 y, 315 (85.1%) had visceral disease, and 43 (11.6%) completed 24 mo of therapy. Median time from enrollment to data cutoff (Sep 26, 2020) was 56.3 mo (range, 51.2-65.3) for all patients and 56.0 mo (range, 51.4-65.2) for the 110 patients (29.7%) with CPS ≥10. Confirmed ORR for all patients was 28.9% (95% CI, 24.3-33.8); complete response, 9.5% (n=35); partial response, 19.5% (n=72). Median DOR was 33.4 mo (range, 1.4+ to 60.7+); 44.8% and 39.4% of patients had DOR ≥36 and ≥48 mo, (Kaplan-Meier estimates). Median OS was 11.3 mo (95% CI, 9.7-13.1); 24- and 36-mo OS rates were 31.5% and 22.1%. Patients with CPS ≥10 had better outcomes than patients with CPS <10 (Table). Treatment-related adverse events (AEs) occurred in 67.3% of patients; 21.1% of treatment-related AEs were grade ≥3, including 1 death (myositis). **Conclusions:** After up to 5 y of follow-up, pembro continued to elicit clinically meaningful, durable antitumor activity in cisplatin-ineligible patients with advanced UC. These effects were more pronounced in patients with CPS ≥10. Clinical trial information: NCT02335424. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Efficacy results.

	CPS <10 n=251	CPS ≥10 n=110	Total N=370
Confirmed ORR, % (95% CI)	20.7 (15.9-26.3)[a]	47.3 (37.7-57.0)[a]	28.9 (24.3-33.8)[b]
DOR, median (range), mo	21.2 (1.6+ to 59.7+)[a]	NR (1.4+ to 60.7+)[a]	33.4 (1.4+ to 60.7+)[b]
DOR ≥36 months, %	34.4	57.6	44.8
DOR ≥48 months, %	27.4	57.6	39.4
OS, median (95% CI), mo	9.7 (7.6-11.5)	18.5 (12.2-28.5)	11.3 (9.7-13.1)
OS at 36 months, % (95% CI)	15.4 (11.2-20.1)	35.8 (26.9-44.7)	22.1 (18.0-26.5)

[a]52 responders. [b]107 responders; 3 had unknown PD-L1 status.

4509 Poster Discussion Session; Discussed in Poster Discussion Session

Nivolumab plus cabozantinib in patients with non-clear cell renal cell carcinoma: Results of a phase 2 trial. *First Author: Chung-Han Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cabozantinib plus nivolumab (CaboNivo) improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) over sunitinib in a phase 3 trial for metastatic clear cell renal cell carcinoma (RCC). (Choueiri, abstract 6960, ESMO 2020) We report the results of a phase 2 trial of CaboNivo in patients (pts) with non-clear cell RCC. **Methods:** Pts had advanced non-clear cell RCC, 0 or 1 prior systemic therapies excluding prior immune checkpoint inhibitors, and measurable disease by RECIST. Cabo 40 mg/day plus Nivo 240 mg every 2 weeks or 480 mg every 4 weeks was given across two cohorts. Cohort 1: papillary, unclassified, or translocation associated RCC; Cohort 2: chromophobe RCC. The primary endpoint was ORR by RECIST; secondary endpoints included PFS, OS, and safety. Cohort 1 was a single stage design that met its primary endpoint and was expanded to produce more precise estimates of ORR. Cohort 2 was a Simon two-stage design that closed early for lack of efficacy. Correlative analyses by next generation sequencing were performed and to be presented. **Results:** A total of 40 pts were treated in Cohort 1, and 7 pts were treated in Cohort 2 (data cutoff: Jan 20, 2021). Median follow up time was 13.1 months (range 2.2 – 28.6). In Cohort 1, 26 (65%) pts were previously untreated, and 14 (35%) pts had 1 prior line: 10 (25%) received prior VEGF-targeted therapy and 8 (20%) received prior mTOR-targeted therapy. ORR for Cohort 1 was 48% (95% CI 31.5–63.9; Table). Median PFS was 12.5 months (95% CI 6.3–16.4) and median OS was 28 months (95% CI 16.3–NE). No responses were seen among 7 patients in Cohort 2 with chromophobe histology (Table). Grade 3/4 treatment emergent adverse events were consistent with that reported in the phase 3 trial; Grade 3/4 AST and ALT were 9% and 15%, respectively. Cabozantinib and nivolumab were discontinued due to toxicity in 17% and 19% of pts, respectively. **Conclusions:** CaboNivo had an acceptable safety profile and showed promising efficacy in metastatic non-clear cell RCC pts with papillary, unclassified, or translocation associated histologies whereas activity in patients with chromophobe RCC was limited. Clinical trial information: NCT03635892. Research Sponsor: Exelixis, BMS.

Cohort 1: Papillary, Unclassified, Translocation Associated	Any Line (N = 40)	1st Line (N = 26)	2nd Line (N = 14)
ORR	19 (48%)	14 (54%)	5 (36%)
PR	19 (48%)	14 (54%)	5 (36%)
SD	20 (50%)	12 (46%)	8 (57%)
PD	1 (3%)	0 (0%)	1 (7%)
Cohort 2: Chromophobe	**Any Line (N = 7)**		
ORR	0 (0%)		
PR	0 (0%)		
SD	5 (71%)		
PD	1 (14%)		
Not Evaluable	1 (14%)		

4510 Poster Discussion Session; Discussed in Poster Discussion Session

Phase II study of nivolumab and salvage nivolumab + ipilimumab in treatment-naïve patients (pts) with advanced non-clear cell renal cell carcinoma (nccRCC) (HCRN GU16-260-Cohort B). *First Author: Michael B. Atkins, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC*

Background: The HCRN GU16-260 trial reported on the efficacy and toxicity of nivo monotherapy in treatment naïve clear cell RCC (Cohort A) and the efficacy of nivo/ipi salvage therapy in pts with tumors resistant to initial nivo monotherapy (Atkins JCO 2020.38.15_suppl.5006). Limited information is available on the effects of such an approach in pts with advanced nccRCC. **Methods:** Eligible pts with treatment-naïve nccRCC received nivo 240mg IV q2 wk x 6 doses followed by 360mg IV q3 wk x 4 doses followed by 480 mg q4 wk until progressive disease (PD), toxicity, or completion of 96 wks of treatment (Part A). Pts with PD prior to or stable disease (SD) at 48 wks (pSD) were potentially eligible to receive salvage nivo (3mg/kg) /ipi (1 mg/kg) q3 wk x 4 doses followed by q4 wk nivo maintenance for up to 48 wks (Part B). All pts were required to submit tissue from a metastatic lesion obtained within 12 months (mo) prior to study entry and prior to enrolling on Part B for correlative studies. **Results:** 35 pts with nccRCC were enrolled between 5/2017 and 12/2019 at 12 participating HCRN sites. Median age 63 (range 35-84 years); 89% male. IMDC favorable 8 (23%), intermediate 18 (51%) and poor risk 9 (26%). Of the 35 pts 19 (54%) had papillary, 6 (17%) chromophobe and 10 (29%) unclassified histology. RECIST defined ORR was 5 of 35 (14.3%) [CR 2 (5.7%), PR 3 (8.6%)], SD 16 (45.7%), PD 14 (40.0%). Immune-related ORR was 8 of 35 (22.9%). RECIST ORR by histology was: papillary - 1/19 (5%); chromophobe - 1/6 (17%); unclassified - 3/10 (30%). 9 pts (26%) had tumors with sarcomatoid features with 3 (33%) (2 unclassified, 1 papillary) responding. Median PFS was 4.0 (2.7, 4.3) mo. 21 pts remain alive. None of the responders have progressed or died. 28 pts (25 PD, 3 pSD) were potentially eligible for salvage nivo/ipi (Part B), but 12 did not enroll due to symptomatic PD (2), grade 3-4 toxicity on nivo (3), or other including no biopsy tissue (7). In the 16 Part B pts, best response to nivo/ipi was: PR (1, 6%) – (unclassified/non-sarcomatoid); SD (7, 44%); PD (8, 50%). Grade 3 Treatment-related adverse events (TrAEs) were seen in 7/35 (20%) on nivo. Grade 3-5 TrAEs were seen in 7/16 (44%) on nivo/ipi with 1 pt experiencing sudden death. Correlative studies including PD-L1 status, WES and RNAseq are pending. **Conclusions:** Nivo monotherapy has limited activity in treatment naïve nccRCC with most responses (4 of 5) seen in pts with sarcomatoid and/or unclassified tumors. Toxicity is consistent with prior nivo studies. Salvage treatment with nivo/ipi was provided in 16 of 28 (57%) pts with PD/pSD on nivo monotherapy, with 1 response observed. Clinical trial information: NCT03117309. Research Sponsor: Bristol Meyers Squibb, Other Government Agency.

4511 Poster Discussion Session; Discussed in Poster Discussion Session

Clinical activity of durvalumab and savolitinib in MET-driven, metastatic papillary renal cancer. *First Author: Cristina Suarez Rodriguez, Vall d' Hebron University Hospital, Barcelona, Spain*

Background: Savolitinib is a potent and selective MET inhibitor with activity in MET-driven papillary renal cancer (PRC). Durvalumab is a PD-L1 inhibitor which has been tested in combination with savolitinib in metastatic PRC with response rates of 29% (12/41). Here we describe the efficacy of this combination in MET-driven metastatic PRC. **Methods:** This single arm phase I/II trial explored durvalumab (1500mg Q4W) and savolitinib (600mg OD) together in metastatic PRC, with a 4wk savolitinib run in. Biomarker analysis results were compared with responses to treatment as planned in the protocol. The analysis presented here focuses on those patients with MET DNA alterations (central analysis:chromosome 7 gain/MET or HGF amplification/MET kinase domain mutations). Confirmed response rate (RR) (RECIST v1.1), progression-free survival (PFS), tolerability (CTCAE v4.03) and overall survival (OS) were analysed. **Results:** 42 patients were enrolled in the metastatic papillary cohort, of which 41 patients received treatment. The median follow up was 26.8 months. The confirmed RR was 29% (12/41) and median PFS was 4.9 months (95% CI 2.5-10.0). 14/41 (34%) of these patients had MET-driven disease. 71% (10/14) of MET-driven patients had not previously received systemic therapy and 7% (1/14) were PD-L1 positive. IMDC good, intermediate, and poor risk disease occurred in 36% (5/14), 57% (8/14), and 7% (1/14) of MET-driven patients respectively. Confirmed RR in MET-driven patients was 57% (8/14) with duration of response at 9.4 months (95% CI 3.9-Not reached [NR]). Median PFS and OS in MET-driven patients were 10.5 months (95% CI 2.9-15.7) and 27.4 months (95% CI 7.3-NR) respectively. No new safety signals were seen. **Conclusions:** The combination of savolitinib and durvalumab has clinical activity in MET-driven PRC. A randomised phase III study is planned based upon these data. Clinical trial information: NCT02819596. Research Sponsor: AstraZeneca.

4512 Poster Discussion Session; Discussed in Poster Discussion Session

Vorolanib, everolimus, and the combination in patients with pretreated metastatic renal cell carcinoma (CONCEPT study): A randomized, phase 3, double-blind, multicenter trial. *First Author: Xinan Sheng, Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: The combination of agents targeting both VEGF- and mTOR-mediated pathways has been investigated in renal cell carcinoma (RCC). We conducted the CONCEPT study to assess vorolanib, everolimus, or their combination as second-line treatment in Chinese patients (pts) with metastatic RCC. **Methods:** Pts with cytologically or histologically confirmed RCC who had disease progression after one prior VEGFR-TKI were eligible for participation in the study. They will be randomized by 1:1:1 ratio to receive matching placebo plus vorolanib or everolimus, or the combination. The primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), objective response rate (ORR), and safety. **Results:** Between November 2016 and June 2019, 399 pts (133 pts in each group) were enrolled. At the data cutoff (October 23, 2020), the median PFS in combination group was significantly longer than that in single-agent everolimus group (10.0 months [95% CI, 8.2-10.4] vs. 6.4 months [95% CI, 4.7-8.3]; HR = 0.70 [95% CI, 0.52-0.94]; P = 0.0171), while the median PFS was similar between single-agent vorolanib group and single-agent everolimus group (6.4 months [95% CI, 4.6-8.3] vs. 6.4 months [95% CI, 4.7-8.3]; HR = 0.94 [95% CI, 0.69-1.24]; P = 0.6856). An objective response was achieved by 33 (24.8%) of 133 pts allocated vorolanib plus everolimus compared with 11 (8.3%) of 133 who received single-agent everolimus and 14 (10.5%) of 133 pts assigned single-agent vorolanib. OS was immature with no significant difference between pts assigned vorolanib plus everolimus (30.4 months [95% CI, 16.5-NE]) and those allocated single-agent everolimus (25.4 months [95% CI 19.4-NE]) or single-agent vorolanib (30.5 months [95% CI, 22.8-NE]). Treatment-related adverse event (TRAE) occurred in 132 (99%) of 133 pts with vorolanib plus everolimus, 127 (96%) of 133 pts with single-agent vorolanib and 131 (99%) of 133 pts with single-agent everolimus, respectively. Grade 3 or higher TRAEs occurred in fewer patients who received single-agent vorolanib (52 [39%]) than in those who received single-agent everolimus (71 [53%]) or vorolanib plus everolimus (96 [72%]). Safety profiles of both agents were consistent with previous studies. **Conclusions:** This is the first phase 3 study of combination of mTOR- and VEGF-targeted agents in second-line treatments. Vorolanib plus everolimus showed a PFS benefit for patients with metastatic RCC who have progressed after one previous VEGF-targeted therapy with a safe tolerance profile. Clinical trial information: NCT03095040. Research Sponsor: Betta pharmaceuticals.

4513 Poster Discussion Session; Discussed in Poster Discussion Session

First results of a randomized phase IB study comparing nivolumab/ipilimumab with or without CBM-588 in patients with metastatic renal cell carcinoma. *First Author: Luis A Meza, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Recent evidence suggests that the gut microbiome is a potent mediator of immune checkpoint inhibitor (ICI) activity in metastatic renal cell carcinoma (mRCC), with both specific bacterial species and cumulative microbial diversity driving response (Routy *et al* Science 2018; Salgia *et al* Eur Urol 2020). We examined whether the butyrate-producing bacterium *Clostridium butyricum*, the key constituent of CBM-588, could modulate the gut microbiome in patients (pts) with mRCC receiving nivolumab/ipilimumab (N/I) and secondarily improve clinical outcome. **Methods:** An open-label, randomized study was conducted, with key eligibility criteria including confirmed clear cell and/or sarcomatoid mRCC, intermediate/poor risk by IMDC criteria and no systemic therapy for metastatic disease. Patients were randomized 2:1 to receive either N/I+CBM-588 or N/I alone. N/I was dosed at 3 mg/kg and 1 mg/kg IV every 3 weeks for 12 weeks, followed by N at 480 mg IV every 4 weeks. CBM-588 was dosed orally at 80 mg bid. Stool was collected for bacteriomic profiling at baseline and 12 weeks. Metagenomic sequencing was employed using previously published methods (Dizman *et al* Cancer Med 2020). The primary endpoint of the study was change in *Bifidobacterium* spp. from baseline to week 12. Secondary endpoints included change in microbial diversity and clinical outcomes including response rate (RR) and progression-free survival (PFS). **Results:** 30 pts were randomized between April 2019 and Nov 2020; 1 pt was excluded after genomic sequencing clarified a diagnosis of sarcoma. Among 29 evaluable patients (21:8 M:F), median age was 66, 10 pts (34%) had sarcomatoid features and 24 pts (83%) were intermediate risk . Metagenomic sequencing of paired stool specimens showed an 8-fold increase in *B. bifidum* and a 6-fold increase in *B. adolescentis* in pts receiving N/I+CBM-588 from baseline to week 12. *C. butyricum* was detected only in pts receiving CBM-588. Pathogenic species (e.g., *Escherichia. coli* and *Klebsiella* spp.) were more prevalent in pts not receiving CBM-588. RR was significantly higher among pts receiving N/I+CBM-588 vs N/I alone (59% vs 11%; P = 0.024). Median PFS was also prolonged with the addition of CBM-588 to N/I (NR vs 11 weeks; $P < 0.001$). No significant difference in grade 3/4 toxicities were observed between study arms. **Conclusions:** This is the first randomized, prospective study to suggest enhancement of ICI response with a live bacterial product. The observed clinical impact is corroborated by biologic findings supporting gut modulation by CBM-588. Clinical trial information: NCT03829111. Research Sponsor: None.

4514 Poster Discussion Session; Discussed in Poster Discussion Session

Outcomes of patients who progressed while receiving avelumab + axitinib (A + Ax) and received subsequent treatment (Tx) in JAVELIN Renal 101. *First Author: Laurence Albiges, Department of Cancer Medicine, Gustave Roussy Cancer Campus, University of Paris Sud, Boston, MA*

Background: There are limited data on the outcomes of patients receiving second-line (2L) therapy following immunotherapies plus tyrosine-kinase inhibitors in the first-line (1L). We describe the outcomes of patients with advanced renal cell carcinoma (aRCC) who had received 1L A + Ax in the phase 3 JAVELIN Renal 101 trial and went on to receive subsequent Tx. **Methods:** At the cutoff date for the third interim analysis (April 28, 2020), patients who received 1L A + Ax (n = 442) and received any subsequent lines of Tx were assessed. We report the overall survival (OS), progression-free survival on next-line systemic therapy (PFS2) per type of Tx, and duration of 2L Tx. **Results:** Anticancer drug therapies were received by 204/442 patients following A + Ax Tx. Of patients who received a follow-up anticancer drug Tx, 163/204 received a single agent (SA), and 41/204 received a combination Tx (CT) regimen. The most common 2L SA was cabozantinib (60/163), and the most frequent 2L CT was everolimus + lenvatinib (12/41). OS, PFS2, and duration of treatment (DOT) for the various subgroups are summarized in the table below. Analyses on additional subgroups will also be presented. **Conclusions:** In patients with aRCC who received 2L CT following 1L treatment with A + Ax, long-term OS and PFS2 were observed. Clinical trial information: NCT02684006. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

	2L SA (n = 163)	2L SA cabozantinib (n = 60)	2L combination (n = 41)
18-mo OS (95% CI), %	75.8 (68.4, 81.7)	68.3 (55.0-78.5)	85.3 (70.2-93.1)
36-mo OS (95% CI), %	44.1 (35.9, 52.0)	36.9 (24.2-49.7)	63.4 (45.7-76.6)
mOS (95% CI), mo	30.4 (24.7, NE)	26.2 (21.3, 34.1)	NE (30.4 to NE)
18-mo PFS2 (95% CI), %	56.2 (48.0, 63.6)	52.6 (39.2-64.4)	65.9 (49.3-78.2)
mPFS2 (95% CI), mo	20.4 (17.6, 23.0)	18.2 (14.7-22.6)	24.1 (17.7 to NE)
mDOT (95% CI), mo	11.1 (8.4, NE)	19.1 (7.3 to NE)	12.9 (7.4 to NE)

mOS, median overall survival; mPFS2, median progression-free survival on next-line therapy; mDOT, median duration of treatment; NE, not estimable.

4515 Poster Discussion Session; Discussed in Poster Discussion Session

Safety and efficacy outcomes with nivolumab plus ipilimumab in patients with advanced renal cell carcinoma and brain metastases: results from the CheckMate 920 trial. *First Author: Hamid Emamekhoo, University of Wisconsin School of Medicine and Public Health, Madison, WI*

Background: Combination therapy with nivolumab plus ipilimumab (NIVO+IPI) has demonstrated long-term efficacy and tolerability in patients with previously untreated advanced renal cell carcinoma (aRCC). Previous phase 3 clinical trials of patients with advanced or metastatic cancers have mostly excluded patients with brain metastases. CheckMate 920 is an ongoing, phase 3b/4 clinical trial of NIVO+IPI treatment in patients with aRCC with a high unmet medical need. We present updated safety and efficacy results for the cohort of patients with aRCC of any histology and brain metastases from CheckMate 920 (NCT02982954). **Methods:** Patients with previously untreated advanced/metastatic aRCC of any histology, with asymptomatic brain metastases (not currently receiving corticosteroids or radiation), and Karnofsky performance status $\geq$ 70% were assigned to treatment with NIVO 3 mg/kg + IPI 1 mg/kg every 3 weeks $\times$ 4 doses followed by NIVO 480 mg every 4 weeks for $\leq$ 2 years or until disease progression/unacceptable toxicity. The primary endpoint was incidence of grade $\geq$ 3 immune-mediated adverse events (imAEs) within 100 days of last dose of study drug. Key secondary endpoints included progression-free survival (PFS) and objective response rate (ORR) by RECIST v1.1 (both per investigator). Exploratory endpoints included overall survival (OS). **Results:** Of 28 treated patients with brain metastases, 85.7% were men; median (range) age was 60 (38–87) years, and 14.3% had sarcomatoid features. With 24.5 months minimum follow-up of the 28 patients enrolled, median duration of therapy (range) was 3.4 (0.0–23.3) months for NIVO and 2.1 (0.0–3.3) months for IPI. No grade 5 imAEs occurred. Grade 3–4 imAEs by category were diarrhea/colitis (7.1%), hypophysitis (3.6%), rash (3.6%), hepatitis (3.6%), and diabetes mellitus (3.6%). Of the 25 patients who were evaluable for ORR, the ORR was 32.0% (95% CI, 14.9–53.5). No patients achieved complete response, 8 achieved partial response, and 10 patients had stable disease. Median time to response (range) was 2.8 (2.4–3.0) months. Median duration (range) of response was 24.0 (3.9–not estimable [NE]) months; 4 of 8 responders remain without reported progression. Of 28 patients, 7 (25%) had intracranial progression. Median PFS (n = 28) was 9.0 (95% CI, 2.9–12.0) months. Median OS (n = 28) was still not reached (95% CI, 14.1 months–NE). **Conclusions:** In patients with previously untreated aRCC and brain metastases, a population with high unmet medical need that is often underrepresented in clinical trials, the approved treatment regimen of NIVO+IPI followed by NIVO for aRCC showed no new safety signals and continues to show encouraging antitumor activity with longer follow-up. Clinical trial information: NCT02982954. Research Sponsor: Bristol Myers Squibb.

4516 Poster Discussion Session; Discussed in Poster Discussion Session

Survival benefit of nephrectomy prior to immunotherapy-based combinations in patients with metastatic renal cell carcinoma: An FDA pooled analysis. *First Author: Jaleh Fallah, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Immunotherapy-based combination therapies (IO-X) are standard of care for metastatic RCC (mRCC) in the frontline setting. Limited data is available on the role of cytoreductive nephrectomy prior to IO-X in patients (pts) with mRCC (Bakouny, et al. GU ASCO 2020). We assessed the correlation between nephrectomy prior to IO-X and overall survival (OS) in pts with de novo mRCC. **Methods:** We pooled data from trials submitted for FDA review of a checkpoint inhibitor combination as first-line treatment for pts with mRCC. We only included trials with available data for stage at initial diagnosis (dx) to identify pts with stage IV disease at initial dx and to exclude those with nephrectomy in the non-metastatic setting. Kaplan-Meier method was used to estimate median OS in pts with de novo mRCC with and without nephrectomy prior to IO-X. **Results:** Five trials met inclusion criteria, all of which evaluated IO in combination with a kinase inhibitor. Data for stage at initial dx was available in 1708 pts who received IO-X. The majority of pts were male (72%) and White (80%). Among the 849 pts (50%) with stage IV RCC at initial dx, 523 pts (62%) had nephrectomy prior to IO-X. All pts had clear cell histology; Sarcomatoid differentiation was present in tumor pathology of 25% and 10% of pts with and without prior nephrectomy, respectively. Proportion of pts with favorable, intermediate and poor risk disease was 10%, 70% and 20%, respectively. OS appeared better in those with stage IV disease at dx who had prior nephrectomy compared to pts without nephrectomy (Hazard ratio (HR) = 0.53, 95% CI: 0.42, 0.68), even after adjusting for age and prognostic risk group (HR = 0.59, 95% CI: 0.46, 0.75) (see table). **Conclusions:** In this retrospective exploratory analysis, nephrectomy prior to IO-X in pts with new dx of stage IV RCC appeared to be associated with improved OS, even when controlling for age and prognostic risk group. The decision for nephrectomy is affected by factors such as medical comorbidities which could not be completely controlled. Results should be considered hypothesis generating. Research Sponsor: None.

Pts with stage IV RCC at initial dx (N = 849)	Prior Nephrectomy (N = 523)	No Prior Nephrectomy (N = 326)	HR (95% CI)
Age, mean (SD)	59.8 (9.3)	62.3 (10.3)	
Months from diagnosis to randomization, median (IQR)	3.4 (1.9 , 8.0)	1.5 (1.0 , 2.5)	
Death events N (%)	139/523 (27%)	134/326 (41%)	
Favorable risk	9/44 (20%)	10/37 (27%)	0.69 (0.28 , 1.72)
Intermediate risk	93/397 (23%)	80/200 (40%)	0.47 (0.35 , 0.64)
Poor risk	37/82 (45%)	44/87 (51%)	0.84 (0.54 , 1.30)
Median OS (unadjusted HR)	NR (31.8 , NR)	24.5 (19.6 , NR)	0.53 (0.42 , 0.68)
Median OS (HR adjusted for age and prognostic risk group)	NR (31.8 , NR)	25.2 (19.8 , NR)	0.59 (0.46 , 0.75)

4517 Poster Discussion Session; Discussed in Poster Discussion Session

Neoadjuvant atezolizumab (A) with gemcitabine and cisplatin (GC) in patients (pts) with muscle-invasive bladder cancer (MIBC): A multicenter, single-arm, phase 2 trial. *First Author: Samuel Aaron Funt, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Neoadjuvant GC is standard for pts with MIBC and can result in pathologic downstaging to non-MIBC (< pT2N0) at radical cystectomy (RC), which correlates with improved survival. Based on the known activity of A in metastatic BC (mBC), we tested the combination of GC+A as neoadjuvant therapy for MIBC in a phase II trial (NCT02989584). **Methods:** Eligible pts with MIBC (cT2-T4aN0M0) received a single dose of A (1200 mg IV) and, two weeks later, began C (as either 70mg/m2 IV on D1 or 35 mg/m2 on D1,D8), G (1000 mg/m2 on D1,D8), and A (1200 mg IV on D8) every 21 days for 4 cycles followed by RC. Pts were also able to receive one additional dose of A 3 weeks after the last dose of A and prior to RC. The primary endpoint was proportion of pts with < pT2N0. Pts were considered not evaluable for the primary endpoint if they received less than 2 cycles due to withdrawal of consent or unrelated adverse events (AEs). Secondary endpoints included the proportion of pts with pT0N0, recurrence-free survival (RFS), and safety. We prespecified null and alternate < pT2N0 rates of 35% and 55%, respectively, with the null being rejected if at least 19 of 39 pts achieved < pT2N0. Pretreatment tumors underwent centralized PD-L1 staining (SP142; positive if ≥5% of immune cells). **Results:** Between Feb 2018 and May 2020, 44 pts were enrolled from five institutions. Five pts were not evaluable (withdrawal of consent before C3, n = 4; unrelated AEs during C1, n = 1). Of the 39 evaluable pts (cT2N0 79%, cT3N0 18%, cT4N0 3%), 1 pt refused surgery and was considered a non-responder. The primary endpoint was met, with 27 of 39 pts (69%) < pT2N0 at RC, including 15 (38%) pT0N0. All pts achieving < pT2N0 are alive and disease free. The median RFS was not reached with a median follow-up of 16.7 months (range: 7.7-33.2). The median time from last dose of chemotherapy to RC was 7.8 weeks (range 5.1 – 17). The most common grade 3-4 treatment related AEs were due to chemotherapy and were neutropenia (36%), lymphopenia (16%), and anemia (11%). Possible grade 3-4 immune related AEs included 2 pts with asymptomatic grade 3 pancreatic enzyme elevation, 1 pt with grade 3 pancreatitis, and 1 pt with hepatitis requiring steroids. Only 4 of 39 (10%) pts had PD-L1 positive tumors, which is low compared to mBC (25% positive; Powles et al. Lancet 2017) and MIBC (40% positive; Powles et al. Nature Med 2019) cohorts also tested with the SP142 clone. All 4 pts with PD-L1 positive tumors achieved < pT2N0. Twelve of 12 (100%) non-responding pts were PD-L1 negative and 23 of 27 (85%) responding pts were PD-L1 negative (p = 0.3). **Conclusions:** Neoadjuvant GC+A is an effective and safe regimen for the treatment of pts with MIBC. The PD-L1 positivity rate was low compared with other studies and was not predictive of pathologic downstaging. Additional interrogation of the genomic and host immune factors mediating response and resistance to GC+A is ongoing. Clinical trial information: NCT02989584. Research Sponsor: Genentech/Roche, Conquer Cancer Foundation of the American Society of Clinical Oncology.

4518 Poster Discussion Session; Discussed in Poster Discussion Session

PrE0807: A phase Ib feasibility trial of neoadjuvant nivolumab (N) without or with lirilumab (L) in cisplatin-ineligible patients (pts) with muscle-invasive bladder cancer (MIBC). *First Author: Petros Grivas, University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA*

Background: Neoadjuvant cisplatin-based chemotherapy (CT) prior to radical cystectomy (RC) improves overall survival (OS) in MIBC, but about half of pts are cisplatin-unfit or refuse it. Neoadjuvant immune checkpoint inhibitors can induce high pathologic complete response rate (ypT0N0). The combination of anti-PD-1 (N) and anti-KIR (L) is hypothesized to be safe and have significant activity based on the complementary and possibly synergistic roles in regulating adaptive and innate immune response in MIBC. **Methods:** This is a phase Ib multi-institutional trial in pts with localized MIBC treated with 2 neoadjuvant doses (4 weeks apart) of N alone (480 mg) in cohort 1 or N (480 mg) + L (240 mg) in cohort 2 prior to RC without adjuvant therapy (NCT03532451). Cohorts were enrolled sequentially and were not randomized. Key eligibility criteria included stage cT2-4aN0-1M0, ≥20% tumor content at TURBT and cisplatin-ineligibility (Galsky criteria) or refusal. Primary endpoint was safety manifested as rate of ≥G3 treatment related adverse events (TRAE) assessed in each cohort with CTCAE v5.0. Key secondary endpoints included the % of pts who had RC > 6 weeks after last neoadjuvant dose due to TRAE, CD8+ T cell density at RC, ypT0N0 and < ypT2N0 rates, CD8+ T cell density change between TURBT and RC, recurrence-free survival (RFS) and biomarkers in tumor tissue, blood and urine. **Results:** Among 43 pts enrolled (13 cohort 1, 30 cohort 2), median age was 75 (51-89), 67% were men, all had PS ECOG 0-1. Pts were cisplatin-ineligible due to impaired renal function (47%) and hearing loss (37%), while 14 % refused cisplatin. At baseline, 37 pts had cT2 stage, 2 had cN1 and 3 cNx. In cohort 1 and 2, 13 and 29 pts, respectively, completed intended neoadjuvant treatment, and 41/43 underwent RC (12/13 cohort 1, 29/30 cohort 2). One pt progressed to metastatic disease prior to RC (cohort 1) and 1 withdrew consent prior to being treated (cohort 2). Additionally, 1 patient was found to have cervical cancer at RC. Median time from last neoadjuvant dose to RC was 27 (95%CI: 24-29) days. There was no RC delayed > 6 weeks from treatment completion due to TRAE. G3 TRAEs occurred in 0% with N and 6.7% (90%CI 1.2-19.5%) in N+L (1: arthralgia, 1: gout, 2: hip pain) that all resolved. No G4/5 TRAEs occurred. Of 40 pts with MIBC and RC, ypT0N0 rates for N and N+L were 8% and 18%, while < ypT2N0 rates were 17% and 29%, respectively. Data on RFS and OS, and biomarker data were not yet mature. **Conclusions:** Neoadjuvant N alone and N+L combination prior to RC were safe, feasible and well tolerated in cisplatin-ineligible pts with MIBC, but ypT0N0 rates were unexpectedly low, especially with N alone. Two phase 3 trials (NCT03661320; NCT04209114) are evaluating the peri-operative role of N + chemotherapy +/- Linrodostat in cisplatin-fit and N +/- Bempeg in cisplatin unfit patients and are also assessing biomarkers. Clinical trial information: NCT03532451. Research Sponsor: Bristol Myers Squibb.

4519 Oral Abstract Session

Inducible T-cell co-stimulatory (ICOS) receptor agonist, feladilimab (fela), alone and in combination (combo) with pembrolizumab (P): Results from INDUCE-1 urothelial carcinoma (UC) expansion cohorts (ECs). *First Author: Arjun Vasant Balar, Perlmutter Cancer Center at NYU Langone Health, New York, NY*

Background: INDUCE-1 is a first-in-human trial evaluating fela, an IgG4 ICOS agonist non-T-cell depleting mAb, as monotherapy (mono) and in combo with P. ECs include tumor types, such as UC, with high ICOS expression and immunotherapy-favorable features. Fela induced IFNγ, increased PD-1/L1 expression, and enhanced antitumor activity in combo with PD-1 blockade nonclinically. We report preliminary efficacy, safety, and biomarker data of fela ± P in INDUCE-1 UC ECs. **Methods:** Eligible patients (pts) had recurrent/metastatic (R/M) UC of the upper or lower urinary tract, ≤6 prior systemic therapy lines in the advanced setting, measurable disease, and no active autoimmune disease. Pts received 0.3 or 1 mg/kg fela (mono EC; anti-PD-1/L1–experienced [exp] pts) or 0.3 mg/kg fela + 200 mg P (combo EC; anti-PD-1/L1–naïve pts) every 3 wks, up to 35 cycles until disease progression or unacceptable toxicity. Disease was assessed every 9 wks through wk 54, then every 12 wks. Archival and/or fresh biopsy tumor tissue was collected for biomarker analyses and safety assessed. **Results:** By Nov 6 2020, 13 anti-PD-1/L1–exp and 32 anti-PD-1/L1–naïve pts were evaluable in the mono and combo ECs, respectively. In the mono EC, median age was 69 yrs (range: 47–82), 92% of pts were male, and 85% received ≥2 prior therapy lines in the metastatic setting. In the combo EC, median age was 70 yrs (range: 42–84), 75% of pts were male, and 72% received ≥1 prior therapy line in the metastatic setting. In the mono EC, median duration of follow-up (mDoF) was 10.6 mo (range: 1.1–22.8); overall response rate (ORR) was 8% (1 partial response [PR]; 95% CI: 0.2, 36.0) with a duration of response (DoR) of 6.1 mo; disease control rate (DCR [response or stable disease for ≥9 wks]) was 23% (95% CI: 5.0, 53.8), and median overall survival (mOS) was 14.5 mo (95% CI: 2.8, NR), with 74% of pts alive at 6 mo. In the combo EC, mDoF was 9.6 mo (range: 0.9–28.3); ORR was 22% (7 PRs; 95% CI: 9.3, 40.0) with a median DoR of 8.3 months (range: 3.5–23.3+); DCR was 63% (95% CI: 43.7, 78.9), and mOS was 10.7 mo (95% CI: 5.2, 18.1), with 64% of pts alive at 6 mo. Grade ≥3 treatment-related AEs were reported for 0% and 9% of pts in the mono (N = 16) and combo (N = 44) safety populations, respectively. PD-L1 expression and ICOS-specific biomarkers are being evaluated, with promising trends observed in enrichment of clinical activity in preliminary analyses. **Conclusions:** Fela is the first ICOS agonist with reported single-agent activity in anti-PD-1/L1–exp relapsed/refractory UC. Fela + P in combo shows promising clinical activity and manageable safety in PD-1/L1–naïve R/M UC. Further study is warranted. Updated data to be presented. Funding: Study 204691 (NCT02723955) funded by GlaxoSmithKline in collaboration with Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA. Clinical trial information: NCT02723955. Research Sponsor: Study 204691 (NCT02723955) funded by GSK in collaboration with Merck Sharp & Dohme Corp, a subsidiary of Merck & Co, Inc, Kenilworth, NJ, USA.

4520 Poster Discussion Session; Discussed in Poster Discussion Session

Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC): Analysis of clinical and genomic subgroups from the JAVELIN Bladder 100 trial. *First Author: Thomas Powles, Barts Cancer Institute, Experimental Cancer Medicine Centre, Queen Mary University of London, St Bartholomew's Hospital, London, United Kingdom*

Background: In the phase 3 JAVELIN Bladder 100 trial, avelumab 1L maintenance + best supportive care (BSC) significantly prolonged overall survival (OS) vs BSC alone in patients (pts) with advanced UC that had not progressed on 1L platinum-based chemotherapy (HR, 0.69 [95% CI: 0.56, 0.86; 1-sided *P*= 0.0005]). We report post hoc analyses in previously unreported clinical and genomic subgroups. **Methods:** In JAVELIN Bladder 100 (NCT02603432), eligible pts had unresectable locally advanced or metastatic UC without progression after 4-6 cycles of 1L gemcitabine + cisplatin or carboplatin, and were randomized to receive avelumab + BSC (n = 350) or BSC alone (n = 350). The primary endpoint was OS, in all randomized pts and pts with PD-L1+ tumors (Ventana SP263 assay). In this exploratory analysis, we analyzed OS in disease stage and site subgroups, in pts with PD-L1+ tumors who received 1L gemcitabine + carboplatin, and in genomic subtypes (RNAseq whole-transcriptome profiling of tumor tissue) defined using data from The Cancer Genome Atlas (TCGA 2017). Interaction tests were not performed. **Results:** Prolonged OS was observed in the avelumab + BSC arm vs the BSC alone arm in pts with upper or lower tract tumors, metastatic or locally advanced (LA) and unresectable disease (prior to chemotherapy), and lymph node-only disease post-chemotherapy (Table). OS was also prolonged with avelumab + BSC in pts in PD-L1+ tumors who had received 1L gemcitabine + carboplatin, consistent with findings in the overall population. In genomic subtypes, the OS benefit for avelumab + BSC was apparent across TCGA subtypes except luminal. **Conclusions:** An OS benefit was seen for avelumab 1L maintenance + BSC vs BSC alone across subgroups of interest. Results are consistent with previously reported findings, further supporting avelumab 1L maintenance as a standard of care for pts with advanced UC that has not progressed with 1L platinum-containing chemotherapy. Clinical trial information: NCT02603432. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

	Pts, n		Median OS (95% CI), months		
Subgroup	Avelumab + BSC	BSC	Avelumab + BSC	BSC	HR (95% CI)
Upper tract	106	81	19.9 (15.3, NE)	17.4 (12.8, 33.0)	0.89 (0.578, 1.373)
Lower tract	244	269	22.5 (19.0, 28.3)	14.1 (11.8, 17.9)	0.62 (0.477, 0.802)
Metastatic disease	216	215	18.2 (13.8, 20.3)	14.1 (11.7, 17.3)	0.88 (0.678, 1.147)
LA and unresectable disease	133	133	NE (25.3, NE)	17.9 (13.5, NE)	0.40 (0.265, 0.617)
Lymph node-only disease*	48	39	NE (23.8, NE)	NE (10.7, NE)	0.55 (0.259, 1.152)
1L gemcitabine + carboplatin, PD-L1+ tumor	74	54	24.0 (18.6, NE)	16.1 (9.4, NE)	0.67 (0.393, 1.137)
TCGA: basal squamous	45	44	24.0 (16.0, NE)	17.9 (12.7, NE)	0.62 (0.326, 1.187)
TCGA: luminal	30	25	23.8 (12.5, NE)	NE (14.3, NE)	1.01 (0.403, 2.509)
TCGA: luminal infiltrated	143	143	19.9 (18.2, NE)	14.3 (12.8, 18.6)	0.68 (0.481, 0.968)
TCGA: luminal papillary	61	63	22.5 (18.2, 26.0)	13.4 (10.1, NE)	0.63 (0.370, 1.079)

NE, not estimable *Post-chemotherapy.

4521 **Poster Session**

Safety and efficacy of rogaratinib in combination with atezolizumab in cisplatin-ineligible patients (pts) with locally advanced or metastatic urothelial cancer (UC) and *FGFR* mRNA overexpression in the phase Ib/II FORT-2 study. *First Author: Jonathan E. Rosenberg, Department of Medicine, Genitourinary Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Rogaratinib (R) is a novel pan-FGFR inhibitor that showed promising efficacy and safety in a Phase I trial in pts with advanced solid tumors, including UC, with *FGFR1-3* mRNA overexpression. The Phase Ib/II FORT-2 study (NCT03473756) of R plus atezolizumab (A) in pts with first-line cisplatin-ineligible, *FGFR*-positive, advanced/metastatic UC previously identified a maximum tolerated dose of R 600 mg twice daily (BID) plus A (1200 mg every 3 weeks). We report updated safety, efficacy, and the recommended Phase II dose (RP2D) for combination therapy from the Phase Ib study. **Methods:** Pts with cisplatin-ineligible, locally advanced/metastatic UC with *FGFR1/3* mRNA overexpression detected by RNA *in situ* hybridization of archival tissue (RNAscope) received oral R 600 mg BID plus A 1200 mg on day 1 of a 21-day cycle. Archival tissue was examined for programmed cell-death ligand 1 (PD-L1) protein expression levels, *FGFR3*-activating mutations via a targeted Illumina NGS panel, and *FGFR* fusions via an Archer fusion plex assay. Primary objectives were safety, tolerability, and determination of the RP2D. **Results:** 26 pts (enrolled May 25, 2018 to Nov 25, 2020) were treated; 89% were male, median age was 76 years (range 47-85), 58% had an ECOG performance status of 1, and 77% displayed low or absent (negative or non-detectable) PD-L1 expression (combined positive score $< 10\%$). Common treatment-emergent adverse events (TEAEs) included diarrhea (n = 17, 65%; 1 grade [G] 3), hyperphosphatemia (n = 15, 58%; all G1 or 2), and nausea (n = 11, 42%; 1 G3). The most common G3/4 TEAEs were elevated lipase without pancreatitis (n = 5, 19%), elevated amylase (n = 3, 12%), and rash and syncope (n = 2, 8% each). TEAEs led to interruption/reduction/discontinuation of R in 69%/46%/19% of pts. R-related unique TEAEs were hyperphosphatemia in 15 pts (58%) and retinal pigment epithelium detachment in 1 pt (4%). G5 events occurred in 3 pts (12%), unrelated to treatment. 13 of 24 evaluable pts (54%) had an objective response (OR) per RECIST v1.1. The disease control rate was 83%, including 3 pts (13%) with a complete response (CR), 10 (42%) with a partial response (PR), and 7 (29%) with stable disease. Median duration of response was not reached. OR rate was 56% (2 CRs and 7 PRs) in the 16 pts with tumors having low/negative PD-L1 protein and *FGFR3* mRNA overexpression without mutation. The RP2D for R+A was 600 mg BID. **Conclusions:** First-line treatment with the RP2D of R+A achieved favorable clinical efficacy and tolerability in pts with cisplatin-ineligible, metastatic UC characterized by high *FGFR1/3* mRNA expression and generally low/negative PD-L1 expression. Encouraging efficacy was observed regardless of PD-L1 expression or *FGFR3* mutation status, warranting future investigation. Clinical trial information: NCT03473756. Research Sponsor: Funding: Bayer AG. Writing support: Complete HealthVizion.

4522 **Poster Session**

Phase I/II study to evaluate the efficacy of TAS0313, a cancer peptide vaccine, combined with pembrolizumab for locally advanced or metastatic urothelial carcinoma. *First Author: Ryuji Matsumoto, Department of Renal and Genitourinary Surgery, Hokkaido University, Sapporo, Japan*

Background: TAS0313 is a cancer vaccine cocktail comprising three long peptides with a total of 12 cytotoxic T lymphocyte epitope peptides. We performed a multicenter phase I/II study including patient (pts) with urothelial carcinoma (UC) treated using TAS0313 combined with pembrolizumab. **Methods:** The enrolled pts with a histologically or cytologically confirmed diagnosis of urothelial carcinoma had at least one of the following HLA types: HLA-A*02:01, -A*02:06, -A*02:07, -A*11:01, -A*24:02, -A*31:01, or -A*33:03. For cohort C1, eligible pts were those who received platinum-based chemotherapy and were naïve to immune checkpoint inhibitors (ICI). For cohort C2, eligible pts were those who progressed onto treatment with pembrolizumab. TAS0313 (9 mg) was subcutaneously administered on days 1, 8, and 15 of cycles 1 and 2 and day 1 of cycle 3 or later in 21-day cycles, while pembrolizumab (200 mg) was intravenously administered on day 1 of cycle 1 or later in 21-day cycles until disease progression or unacceptable toxicity occurred. Tumor response was evaluated using the RECIST v1.1 criteria. The TAS0313 target antigen-specific immunoglobulin G (IgG) was analyzed before and after treatment. The primary objective was to evaluate efficacy, while the secondary objective was to evaluate the safety and tolerability of the combination therapy. **Results:** As of 10th September 2020, 46 pts with a median age of 71.0 and 65.5 years, in cohort C1 (n = 36) and cohort C2 (n = 10), respectively, have been treated with the combination therapy. For cohorts C1 and C2, the median follow-up duration was 6.47 and 6.95 months, while the median treatment duration was 4.86 and 2.56 months, respectively. In cohort C1, the overall response rate and disease control rate (DCR) were 33.3% (16.7% complete response, 16.7% partial response) and 66.7% (33.3% stable disease), respectively. The median progression-free survival was 5.0 months, median overall survival (OS) was not yet reached, and 1-year OS rate was 74.3%. The best overall response in cohort C2 was stable disease in 5/10 pts, resulting in a DCR of 50.0%. Increase in IgG level was detected after treatment in both the cohorts. The most common adverse drug reactions (ADRs) of TAS0313 and/or pembrolizumab were grade 1–2 injection site reactions and pyrexia. There were no grade 3–5 ADRs with an incidence of $\geq$10%. **Conclusions:** This study confirmed the tolerability, safety, and immune response of TAS0313 combined with pembrolizumab in cohorts C1 and C2. We observed promising efficacy in pts with ICI-naïve UC in cohort C1; however, in pts with pembrolizumab-refractory UC in cohort C2, limited efficacy was seen. Therefore, a large-scale randomized study is needed to clarify the benefits of TAS0313 combined with ICI in ICI-naïve pts. Clinical trial information: 183824. Research Sponsor: Taiho Pharmaceutical Co., Ltd.

4523 **Poster Session**

Circulating tumor cell-driven use of neoadjuvant chemotherapy in patients with muscle-invasive bladder cancer. *First Author: Nick Beije, Department of Medical Oncology, Erasmus MC Cancer Institute, Erasmus University Medical Center, Rotterdam, Netherlands*

Background: International guidelines for the treatment of non-metastatic muscle-invasive bladder cancer (MIBC) recommend neoadjuvant chemotherapy (NAC), which, however, is underutilized in practice. We hypothesized that the absence of circulating tumour cells (CTCs), an established prognostic marker in MIBC, may identify patients with such a favourable prognosis that NAC may be withheld. **Methods:** The *CirGuidance* study included adults with clinical stage T2-T4aN0-N1M0 muscle-invasive urothelial carcinoma of the bladder who were fit to undergo radical cystectomy. CTCs were enumerated using the CellSearch system. CTC-negative patients (no CTCs detectable) underwent radical surgery without NAC; CTC-positive patients ($\geq$1 detectable CTCs) were advised to receive NAC followed by radical surgery, but NAC could be withheld at the discretion of the treating physician. The primary endpoint was the two-year overall survival (OS) in the CTC-negative group, analysed in the intention-to-treat population. The prespecified criterion for trial success was a two-year OS of minimally 75% (95% confidence interval (CI) ±5%) in the CTC-negative group. **Results:** Of 315 patients screened for eligibility, 273 were enrolled in the study. The median age was 69 years; the median follow-up was 36 months. The two-year OS in the CTC-negative group was 69.5% (n = 203; 95% CI 62.6%-75.5%); in the CTC-positive group it was 58.2% (n = 70; 95% CI 45.5%-68.9%). CTC-positive patients had a higher rate of cancer-related mortality (hazard ratio (HR) 1.61, 95% CI 1.05-2.45, p = 0.03) and disease relapse (HR 1.87, 95% CI 1.28-2.73, p = 0.001) than CTC-negative patients. Explorative analyses suggested that CTC-positive patients who had received NAC (n = 22) survived longer than CTC-positive patients who had not (n = 48), with a two-year OS of 74.8% (95%CI 49.5%-88.8%) versus 52.0% (95% CI 37.2%-65.0%), respectively. **Conclusions:** The two-year OS in the CTC-negative group did not meet the prespecified criterion for trial success. However, given the trial population's advanced age and high rate of non-cancer related mortality, the benefit of NAC is likely to be limited in CTC-negative MIBC patients. CTC enumeration at the moment of diagnosis could aid in the decision to prescribe neoadjuvant chemotherapy for a muscle-invasive bladder cancer patient as a criterion in addition to clinical characteristics. Clinical trial information: NL3954. Research Sponsor: Erasmus MC Grants & Cancer Genomics Netherlands.

4524 **Poster Session**

Enfortumab vedotin in cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer who received prior PD-1/PD-L1 inhibitors: An updated analysis of EV-201 Cohort 2. *First Author: Bradley Alexander McGregor, Dana-Farber Cancer Institute, Boston, MA*

Background: Cisplatin (cis)-ineligible, platinum-naive patients (pts) with locally advanced or metastatic urothelial carcinoma (la/mUC) who progress on/after anti-PD-1/L1 treatment (tx) have a poor prognosis and few tx options. Enfortumab vedotin (EV), a Nectin-4-directed antibody-drug conjugate, demonstrated overall survival (OS) benefit in pts with la/mUC who previously received anti-PD-1/L1 tx and platinum-containing chemotherapy (EV-301). EV-201 (NCT03219333) is a pivotal, single-arm, 2-cohort (C) study. C2 enrolled cis-ineligible pts with prior anti PD-1/L1 tx and no prior platinum for la/mUC. Results of the C2 primary analysis were previously presented. In this updated analysis, with 3 additional mo of follow-up (f/u), all responders were followed for $\geq$6 mo after onset of response. **Methods:** Pts received 1.25 mg/kg EV on Days 1, 8, and 15 of each 28-day cycle. The primary endpoint was confirmed objective response rate (ORR) per RECIST 1.1 by blinded independent central review (BICR). Secondary endpoints were duration of response (DOR), progression-free survival (PFS), OS, and safety. **Results:** 91 pts were enrolled and 89 treated in C2. Median (m) age was 75 y (range: 49-90). Pts were cis-ineligible at baseline, primarily due to CrCl < 60 mL/min (78%). Primary tumor site was upper tract in 43%, and 79% had visceral mets, including 24% with liver mets. As of 04 Dec 2020 (data cut-off), m f/u was 16.0 mo and m tx duration was 6.0 mo (range: 0.3-24.6). Confirmed ORR per BICR was 51% (95% confidence interval [CI] 39.8-61.3), including 22% complete response (CR) among treated pts. mDOR was 13.8 mo (95% CI 6.4-not reached). mPFS and mOS were 6.7 mo (95% CI 5.0-8.3) and 16.1 mo (95% CI 11.3-24.1), respectively. All-grade and grade (G) $\geq$3 tx-related adverse events (TRAEs) were reported in 97% and 55% of pts, respectively. Most common all-grade TRAEs were alopecia (51%), peripheral sensory neuropathy (49%), and fatigue (34%). For TRAEs $\geq$G3, each preferred term occurred in $< 10\%$ pts. TRAEs of interest included skin reactions (61% all grade, 17% $\geq$G3), peripheral neuropathy (56% all grade, 8% $\geq$G3), and hyperglycemia (10% all grade, 6% $\geq$G3). Four deaths were previously reported as tx related by investigators: 3 events $\leq$30 d of first EV dose (acute kidney injury, metabolic acidosis, multiple organ dysfunction syndrome) and 1 $>$ 30 d of last EV dose (pneumonitis). **Conclusions:** Efficacy and safety in this updated analysis of EV-201 C2 are consistent with the primary analysis. The majority of platinum-naive, cis-ineligible la/mUC pts who progressed on/after anti-PD-1/L1 tx responded to EV, with 22% achieving CR and mDOR exceeding a year. PFS and OS continue to be encouraging in this elderly population, with no new safety signals. These data show the potential for EV as a non-platinum option for cis-ineligible pts following anti-PD-1/L1 tx. Clinical trial information: NCT03219333. Research Sponsor: Astellas Pharma Global Development, Inc. and Seagen Inc.

4525 **Poster Session**

Avelumab first-line (1L) maintenance plus best supportive care (BSC) versus BSC alone for advanced urothelial carcinoma (UC): Analysis of time to end of next-line therapy in JAVELIN Bladder 100. *First Author: Petros Grivas, University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA*

Background: Avelumab 1L maintenance is approved in various countries for patients (pts) with advanced UC that has not progressed with 1L platinum-based chemotherapy based on significantly prolonged overall survival (OS) seen with avelumab + BSC vs BSC alone in the phase 3 JAVELIN Bladder 100 trial. OS was prolonged despite the more frequent use of subsequent anticancer therapy in the BSC alone arm (42.3% in the avelumab + BSC arm vs 61.7% in the BSC alone arm), most commonly with immune checkpoint inhibitors (6.3% vs 43.7%, respectively). To further characterize the efficacy benefits of avelumab 1L maintenance, we report a post hoc analysis of the time to end of next-line therapy (for any reason) in the randomized trial population. **Methods:** In JAVELIN Bladder 100 (NCT02603432), eligible pts had unresectable locally advanced or metastatic UC without disease progression with 4 to 6 cycles of 1L gemcitabine + either cisplatin or carboplatin. The primary endpoint was OS from randomization, assessed in 2 populations: all pts and pts with PD-L1+ tumors (Ventana SP263). In this exploratory analysis, time from randomization until end of next-line treatment received after first progression (due to death or discontinuation) was assessed. **Results:** A total of 700 pts were randomized 1:1 to avelumab 1L maintenance + BSC or BSC alone. Among all randomized pts, time to end of next-line therapy was prolonged in the avelumab + BSC arm vs the BSC alone arm (Table). Time to end of next-line therapy was also longer in the avelumab + BSC arm vs the BSC alone arm in pts with PD-L1+ tumors (n = 358) or PD-L1− tumors (n = 270). **Conclusions:** Pts who received avelumab 1L maintenance + BSC had prolonged time to end of next-line treatment compared with those who received BSC alone, irrespective of PD-L1 status. These data provide further evidence of the efficacy of a maintenance approach with avelumab in pts with advanced UC that has not progressed with 1L platinum-based chemotherapy. Clinical trial information: NCT02603432. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

	Patients, n		Median time to end of next-line therapy (95% CI), months		
	Avelumab + BSC	BSC alone	Avelumab + BSC	BSC alone	Hazard ratio (95% CI)
All randomized pts	350	350	14.8 (12.0, 17.0)	9.2 (8.0, 11.5)	0.67 (0.545, 0.815)
Pts with PD-L1+ tumors	189	169	18.1 (12.5, 19.2)	9.0 (7.9, 12.5)	0.61 (0.451, 0.818)
Pts with PD-L1− tumors	139	131	11.9 (9.1, 15.4)	9.3 (7.6, 12.8)	0.76 (0.560, 1.035)

4526 **Poster Session**

Large cell neuroendocrine carcinoma of the urothelial tract (LNEC): The MSKCC experience. *First Author: Brendan John Guercio, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: LNEC is a rare, poorly characterized entity morphologically resembling small cell NEC of the urothelial tract (SNEC). **Methods:** Pure and partial LNEC and SNEC cases were identified by histopathologic re-review; clinical outcomes were compared. A subset was sequenced with MSK-IMPACT (279-505 genes). **Results:** Between 1992-2020, 43 patients (pts) with LNEC were identified (42 bladder, 1 upper tract); 19 (44%) had concomitant SNEC. LNEC cases were compared to 192 SNEC without LNEC (SNEC-only) (Table 1). Compared to SNEC-only pts, LNEC pts experienced longer overall survival (OS), adjusting for age and M0 vs M1 (median OS not reached vs 22.4 months [mos]; HR 0.34, 95% CI 0.16-0.74, p = .006). Neoadjuvant chemo (NAC) use increased over time. Pathologic response rate (<ypT2N0) after NAC was 25% for LNEC and 50% for SNEC-only (p = .13); the ypTONO rate was 25% for LNEC and 40% for SNEC-only (p = .52). Perioperative chemo did not improve OS compared to surgery alone in LNEC, adjusting for age and concurrent SNEC (HR 1.46, 95% CI 0.12-17.5, p = .76), but was associated with longer OS among SNEC-only pts (n = 98; HR 0.39, 95% CI 0.22-0.69, p = .001). Two M1 LNEC pts received immunotherapy (IO) in the first-line: 1 atezolizumab, 1 atezolizumab + chemo. Both remained free of progression on IO at a follow-up of 20 and 12 mos, respectively. Of 18 sequenced LNEC tumors, 89% had *TERT* promoter alterations (alts), similar to 85% seen in 52 SNEC tumors. All LNEC tumors had alts of *TP53* or *RB1*, and 10 (56%) had both. Median tumor mutational burden (TMB) was 14 (IQR 8-38) in LNEC and 30 (IQR 15-55) in SNEC. Epigenetic modifiers were altered in 78% LNEC and 79% SNEC. Two LNEC pts had *ERCC2* alts and received platinum chemo; both were alive at last follow-up from NEC diagnosis of 30.7-39.1 mos. **Conclusions:** LNEC pts experienced longer OS compared to pts with SNEC-only in this cohort, but did not appear more chemo-sensitive. Genomic profiles of LNEC and SNEC-only tumors were similar; *TERT* promoter mutations suggest a potential urothelial precursor. Further investigation of IO for LNEC is warranted. Research Sponsor: U.S. National Institutes of Health.

LNEC (includes LNEC with concurrent SNEC) vs SNEC-only cases.

Characteristics	LNEC (n = 43)	SNEC-only (n = 192)
Age, median (range)	69 (44-84)	68 (38-94)
% Male	74%	81%
% M0 at diagnosis	81%	74%
NAC (14 LNEC, 62 SNEC-only)	Platinum + etoposide (64%) Platinum + gemcitabine (29%) MVAC (7%)	Platinum + etoposide (81%) Platinum + gemcitabine (10%) MVAC (5%) Other chemo/unknown (5%)
Other treatments (tx) for M0 pts (20 LNEC, 72 SNEC-only)	Surgery alone (30%) Surgery + adjuvant chemo (10%) RT ± chemo (35%) Chemo only (5%) Other/unknown (20%)	Surgery alone (32%) Surgery + adjuvant chemo (18%) RT ± chemo (18%) Chemo only (19%) Other/unknown (13%)
First-line tx for M1 pts (8 LNEC, 46 SNEC-only)	Platinum + etoposide (50%) Platinum + taxane (13%) IO + chemo (13%) IO alone (13%) No systemic tx (13%)	Platinum + etoposide (70%) Platinum + taxane (2%) MVAC (2%) Other chemo (17%) No systemic tx (9%)

4527 **Poster Session**

Avelumab first-line (1L) maintenance for advanced urothelial carcinoma (UC) in the JAVELIN Bladder 100 trial: Subgroup analysis by duration of treatment-free interval (TFI) from end of chemotherapy to start of maintenance. *First Author: Srikala S. Sridhar, Princess Margaret Cancer Center, University Health Network, Toronto, ON, Canada*

Background: The phase 3 JAVELIN Bladder 100 trial, which enrolled patients (pts) with advanced UC that had not progressed with 1L platinum-containing chemotherapy, showed that maintenance therapy with avelumab + best supportive care (BSC) significantly prolonged overall survival (OS) compared with BSC alone (hazard ratio [HR], 0.69 [95% CI: 0.56, 0.86; 1-sided P= 0.0005]). However, the optimal timing for starting avelumab after completing 1L chemotherapy is unknown. In this post hoc analysis, we report efficacy by duration of the TFI from completion of 1L chemotherapy. **Methods:** In the JAVELIN Bladder 100 trial (NCT02603432), eligible pts had unresectable locally advanced or metastatic UC without disease progression following 4 to 6 cycles of 1L platinum-containing chemotherapy. Pts were randomized to receive avelumab + BSC (n = 350) or BSC alone (n = 350) after a TFI of 4 to 10 weeks from the last dose of chemotherapy. In this exploratory analysis, subgroups with a TFI of 4 to < 6 weeks (< 42 days), 6 to < 8 weeks (42 to < 56 days), or 8 to 10 weeks (≥56 days) were evaluated. **Results:** In the avelumab + BSC and BSC alone arms, the TFI was 4 to < 6 weeks in 143 and 158 pts, 6 to < 8 weeks in 109 and 80 pts, and 8 to 10 weeks in 98 and 110 pts, respectively. Baseline characteristics in these subgroups were generally well balanced between arms. For both arms combined, however, the TFI 4 to < 6 weeks subgroup vs the other 2 subgroups included more pts with visceral metastases (57.8% vs 54.0% and 50.0%), an objective response with 1L chemotherapy (76.4% vs 69.3% and 68.3%), and an ECOG performance status of 1 (44.5% vs 33.3% and 35.6%). OS was prolonged with avelumab + BSC vs BSC alone in all subgroups; the HR was 0.76 (95% CI: 0.546, 1.059) in the TFI 4 to < 6 weeks subgroup (median OS, 19.9 months [95% CI: 16.3, 25.3] vs 13.5 months [95% CI: 11.7, 17.4]), 0.64 (95% CI: 0.404, 1.021) in the TFI 6 to < 8 weeks subgroup (median OS, 26.1 months [95% CI: 19.9, not estimable] vs 21.0 months [95% CI: 10.7, not estimable]), and 0.70 (95% CI: 0.468, 1.035) in the TFI 8 to 10 weeks subgroup (median OS, 20.1 months [95% CI: 13.8, not estimable] vs 14.1 months [95% CI: 11.7, 19.6]). **Conclusions:** In patients with advanced UC that had not progressed with 1L platinum-containing chemotherapy, avelumab 1L maintenance prolonged OS irrespective of the TFI assessed in this study (4-10 weeks), supporting this new treatment strategy as a standard of care. Differences in duration of TFI were likely related to individual patient- and disease-specific characteristics or logistics and did not impact the OS benefit observed with avelumab 1L maintenance. Clinical trial information: NCT02603432. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

4528 **Poster Session**

Study EV-103: Update on durability results and long term outcome of enfortumab vedotin + pembrolizumab in first line locally advanced or metastatic urothelial carcinoma (la/mUC). *First Author: Terence W. Friedlander, University of California San Francisco Medical Center, San Francisco, CA*

Background: Significant unmet need remains for people with cisplatin-ineligible (cis-ineligible) locally advanced or metastatic urothelial carcinoma (la/mUC). In the first-line (1L) setting, carboplatin-based regimens have demonstrated poor tolerability, modest objective response rate (ORR) and limited durability. PD-1/PD-L1 inhibitors demonstrate durable responses; however, only a minority of pts achieve a response (ORR 24-29%). Enfortumab vedotin (EV) is an antibody-drug conjugate (ADC) delivering the microtubule-disrupting agent monomethyl auristatin E (MMAE) to targeted tumor cells expressing Nectin-4. EV has shown an overall survival benefit versus chemotherapy in previously treated la/mUC. Preclinical studies show that ADCs utilizing MMAE can induce immunogenic cell death and may enhance antitumor immunity. Clinical data suggests the combination of EV + pembrolizumab (P) may have the potential to induce greater antitumor activity compared to either agent alone. Preliminary data on EV + P was previously presented, and the FDA granted breakthrough therapy designation to EV + P for the treatment of pts with 1L cis-ineligible la/mUC in Feb 2020. Here we report updated data with 24.9 months median follow-up. **Methods:** This multi-cohort EV-103 study (NCT03288545) evaluates the safety/activity of EV + P (Dose Escalation/Cohort A). This report highlights 1L cis-ineligible pts treated with 3-week cycles of EV 1.25 mg/kg (Days 1, 8) and P (Day 1). Endpoints include safety/tolerability, investigator response per RECIST v1.1, DOR, PFS, and OS. **Results:** As of 13 Oct 2020, the median follow-up for the 45 1L la/mUC pts (median age 69 yrs [51-90]) was 24.9 months. The median number cycles of EV + P was 9 (range 1-34). The most common treatment-related adverse events were peripheral sensory neuropathy (56%, 4% ≥G3), fatigue (51%, 11% ≥G3), and alopecia (49%). There was one death reported as possibly related to study treatment (multiple organ dysfunction syndrome) per investigator assessment. Confirmed ORR is 73.3% (95% CI: 58.1, 85.4) including 17.8% CR and an ORR of 57.1% (8/14) in pts with liver metastasis. The median DOR was 25.6 months (95% CI: 8.3, -). Fifty-three percent of the responders had DOR at 24 months. Additionally, the DCR is 93.3%, the median PFS is 12.3 months (95% CI: 8.0, -), and the median OS is not reached. The OS rate at 24 months is 56.3% (95% CI: 39.8, 69.9). **Conclusions:** EV + P, a platinum-free option, continues to demonstrate promising activity with a durable response profile in 1L cis-ineligible pts with la/mUC. The safety profile is manageable and stable over time with no new safety signals. Cohort K of EV-103 in cis-ineligible pts with la/mUC is actively randomizing pts to EV monotherapy or EV + P to evaluate the contribution of each agent. Clinical trial information: NCT03288545. Research Sponsor: Astellas and Seagen Inc.

4529 **Poster Session**

Effect of Bacillus Calmette-Guerin (BCG) exposure on severity of COVID-19 infection: A COVID-19 and Cancer Consortium (CCC19) study. *First Author: Andrew Lachlan Schmidt, Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Oncology patients experience more severe disease outcomes from COVID-19 infection than the general population. BCG is a live bovine tuberculosis bacillus with immunotherapeutic effects in urothelial cancers; it is also used as vaccination against *Mycobacterium tuberculosis* in parts of the world. As BCG vaccination has been associated with broad protection against viral pathogens, BCG exposure through vaccination or intravesical therapy may modulate host immunity and reduce the severity of COVID-19 infection. We report the effect of BCG exposure on COVID-19 severity in oncology patients from the CCC19 registry. **Methods:** The CCC19 registry (NCT04354701) was used to identify patients with prior BCG exposure. Cohort A received intravesical treatment for bladder carcinoma, and cohort B received prior BCG vaccination. Each cohort was matched 3:1 to non-BCG-exposed controls by age, sex, race, primary cancer type, cancer status, ECOG performance status (PS) and calendar time of COVID-19 infection. The primary endpoint was COVID-19 severity reported on an ordinal scale (uncomplicated, hospitalized, admitted to ICU +/- ventilated, died within 30 days) of patients exposed to prior BCG compared to matched non-exposed controls. 2-sided Wilcoxon rank-sum tests were used. **Results:** As of 6-Feb-2021 we included 124 patients with BCG exposure, 68 patients with bladder carcinoma who had received intravesical BCG (Cohort A), and 64 cancer patients with prior BCG vaccination (Cohort B). Median age was 76 years, IQR 69-83 (Cohort A) and 67 years, IQR 62-74 (Cohort B). Bladder cancer pts were predominately male (78%) vs 55% for Cohort B. Patients with PS 2+ were uncommon, 18% in Cohort A and 16% in Cohort B. COVID-19 illness severity was no different in patients exposed to prior intravesicular BCG (p=0.87). COVID-19 illness severity was no different in patients exposed to prior intradermal BCG vaccination (p=0.60). **Conclusions:** Despite this being the largest such cohort reported to date, we failed to demonstrate an association of prior BCG exposure with modulation of severity of COVID-19 illness. Prospective trials evaluating the protective effect of BCG vaccination are ongoing and will add further insight into the effect of BCG on COVID-19 illness. Research Sponsor: P30 CA068485.

COVID-19 severity and relationship to BCG exposure.

COVID-19 severity	Uncomplicated (n, %)	Hospitalized (n, %)	ICU +/- Ventilated (n, %)	30 day mortality (n, %)	P value
Intravesicular					0.87
Cohort A					
BCG Exposed (n, %)	25 (37)	20 (29)	8 (12)	14 (21)	
BCG Non-exposed (n, %)	60 (31)	78 (41)	18 (9)	36 (19)	
Intradermal					0.60
Cohort B					
BCG Exposed (n, %)	21 (33)	27 (42)	5 (8)	9 (14)	
BCG Non-exposed (n, %)	57 (30)	67 (39)	18 (11)	29 (17)	

4530 **Poster Session**

Fibroblast growth factor receptor alteration (*FGFRa*) status and progression outcomes of patients with advanced or metastatic urothelial cancer (mUC). *First Author: Sarah Fleming, Janssen Research & Development, LLC, Raritan, NJ*

Background: *FGFRa* appear in approximately 15% of cases of mUC. Data on whether *FGFRa* in mUC have a prognostic impact or predictive benefit for particular treatments have been limited by small sample sizes. The objective of this study was to evaluate the association between tumor *FGFRa* and clinical outcomes of patients with advanced UC or mUC regardless of therapy type and status. **Methods:** A convenience sample of oncologists and urologists across the United States provided patient level data on 400 patients with stage IIIb or IV UC via a standardized questionnaire over a 1-month period (August 17, 2020 – September 20, 2020). Study design enriched for *FGFRa* by requiring physicians to provide ≥1 *FGFRa* patient record. The questionnaire included physician characteristics, patient demographic information, FGFR status, therapy given, response, and clinical and radiographic measures of progression. Patient records were eligible for inclusion if they were identified and treated during July 1, 2017, to June 30, 2019. Cox proportional hazards models were used to estimate adjusted risk of disease progression by FGFR status. **Results:** A total of 104 physicians (58.7% medical oncologists, 31.7% hematologic oncologists, and 9.6% urologic oncologists) contributed 414 patient records Overall, 73.9% of the patients were male and the average age was 64.5 years (SD ±10.6). Median follow-up was 15 months. Of the 414 patients, 218 (52.7%) had *FGFRa* and 196 (47.3%) had FGFR wild-type (*FGFRwt*) mUC. Of the 218 patients with *FGFRa*, 47.2% were treated with front-line chemo, 27.5% with a programmed death-ligand 1 inhibitor (PD-L1), 11.5% with chemo + PD-L1, and 13.8% with other treatments. Of the 196 *FGFRwt* patients , 63.2% were treated with front-line chemo, 21.9% with PD-L1, 12.2% with chemo + PD-L1, and 2.6% with other treatments. There was no difference in response or progression status for those receiving front-line chemo (HR, 1.15; 95% CI, 0.86-1.55). Among 97 patients (55 *FGFRa* and 42 *FGFRwt*) who received PD-L1 alone as front-line therapy, those who had *FGFRa* had an adjusted risk of progression 2 times higher than their *FGFRwt* counterparts (HR, 2.12; 95% CI, 1.13-4.00). **Conclusions:** Patients with *FGFRa* mUC progressed earlier than *FGFRwt* patients treated with front-line PDL-1 inhibitors; however, there was no difference in progression in patients treated with chemo based upon FGFR status. This real-world study using a survey design efficiently generated a relatively large *FGFRa* dataset, mitigating a core limitation of other studies assessing the patient population with *FGFRa*. Further work is warranted to validate these results and determine the optimal strategy for treating the patient with *FGFRa* mUC. Gene expression profiling of *FGFRa* mUC samples from clinical trials will help determine the potential impact of subtype or other features that may associate with benefit from therapy. Research Sponsor: Janssen Research & Development, LLC.

4531 **Poster Session**

Safety evaluation of combined PD-1+CTLA4 inhibition concurrently to chemoradiotherapy (CRT) in localized muscle invasive bladder carcinoma (MIBC). *First Author: Ben-Max de Ruiter, Amsterdam UMC, University of Amsterdam, Department of Urology, Cancer Center Amsterdam, Amsterdam, Netherlands*

Background: Neoadjuvant nivolumab (nivo) + ipilimumab (ipi) prior to radical cystectomy showed efficacy in localized MIBC. The safety of PD-1 and PDL-1+CTLA4 inhibition concurrent with CRT in localized MIBC has not been assessed. We present the first clinical trial data on concurrent 3 doses of q4w nivo 480mg (cohort1) and concurrent 4 doses of q3w nivo 3mg/kg + ipi 1kg/mg (nivo3+ipi1, cohort2) in combination with Mitomycin C/Capecitabin (MMC/Cape) CRT. **Methods:** We report the first 2 cohorts of a phase 1b, EC approved, study with nivo only or nivo3+ipi1 added to MMC/Cape CRT. CRT consists of MMC i.v. on day 1 with Cape 750mg/m2 on days of radiotherapy. Radiotherapy schedule comprises a 20x2Gy whole bladder irradiation with a simultaneous tumorboost of 20x0.75Gy. Patients with MIBC, T2-4N0-1, ECOG performance status <2 were included. A dose escalation scheme, with a staggered enrollment is used. The first 10 patients received nivo 480mg on week 1, 5, 9. Cohort2 of 10 patients received nivo3+ ipi1 at week 1, 4, 7 and 10. Relevant severe Adverse Events (AEs) were registered as Dose Limiting Toxicity (DLT) when they occurred within 6 weeks after start of treatment. Clinical efficacy is evaluated by cystoscopy and CT at week 12 and 24. **Results:** Both cohorts enrolled 10 patients. Median age was 68 [IQR 61-75] and 70 [IQR 66-75] years in cohort1 and 2, respectively. In cohort1 no patients experienced DLT. No dose reductions were applied. In cohort2, 2 patients experienced DLT, 1 trombocytopenia (grade 4) and 1 asystole (grade 5). 50% of patients did not receive all 4 q3w nivo3+ipi1 infusions, due to AEs. Table 1 reports an overview of AEs. In cohort2 6 SAE's occurred in 3 patients. Median follow up is 71 [IQR 59-86] and 30 weeks [IQR 12-45] in cohort1 and 2, respectively. 1year OS and DFS is 100% in cohort1. **Conclusions:** Concurrent 3 doses nivo 480mg q4w added to MMC/Cape based CRT is feasible with a favorable toxicity profile and shows promising efficacy in MIBC patients. An escalated regimen with 4 doses nivo 3mg/kg + ipi 1mg/kg q3w concurrent to CRT shows acceptable toxicity. Cohort3 with ipi 3mg/kg and nivo 1mg/kg is enrolling. Clinical trial information: NCT03844256. Research Sponsor: Cure for Cancer Foundation & Dutch Cancer Society.

		Nivo only		Nivo3 + ipi1	
AE		**All grade, n (%)**	**Grade ≥3, n (%)**	**All grade, n (%)**	**Grade ≥3, n (%)**
Total patients with AEs		9 (90)	**1 (10)**	10 (100)	**3 (30)**
GI	Diarrhea	7 (70)	**1 (10)**	6 (60)	**1 (10)**
	Duodenal ulcer			2 (20)	**1 (10)****
	Vomiting	2 (20)		1 (10)	**1 (10)**
	Nausea	3 (30)		2 (20)	
	Abdominal pain			1 (10)	
Renal & urinary	UTI			1 (10)	**1 (10)****
	AKI Urgency	1 (10)		1 (10)	
				2 (20)	
Blood	Anemia	2 (20)		1 (10)	**1 (10)**
	Hyponatremia			1 (10)	**1 (10)****
	Hypercalcemia			1 (10)	**1 (10)****
	Thrombocytopenia			1 (10)	**1 (10)**
Cardiac	Asystole			1 (10)	**1 (10)*****
Auto-immune	Colitis			1 (10)	**1 (10)****
	Hepatitis	1 (10)		1 (10)	
	Pancreatitis				
Endocrine	Adrenal insuff.			1 (10)	
	Hypothyroidism	1 (10)		1 (10)	
	hyperthyroidism			1 (10)	
Skin	Pruritus			2 (20)	
	Rash			2 (20)	
Nervous system	Dysgeusia	1 (10)		3 (30)	
	Ataxia			1 (10)	
General	Fatigue	6 (60)		6 (60)	

CTCAE scored AE, * = Grade V ** = SAE.

4532 **Poster Session**

Pembrolizumab (pembro) versus investigator's choice of paclitaxel, docetaxel, or vinflunine in recurrent, advanced urothelial cancer (UC): 5-year follow-up from the phase 3 KEYNOTE-045 trial. *First Author: Joaquim Bellmunt, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

Background: Pembro was approved for the treatment of locally advanced or metastatic UC that progressed during or after a platinum-containing regimen, based on the phase 3 KEYNOTE-045 (NCT02256436) trial that showed significantly improved OS with use of pembro. Updated results are presented from KEYNOTE-045 after >5 y of follow-up since the last patient (pt) was randomized. **Methods:** KEYNOTE-045 is a randomized, multisite, open-label, phase 3 trial. Pts with histologically or cytologically confirmed UC, progression after platinum-containing chemo, ECOG PS 0-2, measurable disease per RECIST v1.1, and ≤2 prior lines of systemic therapy were eligible. Pts were randomly assigned 1:1 to receive pembro 200 mg Q3W or investigator's choice of paclitaxel 175 mg/m^2 Q3W, docetaxel 75 mg/m^2 Q3W, or vinflunine 320 mg/m^2 Q3W. Primary end points are PFS (RECIST v1.1, blinded central review) and OS. ORR and duration of response (DOR) were key secondary end points. **Results:** As of Oct 1, 2020, among 542 enrolled pts, median time from randomization to data cutoff was 62.9 mo (range 58.6-70.9). 9.4% and 0% of pts in the pembro and chemo arms, respectively, completed 2 years of therapy. Median OS was longer for pembro vs chemo (10.1 vs 7.2 mo; HR, 0.71 [95% CI, 0.59-0.86]) overall and in pts with CPS ≥10 (8.0 vs 4.9 mo; HR, 0.59 [95% CI, 0.40-0.86]). For pts with CR or PR, median OS was not reached and 16.4 (95% CI, 11.3-25.1) mo in the pembro and chemo arms, respectively (Table). OS rates at 48 mo were 16.7% for pembro and 10.1% for chemo; 60-mo OS rates were 14.9% and 8.7%, respectively. OS benefit with pembro vs chemo continued regardless of age, ECOG PS, prior therapy, liver metastases, baseline hemoglobin, time from last chemo, histology, risk factors, and chemo choice. Median DOR for responders was longer for pembro vs chemo (29.7 mo [1.6+ to 60.5+] vs 4.4 mo [1.4+ to 63.1+]), and a greater proportion of responses lasted ≥48 mo (40.9% vs 28.3%, Kaplan-Meier) and ≥60 mo (32.8% vs 28.3%). ORR was higher for pembro vs chemo (21.9% vs 11.0%; difference 10.8% [95% CI, 4.6-17.0]). Fewer pts given pembro vs chemo experienced a treatment-related AE of any grade (62.0% vs 90.6%) or grade ≥3 (16.9% vs 50.2%). **Conclusions:** After 5 y, pembro maintained clinically meaningful OS benefit vs chemo in pts with locally advanced or metastatic UC that progressed during or after platinum-based chemo. Pts who responded to pembro experienced a durable response (median >2 y). Clinical trial information: NCT02256436. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

5-y survival and OS by best response.

	Pembrolizumab	Chemo
5-y survival, % (95% CI)	14.9 (10.9-19.6)	8.7 (5.6-12.7)
OS by best response, median (95% CI), mo		
CR or PR	n=59 NR	n=30 16.4 (11.3-25.1)
SD	n=47 16.4 (13.7-18.9)	n=92 10.5 (8.8-12.6)
PD	n=129 6.2 (4.9-7.6)	n=90 4.7 (3.8-5.5)

4533 **Poster Session**

Stool microbiota profiling of patients with muscle invasive bladder cancer receiving neoadjuvant pembrolizumab. *First Author: Filippo Pederzoli, Vita-Salute San Raffaele University, Milan, Italy*

Background: Immune checkpoint inhibitors (ICIs) showed efficacy in metastatic urothelial carcinoma (UC) and promising activity in muscle-invasive and non-muscle invasive UC of the bladder. Recent studies revealed the immunomodulatory effect of the gut microbiota on ICIs efficacy across several malignancies, identifying microbial "signatures" associated with response to therapy and effective antitumoral T-cell activity. In our study, we aimed to study the stool microbiota in patients undergoing neoadjuvant immunotherapy (IO) for muscle-invasive UC. **Methods:** Pre-IO stools were available for analysis from 42 patients enrolled in the PURE-01 trial (NCT02736266), testing 3x200mg flat-dose pembrolizumab every 21 days before radical cystectomy (RC). All samples were collected using Stool Nucleic Acid Collection and Preservation Tubes (Norgen) and extracted using the Stool DNA Isolation Kit (Norgen), according to the manufacturer's protocol. 16s sequencing was performed using standardized protocols at the internal facility, using mock communities and DNA standards (ZymoBIOMICS) to control for extraction and sequencing contaminations. A QIIME-based bioinformatic pipeline was used for microbiome analyses. Complete response (CR) to neoadjuvant IO was defined as ypT0N0 at pathologic examination on radical cystectomy specimens, while partial response (PR) was defined as < ypT2N0. Concomitant antibiotic therapy (ABT) was defined as any ATB between 30 days prior to the first pembrolizumab dose and the planned RC. **Results:** In our study sample, 23 patients responded to IO (21 CR + 2 PR). Overall median age was 68.5 years. Among responders, 20 (87%) patients had a smoking history (vs. 15 (79%) in non-responders) and 4 (17%) underwent concomitant ABT (vs. 6 (32%) in non-responders). Alpha-diversity assessed by richness (ACE index) was higher in responders vs. non-responders ($p = 0.05$), while no significant diversity was found. Beta-diversity did not show clear clustering of responders vs. non-responders. LEfSe identified 16 bacterial taxa with a linear discriminant analysis (LDA) score ≥2.5 that were differently enriched between responders and non-responders. Among them, we identified the genus *Sutterella* enriched in responders ($p = 0.02$), while the species *Ruminococcus bromii* was enriched in non-responders ($p = 0.02$). **Conclusions:** Our analyses showed an association between response to neoadjuvant-IO and microbiome composition in an intention-to-cure population with muscle invasive UC. We found bacterial taxa specifically enriched in responders or non-responders using pre-therapy stool specimens. The identified taxa may be tested in future studies as potential indicators of therapy outcomes, alone or in combination with other IO biomarkers. These results may also inspire new strategies of gut microbiota modulation to promote response in immunotherapy-refractory patients. Research Sponsor: None.

4534 **Poster Session**

RC48-ADC combined with toripalimab, an anti-PD-1 monoclonal antibody (Ab), in patients with locally advanced or metastatic urothelial carcinoma (UC): Preliminary results of a phase Ib/II study. *First Author: Li Zhou, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: RC48-ADC is a novel humanized anti-HER2 antibody-drug conjugate (ADC), which showed promising data in HER2-positive and even negative patients (pts). Anti-PD-1 Abs have durable antitumor effect for mUC especially in PD-L1 positive patients. The combination may have synergistic antitumor effect. This phase 1b/II study evaluated the safety and activity of RC48-ADC combined with toripalimab in mUC. **Methods:** In dose-escalation cohort, pts received 1.5 or 2 mg/kg RC48-ADC + 3mg/kg toripalimab with the traditional 3+3 escalation design. In expansion cohort, patients received the recommended dose of RC48-ADC + toripalimab every 2 weeks. The primary endpoints were safety/tolerability and recommended RC48-ADC dose; secondary endpoints included pharmacokinetics, ORR per RECIST 1.1, PFS, and OS stratified by HER2 and PD-L1 expression. HER2 positivity was determined by IHC and in situ hybridization (ISH). PD-L1 expression was tested with IHC 22C3 pharmDx assay. **Results:** As of 8 Jan 2021 (data cutoff), 14 mUC pts (9 males, median age 66 y [52-76]) were enrolled. Most pts were systemic treatment naïve (57%) in the locally advanced or metastatic setting. The primary site was in upper tract UC in 50%; 50% had visceral metastases (mets), including 36% with liver mets; HER2 expression was positive (IHC 3+ or 2+ ISH+) in 28%, and 43% PD-L1 CPS≥10. A total of 36 pts is anticipated to be enrolled by Apr 2021. No dose limiting toxicity was reported and the recommended dose for RC48-ADC was 2mg/kg. At data cutoff, 10/14 patients were evaluable for response, with 8 PR, 1 SD (tumor shrinking), and 1 PD. The objective response rate (ORR) was 80%, and disease control rate (DCR) was 90%. All responsive patients have durable efficacy and are still on treatment. Follow-up continues for PFS and OS. Most common treatment-related AEs were grade 1-2, including aminotransferase level increased (7/14, 50%), weight loss (6/14, 43%), alopecia (6/14, 43%), asthenia (4/14, 29%), anemia (3/14, 21%), leukopenia (21%), peripheral sensory neuropathy (21%), hypothyroidism (21%), blood triglycerides increased (21%), and creatine phosphokinase increase (21%). One pt had G3 intestinal obstruction attributed to study drug and went back to treatment after recovery. **Conclusions:** RC48-ADC in combination with toripalimab had a good tolerance and promising anti-tumor activity in pts with mUC. Further evaluation of safety and efficacy is ongoing. Clinical trial information: NCT04264936. Research Sponsor: Remegen.

4535 **Poster Session**

Influence of first-line chemotherapy regimen on survival outcomes of patients with advanced urothelial carcinoma who receive second-line immunotherapy. *First Author: Benjamin Miron, Fox Chase Cancer Center, Philadelphia, PA*

Background: Treatment of advanced urothelial carcinoma (mUC) has improved following approvals of PD-1/PD-L1 inhibitors. Platinum chemotherapy remains the standard-of-care in the first-line (1L). Cisplatin (Cis) regimens are accepted to be superior to carboplatin (Carbo) regimens for patients (pts) who are Cis-eligible. We sought to evaluate if differences in efficacy of 1L Cis vs. Carbo have meaningful impact on overall survival (OS) in the era of second-line (2L) immunotherapy (IO). **Methods:** We conducted a retrospective, observational cohort study to compare OS for pts treated with 1L Cis or Carbo combined with gemcitabine (Gem) followed by 2L IO using patient-level data from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database. Pts included were diagnosed with mUC between 9/1/2015 and 9/15/2020. 2L IO was defined as single-agent atezolizumab, avelumab, durvalumab, nivolumab, or pembrolizumab. OS was calculated from start of 1L and 2L therapy and compared using Kaplan-Meier curves. Time to 2L IO was calculated from start of 1L to start of IO. Adjusted OS was calculated using multivariable Cox regression models, adjusting for age, gender, race, ECOG performance status, primary site, prior cystectomy, smoking status, and year of diagnosis. **Results:** A total of 1882 pts were included, 924 (49.1%) received Gem/Cis and 958 (50.9%) received Gem/Carbo in 1L. A similar percentage of pts did not receive any 2L therapy following Gem/Cis (46.4%) or Gem/Carbo (46.0%). Our analysis focused on the 780 pts (41.4%) who received 2L IO—381 after Gem/Cis and 399 after Gem/Carbo. Median follow-up time for the group was 35 months (mo). Pts in the Gem/Cis cohort were younger, had better performance status and lower incidence of upper tract disease (Table). OS from start of 1L therapy was numerically longer in pts who received Gem/Cis compared to Gem/Carbo on unadjusted (median 18.0 v 16.2 mo, $p = 0.06$) and adjusted analyses (HR = 0.83, 95% CI 0.69-1.00, $p = 0.055$) but neither result was statistically significant. Time to 2L IO was longer for pts receiving Gem/Cis (6.5 mo) vs Gem/Carbo (5.5 mo, $p = 0.008$). Survival time on 2L IO did not differ significantly by 1L regimen (Gem/Cis 8.0 mo vs Gem/Carbo 8.2 mo $p = 0.36$). **Conclusions:** Real world data suggests that in pts with mUC who are able to receive second-line IO, the choice of first-line platinum chemotherapy may not provide a distinguishable OS benefit. Despite methodologic limitations of this data, a greater focus in discussions with patients on toxicity associated with cisplatin vs carboplatin may be warranted. Research Sponsor: None.

	Gem/Cis (N = 381)	Gem/Carbo (N = 399)	p-value
Median age at mUC dx [SD]	69 [41-84]	73 [31-85]	< 0.001
ECOG PS			0.084
0	145 (48.5%)	132 (41.9%)	
1	128 (42.8%)	154 (48.9%)	
2	20 (6.7%)	27 (8.6%)	
Primary Site			0.025
Bladder	292 (76.6%)	274 (68.7%)	
Renal Pelvis	57 (15.0%)	80 (20.1%)	
Ureter	28 (7.3%)	44 (11.0%)	

4536 **Poster Session**

Use of neoadjuvant chemotherapy in elderly patients with muscle invasive bladder cancer: A population-based study, 2006 to 2017. *First Author: Natasza Posielski, Virginia Mason Medical Center, Seattle, WA*

Background: Current guidelines recommend neoadjuvant chemotherapy (NAC) prior to radical cystectomy (RC) for muscle invasive bladder cancer (MIBC). NAC has been shown to confer a survival benefit across all ages. Yet, many elderly patients are not offered NAC due to concern regarding physiologic reserve and postoperative complications. Our objective was to evaluate age-based disparity in treatment and outcomes of MIBC. **Methods:** Using the National Cancer Database, we identified patients with MIBC from 2006-2017. First, use of different treatments, RC, RC and adjuvant chemotherapy, RC with NAC ("optimal treatment"), chemo-radiation, and no treatment, was compared between age groups. A second analysis was performed in the cohort of elderly patients, ≥70, undergoing cystectomy. Propensity weighting was used to compare peri-operative and mortality outcomes in those who received NAC vs. no NAC. **Results:** In 70,911 patients with non-metastatic MIBC, use of RC with NAC was lower in patients ≥70, 7.2 vs. 20.9%, $p<0.001$ (Table). Patients receiving RC with NAC were younger, had private insurance, higher high school completion rate and median income, shorter distance to hospital, lower CCI, diagnosis in recent years, and higher stage disease. NAC use was also associated with pelvic lymph node dissection (OR 4.55, $p<0.001$). In patients ≥70 undergoing RC, NAC was associated with shorter length of stay (LOS) (8.5 vs 9.6 days, $p<0.001$), decreased 30-day readmission (8.6 vs 10.6%, $p=0.003$), lower 30- and 90-day mortality (1.9 vs 3.6%, $p=0.01$ and 4.9 vs 7.7%, $p=0.004$, respectively), and better overall survival (OS) (43.8% vs. 37.5%, $p<0.001$). Multivariate logistic regression found NAC as an independent predictor of shorter LOS, lower 30-and 90-day mortality, and improved OS. **Conclusions:** Despite increased omission of NAC in patients ≥70, NAC is not associated with worse peri-operative outcomes or mortality in elderly patients. Advanced age in properly selected patients should not preclude offering NAC prior to radical cystectomy. Research Sponsor: None.

Treatment differences between age groups.

	Pre-Weights			Post-Weights		
Treatment	**< 70 (n=27,228)**	**70+ (n=43,683)**	**p**	**< 70 (n=15,143)**	**70+ (n=24,442)**	**p**
RC, no. (%)	5627 (20.7)	7858 (18.0)	<0.001	2959 (19.5)	4483 (18.3)	<0.001
RC + AC, no. (%)	3818 (14.)	2316 (5.3)		2250 (14.9)	1401 (5.7)	
Chemo-Radiation, no. (%)	1830 (6.7)	5620 (12.9)		857 (5.7)	2785 (11.4)	
NAC + RC, no. (%)	4872 (17.9)	2643 (6.1)		3163 (20.9)	1760 (7.2)	
No Treatment, no. (%)	197 (0.7)	593 (1.4)		0 (0)	0 (0)	
Missing, no. (%)	10884 (40.0)	24653 (56.4)		5914 (39.1)	14013 (57.3)	

*Propensity score weighted adjustment for age, race, year of diagnosis, insurance status, percentage of non-high school completion, area of residence, proximity to hospital, Charlson score, histology, clinical T stage, LN dissection, and surgery type.

4537 **Poster Session**

Response and outcomes to immune checkpoint inhibitors (ICI) in advanced urothelial cancer (aUC) based on prior intravesical BCG. *First Author: Rafee Talukder, University of Washington, Seattle , WA*

Background: Little is known regarding response and outcomes to ICI for patients (pts) with aUC who were previously treated with BCG for non-muscle invasive bladder cancer. We hypothesized that prior intravesical BCG would not be associated with changes in objective response or survival in pts with aUC treated with ICI. **Methods:** We performed a retrospective cohort study across 25 institutions. Demographic, intravesical BCG history, treatment and outcomes data were collected for pts with aUC who received ICI. Pts with aUC treated with ICIs were included, pts with pure non-UC, those treated with combination or on clinical trials, pts with multiple ICI treatment lines and those with upper tract UC were excluded. Pts were stratified to prior exposure versus no exposure to BCG. We compared overall response rate (ORR) using logistic regression; and progression-free survival (PFS) and overall survival (OS) using Kaplan-Meier and Cox proportional hazards. All analyses were performed in the overall population and further stratified by treatment line (first-line [1L] vs salvage [2+L]) and multivariable models. The stratified analysis was also adjusted for an internally developed risk score for 1L and Bellmunt risk score for 2+L; $p<0.05$ was significant. **Results:** 1026 aUC pts treated with ICI were identified; 614 pts, 617 pts, and 641 pts were included in ORR, OS and PFS analyses, respectively. Overall, mean age at CPI initiation was 70, 76% were men, 70% were current or former smokers, 75% White, 29% with mixed histology, and 24% had prior exposure to BCG. ORR to ICI in pts with or without prior exposure to BCG was similar, 27% and 28% respectively (OR=0.93 [95% CI 0.61-1.42], p=0.73). Median OS (mOS) for pts with vs without prior BCG exposure was 9 vs 10 mo (HR=1.13 [95% CI 0.88-1.44], p=0.35). Median PFS (mPFS) was 4 months (mo) in both groups (HR=1.02 [95% CI 0.82-1.27], p=0.83). ORR, PFS and OS analyses stratified by ICI treatment line (1L vs 2+L) are listed in the table. **Conclusions:** In this multi-institutional retrospective analysis, prior intravesical BCG was not associated with objective response or survival in pts with aUC treated with ICI. Limitations of this study include retrospective nature, lack of randomization and possible confounding, but it does provide important preliminary data that selection for ICI treatment should not be impacted by prior exposure to BCG. Further clinical and molecular biomarker exploration is needed to refine patient selection for ICI in aUC. Research Sponsor: None.

	N	ORR % (95% CI)	OR (95% CI)	p	N	mOS, months (95% CI)	HR (95% CI)	p	N	mPFS, months (95% CI)	HR (95% CI)	p
First Line												
No BCG	273	31 (26-37)	Ref	0.08	279	11 (8-14)	Ref	0.79	286	4 (4-6)	Ref	0.55
Hx of BCG	71	23 (14-34)	0.55 (0.28-1.06)		74	11 (6-15)	1.05 (0.71-1.56)		77	3 (2-7)	1.12 (0.77-1.62)	
2+ Line												
No BCG	198	24 (18-30)	Ref	0.12	191	10 (8-12)	Ref	0.49	203	4 (3-4)	Ref	0.39
Hx of BCG	72	31 (21-42)	1.65 (0.88-3.10)		73	7 (5-12)	1.13 (0.79-1.63)		72	4 (3-7)	0.87 (0.63-1.19)	

4538 **Poster Session**

Real-world treatment patterns and clinical outcomes among patients with metastatic urothelial carcinoma. *First Author: Daniel M. Geynisman, Fox Chase Cancer Center, Department of Hematology and Oncology, Philadelphia, PA*

Background: Knowledge of large-scale real-world treatment patterns and clinical outcomes in patients (pts) with metastatic urothelial carcinoma (mUC) is limited. We conducted this study to address the lack of knowledge and identify unmet needs in pts with mUC in real-world clinical practice. **Methods:** The US nationwide Flatiron Health electronic health records–derived, de-identified database, comprised of 280 oncology practices across the US, was utilized to conduct a retrospective cohort analysis of pts diagnosed with mUC between Jan 1, 2011, and Aug 31, 2020. Baseline pt characteristics were assessed descriptively, and treatment patterns were classified by cisplatin (CIS) eligibility. Kaplan–Meier methods were used to evaluate overall survival (OS) and progression-free survival (PFS). In a subgroup analysis of cisplatin-ineligible (CIS-inelig) pts, a multivariable model adjusting for baseline covariates was used to assess survival outcomes. **Results:** Of 8183 pts with mUC, median age was 73.0 years at diagnosis. Primary tumor sites were bladder (78.5%), upper tract (20.6%), and urethra (0.9%). Median (range) follow-up from mUC diagnosis was 9.7 (0.2-116.6) months. Of 5855 (71.6%) pts who received first-line (1L) systemic therapy, 1764 (30.1%) were CIS eligible (CIS-elig), 2293 (39.2%) were CIS-inelig, and 616 (10.5%) did not receive CIS despite qualifying ECOG PS (0–1) and renal function; CIS eligibility was unknown in 1182 (20.2%). Among all 1L pts, 4380 (74.8%) received chemotherapy and 1410 (24.1%) received immunotherapy (IO); of the IO users, 1345 (95.4%) received monotherapy. Among CIS-elig pts, CIS plus gemcitabine (GC) and methotrexate, vinblastine, doxorubicin, CIS (MVAC) accounted for 1562 (88.5%) of 1L therapy. Among CIS-inelig pts, carboplatin plus gemcitabine (GCa; 36.1%), pembrolizumab (pembro) monotherapy (18.5%), and atezolizumab (atezo) monotherapy (15.1%) were the most common 1L therapies. Across CIS eligibility groups, the most common second-line therapies included pembro, atezo, and GCa; the most common third-line therapies included atezo, pemetrexed, paclitaxel, and GCa. Median OS (95% CI) was longer in pts who received $\geq$ 1 line of systemic therapy (14.5 [14.0–15.2] months) than in those who did not receive therapy (6.8 [6.2–7.3] months). Median (95% CI) OS and PFS were also longer in CIS-elig pts (OS, 19.7 [18.2–21.4] months; PFS, 11.5 [10.8–12.1] months) than in CIS-inelig pts (OS, 11.4 [10.8–12.0] months; PFS, 7.0 [6.7–7.4] months), irrespective of receiving treatment. In a subgroup analysis of CIS-inelig pts, 1L IO monotherapy was associated with worse OS than 1L chemotherapy (HR, 1.26; 95% CI, 1.13–1.40, $P < 0.0001$). **Conclusions:** This study of > 8000 mUC pts, of whom almost 30% never received systemic therapy, demonstrates real-world treatment patterns in mUC and highlights the substantial unmet need in this population, in particular for CIS-inelig pts. Research Sponsor: None.

4539 **Poster Session**

Quality of life, functioning, and symptoms in patients with previously treated locally advanced or metastatic urothelial carcinoma from EV-301: A randomized phase 3 trial of enfortumab vedotin versus chemotherapy. *First Author: Ronac Mamtani, University of Pennsylvania, Philadelphia, PA*

Background: In EV-301, a randomized, open-label phase 3 study (NCT03474107), enfortumab vedotin (EV), a Nectin-4–directed therapy, significantly prolonged median overall survival by ~3.9 months and reduced the risk of death by 30% compared with standard chemotherapy (SC; docetaxel, paclitaxel, or vinflunine) in patients with previously treated locally advanced/metastatic urothelial carcinoma. Understanding patient perspectives and experiences is important to further contextualize the benefits/risks of EV. Here, we report key prespecified quality-of-life (QoL) endpoints, a secondary objective of EV-301. **Methods:** Patients completed the validated European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire Core 30 (QLQ-C30) at baseline, on Day 1 of each week for the first 12 weeks, and then every 12 weeks until discontinuation. The QLQ-C30 assessed functional domains, symptom scales/items, financial impact, and overall health/QoL. Descriptive statistics were used to summarize instrument compliance rates and scores; mixed model repeated measures were used to evaluate changes from baseline over time. Logistic regressions were conducted to assess confirmed improvement rates, defined as clinically meaningful improvement (predefined per domain) over two subsequent visits. **Results:** Of the 608 randomized patients (EV, n = 301; SC, n = 307), 77.3% were male, median age was 68 (range: 30-88), and 30.9% had liver metastasis. Questionnaire compliance rates at baseline were ~90% in both groups; during the study, average rates were 70.2% (EV) and 66.9% (SC). Baseline QLQ-C30 scores were similar between groups. At Week 12, scores on the global health status (GHS) scale were similar between groups (EV: -2.8, SC: -5.0; P= .2429), but SC was associated with numerically greater deterioration and more variability in QoL over the first 12 weeks. Patients receiving EV had significant reduction in pain symptoms (EV: -5.62, SC: +0.11; adjusted difference: -5.73, $P< .05$), but significant worsening of appetite loss (EV: +8.55, SC: +1.26; adjusted difference: 7.29, $P< .05$) compared with SC. Other symptom scores were not significantly different between groups. Higher proportions of patients on EV vs SC had significant confirmed improvements across all functioning domains (role, physical, emotional, social, cognitive), GHS, and several symptom scales (pain, fatigue, dyspnea, constipation). The greatest difference in improvement was reported for pain (EV: 51.6%, SC: 28.8%; OR = 2.76[1.81, 4.22]). **Conclusions:** Compared with SC, patients receiving EV had numerically less deterioration and variability in QoL during the first 12 weeks of treatment. More patients in the EV group had improvements over SC in 10 of 15 QLQ-C30 domains; improvement in pain showed the largest benefit. Clinical trial information: NCT03474107. Research Sponsor: Astellas Pharma, Inc, Pharmaceutical/Biotech Company.

4540 **Poster Session**

Impact of recurrence on health-related quality of life in patients at high risk of recurrence after radical surgery for muscle-invasive urothelial carcinoma (MIUC): Results from the phase 3 CheckMate 274 trial. *First Author: Matt D. Galsky, Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Patients (pts) undergoing radical surgery for MIUC face a high risk of disease recurrence. Recurrence is associated with worse survival, but its effect on health-related quality of life (HRQoL) is unclear. This post hoc analysis assessed the impact of recurrence on HRQoL using data from the phase 3 CheckMate 274 trial. **Methods:** Pts who had undergone radical surgery for high-risk MIUC ($\leq$ 120 days previously) were randomized 1:1 to nivolumab 240 mg Q2W or placebo for $\leq$ 1 year. HRQoL was assessed using the EORTC QLQ-C30 and EQ-5D-3L every 4–6 weeks during treatment; 35 and 115 days after the last dose; and every 3 months after that until the end of the study (EQ-5D-3L only). The analysis included pts with a valid HRQoL assessment at baseline and at $\geq$1 post-baseline visits. Confirmed deterioration in HRQoL was defined as worsening exceeding an a priori points threshold (± 10 for the EORTC QLQ-C30 domains, –7 for the EQ-5D visual analogue scale [VAS]) at $\geq$ 2 consecutive visits. Recurrence was classified as local only or distant (with or without local recurrence). The effect of recurrence on HRQoL deterioration was assessed by Cox proportional hazards regression with recurrence as a time-dependent covariate. The models controlled for treatment arm and baseline HRQoL score, and were stratified by PD-L1 expression, pathologic nodal status, and use of neoadjuvant cisplatin-based chemotherapy. **Results:** The analysis included 645 pts for EORTC QLQ-C30, of whom 71 (11%) had local recurrence only and 136 (21%) had distant recurrence during the HRQoL assessment period; and 648 pts for EQ-5D-3L. with recurrence had a significantly higher risk of confirmed deterioration in all HRQoL domains than those without recurrence (see table). However, hazard ratios were consistently greater for distant recurrence than for local recurrence across all HRQoL domains. For local recurrence only, a higher risk of confirmed deterioration in HRQoL compared to no recurrence was observed only for global health status/QoL. **Conclusions:** Recurrence, particularly distant recurrence, had a significant, negative impact on HRQoL. This suggests that treatment delaying recurrence after radical surgery for high-risk MIUC may prevent or delay HRQoL deterioration in these pts. Clinical trial information: NCT02632409. Research Sponsor: Bristol Myers Squibb.

Adjusted hazard ratios (95% confidence interval) for recurrence vs. no recurrence.

	Any Recurrence	Local Recurrence Only	Distant Recurrence
EORTC QLQ-C30 (N = 645)	n = 207 (32%)	n = 71 (11%)	n = 136 (21%)
Global health status/QoL	**3.5 (2.3–5.3)**	**3.0 (1.6–5.7)**	**3.8 (2.4–6.2)**
Physical functioning	**4.2 (2.8–6.3)**	1.2 (0.4–3.2)	**6.6 (4.2–10.2)**
Role functioning	**3.1 (2.1–4.5)**	1.5 (0.7–3.1)	**4.3 (2.8–6.6)**
Fatigue	**1.7 (1.1–2.6)**	0.9 (0.4–2.0)	**2.3 (1.4–3.7)**
EQ-5D-3L (N = 648)	n = 209 (32%)	n = 72 (11%)	n = 137 (21%)
VAS	**1.8 (1.2–2.8)**	1.1 (0.5–2.5)	**2.3 (1.4–3.9)**

Bold values denote $P < 0.05$.

4541 **Poster Session**

Phase II trial of atezolizumab in BCG-unresponsive non-muscle invasive bladder cancer: SWOG S1605 (NCT #02844816). *First Author: Peter C. Black, Vancouver Prostate Centre, University of British Columbia, Vancouver, BC, Canada*

Background: Radical cystectomy (RC) is the standard of care for patients with BCG-unresponsive high risk non-muscle invasive bladder cancer (NMIBC), but many patients are unfit for surgery or elect bladder preservation. This trial was designed to evaluate the activity of atezolizumab in BCG-unresponsive high risk NMIBC. **Methods:** This single arm phase II registration trial testing systemic atezolizumab (1200 mg IV) every 3 weeks for one year aimed to enroll 135 (70 CIS and 65 non-CIS) eligible patients with histologically proven BCG-unresponsive high risk NMIBC who were unfit for or declined RC. Here we report the 18 month results for all eligible patients who received at least one protocol treatment. The co-primary endpoints were pathological complete response (CR) rate at 6 months in patients with CIS (reported at ASCO 2020), and event-free survival (EFS) in all patients at 18 months using Kaplan-Meier methods (KM), conditional on a positive CIS response rate. A sample size of 135 evaluable patients provided 93% statistical power for detecting a 30% 18-month EFS rate versus 20% using a one-sided alpha = 0.05. EFS in the subset with Ta/T1 disease and duration of response in CIS patients were secondary endpoints. **Results:** 172 patients were enrolled, 166 received at least one dose of atezolizumab and are included in the safety analysis, and, of those, 128 were eligible and included in the efficacy analysis. As previously reported, 20 (27%) out of 74 patients with CIS attained a pathologic CR at 6 months. The KM estimate of 12 month (actual 11.9 mo) duration of response after 6 month CR for CIS patients was 54% (95% CI 30%, 78%) and the median duration of response was 16.5 months. The KM EFS rate at 18 months in 74 patients with CIS was 17% (90% CI 9%, 25%). The 18 month KM EFS rate in the overall population of 128 patients with Ta, T1 and CIS was 29% (90% CI 22%, 36%). The 18 month actuarial EFS rate in 54 patients with Ta/T1 disease was 45% (90% CI 34, 57%). Any possibly or probably treatment-related adverse event (TRAE) was observed in 142 out of 166 (86%) patients who received any atezolizumab regardless of eligibilty. The most frequent TRAEs were fatigue 72 (43%), diarrhea 34 (20%), and anemia 38 (23%). Grade 3-5 TRAEs occurred in 28 (17%) patients, including rash in 4 (2%), hyponatremia in 4 (2%), hypertension in 3 (2%) and elevated liver function tests in 3 (2%). There were two treatment-related deaths (sepsis and respiratory failure due to myasthenia gravis). **Conclusions:** The observed response of atezolizumab at 6 and 18 months in patients with BCG-unresponsive CIS suggests that this could be a valuable treatment to address a critical unmet need in this patient population. The 18 month EFS in patients with Ta/T1 disease suggests activity in this patient subset. This trial provided no new safety concerns. Funding: NIH/NCI grants: CA180888, CA180819, CA180820, CA180821, CA180863 and in part by Genentech. Clinical trial information: NCT02844816. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

4542 **Poster Session**

Genomic predictors of response to PD-1 axis inhibitors in metastatic urothelial cancer (mUC) patients using machine learning analysis of tissue comprehensive genomic profiling (CGP). *First Author: Raquel Reisinger, University of Utah School of Medicine, Salt Lake City, UT*

Background: Immune check point inhibitors (ICI), specifically PD-1 axis inhibitors, are an established treatment for mUC patients (pts), though molecular markers of response are not well-established. Probabilistic Graphical Models (PGMs) are artificial intelligence (AI) algorithms that capture multivariate, multi-level dependencies in complex patterns in large datasets while retaining human interpretability. We hypothesize that machine learning analysis can reveal biomarkers of response to ICI beyond Tumor Mutational Burden (TMB) and PD-L1 expression. **Methods:** Pts with mUC receiving systemic therapy and available tumor CGP were included in the analysis. CGP was performed by a CLIA validated NGS panel (Foundation Medicine). 17 clinically relevant variables were included in the analyses. Multilevel molecular and clinical interdependencies between ICI response were assessed using a Bayesian network (BN) machine learning approach. To account for high computational cost of the BN dependence structure discovery, variables were selected based on primary and secondary dependencies to ICI Objective Response Rate (ORR) via Hill Climbing Algorithm. Genes selected for analysis included those present in $>$ 5% of the cohort. All variants of unknown significance were removed. Kaplan-Meyer (KM) survival analysis was also performed. **Results:** 174 pts were eligible and included: median age was 67 (33 – 86), 54.6% were smokers, 27.6% male, 14.4% had upper tract disease at diagnosis and 77 pts were treated with an approved ICI. Results from BN analysis revealed strong positive interdependencies between ICI ORR and TMB $\geq$ 10 or mutated *PIK3CA* gene. KM analysis was in agreement with BN results, a low TMB ($<$ 10 muts/MB) and wild-type PIK3CA were predictive of poor PFS (Table). PGMs will be presented at the meeting. **Conclusions:** BN and KM survival analysis supported TMB $\geq$ 10 as a biomarker of improved outcomes to ICI. Moreover, these results reveal mutated PIK3CA as a novel biomarker of improved outcomes to ICI. Study has limitations as expected in a retrospective analysis. These hypothesis-generating data require external validation. Research Sponsor: U.S. National Institutes of Health.

Biomarker	RR of ICI ORR[1] (± Std Dev)
High TMB (≥10 Muts/MB)	1.31 (0.22)
PIK3CA (mutant)	1.61 (0.25)
PFS HR (95% CI), p-value	
TMB (< 10 vs ≥10 Muts/MB)	2.411 (1.244 - 4.672), p < 0.01
PIK3CA (wild-type vs mutant)	2.223 (1.160 - 4.260), p < 0.02

[1]Relative risk of codependency of biomarker and ICI ORR compared to biomarker alone.

4543 **Poster Session**

Survival outcomes in patients receiving immune checkpoint inhibitor (ICI) for metastatic small cell urothelial cancer (SCUC). *First Author: Omar Alhalabi, Beaumont Health, Royal Oak, TX*

Background: The prognosis in patients with metastatic SCUC (mSCUC) remains poor with median survival around 1 year with systemic chemotherapy. We aimed to investigate the impact of ICI on survival of patients with mSCUC. **Methods:** Patients who received systemic therapy at MD Anderson Cancer Center (MDACC) for de novo or metachronous mSCUC after completing local management. within 12 months of neoadjuvant or adjuvant chemotherapy were included in this cohort, with overall survival (OS) calculated from the time of receipt of initial chemotherapy. Hazard ratios (HR) and 95% confidence intervals (95% CI) were calculated using logrank test. **Results:** 102 patients with mSCUC received systemic therapy at MDACC between April 2006 and June 2020. Median age was 66 (range 24 – 86 years), male to female ratio was 5. Bladder was the primary site in 85 (83%), 45 (44%) had prior cystectomy and 9 (9%) had prior nephroureterectomy. Histologies included 51 (50%) with predominant small cell (SC) features, 28 (27%) with focal SC features, 20 (20%) with pure SC, and 3 (3%) mixed with large cell component. Thirty-nine (38%) received ICI during their disease course: 29 (28%) following front-line chemotherapy (15 of whom within 12 months of neoadjuvant/adjuvant platinum therapy), 5 (5%) combined with front-line chemotherapy, and 5 (5%) received ICI front-line (two of whom were able to receive second-line chemotherapy). ICI agents used included anti-PD-1 (n=19), anti-PD-L1 (n=12), anti-PD-1/anti-CTLA-4 (n=5), anti-PD-1/anti-TIM3 (n=1), anti-PD-1/anti-STAT3 (n=1), anti-PD-L1/PARPi (n=1). Those who received ICI at any time had an improved median OS compared to those treated with chemotherapy alone (20.1 vs 12 months), [HR=0.45, 95% CI 0.27-0.72, p=0.003]. When we limited the analysis to those with de novo mSCUC (n=36), those who received ICI at any time (n=13) had an improved median OS compared to those treated with chemotherapy alone (n=23) (not reached vs 9.41 months), [HR=0.28, 95% CI 0.12-0.68, p=0.03]. Among patients who received ICI (n=39), median OS in those with liver metastases (n=11) was numerically shorter than those without (n=28) (13.1 vs 21.6 months), [HR=1.83, 0.59-5.7, p=0.21]. **Conclusions:** ICI improves OS for patients with mSCUC. Although clinical trials remain difficult in these rare variants, further prospective studies are indicated to confirm this finding. Research Sponsor: None.

4544 **Poster Session**

Phase I/II trial of pembrolizumab and cabozantinib in the treatment of metastatic renal cell carcinoma (mRCC). *First Author: Elizabeth R Kessler, University of Colorado Cancer Center, Anschutz Medical Campus, Aurora, CO*

Background: Checkpoint inhibitors (CPI) and vascular endothelial growth factor receptor inhibitors (VEGFi) are standard treatments for patients (pts) with mRCC. This phase I/II study evaluated the safety and efficacy of the novel combination of pembrolizumab (pembro) and cabozantinib (cabo). The phase I dose escalation data was presented at ASCO GU 2019. We now report the objective response rate (ORR), progression free survival (PFS), overall survival (OS), and toxicity of patients in the phase II dose expansion. **Methods:** Eligible pts had metastatic clear cell (ccRCC) or non-clear cell (nccRCC) histology, normal organ function, ECOG 0-1, and no prior exposure to pembro or cabo. Pts could be treatment-naïve or have received prior CPI and/or VEGFi. Pts were dosed at the recommended phase 2 dose of pembro 200 mg IV Q3W in combination with cabo 60 mg PO QD. Scans were obtained every 9 weeks. Treatment beyond progression, in the setting of continued clinical benefit, was allowed. The primary endpoint was ORR. Simon's two-stage design was implemented to test the null hypothesis that ORR $\leq$ 0.20 versus the alternative that ORR $\geq$ 0.50. **Results:** Forty pts were enrolled, of which 34 pts (85%) had ccRCC and 6 pts (15%) had nccRCC. This was first-line treatment for 15 pts (38%) and second- and subsequent-line therapy for 25 pts (62%). IDMC risk category was favorable in 15%, intermediate in 72.5%, and poor in 12.5% of pts. Prior therapies included VEGFi in 17 pts (43%), CPI in 17 pts (43%), and 9 pts (23%) had both prior VEGFi and CPI in combination or sequentially. At a median follow up of 17.8 months (mo), the ORR was 60% (95% CI 0.458-1.00), clinical benefit rate (CBR) was 92.5% (95% CI 0.817-1.00), median time to response was 4.2 mo; median duration of response was 8.4 mo. Three of six nccRCC pts achieved partial response. Median PFS was 10.4 mo (95% CI 6.3 mo-NR). Median OS was not reached. Twelve patients remain on treatment. The most common grade 1 and 2 (G1/2) treatment-related AEs were diarrhea (53%), fatigue (49%), weight loss (47%), nausea (43%), and dysgeusia (43%). Twenty-five patients (47%) experienced a treatment-related G3 AE and there were no G4 related AEs. Thirteen pts experienced serious adverse events, 8 of which were related to treatment: G3 transaminitis and hypoglycemia were attributed to the combination; G3 pancreatitis, nephritis, and pneumonitis attributed to pembro; G3 pulmonary embolus, confusion due to reversible posterior leukoencephalopathy (RPLS), and stroke attributed to cabo. There was one treatment-related death in the pt with RPLS, possibly related to cabo. **Conclusions:** This study of the combination of pembrolizumab 200mg and cabozantinib 60mg met the primary endpoint of ORR. Benefit was seen in first- and subsequent-line therapy. The safety profile was manageable. This combination warrants further confirmation in a randomized controlled trial. Clinical trial information: NCT03149822. Research Sponsor: Merck.

4545 **Poster Session**

Health care disparities and barriers to palliative care among metastatic renal cell carcinoma patients: An NCDB analysis. *First Author: Janvi Wadiwala, Houston Healthcare, Perry, GA*

Background: Palliative care improves quality of life for both patients and caregivers but may be underutilized due to socioeconomic barriers to access. An NCDB analysis was performed to analyze the effect of socioeconomics on palliative care receipt among patients with metastatic renal cell carcinoma. **Methods:** A retrospective hospital-based analysis was performed using the National Cancer Database to identify variables that significantly affect receipt of palliative care among patients diagnosed with metastatic renal cell carcinoma diagnosed between 2004 and 2016. Sub-cohort analysis was also performed among patients with the most severe disease. Multivariate binominal logistic regression was performed to determine the association of underlying socioeconomics with receipt of palliative care. The odds of receiving palliative care based on socioeconomic factors was reported as odds ratios (OR) with 95% CI. **Results:** There were 50405 patients meeting inclusion criteria with 40448 (80.2%) undergoing no palliation and 9957 (19.8%) undergoing palliative care. Both Black and Spanish/Hispanic patients had decreased odds of receiving palliative care (OR, 0.816, 95% CI, 0.753 to 0.885 and OR, 0.599, 95% CI, 0.540 to 0.665, respectively). Increasing age, papillary histology, increasing income, and increasing distance were also significantly associated with decreased odds of receiving palliation while treatment at an integrated network cancer program or comprehensive community cancer program and higher educational attainment were associated with increased odds of receiving palliative care. Similar findings were demonstrated among patients with the most severe disease. Limitations include the retrospective design and potential underlying selection biases of this study. **Conclusions:** Significant associations between receipt of palliative care and socioeconomic factors exist among patients with metastatic renal cell carcinoma. In this study among patients with metastatic renal cancer, we found associations between socioeconomics and palliative care access including age, race, Spanish/Hispanic origin, income, education, and other factors. Research Sponsor: None.

4546 **Poster Session**

TIVO-3: Durability of response and updated overall survival of tivozanib versus sorafenib in metastatic renal cell carcinoma (mRCC). *First Author: Elena Verzoni, Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy*

Background: Tivozanib is a potent and highly selective VEGF receptor (R) tyrosine kinase inhibitor in clinical development for mRCC. **Methods:** The TIVO-3 study enrolled subjects with mRCC who failed 2 or 3 prior systemic regimens, one of which included a VEGFR TKI, stratified by IMDC risk category and type of prior therapy (two TKIs; TKI plus checkpoint; TKI + other) then randomized 1:1 to T or sorafenib. Tivozanib demonstrated PFS and ORR advantages over sorafenib. Here we report long term durability of response based on investigator assessment and updated overall survival. **Results:** There were 41 responders (23%) to tivozanib and 20 responders (11%) to sorafenib. The median duration of response (mDoR) was 20.3 months (95% CI: 9.8, 29.9) and 9.0 months (95% CI: 3.7, 16.6) for tivozanib and sorafenib, respectively. With prolonged follow up there were 270 deaths; the HR for overall survival favored tivozanib at 0.91 (95% CI: 0.716, 1.165). Clinical trial information: NCT02627963. **Conclusions:** Tivozanib treatment in third and fourth line mRCC results in longer PFS, higher objective response rate and more durable responses compared to sorafenib. There is no difference in overall survival. Research Sponsor: AVEO Oncology.

Treatment	N	Objective Response	Ongoing Response	mDoR in Months (95% CI)	HR (95% CI)
Sorafenib	175	20 (11%)	3	9.0 (3.7, 16.6)	0.55 (0.30, 1.00)
Tivozanib	175	41 (23%)	13	20.3 (9.8, 29.9)	

4547 **Poster Session**

Integrating peripheral biomarker analyses from JAVELIN Renal 101: Avelumab + axitinib (A + Ax) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). *First Author: Toni K. Choueiri, Dana-Farber Cancer Institute, The Lank Center for Genitourinary Oncology, Boston, MA*

Background: In the phase 3 JAVELIN Renal 101 trial (NCT02684006), treatment-naive patients (pts) with aRCC demonstrated prolonged progression-free survival (PFS) and a higher objective response rate with A + Ax vs S. We report the association of blood-based biomarkers with differential responses to treatment. **Methods:** Biomarkers in pretreatment (pre-tx) and on-treatment (on-tx) blood samples from 886 enrolled pts were correlated with clinical outcomes and molecular profiling data from corresponding tumor samples. Analyses include blood counts of unique populations, T-cell receptor sequencing, circulating cytokines, and serum proteomics by mass spectrometry MALDI-TOF. **Results:** At baseline, higher pre-tx monocyte counts were associated with shorter PFS in the A + Ax arm (Table). In the S arm, higher pre-tx levels of multiple T-cell–related metrics, including the percent of productively rearranged peripheral T cells, were associated with longer PFS but had no association in the A + Ax arm (Table). Higher pre-tx neutrophil counts were associated with shorter PFS in both arms, but neutrophil-to-lymphocyte ratio (NLR) was only associated with PFS for the S arm (Table). On-therapy biomarkers showed differential post-tx changes in T-cell numbers and clones at C2D1. Tx-specific differences were also seen in non–T-cell populations such as monocytes and neutrophils at multiple time points through C3D1. Serum levels of pre- and on-tx VEGF, CRP, and several interleukins showed differential associations with PFS (eg, higher pre-tx VEGF was associated with shorter PFS in only the S arm) (Table). Specific genomic alterations in tumor tissues were associated with differences in several pre- and on-tx angiokines & cytokines. **Conclusions:** Response to treatment with first-line A + Ax or S was associated with immune fitness and tx-specific immunomodulation. We identified peripheral biomarkers in pts with aRCC associated with the presence of impactful genomic alterations and differential clinical outcomes. Clinical trial information: NCT02684006. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

Pre-Tx Biomarker (≥ < med)	A + Ax (N = 442)	S (N = 444)
Monocyte counts (n)	200 vs 183	195 vs 201
mPFS, (95% CI), mo	11.07 (8.54-12.55) vs 16.62 (12.45-23.49)	8.54 (7.16-9.96) vs 9.23 (7.00-10.84)
HR* (95% CI)	1.50 (1.14-1.97)	1.09 (0.85-1.39)
T-cells % (n)	177 vs 198	193 vs 171
mPFS, (95% CI), mo	15.08 (11.11-20.73) vs 12.45 (9.79-17.77)	9.82 (8.31-12.45) vs 8.35 (6.24-9.69)
HR* (95% CI)	0.86 (0.66-1.14)	0.73 (0.57-0.94)
NLR (n)	220 vs 214	217 vs 222
mPFS, (95% CI), mo	12.45 (9.89-17.77) vs 15.08 (11.11-18.20)	7.16 (5.75-9.04) vs 11.07 (8.38-12.49)
HR* (95% CI)	1.10 (0.85-1.42)	1.58 (1.25-2.00)
VEGF (n)	189 vs 193	192 vs 183
mPFS, (95% CI), mo	13.77 (11.11-17.97) vs 12.22 (9.79-16.59)	8.21 (5.68-8.54) vs 11.07 (9.69-12.49)
HR* (95% CI)	0.92 (0.70-1.20)	1.49 (1.16-1.92)

HR, hazard ratio; med, global median *Unstratified.

4548 **Poster Session**

Association of C-reactive protein (CRP) with efficacy of avelumab + axitinib (A + Ax) in advanced renal cell carcinoma (aRCC): Long-term follow-up results from JAVELIN Renal 101. *First Author: Yoshihiko Tomita, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Japan*

Background: CRP is an important prognostic and predictive factor in patients with aRCC receiving various therapies, such as cytokines and tyrosine kinase inhibitors. In this extended follow-up to the phase 3 JAVELIN Renal 101 trial (NCT02684006), we report the association of CRP levels at baseline (BL) and early after treatment with the efficacy of A + Ax or sunitinib (S). **Methods:** CRP levels were assessed at screening and day 1 of each 6-week cycle. Patients were categorized into CRP normal (BL CRP $<$ 10 mg/L), normalized (BL CRP $\geq$10 mg/L and $\geq$1 CRP value decreased to $<$ 10 mg/L during 6 weeks of treatment), and non-normalized (CRP $\geq$10 mg/L at BL and during 6 weeks of treatment) groups. Multivariate analysis of BL characteristics, including CRP for efficacy, was also conducted. Progression-free survival (PFS) and best overall response per independent central review (RECIST 1.1) from the second interim analysis (IA2) of overall survival (OS) and OS from the third interim analysis (IA3) were assessed. **Results:** Minimum duration of follow-up for IA2 and IA3 were 13 and 28 months, respectively. The table shows objective response rate (ORR), PFS, and OS by CRP group. Efficacy outcomes in the normal and normalized groups were favorable compared with the non-normalized group with both A + Ax and S. In the A + Ax arm, the complete response rate was 11.8% (normalized group), 3.8% (normal group), and 0.9% (non-normalized group). With A + Ax, the PFS in the normalized group was longer than in the normal group, but this was not observed with S. In each CRP group, all efficacy outcomes were favorable with A + Ax vs S. In the multivariate analysis, normalized or non-normalized CRP was an independent predictive factor of ORR or OS with A + Ax. **Conclusions:** Normal and normalized CRP levels were associated with improved A + Ax efficacy. A + Ax demonstrated favorable efficacy across CRP groups. OS in this study was immature; follow-up for the final analysis is ongoing. Further research in defining predictive value of CRP is warranted. Clinical trial information: NCT02684006. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

CRP group	A + Ax Normal n = 234	A + Ax Normalized n = 51	A + Ax Non-normalized n = 108	S Normal n = 232	S Normalized n = 36	S Non-normalized n = 128
ORR (95% CI), %	56.0	66.7	45.4	30.6	41.7	19.5
Odds ratio (95% CI)*	(49.4-62.4)	(52.1-79.2)	(35.8-55.2)	(24.7-37.0)	(25.5-59.2)	(13.1-27.5)
	Ref	1.572	0.653	Ref	1.620	0.550
		(0.832-2.973)	(0.413-1.033)		(0.789-3.324)	(0.328-0.924)
mPFS (95% CI), mo	15.2	NE	7.0	11.2	11.2	4.2
HR (95% CI)*	(12.5-21.0)	(11.1-NE)	(5.6-9.9)	(8.4-13.9)	(6.7-13.8)	(2.8-5.6)
	Ref	0.724	1.923	Ref	1.099	2.090
		(0.453-1.156)	(1.428-2.590)		(0.689-1.753)	(1.585-2.757)
mOS (95% CI), mo	NE	NE	23.0	NE	39.8	19.1
HR (95% CI)*	(42.2-NE)	(30.4-NE)	(18.4-33.1)	(39.0-NE)	(21.7-NE)	(16.3-25.3)
	Ref	1.218	2.428	Ref	1.343	2.494
		(0.734-2.022)	(1.722-3.423)		(0.774-2.331)	(1.823-3.412)

HR, hazard ratio; m, median; NE, not estimable; Ref, reference. *Unstratified.

4549 **Poster Session**

Association between neutrophil-to-eosinophil ratio (NER) and efficacy outcomes in the JAVELIN Renal 101 study. *First Author: Matthew D Tucker, Vanderbilt University Medical Center, Nashville, TN*

Background: Baseline NER has been reported to be associated with outcomes of immuno-oncology based combination treatment in advanced renal cell carcinoma (aRCC). We report outcomes by baseline NER of patients with aRCC in the JAVELIN Renal 101 trial who received avelumab + axitinib (A + Ax) or sunitinib (S). **Methods:** We calculated the median NER (mNER) for patients in the A + Ax and the S arms at the data cutoff (April 20, 2020) for the 3rd interim analysis (IA3). Progression-free survival (PFS), overall survival (OS), and objective response (OR) by NER are reported. Multivariate Cox regression analyses of PFS and OS were also conducted. **Results:** At the IA3 cutoff date, the mNERs for the A + Ax arm (n = 383) and S arm (n = 396) were 29.2 and 27.0, respectively. OR, PFS and OS for both arms are summarized in the table below. Better observed treatment outcomes in OR (63.9% vs 55.2%) and median PFS (15.5 vs, 11.1 months) were observed for patients with a NER $<$ median vs. NER $\geq$ median in the A + Ax arm, while there were not major differences in outcome based on NER in the S arm. The stratified hazard ratio (HR) for PFS in patients with a NER $<$ median compared with those with a NER $\geq$ median in the A + Ax arm was 0.81 (95% CI, 0.630-1.035) and 0.93 (95% CI, 0.728-1.181) in the S arm. Patients with a NER $<$ median had improved OS compared with those with a NER $\geq$ median in the A + Ax arm (stratified HR, 0.67; 95% CI, 0.481-0.940) and the S arm (stratified HR, 0.57; 95% CI, 0.424-0.779). Multivariate analysis showed that a low NER was associated with longer PFS and OS by treating baseline NER as either a continuous variable or a binary variable (dichotomized by median). **Conclusions:** Baseline NER may be predictive of OR and PFS in aRCC patients treated with A + Ax, and prognostic for overall survival regardless of therapy. Clinical trial information: NCT02684006. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

	A + Ax	A + Ax	S	S
	NER < mNER (n = 191)	NER ≥ mNER (n = 192)	NER < mNER (n = 195)	NER ≥ mNER (n = 201)
OR, %	63.9	55.2	32.8	30.8
mPFS, mo	15.5	11.1	9.7	8.3
18-mo PFS, %	45.6	37.6	29.6	25.0
36-mo PFS, %	23.7	18.5	10.6	10.6
mOS, mo	NE	NE	NE	28.1
18-mo OS, %	81.4	73.5	79.3	64.4
36-mo OS, %	66.0	52.2	62.6	41.7

4550 **Poster Session**

Camrelizumab plus famitinib for advanced renal cell carcinoma or unresectable urothelial carcinoma: Updated results from a phase II trial. *First Author: Yuan-Yuan Qu, Department of Urology Surgery, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Considering the synergistic/additive effect of PD-1 blockade and angiogenesis inhibition, we conducted an open-label, multi-center phase II study of camrelizumab (an anti-PD-1 antibody) plus famitinib (a TKI against VEGFR-2, PDGFR, c-kit, and FGFR) in pts with heavily treated advanced renal cell carcinoma (RCC) and unresectable urothelial carcinoma (UC). **Methods:** Based on an adaptive two-stage design, 22 pts were enrolled in the RCC and UC cohort, respectively, at stage 1; if there were $\geq$7 responders of the 22 pts, enrollment would be extend to 33 at stage 2. Pts received famitinib 20 mg orally QD plus camrelizumab 200 mg IV Q3W. Primary endpoint was ORR per RECIST v1.1. Preliminary data at stage 1 were reported at ASCO 2020 annual meeting (#5085). More than 7 pts in each cohort had CR/PR during stage 1; enrollment of stage 2 had been completed, and the data are firstly reported here. **Results:** 74 pts (38 advanced RCC and 36 unresectable UC) were enrolled from Jan 23, 2019 to Dec 14, 2020. In RCC cohort, 65.8% of pts had received $\geq$1 prior VEGFR inhibitors. In UC cohort, all pts had progressed on or relapsed after a platinum-containing chemotherapy. As of Jan 10, 2021, median time from enrollment to data cutoff was 18.8 mos (range, 8.5-22.7) for RCC cohort and 7.0 mos (range, 0.9-23.6) for UC cohort. In RCC cohort, ORR was 63.2% (95% CI, 46.0-78.2; 24 PRs), DCR was 89.5% (95% CI, 75.9-95.8), median DOR was not reached (range 2-19+ mos), mPFS was not reached, and 12-mo OS rate was 88.0%. Most pts (92.1%) had reduction in target lesions, and median reduction was 47% from baseline. ORR was 84.6% (95% CI, 57.8-97.3; 11/13) for untreated RCC pts and 52.0% (95% CI, 31.3-72.2; 13/25) for pre-treated pts; DCR was 100% (95% CI, 77.2-100.0) and 84.0% (95% CI, 65.3-93.6), mPFS was not reached and 13.4 mos (95% CI: 4.1-21.0), respectively. In UC cohort, of the 33 pts with post-baseline efficacy evaluation, ORR was 33.3% (95% CI, 19.8-50.4; 1 CR, 10 PRs), DCR was 60.6% (95% CI, 43.7-75.3), median DOR was not reached (range 1.0+-16.7+ mos), mPFS was 6.4 mos (95% CI, 2.1-11.8), and mOS was not reached. ORR trended to be higher for bladder cancer (43.8%, 7/16) than upper tract urothelial carcinoma (25.0%, 4/16). Treatment-related AEs (TRAEs) occurred in 97.3% of 74 pts. Grade 3 or 4 TRAEs occurred in 63.5% of pts, mainly hypertension (23.4%), decreased platelet count (21.3%), proteinuria (17.0%), anemia (14.9%), and palmar-plantar erythrodysesthesia syndrome (14.9%). 1 pt died of TRAE (multiple organ dysfunction syndrome). **Conclusions:** Camrelizumab plus famitinib showed potent anti-tumor activity in pts with advanced RCC and UC with no new safety concerns. Additionally, promising ORR and durable DOR were observed in pts with heavily-treated RCC. These results support further investigation in these settings. Clinical trial information: NCT03827837. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

4551 **Poster Session**

Real-world outcomes in patients with metastatic clear cell renal cell carcinoma receiving front-line axitinib plus pembrolizumab versus ipilimumab plus nivolumab. *First Author: Kevin Zarrabi, Fox Chase Cancer Center, Philadelphia, PA*

Background: Front-line treatment for patients (pts) with metastatic clear cell renal cell carcinoma (mRCC) has undergone rapid advances in the last five years. This evolution has led to uncertainty about the optimal first line combination regimen. Herein, we compare real-world outcomes in pts treated with either axitinib/pembrolizumab (A/P) or ipilimumab/nivolumab (I/N) reported by International Metastatic RCC Database Consortium (IMDC) score. **Methods:** The nationwide Flatiron Health electronic health records-derived database was used to select pts diagnosed with mRCC and treated with front-line A/P or I/N from 2018-2020. The primary endpoints were overall-survival (OS) and real-world progression free survival (rwPFS). The survival analyses were adjusted using propensity score-based Inverse Probability of Treatment weighting, providing balance on age, gender, insurance, race, IMDC, practice type, and nephrectomy. Survival was assessed from beginning of therapy, and survival by treatment groups was compared using weighted and unweighted Kaplan-Meier curves with log-rank tests and weighted Cox proportional hazards regressions. Disease characteristics between the treatment groups were compared using chi-square and T-tests. **Results:** 821 pts received frontline A/P (n=259) or I/N (n= 562). Demographics and clinical parameters were similar between the two cohorts. Median age was 66 years, 73% were male, and 54.9% had a nephrectomy. 459 pts had all IMDC criteria factors available, 242 pts had missing factors but enough to define as intermediate/poor risk, 120 pts had unknown IMDC risk. Adjusted median OS was not statistically different: mOS for A/P was not reached (NR) while I/N was 22 mo (95% CI, 19.8-NR; p=0.40). Twelve-month survival was 68.5% for A/P treated pts and 65.8% for I/N treated pts (P=0.41). Twelve-month rwPFS was 41.4% for A/P treated pts and 39.7% for I/N treated pts (P=0.14). No statistical difference in survival was seen within IMDC risk strata (see table). **Conclusions:** In this retrospective, real-world study of pts treated with front-line A/P or I/N, 12-month survival was not statistically different irrespective of IMDC risk. Longer follow-up will be necessary to discern any significant differences. Research Sponsor: None.

Adjusted 12-month survival.

IMDC Score	A/P n=259	I/N n=562	p-value
Favorable (n=69)	93.2%	72.5%	0.31
Intermediate/Poor (n=632)	64.6%	56.1%	0.61
Int.	73.9%	65.9%	0.29
Poor	52.1%	51.9%	0.80
Unknown (n=120)	76.4%	76.7%	0.61
Full cohort (n=821)	68.5%	65.8%	0.41

4552 **Poster Session**

The impact of antibiotic (Ab) exposure on clinical outcomes in patients with metastatic renal cell carcinoma (mRCC) treated with immune checkpoint inhibitors (ICI) or VEGF targeted therapy (VEGF-TT). *First Author: Matthew Scott Ernst, Tom Baker Cancer Center, University of Calgary, Calgary, AB, Canada*

Background: Retrospective studies have shown an association between Ab exposure and inferior clinical outcomes in patients receiving ICI across various tumor types, including mRCC. However, it is unclear whether Ab exposure has a unique interaction with ICI or is an independent prognostic marker, regardless of treatment. We sought to examine Ab exposure and its association with clinical outcomes in patients with mRCC treated with ICI compared to VEGF-TT. **Methods:** We identified patients treated with ICI (anti-PD-L1 alone or in combination with VEGF or CTLA4 inhibitor) or VEGF-TT alone in first to fourth line settings from 2009-2020 across 3 academic centers in North America. Ab exposure was defined as administration of Ab within 60 days prior to initiation of systemic therapy. Outcomes of interest were response rate (RR), time to treatment failure (TTF) and overall survival (OS). Multivariable Cox regression was performed to control for imbalances in International mRCC Database Consortium (IMDC) risk factors, histology, and treatment line. **Results:** We identified 748 patients. Among the ICI (n=427) and VEGF-TT (n=321) cohorts, 13% vs 15% (p=0.47) had Ab exposure and 57% vs 48% (p=0.046) were treated in the first line setting. The proportion of favorable, intermediate, and poor risk disease by IMDC criteria differed between Ab exposed and unexposed patients in the ICI (14% vs 18%, 47% vs 62%, 39% vs 21% p=0.03) and VEGF-TT (7% vs 13%, 43% vs 60%, 50% vs 27%, p=0.01) cohorts. RR, TTF and OS results are displayed in Table 1. Multivariable analysis did not show a significant independent association between Ab exposure and OS in both the ICI (HR 1.13, p=0.62) and VEGF-TT (HR 1.32, p=0.16) cohorts. Treatment modality (ICI vs VEGF-TT) did not modify the effect of Ab exposure on OS (p=0.84). **Conclusions:** Ab exposure was associated with higher IMDC risk scores in both the ICI and VEGF-TT cohorts as well as inferior OS on univariable analysis. After adjusting for IMDC risk factors, histology and treatment line, we were unable to find an independent association between Ab exposure and OS in multivariable analysis for either cohort. Research Sponsor: None.

	ICI Cohort			VEGF-TT Cohort		
	Ab	No Ab	P-value	Ab	No Ab	P-value
RR (%)	36	38	0.81	21	24	0.66
Median TTF, mo (95% CI)	6.2 (4.7-10.7)	8.1 (6.4-10.3)	0.23	5.5 (4.3-7.6)	6.3 (3.6-8.6)	0.14
Median OS, mo (95% CI)	22.5 (11.5-79.6)	36.8 (30.1-47.1)	0.02	13.5 (6.0-21.1)	21.6 (17.2-25.6)	<0.01

4553 **Poster Session**

Nivolumab plus cabozantinib (N+C) versus sunitinib (S) for advanced renal cell carcinoma (aRCC): Outcomes by baseline disease characteristics in the phase 3 CheckMate 9ER trial. *First Author: Andrea B. Apolo, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: First-line N+C significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in aRCC patients (pts) in the phase 3 CheckMate 9ER trial, leading to FDA approval of N+C in this setting. A deeper understanding of how baseline disease characteristics may impact clinical outcomes with N+C vs S may inform clinical decision making. **Methods:** Pts with clear cell aRCC were randomized to N 240 mg IV Q2W + C 40 mg PO QD vs S 50 mg PO QD (4 weeks of 6-week cycles). In this post hoc exploratory analysis, PFS, OS, and ORR were evaluated across pt subgroups defined by baseline IMDC risk status, organ sites of metastases (mets), number of organs with any lesions, or target lesion size. Consistent with primary/secondary efficacy endpoints in ITT pts, PFS and ORR were evaluated per RECIST v1.1 by blinded independent central review in subgroups. **Results:** Median follow-up in ITT pts was 23.5 months. PFS, OS, and ORR (including complete response [CR]) outcomes are summarized in the table across subgroups: IMDC risk (favorable [FAV], intermediate [I], poor [P]); number of organs with ≥ 1 target/nontarget lesion (T/NT; 1 and ≥ 2); sum of diameters of target lesions (sDTL; < and ≥ median [72.1 mm]), and in pts with liver, bone, or lung mets. The PFS HR favored N+C vs S and median (m) PFS was longer with N+C vs S across all subgroups. The OS HR also favored N+C vs S across most subgroups. ORR ranged from 38%–66% (N+C) vs 10%–44% (S) across subgroups, and CR benefits were seen with N+C in most subgroups. Additional outcomes including landmark OS and response details in subgroups will be reported. **Conclusions:** Consistent with outcomes in ITT pts, efficacy benefits with N+C vs S were observed regardless of IMDC risk status, organ site of mets, or extent of tumor burden at baseline. These results support N+C as a new first-line treatment option for pts with aRCC. Clinical trial information: NCT03141177. Research Sponsor: Bristol Myers Squibb.

Subgroup (N+C v S, n)	FAV risk (74 v 72)	I risk (188 v 188)	P risk (61 v 68)	1 organ site with T/NT (61 v 68)	≥ 2 organ sites with T/NT (261 v 258)	sDTL < 72.1 mm (160 v 167)	sDTL ≥ 72.1 mm (163 v 161)	Pts w/ lung mets (240 v 251)	Pts w/ bone mets (79 v 72)	Pts w/ liver mets (73 v 54)
PFS, HR (95%)	0.58 (0.36–0.93)	0.58 (0.45–0.76)	0.36 (0.23–0.56)	0.53 (0.32–0.88)	0.53 (0.43–0.67)	0.52 (0.39–0.71)	0.53 (0.40–0.70)	0.51 (0.40–0.64)	0.38 (0.25–0.59)	0.51 (0.33–0.79)
mPFS, mo	25 v 13	17 v 9	10 v 4	25 v 13	15 v 7	20 v 10	11 v 6	17 v 8	18 v 4	11 v 6
OS, HR (95%)	0.94 (0.46–1.92)	0.74 (0.50–1.08)	0.45 (0.27–0.76)	0.79 (0.33–1.90)	0.63 (0.47–0.84)	0.64 (0.38–1.06)	0.64 (0.46–0.89)	0.63 (0.46–0.86)	0.64 (0.39–1.06)	0.47 (0.27–0.82)
ORR per RECIST v1.1 (95% CI), %	66 (54–77) v 44 (33–57)	56 (48–63) v 29 (22–36)	38 (26–51) v 10 (4–20)	62 (49–74) v 35 (24–48)	53 (47–59) v 27 (21–33)	62 (54–69) v 36 (29–44)	48 (40–56) v 20 (15–28)	56 (49–62) v 29 (24–36)	48 (37–60) v 11 (5–21)	49 (37–61) v 20 (11–34)
CR, %	9 v 10	11 v 3	5 v 1	20 v 4	7 v 4	16 v 8	2 v 0	8 v 4	6 v 0	1 v 2

4554 **Poster Session**

Outcomes of first-line (1L) ipilimumab and nivolumab (IPI-NIVO) and subsequent therapy in metastatic renal cell carcinoma (mRCC): Results from the International mRCC Database Consortium (IMDC). *First Author: Chun Loo Gan, Tom Baker Cancer Center, University of Calgary, Calgary, AB, Canada*

Background: IPI NIVO is approved for 1L treatment of IMDC intermediate/poor risk mRCC based on the CHECKMATE 214 trial. Herein, we report the clinical effectiveness of 1L IPI NIVO and second line (2L) therapy in the real-world setting. **Methods:** Using the IMDC dataset, patients (pts) treated with 1L IPI NIVO were identified. The outcomes of interest were 1L and 2L overall response rate (ORR), treatment duration (TD), time to next treatment (TTNT), and overall survival (OS). **Results:** 706 pts were included: 9% (57/614), 58% (354/614), and 33% (203/614) were IMDC favorable (fav), intermediate (int), and poor risk, respectively. Median age was 61 years. The majority of pts were males (71%), had clear cell histology (85%), and underwent nephrectomy (61%). 36%, 19%, and 8% of patients had bone, liver, and brain metastases, respectively. The 12-month OS for pts with IMDC fav, int, and poor risk disease was 92%, 79%, and 56%, respectively (p<0.01). The corresponding estimates for 24 months were 80%, 69%, and 38% (p<0.01). Pts who responded (39%) were more likely to have better IMDC risk category (p=0.02), received nephrectomy (p=0.04), normal neutrophil count (p<0.01), and clear cell histology (p=0.01). Pts with progressive disease as best response (27%) were more likely to have not received nephrectomy (p<0.01), worse IMDC risk category (p=0.02), bone metastases (p=0.01), liver metastases (p=0.04), and non-clear cell histology (p=0.01). Of the 66% (466/706) of pts who discontinued 1L IPI NIVO, 51% (236/466) received 2L therapy: sunitinib (40%), cabozantinib (25%), pazopanib (18%), axitinib (8%), and others (9%). The ORR, median TD, and median OS for those who received either sunitinib, cabozantinib, pazopanib or axitinib was 16%, 4.5 months (mo) (95% CI 3.7-5.6), and 14.5 mo (95% CI 10.9-25.9), respectively. 33% (129/386) of pts discontinued IPI NIVO due to irAEs. **Conclusions:** Our study benchmarks the real-world experience of 1L IPI NIVO in mRCC. IMDC criteria is prognostic for clinical outcome. Tyrosine kinase inhibitors have clinical activity post IPI NIVO. Research Sponsor: None.

1L IPI NIVO Clinical Outcome	All IMDC risk category				IMDC Int/Poor		
	Overall	Fav*	Int	Poor	All	Clear Cell histology	Non clear cell
ORR %, (n/n)	39% (201/518) P=0.02	45% (23/51)	43% (129/303)	30% (49/164)	38% (170/467)	43% (151/352)	30% (14/46)
Median TD (mo) (95% CI)	5.0 (4.0-6.4) P=0.03	6.9 (4.3-13.6)	6.4 (4.3-7.9)	3.0 (2.5-5.4)	5.0 (3.9-6.6)	6.2 (4.6-7.9)	4.2 (2.6-8.5)
Median TTNT (mo) (95% CI)	11.3 (9.6-13.9) P<0.01	24.0 (10.9-NR)	12.9 (9.9-17.9)	7.5 (5.4-9.8)	10.5 (9.1-12.6)	11.3 (9.4-15.4)	9.3 (4.1-NR)
Median OS (mo) (95% CI)	41.4 (27.6-53.4) P<0.01	47.8 (40.8-NR)	48.0 (35.1-NR)	14.0 (11.2-22.1)	40.2 (25.7-NR)	48.1 (35.1-NR)	17.6 (7.9-NR)

*Interpret with caution as the use of IPI NIVO in IMDC fav was highly selected in the real-world.
NR= not reached.

4555 **Poster Session**

Phase 2 study of belzutifan (MK-6482), an oral hypoxia-inducible factor 2α (HIF-2α) inhibitor, for Von Hippel-Lindau (VHL) disease-associated clear cell renal cell carcinoma (ccRCC). *First Author: Ramaprasad Srinivasan, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: Inactivation of *VHL* leads to aberrant stabilization and accumulation of HIF-2α, which drives tumor growth. Patients (pts) with VHL disease are at risk for ccRCC, pancreatic neuroendocrine tumors (pNETs), and hemangioblastomas. Repeated surgeries are often needed to control ccRCC and other VHL disease manifestations. Prior results of this ongoing open-label phase 2 study (NCT03401788) showed activity with belzutifan in VHL disease. Updated results are presented. **Methods:** Adults with germline *VHL* alterations, measurable and localized/nonmetastatic ccRCC, no prior systemic anticancer therapy, and ECOG PS 0 or 1 received belzutifan 120 mg once daily until progression, intolerable toxicity, or decision to withdraw. The primary end point is ORR of VHL-associated ccRCC tumors per RECIST v1.1 by independent review committee (IRC). Secondary end points include DOR, time to response (TTR), PFS, and safety. **Results:** As of June 1, 2020, 61 pts enrolled. Most pts (82%) had ECOG PS 0, and the median number of prior tumor reduction procedures (eg, partial nephrectomy, craniotomy, radiation therapy) per pt was 5 (range, 0-15). Lesions outside the kidney (non-RCC tumors) evaluable by IRC included pNETs (33%) and CNS hemangioblastomas (82%). Median follow-up was 69 wk (range, 18-105), median duration of treatment was 68 wk (range, 8-105), and 56 pts (92%) remain on therapy. There were 22 confirmed responses (ORR, 36% [95% CI, 24-49]) and 7 (11%) unconfirmed responses (documented at 1 time point, to be confirmed at subsequent time point); all were PRs. In pts with confirmed PR, median DOR was not reached (range, 12+ to 62+ wk), median TTR was 31 wk (range, 12-61), and 56 pts (92%) had some reduction in the sum of all target lesion diameters. PFS rate at 52 wk was 98% (95% CI, 89-100). For non-RCC tumors, ORR was 80% (16/20; 1 CR) in pNETs and 32% (16/50; 1 CR) in CNS hemangioblastomas. Of 16 pts with evaluable retinal hemangioblastomas at baseline, 11 (69%) showed improvement per IRC. In those 16 pts, 29 eyes were monitored for retinal hemangioblastomas: 16 eyes (55%) showed improvement, 12 (41%) were stable, and no evaluation was available for 1 eye (3%). All 61 pts (100%) had at least one AE. The most common all-cause AE was anemia (90%), which is considered an on-target toxicity. Treatment-related AEs (TRAE) were reported by 60 pts (98%), and 8 pts (13%) had a grade 3 TRAE. No pts had grade 4/5 TRAEs. One pt discontinued treatment because of a TRAE (grade 1 dizziness). **Conclusions:** Belzutifan demonstrates clinical benefit and has a favorable safety profile in patients with VHL disease–associated ccRCC, pNETs, and hemangioblastomas. Clinical trial information: NCT03401788. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4556 **Poster Session**

Randomized phase Ib study to evaluate safety, pharmacokinetics and therapeutic activity of simlukafusp α in combination with atezolizumab ± bevacizumab in patients with unresectable advanced/ metastatic renal cell carcinoma (RCC) (NCT03063762). *First Author: Jose Luis Perez-Gracia, Department of Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain*

Background: Simlukafusp α ([SIM], FAP-IL2v) is a novel IL-2v immunocytokine engineered to preferentially activate effector CD8 T and NK cells, but not regulatory T cells (Tregs), due to abolished binding to Interleukin-2 receptor α (IL-2Rα) and retained affinity to IL-2Rβγ. High affinity binding of SIM to fibroblast activation protein (FAP), expressed on cancer-associated fibroblasts, mediates its accumulation in malignant lesions. **Methods:** The Dose-Escalation (DE) consisted of: Arm A: SIM 5-25 mg weekly for 4 weeks, and every 2 weeks (Q2W) thereafter in combination with atezolizumab [ATZ] 840mg Q2W; and Arm B: same as Arm A + bevacizumab [BEV] 10 mg/kg Q2W. Patients (pts) not previously treated were evaluated in the Extension Part: Arm C (n=3): SIM + ATZ every 3 weeks (Q3W); or Arm D (n=25): SIM + ATZ + BEV ("triplet") Q3W. Primary objectives were: finding the recommended dose of SIM and assessment of objective response rate (ORR) by RECIST v1.1. **Results:** We enrolled 69 pts with unresectable advanced/ metastatic clear-cell and/or sarcomatoid RCC. Median age of patients was 57 years (range: 35-78). The recommended dose for extension of SIM was 10 mg. Median treatment duration in days in each arm were: A: 106 (range: 1-877); B: 324 (8-940); C: 659 (71-768); D: 437 (1-682). Twenty-five pts are evaluable for therapeutic activity in Arm A [ORR: 24% (6 PR; 90% CI 12.95, 40.12)]; 15 in Arm B [46.7% (1 CR, 6PR; 90% CI 27.67, 66.68)]; 3 in Arm C [33.3% (1PR; 90% CI 7.83, 74.65)]; and 23 in Arm D [47.8% (2 CR, 9 PR; 90% CI 35.74, 68.15)]. Twelve patients are ongoing on study treatment. Treatment related grade 3 and 4 adverse events (AE) occurred respectively in 69.7% and 9.1% patients. The most common serious AEs were pyrexia (10.6 %) and infusion-related reactions (9.1%). 65.2% Of the patients reported at least one AE of elevations in liver transaminases/GGT/ alkaline phosphatase/bilirubin. Drug-related AEs led to dose modification/interruption in 37.9 % of the pts, and treatment discontinuation in 3% of the patients. SIM led to preferential expansion and activation of NK and CD8 T cells (but not Tregs) in peripheral blood and augmented tumor infiltration and tumor inflammation. Intriguingly responses were observed not only in pts with PD-L1 positive or inflamed tumors, but also in pts with PD-L1 negative tumors (n=13) or poorly infiltrated tumors classified as immune deserts (n=2). **Conclusions:** The combination of SIM with ATZ ± BEV was feasible with an acceptable safety profile. Clinical activity was more favorable for the triplet among the study Arms, but comparable to the ATZ + BEV combination in the IMmotion151 (Rini B, et al 2019). Observed pharmacodynamic findings were consistent with the expected effects. Clinical trial information: NCT03063762. Research Sponsor: Roche.

4557 **Poster Session**

Treatment outcomes in renal cell carcinoma patients with metastases to the pancreas and other sites. *First Author: Cassandra Duarte, University of Colorado Denver, Denver, CO*

Background: Metastatic RCC (mRCC) involving the pancreas is distinct from RCC involving other metastatic sites and is characterized by an indolent clinical course, heightened angiogenesis, and an inflamed stroma (PMID: 32271170). We previously reported on outcomes of RCC patients (pts) with pancreatic oligometastasis (ASCO GU 2020). We now report on outcomes in pts with mRCC involving the pancreas in conjunction with other metastases (mets). **Methods:** We conducted a retrospective, multi-institutional study of mRCC pts with mets to the pancreas and other sites. Data on pt demographics, tumor characteristics, systemic therapy, and outcomes were collected. Pts were classified based on treatment category: immunotherapy (IO) or vascular endothelial growth factor/receptor inhibitors (VEGFI). Outcomes measured included objective response rates (ORR), time-on-treatment (TOT), and overall survival (OS). **Results:** The analysis included 229 pts from 9 institutions, diagnosed between 1985-2020. Of these, 211 (92%) had clear-cell histology; 131 (57%) had nephrectomy; 41 (18%) had local pancreas-directed therapy; 111 (48%) had synchronous presentation of disease in the pancreas and other sites at time of mets. IMDC risk was favorable in 33%, intermediate in 41%, poor in 11%, and unknown in 15% pts. Median lines of therapy was 2 (range 0-9). Of 219 pts who received first-line (1L) therapy, 151 (69%) had VEGFI therapy, 41 (19%) had IO, and 18 (8%) had VEGFI/IO combination (Table). The IO group included 21 pts on checkpoint inhibitor (CPI), 16 pts on HD-IL2, 4 pts on other IO. 1L ORR was 39.7% for VEGFI (95% CI 31.8-48.0) and 31.7% for IO (95% CI 18.1-48.1) and was not statistically significant (NS, OR 1.4, 95% CI 0.65-3.23, p = 0.371). Median TOT for 1L therapy was 11.6m for VEGFI and 6.5m for IO (p = 0.0106). With a median follow-up of 51.5m, the median OS (mOS) for all pts from time of metastatic disease was 7.7 years (y) (95% CI 6.3-10.3). The mOS for pts who received 1L VEGFI was 7.6y (95% CI 5.5-9.5) and was not reached (NR) for those who got 1L IO (95%CI 6.5-NR); this difference was significant with an unadjusted p-value of 0.029. The pair-wise comparison between mOS of the 1L CPI subgroup compared to that of the 1L VEGFI group was significant (p = 0.0148). **Conclusions:** Consistent with the literature, mRCC pts with involvement of the pancreas in this study have prolonged OS compared to historical OS for the standard mRCC population. Additionally, our findings suggest that the choice of first-line therapy may impact outcomes. Additional analyses will be presented. Research Sponsor: None.

First-Line therapy.

	N=219	ORR %	Median TOT, months [IQR]	Median OS, years (95% CI)
VEGFI	151	39.7	11.6 [4.0-28.1]	7.6 (5.5, 9.5)
Immunotherapy	41	31.7	6.5 [3.0-10.0]	NR (6.5, NR)
CPI	21	38	4.3 [2.0-11.6]	NR (NR, NR)
HD-IL2	16	25	7.5 [4.0-9.0]	7.4 (6.5, NR)
Other Immuno	4	25	9.5 [2.0-33.0]	6.0 (5.8, NR)
VEGFR + CPI	18	44	15.0 [5.7-21.3]	6.2 (2.8, NR)
Other	9	11	19.6 [8.6-34.0]	3.3 (2.1, NR)

4558 **Poster Session**

Programmed death ligand-1 (PD-L1) expression in patients (pts) with metastatic renal cell carcinoma (mRCC) treated with nivolumab (NIVO) in combination with stereotactic body radiotherapy (SBRT) in NIVES study. *First Author: Cristina Masini, Medical Oncology Unit, Clinical Cancer Centre, AUSL-IRCCS di Reggio Emilia, Reggio Emilia, Italy*

Background: The NIVES study represents the first prospective trial with NIVO in combination with SBRT in pre-treated mRCC patients . This study did not meet the primary endpoint in terms of objective response rate (ORR) as previously reported. However this combination showed a faster time to treatment response, a long progression free survival and median duration of response without increasing toxicities. Here we have tested with an exploratory analysis the correlation between PD-L1 expression and clinical outcomes in pts treated with NIVO plus SBRT. **Methods:** PD-L1 expression was assessed in archival collected tumour samples in our central laboratory using 4 commercial kits for immunoistochemical (ICH) analysis (clone 22C3 pharm DX Dako Agilent, 28.8 Abcam and SP142 and SP263 Ventana Medical System). A tumor cell was considered positive if any membranous staining was found regardless of the intensity. In particular the immunostaining was scored 0 when all tumor cells were unstained (PD-L1-negative), 1+ when $<$ 1% positive tumor cells were counted, 2+ when the percentage was between 1% and 50%,3+ when the number of stained cells was more than 50%. ORR and overall survival (OS) were correlated with PD-L1 staining. **Results:** Formalin-fixed paraffin-embedded (FFPE) specimens were obtained from 44 of 69 pts enrolled in the NIVES study. Twenty-two pts of 44 (50%) were considered PD-L1-negative using all the 4 commercial kits for ICH analysis, while 14 of 44 pts (31,8%) were defined PD-L1 weakly positive (positive tumor cells $<$ 1% at least in one kit for ICH). Eight of 44 pts (18.1%) were defined PD-L1 strong positive when at least one kit for ICH scored 2+ or 3+. About the correlation between ORR and PDL1 staining in the 42 pts (2/44 pts are not evaluable for ORR), ORR was 18.2% (95% CI, 5.2% to 40.3%) in the PD-L1-negative group vs 20% (95% CI, 5.7% to 43.7%) in weakly/strongly PD-L1 positive (p = 1.00). Among the 44 pts in the intention-to-treat population with available PD-L1 status, median OS was not significantly different between pts with PD-L1 negative (20.56 months, 95% CI, 7.16 to NR) and PD-L1 positive (18.33 months, 95% CI, 6.83 to NR) (p = 0.56). **Conclusions:** For the first time four commercial kits for ICH analysis were used to test PD-L1 expression in pretreated mRCC pts. Data from these small sample size seem to confirm that PD-L1 in pre-treated mRCC cancer is not a predictive biomarker for selecting pts to receive NIVO-based treatment. Clinical trial information: NCT03469713. Research Sponsor: GOIRC, Pharmaceutical/Biotech Company.

4559 **Poster Session**

An FDA-pooled analysis of frontline combination treatment benefits by risk groups in metastatic renal cell carcinoma (mRCC). *First Author: Daniel Lee, Natl Cancer Inst, Germantown, MD*

Background: The International Metastatic RCC Database Consortium (IMDC) risk model was developed for prognosis of patients with mRCC treated with vascular endothelial growth factor (VEGF)-targeted monotherapy in the first-line setting. Efficacy in trials of anti-VEGF therapy has been generally consistent across risk groups, including for overall survival (OS). For trials of immunotherapy combinations, the small numbers of OS events for the favorable risk group in each trial limited reliable conclusions; however, there was a suggestion of possible differential effects on OS between favorable risk and other risk groups. **Methods:** We pooled individual patient data (n=3447) from four phase III randomized trials of combinations of immunotherapy + immunotherapy (n=1) or immunotherapy + anti-VEGF therapy (n=3) submitted to the US Food and Drug Administration in support of marketing applications. All trials calculated IMDC risk group for each patient and used a control arm of sunitinib. We combined intermediate and poor prognostic groups (“intermediate/poor”) and compared their OS to that of the favorable risk group using Kaplan-Meier and Cox Proportional Hazards methods. **Results:** In this pooled analysis, treatment with combination immune checkpoint therapy did not demonstrate an improvement in OS compared to sunitinib in the favorable risk group (HR 0.953; 95% CI: 0.72, 1.27). An improvement in OS was observed in the intermediate/poor risk group (HR 0.696; 95% CI: 0.62, 0.78). **Conclusions:** Our analysis of OS in patients treated with immunotherapy combinations compared to sunitinib suggests possible differential benefit in the favorable risk compared to the intermediate/poor risk group. These results are not conclusive and considered exploratory due to the relative immaturity of OS in the favorable risk group. Follow-up for survival continues in each study to allow for more definitive results. Research Sponsor: FDA.

Overall survival by risk status.

Favorable Risk				
Arm	**N**	**Deaths (%)**	**Median (95% CI)***	**HR (95% CI)**
Combination	422	93 (22.0)	NR (NR, NR)	0.953 (0.72, 1.27)
Sunitinib	404	93 (23.0)	NR (NR, NR)	
Intermediate/Poor				
Arm	**N**	**Deaths (%)**	**Median OS (95% CI)**	**HR (95% CI)**
Combination	1,308	534 (40.8)	46.8 (39.9, NR)	0.696 (0.62, 0.78)
Sunitinib	1,313	668 (50.9)	29.3 (26.0, 32.9)	

*Months.

4560 **Poster Session**

Analysis of the CLEAR study in patients (pts) with advanced renal cell carcinoma (RCC): Depth of response and efficacy for selected subgroups in the lenvatinib (LEN) + pembrolizumab (PEMBRO) and sunitinib (SUN) treatment arms. *First Author: Viktor Grünwald, University Hospital Essen, Essen, Germany*

Background: In the multicenter, open-label, randomized, phase 3 CLEAR study, LEN + PEMBRO had significant PFS and OS benefits, and improved ORR vs SUN in first-line advanced RCC. Herein, we explore efficacy according to selected subgroups and the association between pts’ depth of response and OS. **Methods:** Pts in the CLEAR study were randomly assigned 1:1:1 to 1 of 3 treatment arms: LEN 20 mg orally QD + PEMBRO 200 mg IV Q3W; LEN 18 mg + everolimus 5 mg orally QD; or SUN 50 mg orally QD (4 weeks on/2 weeks off). We report PFS, OS, and ORR based on IMDC risk group (favorable and intermediate/poor) and presence of a target kidney lesion at baseline (post hoc analysis). Post hoc 6-month landmark analyses assessed the association between tumor shrinkage and OS. Pts who were alive at 6 months were grouped based on maximum tumor shrinkage from baseline or confirmed complete response (CR) up to 6 months. Tumor assessments were performed by independent review committee per RECIST v1.1. Odds ratios were calculated using the Cochran-Mantel-Haenszel method; HRs were based on stratified Cox proportional hazards model. **Results:** Among 1069 pts randomized in the CLEAR study, 355 were assigned to LEN + PEMBRO and 357 to SUN. Median follow-up was 27 months for the LEN + PEMBRO group and 26 months for the SUN group. PFS favored LEN + PEMBRO (median 22.1 months, n=243) vs SUN (median 5.9 months, n=229) in the IMDC-intermediate/poor subgroup (HR 0.36 [95% CI 0.28-0.47]); and in the IMDC-favorable subgroup (median 28.1 months, n=110 vs median 12.9 months, n=124; HR 0.41 [95% CI 0.28-0.62]). OS favored LEN + PEMBRO vs SUN in the IMDC-intermediate/poor subgroup (HR 0.58 [95% CI 0.42-0.80]); few events were observed in the IMDC-favorable subgroup thus, it was inadequate to evaluate OS. ORR favored LEN + PEMBRO vs SUN in the IMDC-intermediate/poor subgroup (72.4% vs 28.8%; odds ratio 6.60 [95% CI 4.39-9.90]) and the IMDC-favorable subgroup (68.2% vs 50.8%; odds ratio 2.00 [95% CI 1.17-3.42]). In pts with target kidney lesions, PFS, OS, and ORR were improved with LEN+PEMBRO vs SUN (table). The 6-month landmark analysis in the LEN + PEMBRO group showed that the OS rate at 24 months was 100% (95% CI not estimable [NE]-NE) for pts with confirmed CR per RECIST v1.1 and 91.7% (95% CI 53.9-98.8) both for pts with $>$75% to $<$100% target-lesion reduction and pts with 100% target-lesion reduction. **Conclusions:** In pts with target kidney lesions, LEN + PEMBRO conferred survival benefits vs SUN similar to benefits observed in the overall population. Overall, pts treated with LEN + PEMBRO who had greater than 75% reduction in target lesions had similar OS rates to pts with CR. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	LEN + PEMBRO (n=78)		**SUN (n=74)**
mPFS (mos)	22.1		7.5
HR (95% CI)		0.40(0.25-0.65)	
mOS (mos)	Not reached		30.7
HR (95% CI)		0.44 (0.26-0.77)	
ORR (%)	71.8		27.0
Odds ratio (95% CI)		10.55 (4.54-24.52)	

m, median.

4561 **Poster Session**

Cabozantinib (C) exposure-response (ER) analysis for the phase 3 CheckMate 9ER (CM 9ER) trial of nivolumab plus cabozantinib (N+C) versus sunitinib (S) in first-line advanced renal cell carcinoma (1L aRCC). *First Author: Amishi Yogesh Shah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: In the phase 3 CM 9ER trial (NCT03141177), N+C significantly improved progression-free survival (PFS; HR 0.51, 95% CI 0.41–0.64; p < 0.0001), overall survival (OS; HR 0.60, 98.89% CI 0.40–0.89; p = 0.0010), and objective response rate (p < 0.0001) vs S in 1L aRCC (Choueiri, 2020). N+C was generally well tolerated with low rates of treatment-related discontinuations, indicating successful adverse event (AE) management with dose modification to maintain tolerability. Here the impact of C exposure on efficacy and safety outcomes in CM 9ER was evaluated using ER analysis. **Methods:** Patients (pts, N = 320) with previously untreated aRCC received C 40 mg QD in combination with N 240 mg Q2W; dose reductions of C to 20 mg QD or 20 mg Q2D were allowed to manage AEs. Time-to-event Cox proportional hazard ER models were developed to characterize the relationship between predicted C exposure or apparent clearance (CL/F) and specified endpoints, including PFS, dose modification, and select AEs (palmar-plantar erythrodysesthesia [PPE; Gr ≥1], diarrhea [Gr ≥3], hypertension [Gr ≥3], fatigue/asthenia [Gr ≥3], and ALT/AST elevation [Gr ≥3]). C exposure was defined as the overall average concentration from time zero to the time of event or censoring (CAVG) and estimated by population pharmacokinetic modeling for a typical patient. ER analysis for OS was not done due to the low number of events at the database lock date (March 30, 2020). **Results:** In the ER analysis of PFS, predicted C exposure at 40-mg and 20-mg QD doses was not significantly associated with the rate of progression or death (HR 1.00, 95% CI 0.78–1.27, for 20-mg vs 40-mg dose). In the ER analysis of AEs, lower predicted C exposure was significantly associated with lower rates of PPE (HR 0.63, 95% CI 0.50–0.78, for 20-mg vs 40-mg dose) and diarrhea (HR 0.48, 95% CI 0.29–0.80) but was not significantly associated with the rates of hypertension, fatigue/asthenia, or ALT/AST elevation. Higher predicted C CL/F was associated with a lower rate of C dose modification; however, this association was not statistically significant (HR 0.80, 95% CI 0.57–1.12, for CL/F 3.2 vs 1.2 L/hr). **Conclusions:** In ER models of pts with 1L aRCC treated with the combination of N+C, C exposure was not significantly associated with PFS; however, higher C exposure was associated with higher rates of PPE and diarrhea. ER modeling predicts that a starting dose of 40 mg QD C in combination with N with appropriate dose modifications to manage C AEs will not adversely affect the efficacy of the combination in 1L aRCC. Clinical trial information: NCT03141177. Research Sponsor: BMS/Exelixis.

4562 **Poster Session**

Post hoc analysis of the CLEAR study in advanced renal cell carcinoma (RCC): Effect of subsequent therapy on survival outcomes in the lenvatinib (LEN) + everolimus (EVE) versus sunitinib (SUN) treatment arms. *First Author: Thomas E. Hutson, Texas Oncology, Dallas, TX*

Background: The multicenter, open-label, randomized, phase 3 CLEAR study showed that LEN + EVE had a significant PFS benefit (HR 0.65, 95% CI 0.53-0.80, *P*<0.001) and improved objective response rate (relative risk 1.48, 95% CI 1.26-1.74) vs SUN in the first-line treatment of patients (pts) with advanced RCC. The difference in overall survival (OS) for LEN + EVE vs SUN was not statistically significant (HR 1.15, 95% CI 0.88-1.50) (Motzer R et al. *NEJM*. 2021). Post hoc subgroup analyses were performed to assess the impact of subsequent therapy on OS. **Methods:** Pts in the CLEAR study were randomly assigned (1:1:1) to 1 of 3 treatment arms, including LEN 18 mg + EVE 5 mg once daily (QD) and SUN 50 mg QD (4 weeks on then 2 weeks off). These post hoc analyses examined OS by subsequent systemic anticancer medication in the LEN + EVE and SUN arms. Hazard ratios (HR; LEN + EVE vs SUN) were based on stratified (geographic region and MSKCC prognostic risk groups) Cox proportional hazards model. **Results:** Among 1069 pts with advanced RCC randomized in the CLEAR study, 714 pts were randomly assigned to the LEN + EVE and SUN arms (N=357/each). The median duration of survival follow-up was 27 months in the LEN + EVE arm and 26 months in the SUN arm. Given the shorter median duration of study treatment with SUN (7.8 months) vs LEN + EVE (11.0 months), more pts in the SUN arm received subsequent anticancer therapy during survival follow-up (LEN + EVE, n=167; SUN, n=206). Among pts who received subsequent therapy, pts in the LEN + EVE arm had a longer median time from randomization to initiation of subsequent therapy vs those in the SUN arm (8.0 vs 6.6 months, respectively). OS for the overall population, for pts with no subsequent anticancer therapy, and for pts with no subsequent immunotherapy is shown in the table. In the US population subgroup (LEN + EVE, n=62; SUN, n=61) of the CLEAR study, in which a similar number of pts received subsequent systemic anticancer therapies in the LEN + EVE vs SUN arms (62.9% vs 65.6%, respectively), OS was comparable among the 2 arms (HR 0.95, 95% CI 0.51-1.76). Overall, the safety profile was consistent with the known safety profiles of LEN + EVE and SUN. In both arms, most treatment-emergent deaths were due to progressive disease; there were few treatment-related deaths (<1%, per arm) and no clustering of events. **Conclusions:** In the CLEAR study, LEN + EVE met the primary endpoint of a significant benefit in PFS vs SUN. The results of these exploratory analyses suggest that subsequent systemic anticancer therapy affected the OS outcome results for LEN + EVE vs SUN in the CLEAR study. Clinical trial information: NCT02811861. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	LEN + EVE	SUN
Overall, n	357	357
Median OS	Not reached (NR)	NR
HR (95% CI)	1.15 (0.88-1.50)	
No subsequent anticancer therapy, n	190	151
Median OS	NR	NR
HR (95% CI)	0.91 (0.58-1.44)	
No subsequent immunotherapy, n	231	203
Median OS	NR	NR
HR (95% CI)	1.09 (0.75-1.57)	

4563 **Poster Session**

Association of baseline neutrophil-to-eosinophil ratio (NER) and neutrophil-to-lymphocyte ratio (NLR) with response to combination immunotherapy (IO) with ipilimumab plus nivolumab (ipi/nivo) in patients with metastatic renal cell carcinoma (mRCC). *First Author: Matthew D Tucker, Vanderbilt University Medical Center, Nashville, TN*

Background: Previous reports have shown that the baseline neutrophil-to-lymphocyte ratio (NLR) is associated with prognosis in patients with mRCC. However, NLR has not been shown to reliably predict for response to IO. Retrospective analyses in metastatic melanoma and mRCC have shown an association of eosinophilia with improved outcomes to single agent immunotherapy. We sought to evaluate and compare the baseline NLR and NER with response to ipi/nivo in patients with mRCC. **Methods:** A retrospective review of patients with mRCC treated at the Vanderbilt-Ingram Cancer Center or Duke Cancer Institute with ipi/nivo was performed. Patients with clear cell histology and a baseline complete blood count with differential were included. Patients previously treated with IO were excluded. Patients were separated into groups (above and below the median) based on baseline median NER and baseline median NLR. Analyses of progression free survival (PFS) and overall survival (OS) were conducted using the log rank test. The odds ratio (OR) for objective response rate (ORR) was analyzed using Fisher's exact test. **Results:** 111 patients met inclusion criteria. The median age was 60, 77% of patients were male, 68% had prior nephrectomy, 74% were naïve to systemic therapy, and 84% were IMDC intermediate/poor risk. The median NER was 25.0 and median NLR was 3.4. Patients with < median baseline NER had significant improvement in PFS, OS, and ORR (see table). Patients with < median baseline NLR had significant improvement in OS but not in PFS or ORR. **Conclusions:** Baseline NER was associated with improved outcomes with ipi/nivo. While both NER and NLR were associated with improved OS, only NER was additionally associated with both improved PFS and ORR. With multiple first-line treatment options for mRCC, baseline NER may serve as an early non-invasive predictor for response to ipi/nivo. Research Sponsor: None.

	<median NER (n = 56)	median NER (n = 55)		<median NLR (n = 56)	median NLR (n = 55)	
mPFS (mo)	8.3	2.9	HR 0.49, p < 0.01	5.6	5.1	HR 1.06, p = 0.81
mOS (mo)	NR	27.3	HR 0.32, P < 0.01	NR	27.3	HR 0.31, p < 0.01
ORR (%)	39.3%	20.0%	OR 2.59, p = 0.04	28.6%	30.9%	OR 0.89, p = 0.84

4564 **Poster Session**

Phase II trial of stereotactic ablative radiation (SAbR) for oligoprogressive kidney cancer. *First Author: Raquibul Hannan, University of Texas Southwestern Medical Center, Dallas, TX*

Background: Metastatic renal cell carcinoma (mRCC) patients on systemic therapy may experience oligoprogression. SAbR has been demonstrated to be safe and is associated with high local control rates in mRCC. In this prospective phase II single arm trial, we investigated SAbR to control oligoprogressive mRCC. **Methods:** Patients with mRCC who demonstrated response to systemic therapy with subsequent radiographic evidence of three or fewer sites of progression were treated with SAbR to all progressive sites. Systemic therapy was held during SAbR at the discretion of the treating oncologist. Follow-up included radiographic imaging at three-month intervals. Sequential SAbR for continued oligoprogression was allowed. The primary objective was extension of ongoing systemic therapy by >6 months in 40% of the patients. Progression was defined by any of these 3 criteria: (1) local failure at a radiated site; (2) progression ineligible for additional SAbR (>3 sites) or involving >30% of metastasis; or (3) progression as clinically determined by treating physicians. An exact binomial test was used to test the probability of postponing systemic therapy. Secondary endpoints focused on overall survival (OS), local control (LC) rates, toxicity, and health-related quality of life (QOL). **Results:** The trial completed accrual with enrollment of 20 patients who received SAbR to a total of 36 sites. At enrollment four, twelve, three, and one patients were on first, second, third, and fourth line of systemic therapy, respectively. Eleven were on immunotherapy and nine on a tyrosine-kinase inhibitor. Three patients required repeat SAbR to a new site for sequential disease control. At a median follow-up of 8.3 months (interquartile range 3.9 – 15.1), SAbR extended the duration of the ongoing systemic therapy by >6 months in 12 out of 17 patients (70.6%, 95% CI: 48.9%-92.3%). Thirteen out of 20 patients progressed with a median PFS of 8.7 months (95% CI: 3.2-12.4). Five patients died and the OS did not reach the median. LC was 36/36 (100%). Treatment related grade 1 and grade 2 toxicity was experienced by three and one patient, respectively; no grade 3 toxicities were reported. When compared to baseline, no significant decline in QOL was detected. **Conclusions:** SAbR extended PFS of ongoing systemic by >6 months in oligoprogressive patients with mRCC. SAbR was safe and did not adversely affect QOL. These data support further evaluation of SAbR for oligoproressive mRCC in a prospective randomized setting. Clinical trial information: NCT03696277. Research Sponsor: UT Southwestern Medical Center Department of Radiation Oncology.

4565 **Poster Session**

Ipilimumab + nivolumab in people with rare variant renal cell carcinoma refractory to nivolumab alone: Part 2 of UNISON (ANZUP 1602) nivolumab then ipilimumab + nivolumab in advanced non-clear cell renal cell carcinoma. *First Author: Craig Gedye, Calvary Mater Newcastle, Waratah, NSW, Australia*

Background: Immunotherapy targeting PD1 is active across many cancers, but many people are failed by PD1 inhibition alone. UNISON (ANZUP 1602/ NCT03177239) has previously reported the activity and outcomes of nivolumab monotherapy in people with nccRCC (OTRR 17%, PFS6 45%; part 1), and here we report the outcomes of combining ipilimumab (I) and nivolumab (N), in people whose cancers are refractory to N alone (part 2). **Methods:** Participants (pts) with advanced nccRCC with good performance status (ECOG 0/1), were initially enrolled and took N alone. 41 pts refractory to N were offered the combination I (1mg/kg) + N (3mg/kg) every 3 weeks for up to 4 doses. Pts with disease control after N, or N + I could continue N for up to 1 year. UNISON was powered to distinguish a clinically relevant improvement in objective tumour response rate (OTRR) from 15% to 30% in people taking I+N in part 2. **Results:** 85 pts were enrolled and received N. 41 pts were refractory to N, were well enough to take I+N, and had a representative spectrum of nccRCC histologies (n=41; papillary 44%, chromophobe 20%, Xp11 translocation 12%, RCC unclassified 7%, other 17%). The median time on treatment was 2.1 months, the median number of doses was 3; median follow up at the time of reporting was 20.3 months. The OTRR of I+N in pts refractory to N was 10% with 1 complete and 3 partial responses. Stable disease was experienced by 36% of pts and disease progression by 52%. The disease control rate at 6 months was 45% (95% CI: 34%, 56%). The median PFS was 2.6 months (95% CI: 2.2, 3.8). The 6 month progression-free survival (PFS) was 25% (95% CI: 13-39). Only 14% of patients were free of progression at 12 months. The safety of I+N appeared similar to previous reports. 68% of pts experienced serious adverse events, 34% treatment related SAE. One pt died from refractory pneumonitis. 11 pts (27%) experienced treatment delays or permanent treatment discontinuation. **Conclusions:** The primary endpoint of the study was not met. A minority of pts with nccRCC refractory to nivolumab derive benefit from combination I+N but many pts remain refractory to immunotherapy. No new safety issues were identified. More effective therapeutic options are needed for people with rare variant renal cell carcinoma. Clinical trial information: NCT03177239. Research Sponsor: Bristol Myers Squibb, Other Government Agency, Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP).

4566 **Poster Session**

Survival trends of men and women with metastatic clear cell renal cell carcinoma. *First Author: Claud Grigg, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Clear cell renal cell carcinoma (ccRCC) is nearly twice as common in men as in women, and women with non-metastatic RCC have a better prognosis than men. The etiology for these disparities is not known, though sex-specific differences in risk factor prevalence and tumor biology have been reported. The differential impact of systemic therapies, including tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), on prognosis in women and men with metastatic ccRCC is not defined. **Methods:** Clinicopathologic features and survival of patients with clinical stage IV ccRCC were obtained from the National Cancer Database (NCDB). Patients were grouped by date of metastatic diagnosis into three eras that correspond to major advances in systemic therapy: 2004-2005 (pre-TKI), 2006-2014 (TKI), and 2015-2016 (ICI). Uni- and multi-variable chi-square, logistic regression, and survival analyses were used for comparisons. Survival differences were assessed using Kaplan-Meier curves. **Results:** 15,025 male and 7,100 female patients with metastatic ccRCC were identified. Demographic features were similar between cohorts though females were slightly older (median 64.8 vs 62.7 mo, $p < 0.0001$), more likely to be black (6.5% vs 6.0%, $p = 0.0119$) or receiving Medicare benefits (46.4% vs 39.9%, $p < 0.0001$). In the combined cohort, median overall survival (OS) was higher in patients diagnosed in the ICI vs TKI (23.0 vs 16.5 mo) and pre-TKI eras (14.4 mo, log-rank $p < 0.0001$). Compared with men of the same age groups, OS was inferior for women age 50-64 yr (median 18.4 vs 21.1mo, $p = 0.0084$) and $>$ 64 yr (15.3 vs 12.6mo, $p = 0.0001$), but not $<$ 50 yr (20.3 vs 21.7mo, $p = 0.6290$). In the ICI era, median OS improved by a lesser absolute but similar relative amount for women compared to men (+5.6mo [+39%] and +7.2mo [+41%]), respectively). After controlling for age, race, Charlson-Deyo score, initial treatment modality, and insurance and socioeconomic status, women remained at increased risk of death in both the ICI era (HR 1.12 [95% CI 1.04-1.22], $p = 0.004$) and the TKI era (HR 1.08 [1.04-1.12], $p < 0.001$). **Conclusions:** Women with metastatic ccRCC have a worse prognosis than men which is not explained by demographic differences. This disparity is observed in both the TKI and ICI eras. This finding contrasts with previous studies suggesting women with localized RCC have a favorable prognosis compared with men. Further investigation into the sex-specific biology of metastatic ccRCC is warranted. Research Sponsor: None.

4567 **Poster Session**

Temporal characteristics of treatment-emergent adverse events and dose modifications with tivozanib and sorafenib in the phase 3 TIVO-3 study of relapsed or refractory mRCC. *First Author: Sumanta K. Pal, Department of Medical Oncology & Therapeutics, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: The randomized phase 3 TIVO-3 study met the primary endpoint of improved PFS with tivozanib (TIVO) vs sorafenib (SOR) in patients with relapsed/refractory mRCC with fewer dose reductions, interruptions and discontinuations despite a longer time on therapy. Greater insight into temporal characteristics of treatment-emergent adverse events (TEAEs) may enable proactive supportive care strategies and improve patient experience. **Methods:** Updated safety from the previously reported TIVO-3 study with a data cutoff August 15, 2019, was analyzed by treatment arm for time-to-onset (TTO, days [d]) of the most commonly reported TEAEs, and TTO of first dose reduction, interruption, and discontinuation occurring with TIVO and SOR. Duration of TEAE (median d and IQ range), and rate of dose reduction, interruption, or discontinuation due to the TEAE was calculated for each arm. **Results:** Patients in the safety analysis randomly assigned to TIVO (n = 173) or SOR (n = 170) received 11.9 and 6.7 cycles, or 336 and 192 mean days of treatment exposure, respectively. Incidence of any Gr, Gr >3, and TTO of any Gr TEAE of special interest occurring with >20% frequency in either arm is shown in Table 1. While TIVO was associated with less Gr>3 diarrhea, rash and PPE and more HTN than SOR, there were few differences in the TTO or duration of these TEAEs. Overall, dose reductions, interruptions, and discontinuations due to TEAEs were less frequent with TIVO than SOR, and TTO of first dose reduction (85 vs 45 d), interruption (81 vs 50 d), and discontinuation (114 vs 49 d) was longer for TIVO than SOR. Among those experiencing the same TEAE in either arm, resulting dose modifications were less frequent with TIVO than SOR. **Conclusions:** TIVO-3 demonstrated improved PFS with TIVO compared to SOR in mRCC, with longer duration of TIVO exposure, but fewer all Gr and Gr >3 TEAEs. Temporal characteristics of TEAEs were similar, but time to dose modifications was longer with TIVO than SOR. Among those with the same TEAEs, unmodified treatment was continued more often with TIVO than SOR. Clinical trial information: NCT02627963. Research Sponsor: AVEO Oncology.

	Any grade (%)		Grade 3 (%)		Time to onset Days (IQ range)		TEAE Duration Days (IQ range)		TEAE Dose modification rate (%)*	
TEAE	TIVO (n = 173)	SOR (n = 170)	TIVO (n = 173)	SOR (n = 170)	TIVO	SOR	TIVO	SOR	TIVO	SOR
HTN	43%	29%	24%	15%	17 (11-35)	15 (6-29)	29 (7-66)	50 (10–)	20%	26%
Diarrhea	43%	54%	2%	11%	58 (27-127)	43 (15-85)	15 (3-57)	31 (4-102)	18%	34%
Asthenia/Fatigue	66%	48%	13%	12%	29 (11-74)	17 (7-68)	90 (28–)	84 (28–)	24%	37%
Nausea/ Vomiting	34%	26%	1%	5%	54 (14-107)	38 (6-85)	15 (3-71)	14 (4-42)	25%	58%
Rash	13%	34%	< 1%	15%	110 (39-294)	12 (10-15)	51 (14–)	15 (7-32)	18%	55%
PPE	16%	41%	1%	10%	40 (29-71)	15 (10-22)	62 (26–)	23 (10-94)	14%	46%

*Proportion of patients with TEAE that resulted in study drug dose interruption, reduction, or discontinuation.

4568 **Poster Session**

Immune checkpoint inhibitors (ICI) in advanced sarcomatoid renal cell carcinoma (sRCC): A multicenter study. *First Author: Dharmesh Gopalakrishnan, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Advanced sRCC is an aggressive disease with limited responsiveness to chemotherapy and VEGF-targeted therapies. Subgroup analyses from randomized trials showed improved outcomes with ICI, though sample sizes were relatively small. **Methods:** We conducted a multi-institutional retrospective analysis of consecutive patients (pts) who had RCC with any sarcomatoid component and received systemic therapy for advanced disease. The pts were classified into ICI^+ and ICI^- groups (gp) based on whether they had received ICI in any treatment line. Overall survival (OS) was measured from the initiation of first systemic therapy. Time to ICI failure (TIF) was defined as the interval from initiation of ICI to subsequent therapy or death. Survival distributions were estimated using the Kaplan-Meier method. Association between covariates and survival was analyzed using multivariate Cox regression. Two-tailed $P < 0.05$ was considered statistically significant. **Results:** 203 pts from 6 US academic cancer centers met the inclusion criteria – 155 in ICI^+ gp and 48 in ICI^- gp. Overall, 137 (67%) pts were male and 181 (89%) were white; median age at mRCC diagnosis was 59.7 (IQR 52.4-67.7) years; 129 (63%) pts presented *de novo* with distant metastases, 154 (76%) had clear cell (CC) histology, and 182 (90%) had intermediate/poor risk by IMDC criteria. ICI^+ had a higher proportion of purely CC tumors (81% vs 64%, $P = .02$); other demographic and clinical features were similar between the two gps. After a median follow-up of 48.1 (95% CI 40.7-55.5) months (mos), median OS and response rates were significantly higher in the ICI^+ gp (Table). OS benefit, compared to ICI^-, was maintained in pts who received ICI in ≥ second line (39.6 vs 7.6 mos, HR 0.33, 95% CI 0.22-0.51, log-rank $P < .001$). TIF was comparable between pts treated with ICI upfront vs in ≥ second line (6.0 vs 5.3 mos, HR 1.27, 95% CI 0.87-1.85, $P = .21$). On multivariate analysis, ICI^- (HR 2.50, 95% CI 1.61-3.88, $P < .001$), non-CC histology (HR 3.14, 95% CI 1.98-5.00, $P < .001$) and sarcomatoid component ≥20% (HR 1.92, 95% CI 1.28-2.90, $P = .002$) were predictive of all-cause mortality. Among pts with non-CC or mixed histology (n=45), ICI^+ had higher OS (18.0 vs 5.5 mos, HR 0.20, 95% CI 0.09-0.44, $P < .001$) and ORR (44% vs 12%, $P = .03$), compared to ICI^-. **Conclusions:** Treatment with ICI led to markedly higher survival and response rates in advanced sRCC. OS benefit was maintained with ICI in the second line and beyond. Significant benefit was also noted among pts with non-CC or mixed histology sRCC. Research Sponsor: None.

	ICI^+ (n = 155)	ICI^- (n = 48)	P value/ HR (95% CI)
Median OS, mos (95% CI)	31.0 (21.5-40.5)	7.6 (5.5-9.7)	HR 0.40 (0.27-0.58), P <.001
Median RCC-specific survival, mos (95% CI)	37.8 (25.0-50.6)	7.6 (5.5-9.7)	HR 0.38 (0.25-0.58), P < .001
Complete response, %	12.0*	4.3	.009
Overall response rate (ORR), %	43.0*	19.6	.004
Disease control rate, %	66.2*	39.1	.001

*Best response to ICI, ¶best response to non-ICI in any line.

4569 **Poster Session**

A phase 2 single-arm study of cabozantinib in patients with advanced or unresectable renal cell carcinoma pretreated with one immune checkpoint inhibitor: The BREAKPOINT trial (MeetUro trial 03-NCT03463681). *First Author: Giuseppe Procopio, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: For many years, vascular endothelial growth factor (VEGF)-targeted therapy (tp) has been a milestone for metastatic renal cell carcinoma (mRCC). Recently, first line tp based on anti-PD-1/PD-L1 immune-checkpoint inhibitors (ICIs) plus tyrosine-kinase-inhibitors (IO-TKI) and anti-PD-1 plus anti-CTLA-4 combos (IO-IO) significantly improved survival of mRCC patients (pts). Prospective data are lacking to determine the efficacy of anti-VEGF tp after IO-IO or IO-TKI. Cabozantinib (Cabo) showed to prolong survival in mRCC pts pre-treated with TKIs and to target kinases involved in immune-escape. So, it may represent an ideal agent to be used sequentially after ICIs. **Methods:** This is an open label, single arm, multicenter, phase II study evaluating efficacy and safety of Cabo in mRCC pts who received an anti-PD-1/PD-L1-based adjuvant (adj) or first line tp. Cabo 60 mg/daily was administered until progressive disease (PD) or unacceptable toxicity. Primary endpoint was progression free survival (PFS) by Brookmeyer-Crowley test, secondary endpoints were overall survival (OS), objective response rate (ORR) and safety. Exploratory endopoints were to investigate tissue PD-L1 expression, to assess the modulating activity of Cabo on local and systemic tumor immunity and to explore bone formation and reabsorption markers. **Results:** From July 2018, 49 pts were enrolled and 48 were included in the analysis. Median age was 62.5 years (range: 30-78), 63% of pts were male. At baseline, 26% of pts had a good Heng risk score, 47% intermediate and 28% a poor risk, while in 2% of pts the class of risk was undetermined. 74% of pts received an IO-IO combo as first line tp, 17% IO-TKI, 9% pts an adj IO monotherapy. Pts received a median of 10 cycles of Cabo (range 5-17 cycles). 25 pts (53%) are still on tp, 1 patient discontinued Cabo for AEs, 13 pts for radiological PD, 6 pts discontinued for clinical PD or death, while 2 pts for reasons other than AEs or PD. Among evaluable cases, 17 pts (43%) achieved a partial response and 15 pts (37%) stable disease. Complete responses were not observed. At a median (m) follow-up of 8.0 months (mo) (4.4-13.5 mo), 71% of pts were alive and mPFS was 9.3 mo (95% CI 7.1-29.0 mo). Grade (G) 3-4 adverse events (AEs) occurred in 34% of pts, including more frequently serum bilirubin increase, hypertension, calcium and sodium serum levels alterations and oral mucositis. G1-2 were observed in 61% of pts, including in most of cases diarrhoea, nausea, oral mucositis, disgeusia, hand-foot syndrome, fatigue and hypothyroidism. Due to AEs, transitory withholding of Cabo was observed in 53.5% of pts and for 23 pts (48%) dose reductions were needed. **Conclusions:** So far, Cabo tp after IO-IO or IO-TKI showed promising results and was well tolerated. Longer follow-up is needed for final OS and exploratory endpoints results. Clinical trial information: NCT03463681. Research Sponsor: Ipsen.

4570 **Poster Session**

Plasma exosome microRNA-155 expression in patients with metastatic renal cell carcinoma treated with immune checkpoint inhibitors: A potential biomarker of response to systemic therapy. *First Author: Maryam Soleimani, BC Cancer, Vancouver, BC, Canada*

Background: The search for a reliable predictive biomarker of response to immune checkpoint-based therapy (ICBT) remains a critically unmet need in the management of metastatic renal cell carcinoma (mRCC). We sought to evaluate the biomarker potential of plasma exosome microRNAs (miRNAs) implicated in RCC and in augmentation of the tumour microenvironment (TME) for such a role. **Methods:** Eleven miRNAs that are over-expressed in RCC and/or immune-associated were evaluated in 40 patients with mRCC (prior to initiating ICBT) and in 30 healthy volunteers. Exosomes were extracted from 500 uL of plasma and were used for miRNAs extraction. MiRNAs expression was evaluated by RT-PCR. Cycle threshold values were normalized to miR-30-3b, and the relative quantity of the expression (RQ) was compared to those of healthy volunteers and calculated using the $2^{\Delta\Delta Ct}$ method. Mann-Whitney U test was used to evaluate the expression of miRNAs between mRCC pts and healthy volunteers according to best response to first line ICBT between responders (n = 27) v non-responders (n = 13). The cut-off value of significant expression was established by Youden's index. Responders were defined as those patients experiencing complete response, partial response or stable disease and non-responders were those who experienced progressive disease. **Results:** The most common first line ICBT was nivolumab + ipilimumab (n = 32), followed by pembrolizumab + axitinib (n = 5), and avelumab + axitinib (n = 3). A significantly higher expression of miRNA-1233 (median 1.85 v 0.81 p = 0.008) and miRNA-155 [miR-155] (3.69 v 0.21 p = 0.006) were found in patients compared to healthy volunteers. Higher miR-155 expression was associated with higher Fuhrman grade (p = 0.002). There was no association with other clinical prognostic factors. MiR-155 was expressed at a significantly lower level in responders than in non-responders (median 0.61 v 35.29, p = 0.042). Response rate amongst patients with low and high expression of miR-155 (RQ $\leq$ 2.5) was statistically different (p = 0.042) and 84.2% of the pts with low miR-155 expression responded to the treatment. **Conclusions:** Lower expression of miR-155 was associated with response to ICBT in patients with mRCC. Functionally, miR-155 is involved in regulation and modulation of the TME. These results underscore the need for further work in this area to elucidate the role of this and other miRNAs as biomarkers of response in mRCC. Research Sponsor: GUMOC Bayer Research Grant Program jointly established by the Genitourinary Medical Oncologists of Canada (GUMOC) and Bayer Canada.

4571 **Poster Session**

A phase 2 prospective trial of cabozantinib as first-line treatment for metastatic collecting ducts renal cell carcinoma: The BONSAI trial (Meeturo 2) clinical trial information—NCT03354884. *First Author: Giuseppe Procopio, Fondazione Istituto Nazionale Tumori Oncologia Medica Genitourinaria, Milan, Italy*

Background: Metastatic collecting ducts carcinoma (mCDC) is a rare disease with bad prognosis and no standard treatments. Due to its rarity, mCDC is biologically poorly characterized and under-represented in prospective randomized trials. We recently identified two different molecular subtypes of mCDC based on relative expression levels of angiogenesis, metabolic and immune-related genes. **Methods: :** This prospective, monocentric, phase II trial evaluated cabozantinib (cabo) 60 mg orally once daily until progression or unacceptable toxicity in untreated mCDC patients (pts). Primary endpoint was objective response rate (ORR) as the proportion of pts with best overall response of confirmed complete (CR) or partial responses (PR) per RECIST 1.1. Secondary endpoints were progression-free survival (PFS), overall survival and safety profile. Exploratory objectives were: to identify somatic mutations by targeted NGS-based sequencing; to define molecular subtypes, signatures and transcript fusions genes by RNA sequencing; to monitor circulating immune cells and study the immunological context of tumor cells. A central pathological review was mandatory. The study was based on a Simon's two stage optimal design: at least 2 responses in 9 pts in the first stage were needed to proceed to the second stage where at least 6 responses in 14 additional pts were needed to prove activity of cabo. **Results:** From January 2018 to November 2020, 25 pts were enrolled, of whom 23 started treatment. Median age was 66 years, 19 pts were male. 19 (83%) pts received a previous nephrectomy. 9 pts presented with only one metastatic site, 8 pts with two, while the remaining part with multiple sites. The most common metastatic sites were lymphnodes and bone (15 and 13 pts respectively), followed by lung and liver (10 and 4 pts respectively). Median follow up was 8 months. As best overall response, 6 pts presented a stable disease (26%),1 pt achieved a confimed CR and 7 a PR for an ORR of 35%. Median PFS was 6 months. Treatment was feasible and well tolerated. All pts reported at least one grade (G) 1-2 adverse event (AE): the most common were fatigue (43%), hypotiroidism (28%), stomatitis (28%), anorexia (26%), Hand-Foot Syndrome (13%), hypertension (17%), and diarrhea (13%). 5 pts reported G3 AEs (2 thromboembolic events, 2 arterial hypertension, 1 fatigue), while no G4-5 AEs were reported. 17% of pts required dose reduction. DNA sequencing on CDC showed to be feasible, finding 256 mutations in 119 genes (missens mutations the majority). Altered genes, molecular subtypes and signatures will be associated to different outcomes and responses to cabo. **Conclusions:** The study met its primary endpoint showing promising efficacy and acceptable tolerability of cabo in mCDC pts. Mature results according to mutational profiles and gene signatures will be presented. Clinical trial information: NCT03354884. Research Sponsor: IPSEN PHARMA.

4572 **Poster Session**

Characterization of the tumor immune microenvironment in clear cell renal cell carcinoma (ccRCC): Prognostic value and therapeutic implications of an M0-macrophage enriched subtype. *First Author: Mark Farha, University of Michigan Medical School, Ann Arbor, MI*

Background: Metastatic clear cell renal cell carcinoma (ccRCC) has a 5-year survival of 12%, but the number of approved immune checkpoint blockade (ICB) agents is growing, necessitating the need to better identify responders. The composition and role of the tumor immune microenvironment (TIME) has yet to be comprehensively characterized in ccRCC. Here, we leveraged a genomic data driven approach to characterize TIME subtypes in ccRCC. **Methods:** Whole transcriptome data from patients with local and metastatic disease in the Cancer Genome Atlas KIRC (TCGA-KIRC) project was utilized (n = 537). CIBERSORT was used for immune cell deconvolution, and unsupervised hierarchical clustering divided the cohort based on similar immune profiles. Progression free (PFS) and overall (OS) survival of each cluster was analyzed, and Gene Set Enrichment analysis was performed among clusters. The tumor immune dysfunction and exclusion (TIDE) tool, which uses a genomic signature validated on immunotherapy treated melanoma patients to model tumor immune evasion, was then used to predict response to ICB in the TCGA-KIRC clusters. **Results:** There was a distinct $M0^{hi}$ cluster identified which demonstrated a higher proportion of patients with stage III/IV disease, decreased PFS and OS (Table). Additionally, the $M0^{hi}$ cluster was characterized by lower PD-L1 expression (ANOVA, p = 0.0045) and an enrichment of epithelial to mesenchymal transition (EMT) hallmark genes [Enrichment Score = 0.64, p = 0.001]. The $M0^{hi}$ cluster also showed a higher degree of T-Cell Exclusion (ANOVA, $p = 2.2x10^{-16}$), predominance of Cancer Associated Fibroblasts (CAFs; ANOVA, $p = 2.2x10^{-16}$) and Myeloid Derived Suppressor Cells (MDSCs; ANOVA, $p = 4.1x10^{-10}$). The $M0^{hi}$ cluster had the lowest predicted response to immunotherapy using the TIDE tool (Table). **Conclusions:** Comprehensive characterization of the TCGA-KIRC cohort led to identification of a distinct cluster of ccRCC defined molecularly by decreased PD-L1 and increased EMT gene expression and cellularly by enrichment of M0 macrophages, CAFs, MDSCs, and an exclusion of T Cells. Patients within this cluster exhibited aggressive disease and poor predicted response to ICB. These findings warrant further validation to identify appropriate therapeutic approaches for this ccRCC subgroup. Research Sponsor: None.

	CL1 ($M2^{hi}$) N = 132	CL2 N = 130	CL3 N = 124	CL4 ($M0^{hi}$) N = 28	CL5 ($CD8^{hi}$) N = 86
Median OS (mo., 95% CI, one-sided)	NR (91.4 –)	123.8 (73 –)	NR (89.9 –)	45.9 (22.6 –)	78.4 (57.7 –)
Median PFS (mo., 95% CI, one-sided)	86.7 (65.5 –)	71.5 (57.1 –)	92.1 (91.7 –)	26.1 (13.0 –)	74.2 (52.2 –)
Stage III/IV (%)	27.3	45.0	33.9	71.4	52.9
PD-L1**	-0.04	-0.04	-0.06	-0.60	0.23
T-Cell Exclusion**	0.28	0.20	0.32	0.79	-0.19
Predicted ICB Response (%)	32	31	19	4	32
CAF**	0.05	0.03	0.04	0.09	-0.04
MDSC**	0.02	0.02	0.03	0.06	0.01

NR: not reached.
**Signatures from TIDE tool, Z scores.

4573 **Poster Session**

Dynamic changes of the immune infiltrate after neoadjuvant avelumab/axitinib in patients (pts) with localized renal cell carcinoma (RCC) who are at high risk of relapse after nephrectomy (NeoAvAx). *First Author: Axel Bex, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Antibodies targeting PD-1/PD-L1 combined with vascular endothelial growth factor (VEGF) inhibitors are a front-line standard of care for metastatic RCC. Neoadjuvant use of these combinations is associated with tumor downsizing, but dynamic effects on key immune biomarkers are uncertain. We report early dynamic changes in the tumour immune environment after neoadjuvant treatment with avelumab/axitinib. **Methods:** Neoavax is an open label, single arm, phase II trial, investigating 12 weeks of neoadjuvant avelumab/axitinib prior to nephrectomy in patients with high-risk non-metastatic clear-cell (cc) RCC (cT1b-4N0-1M0). Partial primary tumour response (RECIST 1.1) occurring in ≥25% is the primary endpoint. Biomarker analysis on sequential tissue is an exploratory endpoint. Expression of PD-L1 (SP263), CD8+, CD8-granzyme-B (CD8/GZMB)+, Foxp3+ cells, CD8/CD39+ and major histocompatibility complex class I (MHC-I) were compared on paired samples (pre-treatment biopsy and nephrectomy) (NCT03341845). **Results:** Paired, sequential tissue from the first 24 patients was analysed for immune biomarker expression. Of these patients, 70% were ≥pT3a, 30% pN1, 58% had ISUP/WHO grade ≥3 with 8% sarcomatoid features. Compared to pre-treatment biopsy there was a significant increase in PD-L1 ($p = 0.0002$) and CD8+ expression ($p = 0.0003$) after therapy, whereas changes in CD8/GZMB+, MHC-I and CD8/CD39+ were not significant. Furthermore, neoadjuvant avelumab/axitinib therapy was associated with a significant decrease in Foxp3+ cells ($p = 0.009$). **Conclusions:** 12 weeks of neoadjuvant axitinib/avelumab treatment in ccRCC leads to significant dynamic changes in the tumour microenvironment for CD8+, PD-L1 and Foxp3+ expression. High baseline Foxp3+ infiltration is associated with an unfavorable outcome in the majority of solid tumours. The significant on-treatment decrease in Foxp3+ may account for the positive interaction seen between VEGF targeted therapy and immune checkpoint inhibitors in mRCC. If these cells represent regulatory T cells (Tregs), activated CD4 T cells or fragile Tregs remains to be determined. Clinical trial information: NCT03341845. Research Sponsor: Pfizer.

4574 **Poster Session**

Efficacy of avelumab + axitinib (A + Ax) versus sunitinib (S) by IMDC risk group in advanced renal cell carcinoma (aRCC): Extended follow-up results from JAVELIN Renal 101. *First Author: John B. A. G. Haanen, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: In the phase 3 JAVELIN Renal 101 trial (NCT02684006), treatment-naive patients with aRCC receiving A + Ax showed improved progression-free survival (PFS) and objective response rate (ORR) across International Metastatic RCC Database Consortium (IMDC) risk groups (favorable [F], intermediate [I], and poor [P]) compared with patients receiving S. Here we report updated efficacy results for A + Ax vs S by IMDC risk groups from the third interim analysis. **Methods:** Patients were randomized 1:1 to receive either A (10 mg/kg intravenously every 2 weeks) plus Ax (5 mg orally twice daily) or S (50 mg orally once daily) for 4 weeks (6-week cycle). Patients were categorized per IMDC risk group into F, I, and P subgroups, and outcomes were assessed for F, I, P, and I + P. Overall survival (OS) and PFS, ORR, complete response (CR), and duration of response (DoR) per investigator assessment (RECIST v1.1) were assessed. **Results:** The study enrolled 886 patients with aRCC. At data cutoff (Apr 2020), median (95% CI) follow-up for OS in the A + Ax was NR (42.2-NE) vs 37.8 (31.4-NE) months with S. The Table shows OS, PFS, ORR, CR, and DOR by IMDC risk group. A + Ax generally showed improved efficacy compared with S across IMDC groups. **Conclusions:** Consistent with previously reported results from prior interim analyses, extended follow-up confirms the efficacy benefits of A + Ax vs S across IMDC risk groups in patients with aRCC. Patients continue to be followed up for the final OS analysis. Clinical trial information: NCT02684006. Research Sponsor: Funded by Pfizer as part of an alliance between Merck KGaA, Darmstadt, Germany and Pfizer.

IMDC risk group	Favorable A + Ax (N = 442)	Favorable S (N = 444)	Intermediate A + Ax (N = 442)	Intermediate S (N = 444)	Poor A + Ax (N = 442)	Poor S (N = 444)	Intermediate + Poor A + Ax (N = 442)	Intermediate + Poor S (N = 444)
n	94	96	270	276	73	71	343	347
mOS	NE	NE	42.2	37.8	21.3	11.0	40.0	29.5
(95% CI), mo	(NE-NE)	(39.8-NE)	(33.1-NE)	(29.6-NE)	(14.7-33.1)	(7.8-16.5)	(30.5-NE)	(24.8-38.0)
HR*	0.66	Ref	0.84	Ref	0.60	Ref	0.79	Ref
(95% CI)	(0.356-1.22)		(0.649-1.08)		(0.399-0.912)		(0.636-0.98)	
mPFS	20.7	13.8	12.9	8.4	8.7	4.2	11.1	8.2
(95% CI), mo	(16.6-26.3)	(11.1-23.5)	(11.1-16.6)	(7.9-10.1)	(5.6-11.1)	(2.8-5.5)	(9.8-14.6)	(6.9-8.4)
HR*	0.71	Ref	0.71	Ref	0.45	Ref	0.66	Ref
(95% CI)	(0.490-1.02)		(0.578-0.866)		(0.304-0.678)		(0.550-0.787)	
ORR	75.5	45.8	59.6	31.2	38.4	15.5	55.1	28
(95% CI), %	(65.6-83.8)	(35.6-56.3)	(53.5-65.5)	(25.7-37.0)	(27.2-50.5)	(8.0-26.0)	(49.7-60.4)	(23.3-33.0)
CR, n (%)	9 (9.6)	5 (5.2)	11 (4.1)	8 (2.9)	1 (1.4)	1(1.4)	12 (3.5)	9 (2.6)
DoR	22.6	20.8	19.3	12.5	18.2	5.6	19.3	9.8
(95% CI), mo	(15.2-31.7) (n = 71)	(14.5-24.9) (n = 44)	(13.9-22.1) (n = 161)	(7.1-16.6) (n = 86)	(6.8-NE) (n = 28)	(2.5-8.3) (n = 11)	(13.9-22.1) (n = 189)	(7.0-15.3) (n = 97)

m, median; mo, months; NE, not estimable; HR, hazard ratio; Ref, reference. * Unstratified.

4575 **Poster Session**

Association with immune checkpoint inhibitor efficacy of a 27-gene classifier in renal cell cancer. *First Author: Robert Seitz, Oncocyte Inc, Nashville, TN*

Background: The 27-gene immuno-oncology (IO) signature that incorporates expression from activated inflammatory cells, cancer associated fibroblasts, and tumor cells to produce a binary classifier has been shown to be associated with efficacy to immune checkpoint inhibitors (ICIs) in breast, lung, and bladder cancers. Here we created clustered heat maps using data from The Cancer Genome Atlas (TCGA) to confirm the classifier function and diagnostic threshold in renal cell carcinoma (RCC), then applied the predefined algorithm to RNAseq data from a community RCC cohort treated with ICI therapy. **Methods:** Previously, we described the selection of 939 genes from the TCGA breast and lung datasets that comprise mesenchymal (M), mesenchymal stem-like (MSL), and immunodulatory (IM) gene expression patterns centered upon the twenty-seven genes selected for the IO score (AACR, 2021). We created an expression dataset using these genes in clear cell (n = 403) and papillary (n = 203) RCC and used k-means clustering to organize the genes and cases (k=3). We assessed the 27-gene classification of cases by utilizing area under the curve for phenotypic classification and determining the sensitivity and specificity of the previously established threshold compared to optimal accuracy for quantitating the fraction of cases enriched into the IM+ cluster (likely sensitive to ICIs) as opposed to the M or MSL clusters (likely insensitive). Finally, the IO score was evaluated in a small multi-institutional RNAseq dataset of forty-three RCC patients treated with an ICI for which there was definitive one-year progression free survival (PFS) data. **Results:** The 27-gene IO signature applied to the TCGA sample data had an AUC of 90.3 for stratification of cases into IM+ as opposed to M and MSL clusters while the established threshold for likely sensitive enriched 90% of cases into the appropriate IM cluster as opposed 28% into the M and MSL. Efficacy was defined by PFS. Given this result, the 27-gene IO signature was applied with the predefined threshold to the forty-three ICI treated patients. Patients who had a IO+ score by the 27-gene signature had significantly better one-year PFS compared to patients with a negative IO score (hazard ratio = 0.235, 95% CI = 0.069 - 0.803, $p < 0.01$). Median PFS was 5.2 months for patients classified as IO score negative versus 8.6 months for those classified as IO score+. **Conclusions:** The 27-gene IO signature has been validated across multiple tumor types and here in RCC to classify the tumor immune microenvironment without changing the algorithm or threshold. Results demonstrate that the 27-gene classifier has a strong correlation with efficacy of ICI therapy in RCC. This is the fourth tumor type in which the same algorithm has been validated as a predictor of ICI efficacy. These data support this assay as a strong pan-cancer immune system classifier worthy of further prospective study for ICI therapy. Research Sponsor: Oncocyte Inc.

4576 **Poster Session**

Efficacy of nivolumab/ipilimumab in patients with initial or late progression with nivolumab: Updated analysis of a tailored approach in advanced renal cell carcinoma (TITAN-RCC). *First Author: Marc-Oliver Grimm, Department of Urology, Universitaetsklinikum Jena, Jena, Germany*

Background: TITAN-RCC uses a tailored immunotherapy approach in renal cell carcinoma (RCC), starting with nivolumab (nivo) induction followed by nivo + ipilimumab (ipi) as immunotherapeutic "boost" in non-responders. Patients with initial partial or complete response (PR/CR) continued with nivo maintenance but received later "boosts" for progressive disease (PD). Here we report updated results focusing on the efficacy of nivo+ipi in patients with initial PD vs. initial responders with later PD. **Methods:** Patients with IMDC intermediate and poor risk advanced clear cell RCC were recruited between OCT 2016 and DEC 2018. Patients started with nivo 240 mg Q2W induction. Patients with early significant PD (week 8) or non-responders at week 16 received 2-4 nivo+ipi "boost" cycles. Responders (PR/CR) to nivo monotherapy continued with maintenance but could receive nivo+ipi for later PD. The primary endpoint is confirmed investigator assessed objective response rate (ORR) per RECIST in first line (1L) and second line (2L). Secondary endpoints included activity of nivo monotherapy, remission rate with nivo+ipi "boost", safety and overall survival (OS). **Results:** 109 1L and 98 2L (after TKI) patients were analyzed for efficacy. Median age was 65 years (range 20-87). 71 % were intermediate and 25 % poor risk. Confirmed ORR with nivo monotherapy was 28 % for 1L and 17 % for 2L. After a median follow-up of 12.8 months best overall response after nivo induction ± nivo+ipi was 36 % in 1L and 30 % in 2L. Of all patients, 38 received nivo+ipi for stable disease (SD) up to week 16, with 1 (3 %), 4 (11 %) and 26 (68 %) achieving CR, PR and SD, respectively. 28 patients in 1L and 43 in 2L were boosted with nivo+ipi for initial PD. Of these, 3 (11 %) and 8 (29 %) achieved PR and SD, respectively, in 1L, whereas 3 (7.0 %) achieved CR, 6 (14 %) PR and 13 (30 %) SD in 2L. 16 and 10 patients received "boosts" later than week 16 for PD during nivo maintenance in 1L and 2L, respectively. Thereof, 3 (19 %) achieved PR and 5 (31 %) SD in 1L, whereas 2 (20 %) achieved PR and 3 (30 %) SD in 2L. Progression-free survival was 6.3 months (95 % CI 3.7 – 10.1) and 3.7 months (95 % CI 2.0 - 4.5) in 1L and 2L, respectively. OS was 27.2 months (95 % CI 19.9 – not estimable (NE)) in 1L and 20.2 months (95 % CI 15.6 – NE) in 2L. Treatment-related adverse events will be presented. **Conclusions:** Our tailored approach with nivo+ipi "boosts" results in improved response rates compared to nivo monotherapy. Our updated analysis suggests that almost half of the patients receiving "boosts" for PD improve to either PR/CR (18 %) or SD (30 %), irrespective of initial or later progression with nivo. Clinical trial information: NCT02917772. Research Sponsor: Bristol-Myers Squibb.

Response to "boost" upon initial or late PD. n (%).

	1L		2L	
	Initial PD n=28	Late PDn=16	Initial PD n=43	Late PDn=10
CR	-	-	3 (7.0)	-
PR	3 (11)	3 (19)	6 (14)	2 (20)
SD	8 (29)	5 (31)	13 (30)	3 (30)
PD	17 (61)	7 (44)	18 (42)	4 (40)
Not evaluable	-	1 (6.3)	3 (7.0)	1 (10)

4577 **Poster Session**

Retrospective study for the characterization of COVID-19 in renal cancer (COVID-REN) patients treated with antiangiogenics or immunotherapy and outcome comparison with non-infected cases. *First Author: Jesus Garcia Donas, Hospital Universitario Madrid Sanchinarro, Madrid, Spain*

Background: Cancer is recognized as a major risk factor for severe COVID19. However little is known about the impact of oncologic treatments in the evolution of the disease. On the other hand, the influence of SARS-CoV2 in cancer response remains to be established. We aim to determine both aspects in renal cancer patients receiving different therapeutic options. **Methods:** We designed a retrospective case-control study to compare the outcome of patients with advanced renal cancer who developed COVID19 under antiangiogenic treatment (cohort A [ChA]) vs immunotherapy (alone or in combination: cohort B [ChB]) vs matched controls (cohort C [ChC]). Controls were renal cancer patients who were not infected during the period of study. One control per case was selected regarding age, gender, kidney cancer histology and type of treatment. **Results:** From May 20 to Feb 21, 80 patients were recruited. We present the first 55 patients included (15 ChA, 16 ChB and 20 ChC, 4 patients were screening failure) from 13 centers in Spain. Median age was 62 (range 25 to 88) overall and 62 (range 44 to 88) in Ch A, 64,5 (range 42 to 83) in ChB and 61 (range 41 to 77) in ChC. 38 patients were male and 13 were female. Overall 45 cases were clear cell carcinoma (13 ChA, 14 ChB and 18 ChC), 4 papillary (1 ChA, 2 ChB and 1 ChC), 1 chromophobe (ChA) and 1 unclassified (ChC). Median number of prior lines of treatment was 2 (range 1 to 6) overall, (1 [range 1 to 4] in ChA, 2 [range 1 to 4] in ChB and 2 [range 1 to 6] in ChC). 25 patients required treatment interruptions (8 in ChA [32%], 14 in ChB [56%] and 3 [12%] in ChC). 9 patients were hospitalized (4 in Ch A, 5 in ChB and none in ChC) for a median of 10 days (range 4 to 16) overall (7 [range 4 to 14] in ChA and 12 [range 5 to 16] in ChB). No patient required ICU admission. Best tumor response was complete or partial (CR+PR) in 25 patients (5 [20%] in ChA, 9 [36%] in ChB and 11 [44%] in ChC). Clinical benefit (CR+PR+stable disease) was observed in 38 patients (11 [28,9%] in ChA, 10 [26,3%] in ChB and 17 [44,7%] in ChC). One patient in ChB died (due to COVID19). Updated results will be presented. **Conclusions:** Patients with renal cancer who developed COVID19 held treatment more frequently and presented lower clinical benefit rates than non infected cases. Patients receiving immunotherapy required more frequent dose interruptions and longer hospitalizations than cases on antiangiogenics. These results point to an impact of SARS-CoV2 in renal cancer outcome. Therapies administered to treat renal cancer, could play a role in the evolution of COVID19. Research Sponsor: unrestricted grant from Pfizer.

4578 **Poster Session**

Efficacy outcomes of nivolumab + cabozantinib versus pembrolizumab + axitinib in patients with advanced renal cell carcinoma (aRCC): Matching-adjusted indirect comparison (MAIC). *First Author: Bradley Alexander McGregor, Dana-Farber Cancer Institute, Boston, MA*

Background: Nivolumab in combination with cabozantinib (N+C) has demonstrated significantly improved progression-free survival (PFS), objective response rate (ORR), and overall survival (OS), compared with sunitinib as a first-line (1L) treatment for aRCC in the phase 3 CheckMate (CM) 9ER trial. As there are no head-to-head trials comparing N+C with pembrolizumab in combination with axitinib (P+A), this study compared the efficacy of N+C with P+A as 1L treatment in aRCC. **Methods:** An MAIC was conducted using individual patient data on N+C (N = 323) from the CM 9ER trial (median follow-up: 23.5 months) and published data on P+A (N = 432) from the KEYNOTE (KN)-426 trialof P+A (median follow-up: 30.6 months). Individual patients within the CM 9ER trial population were reweighted to match the key patient characteristics published in KN-426 trial, including age, gender, previous nephrectomy, International Metastatic RCC Database Consortium risk score, and sites of metastasis. After weighting, hazards ratios (HR) of PFS, duration of response (DoR), and OS comparing N+C vs. P+A were estimated using weighted Cox proportional hazards models, and ORR was compared using a weighted Wald test. All comparisons were conducted using the corresponding sunitinib arms as an anchor. **Results:** After weighting, patient characteristics in the CM 9ER trial were comparable to those in the KN-426 trial. In the weighted population, N+C had a median PFS of 19.3 months (95% CI: 15.2, 22.4) compared to a median PFS of 15.7 months (95% CI: 13.7, 20.6) for P+A. Using sunitinib as an anchor arm, N+C was associated with a 30% reduction in risk of progression or death compared to P+A, (HR: 0.70, 95% CI: 0.53, 0.93; $P = 0.015$; table). In addition, N+C was associated with numerically, although not statistically, higher improvement in ORR vs sunitinib (difference: 8.4%, 95% CI: -1.7%, 18.4%; $P = 0.105$) and improved DoR (HR: 0.79; 95% CI: 0.47, 1.31; $P = 0.359$). Similar OS outcomes were observed for N+C and P+A (HR: 0.99; 95% CI: 0.67, 1.44; $P = 0.940$). **Conclusions:** After adjusting for cross-trial differences, N+C had a more favorable efficacy profile compared to P+A, including statistically significant PFS benefits, numerically improved ORR and DoR, and similar OS. Research Sponsor: BMS.

Post-weighting efficacy comparison for N+C vs. P+A using anchor-based MAIC.

	N+C vs. sunitinib (CheckMate 9ER)	P+A vs. sunitinib (KEYNOTE-426)	N+C vs. P+A (anchor-based comparison)
PFS, HR (95% CI)	0.50 (0.40, 0.63)*	0.71 (0.60, 0.84)*	0.70 (0.53, 0.93)*
ORR, Difference (95% CI)	28.7% (21.0%, 36.4%)*	20.3% (13.8%, 26.9%)*	8.4% (-1.7%, 18.4%)
DOR, HR (95% CI)	0.55 (0.35, 0.85)*	0.70 (0.53, 0.92)*	0.79 (0.47, 1.31)
OS, HR (95% CI)	0.67 (0.49, 0.92)*	0.68 (0.55, 0.85)*	0.99 (0.67, 1.44)

* indicates a $P < 0.05$.

4579 **Poster Session**

Patient-reported experience of diagnosis, management, and burden of renal cell carcinomas: Results from the 2020 Global Patient Survey from 41 countries. *First Author: Rachel H. Giles, International Kidney Cancer Coalition, Duivendrecht, Netherlands*

Background: The sustained increased global prevalence of kidney cancer (renal cell carcinoma, RCC) has increased the burden to health systems, and most of all, to individual patients and their families. Although individual national surveys have been held, no conclusions could be drawn about country-level variation in patient experience or best practice. Here, we report on the second biennial Global Patient Survey on the diagnosis, management, and burden of RCC. Conducted by the International Kidney Cancer Coalition (IKCC) and involving its Affiliate Organizations worldwide, the survey aims to improve collective understanding and to contribute toward the reduction of the burden of kidney cancer around the world. **Methods:** A 35-question survey on the diagnosis, management, and burden of RCC was designed by a multi-country steering committee of patient leaders to identify geographic variations in 6 key dimensions: patient education, experience and awareness, access to care and clinical trials, best practices, quality of life, and unmet psychosocial needs. The survey was distributed in 13 languages to patients with kidney cancer and their caregivers, through IKCC's 46 Affiliate Organisations and social media. It was completed online or in paper form between 29 Oct 2020 and 5 Jan 2021. **Results:** 2,012 (1,586 patients, 417 carers, 9 undisclosed) responses were recorded from 41 countries in 13 languages. Survey results were analyzed using cross-tabulations by an independent third-party organization. The full global report will be publicly available, as well as 7 individual country reports where at least 100 responses were received. 52% lacked understanding of subtype at diagnosis. 42% reported that the likelihood of surviving their cancer beyond 5 years was not explained. 51% reported that they were involved as much as they wanted to be in developing their treatment plan. 41% indicated that "No one" discussed cancer clinical trials with them. 31% were invited to take part in a clinical trial. 56% experienced barriers to their treatment. 45% self-reported that they were insufficiently physically active; 15% were completely sedentary. 50% indicated that they 'very often' or 'always' experienced disease-related anxiety. 55% indicated that they 'very often' or 'always' experienced a fear of recurrence. 52% reported having talked to their doctor/healthcare professional about their concerns. **Conclusions:** The IKCC and its global affiliates will use these results to ensure that patient and caregiver voices are heard and acted upon, with ultimate incorporation of these findings by much broader communities into care pathways, clinical practice, or health technology assessments. Furthermore, individual countries can use their reports to advance understanding of patient experiences and to drive improvements in providing care locally. Research Sponsor: International Kidney Cancer Coalition.

4580 **Poster Session**

Outcomes with novel combinations in non-clear cell renal cell carcinoma(nccRCC): ORACLE study. *First Author: Deepak Kilari, Medical College of Wisconsin, Milwaukee, WI*

Background: Despite advances in the treatment of clear cell RCC, there is a paucity of data to guide management of nccRCC due to the heterogeneity and rarity of these tumors. The clinical activity of new combination therapies (including immunotherapy (IO), anti-vascular endothelial growth factor inhibitors (VEGF), and mammalian target of rapamycin (mTOR) inhibitors) in metastatic nccRCC is not known. **Methods:** In this multicenter retrospective analysis, we explored the efficacy of combination systemic therapies in patients with nccRCC. Baseline and follow-up demographic, clinical, treatment, and radiographic data were collected. The primary endpoint was objective response rate (ORR) assessed by investigator review. Secondary endpoints include progression- free survival (PFS), disease control rate (DCR), median duration of response (DOR), overall survival (OS), and biomarker correlates. **Results:** Among 66 included patients, median age was 59 yr; 60% were male and 62% white. Histologies included papillary (38%), chromophobe (17%), unclassified (24%), translocation (12%), and other (9 %). Sarcomatoid and/or rhabdoid differentiation was present in 18%, 70% had prior nephrectomy, 86% were IMDC intermediate/poor risk, 29% and 32% had liver and bone metastasis respectively. 67% received combination treatment in the first line. Comparison of outcomes based on treatment regimen is shown in the table. **Conclusions:** Antitumor activity was observed with novel combinations in nccRCC which warrants further prospective studies. Response rates and survival with combination therapy in this dataset remain inferior to rates seen in clear cell RCC. Research Sponsor: None.

	IO/VEGF	IO/IO	VEGF/mTOR
n	19	40	7
ORR(%)	21	19	0
DCR(%)	69	46	72
Median PFS (mo.) 1st line	16.8	13.6	2.1
Median DOR (mo.)	23.6	13.6	NR
Median OS (mo.)	24.7	19.2	23.1

n- number of patients; mo.-months; NR – not reached. IO/VEGF (pembrolizumab + axitinib/ atezolizumab + bevacizumab /avelumab + axitinib); IO/IO (Ipilimumab and nivolumab); VEGF/mTOR (lenvatinib plus everolimus).

4581 **Poster Session**

Disease-free survival as a predictor of overall survival in localized renal cell carcinoma (RCC) following first nephrectomy. *First Author: Naomi B. Haas, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: Intermediate endpoints (e.g., disease free survival [DFS]) have gained traction lately as potential surrogates for OS in oncology as they require shorter follow up to show clinical benefit. Given the high post-nephrectomy survival in patients (pts) with localized RCC, evidence on if DFS can be used as a predictor of OS in the disease is warranted. We assessed the association between DFS and OS in pts with newly diagnosed, completely resected, intermediate-high (pT2N0 high grade, pT3N0) or high-risk (pT4N0, pTanyN1) RCC post-nephrectomy. **Methods:** This retrospective observational study used the SEER-Medicare database (2007–2016). DFS was defined as time from initial nephrectomy date to first recurrence (diagnosis of metastatic disease, additional surgery, starting systemic treatment for advanced RCC) or death, whichever occurred first. OS from time of recurrence in pts with recurrence were compared with OS from comparable time point in pts without, using Kaplan-Meier analyses and adjusted Cox models. OS was also compared between pts with and without recurrence by landmark time points at 1, 2, 3, 4 and 5 years (yrs) post-nephrectomy; hazard ratios (HRs) between the two cohorts were estimated using adjusted Cox models. Correlation between DFS and OS was assessed using the Kendall's τ rank correlation. Monthly healthcare costs were compared between the two cohorts using generalized linear model. **Results:** 643 post-nephrectomy RCC pts (269 with recurrence vs 374 without) met the inclusion criteria (Median follow-up: 23 months). The mean age was 75.5 yrs, 61% male, and 86% white. The median post-nephrectomy OS and DFS was 8.61 and 4.44 yrs, respectively. Pts with and without recurrence had comparable baseline characteristics. Pts with recurrence had significantly shorter OS than those without [median: 2.53 yrs vs not reached; adjusted HR (95% confidence interval [CI]): 6.00 (4.24–8.48)]. Pts with recurrence by each landmark time point had significantly shorter OS than those without [1 yr post-nephrectomy median OS: 2.35 vs 9.66 yrs, and the OS 1, 3, and 5 after the 1 yr landmark was 69.9 vs 96.5%, 41.8 vs 83.8%, and 37.0 vs 70.1%, respectively; all Ps (log-rank test) < 0.001]. Cox models indicated that pts with recurrence by each landmark time point had 2.6–3.5 times increased risk of death compared with those without. Kendall's τ rank correlation model demonstrated a statistically significant correlation between DFS and OS (Kendall's $\tau = 0.70$; 95% CI: 0.65–0.74; $P < 0.001$). Pts with recurrence had $4,924 and $1,387 higher adjusted all-cause medical costs and pharmacy costs per month ($P < 0.001$). **Conclusions:** Post-nephrectomy recurrence is associated with significantly shorter OS among pts with intermediate-high or high-risk RCC, resulting in a strong positive association between DFS and OS in the population. Higher healthcare cost was also seen among pts with recurrence. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

4582 **Poster Session**

Role of cytoreductive nephrectomy (CN) in metastatic renal cell carcinoma (mRCC). *First Author: Pooja Ghatalia, Fox Chase Cancer Center, Philadelphia, PA*

Background: The role of CN in mRCC was challenged by the results of the CARMENA trial in the targeted therapy (TT) era. We sought to evaluate the role of both upfront and deferred CN in pts receiving modern IO-based and TT regimens. **Methods:** Pts with synchronous mRCC who received systemic therapy (tx) for mRCC after 2011 were included from the de-identified nationwide Flatiron Health database. We evaluated 3 groups: systemic tx alone, systemic-> CN, and CN-> systemic tx. Overall survival (OS) was calculated from the time of initiation of first therapy – systemic or CN. Patient characteristics were compared using chi-squared tests or t-test. Weighted Kaplan-Meier curves, log-rank tests, and Cox proportional hazards regressions with time-varying covariates were used to assess the effect of tx on survival. Adjustment was conducted via inverse probability of treatment weighing based on the generalized propensity score, estimated via Bayesian Additive Regression Trees. Covariates in the model were age, gender, race, insurance at mRCC diagnosis, and IMDC risk group. **Results:** Of 1719 pts with mRCC, 972 (56.5%) received systemic tx alone, 605 (35.1%) received CN-> systemic tx, and 142 (8.2%) received systemic->CN. 310 pts received IO or IO/IO, 123 pts received IO+TT and 1152 pts received only TT. The median follow-up was 37.1 months. In adjusted analyses using propensity score weighting and time-varying covariates, CN-> systemic was significantly associated with improved OS compared with systemic tx alone (Table). When stratifying groups by type of systemic treatment (IO and TT), there was improvement of OS in the CN groups compared to systemic tx alone, although we lacked power to reach statistical significance. Among CN-treated patients, the order of systemic tx relative to CN did not change OS (hazard ratio [HR] = 1.00, 95% CI 0.76-1.32, p=0.96). **Conclusions:** Using a national, EHR-based cohort, which includes a large number of IO treated pts, our findings support an oncologic role for CN in select mRCC pts. The timing of CN, for pts who were able to receive both systemic therapy and CN, may not affect overall outcome. The associated improvement in survival of CN is seen in pts receiving IO and TKI based systemic tx. Research Sponsor: None.

Adjusted median OS from weighted Kaplan-Meier curves and HR from weighted time-varying Cox model.

Tx	N for adjusted analysis	Systemic tx alone	CN- systemic tx	Systemic tx- CN
IO, IO/IO or IO/TT		15.1 mo	40.2 mo	Not reached
	400	(N=255)	HR=0.84 (0.56-1.27), p=0.4 (N=113)	HR=0.58 (0.22-1.54), p=0.28 (N=32)
TT		11.0 mo	25.4 mo	37.7 mo
	1087	(N=570)	HR=0.85 (0.72-1.01), p=0.06 (N=417)	HR=0.85 (0.63-1.13), p=0.26 (N=100)
Overall		12.1 mo	26.1 mo	37.7 mo
	1615	(N=891)	HR=0.82 (0.70-0.95), p=0.008 (N=586)	HR=0.82 (0.62-1.07), p=0.14 (N=138)

4583 **Poster Session**

Effect of high-dose corticosteroid use on efficacy of immune checkpoint inhibitors in patients with renal cell carcinoma (RCC). *First Author: Chris Labaki, Dana Farber Cancer Institute - (Individuals), Boston, MA*

Background: The use of High-Dose Corticosteroids (HDC) has been linked to poor outcomes in patients with lung cancer treated with immune checkpoint inhibitors (ICIs) (Ricciuti B, JCO, 2019). There is no data on the effect of HDC on renal cell carcinoma patients (RCC) treated with immunotherapy. We hypothesized that HDC use would be associated with worse outcomes in RCC patients receiving ICIs. **Methods:** This study evaluated a retrospective cohort of patients with RCC at Dana-Farber Cancer Institute in Boston, MA. Clinical information including demographics, IMDC risk score, RCC histology, steroid administration, ICI regimen, line of therapy, time to treatment failure (TTF) and overall survival (OS) were collected. Patients were divided into those receiving HDC (prednisone $\geq$10 mg or equivalent for $\geq$ 1 week, HDC group) or not receiving HDC (No-HDC group). HDC administration was evaluated in relation to TTF and OS in a univariate analysis (Log-rank test) and a multivariate analysis (Cox regression). **Results:** 190 patients with RCC receiving ICIs were included, with a median age of 59 years. HDC were administered to 56 patients and 134 patients received no (N= 116) or only low-dose (N=18) steroids. In the HDC group, 40 patients received steroids for immune-related adverse events, 8 for other cancer-related indications, and 8 for non-oncological indications. There was no difference in TTF between the HDC and No-HDC groups (12-mo TTF rate: 34.8 vs. 32.3%, respectively; log-rank p=0.65). Similarly, there was no difference in OS between the HDC and No-HDC groups (36-mo OS rate: 56.7 vs. 62.4%, respectively; log-rank p=0.97). After adjusting for IMDC risk group, RCC histology, ICI regimen type, and line of therapy, TTF and OS did not differ in the HDC group as compared to No-HDC group (HR=1.14 [95%CI: 0.80-1.62], p=0.44 and HR=1.17 [95%CI: 0.65-2.11], p=0.59, respectively). **Conclusions:** In this retrospective study of patients with RCC treated with ICIs, administration of high-dose corticosteroids was not associated with worse outcomes. Research Sponsor: None.

Clinical characteristics, 12-mo TTF and 36-mo OS rates in study groups.

Variable	Category	Patients receiving HDC (n=56)	Patients not receiving HDC (n=134)	P-value*
IMDC groups	Intermediate risk, n(%)	24 (42.8)	89 (66.4)	Ref.
	Favorable risk, n(%)	19 (34.0)	24 (18.0)	0.005
	Poor risk, n(%)	13 (23.2)	21 (15.6)	0.04
Histology	ccRCC, n(%)	48 (85.7)	107 (79.8)	Ref.
	nccRCC, n(%)	8 (14.3)	27 (20.2)	0.34
Line of therapy	1st line, n(%)	46 (82.1)	94 (70.1)	Ref.
	2nd line, n(%)	10 (17.9)	40 (29.9)	0.09
Regimen	ICI + anti-VEGF, n(%)	25 (44.7)	58 (43.3)	Ref.
	Dual ICI therapy, n(%)	17 (30.3)	33 (24.6)	0.64
	ICI monotherapy, n(%)	14 (25.0)	43 (32.1)	0.47
Survival	12-month TTF rate, % [95%CI]	34.8 [24.1-50.1]	32.3 [24.9-41.9]	0.65
	36-month OS rate, % [95%CI]	56.7 [41.2-78.0]	62.4 [53.2-73.1]	0.97

*Logistic regression for clinical variables, log-rank test for survival outcomes.

4584 **Poster Session**

An open-label, single-arm, multicenter, phase II study of RC48-ADC to evaluate the efficacy and safety of subjects with HER2 overexpressing locally advanced or metastatic urothelial cancer (RC48-C009). *First Author: Xinan Sheng, Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: There is still urgent medical needs in the patients with locally advanced or metastatic urothelial cancer (mUC) post to the failure of at least one line chemotherapy. RC48-ADC, a novel humanized anti-HER2 antibody-drug conjugate (ADC), has proved its efficacy in these patients (RC48-C005, NCT03507166), most of whom had received gemcitabine and platinum. Taking into consideration that taxane is another possible active agent for mUC, this study aims to further evaluate the efficacy of RC48-ADC in HER2 overexpressing mUC post to the failure of platinum, gemcitabine and taxane. **Methods:** This study was an open-label, multicenter, single-arm, non-randomized phase II study. Eligibility criteria included: histologically confirmed UC, HER2 overexpressing (IHC 2+ or 3+), ECOG PS 0-1, failed platinum, gemcitabine and taxane. The patients received RC48-ADC treatment alone (2 mg/kg IV infusion, q2w) until disease progression, unacceptable toxicity, withdrawal, death or study termination. The primary endpoint was objective response rate (ORR) assessed by blinded independent review committee (BIRC) according to RECIST v1.1. Progress-free survival (PFS), duration of response (DOR), overall survival (OS), and safety was also assessed. **Results:** Patient enrollment for this study started in December 2018 and completed in September 2020. A total of 64 patients were enrolled, with a median age of 62.5 years. At baseline, most patients (82.8%) had visceral metastasis. Fifty-five patients (85.9%) had received $\geq$ 2 lines treatment and 19 (29.7%) patients had prior immune checkpoint inhibitor (CPI) therapy. As of Nov 30, 2020, the confirmed ORR assessed by BIRC was 46.9% (95% CI: 34.3%, 59.8%) and the median DOR was 8.3 months (95% CI: 4.3, NE), the median PFS was 4.3 months (95% CI: 4.0, 6.8). The median OS was 14.8 months (95% CI: 8.7, 21.1). The ORR was 60.0% (15/25) in patients with HER2 IHC3+ or FISH test positive, 45.3% (24/53) in patients with visceral metastasis, 42.1% (8/19) in patients post to CPI therapy. The ORR was 55.6% (5/9), 50.0% (21/20) and 30.8% (4/13), in patients who had received 1 line, 2 lines and $\geq$ 3 lines treatment, respectively. Most commonly reported TRAEs were leukopenia (45.3%), AST increase (43.8%), neutropenia (42.2%), hypoesthesia (42.2%), ALT increase (37.5%) and fatigue (35.9%); Most commonly reported $\geq$ grade 3 TRAEs were neutropenia (9.4%) and hypoesthesia (6.3%) **Conclusions:** In patients with HER2 overexpressing (IHC 2+ or 3+) mUC who had failed platinum, gemcitabine and taxane, and the great majority of whom had received $\geq$2 prior lines treatment, RC48-ADC has demonstrated consistently excellent efficacy and benefit-risk profile compared with the RC48-C005 study which enrolled patients with mUC who had received $\geq$1 line prior chemotherapy. Clinical trial information: NCT03809013. Research Sponsor: remegen.

4585 **Poster Session**

Circulating tumor DNA (ctDNA) in patients with advanced adrenocortical carcinoma. *First Author: Bassel Nazha, Emory University Department of Hematology and Medical Oncology, Atlanta, GA*

Background: Adrenocortical Carcinoma (ACC) is a rare and aggressive malignancy with poor prognosis and limited treatments in the advanced setting. Molecular pathways with tumor suppressor genes (e.g. TP53, CDKN2A) and oncogenes (e.g. CTNNB1 and RAS) are implicated in oncogenesis. To our knowledge, the genomic landscape of ctDNA alterations for ACC has not been described in a large cohort. We report plasma-based ctDNA alterations in patients with advanced ACC. **Methods:** We retrospectively evaluated genomic data from 102 patients with ACC who had ctDNA testing between 12/2016 – 10/2020 using Guardant360 (Guardant Health, CA). ctDNA analysis interrogated single nucleotide variants (SNV), fusions, indels and copy number variations (CNV) of up to 83 genes. We evaluated the frequency of genomic alterations, the landscape of co-occurring mutations, and pathogenic or likely pathogenic alterations with potential targeted therapies. The prevalence of alterations identified in ctDNA were compared to those detected in tissue using a publicly available database (cBioPortal). **Results:** The median age was 54 years (range 24-81), and 55% of patients were male. Among the entire cohort, 84 pts (82.4%) had ≥1 somatic alteration detected. Mutations were most frequently detected in TP53 (52%), EGFR (23%), CTNNB1 (18%), MET (18%), and ATM (14%). The frequencies detected in ctDNA were similar to the results detected in tissue. Pathogenic and/or likely pathogenic mutations in therapeutically relevant alterations were observed in 36 patients (35%), including EGFR, BRAF, MET, CDKN2A, and CDK4/6 (Table 1). The most frequently co-occurring mutations were EGFR + TP53 (14%), EGFR + MET (11%), BRAF + MET (10%). **Conclusions:** Blood-based ctDNA profiling in advanced ACC provided comprehensive genomic data in most patients, with a similar profile to tumor tissue analyses. Over one third of patients had actionable mutations with approved therapies in other cancers. This approach might inform the development of personalized treatment options for this aggressive malignancy. Research Sponsor: None.

	ACC patients with mutations in the rapeutically relevant alterations	
Gene	N	%
EGFR	10	11.9%
BRAF	9	10.7%
MET	9	10.7%
CDKN2A	7	8.3%
NF1	7	8.3%
CDK4	7	8.3%
CDK6	6	7.1%
GNAS	6	7.1%
FGFR 1 or FGFR2	5	6.0%
ATM	4	4.8%

TPS4586 **Poster Session**

A phase 3, multicenter, randomized study evaluating the efficacy of TAR-200 in combination with cetrelimab versus concurrent chemoradiotherapy in participants with muscle-invasive urothelial carcinoma of the bladder. *First Author: Stephen B. Williams, University of Texas Medical Branch (UTMB), Galveston, TX*

Background: The standard of care for patients with muscle-invasive bladder cancer (MIBC) consists of neoadjuvant chemotherapy and radical cystectomy (RC) or chemoradiotherapy (CRT). However, RC is associated with potential morbidity or mortality from the procedure. TAR-200 is an intravesical drug-delivery system designed for the local continuous release of gemcitabine within the bladder. Cetrelimab is an investigational immunoglobulin G4 anti–programmed cell death protein-1 antibody. In patients with MIBC, this clinical trial will evaluate whether combination treatment with intravesical TAR-200 and systemic cetrelimab will result in enhanced local and systemic antitumor activity versus concurrent CRT. **Methods:** SunRISe-2 (NCT04658862) is a prospective, multicenter, open-label, randomized phase 3 study evaluating the efficacy and safety of intravesical TAR-200 plus systemic cetrelimab versus CRT in participants with MIBC. Eligible participants are aged ^{3}18 years with an ECOG performance status of 0, 1, or 2, and histologically proven, cT2-T4a, N0, M0 urothelial carcinoma of the bladder diagnosed within 90 days of the randomization date, and who refuse or are ineligible for RC. Approximately 550 participants will be randomized in a 1:1 ratio and with stratification by 2 factors: transurethral resection of bladder tumor screening results (visibly complete vs incomplete) and screening tumor stage (T0 vs Ta/T1/Tis vs T2-T4a). Participants in Arm 1 will receive intravesical TAR-200 every 3 weeks for the first 18 weeks on study; and, beginning at week 24, every 12 weeks through study year 3. Cetrelimab will be dosed every 3 weeks until month 18. Participants in Arm 2 will receive standard of care CRT (with either cisplatin or gemcitabine, for up to 6 weeks). A primary disease assessment will be performed at week 18 to evaluate treatment response in both arms. Subsequent assessments (axial imaging and cystoscopy) will occur at week 24 and every 12 weeks thereafter through study year 2, and then every 24 weeks through study year 5. The primary endpoint is bladder intact event-free survival. Key secondary endpoints include metastasis-free survival, overall survival, overall response rate (at week 18), and safety and tolerability. Other/exploratory end points include assessments of cancer-specific survival, time to symptomatic progression, pharmacokinetics, immunogenicity, health-related quality of life, healthcare resource utilization, and biomarkers. Participants are being enrolled at approximately 272 study sites worldwide. The study opened for enrollment in December 2020. Clinical trial information: NCT04658862. Research Sponsor: Janssen Research & Development, LLC.

TPS4587 **Poster Session**

KEYNOTE-B15/EV-304: Randomized phase 3 study of perioperative enfortumab vedotin plus pembrolizumab versus chemotherapy in cisplatin-eligible patients with muscle-invasive bladder cancer (MIBC). *First Author: Christopher J. Hoimes, Duke University, Durham, NC*

Background: Standard of care for MIBC is neoadjuvant cisplatin-based chemotherapy followed by radical cystectomy and pelvic lymph node dissection (RC+PLND); however, in time, patients experience disease recurrence or progression. Enfortumab vedotin (EV) is a Nectin-4–directed antibody–drug conjugate comprising a fully human, monoclonal antibody and the microtubule-disrupting agent monomethyl auristatin E. The KEYNOTE-869/EV-103 phase 1/2 study (NCT03288545) showed that the PD-1 inhibitor pembrolizumab + EV had encouraging antitumor activity and acceptable safety as first-line treatment for cisplatin-ineligible patients with metastatic urothelial cancer (Rosenberg JE et al. J Clin Oncol. 2020;38[15 suppl]:5044). Based on these data, investigating EV + pembrolizumab in an earlier setting such as MIBC and in a perioperative fashion is appropriate. KEYNOTE-B15/EV-304 (NCT04700124) is a randomized, open-label, phase 3 study to evaluate the efficacy and safety of perioperative EV + pembrolizumab versus neoadjuvant chemotherapy using gemcitabine/cisplatin in cisplatin-eligible patients with MIBC. **Methods:** Patients must have histologically confirmed urothelial cancer/MIBC (clinical stage T2-T4aN0M0 or T1-T4aN1M0) with predominant (≥50%) urothelial histology, have nonmetastatic disease (≥N2 disease and/or M1 excluded) confirmed by blinded independent central review (BICR), have ECOG PS 0 or 1, and not have previously received systemic therapy for MIBC. Approximately 784 patients will be randomly assigned 1:1 to receive either 4 cycles of neoadjuvant EV + pembrolizumab followed by 5 cycles of adjuvant EV + 13 cycles of adjuvant pembrolizumab after RC+PLND or 4 cycles of neoadjuvant cisplatin-based chemotherapy followed by observation after RC+PLND. Neoadjuvant and adjuvant pembrolizumab 200 mg + EV 1.25 mg/kg will be administered intravenously every 3 weeks (Q3W), and neoadjuvant chemotherapy will consist of gemcitabine 1000 mg/m^2 + cisplatin 70 mg/m^2 Q3W. Randomization will be stratified by centrally determined (pathology or imaging) initial T and N stage (T2N0 or T3/T4aN0 or T1-T4aN1), PD-L1 combined positive score (CPS ≥10 or CPS < 10), and geographic region (United States or Europe or most of world). Imaging (CT or MRI) will be performed ≤6 weeks before cystectomy and 6 weeks after cystectomy. After postcystectomy imaging, additional imaging will be performed Q12W up to the end of year 2 (week 96) and at discontinuation. In year 3 and beyond, imaging will be performed Q24W. Primary end points are pathological complete response and event-free survival by BICR. Secondary end points are overall survival, disease-free survival, pathological downstaging, and safety and tolerability. Clinical trial information: NCT04700124. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS4588 **Poster Session**

Consolidative radiotherapy for metastatic urothelial bladder cancer patients without progression and with no more than three residual metastatic lesions following first line systemic therapy: A prospective randomized comparative phase II trial (BLAD RAD01/GETUG-AFU V07). *First Author: Jonathan Khalifa, Institut Claudius Regaud/IUCT-Oncopole, Toulouse, France*

Background: Consolidative local treatment of the primary tumor in the treatment of metastatic malignancies has shown promising results in several types of tumors, mostly relying on the seed-and-soil theory. Furthermore, the local treatment of the residual metastases following systemic treatment is a promising approach, in part due to the high incidence of progression at prior sites of disease in patients who had initially responded to chemotherapy. To date, no prospective data exists on such consolidative approach in metastatic urothelial bladder cancer (mUBC). The phase II trial BLAD-RAD01 GETUG-AFU V07 was designed to investigate the role of local consolidative radiotherapy in patients with limited mUBC and without progression following the initial phase of first-line systemic therapy. **Methods:** This is a phase II, multicenter, randomized open-label and comparative study. Patients with mUBC (excluding brain and liver metastases), without progression following standard first-line systemic therapy according to RECIST v1.1, and with no more than 3 residual metastatic lesions on 18FDG-PET scanner and/or contrast-enhanced CT-scanner are eligible for the study. After the completion of systemic treatment, an estimated 130 patients will be randomized in a 1:1 ratio between consolidative local treatment (pelvic radiotherapy +/- previous transurethral resection of bladder tumor, associated with stereotactic body radiotherapy (SBRT) to the residual metastases) plus standard of care (arm B) and standard of care only (arm A). Stratification is performed based upon: the center, the ECOG performance status, the administration of immunotherapy or not, the number of residual metastatic lesions and the imaging modality for assessment of the number of residual lesions. To date, standard of care for this population is maintenance treatment with avelumab. Radiotherapy regimens consist in conventionally fractionated (64Gy in 32 fractions) or hypofractionated (55Gy in 20 fractions) irradiation of the bladder, optional pelvic nodes irradiation, and 3 to 5 fractions of 6 to 18 Gy in SBRT for metastases, depending on the location. The main objective is to detect an increase in 20-month overall survival rate following chemotherapy from 50% (based upon the JAVELIN 100 trial) to 66%; this corresponds to a hazard ratio of 0.6. A total of 83 events are necessary for 85% power to detect this difference if it is true using a one-sided logrank test at the 10% of significance. Target difference, type I and II error rates are relaxed and compatibles with recommendations for comparative phase II trials. Key secondary endpoints are progression free survival, safety and quality of life. To date, one patient has been enrolled and eight centers are open for accrual. Clinical trial information: NCT04428554. Research Sponsor: PHRC-K 2019 (programme hospitalier de recherche clinique national en cancérologie).

TPS4589 **Poster Session**

AUREA study: Atezolizumab (Atezo) combined with split-dose gemcitabine plus cisplatin (s-GC) in locally advanced or metastatic urothelial cancer (LA/mUC): A SOGUG study. *First Author: Alfonso Gomez De Liano Lista, Medical Oncology Department, Complejo Hospitalario Universitario Insular-Materno Infantil, Las Palmas, Spain*

Background: First-line cisplatin-based chemotherapy (70 mg/m^2) is the standard of care for LA/mUC patients (pts). However, about 50% will be ineligible for Cisplatin according to Galsky's criteria. Moreover, a significant proportion of cisplatin-fit pts will receive carboplatin based on physician criteria. s-GC represents a feasible alternative in such situations, and could improve response rate compared to carboplatin regimens. Atezo is a programmed death-ligand 1 (PD-L1) inhibitor that is approved as first line treatment for cisplatin-ineligible LA/mUC pts with PD-L1 expression ≥5% (Ventana SP142). We present the study design of a phase II single arm trial of Atezo +s-GC in previously untreated pts with LA/mUC (NCT04602078). **Methods:** This single arm, open-label, multicenter study evaluates the efficacy and safety of Atezo +s-GC in previously untreated pts with LA/mUC. 66 pts will be enrolled and receive s-GC x 6 cycles (Cisplatin 35mg/m2 + Gemcitabine 1000mg/m2 on days 1 and 8 Q3W) and Atezo (1200 mg IV Q3W), followed by Atezo (1200 mg IV Q3W) until disease progression, toxicity or absence of clinical benefit. Eligibility criteria include histologically confirmed unresectable LA/mUC, measurable disease per RECIST 1.1 and adequate organ and marrow. Pts must be unfit for full cisplatin dose based on: age > 70 years, PS ECOG 0-2, creatinine Clearance >30 and <60 mL/min per Cockroft-Gault formula or by 24-hour urine collection. Other reasons for cisplatin ineligibility as considered by investigator, including those uncovered by Galsky's criteria, will be allowed, prior discussion with PI. Exclusion criteria include prior systemic therapy for LA/mUC (adjuvant/neoadjuvant allowed if finished > 12 months prior to inclusion), prior autoimmune disease and uncontrolled significant illnesses. The primary endpoint is ORR per RECIST 1.1 assessed by investigator; the secondary endpoints are DoR, OS, PFS and safety. Biomarker analysis, including PD-L1 expression and microbiome relationship, will be an exploratory objective. The first two patients were enrolled in February 2021. Clinical trial information: NCT04602078. Research Sponsor: Roche, Spanish Oncology Genito Urinary Group (SOGUG).

TPS4590 **Poster Session**

EA8185: Phase 2 study of bladder-sparing chemoradiation (chemoRT) with durvalumab in clinical stage III, node positive urothelial carcinoma (INSPIRE)—An ECOG-ACRIN and NRG Collaboration. *First Author: Monika Joshi, Penn State Cancer Institute, Hershey, PA*

Background: Patients [pts] withlymph node positive (LN+), non-metastatic bladder cancer (BC) have a better prognosis than those with metastatic (M1) disease. However, this population is under-represented in advanced bladder trials and ineligible for bladder-sparing trials. Therefore, there have been no larger prospective trials establishing the standard of care in LN+ BC. Given the promise of immunotherapy in advanced BC and potential synergy between immunotherapy and radiation, INSPIRE was designed to determine the role of concurrent and adjuvant durvalumab (durva) in this patient population when treated with induction chemotherapy (IC) followed by concurrent chemoRT. **Methods:** This is a randomized phase II study that is enrolling BC pts with stage III [N1-2 M0], pure or mixed urothelial cancer. Pts must have received ≥3 cycles of IC [either before or after registration, prior to randomization] without progression. LN+ is defined as radiologically LN ≥1.0 cm in short axis, with or without biopsy prior to IC. As long as pts do not progress on induction chemotherapy, they will be randomized to chemoRT+/- durva using 5 stratification factors (Simon Pocock minimization method) a) IC prior vs. post registration b) cisplatin vs non-cisplatin regimen during RT c) LN size d) response to IC e) extent of TURBT. Pts on the chemoRT+durva arm will get chemotherapy per physician choice + IMRT + 3 x doses of Q3wk durva for 6.5-8 wks, whereas those on the control arm will get chemoRT alone. The primary end point is clinical complete response [CR], defined as no radiologically measurable disease in the LNs and negative cystoscopy and bladder biopsy 8-10 weeks post-chemoRT +/- durva. Pts on the chemoRT + durva arm who have a CR or clinical benefit (> T0 and ≤T2 in bladder per cystoscopy, biopsy + CR/PR/SD in LN by imaging) will get adjuvant Q4wk durva for 9 doses, while those on the chemoRT arm will undergo observation. Secondary end points include OS, PFS, bladder-intact event-free survival, rate of toxicity and salvage cystectomy. This study is designed to detect an improvement of 25% in clinical CR between both arms (37.5% to 62.5%). A total accrual of 114 pts (in order to enroll 92 evaluable pts) will provide 81% power to detect this difference using a Fisher's exact test (assuming 10% drop out + anticipating that 20% chemotherapy-naïve pts will progress post IC). We are banking blood and primary tumor tissue pre- and post-chemoRT in both groups. The study was activated in August 2020 and accrual is ongoing. INSPIRE is the first prospective study designed for only LN+ BC and will define both short-term and long-term outcomes for bladder sparing in this patient population and has the potential to define a new treatment strategy for stage III BC. Clinical trial information: NCT04216290. Research Sponsor: U.S. National Institutes of Health.

TPS4591 **Poster Session**

A phase 2 study of cabozantinib in combination with atezolizumab as neoadjuvant treatment for muscle-invasive bladder cancer (HCRN GU18-343) ABATE study. *First Author: Deepak Kilari, Medical College of Wisconsin, Milwaukee, WI*

Background: ABACUS and PURE-01 trials demonstrated the activity of single agent atezolizumab and pembrolizumab respectively as neoadjuvant therapy for muscle invasive urothelial carcinoma (MIUC). However, downstaging to non-muscle invasive disease was noted in only 50 percent of patients. Resistance to programmed death (PD)- 1/L-1 antibodies is likely to include factors such as impaired dendritic cell maturation/function, infiltration of T-Regs and myeloid derived suppressor cells, impaired T-cell priming and T-cell trafficking in tumors. Cabozantinib is a tyrosine kinase inhibitor which targets MET, AXL, MER, Tyro3 and VEGFR2. Cabozantinib has a unique immunomodulatory profile and has demonstrated clinical activity as monotherapy and in combination with PD-1/L1 antibodies in various solid tumors including UC, renal cell cancer, castrate- resistant prostate cancer, and non-small cell lung cancer. We hypothesize that the combination of cabozantinib and atezolizumab as neoadjuvant therapy for MIUC would improve rates of pathologic downstaging compared to single-agent checkpoint inhibitors. **Methods:** ABATE(NCT04289779) is an open-label, single arm, multi-center study to assess the efficacy and safety of cabozantinib with atezolizumab as neoadjuvant therapy for cT2-T4aN0/xM0 MIUC. An estimated 38 patients will be enrolled and receive cabozantinib 40 mg PO daily with atezolizumab 1200mg every 3 weeks for a total duration of 9 weeks followed by radical cystectomy. Adults (≥18 years) with resectable UC who are either cisplatin-ineligible or decline cisplatin are eligible. Patients are required to have an ECOG PS of 0-2 and provide tumor tissue for PD-L1 analysis. UC should be predominant component (≥ 50%). Previous systemic anticancer therapies for MIUC are not permitted. CT/MRI will be performed before investigational therapy and cystectomy. Primary endpoint is pathologic response rate defined as the absence of residual muscle-invasive cancer in the surgical specimen (< pT2). Secondary endpoints are safety and toxicity, pathologic complete response rate and event-free survival. Exploratory end points include patient-reported outcomes and outcome associations with biomarkers. Accrual began May 2020. Clinical trial information: NCT04289779. Research Sponsor: Exelixis and Genentech.

TPS4592 **Poster Session**

Cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) (CaNI) for advanced renal cell carcinoma with variant histology (aRCCVH). *First Author: Bradley Alexander McGregor, Dana-Farber Cancer Institute, Boston, MA*

Background: Despite advances in therapy of clear cell renal cell carcinoma, outcomes for patients with aRCCVH remain poor and these patients have typically been excluded from pivotal phase III studies. COSMIC-313 (NCT03937219) exploring C/N/I vs N/I excludes those with aRCCVH. Given responses seen with C as well as N/I in aRCCVH, there is reason to explore this triplet combination in this population. **Methods:** NCT04413123 is single arm phase 2 trial multi-institutional study involving Dana-Farber Cancer Institute, Beth Israel Deaconess Medical Center, Winship Cancer Institute, Karmanos Cancer Center, University of California in San Diego and University of Texas Southwestern. The primary objective is to assess the objective response rate (ORR) by investigator-assessed Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 of C in combination with N/I in aRCCVH. Key secondary endpoints are progression-free survival (PFS), overall survival (OS) and toxicity by Common Terminology Criteria for Adverse Events (CTCAE) version 5. Mandatory pretreatment biopsy (unless medically infeasible) is required for correlative analysis to define the composition and transcriptional states of tumor and immune cells within the aRCCVH microenvironment in addition to determining the number and state of tumor-infiltrating T cell clones in aRCCVH and relation to response. Any variant histology is allowed, including clear-cell RCC with over 80% sarcomatoid features. Patients may be treatment naïve or received prior therapy including up to one anti-vascular endothelial growth factor agent not including C; prior therapy with immune checkpoint inhibitors is exclusionary. All International Metastatic RCC Database Consortium risk classifications are allowed; patients should have adequate organ function with performance status 0-1. C will be administered at a starting dose of 40 mg daily. N will be dosed at 3 mg/kg with I 1 mg/kg every 3 weeks followed by maintenance N 480 mg IV every 4 weeks and will be continued until progressive disease or unacceptable toxicity. C can be reduced to. 20 mg daily or 20 mg every other day as needed for toxicity. Dose reductions of N or I are not permitted but delays up to 12 weeks are allowed; N may be continued without I if toxicity can be directly attributed to I. Radiographic imaging is performed at baseline with first scheduled assessment at 12 weeks then every 8 weeks thereafter. A one-stage design is employed to enroll 40 eligible patients, which provides 93% power at 1-sided alpha of 0.09 to distinguish an ORR of 40% versus 20%. 12 or more responses are required to deem treatment promising. Seven of the planned 40 patients have been enrolled as of 2/1/2021. Clinical trial information: NCT04413123. Research Sponsor: Exelixis, Pharmaceutical/Biotech Company.

TPS4593 **Poster Session**

A randomized trial of radium-223 (Ra-223) dichloride and cabozantinib in patients (pts) with advanced renal cell carcinoma (RCC) with bone metastases (RADICAL/Alliance A031801). *First Author: Rana R. McKay, University of California San Diego, Moores Cancer Center, La Jolla, CA*

Background: Bone metastases are prevalent in approximately 30% of pts with advanced RCC. Pts with bone metastases have a worse prognosis compared to pts without bone metastases and are at risk of symptomatic skeletal events (SSEs). Cabozantinib, a multitargeted inhibitor of multiple kinases, including vascular endothelial growth factor (VEGF) receptor and MET, has improved survival in pts with metastatic RCC and has enhanced activity in bone. Ra-223, an alpha-emitting radioisotope with natural bone-seeking proclivity, has been shown to prolong survival in men with castration-resistant prostate cancer. We previously conducted a pilot study of Ra-223 with VEGF inhibition and demonstrated safety and declines in markers of bone formation and resorption with the combination (McKay et al, CCR 2018). Given that decreasing rates of SSEs and improving outcomes for pts with RCC with bone metastases are unmet needs in pts with RCC, we designed a randomized phase 2 study through the National Clinical Trials Network (NCTN) investigating cabozantinib with or without Ra-223 in patients with RCC with bone metastases. **Methods:** This is an open-label multicenter study. Eligible pts have metastatic RCC of any histology with ≥2 metastatic bone lesions untreated with prior radiation therapy and no more than 2 prior lines of systemic therapy. Pts with non-clear cell RCC are eligible and will be capped at 20% of the total accrual goal. Pts must have a Karnofsky performance status of ≥60%, have symptomatic bone pain defined as a prior SSE or need of analgesics, and be on osteoclast-targeted therapy unless otherwise contraindicated. Pts are randomized 1:1 to cabozantinib with (Arm A) or without (Arm B) Ra-223. Starting dose of cabozantinib for Arm A is 40 mg by mouth daily to be escalated to 60 mg daily after cycle 1 (1 cycle = 28 days) if no persistent grade 2 or grade ≥3 toxicity. Ra-223 is administered at a fixed dose of 1.49 microcurie/kg IV every 28 days x 6 doses. The primary endpoint is SSE-free survival. Secondary endpoints include safety, progression-free survival, overall survival, quality of life measures, and correlative analyses including liquid biopsy studies and tumor tissue analysis. The study has 90% power to detect an improvement in 6-month SSE-free survival rate from 65% to 78% with one-sided $\alpha = 0.025$ significance. To ensure 191 evaluable patients, target accrual is 210 pts. This design includes a safety run-in and an interim analysis for futility when 50% of the expected number of events (72 SSE events) have been observed. Final data analysis will occur when 143 events have been observed. The study was activated in December 2019 and accrual is currently ongoing throughout the NCTN. Clinical trial information: NCT04071223. Research Sponsor: U10CA180821, U10CA180882, U24CA196171, https://acknowledgments.alliancefound.org. U10CA180820 and UG1CA233302 (ECOG-ACRIN).

TPS4594 **Poster Session**

A phase 1b/2 umbrella study of investigational immune and targeted combination therapies as first-line therapy for patients with advanced renal cell carcinoma (RCC). *First Author: Elizabeth R. Plimack, Fox Chase Cancer Center, Philadelphia, PA*

Background: For advanced clear cell RCC (ccRCC), first-line treatment with PD-1/PD-L1 inhibitors in combination with CTLA-4 inhibitors or VEGF TKIs are established treatment options. However, patients eventually experience progression; therefore, more effective therapies are needed. This umbrella platform study is an open-label, rolling-arm, multicenter, phase 1b/2 trial with an adaptive design that will evaluate the safety and efficacy of experimental combinations of investigational agents in advanced ccRCC based on their mechanisms of action and toxicity profile. Substudy 03A (NCT04626479) will evaluate treatment combinations as first-line therapy for patients with advanced ccRCC. Given promising results of the phase 1b/2 KEYNOTE-146 (NCT02501096) and phase 3 KEYNOTE-581/CLEAR (NCT02811861) studies, pembrolizumab (400 mg IV Q6W) + lenvatinib (20 mg orally QD) will be used as the reference arm. **Methods:** Patients must be aged ≥18 years with histologically confirmed ccRCC, measurable disease per RECIST v1.1, and KPS score ≥70 and must have not received prior systemic therapy for advanced RCC (neoadjuvant therapy is acceptable if completed ≥12 mo before randomization). The study will comprise a safety lead-in phase for experimental combinations with investigational agents without an established recommended phase 2 dose (RP2D) and an efficacy phase. Patients will be randomly assigned 2:1 to an experimental arm or a reference arm. Each experimental arm will contain approximately 80 patients. During the efficacy phase, if more than 1 experimental arm is open for enrollment, patients in the reference arm can be shared. Treatments in the experimental arms are composed of the following: MK-1308A (coformulation of quavonlimab [MK-1308] 25 mg + pembrolizumab 400 mg IV Q6W) + lenvatinib (20 mg orally QD), MK-4280A (coformulation of MK-4280 800 mg + pembrolizumab 200 mg IV Q3W) + lenvatinib (20 mg orally QD), and pembrolizumab (400 mg Q6W IV) + belzutifan (MK-6482, 120 mg orally QD) + lenvatinib (20 mg orally QD). Treatment with pembrolizumab (including coformulations with MK-1308 and MK-4280) will continue up to 2 years, whereas treatment with lenvatinib and belzutifan will continue until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be stratified by IMDC risk group (favorable vs intermediate/poor). Tumor imaging will occur 12 weeks after randomization, then Q6W until week 54, and Q12W thereafter. Coprimary end points are safety and tolerability, establishing the RP2D during the safety lead-in phase (if applicable) and objective response rate per RECIST v1.1 by blinded independent central review (BICR) during the efficacy phase. Secondary end points during the efficacy phase are duration of response, progression-free survival and clinical benefit rate per RECIST v1.1 (BICR), and overall survival. Clinical trial information: NCT04626479. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and Eisai Inc., Woodcliff Lake, NJ, USA.

TPS4595 **Poster Session**

KEYNOTE-B61: Open-label phase 2 study of pembrolizumab in combination with lenvatinib as first-line treatment for non-clear cell renal cell carcinoma (nccRCC). *First Author: Chung-Han Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Most RCCs contain clear cell histology; the remainder of cases are summarized as nccRCC. nccRCC is a heterogeneous group of tumors and, with advanced metastases, survival is uniformly worse than with clear cell RCC (ccRCC) because of the aggressiveness of these cancers and a lack of effective systemic treatment options. Because data are limited for patients with nccRCC, the role of various agents in the treatment of nccRCC is poorly defined and there is no standard of care; treatment guidelines recommend clinical trials as preferred strategy. Inhibition of the PD-1/PD-L1 pathway is an effective treatment option for nccRCC, and pembrolizumab monotherapy has shown efficacy with an acceptable safety profile as first-line treatment. The VEGF TKI lenvatinib has also shown efficacy with a tolerable safety profile as combination therapy with everolimus for nccRCC. Also, in the phase 3 KEYNOTE-581 study (NCT02811861), the combination of lenvatinib + pembrolizumab as first-line therapy showed antitumor activity in patients with metastatic ccRCC, suggesting this combination might be an excellent therapeutic option for nccRCC. The phase 2, open-label, single-arm, KEYNOTE-B61 study (NCT04704219) is being conducted to evaluate pembrolizumab in combination with lenvatinib as first-line treatment for nccRCC. **Methods:** Patients with centrally confirmed nccRCC, locally advanced/metastatic measurable disease per RECIST v1.1 per blinded independent central review (BICR), no prior systemic therapy for nccRCC, and KPS score ≥70 will be enrolled. Approximately 152 patients will receive pembrolizumab 400 mg every 6 weeks and lenvatinib 20 mg once daily. Pembrolizumab treatment will continue for up to approximately 2 years or until a discontinuation criterion is met (disease progression, unacceptable toxicity, or withdrawal of consent); lenvatinib treatment can continue beyond 2 years or until one of the same discontinuation criterion is met. Participants who discontinue one of the treatments can continue to receive the other treatment as monotherapy. A second-course treatment phase is available for patients who meet specific criteria. CT/MRI will be performed at 12 weeks from the start of treatment, every 6 weeks until week 54, and every 12 weeks thereafter. Adverse events will be monitored throughout the study and graded using CTCAE, version 5.0, guidelines. The primary end point is objective response rate based on RECIST v1.1 per BICR. Secondary efficacy end points for this study are clinical benefit rate, disease control rate, duration of response, progression-free survival, overall survival, and safety. Tertiary/exploratory end points are biomarker analysis and association with clinical response/disease etiopathogenesis. Clinical trial information: NCT04704219. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and Eisai Inc., Woodcliff Lake, NJ, USA.

TPS4596 **Poster Session**

PROSPER: Phase III RandOmized Study Comparing PERioperative nivolumab versus observation in patients with renal cell carcinoma (RCC) undergoing nephrectomy (ECOG-ACRIN EA8143). *First Author: Mohamad E. Allaf, James Buchanan Brady Urological Institute, Dept. of Urology, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: There is no standard adjuvant systemic therapy that increases overall survival (OS) over surgery alone for non-metastatic RCC. Anti-PD-1 nivolumab (nivo) improves OS in metastatic RCC and is well tolerated. In mouse models, priming the immune system prior to surgery with anti-PD-1 results in superior OS compared to adjuvant dosing. Remarkable pathologic responses have been seen with neoadjuvant PD-1 in multiple ph 2 studies in bladder, lung and breast cancers. Phase 2 neoadjuvant RCC trials of nivo show preliminary feasibility and safety with no surgical delays. PROSPER RCC seeks to improve clinical outcomes by priming the immune system with neoadjuvant nivo prior to nephrectomy followed by continued immune system engagement with adjuvant blockade in patients (pts) with high risk RCC compared to standard of care surgery alone. **Methods:** This global, unblinded, phase 3 National Clinical Trials Network study is accruing pts with clinical stage ≥T2 or $T_{any}N+$ RCC of any histology planned for radical or partial nephrectomy. Select oligometastatic disease is permitted if the pt can be rendered 'no evidence of disease' within 12 weeks of nephrectomy (≤3 metastases; no brain, bone or liver). In the investigational arm, nivo is administered 480mg IV q4 weeks with 1 dose prior to surgery followed by 9 adjuvant doses. The control arm is nephrectomy followed by standard of care surveillance. There is no placebo. Baseline tumor biopsy is required only in the nivo arm but encouraged in both. Randomized pts are stratified by clinical T stage, node positivity, and M stage. 805 pts provide 84.2% power to detect a 14.4% absolute benefit in recurrence-free survival at 5 years assuming the ASSURE historical control of ~56% to 70% (HR = 0.70). The study is powered to evaluate a significant increase in OS (HR 0.67). Critical perioperative therapy considerations such as safety, feasibility, and quality of life metrics are integrated. PROSPER RCC embeds a wealth of translational studies to examine the contribution of the baseline immune milieu and neoadjuvant priming with anti-PD-1 on clinical outcomes. As of February 10, 2021, 704 patients have been enrolled (N = 805). Clinical trial information: NCT03055013. Research Sponsor: U.S. National Institutes of Health, Bristol Myers Squibb.

TPS4597 **Poster Session**

A randomized phase II study of nivolumab plus ipilimumab versus standard of care in previously untreated and advanced non-clear cell renal cell carcinoma (SUNIFORECAST). *First Author: Marit Ahrens, Medical Clinic II, University Hospital, Frankfurt Am Main, Germany*

Background: Non-clear cell renal cell carcinomas (nccRCC) account for approximately 25% of RCC patients (pts.). Data on treatment strategies for this heterogenous group of RCC are still limited, since most clinical trials focus on clear-cell RCC (ccRCC) histology. Recently combination therapies with immune checkpoint inhibitors (IO, avelumab or pembrolizumab) and tyrosinekinaseinhibitors (TKI) (axitinib) have been approved for treatment in RCC in all International Metastatic RCC Database Consortium (IMDC) risk groups. Additionally nivolumab and ipilimumab (IO/IO) has been approved for treatment in intermediate and high risk pts. showing a significant improvement in overall response rate (ORR), progression free (PFS), and overall survival (OS) compared to sunitinib. Moreover retrospective analysis in nccRCC pts. have shown promising results for IO-based therapies as well in these entities. **Methods:** In this prospective randomized phase-II multicenter European trial adults with advanced or metastatic nccRCC without prior systemic therapy are eligible. Other key inclusion criteria include: available tumor tissue, Karnofsky >70% and measurable disease per RECIST 1.1. All histological diagnoses are reviewed by a central pathologist. The study plans to randomize ~306 pts. stratified for papillary or non-papillary non-clear cell histology and by the IMDC risk score. Pts. will be randomized 1:1 to either i) nivolumab 3mg/kg intravenously (IV) plus Ipilimumab 1mg/kg IV every 3 weeks for 4 doses followed by nivolumab fixed dose 240mg IV every 2 weeks or fixed dose 480mg IV every 4 weeks or ii) standard of care therapy according to the approved schedule. Treatment will be discontinued in case of unacceptable toxicity or withdrawal of informed consent. Pts may continue treatment beyond progression, if clinical benefit is achieved and treatment is well tolerated. Primary endpoint is the OS rate at 12 months. Secondary endpoints include OS rate at 6 and 18 months, median OS, PFS, ORR and quality of life. The trial is in progress and 214 patients (132 pts with papillary, 76 pts with non-papillary histology) have been enrolled until now. Clinical trial information: NCT03075423. Research Sponsor: Bristol-Myers Squibb.

TPS4598 **Poster Session**

Cyto-KIK: A phase II trial of cytoreductive surgery in kidney cancer plus immunotherapy (nivolumab) and targeted kinase inhibition (cabozantinib). *First Author: Karie Runcie, Columbia University Medical Center, New York, NY*

Background: Despite recent therapeutic advancements in metastatic renal cell carcinoma (mRCC), only 5-10% of patients will achieve a complete response (CR) to therapy. Cytoreductive nephrectomy removes a large portion of the tumor which may be a source of immunosuppression driven by tumor cell-intrinsic factors in the tumor microenvironment. A pre-clinical orthotopic mouse model of aggressive metastatic triple negative breast cancer showed that neoadjuvant anti-PD-1 checkpoint inhibition generated enhanced and sustained antitumor immune responses with improved survival compared to adjuvant therapy (Liu J et al. *Cancer Discov.* 2016:1382). Clinical validation of improved outcomes with neoadjuvant compared to adjuvant immune checkpoint inhibitors has been demonstrated in trials for patients with non-small cell lung cancer, advanced melanoma, and recurrent glioblastoma (Forde, P.M., et al. *N Engl J Med.* 2018:1976; Amaria, R.N., et al *Nat Med.* 2018:1649; Cloughesy T.F., et al. *Nat Med* 2019:477). Recent data from a phase III trial in subjects with untreated mRCC, demonstrated the superiority of combination cabozantinib and nivolumab over sunitinib and established a new standard of care for mRCC (Choueiri T.K., et al. *Annals of Onc*, 2020;31 (suppl; abstr 6960). We hypothesize that if tumor specific immune responses to immunotherapy are greatest prior to nephrectomy, then treatment with nivolumab (nivo) and cabozantinib (cabo) prior to cytoreductive nephrectomy will lead to maximal peripheral and intra-tumoral specific immune responses and higher rates of CR during the course of treatment. **Methods:** This is an open label phase II, multicenter clinical trial of combination nivo and cabo prior to cytoreductive nephrectomy in patients with mRCC (NCT04322955). 48 treatment- naïve subjects with radiological or histological diagnosis of mRCC will be enrolled with the primary endpoint of CR rate according to RECIST version 1.1. Subjects will receive cabo (40mg) daily and nivo (480mg) every 4 weeks for 12 weeks prior to nephrectomy and a 3+3 design will be used to evaluate the safety of the interval (21 or 14 days) between the discontinuation of cabo and nephrectomy. Post-operatively, subjects will resume treatment with cabo and nivo until evidence of disease progression. Secondary endpoints include median size reduction of the primary tumor, response rate, PFS, OS, and surgical outcomes using the Clavien-Dindo classification system. Tissue based assays will quantify treatment related changes in the renal tumor microenvironment through polychromatic immunofluorescence, single cell RNA sequencing of the biopsy and nephrectomy specimen, and multiplex assessment of circulating serum cytokines. Dynamic contrast-enhanced MRI will be performed in a subset of subjects to assess radiologic correlates of response. The study is currently open to enrollment. Clinical trial information: NCT04322955. Research Sponsor: Exelixis, Bristol-Myers Squibb.

TPS4599 **Poster Session**

A phase I study of bintrafusp alfa (M7824) and NHS-IL12 (M9241) alone and in combination with stereotactic body radiation therapy (SBRT) in adults with metastatic non-prostate genitourinary malignancies. *First Author: Scot Anthony Niglio, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: The majority of non- prostate genitourinary (GU) cancers are lethal when metastatic and rare GU cancers have limited treatment options. Bintrafusp alfa is a bifunctional fusion protein composed of human TGF-β receptor II, which sequesters or "traps" all three TGF-β isoforms and a monoclonal PD-L1 antibody. NHS-IL12 is an immunocytokine composed of two IL-12 heterodimers, each fused to the H-chain of the NHS76 antibody. The NHS76 IgG1 antibody has affinity for both single- and double-stranded DNA (dsDNA) allowing for targeted delivery of pro-inflammatory cytokine, IL-12, to necrotic portions of tumor with DNA exposure to promote local immunomodulation. Preclinical data suggest synergy between these two agents. There is also evidence suggesting that stereotactic body radiation therapy (SBRT) can promote anti-tumor immune responses both locally and systemically while also synergizing with immune checkpoint inhibitors. Therefore, the combination of Bintrafusp alfa, NHS-IL12 and radiation is a potential strategy for metastatic non-prostate GU tumors. **Methods:** This is an open label, non-randomized, three-stage phase I trial of bintrafusp alfa and NHS-IL12 or bintrafusp alfa and NHS-IL12 in combination with either sequential or concurrent SBRT. Bintrafusp alfa (IV 1200 mg q2w) and SBRT (8 Gy x 3 fractions) are planned with a deescalating NHS-IL12 (subQ q4w) dose schedule. The accrual ceiling has been set at 66 patients. The trial will enroll patients with a pathologically confirmed diagnosis of metastatic non-prostate genitourinary cancer with an ECOG $\leq$ 2 (KPS $\geq$60%). Participants may have had prior cancer immunotherapy but excluding prior treatment with bintrafusp alfa and/or NHS-IL12. 9 patients will receive treatment in cycles consisting of 4 weeks. The primary objective is to determine the safety and highest tolerated doses with acceptable toxicity (recommended phase II dose) of bintrafusp alfa and NHS-IL12 alone or in combination with SBRT administered sequentially or concurrently in patients with metastatic non-prostate genitourinary cancers. Secondary objectives are objective response rate (ORR), progression free survival (PFS) and overall survival (OS). Exploratory objectives are to determine peripheral immune modulation and the status of the immune microenvironment using cytokine analysis, circulating tumor cells, multiplex immunohistochemistry, T-cell receptor sequencing, and RNA-sequencing. The study is open and enrolling. Clinical trial information: NCT04235777. Research Sponsor: U.S. National Institutes of Health.

5000 **Oral Abstract Session**

A phase 3 trial with a 2x2 factorial design of abiraterone acetate plus prednisone and/or local radiotherapy in men with *de novo* metastatic castration-sensitive prostate cancer (mCSPC): First results of PEACE-1. *First Author: Karim Fizazi, Institut Gustave Roussy, University of Paris-Saclay, Villejuif, France*

Background: Historically, androgen deprivation therapy (ADT) was the standard of care (SOC) for men with mCSPC. Since 2015, combining ADT with either docetaxel, novel hormonal therapies, or radiotherapy to the primary tumor (RXT) (for those with low burden metastases) was shown to improve overall survival (OS) and thus has become the new SOC. It is unknown whether combining these new treatments on top of ADT further increments outcomes. **Methods:** Men with *de novo* mCSPC were randomized to SOC, SOC + abiraterone acetate-prednisone (abiraterone), SOC + RXT, or SOC + abiraterone + RXT. SOC was initially ADT alone, then from Oct 2015 onwards the use of docetaxel was authorized as part of SOC (at the investigator's discretion until 2017, then, following the publication of the LATITUDE and STAMPEDE trials, accrual was restricted to men receiving ADT+docetaxel). The trial has two co-primary endpoints of radiographic progression-free survival (rPFS) and OS with type I error of 0.1% and 4.9%, respectively. The required number of rPFS events to achieve 80% power has been reached for the abiraterone question (not yet for the RXT question). The interaction between abiraterone and RXT was first tested using a Cox model adjusted for stratification factors (performance status, type of castration, metastatic burden, and when applicable, docetaxel). A hierarchical testing was used to test the effect of abiraterone: overall population, then ADT+docetaxel population. Results: From Nov 2013 to Dec 2018, 1173 men were enrolled (SOC was ADT+docetaxel in 710 pts and ADT alone in 463 pts), median age 67y (IQR: 60-72), high volume 57%, low volume 43%. The median follow-up is 3.5y. No interaction was detected between the effect of abiraterone and that of RXT ($p = 0.64$), allowing to pool abiraterone arms for comparisons. rPFS was significantly improved in the abiraterone arm in the overall population (HR: 0.54 (0.46-0.64), $p < 0.0001$; medians: 2.2 vs 4.5 years) and in the ADT+docetaxel population: (HR: 0.50 (0.40-0.62), $p < 0.0001$; medians: 2.0 vs 4.5 years). bPFS (PFS including PSA progression as an event) also significantly favored abiraterone in the overall population (HR: 0.40 (0.35-0.47), $p < 0.0001$; medians: 1.5 vs 3.8 years) and in the ADT+docetaxel population (HR: 0.38 (0.31-0.47), $p < 0.0001$; medians: 1.5 vs 3.2 years). OS is maturing. Grade 3-4 adverse events reported in > 5% of pts within the first 6 months in the ADT+docetaxel population included neutropenic fever (4.5% vs 5.4%), liver toxicity (19.7% vs 13%), and hypertension (12.2% vs 8.6%) in the abiraterone and control arms, respectively. Conclusion: Adding abiraterone to ADT + docetaxel significantly improves rPFS in men with *de novo* metastatic prostate cancer, with about 2.5 years of absolute benefit in medians, and no meaningful additional short-term toxicity. Clinical trial information: NCT01957436. Research Sponsor: PHRC, Pharmaceutical/Biotech Company.

5001 **Oral Abstract Session**

SWOG S1216: A phase III randomized trial comparing androgen deprivation therapy (ADT) plus TAK-700 with ADT plus bicalutamide in patients (pts) with newly diagnosed metastatic hormone-sensitive prostate cancer (mHSPC) (NCT01809691). *First Author: Neeraj Agarwal, University of Utah, Salt Lake City, UT*

Background: Tak is an oral selective nonsteroidal 17, 20-lyase inhibitor that blocks the synthesis of gonadal and adrenal androgens. We evaluated the clinical benefit of Tak with ADT in pts with newly diagnosed mHSPC. **Methods:** Pts with mHSPC with a Zubrod performance status (PS) of 0-2 and a PSA of ≥ 2 ng/ml were randomized 1:1 to ADT+Tak (300 mg twice daily) or ADT+Bic (50 mg daily). Stratification factors included PS (0-1 vs ≥2), extent of disease (minimal vs extensive), and receipt of ADT prior to registration (yes vs no). The primary endpoint was overall survival (OS). Secondary endpoints were progression free survival (PFS; based on PSA, imaging or clinical progression), PSA at 7 months (≤0.2 vs $0.2 <$ PSA; ≤-4 vs. > 4 ng/ml) and adverse event (AE) profile. With 2.75 yrs to accrue 1,186 eligible pts and 3 additional yrs of follow-up, we would have 90% power to determine a 33% improvement in OS from 54 to 72 mos (1-sided $\alpha = 0.025$). A final analysis was pre-specified after 523 deaths using a 1-sided $\alpha = 0.022$ to account for interim analyses. **Results:** Between 3/2013 and 7/2017, 1,313 pts were randomized and 1,279 were included in the intention-to-treat (ITT) analysis (32 pts were ineligible and 2 pts withdrew consent). Median age was 68 yrs and 10% of subjects were Black. Median PSA was 30 ng/mL (range 2-6710) and 49% of pts had extensive disease. After a median follow-up of 4.9 yrs, PFS and PSA response were significantly improved with Tak over Bic but no significant improvement in OS was observed (Table). More grade 3/4 AEs occurred in Tak vs. Bic arms (43% vs. 14%), and included hypertension (20% vs. 5%) and fatigue (5% vs. 2%). Five pts in Tak and 1 pt in the Bic arm had grade 5 AE. **Conclusions:** Despite clinically meaningful improvement in various outcome measures with Tak+ADT over Bic+ADT in this representative population of mHSPC, the improvement in OS did not meet the pre-specified criteria for statistical significance. The median OS of 70 mos in the control arm (standard ADT) was higher than that reported in contemporary phase 3 trials in this setting, and 16 mos higher than originally estimated. This trial sets a new landmark for survival estimates when pts with mHSPC have access to multiple approved subsequent life-prolonging therapies. Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819, U10CA180820; U10CA180821; and in part by Millennium Pharmaceuticals, Inc. (Takeda Pharmaceutical Company LTD) Clinical trial information: NCT01809691. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Outcome	ADT + Tak (n = 638)		ADT + bic (n = 641)		HR (95% CI) P-value*
Median OS, mos (525 deaths)	81.1		70.2		0.86 (0.72, 1.02) P = 0.04
Median PFS, mos (787 events)	47.6		23.0		0.58 (0.51, 0.67) P < 0.0001
	PSA ≤ 0.2 ng/ml	0.2 < PSA≤4.0	PSA ≤ 0.2 ng/ml	0.2 < PSA≤4.0	P-value**
PSA response, N (%)	372 (58.3%)	142 (22.3%)	282 (44.0%)	201 (31.4%)	P < 0.0001

* One-sided; ** Two-sided from Cochran–Mantel–Haenszel statistic.

5002 **Oral Abstract Session**

Decreased fracture rate by mandating bone protecting agents in the EORTC 1333/PEACEIII trial combining Ra223 with enzalutamide versus enzalutamide alone: An updated safety analysis. *First Author: Silke Gillessen, Kantonsspital St. Gallen, St. Gallen, Switzerland*

Background: The randomized phase III EORTC-1333-GUCG (NCT02194842) trial compares enzalutamide vs. a combination of Radium 223 and enzalutamide in asymptomatic or mildly symptomatic metastatic castration resistant prostate cancer (mCRPC) patients. The premature unblinding of ERA223 (NCT02043678) in Nov 2017 due to a significant increase in the rate of fractures in the combination of abiraterone and Ra223 arm led to the implementation of the mandatory use of bone protecting agents (BPA) in the EORTC-1333-GUCG trial. Skeletal fractures, pathological or not, are a frequent and underestimated adverse event of systemic treatment of advanced prostate cancer. Whether this mandated use of BPA (zoledronic acid or denosumab) would mitigate the risk of fractures in this patient population was unclear. An early safety analysis (Tombal, ASCO, 2019) suggested that the risk of fractures was well controlled in both arms when patients receive BPA. We present here an updated analysis of fracture incidence with longer follow-up. **Methods:** As of 28/01/2021, a total of 253 patients (134 after making BPA mandatory) were randomized between enzalutamide/Ra223 and enzalutamide. The fracture rate was estimated with the cumulative incidence method in the safety population of 237 (122 after making BPA mandatory) treated patients. Death in absence of fracture was analyzed as competing risk and censoring was applied at last follow-up. **Results:** Overall, 69.5% of enzalutamide/Ra223 patients (95.2% after making BPA mandatory) and 73.1% of enzalutamide patients (95% after making BPA mandatory) received BPA on treatment: 13.6% in the enzalutamide/Ra223 arm and 21.8% in the enzalutamide arm did not use BPA at registration, but started during protocol treatment and 55.9% and 51.3% respectively, received BPA since entry. At 36.7 months median follow-up in patients without BPA and 23.1 months median follow-up in patients receiving BPA, a total of 39 patients reported a fracture. Among them, 30 patients (20 in enzalutamide/Ra223 arm) did not receive BPA and 9 (4 in the enzalutamide/Ra223 arm) received BPA (see table). **Conclusions:** The updated safety analysis confirms the early fracture rate results. In the absence of BPA, the risk of fracture is increased when RA223 is added to enzalutamide. Strikingly, in both arms, the risk remains almost abolished by a preventive continuous administration of BPA, thus stressing the importance of complying to international recommendations in terms of giving BPA to mCRPC patients. This study is sponsored by EORTC and supported by Bayer and Astellas. Clinical trial information: NCT02194842. Research Sponsor: Bayer-Astellas.

Cumulative incidence (%) of fractures (95% CI).

	Received BPA		No BPA	
	Enza+Ra223 (N=82)	Enza (N=87)	Enza+Ra223 (N=36)	Enza (N=32)
At 1 year	2.8 (0.5-8.8)	3.9 (1.0-10.1)	37.1 (21.3-53.0)	15.8 (5.6-30.7)
At 1.5 years	2.8 (0.5-8.8)	3.9 (1.0-10.1)	45.9 (28.6-61.6)	22.3 (9.6-38.2)

5003 **Oral Abstract Session**

Ancestral characterization of the genomic landscape, comprehensive genomic profiling utilization, and treatment patterns may inform disparities in advanced prostate cancer: A large-scale analysis. *First Author: Smruthy Sivakumar, Foundation Medicine, Inc., Cambridge, MA*

Background: Prostate cancer (PCa) incidence, mortality, and outcomes vary widely across race/ethnicity. The underlying drivers of these differences are multifactorial, including systemic barriers that lead to wide variation in access to care including genomic and precision medicine. Men of African ancestry (AFR) are particularly underrepresented in genomic and precision medicine studies. Therefore, we sought to comprehensively assess patterns of gene alterations, comprehensive genomic profiling (CGP) utilization, and treatment patterns in a large, diverse advanced PCa cohort. **Methods:** 11,741 PCa patients with CGP, as part of routine clinical care (Foundation Medicine Inc., FMI) were evaluated for their genomic landscape. Predominant ancestry was inferred using a SNP-based approach (Connelly et al, AACR 2018). Independently, the US-based de-identified Flatiron Health (FH)-FMI clinico-genomic database (CGDB) of 897 evaluable PCa patients was also queried. Clinical characteristics and treatment selections were described for patients who received metastatic or castrate-resistant diagnosis between 1/2011 and 6/2020. **Results:** The FMI cohort included 1,422 (12%) men of AFR and 9,244 (79%) men of European ancestry (EUR). Median age was lower in AFR compared with EUR men (64 vs. 67, $p < 0.001$). *TP53* and *PTEN* alterations and *TMPRSS2-ERG* rearrangements occurred less frequently in AFR than EUR men (35% vs. 43%, 21% vs. 33%, 15% vs. 33% respectively, $p < 0.05$). In contrast, alterations in *SPOP* (11.9% vs. 7.3%), *CDK12* (10.0% vs. 5.2%), *CCND1* (6.0% vs. 3.8%), *KMT2D* (7.7% vs. 5.1%), *HGF* (4.1% vs. 2.5%), and *MYC* (13.4% vs. 10.6%) were enriched in the AFR cohort ($p < 0.05$). Alteration frequency in *BRCA1/2*, *AR*, DNA damage response pathway genes, and actionable genes with therapy implications, were similar across ancestry. Of note, *BRAF* alterations were slightly enriched in AFR (5.0% vs. 3.2%, $p < 0.05$). In the CGDB cohort (79 AFR, 762 EUR), AFR men received a median of 2 lines of therapy prior to CGP, compared to 1 line for EUR men. Notably, the proportion of patients receiving immunotherapy and PARPi was similar across ancestry, however AFR men were less likely to receive clinical study drug compared with EUR men (11% vs 30%, $p < 0.001$), even among men with actionable alterations (1% vs 6%, $p < 0.001$). **Conclusions:** To our knowledge, this study encompasses the largest cohort, particularly of AFR men in a genomic study, that defines CGP utilization, the genomic landscape and therapeutic implications of CGP in PCa across ancestry. Overall, there were largely similar rates of actionable gene alterations across ancestry. Notably, AFR men were less likely to receive CGP earlier in their treatment course, and less likely to be treated on clinical trials, which could impact the genomic landscape, outcomes, and ultimately disparities. Research Sponsor: Foundation Medicine, Inc.

5004 **Oral Abstract Session**

Association of increased intensity of prostate-specific antigen screening in younger African American men with improved prostate cancer outcomes. *First Author: Edmund M. Qiao, Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA*

Background: African-American (AA) men are substantially more likely to present with lethal prostate cancer (PCa) at younger ages than non-Hispanic White men. Despite this disparity, AA men are poorly represented in the prostate-specific antigen (PSA) screening studies on which evidence-based PCa screening guidelines are based. This limits proper PSA screening guidance for AA men, especially for those younger than 55. We examined associations of PSA screening intensity with disease severity at diagnosis and prostate cancer-specific mortality (PCSM) in AA men $<$ 55 years of age. **Methods:** The earliest recommended age to begin discussion of PSA screening is 40 years. We identified AA men aged 40-55 years, diagnosed with PCa from 2004 to 2017 within the Veterans Health Administration. PSA screening was identified using procedural codes. Screening intensity was defined as percentage of years screened within the pre-diagnostic observation period. This included up to 5 years prior to diagnosis. Multivariable logistic regression assessed the influence of PSA screening intensity on metastatic disease at diagnosis. Lead-time correction using published screening-dependent lead times was performed. PCSM was evaluated using Fine-Gray regression and non-cancer death as a competing event. Additional analysis was performed stratifying PSA screening into 'High' and 'Low' groups centered on the mean. **Results:** The cohort included 4,654 AA men at a mean age of 51.8 years with mean PSA screening rate of 53.2%. The pre-diagnostic observation period ranged from 1 to 5 years (median = 5 years). Median follow-up was 7 years. At diagnosis, there was a higher prevalence of Gleason sum $\geq$ 8 (Grade Group $\geq$ 4) and metastatic disease in the 'Low' group compared with the 'High' group ([Gleason sum $\geq$ 8 (Grade Group $\geq$ 4)]: 18.6% vs. 14.4%, $p < 0.01$; Metastatic disease at diagnosis: 3.7% vs. 1.4%, $p < 0.01$). Increased PSA screening intensity was associated with significantly reduced odds of metastatic disease at diagnosis (odds ratio: 0.61, 95% confidence interval (CI) = [0.47-0.81], $p < 0.01$) and decreased risk of PCSM (sub-distribution hazard ratio: 0.75, 95% CI = [0.59-0.95], p = 0.02). **Conclusions:** In this large national cohort of AA men aged 40 to 55 years, PSA screening increased intensity was associated with decreased risk of lethal disease and metastases at time of diagnosis and decreased PCSM. These data support the hypothesis that PSA screening and early prostate cancer detection may improve outcomes in younger AA men. Research Sponsor: U.S. National Institutes of Health.

5005 **Oral Abstract Session**

A prospective validation of the genomic classifier to define high-metastasis risk in a subset of African American men with early localized prostate cancer: VanDAAM study. *First Author: Kosj Yamoah, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Risk stratification of prostate cancer (PC) using routine clinical variables remains suboptimal as they do not account for underlying tumor biology. The genomic classifier provides information on underlying biology and independently predicts an individual patient's risk of metastasis. Although the performance of the genomic classifier has been tested across different cohorts primarily comprised of White men, its validation as an optimal genomic risk classifier for African American men (AAM) is thus far lacking in a prospective trial. We report the initial results on the prospective validation of the genomic classifier in a matched cohort of AAM and non-AAM (NAAM). **Methods:** This was a multisite, prospective validation trial of the genomic classifier i.e. Decipher score in AAM. Participants were recruited on a 1:1 enrollment ratio of AAM to NAAM diagnosed with low-intermediate risk PC. Patient on active surveillance were ineligible. NAAM were matched to AAM on PSA, age, biopsy Gleason score, clinical stage, and percent positive biopsy cores. Diagnostic biopsy specimens were processed at a CLIA certified laboratory and Decipher score was assessed using whole transcriptome profiling platform. Total target accrual was 250 men treated for low-intermediate PC over three years. Statistical analyses include categorical comparison of race dependent risk group migration between NCCN risk group and genomic classifier. Relative risk of metastasis was estimated using negative binomial model. **Results:** Final analytical cohort included 207 evaluable cases (AAM = 102 and NAAM = 107) with comprehensive genomic information. Risk of metastasis was determined based on pretreatment biopsy Decipher score, and patients were classified as low, favorable-, and unfavorable intermediate risk. Despite achieving a robustly matched clinical cohort, we observed significant genomic heterogeneity between AAM and NAAM across NCCN risk groups. In a comparative analysis, 49% of low-favorable intermediate risk AAM harbored high genomic risk tumors as compared to only 10% NAAM, p = 0.02. Similarly, using the modified clinico-genomic risk classifier (cGC), comprised of both Decipher score and clinical variables, AAM experienced an extreme deviation of risk status (difference [δ] between cGC and NCCN $\geq$ 2) as compared to NAAM (26.8% vs 8.1%, p = 0.03). In a binomial model, low-favorable NCCN risk AAM were 3.9 times more likely to be reclassified as high genomic risk for distant metastasis compared to NAAM (RR = 3.99, 95% CI, 1.15 – 13.86, p = 0.02). **Conclusions:** Clinical NCCN risk classification is an inadequate surrogate of tumor biology and offers suboptimal risk stratification for AAM with PC. Integration of patient specific genomic classifier into standard of care will improve accuracy in disease risk classification and treatment recommendations for AAM. Clinical trial information: NCT02723734. Research Sponsor: U.S. National Institutes of Health.

5006 **Oral Abstract Session**

Testicular cancer in the cisplatin era: Causes of death and mortality rates in a population-based cohort. *First Author: Ragnhild Hellesnes, Department of Oncology, University Hospital of North Norway, Tromso, Norway*

Background: Previous studies have reported an increased risk of premature mortality in testicular cancer (TC) survivors, probably associated with previous platinum-based chemotherapy (PBCT) or radiotherapy (RT). However, complete data regarding PBCT cycles are lacking in available literature. Using complete TC treatment data, this population-based cohort study aimed to investigate non-TC mortality in relation to TC treatment. **Methods:** Overall, 5,707 men diagnosed with TC 1980-2009 were included, identified from the Cancer Registry of Norway. Clinical parameters and treatment data were abstracted from medical records and linked with the Norwegian Cause of Death Registry. Causes of death were classified by the European Shortlist. Standardized mortality ratios (SMRs) were calculated to compare the cause-specific mortality in the cohort to an age-matched general population. Age-adjusted hazard ratios (HRs) were estimated to evaluate the impact of number of PBCT cycles on non-TC mortality. **Results:** During a median follow-up of 18.7 years, 665 (12%) men were registered with non-TC death. The overall excess non-TC mortality was 23% (SMR 1.23, 95% CI 1.14-1.33) compared with the general population, with increased risks after PBCT (SMR 1.23, 95% CI 1.06-1.42) and RT (SMR 1.28, 95% CI 1.15-1.43), but not after surgery (SMR 0.95, 95% CI 0.79-1.14). SMRs increased significantly with increasing follow-up time $\geq$10 years, and the overall risk of non-TC death reached a maximum after $\geq$30 years follow-up (SMR 1.64, 95% CI 1.31-2.06). The most important cause of death was non-TC second cancer with an overall SMR of 1.53 (95% CI 1.35-1.73). Increased risks appeared after PBCT (SMR 1.43, 95% CI 1.12-1.83) and RT (SMR 1.59, 95% CI 1.34-1.89). Treatment with PBCT was associated with significantly 1.69-6.78-fold increased SMRs for cancers of the oral cavity/pharynx, esophagus, lung, bladder, and leukemia. After RT, significantly 3.02-4.91-fold increased SMRs emerged for cancers of the oral cavity/pharynx, stomach, liver, pancreas and bladder. Non-cancer mortality was also increased by 15% (SMR 1.15, 95% CI 1.04-1.27), and excesses appeared after PBCT (1.23, 95% CI 1.03-1.47) and RT (SMR 1.17, 95% CI 1.01-1.34). Importantly, we report excess suicides after PBCT (SMR 1.65, 95% CI 1.01-2.69). Long-term overall cardiovascular mortality was not increased in the study cohort nor according to treatment modality. Compared with surgery, the overall non-TC mortality was increased after 4 (HR 1.41, 95% CI 1.00-1.98) and $>$4 (HR 2.03, 95% CI 1.24-3.33) PBCT cycles after $>$10 years of follow-up. **Conclusions:** TC treatment with PBCT or RT is associated with significantly increased long-term non-TC mortality, with non-TC second cancer being the most important cause of death. Significantly elevated risks for non-TC mortality emerged after $\geq$4 PBCT cycles after $>$10 years of follow-up. Research Sponsor: Helse Nord (HNF1582-21).

5007 **Oral Abstract Session**

Late relapse of germ cell tumors: Detection and treatment outcomes. *First Author: Noah Hunter Richardson, Indiana University Department of Medicine, Indianapolis, IN*

Background: Late relapse (LR) of germ cell tumors (GCT) is defined as relapsed disease $>$ 2 years from initial treatment. LR remains a challenge both for optimal screening methods and treatment. We report the method of detection, treatments received, and outcomes in patients with LR GCT. **Methods:** The prospectively maintained Indiana University testicular cancer database was queried identifying 2712 pts with GCT treated at Indiana University from January 2000 to January 2019. Method of detection of LR was recorded along with site, treatment received, chemo-naive vs chemo-exposed LR, and survival outcomes. **Results:** 90 pts with LR were identified. Median age at LR was 35.2 yr (range, 19.2-56.8). Primary tumor site was testis in 88 (98%), retroperitoneum in 1 (1%), and mediastinum in 1 (1%). Chemo-exposed accounted for 42 (47%) and chemo-naïve for 48 (53%) of cases. Table compares clinical characteristics and survival outcomes of chemo-exposed vs. chemo-naïve late relapse. 62% of chemo-exposed LR were diagnosed with elevated AFP. For the 42 chemo-exposed LR pts, 2-yr PFS based on treatment: surgery vs. chemo vs surgery+chemo was 48% vs 10% vs 45% (p = 0.105). For the 48 chemo-naïve LR pts, 2-yr PFS based on treatment: surgery vs. chemo vs. surgery+chemo was 100% vs 74% vs 37% (p = 0.004). Next generation sequencing was available for 9 patients. No actionable findings were found. Tumor mutational burden was low in all patients where genomic testing was available. **Conclusions:** Most pts with chemo-exposed LR will be diagnosed with an elevated AFP. GCT pts require lifetime follow-up with annual physical exam and tumor markers. Surgical resection, when feasible, remains our preferred treatment for chemo-exposed LR as chemotherapy alone offers only brief responses. Pts with chemo-naïve LR have more chemo-sensitive biology. Research Sponsor: None.

Late Relapse (N = 90)	Chemo-exposed (N = 42)	Chemo-naïve (N = 48)
Time from initial chemotherapy to late relapse		
· 2-5yrs	21 (50%)	
· 5-10yrs	15 (36%)	
· > 10yrs	6 (14%)	
Method of detection of late relapse		
· AFP	26 (62%)	7 (15%)
· hCG	6 (14%)	5 (10%)
· Routine imaging	10 (24%)	24 (50%)
· Symptoms	3 (7%)	17 (35%)
Site of late relapse		
· Retroperitoneum	22 (52%)	31 (65%)
· Mediastinal LN	9 (21%)	7 (15%)
· Lung	7 (17%)	5 (10%)
· Liver	6 (14%)	0
Treatment of late relapse		
· Surgery only	13 (31%)	10 (21%)
· Chemotherapy only	10 (24%)	19 (40%)
· Surgery + Chemo	19 (45%)	16 (33%)
Status at last f/u		
· No evidence of disease	14 (33%)	36 (75%)
· Alive with disease	10 (24%)	2 (4%)
· Dead of GCT	15 (36%)	3 (6%)
· Dead of other cause	1 (2%)	1 (2%)
2- yr PFS (95% CI)	36.5% (21.7-51.4%)	70.1% (53.1-81.9%)
5-yr PFS (95% CI)	17.0% (6.1-32.7%)	70.1% (53.1-81.9%)
2- yr OS (95% CI)	70.5% (52.0-83.0%)	97.4% (82.8-99.6%)
5-yr OS (95% CI)	49.4% (29.3-66.7%)	88.0% (65.6-96.2%)

5008 **Poster Discussion Session**

The CADMUS trial: A paired cohort, blinded study comparing multiparametric ultrasound targeted biopsies with multiparametric MRI targeted biopsies in the detection of clinically significant prostate cancer. *First Author: Alistair Grey, University College London, London, United Kingdom*

Background: Multiparametric MRI (mpMRI) of the prostate followed by targeted biopsy is recommended in men at risk of prostate cancer. Dissemination of this pathway may be limited by cost, variable scan and reporting quality, and contraindicated in the presence of metallic implants and claustrophobia. Multi-parametric ultrasound (mpUSS) is a point of care test with low cost that combines b-mode, colour Doppler, elastography and contrast enhancement. CADMUS compared the diagnostic performance of mpUSS to mpMRI. **Methods:** CADMUS recruited 370 patients from seven sites to a prospective, multicentre, paired-cohort trial (ISRCTN 38541912). Ethics committee approval was obtained. Patients underwent both mpUSS and mpMRI independently, each with a positive test defined as a Likert score of >3. Those with either a positive mpUSS or mpMRI, or both, were advised to undergo targeted biopsies. Reporting of each scan was carried out blind to the other and prior to biopsy; patients advised for biopsy were blinded to which test was positive. The order of mpUSS and mpMRI targeting was randomised. Primary outcomes were proportion of positive tests and detection of clinically significant cancer (csPCa) defined as Gleason >4+3 of any length and/or maximum cancer core length of >6mm of any grade [PROMIS definition1]. **Results:** 306 completed both mpUSS and mpMRI. Agreement in lesion detection between mpUSS and mpMRI was 73.2% (kappa 0.06, p = 0.14). 257 with positive results on mpUSS, mpMRI or both had targeted biopsies. Agreement on detection of csPCa was 91.1% (expected 59.8%, kappa 0.78, $p < 0.01$) . Overall, mpUSS detected 4.3% fewer csPCa than mpMRI (95% CI = [-8.3%, -1.5%]; p = 0.042 [Bonferroni correction]). mpUSS detected 7.2% (6/83) csPCa missed by mpMRI; mpMRI detected 20.5% (17/83) csPCa that mpUSS missed. At a less stringent definition of significant cancer, Gleason grade >3+4 of any length (definition 3), agreement was 89.1% (expected 55.6%, kappa 0.75, $p < 0.01$) mpUSS detected 5.4% fewer definition 3 cancers than mpMRI overall. mpUSS detected 7% (7/99) definition 3 cancers that mpMRI missed; mpMRI detected 21% (21/99) definition 3 cancers that mpUSS missed. **Conclusions:** The CADMUS trial shows mpUSS has a diagnostic performance approaching that of mpMRI and significant cancer detection is improved by the use of both scans over mpMRI alone. Clinical trial information: 38541912. Research Sponsor: JP Moulton Charitable Foundation, Prostate Cancer UK, UCLH and Barts Charitable Trustees.

		Definition 1 detection by mpMRI		
		No cancer detected	Cancer detected	Total
Definition 1 detection by mpUSS	No cancer detected	174	17	191
	Cancer detected	6	60	66
	Total	180	77	257

5009 **Poster Discussion Session**

MRI and targeted biopsies compared to transperineal mapping biopsies for targeted ablation in recurrent prostate cancer after radiotherapy: Primary outcomes of the FORECAST trial. *First Author: Taimur T. Shah, Imperial College London, London, United Kingdom*

Background: Radiotherapy is a common and effective treatment for localised prostate cancer. However, recurrence of cancer can occur in 10-15% of men in the following 5 years. Most patients with recurrence are managed using hormonal therapy with associated systemic side-effects and subsequent development of castrate resistance. Salvage prostatectomy confers a high risk of urine incontinence and rectal injury. Accurately localising and ablating only areas of recurrence within the prostate might be effective with fewer side-effects. The FOcal RECurrent Assessment and Salvage Treatment (FORECAST) trial assessed this diagnostic and treatment pathway for men with radiorecurrent cancer (NCT01883128). **Methods:** We first compared the accuracy of multiparametric MRI (mp-MRI) and MRI-targeted biopsy in identifying areas of recurrent cancer to a transperineal template prostate mapping (TTPM) biopsy (Apr/2014-Jan/2018) in 181 patients from 6 UK centres. We then assessed the functional and cancer control outcomes of focally ablating areas of intraprostatic recurrence in 93 patients with localised or metastatic cancer (using cryotherapy or HIFU). Primary outcomes were sensitivity of mpMRI and MRI-targeted biopsies and urinary continence after focal ablation. A key secondary outcome was progression free survival (PFS) defined as no new metastases or hormone use (localised group only), or chemotherapy or further local treatment. **Results:** Of 181 men with suspicion of recurrence following radiotherapy, restaging whole-body imaging (Choline PET and Bone Scan) showed localised disease in 128 (71%), nodal disease only in 13 (7%) and 38 (21%) metastatic. The sensitivity of MRI-targeted biopsy was 92% (95%CI 83-97%). Specificity, and positive and negative predictive values, were 75% (95%CI 45-92%), 94% (95%CI 86-98%) and 65% (95%CI 38-86%). 4/72 (6%) cancers were missed on TTPM biopsies alone and 6/72 (8%) were missed on MRI-targeted biopsies alone. Overall sensitivity of mpMRI was 81% (95%CI 73-88%) using Likert score 4-5 to denote a positive test. Specificity, and positive and negative predictive values, were 88% (95%CI 73-98%), 96% (95%CI 90-99%) and 57% (95%CI 42-70%). In the 93 men undergoing focal ablation, urinary continence was preserved in 78/93 (84%); 5/93 (5%) had a CTCAE grade 3+ adverse events. There were no rectal injuries. With a median follow-up of 27.8 [SD 1.3] months, PFS was 66% [54-75] at 24-months. Metastases-free survival in the 73 men with localised disease was 80% [95%CI 68–88] at 24-months. There were no cancer specific deaths. **Conclusions:** Prostate mpMRI and MRI-targeted biopsies can accurately detect and localise recurrent prostate cancer following radiotherapy. Focal ablation to areas of intra-prostatic recurrence preserves continence in the majority of men with good cancer control. Clinical trial information: NCT01883128. Research Sponsor: Funded by Pelican Cancer Foundation, National Institute of Health and Research and the Medical Research Council [UK].

5010 **Poster Discussion Session**

Validation of the decipher genomic classifier (GC) in SAKK 09/10: A phase III randomized trial of dose-escalated salvage radiotherapy (SRT) after radical prostatectomy (RP). *First Author: Alan Dal Pra, Miller School of Medicine, University of Miami, Miami, FL*

Background: GC has been shown to independently prognosticate outcomes in prostate cancer. Herein, we validate the GC in a European randomized phase III trial of dose escalated SRT after RP. **Methods:** SAKK 09/10 (NCT01272050) randomized 350 patients with biochemical recurrence after RP to 64Gy vs 70Gy. No patients received androgen deprivation therapy (ADT) or pelvic nodal radiotherapy. A pre-specified statistical plan was developed to assess the impact of the GC on clinical outcomes. RP samples were centrally reviewed for the highest-grade tumor and those passing quality control (QC) were run on a clinical-grade whole-transcriptome assay to obtain the GC score (0 to 1; < 0.45, 0.45-0.6, > 0.6 for low-, intermediate-, and high, respectively). The primary aim of this study was to validate the GC for the prediction of freedom from biochemical progression (FFBP) using Cox multivariable analysis (MVA) adjusting for age, T-category, Gleason score, persistent PSA after RP, PSA at randomization, and randomization arm. The secondary aims were to evaluate the association of GC with clinical progression-free survival (CPFS) and use of salvage ADT. **Results:** Of 233 patients with tissue available, 226 passed QC and were included for analysis. The final GC cohort was a representative sample of the overall cohort, with a median follow-up of 6.3 years (IQR 6.0-7.2). GC score (continuous per 0.1 unit, score 0-1) was independently associated with FFBP (HR 1.14 [95% CI 1.03-1.25], p = 0.009). Higher GC scores were independently associated with CPFS, use of salvage ADT, and rapid biochemical failure (< 18 months after SRT). High- vs. low/intermediate-GC showed a HR of 2.22 ([95% CI 1.37-3.58], p = 0.001) for FFBP, 2.29 ([95% CI 1.32-3.98], p = 0.003) for CPFS, and 2.99 ([95% CI 1.50-5.95], p = 0.002) for use of salvage ADT. Patients with high-GC had 5-year FFBP of 45% [95% CI 32-59] vs 71% [95% CI 64-78] in low-intermediate GC. Similar estimates for GC risk groups were observed in the 64Gy vs 70Gy in GC high (5-year FFBP of 51% [95% CI 32-70] vs 39% [95% CI 20-59]) and in low-intermediate GC (75% [95% CI 65-84] vs 69% [95% CI 59-78]). **Conclusions:** This study represents the first contemporary randomized controlled trial in patients with recurrent prostate cancer treated with early SRT without ADT that has validated the prognostic utility of the GC. Independent of standard clinicopathologic variables and radiotherapy dose, patients with a high-GC were more than twice as likely than a lower GC score to experience biochemical and clinical progression and receive salvage ADT. This data confirms the clinical value of Decipher GC for tailoring treatment in the postoperative salvage setting. Research Sponsor: Decipher Biosciences.

5011 **Poster Discussion Session**

Radiation and androgen deprivation therapy with or without docetaxel in the management of non-metastatic unfavorable-risk prostate cancer: A prospective randomized trial. *First Author: Anthony Victor D'Amico, Dana-Farber Cancer Institute/Brigham and Women's Hospital, Boston, MA*

Background: For men with unfavorable-risk non-metastatic (M0) prostate cancer (PC) the addition of docetaxel to radical prostatectomy (RP) or radiation therapy (RT) and androgen deprivation therapy (ADT) has been studied in 6 randomized controlled trials with negative or inconclusive results. Specifically, an overall survival (OS) benefit with a non-significant reduction in PC-specific mortality (PCSM) has been observed in two of the 6 studieswhere > 80% of the patients had high-grade PC. A plausible hypothesis for the OS benefit and a non-significant reduction in PCSM is that docetaxel reduces PCSM in the small subset of men with low prostate-specific antigen (PSA)-producing, high-grade PC that may be resistant to conventional ADT while also reducing non-PCSM by reducing death from RT-induced cancers. Given that docetaxel even at low doses (i.e. 20 mg/m^2) is a potent radiosensitizer,it is plausible that it can sterilize cells that survive RT-induced damage and later develop into RT-induced cancers. Therefore, while docetaxel is not recommended when managing men with unfavorable-risk prostate cancer given inconclusive results from prior randomized trials, unstudied benefits may exist. **Methods:** This multicenter international randomized phase 3 trial (National Clinical Trial # 00116142) assigned 350 men with T1c-4N0M0 unfavorable-risk PC to receive ADT+RT and Docetaxel (60 mg/m^2 q3 weeks for 3 cycles before RT and 20 mg/m^2 weekly during RT) versus ADT+RT (1:1 ratio). Collection of data at each follow-up visit on second cancer incidence and survival status was recorded. We evaluated the treatment effect of adding docetaxel to ADT+RT on the primary endpoint of OS and the incidence of RT-induced cancers and explored whether the treatment effect impacted OS differed differently within PSA subgroups (< 4, > 20 versus 4-20 ng/mL) using the interaction test for heterogeneity adjusted for age and known PC prognostic factors. **Results:** After a median follow-up of 10.2 years, 89 men died (25.43%); of these 42 from PC (47.19%). While OS was not significantly increased on the docetaxel arm [restricted mean survival time over 10-years was 9.11 versus 8.82 years with a difference of 0.29 (95% CI: -0.19, 0.76) years (p = 0.22)], significantly fewer RT-induced cancers were observed [10-year estimates: 0.61% versus 4.90%: age-adjusted HR of 0.13: 95% CI: 0.02, 0.97; p = 0.046]. For men with a PSA < 4 ng/mL versus 4-20 ng/mL the treatment effect of adding docetaxel to ADT+RT on OS differed significantly [Adjusted HR: 0.27, 1.51; $p_{interaction}$ = 0.047] due to less PCSM on the docetaxel arm [0/13 (0.00%) versus 4/14 (28.57%)] among men with PSA < 4 ng/mL. **Conclusions:** Adding docetaxel to ADT+RT did not prolong OS in men with unfavorable-risk PC, but decreased RT-induced cancer incidence, and may prolong OS in the subgroup of men with a PSA < 4 ng/mL by reducing PCSM. Clinical trial information: NCT00116142. Research Sponsor: Sanofi-Aventis and Astra-Zeneca.

5012 **Poster Discussion Session**

Interim results of aasur: A single arm, multi-center phase 2 trial of apalutamide (A) + abiraterone acetate + prednisone (AA+P) + leuprolide with stereotactic ultra-hypofractionated radiation (UHRT) in very high risk (VHR), node negative (N0) prostate cancer (PCa).

First Author: Sean Matthew McBride, Memorial Sloan Kettering Cancer Center, New York, NY

Background: Standard of care in VHR PCa is radiation therapy (RT) with 18-36 months (mos) of androgen-deprivation therapy (ADT). With this regimen, chronic ADT toxicity is significant and biochemical recurrence (BCR) frequent. We sought to improve tumor control and minimize toxicity with intensified short course ADT with dual androgen receptor signaling inhibitors (ARSI) and UHRT. **Methods:** 64 patients (pts) with VHR, N0 PCa were enrolled from 4 centers. VHR PCa was defined as Gleason score (GS) 9-10, >4 cores of GS 8 disease, or 2 high-risk features (including rT3/T4 disease). Treatment (tx) involved 6 mos of A, AA+P, and leuprolide with prostate/seminal vesicle-directed RT (7.5-8 Gy x 5 fractions). The primary endpoint was BCR defined as nadir PSA + 2ng/mL. Biochemical recurrence-free survival (bRFS) is reported herein. Our hypothesized reduction in BCR from 25% to 10% at 3 years (yrs) required 53 pts to provide a power of 0.84 and an alpha of 0.03. Undetectable PSA was defined as <0.10 ng/mL. Non-castrate testosterone (T) was a post-tx value >150 ng/mL. All analyses were intention-to-treat. Toxicity and health-related quality of life measures were evaluated using CTCAEv4.0 and the EPIC-26 questionnaire. **Results:** Baseline characteristics are summarized in the Table; 63 of 64 pts completed protocol tx. Median time to nadir PSA from tx start was 2 mos (range, 1-9); 63 of 64 pts (98.4%) achieved an undetectable nadir PSA. Median time to post-tx, non-castrate T was 6.5 mos (range, 2.5-25.5). Median follow-up (f/u) for pts without BCR was 30 mos (range, 15-44). Seven pts had BCR; 2-yr bRFS was 95.0% (95% CI, 89.7-100); 3-yr bRFS was 89.7% (95 CI, 81.0-99.3). For the 57 pts without BCR, 56 (98.2%) had T > 150ng/mL at last f/u; median PSA at last f/u was 0.10 ng/mL (IQR, <0.10-0.30); of these, 40 (70.2%) pts had PSAs ≤ 0.20 ng/mL with 24 (42.1%) undetectable. Fifteen pts experienced transient Grade 3 toxicities: 12 (18.8%) with hypertension and 3 with rash (4.7%). EPIC-26 scores for a subset of pts (n=21) at baseline and 12 mos showed no significant decline in urinary or bowel domains; declines in sexual (-11.9) and hormone (-5.7) domains met significance. **Conclusions:** Compared to historic controls with the long course ADT, AASUR demonstrated impressive 3-yr bRFS, rapid T recovery, and limited toxicities; the safety profile of this regimen was consistent with the known AE profile of the ARSI and RT. This regimen warrants further, randomized evaluation. Funded by Janssen Pharmaceuticals. Managed by the Prostate Cancer Clinical Trials Consortium. Clinical trial information: NCT02772588. Research Sponsor: Janssen Pharmaceuticals.

Age, yrs	69 (50-90)
PSA at Screening, ng/dL	12.0 (3.1-209.5)
Gleason Score (GS) at Diagnosis	N (%)
GS 6-7	5 (7.9)
GS 8	14 (21.9)
GS 9-10	45 (70.3)
Radiographic T Stage (MRI)	N (%)
T2	45 (70.3)
T3a	12 (18.7)
T3b	7 (10.9)

5013 **Poster Discussion Session**

Results of an ongoing phase 1/2a dose escalation study of HPN424, a tri-specific half-life extended PSMA-targeting T-cell engager, in patients with metastatic castration-resistant prostate cancer (mCRPC).

First Author: Johann S. De Bono, The Institute of Cancer Research and Royal Marsden Hospital, London, United Kingdom

Background: HPN424 is a prostate-specific membrane antigen (PSMA)-targeting T cell engager designed to redirect T cells to kill PSMA-expressing prostate cancer cells; engineered with three binding domains: anti-PSMA for tumor cell engagement, anti-albumin for half-life extension and anti-CD3 for T cell engagement. HPN424 is optimized for small size and increased stability compared to other bispecific platforms. **Methods:** This Ph1/2a study is evaluating HPN424 in mCRPC patients (pts) who have received > 2 prior systemic therapies. Primary endpoints are safety, tolerability and determination of MTD/RP2D. Secondary objectives are pharmacokinetics (PK), pharmacodynamics, immunogenicity and preliminary anti-tumor activity. HPN424 is administered IV once weekly. Tumor assessments include PSA, CT and bone scans every 9-weeks. **Results:** As of 2/8/21, 80 pts were dosed in 15 cohorts with target doses ranging from 1.3 to 160ng/kg fixed dose, and up to 300ng/kg with step dosing to the target dose after initial priming dose. Pts had received a median of 6 prior systemic regimens, 75% received prior chemotherapy for mCRPC. Median age was 70 (43 – 91). Most common grade > 3 TEAEs were AST increase (18%), anemia (11%) and ALT increase (11%). DLTs include CRS G3 (n = 3), elevated lipase G3 (n = 1) and seizure G3 (n = 1). These events did not limit escalation, MTD has not been reached and escalation continues. All grade CRS occurred in 63% of pts, 4% grade 3 per ASTCT and no Grade 4/5 CRS. CRS G3 events occurred after first administration of target dose (n = 2 fixed dose, n = 1 step dose). Transaminase elevation occurred predominantly during Cycle 1, was transient and had no clinical sequelae. Disease progression was the primary reason for drug discontinuation; 2 pts (3%) discontinued due to TRAE. Reduction in circulating tumor cells (CTC) was seen in 32 of 56 pts (57%) with measurable CTC at baseline. Fifteen of 62 pts (24%) with > 24 weeks follow-up remained on treatment ≥ 24 weeks. Thirteen of 63 pts (21%) with post-baseline levels had PSA declines from baseline, including 3 PSA50, 2 PSA30 responses. In chemo-naïve pts, 5 of 15 (33%) showed PSA declines post-baseline. In the highest fixed dose cohort (160ng/kg) tested to-date, 3 of 7 evaluable pts had PSA declines from baseline and 1 had a confirmed partial response per RECIST. **Conclusions:** HPN424, a novel half-life extended PSMA-targeting T cell engager, was well tolerated when administered once weekly. AEs were transient, manageable and consistent with class of agent. Grade 3 CRS was observed in 4% of patients, occurring with first administration of target dose. Evidence of antitumor activity included PSA and CTC reductions and treatment duration > 24 weeks in 15/62 pts. Encouraging signals were seen at the highest fixed dose cohort including a confirmed RECIST partial response. NCT03577028 Clinical trial information: NCT03577028. Research Sponsor: Harpoon Therapeutics.

5014 **Poster Discussion Session**

COMBAT-CRPC: Concurrent administration of bipolar androgen therapy (BAT) and nivolumab in men with metastatic castration-resistant prostate cancer (mCRPC).

First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD

Background: During BAT, intramuscular (IM) testosterone (T) is administered, which results in rapid cycling of serum T levels from supraphysiologic to near-castrate in men with metastatic castration resistant prostate cancer (mCRPC). We previously observed anecdotal clinical responses to immune checkpoint blockade (ICB) in mCRPC patients (pts) previously treated with BAT and hypothesized that that a BAT/ICB combination would be synergistic. Here we report a prospective phase 2 study of men with mCRPC treated with BAT in combination with nivolumab. **Methods:** This was a multi-center, single arm, open label phase 2 trial (NCT03554317) of men with mCRPC who received T cypionate 400mg IM (BAT) every 28 days and nivolumab 480mg IV every 28 days. LHRH agonist treatment was continued. All pts received BAT as single agent therapy for a 12-week lead-in prior to the addition of nivolumab. Eligible pts were those with asymptomatic mCRPC who had soft tissue disease amenable to biopsy and progressed on at least one prior novel AR targeted therapy. Up to one line of chemotherapy was allowed for the treatment of mCRPC disease. The primary endpoint was confirmed PSA_{50} response rate. Key secondary endpoints included safety, objective response rate (ORR), and radiographic progression-free survival (rPFS). The trial was designed to detect a 20% absolute increase in PSA_{50} response rate from the null of 25%. **Results:** 45 pts were enrolled on study and treated. The confirmed PSA_{50} response rate was 40.0% (N=18/45, 95% CI: 26-56%, P=0.02 against the 25% null hypothesis). For pts with measureable disease, the ORR was 23.8% (N=10/42). Median rPFS on BAT and nivolumab was estimated at 5.7 months (95% CI: 4.9-7.8 months). 11.1% (N=5/45) of pts were free from radiographic progression for 11 or more months. One patient achieved a complete radiographic response, which is ongoing (>13 months). The majority of adverse events (AE) were Grade <2. The most common AEs were edema (20%), nausea (20%), and back pain (13%). Immune related AE (irAE) were generally mild (Grade <2) with N=2 Grade 3 irAE observed (pericarditis, lipase elevation). Serial biopsies were obtained on trial for translational studies. **Conclusions:** BAT plus nivolumab was well tolerated without concerning safety signals. The combination met the pre-specified primary endpoint of confirmed PSA_{50} response in a heavily treated population. Durable responses were observed in a subset of pts. Biomarker analysis is ongoing to identify a molecular signature predictive of response. Clinical trial information: NCT03554317. Research Sponsor: Bristol-Myers Squibb, Other Foundation.

	N = 45
Age (years)	
Median	69
Baseline PSA (ng/mL)	
Median	57.6
Lines of Prior Novel AR Targeted Therapy, N (%)	
1	21 (46.7%)
>2	24 (53.3%)
Prior Taxane Chemotherapy, N (%)	
Yes	20 (44.4%)
No	25 (55.6%)
Confirmed PSA50 RR	40.0% (N=18)
Objective RR (N=41)	23.8% (N=10)
Radiographic PFS (months)	5.7 (95% CI:4.9-7.8)

5015 **Poster Discussion Session**

Phase I study of ^{225}Ac-J591 for men with metastatic castration-resistant prostate cancer (mCRPC).

First Author: Scott T. Tagawa, Weill Cornell Medicine, New York, NY

Background: Antibodies and small molecule ligands target PSMA with different kinetics and biodistribution, with certain sites of PSMA expression such as salivary/lacrimal glands, kidneys, and small bowel less accessible to large antibodies. Alpha emitters such as ^{225}Ac have high potency, but short range. We report dose-escalation plus expansion cohort results of a first in human study of ^{225}Ac-J591. **Methods:** Men with progressive mCRPC following at least 1 potent AR-pathway inhibitor (ARPI, e.g. abi/enza) and chemo (or unfit/refuse chemo) without limit of # prior therapies (including Ra-223 or prior ^{177}Lu-PSMA) provided adequate organ function were eligible. Baseline ^{68}Ga-PSMA11 PET was performed, but not used for eligibility. Dose-escalation was in single-subjects x4 followed by 3+3 with a single infusion of ^{225}Ac-J591 (13.3 KBq/kg with planned escalation up to 93.3 KBq/kg). Dose-limiting toxicity (DLT) was defined as attributable grade (Gr) 4 heme toxicity or Gr 3/4 non-heme tox. Imaging, genomic, patient-reported outcomes (PRO), and immune correlates embedded. **Results:** 32 men were treated with a single dose of ^{225}Ac-J591 on 7 dose levels with expansion at the highest dose level (n = 16). Median age 69.5 (range 52-89), PSA 149.1 (4.8-7168.4); 75% with >2 prior ARPI, 62.5% chemo, 28% Ra-223, 43.7% ^{177}Lu-PSMA. One (3.1%) CALGB (Halabi) good prognostic risk, 8 (25%) intermediate, and 23 (71.9%) poor risk. While PSMA uptake was not a prerequisite for treatment, of 28 with pre-treatment PSMA PET, none had tumor SUVmax < liver, 5 (17.8%) with tumor SUVmax 1-2.5x liver, 2 (7.2%) with tumor SUVmax 2.5-5x liver, and 21 (75%) with tumor SUVmax > 5x liver SUVmean. 1 of 6 in cohort 6 (80 KBq/kg) had DLT (Gr 4 anemia and platelets) with 0 of 6 at the highest dose level (93.3 KBq/Kg) and this dose was expanded. High Gr AEs were restricted to hematologic: In addition to DLT, 4 (12.5%) Gr 3 platelets and 2 (6.2%) with Gr 3 neutropenia. Non-heme AE's were restricted to Gr 1/2 and included: 10 (31.2%) fatigue, 5 (15.6%) pain flare, 14 (43.7%) nausea, 8 (25%) with Gr 1 xerostomia (of which 5 received prior ^{177}Lu-PSMA), 12 (37.5%) AST elevation. Despite prior treatment including ^{177}Lu-PSMA and no selection for PSMA expression, 22 (68.7%) with any PSA decline, 12 (37.5%) with > 50% PSA decline. Of 21 with paired baseline and 12-wk CTC counts, 12 declined (5 converting from unfavorable to favorable and 5 converting detectable to 0), 5 remained 0, 4 increased. In the subset with PRO data, pain scores by BPI-SF tended to improve by wk 12. Following a single dose of ^{225}Ac-J591, median PFS 7.2 months [95% CI 4.6-NR], median OS 10.9 months [7.6-21.1]. **Conclusions:** PSMA-targeted alpha-emitter ^{225}Ac utilizing intact antibody J591 is tolerable with early evidence of clinical activity. Based upon these results, a follow up study [NCT04506567] testing multiple and fractionated dosing of ^{225}Ac-J591 is underway. Clinical trial information: NCT03276572. Research Sponsor: Weill Cornell Medicine, Other Foundation, Other Government Agency, U.S. National Institutes of Health.

5016 **Poster Discussion Session**

Hearing loss after cisplatin-based chemotherapy: Patient-reported outcomes versus audiometric assessments. *First Author: Shirin Ardeshirrouhanifard, Indiana University School of Medicine, Indianapolis, IN*

Background: Although pure-tone audiometry is the gold standard to evaluate hearing loss (HL), patient-reported outcomes are practically more time and cost effective. However, no data exist on factors associated with discrepancies between patient-reported and audiometrically-defined HL in adult-onset cancer survivors after cisplatin-based chemotherapy (CBCT); and few comprehensive assessments of factors associated with audiometrically-defined HL have been conducted. **Methods:** A total of 1,410 testicular cancer survivors (TCS) ≥6 months post-CBCT completed comprehensive audiometric assessments (0.25-12 kHz) and detailed questionnaires of sociodemographic, clinical, and health behaviors. Audiometrically-defined HL severity was defined using American Speech-Language-Hearing Association (ASHA) criteria. Multivariable multinomial logistic regression identified factors associated with discrepancies (overestimation and underestimation vs. concordance), between patient-reported and audiometrically-defined HL and multivariable ordinal logistic regression evaluated factors associated with the HL severity. **Results:** Overall, 34.8% of TCS self-reported HL, while 77.8% had audiometrically-defined HL. Among TCS without tinnitus, those with audiometrically-defined HL at only extended high frequencies (EHFs) (10-12 kHz) (17.8%) or at both EHFs and standard frequencies (0.25-8 kHz) (23.4%) were significantly more likely to self-report HL than those with no audiometrically-defined HL (8.1%) (OR = 2.48; 95%CI, 1.31-4.68 and OR = 3.49; 95%CL,1.89-6.44, respectively). Older age (OR = 1.09; $P<$ 0.0001), absence of prior noise exposure (OR = 1.40; $P=$ 0.02), and mixed/conductive HL (OR = 2.01; $P=$ 0.0007) were associated with greater underestimation of audiometrically-defined HL severity. Hearing aid use (OR = 0.18; $P=$ 0.003) and higher education ($P=$ 0.004) were associated with less underestimation of audiometrically-defined HL severity, while tinnitus was associated with greater overestimation ($P<$ 0.0001). Older age (OR = 1.13; $P<$ 0.0001), cumulative cisplatin dose ($>$ 300 mg/m^2, OR = 1.47; $P=$ 0.0001), and hypertension (OR = 1.80; $P=$ 0.0007) were associated with greater ASHA-defined HL severity, whereas post-graduate education (OR = 0.58; $P=$ 0.005) was associated with less severe HL. **Conclusions:** Discrepancies between patient-reported and audiometrically-defined HL after CBCT are associated with several factors including age, education, tinnitus, prior noise exposure, use of hearing aids, and conductive HL. Understanding these factors will help clinicians to better interpret self-reported HL as a surrogate for audiometric assessments. For survivors who self-report HL, but have normal audiometric findings at standard frequencies, referral to an audiologist for additional testing and inclusion of EHFs in audiometric assessments, should be considered. Research Sponsor: U.S. National Institutes of Health.

5017 **Poster Discussion Session**

Immunity to childhood vaccines following high dose chemotherapy (HDCT) and autologous stem cell transplantation (ASCT) for germ cell tumors (GCT) with comparison to Hodgkin lymphoma (HL). *First Author: Darren R. Feldman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: HDCT/ASCT represents a curative salvage treatment for patients with GCT but is rarely used for other solid tumors. Patients undergoing HDCT/ASCT for hematologic neoplasms require revaccination for their childhood immunizations. Whether this is necessary in patients with GCT is unknown. **Methods:** In this prospective longitudinal study, patients with GCT undergoing HDCT-ASCT from 11/2010 to 5/2018 had serologies for Measles, Mumps, Rubella, Diphtheria, Tetanus, Polio, and Varicella Zoster measured before HDCT and at 3, 6, and in a subset, 12+ months after the last HDCT with results at these timepoints compared using descriptive statistics. In addition, titer levels at ≥6 months post-transplant were matched 1:1 for age and gender with HL patients who underwent HDCT/ASCT during the same time period. Immunity was compared between cohorts using the Cochran-Mantel-Haenszel test. **Results:** Of 80 patients with GCT (median age 30, 84% nonseminoma), 91% received 3 sequential transplants and 68 had repeat titers at ≥6 months. Immunity at baseline was >95% for Diphtheria, Tetanus and Polio and 89% for Varicella Zoster but lower for Measles (74%), Mumps (85%), and Rubella (83%) (Table). Compared to baseline, proportional immunity for all infections was similar at 3, 6, and 12 months post-transplant in the GCT population (≥6 months shown in Table). Matching resulted in 58 GCT-HL pairs. One-year immunity was numerically lower for most infections in the HL vs. GCT patients and significantly decreased for Measles and Rubella (Table). **Conclusions:** To our knowledge, this is the first study to assess vaccine titers following HDCT/ASCT for GCT. We demonstrate that HDCT/ASCT does not result in loss of immunity to childhood vaccines and that GCT patients retain protective titers more frequently than those with HL. However, 15-31% of GCT patients lack MMR immunity at baseline and at 1-year post-ASCT. Therefore, we recommend checking MMR titers at 1-year post-ASCT with revaccination of those lacking immunity. Titer evaluation and revaccination is not necessary for other childhood immunizations. Research Sponsor: Craig D. Tifford Fund and the The Louise B. Blackman Foundation.

Proportion of patients with immunity to childhood vaccines.

	GCT Cohort				Matched GCT/HL Cohorts at ≥ 6 months				
	Baseline		≥ 6 months		GCT		HL		
Disease/Vaccine	N	N (%)	N	N (%)	N	N (%)	N	N (%)	P
Diphtheria	78	78 (100)	68	68 (100)	58	58 (100)	58	57 (98)	0.32
Tetanus	80	78 (98)	67	66 (99)	58	57 (98)	57	54 (95)	0.30
Polio 1	79	75 (95)	68	64 (94)	58	55 (95)	58	52 (90)	0.29
Polio 3	79	77 (98)	68	68 (100)	58	58 (100)	58	58 (100)	-
Measles	80	59 (74)	65	47 (69)	58	42 (72)	58	28 (48)	0.03
Mumps	79	67 (85)	68	56 (82)	58	49 (85)	58	43 (74)	0.37
Rubella	80	80 (83)	68	52 (77)	58	48 (83)	58	37 (64)	0.05
Var. zoster	80	71 (89)	68	58 (87)	58	50 (86)	55	45 (82)	0.57

5018 **Poster Discussion Session**

Surveillance after complete response in patients with metastatic non-seminomatous germ-cell tumor (NSGCT). *First Author: Jennifer King, Indiana University School of Medicine, Indianapolis, IN*

Background: The optimal management of patients (pts) with complete response (CR) after first-line chemotherapy remains unsettled with guidelines recommending either surveillance or retroperitoneal LN dissection (RPLND). We present long-term outcomes from a large dataset of pts managed with surveillance after achieving CR to first-line chemotherapy. **Methods:** The prospectively maintained Indiana University testicular cancer database was queried for pts with metastatic NSGCT treated between 1990-2017 who achieved a CR after first-line chemotherapy. CR was defined as normalization of tumor markers (AFP+hCG) and no residual mass > 1cm. Kaplan-Meier methods were used to analyze progression-free survival (PFS) and overall survival (OS). **Results:** 388 pts met eligibility and were included in this analysis. Median age at diagnosis was 28.4 (range, 13-61.5). Primary site was testis in 385 pts (99%). Primary tumor predominant histology was embryonal ca (241), mixed (61), seminoma (31), yolk sac tumor (20), choriocarcinoma (10), and teratoma (14). 126 pts (32.5%) had teratoma in the primary tumor. Metastasis sites were retroperitoneum (295), mediastinal LN (15), pulmonary (149), liver (15), bone (7), and brain (6). IGCCCG risk was good in 325, intermediate in 25, and poor in 32 pts. Pre-chemotherapy retroperitoneal LN size was available in 232 pts: < 3cm in 170 and ≥3cm in 62. Median pre-chemo AFP was 10.7 (1-31,000) and hCG was 16.5 (0-595,930). First-line chemo was BEPx3 in 274, BEPx4 in 30, other regimens in 82 pts. With a median follow-up of 3.9 yrs, 34 pts (8.8%) progressed. At most recent follow-up, 363 (93.6%) pts were alive with no evidence of disease and 10 pts (2.6%) died of their disease. The estimated 2-yr PFS was 90.1% (95% CI: 86.2-93%) and 2-yr OS was 97.8% (95% CI: 95.2-99%). The estimated 2-yr PFS by IGCCCG risk category was 90.4% for good vs 90.4% for intermediate vs 86.5% for poor risk (p = 0.23), and the estimated 2-yr OS was 98.6% for good vs 95.5% for intermediate vs 92.9% for poor risk disease respectively (p = 0.002). For the 34 pts who progressed on surveillance, 16 (4%) progressed in the retroperitoneum only. 3 pts had malignant transformation of teratoma to PNET, adenocarcinoma, or other elements. 11 of progressed pts were treated with surgery, 12 were treated with salvage chemo, and 11 were treated with surgery+chemo. At most recent follow up, 21 of progressed pts had NED, 10 had died of disease, and 3 were lost to follow up. **Conclusions:** Pts with metastatic NSGCT who achieve CR after first-line chemotherapy can be safely observed with surveillance. Most pts who relapse can be salvaged with surgery and/or chemotherapy. Research Sponsor: None.

5019 **Poster Discussion Session**

Effect of pretreatment central adiposity on the cardiometabolic risk of male germ cell tumor survivors after cisplatin-based chemotherapy. *First Author: Andreas Georg Wibmer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Preferential fat accumulation in the visceral compartment (i.e. central adiposity) increases cardiovascular risk in the general population independent of body mass index (BMI). We investigated how body fat distribution modulates the cardiometabolic risk of male germ cell tumor (GCT) survivors after cisplatin-based chemotherapy. **Methods:** For 456 patients in The Platinum Study enrolled at Memorial Sloan Kettering Cancer Center, visceral (VAT) and subcutaneous (SAT) adipose tissue compartments were quantified on pre-chemotherapy computed tomography (CT) scans (median time between CT and chemotherapy: 13 days, range: 0-56). The VAT/SAT ratio was calculated as a quantitative indicator of central adiposity. Endpoints were (I) post-chemotherapy cardiovascular risk as per the office-based Framingham risk calculator, and (II) incidence of post-chemotherapy cardiometabolic disease defined as need for new anti-hypertensive drugs, or lipid-lowering drugs, or medication used to treat diabetes. Changes in fat distribution after chemotherapy were analyzed in a subgroup with post-chemotherapy CTs (n = 108; median interval from chemotherapy start: 18 months, range: 7-185). Linear regression with interaction terms (endpoint 1, subgroup analysis) and Cox proportional hazard regression (endpoint 2) were applied. **Results:** For all 456 patients, median age at chemotherapy initiation was 31 years and median follow-up was 27 months (range: 7, 207). At baseline (pre-chemotherapy), the median BMI was 26.2 kg/m^2, and 102 patients (22.4%) had a BMI of ≥30 kg/m^2. The median VAT/SAT ratio at baseline CT was 0.49, and positively associated with higher post-chemotherapy Framingham risk scores after adjustment for age, BMI, and blood pressure measurements at chemotherapy start, as well as post-therapy follow-up time (adjusted β-estimate: 1.36, 95% CI: 1.15, 1.59, p < 0.001). A higher VAT/SAT ratio also inferred a higher likelihood of new onset cardiometabolic disease in patients with BMI ≥30 kg/m^2 (age-adjusted HR: 3.11, 95%CI: 1.01, 9.62, p = 0.048), but not in those with BMI < 30 kg/m^2. In the subgroup analysis, we observed a significant increase of BMI after chemotherapy (mean: +1.1 kg/m2, 95% CI: +0.58, +1.54; p < 0.001). Changes in BMI were positively associated with changes of the VAT/SAT ratio (β-estimate: 3.0, 95% CI: 2.23, 4.04; p < 0.001), meaning that weight gain occurred preferentially in the VAT compartment, while weight loss tended to be paralleled by an improved body fat distribution. **Conclusions:** In male GCT patients, central adiposity at baseline increases cardiometabolic risk after cisplatin-based chemotherapy, particularly for obese individuals. Quantification of an individual's body fat distribution on pre-chemotherapy CT could potentially help to identify high risk individuals who may benefit from intensified risk-modulating interventions. Research Sponsor: None.

5020 **Poster Session**

Concordance of DNA damage repair (DDR) gene mutations in paired primary and metastatic prostate cancer (PC) samples. *First Author: Michael Thomas Schweizer, University of Washington/Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Mutations in DDR genes represent actionable alterations that can be used to guide precision medicine strategies in men with advanced PC. However, acquisition of contemporary tissue samples for advanced molecular testing can be a barrier to deploying precision medicine approaches. We hypothesized that most DDR alterations represent early truncal events in PC and that archival primary tissue would faithfully reflect mutations found in cell-free circulating tumor (ctDNA) and/or metastatic tissue. **Methods:** Patients were included in this study if a DDR pathway mutation was detected in metastatic tissue or ctDNA and primary tissue sequencing was available for comparison. Sequencing data from three cohorts were analyzed: 1) FoundationOne, 2) University of Washington (UW-OncoPlex or SU2C/PCF International Dream Team sequencing pipelines) and 3) University of Washington rapid autopsy series. Only pathogenic somatic mutations were included and we required ≥30 days between primary tumor tissue and ctDNA/tumor tissue acquisition. Clonal hematopoiesis of indeterminant potential (CHIP) and germline events were adjudicated by an expert molecular pathologist and excluded. Variants detected only in plasma were considered likely to be CHIP or low subclones if the variant fraction was <1% and/or >5-fold less than the estimate tumor content in plasma. **Results:** Paired primary and ctDNA/metastatic samples were sequenced from 72 individuals with known DDR alterations. After excluding ctDNA cases where only CHIP (N=13) and/or germline events (N=7) were observed, 51 subjects remained and were included in the final analysis. The median time from acquisition of primary tissue to acquisition of ctDNA or tumor tissue was 52 mos (range: 1 – 193 mos). Concordance in DDR genes across samples was 86% (95% CI: 74-93%). Rates of concordance between metastatic-primary and ctDNA-primary pairs were similar when CHIP cases were excluded (87% and 85%, respectively). *BRCA2* reversion mutations associated with resistance to PARP inhibitors and platinum chemotherapy were detected in ctDNA from two subjects. **Conclusions:** These data provide evidence that primary prostate tissue accurately reflect the mutational status of actionable DDR genes in men with metastatic PC, supporting the hypothesis that DDR alterations are early truncal events. After excluding likely CHIP events, ctDNA profiling accurately captured these truncal DDR mutations, while also detecting reversion alterations that may suggest potential resistance mechanisms. Research Sponsor: None.

Summary of DDR gene alterations in paired primary PC and ctDNA/metastatic tissue. Only gene alterations identified in ≥2 subjects are presented. Note: Several patients had alterations in more than one gene.

Gene	Number of mutations (N)	Concordance (%)
CDK12	17	16 (94%)
BRCA2	16	13 (81%)
ATM	9	8 (89%)
PALB2	2	2 (100%)
FANCA	2	2 (100%)
ATR	2	1 (50%)
	Total	48 (86%)

5021 **Poster Session**

Copy number profiles of primary tumors for risk stratification of advanced prostate cancer: A biomarker study embedded in the multicenter STAMPEDE trial. *First Author: Emily Grist, University College London Cancer Institute, London, United Kingdom*

Background: Men with advanced hormone-sensitive prostate cancer (HSPC) starting long term androgen deprivation therapy (ADT) follow a highly variable clinical course. Treatment intensification with docetaxel or AR targeted therapies improves outcomes but there is a risk of overtreatment, especially in non-metastatic (M0) or metastatic (M1) low volume disease. We established a framework for biomarker evaluation in the STAMPEDE trial. We aimed to evaluate the feasibility and clinical utility of assessing the burden of copy number (CN) aberrations in newly diagnosed advanced HSPC. We hypothesised that increased percentage genome altered (PGA) would associate with higher disease burden and worse prognosis. **Methods:** We implemented a scalable strategy using low coverage whole genome sequencing (lpWGS) of formalin fixed paraffin embedded (FFPE) diagnostic core biopsies from STAMPEDE participants randomised to the standard of care ADT arm, between 2005 and 2016. Tissue was retrieved from 136 trial sites. 315 cases were randomly selected, aiming for a biomarker population of 300, anticipating an assay failure rate ~5%. We defined 40% as the minimum histopathologically determined tumor cellularity (TC) for inclusion. We performed a survival analysis investigating PGA at diagnosis as a continuous measure with fractional polynomial specification in Cox models adjusting for disease burden, Gleason grade, pre-ADT PSA (log-transformed), age at randomisation and TC. We pre-specified that all hypothesis tests required evidence at the 5% significance level to consider rejecting the null hypothesis. **Results:** We successfully CN profiled 300/315 cases. There were no significantly different baseline clinico-pathological features between the full trial comparison n = 3106 and final biomarker population n = 300, 290/300 cases were *de novo* presentations. PGA in the core with highest Gleason grade and TC was median 18% (range 0%-75%; n = 300). PGA was significantly higher in M1 (n = 169) compared to M0 (n = 131) cases (median: 21% vs 14%; p = 0.00006). 284/300 were subclassified by disease burden into M0 node negative and node positive, and M1 low and high volume. PGA was significantly associated with increased disease burden (p = 0.00002). Increased PGA was significantly and non-linearly associated with an increased hazard of failure-free survival (p = 0.004), progression-free survival (p = 0.002), metastatic progression-free survival (p = 0.003), overall survival (p = 0.045) and prostate cancer-specific survival (p = 0.011). **Conclusions:** Evaluation of the burden of CN aberrations in archival, poor quality FFPE diagnostic tissue from men randomised in the STAMPEDE trial is feasible using lpWGS and has potential clinical utility to identify better prognosis advanced HSPC patients, who may not require treatment intensification. Research Sponsor: Prostate Cancer UK, Other Foundation.

5022 **Poster Session**

Characterization of findings on prostate cancer tumor sequencing that should prompt consideration for germline testing. *First Author: Hong Truong, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Tumor sequencing is increasingly used for therapeutic selection in men with advanced prostate cancer (PC). If tumor-only sequencing is performed without matched germline, identified mutations could be of somatic or germline origin. Germline mutations could confer additional risk for other cancers to the patient and at-risk family members. The objective of this study is to determine the overall and gene-specific probability of pathogenic/likely pathogenic germline mutations based on tumor-only sequencing. **Methods:** We investigated mutations found in a cohort of men with PC who underwent targeted next generation sequencing of PC tumor and matched peripheral blood using the MSK-IMPACT assay between 01/2015 and 01/2020. A germline probability for each gene was determined by dividing the number of germline mutations by the total number of somatic and germline mutations. Cancer susceptibility genes commonly sequenced on tumor-based tests for PC were assessed, including *ATM*, *BRCA1/2*, *BRIP1*, *CHEK2*, *HOXB13*, *MLH1*, *MSH2*, *MSH6*, *NBN*, *PALB2*, *PMS2* (henceforth referred to as PC genes). **Results:** A total of 1883 men with PC were included, with median age of diagnosis of 62.0 ± 8.8 years. 84% had high risk PC, 52% had metastasis, 38% had family history of PC. A total of 364 (19%) men had at least one mutation (either somatic or germline) in PC genes. Overall, 189 (10%) men had at least one germline mutation that would not have been reported as germline without matched normal. The average germline probability of PC genes was 40% (range: 0% in *MLH1* to 83% in *CHEK2*). The number of total mutations, germline mutations, and germline probability of genes found in > 0.5% of the study cohort are summarized in Table. All these genes are moderate/high penetrance autosomal dominant genes with established guidelines for cascade testing, enhanced cancer screening, or potential risk-reducing surgery. **Conclusions:** In this study, an average of 40% of mutations found in cancer susceptibility genes on PC tumor sequencing were germline mutations. Men undergoing tumor-only sequencing should be counseled on the possibility of uncovering a germline mutation. In addition to *BRCA1/2*, mutations in certain genes, such as *CHEK2* and *PALB2*, have a high probability of being germline and should prompt referral for genetic counseling and germline testing. Research Sponsor: U.S. National Institutes of Health.

Genes	Total mutations (n, %)	Germline mutations (n, %)	Germline probability (%)
BRCA2	158, 8.4	74, 3.9	47
ATM	77, 4.1	24, 1.3	31
CHEK2	58, 3.1	48, 2.5	83
MSH2	34, 1.8	7, 0.4	21
MSH6	26, 1.4	4, 0.2	15
BRCA1	20, 1.1	11, 0.6	55
PALB2	16, 0.9	11, 0.6	69
BRIP1	13, 0.7	4, 0.2	31

5023 **Poster Session**

PSMA-targeted imaging with ^{18}F-DCFPyL-PET/CT in patients (pts) withbiochemically recurrent prostate cancer (PCa): A phase 3 study (CONDOR)—A subanalysis of correct localization rate (CLR) and positive predictive value (PPV) by standard of truth. *First Author: Frederic Pouliot, Cancer Research Center, Centre Hospitalier Universitaire (CHU) de Québec-Université Laval, Québec City, QC, Canada*

Background: PSMA-targeted PET/CT is superior to conventional imaging modalities to localize biochemically recurrent (BCR) PCa after local therapy, particularly in pts with low PSA (< 2 ng/mL). However, few studies have reported PSMA-targeted PET/CT accuracy compared to a pre-specified rigorous standard of truth (SOT) including histopathology, correlative imaging or treatment response in this population. Here, we report the CLR and PPV of PSMA-targeted ^{18}F-DCFPyLPET/ CT, for each of the pre-defined SOT criteria for the CONDOR prospective phase 3 study. **Methods:** The study enrolled men with rising PSA after definitive therapy and negative or equivocal standard of care imaging (e.g., CT/MRI, bone scintigraphy, F-18 fluciclovine). A single 9 mCi (333 MBq) ± 20% dose of ^{18}F-DCFPyL was injected, followed by PET/CT 1-2 hours later. Pts with positive ^{18}F-DCFPyL-PET/CT scans based on local interpretation were scheduled for follow up within 60 days to verify suspected lesion(s) using a composite SOT. The primary endpoint was CLR defined as PPV with the requirement of anatomic lesion co-localization between ^{18}F-DCFPyL-PET/CT and the SOT. The SOT consisted of, in descending priority: 1) histopathology, 2) subsequent correlative imaging findings determined by twocentral readers, or 3) post-radiation PSA response. The trial was successful if the lower bound of the 95% confidence interval for CLR exceeded 20% for at least two of three independent, blinded central ^{18}F-DCFPyL-PET/CT reviewers. **Results:** 208 men (median PSA 0.8 ng/mL) underwent ^{18}F-DCFPyL-PET/CT and the study achieved its primary endpoint: CLR was between 84.8% to 87.0% (lower bound of 95% CI: 77.8%-80.4%) among the three ^{18}F-DCFPyL-PET/CT readers, against the composite SOT. The performance of ^{18}F-DCFPyL-PET/CT by CLR (≥1 lesion co-localized) and PPV (≥1 lesion confirmed) was maintained through all 3 SOT categories. Histopathology (N = 31): 78.6-82.8% and 92.9-93.3% for CLR and PPV, respectively; correlative imaging (N = 100): 86.1-88.6% and 87.0-89.5% for CLR and PPV, respectively; and PSA response (N = 1): 100% for both CLR and PPV. Further analyses of the correlative imaging results showed CLR remained high across the different modalities used a) ^{18}F-fluciclovine-PET/CT (N = 71): (86.8-90.9%); b) MRI (N = 23): (80.0-86.7%); and c) CT (n = 6): (80.0-100%). **Conclusions:** PSMA-targeted ^{18}F-DCFPyL-PET/CT detected and localized metastatic lesions with high CLR and PPV regardless of which criterion defined CLR that was used, in men with BCR who had negative or equivocal baseline imaging. Clinicaltrials.gov: NCT03739684 Clinical trial information: NCT03739684. Research Sponsor: Progenics Pharmaceuticals, Inc.

5024 **Poster Session**

Evaluation of PSA progression after initiation of enzalutamide or abiraterone: Real-world data on metastatic castration-resistant prostate cancer (mCRPC). *First Author: Fernando López-Campos, Radiation Oncology Department, Hospital Universitario Ramón y Cajal, Madrid, Spain*

Background: PSA value is widely used for the monitoring of treatment outcome in mCRPC in the clinical real-world setting. Early PSA changes are not considered in the definition of PSAProg due to the potential for spurious "flare" reactions. We aimed to evaluate the significance of an early PSA increase in mCRPC patients (pts) treated with enzalutamide or abiraterone (Enz/Abi). **Methods:** We retrospectively evaluated Enz/Abi-treated mCRPC pts from 11 hospitals between 2011-2020. Early PSAProg was defined as a 25% increase in PSA from baseline at 4 (PSAProg4) or 8 (PSAProg8) weeks after treatment initiation. PSA progression at 12 weeks (PSAProg12) was confirmed by a second reading. Uni- and multivariable (MV) Cox regression models were conducted to explore the association of PSAProg and overall survival (OS) in chemotherapy naïve patients treated with Abi or Enz. Interaction tests were conducted to explore differences in the impact of PSA progression on OS in Abi or Enz-treated pts. **Results:** We analyzed 511 chemotherapy-naïve mCRPC pts treated with Abi (N=391; 76.5%) or Enz (N=120; 23.5%). Median follow-up: 30.2 months. OS was longer in Enz-treated pts (38.1 vs 29m; HR 1.4; p=0.027). 59 (15.1%), 70 (17.9%) and 48 (12.3%) of Abi-treated and 9 (7.5%), 11 (9.2%) and 10 (8.3%) of Enz-treated pts experienced PSAProg4, PSAProg8 and PSAProg12, respectively, although differences were not statistically significant. PSAProg was associated with worse OS at all 3 timepoints only in Abi-treated pts. In Enz-treated pts, PSAProg4 had a large impact on OS, not observed in PSAProg8 or PSAProg12. We observed no significant interaction between agent (Enz/Abi) and PSA progression (Table). **Conclusions:** PSA progression at 4 weeks after Enz/Abi is significantly associated with shorter OS and may help identify pts not benefitting from Abi/Enz before clinical or radiographic progression. PSA pattern progression and its association with OS might differ depending on the drug used (Enz/Abi). Prospective validation studies are needed. Research Sponsor: None.

Association between PSA prog and OS in abi- and enz-treated pts.

		Abiraterone		Enzalutamide		Interaction test
		OS	HR (p-val)	OS	HR (p-val)	
PSAProg4	Yes	25.9 m	1.47 (p=0.018)	15.2 m	3.57 (p=0.004)	p=0.103
	No	30.4 m		41.7 m		
PSAProg8	Yes	22.9 m	1.69 (p<0.001)	17 m	2.14 (p=0.06)	p=0.624
	No	31.1 m		38.1 m		
PSAProg12 (confirmed)	Yes	14.5 m	2.58 (p<0.001)	39.5 m	1.82 (p=206)	p=0.463
	No	31.6 m		41.7 m		

5025 **Poster Session**

Factors associated with use of medications for anxiety and depression in testicular cancer survivors after cisplatin-based chemotherapy. *First Author: Shirin Ardeshirrouhanifard, Indiana University School of Medicine, Indianapolis, IN*

Background: Cancer survivors are at increased risk of anxiety and depression that can affect health-related quality of life. There is no study to date that has examined the characteristics of testicular cancer survivors (TCS) taking medications for anxiety or depression since pharmacological interventions are typically reserved for more severe cases of these disorders. In this study, we aimed to examine sociodemographic factors, cisplatin-related adverse health outcomes (AHOs), and cumulative burden of morbidity (CBM_{Pt}) scores associated with medication use for anxiety and/or depression in TCS. **Methods:** A total of 1,802 TCS who completed CBCT ≥12 months previously completed validated questionnaires regarding sociodemographic features and cisplatin-related AHOs (hearing impairment, tinnitus, peripheral sensory neuropathy (PSN), kidney disease). Patients were recognized as users of medications for anxiety and/or depression if they used pharmacological classes of these medications and also indicated that the reason for use was for anxiety or depression. Individual AHOs were graded 0-to-4 based on severity according to NCI Common Terminology Criteria for Adverse Events version 4.03. A CBM_{Pt} score encompassed the number and severity of cisplatin-related AHOs. Multivariable logistic regression models assessed the relationship of individual AHOs and CBM_{Pt} with medication use for anxiety and/or depression. **Results:** A total of 151 TCS (8.4%) used medications for anxiety and/or depression. Any grade of HL, tinnitus, PSN, and kidney disease were reported by 37.9%, 39.5%, 55.2%, and 2.4% of 1,802 participants, respectively. No cisplatin-related AHO were reported by 511 (28.4%) participants, whereas 622 (34.5%), 334 (18.5%), 287 (15.9%), and 48 (2.7%), respectively, had very low, low, medium, and high CBM_{Pt} scores. Higher CBM_{Pt} scores were significantly associated with greater medication use for anxiety and/or depression (CBM_{Pt} scores of low (OR = 2.96, 95%CI, 1.67-5.24), medium (OR = 3.47, 95%CI, 1.95-6.18), and high (OR = 3.18, 95%CI, 1.22-8.3). A multivariable model including individual AHOs indicated that tinnitus (P= 0.0009), PSN (P= 0.02), and having health insurance (OR = 2.15, 95%CI, 1.01-4.56) were associated with significantly greater use of these medications; whereas being employed (OR = 0.39, 95%CI, 0.23-0.66) and vigorous physical activity (OR = 0.63, 95%CI,0.44-0.89) were associated with significantly diminished use. **Conclusions:** We found that TCS with higher CBM_{Pt} scores had a higher probability of using medications for anxiety and/or depression and conversely, those who were employed and physically active tended to have reduced use. These findings deserve further investigation in longitudinal studies. In the interim, healthcare providers should be aware of these associations in formulating survivorship care plans. Research Sponsor: U.S. National Institutes of Health.

5026 **Poster Session**

Adjuvant chemotherapy with CAV/IE for malignant transformation of teratoma to primitive neuroectodermal tumor (PNET): An institutional analysis from Indiana University. *First Author: Cynthia Wei, Indiana University School of Medicine, Indianapolis, IN*

Background: Malignant transformation of teratoma to PNET has an aggressive disease biology and generally poor outcomes when metastasis occurs. The optimal management of patients (pts) with PNET who have complete surgical extirpation is unknown. Most pts who are monitored with surveillance will relapse. We report results from pts with metastatic PNET who had complete surgical resection to NED status followed by adjuvant chemotherapy, most commonly cyclophosphamide + doxorubicin + vincristine alternating with ifosfamide + etoposide (CAV/IE) for 4 cycles. **Methods:** We reviewed records for pts with histologically confirmed malignant transformation of teratoma at Indiana University from 1990 to 2020. We identified 13 pts with PNET who underwent resection of metastatic disease to NED status followed by treatment with adjuvant chemotherapy, most commonly CAV/IE comprising of cyclophosphamide (1200 mg/m2), doxorubicin (75 mg/m2), and vincristine (2 mg/m2) alternating with ifosfamide (1.8 g/m2) plus etoposide (100 mg/m2). Treatment was delivered every 3 weeks for 4 cycles or until unacceptable toxicity. **Results:** Thirteen pts with metastatic PNET resected to NED status and received adjuvant chemotherapy were identified. Median age at diagnosis was 29 (range, 20 to 55). Primary tumor site was testis in 11 pts, retroperitoneum in 1 pt, and mediastinum in 1 pt. Metastasis site was retroperitoneal lymph nodes in 11 pts, mediastinal lymph nodes in 1 pt, and local mediastinal recurrence in 1 pt. After resection to NED status, all 13 pts were treated with adjuvant chemotherapy: 11 pts were treated with CAV/IE and 2 received etoposide-ifosfamide-cisplatin (VIP) x 2. Among the 11 pts who received CAV/IE: 3 pts received $<$ 4 cycles due to toxicity and 8 completed 4 cycles. With a median follow-up of 16.3 months, 3 of 13 pts relapsed (23%) and 10 of 13 remained continuously disease free (77%). Of those who relapsed, median time to relapse was 9.3 months, 2 remained alive with disease at follow up and one patient died of disease progression. **Conclusions:** Adjuvant CAV/IE improves the outcomes of pts with malignant transformation of teratoma to PNET and who had resection of metastasis to NED status. Most pts who received adjuvant therapy remain continuously disease-free in comparison to historically high relapse rates in pts with resected PNET monitored with surveillance. Research Sponsor: None.

5027 **Poster Session**

Clinical utility of FDG PET-CT in stage 1 and advanced testicular seminoma. *First Author: Ciara Conduit, Peter MacCallum Cancer Centre, Melbourne, VIC, Australia*

Background: Testicular seminoma is highly curable; however, treatments can cause long-term morbidity in survivors. Following chemotherapy for advanced seminoma, positron emission tomography with 2-[18F]fluoro-2-deoxy-D-glucose together with computerised tomography (PET-CT) can identify patients with residual masses who do not need additional treatment. Its role in detecting recurrence during active surveillance, particularly in patients with small indeterminate masses, is unknown. We assessed the clinical utility of PET-CT in testicular seminoma undergoing active surveillance for stage 1 disease and following curative-intent treatment for advanced disease. **Methods:** An institutional database was interrogated to identify patients with testicular seminoma who underwent PET-CT between 2000-2020. Demographic, clinicopathological, PET-CT findings and outcome data were retrieved. The positive predictive value (PPV) of PET-CT for correctly identifying disease recurrence was calculated, with disease recurrence (true positive) defined as progressive radiological change, response to treatment or histological confirmation. Negative predictive value (NPV) was calculated for correctly identifying non-recurrence (true negative) at 24-months post PET-CT. **Results:** We identified 193 PET-CT in 181 stage 1 patients. Of these, 18 (10%) PET-CT were positive, with all correctly diagnosing recurrence, PPV 100%. Of the 138 negative PET-CT with at least 24 months follow up, 5 recurrences developed, NPV 96%. In the subset of PET-CT conducted for suspicion of recurrence in stage 1 patients (n = 71: abnormal imaging n = 65, elevated markers n = 4, other clinical suspicion n = 2), 16 (23%) PET-CT were positive, with all correctly diagnosing recurrence, PPV 100%. In this subset, the NPV is 93% at 24 months (3 recurrences in 44 negative PET-CT). We also identified 154 PET-CT in 77 post-treatment, advanced stage patients. Of these, 69 (45%) PET-CT were positive, with 51 correctly diagnosing recurrence, PPV 74%. Of the 66 negative PET-CT with at least 24 months follow up, 5 recurrences developed, NPV 92%. In the subset of PET-CT performed for suspicion of recurrence following treatment for advanced disease (n = 61: abnormal imaging n = 49, elevated markers n = 5, other clinical suspicion n = 7), 41 (67%) PET-CT were positive, with 36 correctly diagnosing recurrence, PPV 88%. In this subset, the NPV is 94% at 24 months (1 recurrence in 17 negative PET-CT). **Conclusions:** At our centre, PET-CT has a very high PPV for recurrence, particularly in stage 1 disease, and a very high NPV for non-recurrence in all disease settings. In the subset of PET-CT performed for suspicion of recurrence, PPV is $>$ 88% and NPV is $>$ 93%. The role of PET-CT should be considered in patients with suspicion of recurrence where it may prevent over-treatment in up to 70% patients in stage 1 or 30% in advanced disease. Research Sponsor: None.

5028 **Poster Session**

Efficacy of TIP (paclitaxel, ifosfamide and cisplatin) as salvage chemotherapy for relapsed germ cell cancer patients stratified by the modified International Prognostic Factors Study Group (IPFSG) score: The Northern Ireland (NI) Experience. *First Author: Adam Uprichard, Belfast City Hospital, Belfast, United Kingdom*

Background: Salvage therapy for relapsed or refractory germ cell tumours (GCTs) after first-line treatment (1LT) failure remain controversial. The ongoing TIGER trial aims to compare conventional-dose chemotherapy (CDCT) using TIP with high-dose chemotherapy (HDCT) and to validate a modified version of the IPFSG stratification system as a secondary objective. We retrospectively analysed data from patients treated with TIP at our institution and stratified by the modified IPFSG (mIPFSG) groupings, correlating this with clinical outcomes. **Methods:** Data from all GCT patients who received TIP in NI between 2005 and 2014 was collected. Patients were scored using known IPFSG factors including progression-free interval (0-1), metastasis site (0-3), response to 1LT (0-2), primary tumour site (0-3), HCG (0-1), AFP (0-2), and histology (-1 to 0), and categorised into the modified strata. Descriptive and inferential statistics using SPSS compared survival measure outcomes and the favourable response rate (FRR) i.e the proportion of patients achieving either a complete response or partial response with normal serum tumour markers, according to mIPFSG group. **Results:** Thirty patients were identified, all of whom received 4 cycles of TIP. The median age was 37 years (range 17-57), 28 patients were non-seminoma histology with 2 patients seminoma. The cohort comprised predominantly of patients with more adverse mIPFSG features and the FRR of the group was 30%, with a median progression-free survival (PFS) of 9 months and 2-year overall survival (OS) of 50%. Clinical outcomes differed by mIPFSG score as shown below. **Conclusions:** Our study shows TIP efficacy comparable to published data, and to our knowledge is the first to show correlation between clinical outcomes with the regimen and the new mIPFSG model. The differences in outcomes to CDCT using TIP across risk groups in real world practice shows potential for a stratified approach to patient selection for salvage therapy, as is under investigation by the TIGER study. Research Sponsor: None.

mIPFSG point score	FRR	2-year OS	
Low (-1 to 0), n= 5	80%	80%	
Intermediate (1-2), n= 11	36.4%	72.7%	P <0.05
High (3+), n= 14	7.1%	21.4%	

5029 **Poster Session**

Outcomes of patients with germ cell tumors diagnosed with stage I disease who subsequently received high dose chemotherapy (HDCT) with peripheral stem cell transplant (PBSCT) following failure of initial therapy for metastatic disease: The Indiana University experience. *First Author: Stephen B Benzinger, Indiana University School of Medicine, Indianapolis, IN*

Background: Pts with stage I testicular germ cell tumors (GCT) have a 15-year DFS of 99%. However, 1% are not cured, despite orchiectomy and systemic therapy at relapse. Predictive variables for relapse in this small population have not been identified. **Methods:** Pts undergoing HDCT with PBSCT as salvage therapy for relapsed GCT after an initial diagnosis of stage I disease managed with orchiectomy and surveillance were evaluated from a database at Indiana University. Patient demographics, disease characteristics, adherence to standard surveillance guidelines for stage I disease, prognostic variables, treatment received in the first-line setting, pattern of relapse, and outcomes were analyzed. **Results:** From 1/92 to 10/19, 71 pts (34 seminoma, 37 NSGCT) initially diagnosed with stage I GCT managed with orchiectomy and surveillance but subsequently relapsed and eventually required HDCT with PBSCT were identified. Median f/u time was 5.1 years (range, 1.1-18.8). Median age was 34.1. First-line chemo consisted of BEP or EP in most pts. Risk category at relapse: good/intermediate/poor (52/8/11). Pattern of initial relapse included 22 (seminoma n=13, NSGCT n=9) with RPLN only. Relapse and death after HDCT occurred in 2 of these 22 pts. Strict adherence to standard surveillance guidelines was observed in 62/71 pts. Relapse and/or death after HDCT occurred in 3 of 9 with inadequate surveillance follow-up. At a minimum of 1 yr follow-up, 54 of 71 (76%) remain alive, including 47 (66%) who have no evidence of disease (NED). **Conclusions:** Most patients in this series progressed despite appropriate surveillance and first-line chemotherapy. Pattern of relapse was also not indicative of further progression in most patients. Further investigation should evaluate disease biology that puts patients with potentially easily curable disease at risk of multiple relapses. Research Sponsor: None.

Status at last follow up.

	Patients with No Evidence of Disease (n=47)	Patients either Dead of Disease, Dead of Other Causes, Alive With Disease, or Lost to Follow Up (N=24)
Histopathology		
Seminoma n=34	27	7
Non-Seminoma n=37	20	17
Appropriate Surveillance		
Yes n=62	41	21
No n=9	6	3
Appropriate First-line Therapy		
Yes n=63	44	19
No n=8	3	5
Risk Group		
Good n=52	40	12
Intermediate n=8	4	4
Poor n=11	3	8
Pattern of Relapse		
RPLN n=43	29	14
Lung n=28	16	12
Posterior Mediastinal n=12		
NPVM 14	6	6
Liver n=5	2	3
CNS n=7	1	6
Bone n=7	4	3
First Line Chemo		
BEPx3-4 n=44	31	13
EPx4 n=19	13	6
VIPx3 n=1	1	0
BEPx3 + EPx1 n=1	0	1
Other n=6	2	4

5030 **Poster Session**

Very late recurrence in germ cell tumor of the testis: Lessons and implications. *First Author: Joseph A Moore, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Up to 30% of patients with germ cell tumor of the testis (TGCT) develop recurrent disease after initial treatment. The majority of recurrences occur in the first 2 years after treatment. Very late recurrence (LR), i.e. > 5 years after initial presentation, occurs in about 1% of patients with TGCT and is associated with poor prognosis. Current guideline does not require follow-up after 5 years to detect LR, except in those presenting with metastatic NSGCT. **Methods:** We retrospectively reviewed the records of patients from the Genitourinary Medical Oncology clinic at the M. D. Anderson Cancer Center, who developed recurrent disease > 5 years after their initial diagnosis of TGCT. Specifically, we examined the pathology and location of their primary and recurrent tumors, treatments rendered (e.g., surgery, radiotherapy, chemotherapy), and overall survival after LR. Overall survival from the time of LR was estimated using Kaplan-Meier estimates and compared for patient subgroups with log rank tests. Fisher's exact test was used to compare proportions in patient subgroups. **Results:** We identified 25 patients who developed LR between July 2007 and August 2020. Age at time of LR: median 46 years (range, 29-61); time of late LR: median 16.1 years (range, 6.8-33.1 years) after diagnosis. Stage at time of diagnosis: I – 5, II-IIIA – 13, IIIB-C – 7. Pathology of primary: nonseminoma with yolk sac tumor or teratoma – 15, nonseminoma without yolk sac tumor or teratoma – 1, not available – 9. Pathology of LR: somatic transformation to carcinoma – 9, somatic transformation to sarcoma – 2, nonseminoma with yolk sac tumor or teratoma – 10, nonseminoma without yolk sac tumor or teratoma – 2, not available – 2. Overall, 5 patients (20%) had LR in retroperitoneum alone, 6 patients (24%) had non-retroperitoneal nodal or pulmonary metastases, and 14 patients (56%) had non-pulmonary visceral metastases. Nine patients (36%) are deceased, ten patients (40%) are alive without evidence of disease (NED), and 6 patients are alive with disease (24%). With a median follow-up of 42 months, 68% of patients are alive 3 years after LR. Patients with prior post-chemotherapy consolidation surgery have longer survival, 80% vs. 53% at 3 years, respectively (p = 0.01). Additionally, at their last follow-up 9/12 vs. 1/13 patients were NED with vs. without prior post-chemotherapy consolidation surgery, respectively (p = 0.001). **Conclusions:** Patients with LR > 5 years after initial presentation tend to harbor nonseminoma (with yolk sac tumor and or teratoma). Among these patients, a majority who did not undergo surgery to remove residual disease after chemotherapy developed somatic transformation and succumbed to their LR. Further investigation into rates of LR among all patients may be warranted given the poor survival after LR. Research Sponsor: None.

5031 **Poster Session**

First-in-human study of TAS3681, an oral androgen receptor (AR) antagonist with AR and AR splice variant (AR-SV) downregulation activity, in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC) refractory to abiraterone (ABI) and/or enzalutamide (ENZ) and chemotherapy (CT). *First Author: Johann S. De Bono, Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, Surrey, United Kingdom*

Background: Second-generation AR signaling inhibitors have improved outcomes from mCRPC; drug resistance, however, invariably evolves with AR overexpression, AR mutation, or AR-SVs and continued AR signaling. TAS3681 is an oral and selective AR antagonist with AR and AR-SV down-regulation and has antitumor efficacy in AR-SV+, ENZ-resistant CRPC models. We report the dose escalation part of the first-in-human trial of TAS3681 in pts with mCRPC (NCT02566772). **Methods:** mCRPC pts with progressing disease after ABI and/or ENZ, and ≥1 additional CT, received TAS3681 in a 3+3 dose escalation design; QD or BID tablets were given in 28-day cycles; BID dosing at ≤600 mg was introduced to increase daily exposure while limiting C_{max}. Primary endpoints: incidence of dose limiting toxicities (DLTs) and adverse events (AEs); other endpoints: pharmacokinetics (PK), and antitumor activity per Prostate Cancer Clinical Trials Working Group 3 (PCWG3). **Results:** As of January 22, 2021, 56 pts in 10 cohorts were dosed (QD: 25, 50, 100, 200, 400, 600, 800, and 1000 mg; and BID: 300 and 400 mg). Median age was 66 (56–79) yrs; pts had a median of 6 prior lines of systemic therapy. Of 41 pts evaluable for DLTs, 3 had confirmed DLTs: 1/10 DLT evaluable pts at 600 mg QD (QT prolongation >480 ms) and 2/3 DLT evaluable pts at 400 mg BID (1 pt with QT prolongation >480 ms, 1 pt with G3 hypertension). The most common treatment-related AEs (TRAEs) were: nausea (32 pts, 57.1%), hyperbilirubinemia (21 pts, 37.5%), fatigue (18 pts, 32.1%), vomiting (17 pts, 30.4%) and diarrhea (16 pts, 28.6%); AEs of QT prolongation were seen in 11 pts (19.6%). TRAEs ≥G3 were reported in 12 pts (21.4%). TAS3681 exposure increased dose-dependently up to 600 mg QD and then plateaued. Steady state was reached by Day 8 and accumulation ratios of AUC were approximately 2 to 6 times. Confirmed PSA declines of >50% from baseline were seen in the 600 mg QD (2 pts) and 300 mg BID cohorts (1 pt). Antitumor activity was observed; tumor response rate was 23.1% in the 600 mg QD cohort (3 confirmed partial responses (cPRs) in 13 dosed pts), 22.2% in the 300 mg BID cohort (1 cPR and 1 unconfirmed complete response in 9 dosed pts), and 14.3% in the 400 mg BID cohort (cPR in 1/7 dosed pts). Responses occurred after 2–4 cycles of treatment. The longest duration of response (DoR) to date is 16.2 mo. The 5 pts with cPR had DoR >6 mo with the exception of 1 pt who had a short follow-up period. 300 mg BID was found to be the best tolerated dose with antitumor activity. **Conclusions:** The recommended phase 2 dose is 300 mg BID. TAS3681 has a manageable safety profile and has antitumor activity against heavily pretreated, multi-drug resistant mCRPC. The study expansion phase is enrolling pts who have progressed on ABI or ENZ +/- taxane CT. Clinical trial information: NCT02566772. Research Sponsor: Taiho.

5032 **Poster Session**

Survival of veterans treated with enzalutamide and abiraterone in advanced prostate cancer. *First Author: Martin W. Schoen, Saint Louis University School of Medicine, St. Louis, MO*

Background: Abiraterone (AA) and enzalutamide (ENZ) are two second generation antiandrogens used to treat advanced prostate cancer, but no large head-to-head trials have been performed. These oral therapies are commonly used in older patients with medical comorbidities who are not candidates for chemotherapy or clinical trials and have different mechanisms of action, adverse events, and drug interactions. To understand survival of patients with prostate cancer, we studied United States veterans treated prior to approval of AA and ENZ for metastatic hormone sensitive prostate cancer when both drugs had approval for metastatic castration resistant prostate cancer. **Methods:** We identified patients treated with AA or ENZ between 9/10/2014 and 6/3/2017 in the Veterans Health Administration and followed them to April 2020. Age, Elixhauser comorbidity score, treatment with androgen deprivation therapy (ADT) and docetaxel were collected. Cox proportional hazards modeling was used to assess the association between first oral treatment (AA or ENZ) and overall survival, while adjusting for covariates. **Results:** Of 5895 patients, 2562 (43.5%) were initially treated with ENZ, 3333 (56.5%) with AA, and 3040 (51.6%) received only one of the two drugs during the study period. Patients initially treated with ENZ compared to AA were older (mean 75.9 vs. 75.0 years, $p = 0.001$), had higher mean comorbidity score (6.2 vs. 5.9, $p < 0.001$), and were less likely to receive both ENZ and AA (45.2% vs. 51.0%, $p < 0.001$) or docetaxel (24.1% vs. 28.4%, $p < 0.001$). Patients who received only AA or ENZ and never received docetaxel were older (mean 78.3 vs. 73.2 years, $p < 0.001$) with higher mean comorbidity scores (6.4 vs. 5.7, $p < 0.001$). In the entire cohort, initial treatment with ENZ was associated with longer median survival (24.1 vs. 22.2 months, $p = 0.003$). After adjusting for age and comorbidities, ENZ was associated with a decreased risk of death compared to AA (HR 0.87, 95% CI 0.82-0.92). In 3317 patients who received two or more therapies (ENZ, AA, docetaxel) there was no difference in median survival between initial treatment with ENZ or AA (28.0 vs. 27.9 months). In 2578 patients (43.7%) who never received docetaxel and either ENZ or AA only, median survival was longer in patients treated with ENZ (18.9 vs. 13.6 months, $p < 0.001$) and was associated with decreased mortality when adjusting for age and comorbidities (HR 0.73, 95% CI 0.67-0.80). **Conclusions:** In the overall cohort, initial treatment with ENZ was associated with increased survival compared to AA. Patients who received only ENZ or AA and never received docetaxel had the largest benefit from ENZ, a difference of 5.3 months median survival. Efforts should be made to improve therapy selection for patients with prostate cancer, especially older patients with comorbidities. Research Sponsor: Saint Louis Veterans Affairs Medical Center.

5033 **Poster Session**

A methodology for the extraction and analysis of real-world radiographic and electronic medical record data to reconstruct treatment arms of historical prostate cancer clinical trials. *First Author: William David Lindsay, Oncora Medical, Inc., Philadelphia, PA*

Background: Real-world evidence (RWE), including synthetic comparator arms created from historical real-world data (RWD), has the potential to support the safety and efficacy evaluation of new medical products. However, many available RWD sources lack the details necessary to reliably identify patients comparable to clinical trial cohorts or to assess essential oncologic efficacy endpoints. This project demonstrates the ability to extract and analyze RWD to identify patients matching eligibility criteria to four historical clinical trials in metastatic castration-resistant prostate cancer (mCRPC), and calculate outcome measures. **Methods:** A total of 5,741 patients treated for prostate cancer at multiple institutions (2010-2020) were analyzed in two cohorts using data extracted from the EMR, Tumor Registry, Oncology Information System, and Picture Archiving and Communication System. Of 3,486 patients with prostate cancer in Cohort 1, 422 mCRPC patients were identified: those treated with ADT who achieved castration-level testosterone (< 50 ng/dL), had evidence of metastatic disease, and exhibited rising PSA (PCWG2). These patients were further matched to four historical clinical trial treatment arms (COU-AA-301: 49, COU-AA-302: 143, AFFIRM: 30, PREVAIL: 79), based on prior chemotherapy and receipt of Abiraterone or Enzalutamide. Overall survival (OS) and time to skeletal related events (SRE) (pathological fracture, spinal compression, surgery to bone, and radiotherapy to bone) were calculated based on diagnosis and procedure codes using the Kaplan-Meier (KM) Estimator. Of 2,255 patients with prostate cancer in Cohort 2, 101 patients received Abiraterone or Enzalutamide and 59 patients had sufficient baseline and follow-up imaging to be scored. Radiographic progression-free survival (rPFS) was calculated from the start of treatment to the time of progression (RECIST 1.1) or loss to follow-up using the KM estimator. **Results:** In Cohort 1, median OS was 37.7 months (95% CI: 31.5-NR), and median time to SRE was 17.9 months (13.5-22.6). Median OS per patient cohort matched to historical trial treatment arm was COU-AA-301: 23.7 months (10.7-NR), COU-AA-302: 45.9 months (34.9-NR), AFFIRM: 35.3 months (6.34-NR), PREVAIL: 41.5 months (21.9-NR). In Cohort 2, median rPFS was 37.2 months (13.3-NR). **Conclusions:** The methodology employed in this analysis not only successfully identified a cohort of RWD patients similar to clinical trial-defined patients, but also curated sufficiently reliable data to calculate essential endpoints (e.g., rPFS). At scale, this methodology can be used to generate RWE, including synthetic comparator arms to support clinical trials with radiographic endpoints. Research Sponsor: Tmunity Therapeutics.

5034 **Poster Session**

A phase 2 study of berzosertib (M6620) in combination with carboplatin compared with docetaxel in combination with carboplatin in metastatic castration-resistant prostate cancer. *First Author: Atish Dipankar Choudhury, Dana-Farber Cancer Institute, Boston, MA*

Background: Alterations in DNA damage repair (DDR) genes are common in metastatic castration-resistant prostate cancer (mCRPC), and are implicated in responses to carboplatin [carbo], PARP inhibitors and immunotherapeutics. Inhibitors of the ATR kinase, which is involved in the DDR response, have been demonstrated to have synergistic activity with platinum compounds in preclinical models. We therefore conducted a phase 2 study of the ATR inhibitor berzosertib [berzo]+carbo vs. docetaxel [doce]+carbo in mCRPC. **Methods:** Patients (pts) previously treated with at least one secondary hormonal therapy and taxane underwent mandatory pre-treatment biopsy and were randomized 1:1 to receive Arm A (doce 60 mg/m2 day 1 + carbo AUC 4 day 1) or Arm B (berzo 90 mg/m2 days 2,9 + carbo AUC 5 day 1) every 21 days. Pts randomized to Arm A who were not candidates for doce received carbo AUC 5 monotherapy. Stratification factors were 1) prior PARP inhibitor (yes vs. no) and 2) evaluable disease by RECIST 1.1 (yes vs. no). Pts on Arm A crossed over to Arm B (berzo+carbo) at the earlier of PSA or radiographic progression. The primary endpoint was overall response rate (ORR; PSA reduction by $\geq$ 50% or radiographic response by RECIST 1.1). Secondary endpoints included time to PSA progression, radiographic PFS (rPFS), PFS by PCWG3 criteria, and adverse events (AEs) in each arm. Planned enrollment was 136 pts (for 130 to be treated), with interim analysis for futility after 65 pts were treated. **Results:** 73 pts were randomized between 6/2019 and 7/2020; 34 pts were treated on Arm A (26 carbo+doce; 8 carbo alone) and 31 on Arm B. Median number of prior systemic therapies (excluding ADT, 5α-reductase inhibitors, 1st generation antiandrogens) was 4 (range 2-8). Median treatment duration was 3 cycles, and 4 pts in each arm discontinued for AEs. Grade 3 or higher treatment-related AEs (TrAE) were seen in 13(38%) pts in Arm A and 21(68%) in Arm B. Pts in Arm B had greater frequency of grade 3-4 thrombocytopenia (8[26%] vs. 3[9%]). 1 pt in Arm B had grade 5 sepsis attributed to study treatment. ORR was 15% in Arm A (5/34; 5/26[19%] in pts who received carbo+doce) and 0% in Arm B (0/31). 14 pts in Arm A crossed over, with no subsequent responses seen. Median rPFS was 2.1(95% CI:2.0,3.2) mo in Arm A and 2.4(1.9,4.2) mo in Arm B. At planned interim analysis, trial enrollment and crossover to Arm B were halted due to futility. **Conclusions:** Carbo+berzo led to fewer overall responses and a higher rate of grade 3 or higher TrAEs compared to carbo+doce. All responses seen were in pts who received carbo+doce despite requirement for prior progression on taxane, suggesting that this combination is favored over carbo+berzo or carbo monotherapy in a heavily pre-treated biomarker-unselected population. Extensive genetic and molecular studies for DDR assessment from tissue and cfDNA are in progress. Clinical trial information: NCT03517969. Research Sponsor: U.S. National Institutes of Health.

5035 **Poster Session**

Cortisol as biomarker for CYP17 inhibition in mCRPC patients treated with abiraterone acetate. *First Author: Maaike Bruin, The Netherlands Cancer Institute–Antoni van Leeuwenhoek, Amsterdam, Netherlands*

Background: Abiraterone acetate is an effective metastatic castration resistant prostate cancer (mCRPC) treatment, however, there is a high variability in response. It inhibits CYP17, thereby preventing the production of androgens. Abiraterone trough concentrations (C_{min}) > 8.4 ng/mL have been associated with an increased progression free survival (PFS) (Eur J Cancer. 2017;72:54-61; Prostate Cancer Prostatic Dis. 2020;23(2):244-251). However, plasma levels do not directly provide information on the level of CYP17 inhibition. Ideally, testosterone levels should be measured, but these levels are below the detection limit of available assays. The synthesis of cortisol is also inhibited by abiraterone via CYP17 inhibition and might therefore be a biomarker for CYP17 inhibition. The objective of this study was to investigate if cortisol levels are related to abiraterone levels and to clinical response. **Methods:** An observational study was performed in mCRPC patients treated with abiraterone acetate. At the outpatient clinic, plasma samples were collected for pharmacokinetic (PK) monitoring at each hospital visit. Reference populations of healthy volunteers and mCRPC patients using enzalutamide were included to investigate the influence of mCRPC and abiraterone treatment on the circadian rhythm of cortisol. Abiraterone and cortisol levels were measured using validated liquid chromatography-mass spectrometry (LC-MS/MS) assays. Clinical (prostate specific antigen (PSA) independent) PFS and PSA response were evaluated. **Results:** In total, 117 mCRPC patients using abiraterone acetate, 100 mCRPC patients using enzalutamide and 12 healthy volunteers were included. A clear circadian rhythm of cortisol was described in healthy volunteers and unaffected in mCRPC patients using enzalutamide. Contrarily, a circadian rhythm of cortisol could not be identified in mCRPC patients using abiraterone acetate, due to continuous suppression throughout the day. Patients with an abiraterone $C_{min} > 8.4$ ng/mL (n = 77) had a median cortisol concentration of 1.03 ng/mL vs. 2.59 ng/mL in patients with an abiraterone $C_{min} \leq 8.4$ ng/mL (n = 40) ($p = 0.020$). The median cortisol concentration in PSA responders (n = 63) was 1.02 ng/mL vs. 2.59 ng/mL for PSA non responders (n = 54) ($p = 0.037$). Patients in the highest cortisol tertile (> 3.03 ng/mL) had a median PFS of 3.7 months (n = 39) vs. 13.8 months in patients with cortisol levels ≤ 3.03 ng/mL (n = 78) ($p = 0.007$). The median PFS was 16.3 months in patients with an abiraterone $C_{min} > 8.4$ ng/mL and cortisol concentration < 3.03 ng/ml vs. 5.3 months in patients with an abiraterone $C_{min} > 8.4$ ng/mL and cortisol concentration > 3.03 ng/ml ($p = 0.02$). **Conclusions:** This study demonstrates that cortisol levels are of additional value to abiraterone concentrations as a marker for abiraterone acetate efficacy. This might help be helpful to assess efficacy of abiraterone treatment. Research Sponsor: None.

5036 **Poster Session**

Biomarker analysis of phase (Ph) IB trial of radium-223 (Rad) and niraparib (Nira) in patients (Pts) with metastatic castrate-resistant prostate cancer (mCRPC) (NiraRad). *First Author: Eddy Shih-Hsin Yang, University of Alabama at Birmingham, Birmingham, AL*

Background: Rad is an alpha particle emitter that causes DNA double strand breaks and has been FDA-approved for use in mCRPC pts with bone metastases. PARP-1 activity critically supports androgen receptor (AR) activity in mCRPC and potentiates AR-dependent DNA damage response pathways that promote prostate cancer cell survival. Nira is a potent and selective PARP-1/2 inhibitor that has shown single agent clinical activity in mCRPC. We previously reported the safety of targeting the PARP-1/AR axis with Nira in combination with Rad. Herein we describe the results of an exploratory biomarker analysis. **Methods:** The primary objective of NiraRad is to determine the optimum Ph II dose of Nira plus Rad (55 kBq/kg of body weight IV every 4 weeks (wks) x 6) in pts with and without prior chemotherapy (docetaxel). Pts were enrolled to one of three dose levels of Nira (100, 200, or 300 mg PO daily). All cohorts were combined for exploratory biomarker analysis using Nanostring PanCancer Driver and Immune Pathways panels and the nSolver Advanced analysis module was performed on blood obtained from 23 pts at baseline, cycle (C) 1 day (D) 15, and C3D15. A favorable response was defined as any PSA reduction at week 12 or treatment (tx) duration $>$ 18 wks, the median time on tx in the cohort of pts analyzed. A threshold of $>$ 2 fold (X) differentially expressed genes was used. **Results:** Of the 23 pts with biomarker data, 7 (30%) experienced PSA reductions and 11 (48%) received tx for $>$ 18 wks, 6 of which also had PSA reductions. Exploratory analysis revealed that the PI3K/Ras, MAPK, and transcriptional misregulation pathways were differentially regulated in pts who had favorable responses. The top downregulated gene, PAX5, which has been shown to promote prostate cancer growth, was decreased at C1D15 (2.7X, $p < 0.01$) and C3D15 (4.8X, $p < 0.001$) in pts with tx duration $>$ 18 wks and at baseline in pts who had PSA reductions (3.1X, $p < 0.05$). Immune pathways analysis suggested downregulation of immunosuppressive B-cell (plasma cell) and upregulation of NK and T cell pathways in pts with tx duration $>$ 18 wks. **Conclusions:** Previously Nira and Rad have been shown to have acceptable tolerability in mCRPC pts. This exploratory analysis suggests potential response biomarkers that warrant further investigation. Managed by: the Prostate Cancer Clinical Trials Consortium; Funded by: Janssen Pharmaceuticals and Bayer Healthcare Pharmaceuticals, Inc. Clinical trial information: NCT03076203. Research Sponsor: Janssen Scientific Affairs, LLC, Pharmaceutical/Biotech Company.

5037 **Poster Session**

Analysis of two poor prognosis subgroups in ACIS evaluating apalutamide + abiraterone acetate plus prednisone (APA + AAP) versus placebo (PBO) + AAP in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Fred Saad, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada*

Background: In the double-blind PBO-controlled ACIS study, investigator-assessed radiographic progression-free survival (rPFS) was significantly improved with APA + AAP vs PBO + AAP in chemo-naive mCRPC, with no significant new safety signals (Rathkopf ASCO GU 2021). Among prespecified subgroups, efficacy and safety were explored in two difficult to treat subgroups: pts with visceral disease (VD; liver, lung, and/or adrenal gland metastasis) or age $\geq$ 75 y. **Methods:** Pts with mCRPC with ongoing ADT and no prior life-prolonging treatment were randomized 1:1 to APA (240 mg QD) + AA (1000 mg QD) + P (5 mg BID) or PBO + AAP. Stratified: presence or absence of VD, ECOG PS 0 or 1, geographic region. Primary end point: rPFS (randomization to radiographic progression or death); secondary end points: overall survival (OS), time to initiation of cytotoxic chemotherapy, time to chronic opioid use, time to pain progression, safety. **Results:** 982 pts enrolled. 14.6% had VD and 35.9% were $\geq$ 75 y. Median rPFS, OS, and time to pain progression favored APA + AAP vs AAP (HR $<$ 1) in both subgroups (Table). For pts $\geq$ 75 y, rPFS and OS were $\geq$ 7 mo longer with APA + AAP. Overall, treatment-emergent adverse events (TEAEs) were similar (all $>$ 94%) in pts with VD, $\geq$ 75 y, and overall safety population; hypertension was more frequent with APA + AAP vs AAP mainly in pts $\geq$ 75 y (31.7% vs 17.6%). Grade 3/4 TEAEs (APA + AAP vs AAP): VD, 60.8%, n = 74 vs 48.5%, n = 68; $\geq$ 75 y, 71.5%, n = 186 vs 68.5%, n = 165; overall, 63.3%, n = 490 vs 56.2%, n = 489. TEAEs leading to discontinuation: VD, 17.6% vs 5.9%; $\geq$ 75 y, 26.3% vs 20.6%; overall, 16.9% vs 12.5%. TEAEs leading to death: VD, 6.8% vs 5.9%; $\geq$ 75 y, 5.4% vs 13.9%; overall, 3.5% vs 7.6%. **Conclusions:** In this analysis of two difficult to treat subgroups, addition of APA to AAP favored rPFS and OS. Safety, while generally consistent with the overall population, showed higher hypertension rate in $\geq$ 75 y and TEAEs leading to discontinuation in VD. Clinical trial information: NCT02257736. Research Sponsor: Janssen Research & Development.

	APA + AAP vs AAP; Median mo, HR (95%CI)		
End Points	**VD[a,b]**	**Age $\geq$ 75 y[b]**	**All[c]**
n	74 vs 69	188 vs 165	492 vs 490
rPFS[d]	16.4 vs 8.3; 0.69 (0.45-1.05)	24.7 vs 16.0; 0.54 (0.40-0.73)[†,e]	22.6 vs 16.6; 0.69 (0.58-0.83)[†]
OS[f]	29.7 vs 24.4; 0.76 (0.52-1.10)	34.9 vs 27.9; 0.75 (0.59-0.96)*,e	36.2 vs 33.7; 0.95 (0.81-1.11)
Time to:			
Initiation of cytotoxic chemotherapy[f]	25.5 vs 27.1; 0.84 (0.53-1.34)	60.7 vs 43.5; 0.68 (0.47-0.99)*,e	36.1 vs 34.2; 0.94 (0.78–1.13)
Chronic opioid use[f]	36.1 vs 39.7; 0.92 (0.54-1.57)	NE vs 62.4; 0.87 (0.60-1.26)	47.0 vs 53.3; 1.07 (0.87–1.32)
Pain progression[f]	31.3 vs 24.9; 0.89 (0.56-1.40)	32.7 vs 19.8; 0.78 (0.58-1.05)	21.8 vs 26.5; 1.12 (0.95-1.33)

ITT *$p < 0.05$, †$p < 0.0001$. [a]n = 135 liver and/or lung; n = 11 adrenal gland, not mutually exclusive; electronic case reports. [b]non-stratified post hoc. [c]stratified. [d]Primary end point. [e]p-value nominal unadjusted. [f]Final analysis.
NE, not estimable.

5038 **Poster Session**

Complementary detection of genomic alterations in metastatic castration-resistant prostate cancer (mCRPC) from CheckMate 9KD through analyses of tumor tissue and plasma DNA. *First Author: Mark Sausen, Bristol Myers Squibb, Princeton, NJ*

Background: Accurate analysis of the genomic alteration landscape within tissue- and plasma-derived tumor DNA using next-generation sequencing (NGS) may provide insights into specific patient populations that benefit from different therapies. The interchangeable use of tissue- and plasma-based assessments may benefit patients when tissue availability is limited, a common occurrence in individuals with mCRPC. To understand the potential sources of technical and biological variability in this setting, we performed comprehensive comparative analyses across 3 NGS platforms, using samples from patients enrolled in CheckMate 9KD, a phase 2 study of nivolumab combined with docetaxel, rucaparib, or enzalutamide for patients with confirmed mCRPC (NCT03338790). **Methods:** We performed retrospective integrated analyses of sequence and structural alterations identified through comprehensive genomic profiling (CGP) of DNA obtained from formalin-fixed, paraffin-embedded tissue specimens and cell-free DNA obtained from plasma. Tissue-based analysis was performed using the FoundationOne assay (F1, 395 genes), while the FoundationACT (FACT, 70 genes) and GuardantOMNI (OMNI, 500 genes) assays were used for plasma-based analysis. Analysis was performed on samples from 103 patients for which datasets from all 3 assays were available. Inter-platform analysis considered variants with $\geq$ 0.50% variant allele fraction and common to the shared pairwise targeted regions, while excluding synonymous variants. **Results:** Through broad profiling of DNA obtained from tissue and plasma, we uncovered previously identified recurrent alteration of *AR*, *TP53*, *PTEN*, and *TMPRSS2* fusion with ETS genes. Additionally, we found that 42% (F1), 45% (FACT), and 34% (OMNI) of patients harbored a combination of germline and somatic mutations in homologous recombination repair pathway genes. Across all samples, median tumor mutational burden was 3.5 mutations per megabase (mut/Mb) by F1 and 8.6 mut/Mb by OMNI. Inter-platform variant analyses demonstrated concordance of 52% for F1 vs FACT, 40% for F1 vs OMNI, and 75% for FACT vs OMNI. **Conclusions:** Overall, these data demonstrate the value of integrated tissue and liquid biopsy profiling in mCRPC. Both technical and biological sources of variation, including panel size, mutation detection algorithms, variant annotation and reporting, analytical performance, circulating tumor DNA levels, and tumor heterogeneity, may be captured differently by tissue- and plasma-based techniques, accounting for the discordance in reported results. Clinical trial information: NCT03338790. Research Sponsor: Bristol Myers Squibb.

5039 **Poster Session**

ARC-6: A phase 1b/2, open-label, randomized platform study to evaluate efficacy and safety of etrumadenant (AB928)-based treatment combinations in patients with metastatic castrate-resistant prostate cancer (mCRPC). *First Author: Sumit Kumar Subudhi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Standard-of-care (SOC) chemotherapy may contribute to immunosuppression by elevating intratumoral levels of adenosine, activating the A_{2a} and A_{2b} receptors on immune cells. Extracellular adenosine is primarily produced by the enzyme CD73; in prostate cancer, additional adenosine is also produced by the highly expressed protein, prostatic acid phosphatase (PAP). Etrumadenant (etruma) is an orally bioavailable, small-molecule, selective dual adenosine receptor antagonist and has been well tolerated in dose escalation studies as monotherapy or combined with chemo/immunotherapy. Adenosine axis inhibition combined with SOC regimens and/or immunotherapy may have a synergistic effect on the induction of sustained antitumor immunity against mCRPC. Initial results from the etruma + zimberelimab (zim; antiPD-1 mAb) + docetaxel (doc) arm are presented herein. **Methods:** ARC-6 (NCT04381832) is an ongoing, phase 1b/2, open-label, multicohort platform study to evaluate efficacy and safety of etruma combination therapy. All eligible patients (pts) have mCRPC that has progressed on androgen deprivation therapy and are checkpoint inhibitor-naive; additionally, for this arm, pts must be androgen signaling inhibitor (ASI)-experienced and taxane-naive. Study pts receive 150 mg etruma orally once daily + 360 mg zim IV every 3 weeks + SOC doc (EZD). The primary objectives are to evaluate safety and antitumor activity (prostate-specific antigen [PSA], radiographic, and composite response rates) of EZD. PSA levels are assessed every 3 weeks, and radiographic scans are performed every 12 weeks. PSA response-evaluable pts have baseline (BL) + $\geq$2 consecutive post-BL PSA assessments; radiographic response-evaluable pts have RECIST measurable or non-measurable disease per BL imaging + $\geq$1 post-BL radiographic assessment. **Results:** As of 22Jan2021, 17 pts have received EZD in phase 1b; 14 are PSA response-evaluable and 8 are radiographic response-evaluable. 15 (88%) pts reported treatment emergent adverse events (TEAEs); the most common ($>$ 30%) were lymphocyte count decreased and neutrophil count decreased (7 pts each; 41%), and hyponatremia and alopecia (6 pts each; 35%). Grade $\geq$3 treatment-related TEAEs were reported by 9 pts (53%). As of 22Jan2021, 16 pts were continuing treatment; median time on EZD for all pts was 9.9 weeks (0.127.4+ weeks). In response-evaluable pts, PSA response rate was 36% (5/14), radiographic response rate was 38% (3/8; 1 CR), and the composite response rate was 43% (6/14). **Conclusions:** Phase 1b results indicate that EZD treatment in pts with mCRPC had a manageable safety profile and was associated with clinical benefit. Having met phase 2 advancement criteria, randomized pt enrollment to EZD vs. doc is ongoing. Clinical trial information: NCT04381832. Research Sponsor: Arcus Biosciences, Inc.

5040 **Poster Session**

Differential responses to taxanes and PARP inhibitors (PARPi) in *ATM*- versus *BRCA2*-mutated metastatic castrate-resistant prostate cancer (mCRPC) patients (pts).

First Author: Christopher T Su, University of Michigan Rogel Cancer Center, Ann Arbor, MI

Background: PARPi have shown promise in mCRPC pts with mutations in DNA repair, but *ATM*- and *BRCA2*-altered pts may respond differently to PARPi. We hypothesized that differences may also exist for taxane therapy, aiding in treatment sequencing decisions. **Methods:** mCRPC pts (N = 137) with deleterious *ATM* or *BRCA2* mutations who received taxanes, PARPi, or both were identified from 8 US academic centers. Demographic, treatment, and survival data were collected. Kaplan-Meier analyses were performed for time-to-treatment-discontinuation (TTD), as well as overall survival (OS), from time of first taxane or PARPi therapy. Cox hazard ratio (HR) regression analyses were performed, adjusting for Gleason sum (≤7 vs. 8-10). For OS, receipt of subsequent therapies following first taxane or PARPi was also included as a covariate. **Results:** 50 *ATM*- and 87 *BRCA2*-mutated pts were identified. 40/50 (80%) of *ATM*-mutated pts received taxane only or taxane prior to PARPi, while 10/50 (20%) received PARPi only or PARPi prior to taxane. *ATM*-mutated pts showed a trend towards longer TTD when taxane was given first vs PARPi given first (P = 0.08, adjusted HR for taxane treatment 0.50 [95% CI: 0.24–1.08]). Considering all pts who received taxane first, *ATM*-mutated pts had longer TTD than *BRCA2*-mutated pts who received taxane first (*P*= 0.04, adjusted HR for *ATM* 0.61 [CI: 0.37–0.99]). Among *ATM*-mutated pts, OS was longer in those receiving taxane first (*P*= 0.06, adjusted HR for taxane treatment 0.33 [CI: 0.10–1.05]). Among *BRCA2*-mutated pts, 43/87 (49%) received taxane first and 44/87 (51%) received PARPi first. *BRCA2*-mutated pts had longer TTD when PARPi was given first vs taxane given first (*P*< 0.0001, adjusted HR for PARPi treatment 0.32 [CI: 0.19–0.56]). Considering all pts who received PARPi first, *BRCA2*-mutated pts also had longer TTD than *ATM*-mutated pts who received PARPi first (*P*= 0.0031, adjusted HR for *BRCA2* 0.29 [CI: 0.12–0.66]). There was no significant OS difference in *BRCA2*-mutated pts regarding which treatment was given first (*P*= 0.63, adjusted HR for PARPi treatment 1.18 [CI: 0.59–2.35]). **Conclusions:** Our data in *ATM*- and *BRCA2*-mutated mCRPC pts suggests a trend towards improved clinical outcomes when taxanes are used prior to PARPi in *ATM*-mutated pts, while the reverse sequence appears to be better for *BRCA2*-mutated pts. Research Sponsor: U.S. National Institutes of Health.

	Taxane given first	PARPi given first	Adjusted Cox p
Median duration of therapy in *ATM*-mutated pts (95% CI)	126 days (105-165) N = 40	87 days (17-222) N = 9	0.08
Median overall survival in *ATM*-mutated pts from time of first taxane or PARPi therapy	509 days (319-987) N = 25	279 days (18-not reached) N = 5	0.06
Median duration of therapy in *BRCA2*-mutated pts	122 days (84-136) N = 43	224 days (111-335) N = 33	< 0.0001
Median overall survival in *BRCA2*-mutated pts from time of first taxane or PARPi therapy	545 days (394-828) N = 32	453 days (343-632) N = 15	0.63

5041 **Poster Session**

Molecular, immunologic, and clinicodemographic landscape of MYC-amplified (MYCamp) advanced prostate cancer (PCa).

First Author: Brandon Arvin Virgil Mahal, University of Miami, Miami, FL

Background: The *MYC* oncogene is one of the most commonly amplified genes in PCa, contributes to androgen independent growth, and is potentially targetable. We sought to define the molecular, immunologic, and clinicodemographic landscape of *MYC*amp in advanced PCa to better understand progression and establish rationale for personalized treatments and combinations. **Methods:** Hybrid capture-based comprehensive genomic profiling (CGP) was performed on tumor samples from predominantly advanced PCa samples. *MYC*amp was defined as copy number (CN) ≥6. PD-L1 IHC was performed using Dako 22C3. A subset of patients (pts) with advanced PCa were selected from the Flatiron Health- Foundation Medicine (FM) clinicogenomic database (CGDB), a nationwide de-identified EHR-derived clinical DB linked to FM CGP data for pts treated from 01/2011-12/2020. The de-identified data originated from approximately 280 US cancer clinics (~800 sites of care). **Results:** The genomic profiles of 12,528 tissue samples from unique PCa pts (including hormone sensitive and castrate resistant) were evaluated. *MYC*amp was detected in 10.6%, with a median *MYC* CN of 8. Median age was 67 years (67 for *MYC*wt versus 68 for *MYC*amp). *MYC*amp occurred at a higher frequency in men with African (N = 190/1,473, 12.9%) versus European (N = 996/9,796, 10.2%) ancestry (P = 0.002), was more frequent in metastatic biopsy sites vs primary (15.7% vs 6.2%, P < 0.001), and was most common in liver mets (20.2%). *MYC*amp CN > 15 was enriched for PD-L1 positivity (26.1%) compared with *MYC*wt (9.8%) or *MYC*amp CN 6-15 (11.5%) (CN > 15 vs wt P = 0.025). In pts with *MYC*amp vs *MYC*wt PCa *AR*, *RAD21*, *PTEN*, *CCND1*, *ZNF703*, *FGF19*, *FGFR1*, and *FGF3* each had significantly higher rates of CN changes (all p < 0.001); *TP53* mutation was also more common with *MYC*amp (47.5% vs 39.7%, P < 0.001). *MYC*amp tumors were less likely to harbor microsatellite instability vs *MYC*wt (0.8% vs 2.4%, P < 0.001) and had higher tumor mutational burden (median 2.6 vs 1.7 mut/Mb, P < 0.001). In liquid samples with evidence of circulating tumor DNA (compositive tumor fraction [cTF] > 0) from PCa pts *MYC*amp was detected in 2.0% (28/1,402), and in 4.5% (20/445) with cTF > 20%. Among evaluable PCa pts in the CGDB, (67 *MYC*amp and 658 *MYC*wt) *MYC*amp did not significantly impact treatment decisions, with the majority receiving novel hormone therapies (35.8% *MYC*amp vs. 31.5% *MYC*wt) or chemotherapy containing regimens (37.3% *MYC*amp vs. 27.7% *MYC*wt) as first therapy after CGP report. **Conclusions:** Herein, we report the largest analysis to date of molecular, immunologic, and clinicodemographic features of *MYC*amp advanced PCa. These findings suggest that *MYC*amp defines a biologically distinct subset of PCa pts for whom personalized combination treatments utilizing targeted and/or immunotherapies may be effective. Independent cohorts are needed to validate these findings. Research Sponsor: Foundation Medicine.

5042 **Poster Session**

Pembrolizumab plus enzalutamide for enzalutamide-resistant metastatic castration-resistant prostate cancer (mCRPC): Updated analyses after one additional year of follow-up from cohorts 4 and 5 of the KEYNOTE-199 study.

First Author: Julie N Graff, OHSU Knight Cancer Institute, Portland, OR

Background: KEYNOTE-199 (NCT02787005) is a multicohort phase 2 study to evaluate pembrolizumab (pembro) in mCRPC. A previous analysis of patients with RECIST-measurable (cohort 4 [C4]) or bone-predominant nonmeasurable (cohort 5 [C5]) disease who were chemotherapy-naive and had progression while on enzalutamide (enza) found that pembro + enza showed antitumor activity and manageable safety. Long-term outcomes are of interest with immunotherapy; hence, updated efficacy and safety data after an additional 1 year of follow-up are presented. **Methods:** Pts were eligible if they had resistance to enza after prior response. Prior treatment with abiraterone was allowed. Pts received pembro 200 mg Q3W for up to 35 cycles + enza QD until progression, unacceptable toxicity, or withdrawal. Primary end point was ORR per RECIST v1.1 by blinded independent central review (BICR) in C4. Secondary end points were DOR (C4), and DCR, rPFS, OS and safety (both cohorts). **Results:** 126 pts (C4, 81; C5, 45) were treated. Median age was 72 years (range 43-92), 32.5% had visceral disease and 87.3% previously received ≥6 mo of enzalutamide; 121 pts (96.0%) discontinued, most because of progressive disease. Median (range) time from enrollment to data cutoff was 31.7 mo (23.1-37.1) in C4 and 35.5 mo (22.9-37.3) in C5. In C4, confirmed ORR was 12.3% (95% CI 6.1-21.5) (2 CRs, 8 PRs); median (range) DOR was 8.1 mo (2.5+ to 15.2), and 62.5% had a response ≥6 mo (Kaplan-Meier estimate). Additional efficacy analyses are outlined in the table. A total of 27.2% and 28.9% of pts in C4 and C5, respectively, experienced grade ≥3 treatment-related adverse events. Two pts in C4 died of immune-related AEs (Miller Fisher syndrome and myasthenia gravis). Incidence of any-grade (34.1%) and grade 3 or 4 (5.6%) rash, regardless of relatedness to treatment, was higher than previously reported for individual agents but manageable with standard-of-care treatments; 2 pts discontinued because of rash. **Conclusions:** After an additional 1 year of follow-up, pembro + enza continued to show antitumor activity and a manageable safety profile in pts with mCRPC who became resistant to enza. The treatment combination is being further evaluated in the ongoing phase 3 KEYNOTE-641 trial (NCT03834493). Clinical trial information: NCT02787005. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Efficacy outcomes.

	Cohort 4 RECIST Measurable N=81	Cohort 5 Bone Predominant Nonmeasurable N=45
ORR, by RECIST v1.1 by BICR, n/N (%)	10/81 (12.3)	NA
DCR, n/N (%)	43/81 (53.1)	23/45 (51.1)
PSA response rate in pts with baseline PSA, n/N (%)	13/80 (16.3)	4/45 (8.9)
Time to PSA progression		
Median (95% CI), mo	5.6 (4.2-10.4)	4.2 (4.2-6.2)
Progression free at 12 mo, %	31.8	19.0
rPFS		
Median (95% CI), mo	4.2 (2.5-6.0)	4.4 (3.2-6.2)
rPFS 12 mo, %	16.8	29.8
OS		
Median (95% CI), mo	17.6 (14.0-22.6)	20.8 (14.1-28.9)
OS 24 mo, %	36.6	44.2

5043 **Poster Session**

A phase (Ph) 1b/2 study of ribociclib (R) in combination with docetaxel (D) plus prednisone (P) in metastatic castration-resistant prostate cancer (mCRPC).

First Author: Ivan de Kouchkovsky, University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA

Background: The survival benefit of D in mCRPC is modest. CDK4/6 inhibitors such as R have shown synergistic activity with taxanes in pre-clinical cancer models. We sought to determine the safety and efficacy of R + D + P in mCRPC patients (pts). **Methods:** This was a Ph 1b/2 multicenter, open-label single arm trial of mCRPC pts with progression (PD) on ≥ 1 prior androgen receptor signaling inhibitor (ARSi) who had not previously received D for mCRPC (NCT02494921). Pts were treated with escalating doses of R in combination with D + P for 6-9 cycles, followed by single agent maintenance R until radiographic or clinical PD. The Ph 2 primary endpoint was 6-month (mo) radiographic progression-free survival (rPFS) rate by PCWG2 criteria, with a target rate of 55% and null hypothesis of 35%. Ph 2 pts underwent baseline circulating tumor cell (CTC) enumeration and genome sequencing (Epic Sciences). Cox proportional hazard model and log-rank test were used to test for associations between rPFS and CTC burden and copy number (CN) variants, respectively. **Results:** 43 pts were enrolled from 11/2015 to 6/2019. Median age was 68 (range 55-84). 20.9% of pts had visceral metastases. 33 (77%) had PD on prior abiraterone, 27 (63%) on enzalutamide, and 17 (40%) on both. In Ph 1b, 19 pts were enrolled. In the first cohort (D 75 mg/m^2 day [d] 1, R 200 mg/d d2-14 of every 21d cycle), 2 pts experienced DLTs (febrile neutropenia [FN] and grade 4 neutropenia). With an alternative dosing schema of D 60 mg/m^2 on d1, and R daily on d1-4 and 8-15 of cycle, with daily G-CSF support on d5-7, the MTD was not reached and D 60 mg/m^2 + R 400 mg/d was chosen as the recommended Ph 2 dose (RP2D). In total, 30 pts were treated at RP2D; median number of D cycles was 8.5 and 60% went on to receive maintenance R. The Ph 2 primary endpoint was met with a 6-mo rPFS rate of 65% (95% CI 50-85%). Median rPFS was 8.0 mos (95% CI 4.1-10.0). PSA response rate (RR) defined as ≥50% reduction was 27.6% (95% CI 12.7-47.2%) and objective RR was 30.8% (95% CI 9.1-61.4%). Among pts treated at RP2D, the most common grade ≥3 treatment-related adverse events were neutropenia (n= 11, 36.7%), lymphocytopenia (n=3, 10%); no cases of FN were observed. Baseline CTC burden was associated with an increased risk of radiographic PD or death (HR 1.038, 95% CI 1.001-1.074, p = 0.038). Pts harboring CTCs without MYC (4/11 pts) or CDK6 CN gain (7/11 pts) had prolonged rPFS compared to those with gene amplification (median rPFS 10.76 vs 4.11 mos, p = 0.03, and 7.01 vs 1.92 mos, p = 0.053, respectively). **Conclusions:** The combination of R + D was well tolerated and showed promising activity in mCRPC pts who had progressed on an ARSi. The Ph 2 study met its primary endpoint, with an encouraging 6-mo rPFS rate of 65%. Lack of MYC or CDK6 amplification on CTC sequencing was associated with longer rPFS. Funding: Novartis Pharmaceuticals, PCF YIA. Managed by the PCCTC. Clinical trial information: NCT02494921. Research Sponsor: Novartis, Other Foundation, Other Government Agency.

5044 **Poster Session**

CheckMate 9KD cohort A1 final analysis: Nivolumab (NIVO) + rucaparib for post-chemotherapy (CT) metastatic castration-resistant prostate cancer (mCRPC). *First Author: Russell Kent Pachynski, Washington University School of Medicine, St. Louis, MO*

Background: CheckMate 9KD is a phase 2 trial of NIVO (anti-PD-1) combined with either rucaparib, docetaxel, or enzalutamide for mCRPC. PARP inhibitors, like rucaparib, increase cellular DNA damage, particularly in tumors with DNA repair defects, leading to genomic instability and cell death. This DNA damage promotes immune priming and adaptive PD-L1 upregulation. Consequently, dual PD-(L)1 and PARP inhibition is a plausible therapeutic strategy for mCRPC. We report final results for cohort A1 (NIVO + rucaparib for post-CT mCRPC) of CheckMate 9KD. **Methods:** Cohort A1 enrolled patients (pts) with post-CT mCRPC (1–2 prior taxane regimens), ongoing ADT, ≤ 2 prior novel hormonal therapies (abiraterone, enzalutamide, etc) for mCRPC, and no prior PARP inhibitor treatment. Pts received NIVO 480 mg Q4W + rucaparib 600 mg BID until disease progression/unacceptable toxicity (NIVO dosing limited to 2 yrs). Coprimary endpoints: objective response rate (ORR) per PCWG3 criteria and prostate-specific antigen response rate (PSA-RR; ≥ 50% PSA reduction) in all treated pts and pts with homologous recombination deficiency positive (HRD+) tumors, determined before enrollment. Secondary endpoints included radiographic progression-free survival (rPFS), overall survival (OS), and safety. **Results:** Of 88 treated pts, median age 66 yrs (range, 46–85), 34.1% had visceral metastases and 65.9% had measurable disease. Median follow-up was 11.9 mo. Pts had a median of 4.5 NIVO doses and 3.8 mo of rucaparib. The table summarizes primary and key secondary efficacy results, and shows better outcomes for HRD+ vs HRD–/not evaluable (NE) tumors. In pts with *BRCA2* mutations, confirmed ORR was 37.5% (3/8 pts) and confirmed PSA-RR was 45.5% (5/11 pts). Any-grade treatment-related AEs (TRAEs) occurred in 93.2% of pts, most commonly nausea (40.9%) and fatigue (33.0%). Grade ≥ 3 TRAEs occurred in 54.5% of pts, most commonly anemia (20.5%) and neutropenia (10.2%). TRAEs led to discontinuation in 27.3% of pts. One pt had a stroke, considered related to rucaparib by the investigator, after 28 days on rucaparib and 2 NIVO doses and died 2 months later due to post-thrombolysis hematoma. **Conclusions:** NIVO + rucaparib is active in pts with HRD+ post-CT mCRPC, although the trial design and short follow-up limit assessment of benefits of the combination vs individual components. Pts with HRD– tumors did not appear to benefit from either drug. No new safety signals were observed with NIVO + rucaparib. Additional biomarker analyses are ongoing. Clinical trial information: NCT03338790. Research Sponsor: Bristol Myers Squibb.

Outcome (95% CI)	Total (N = 88)	HRD–/NE (N = 43)	HRD+ (N = 45)
ORR, %	n = 58[a] 10.3 (3.9–21.2)	n = 29[a] 3.4 (0.1–17.8)	n = 29[a] 17.2 (5.8–35.8)
Confirmed PSA-RR, %	n = 84[a] 11.9 (5.9–20.8)	n = 40[a] 5.0 (0.6–16.9)	n = 44[a] 18.2 (8.2–32.7)
Median rPFS, mo	4.9 (3.7–5.7)	3.7 (1.8–5.5)	5.8 (3.7–8.4)
Median OS, mo	13.9 (10.4–15.8)	9.4 (7.2–14.7)	15.4 (11.4–18.2)

[a]No. of evaluable pts.

5045 **Poster Session**

The impact of prior radiation therapy on outcome in a phase 2 trial combining sipuleucel-T (SipT) and ipilimumab (Ipi) in patients (pts) with metastatic castration resistant prostate cancer (mCRPC). *First Author: Li Zhang, University of California San Francisco, San Francisco, CA*

Background: SipT is an FDA-approved autologous cellular immunotherapy targeting Prostatic Acid Phosphatase (PAP) that improves survival in patients with mCRPC. Combining immunotherapies could provide opportunities to enhance efficacy. We performed a randomized phase II trial adding CTLA-4 blockade with Ipi following SipT treatment and assessed whether timing of this sequence could modify immune and/or clinical responses to this treatment. **Methods:** Fifty chemotherapy-naïve mCRPC pts were randomized to receive ipi (4 doses of 3mg/kg every 3 weeks) either immediately (n = 24) or 3 weeks (n = 26) following completion of sipT. Blood was collected at various time points of the study. Immune-related adverse events (irAE) were recorded. The primary endpoint was to determine the proportion of pts who achieved an antibody titer of ^{3}1:400 to PA2024, the targeting cassette in SipT and/or PAP. Clinical response was defined as ^{3}30% reduction in serum prostate specific antigen (PSA) compared to pre-treatment levels. Radiographic progression-free survival (rPFS) and overall survival (OS) were defined as from the date of randomization to the date of radiographic progression and the date of death, respectively, or last follow-up date. Luminex assays for anti-PAP and anti-PA2024 specific serum IgG and ELISpot for IFN-g production against PAP and PA2024 were used to assess antigen-specific B and T cells responses, respectively. Modulation of circulating immune cells was evaluated by CyTOF. **Results:** SipT + Ipi did not induce any unexpected irAEs. The timing of Ipi did not significantly alter the rates of clinical response, rPFS, OS, toxicity, nor antigen-specific B and T cell responses. Clinical responses were observed in 6 of 50 (12%) pts and were often durable (median 140 days, range 55-689 days). Pts experiencing irAEs were more likely to have a PSA response (P = 0.001). The median rPFS was 5.7 months (mos). The median OS was 31.9 mos. This treatment induced antibody and T cell immune responses irrespective of treatment arm. Single cell assessment bt CyTOF demonstrated that treatment induced CD4 and CD8 T cell activation that was more pronounced with the immediate schedule. Lower frequencies of CTLA-4 positive circulating T cells were associated with better clinical outcomes even at baseline. Lower frequencies of CTLA-4 positive T cells was associated with prior radiation therapy. Prior radiation treatment was associated with improved rPFS (6.5 vs. 3.9 mos, P = 0.004). **Conclusions:** These findings suggest that pre-existing immunity may help dictate responsiveness to Ipi and SipT combination immunotherapy in mCRPC pts. Prior radiation therapy seems to leave not only a lasting impression on the T cell compartment, but also can associate with improved clinical outcomes with subsequent immunotherapy. Clinical trial information: NCT01804465. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company, Prostate Cancer Foundation.

5046 **Poster Session**

ODENZA: A French prospective, randomized, open-label, multicenter, cross-over phase II trial of preference between darolutamide and enzalutamide in men with asymptomatic or mildly symptomatic metastatic castrate-resistant prostate cancer (CRPC). *First Author: Emeline Colomba, Cancer Medicine Department, Gustave roussy Paris Saclay University, Villejuif, France*

Background: Darolutamide (Daro) and enzamutamide (Enza) are both next generation androgen receptor inhibitors with demonstrated activity in men with CRPC. Although both agents are associated with survival improvement, their toxicity profiles are different. To help decipher whether this may impact on patient preference, we designed the ODENZA trial. **Methods:** ODENZA is a prospective, randomized, open-label, multicenter, cross-over, phase II trial of preference between Daro and Enza in men with asymptomatic or mildly symptomatic metastatic CRPC. Patients were randomized 1/1 to receive Daro 1200 mg/d for 12 weeks followed by Enza 160 mg/d for 12 weeks (Daro-Enza arm) or the reverse sequence (Enza-Daro arm). In both arms, the second treatment was given in absence of evidence of cancer progression at week 12. The primary endpoint was patient preference between the two drugs, as assessed by a questionnaire at week 24. The Prescott's test was used to determine treatment preference in patients fullfilling pre planned criteria (exposure to both treatments, no progression at week 12, and completion of the preference questionnaire). A p-value greater than 0.05 indicates that there is no difference in preference between treatments. Stratification factors were performance status and prior taxane for mCSPC. After week 24, patients went on to an extension period during which they received the chosen treatment until progression or toxicity. The main secondary objectives included reasons for preference, response at week 12, cognitive assessment, and toxicity. **Results:** Overall 249 pts were randomized, median age 72y (68; 79), ECOG PS 0 (56%), prior taxanes (22%). Two hundred pts fulfilled the pre-planned criteria for evaluation of the preference primary endpoint : 97 (48.5% [41.3;55.7]), 80 (40.0% [33.0;47.0]), and 23 (11.5% [6.8;16.2]) chose Daro, Enza, and had no preference, respectively (unilateral p-value of 0.92). After preference assessment, 186 patients entered the extension period: 103 (55.4%) and 83 (44.6%) received Daro and Enza respectively. The most common factors influencing patient preference all numerically favored Daro over Enza, without significant differences were: less fatigue (44% vs 29%), ease of taking the medication (37% vs 31%), better quality of life (36% vs 28%), ability to be more active (26% vs 15%), ability to concentrate (22% vs 15%) and less falls (6% vs 3%). A PSA50 response was achieved in 76.2% and 83.9% at week 12 with Daro and Enza respectively (p = 0.13). Fatigue was the most frequently reported all grade adverse event at week 12, in 21% and 36% with Daro and Enza, respectively. **Conclusions:** More patients with early mCRPC preferred Daro over Enza, although the difference did not reach significance, with fatigue as the key influencing factor. Clinical trial information: NCT03314324. Research Sponsor: ODENZA.

5047 **Poster Session**

Talazoparib (TALA), an oral poly (ADP-ribose) polymerase (PARP) inhibitor for men with metastatic castration-resistant prostate cancer (mCRPC) and DNA damage response (DDR) alterations: Detailed safety analyses from TALAPRO-1 trial. *First Author: Niven Mehra, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

Background: PARP inhibitors have recently been approved for the treatment of mCRPC. In this Phase 2 study, we explore the safety profile of TALA in men with mCRPC with the aim of understanding how patients (pts) with adverse events (AEs) were managed during the trial. **Methods:** TALAPRO-1 (NCT03148795) is a single-arm, open-label, phase 2 study of TALA in pts with progressive mCRPC, measurable soft tissue disease, and DDRm likely to sensitize to PARPi (*ATM, ATR, BRCA1/2, CHEK2, FANCA, MLH1, MRE11A, NBN, PALB2, RAD51C*), who received ≥1 taxane-based chemotherapy and progressed on ≥1 novel hormonal therapy (enzalutamide/abiraterone). The primary objective was confirmed objective response by central independent review; the assessment of safety included AEs, incidence of dose modifications and of permanent treatment discontinuation due to AEs, and clinical laboratory tests. **Results:** In the TALA-treated population (1 mg/daily; n=127), 95.3% (121/127) experienced all-causality AEs. The most common (≥15%) hematologic AEs were anemia (any grade, 48.8%; G3, 30.7% [no G4 events]), thrombocytopenia (all grade, 18.9%; G3/4, 8.7%), and neutropenia (all grade, 16.5%, G3, 7.9% [no G4]). Median time from first dose of TALA to onset of first episode of G≥3 anemia, neutropenia, and thrombocytopenia was 56, 48, and 17 days, respectively. G3 anemia lasted a median of 7 days, G3 neutropenia lasted a median of 12 days, G3 and G4 thrombocytopenia lasted a median of 8 and 11 days, respectively. Hematologic AEs typically occurred during the first 4–5 months of TALA treatment and were managed by dose modifications and supportive care. 34.6% of pts received a blood transfusion product, and most transfusions occurred when hemoglobin was between 7.0–10.0 g/dL. Overlapping G3/4 hematologic AEs were infrequent on TALA (anemia + neutropenia 4.7%; anemia + thrombocytopenia 5.5%; neutropenia + thrombocytopenia 1.6%). In pts who had anemia, 12.6% also had fatigue; in those with thrombocytopenia, 4.7% had a subsequent bleeding event; in those with neutropenia, 1.6% had an overlapping infection. The most common non-hematologic AEs (≥15%) were nausea (any grade, 33.1%; G3/4, 2.4%), decreased appetite (any grade, 28.3%; G3/4, 3.1%), and asthenia/fatigue (any grade, 23.6%/19.7%; G3/4, 3.9%/1.6%). In the treated population, dose reduction of TALA due to all-causality AE occurred in 33 pts (26.0%). Treatment discontinuation due to all-causality AEs was low and occurred in 15 pts (11.8%); the most frequent (≥2 pts) AEs leading to discontinuation of TALA were back pain and platelet count decrease (each, 1.6% [2/127 pts]). There were no treatment-related deaths. **Conclusions:** A manageable safety profile and durable antitumor effects were observed with TALA in men with heavily pretreated mCRPC in this phase 2 study. Clinical trial information: NCT03148795. Research Sponsor: Pfizer.

5048 **Poster Session**

Association of plasma tumor DNA (ptDNA) with increased risk of venous thromboembolism (VTE) in metastatic castration resistant prostate cancer patients (mCRPC). *First Author: Vincenza Conteduca, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori IRCCS, Italy, Meldola, MA, Italy*

Background: Cancer is a risk factor for VTE. In mCRPC, ptDNA is an independent predictor of outcome (*Romanel, Sci Transl Med 2015; Conteduca, Br J Cancer 2020*). We firstly aimed to investigate the association between ptDNA and VTE in mCRPC men treated with androgen receptor signaling inhibitors (ARSI) **Methods:** This prospective biomarker study included mCRPC patients treated with abiraterone and enzalutamide from April 2013 to December 2018. We excluded patients with a previous VTE history and/or ongoing anticoagulation. Targeted next-generation sequencing was performed to determine ptDNA fraction from pre-treatment plasma samples. Assessment of VTE risk based on survival analysis was performed using cumulative incidence function and estimating sub-distributional hazard ratio (SHR) **Results:** Median age of 180 enrolled patients was 74 years (range 42-90). Of these, 60 (33.3%) were chemotherapy-naive. At a median follow-up of 58 months (range 0.5-111.0), 21 patients experienced VTE (venous thrombosis and/or pulmonary embolism) with a cumulative incidence of VTE at 12 months of 17.1% (95% CI 10.3-23.9). Before starting ARSI, ptDNA fraction above median value of 0.175, presence of visceral metastasis (mets), prior chemotherapy and serum lactate dehydrogenase (LDH) were significantly associated with higher incidence of VTE compared with patients with no thrombosis (12-month estimate, 18.6 *vs* 3.5%, P=0.0003; 44.4 *vs* 14.8%, P=0.015; 24.7 *vs* 4.5%, P=0.006; and 30.0 *vs* 13.5%, P=0.050, respectively). In the multivariate analysis (Table) including baseline ptDNA level, visceral, liver and lung mets, number of lesions, LDH, high ptDNA fraction was the only independent factor associated with the risk of thrombosis (HR 5.78, 95% confidence interval [CI] 1.63-20.44, P=0.006). All these patients received anticoagulant therapy for VTE. No ARSI discontinuation and VTE-related death were reported, and no significant difference in progression-free/overall survival was observed in mCRPC patients with and without VTE. **Conclusions:** These results suggest that baseline ptDNA fraction in mCRPC patients treated with ARSI is associated with increased risk of VTE. These patients may be followed up more closely for the risk of VTE and the need for a primary thromboprophylaxis should be taken into account in mCRPC with elevated ptDNA concentration. Validation of these findings in larger multicenter trials is warranted. Research Sponsor: None.

Multivariable analysis of risk factors associated with VTE events.

	SHR (95% CI)	p
ptDNA fraction (high *vs* low)	5.78 (1.63-20.44)	0.006
Visceral mets (yes *vs* no)	1.12 (0.21-6.13)	0.893
Liver mets (yes *vs* no)	2.22 (0.25-19.28)	0.470
Lung mets (yes *vs* no)	2.57 (0.70-9.42)	0.153
Median number of lesions (high *vs* low)	0.73 (0.24-2.22)	0.584
Prior chemotherapy (yes *vs* no)	3.87 (0.76-19.76)	0.104
LDH (> *vs* ≤ Upper Normal Limit)	1.61 (0.53-4.87)	0.395

5049 **Poster Session**

Circulating tumor DNA fraction (ctDNA%) to independently predict for clinical outcomes in patients (pts) with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Corinne Maurice-Dror, BC Cancer, Vancouver, BC, Canada*

Background: CtDNA% (the tumour-derived proportion of cell-free DNA (cfDNA)) is abundant in >60% of mCRPC pts and associates with adverse clinical prognostic factors. However, prognostic associations have not been comprehensively tested across clinical contexts. We evaluated the utility of ctDNA% as an independent prognostic biomarker in patients with mCRPC prior to first-line (1L) therapy. **Methods:** 410 treatment-naïve mCRPC pts had blood samples drawn prior to 1L therapy and followed prospectively for outcomes. Plasma cfDNA was subjected to deep targeted sequencing and ctDNA% was calculated using validated methods (Annala, *Cancer Discov*, 2018). Overall survival (OS), PSA progression free survival (PSA PFS) and PSA declines ≥50% from baseline (PSA50 response rate (RR)) were stratified by ctDNA% and compared using Kaplan--Meier and Cox proportional hazards analysis. **Results:** Median age was 73 yrs. (range 45-98), the majority of pts had ECOG PS 0-1 (78%) and 9.5% had liver metastases at baseline. The most common 1L therapy employed was androgen receptor pathway inhibitors (90%). Median follow-up was 21 mo. (range 1-75) and median ctDNA% was 4.9% (range: 0-89%). Stratifying patients into high ctDNA (>30%) and Low ctDNA (≤2%) groups showed stronger association with OS and PSA PFS than grouping by median (Table). In a univariate comparison to pts with low ctDNA (≤2%), pts with high ctDNA% (>30%) had significantly shorter median PSA PFS, median OS and a lower PSA50 RR (Table). In a multivariable adjustment for clinical prognostic factors and cfDNA concentration, high ctDNA% remained strongly associated with OS (HR= 3.3, 95%CI: 2.1-5.3, p<0.001) and PSA PFS (HR: 3.7, 95%CI: 2.4-5.9, p<0.001). Although ctDNA% and total cfDNA concentration were correlated (R^2=0.55), association with OS was stronger for ctDNA% than cfDNA concentration (stratified at median; HR: 2.9 (2.3-3.7), p<0.001 vs HR: 2.1 (1.7-2.6), p<0.001). **Conclusions:** In a large cohort of treatment-naïve mCRPC pts, ctDNA% prior to 1L treatment provided strong prognostic information independent of known clinical factors. These data further demonstrate the multipronged clinical utility of ctDNA-based profiling for actionable genomic alterations. Research Sponsor: BC Cancer Foundation, Other Foundation.

Outcomes.

	ctDNA ≤2% (n =169)	ctDNA >30% (n = 89)	ctDNA ≤ median (n = 208)	ctDNA > median (n = 202)
Median OS (months)	39.8	9.9	37.6	15.9
HR (95% CI)	4.8 (3.5-6.5) p<0.001		2.9 (2.3-3.7) p<0.001	
Median PSA PFS (months)	13.0	2.9	12.8	5.6
HR (95% CI)	4.4 (3.2-6.2) p<0.001		2.5 (2.0-3.1) p<0.001	
PSA50 RR	77%	51%	76%	62%
χ^2	p<0.001		p=0.004	

5050 **Poster Session**

An open-label, pharmacokinetic study to determine the bioavailability, safety and tolerability of single dose oral docetaxel in metastatic prostate cancer (mPC) patients treated with IV docetaxel. *First Author: Christopher G. C. A. Jackson, Dunedin Hospital, Dunedin, New Zealand*

Background: Docetaxel has poor oral bioavailability in part due to extrusion by intestinal p-glycoprotein. To improve IV solubility, it is fomulated with the nonionic surfactant polysorbate 80, requiring steroid premedication to manage hypersensitivity type reactions. Oral administration has the potential to improve tolerability, reduce day-stay utilization and improve patient convenience and allows investigation of alternative dosing schedules. Oradoxel is a new combination of oral docetaxel capsules plus the novel gut-selective P-glycoprotein inhibitor encequidar (HM30181A). **Methods:** Patients with mPC receiving IV docetaxel were enrolled in 3 cohorts with a dose escalation schedule of Oradoxel 75 mg/m^2 in Cohort 1, 150 mg/m^2 in Cohort 2, 300mg/m^2 in Cohort 3. Oradoxel was given 3 weeks before or after IV docetaxel treatment. Intensive PK samples were taken on days 1-5 for Oradoxel and days 1-4 for IV docetaxel. Dose limiting toxicity (DLT) or serious adverse events (SAE) were assessed per CTCAE v4.03. **Results:** 3 evaluable patients in each Cohort were studied. No DLT, MTD, or drug-related SAE were observed. PK parameters of Oradoxel vs IV docetaxel are summarized in the table below. Mean absolute bioavailability of Oradoxel was 15.9% (range 8-25%). PK became non linear at 300mg/m^2. **Conclusions:** Oradoxel was well tolerated. Based on the results of this and related studies, Oradoxel 300mg/m^2 in divided doses is being further evaluated in phase 2 studies. Clinical trial information: 12616000983404. Research Sponsor: Athenex.

	Oradoxel (N = 3/group)			IV (N = 9)
Docetaxel Dose (mg/m^2)	**75**	**150**	**300**	**57 (49 – 74)[a]**
Absolute bioavail. F (%)	18.4±6.4	18.1±5.7	11.0±3.0	N/A
C_{max} (ng/mL)	103±19	192±69	264±120	1388±237
AUC_{0-t} (ng·h/mL)	395±78	918±385	1213±422	1965±336
$AUC_{0-\infty}$ (ng·h/mL)	478±98	1003±383	1346±451	2053±325
t_{max} (h)[b]	2.00 (1.00-2.50)	2.75 (0.75-3.00)	2.50 (2.50-6.00)	1.00 (0.67-1.07)
$t_{½}$ (h)	21.1±4.6	19.7±7.4	30.0±4.3	21.5±6.1

Results are in mean ± SD or otherwise specified. [a]Mean (range). [b]Median (range).

5051 **Poster Session**

Indirect treatment comparison of the efficacy of olaparib 300 mg tablets BID and cabazitaxel 25 mg/m^2 every 3 weeks plus daily prednisolone and granulocyte colony-stimulating factor in the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Tim Reason, Estima Scientific, London, United Kingdom*

Background: In PROfound, olaparib demonstrated improved radiological PFS (rPFS) and overall survival (OS) versus new hormonal agent (NHA) in patients with homologous recombination repair mutated (HRRm) mCRPC that had progressed on prior NHA. This efficacy was observed across prespecified subgroups including patients treated with prior taxane therapy and for whom intravenous cabazitaxel is an alternative treatment option. The relative efficacy of olaparib versus cabazitaxel has not been assessed in head-to-head studies. An indirect treatment comparison (ITC) was performed to simulate the comparative efficacy of olaparib and cabazitaxel in patients with HRRm mCRPC after prior taxane and NHA. **Methods:** Fixed-effects frequentist ITCs were conducted using efficacy data from the prior taxane subgroup of PROfound (NCT02987543) and published data from the Phase IV CARD study of cabazitaxel versus NHA after prior NHA and taxane treatment (NCT02485691). Baseline variables feasible for comparison across studies were assessed for effect modification. Efficacy analyses were performed on the hazard ratios (HR) of rPFS by independent central review and OS. The OS analysis was performed using the final PROfound OS results, which included switching from NHA to olaparib after progression, and using results that were adjusted for switching. In the absence of biomarker subgroup data, the efficacy results of the overall population in CARD were assumed generalizable to the HRRm biomarker population of PROfound, such that mutation status is not a modifier of relative treatment effect for cabazitaxel versus NHA. Results were presented for the comparison of olaparib with cabazitaxel in the BRCA1-/BRCA2-mutated (BRCAm) and BRCAm/ATM populations. **Results:** The ITC HR for rPFS was 0.36 (95% confidence interval 0.20–0.64) in BRCAm and 0.51 (0.31–0.84) for the BRCAm/ATM population. Without adjustment for switching in PROfound, the ITC HRs for OS in the BRCAm population and BRCAm/ATM population were 0.99 (0.55–1.78) and 0.88 (0.52–1.47), respectively; after switch adjustment, the OS HRs were 0.47 (0.12–1.79) and 0.44 (0.17–1.10), respectively. **Conclusions:** The ITC results suggest that olaparib is associated with significantly improved rPFS versus cabazitaxel in the treatment of BRCAm and BRCAm/ATM patients who have progressed on taxane and NHA therapy. After removing the effect of switching from NHA to olaparib in PROfound, olaparib appears associated with a non-significant OS improvement versus cabazitaxel in both populations. The results require confirmation in comparative studies. Analysis limitations include uncertainty over the efficacy of cabazitaxel versus NHA in HRRm mCRPC patients, and heterogeneity in prior taxane and NHA therapy. Clinical trial information: NCT02987543. Research Sponsor: AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

5052 **Poster Session**

A phase II study evaluating the efficacy of enzalutamide and the role of ARv7 in metastatic castration-resistant prostate cancer (mCRPC) patients (pts) with visceral disease. *First Author: Pierangela Sepe, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Enzalutamide is a second-generation androgen receptor inhibitor that showed to prolong survival in different setting of prostate cancer. Visceral metastases, occurring in 10–30% of mCRPC pts, have been associated with poor outcomes. Given the poor prognosis, trial investigating hormone therapies often excluded men with visceral disease, especially in the pre-docetaxel setting. To date, there are no prospective studies designed ad hoc to test hormone therapies in this subgroup of pts. **Methods:** In this open label phase II multicentre study mCRPC pts with visceral metastases were treated with enzalutamide 160 mg orally once daily as first or second line after docetaxel until progressive disease or unacceptable toxicity. Pts were eligible if they had documented measurable metastatic visceral disease (according to RECIST 1.1 criteria), including lesions in lung or liver or extraregional lymphnodes. Pts must have PSA progression or radiographic progression (according to PCWG2). Primary endpoint was to determine the clinical benefit, as measured by 3-months (mo) disease control rate (DCR) defined as the proportion of pts with best overall response of confirmed complete (CR) or partial responses (PR) or stable disease as per RECIST 1.1 at mo 3. Secondary endpoints were safety, quality of life (assessed by EQ-5D-5L e FACT-P questionnaire), pain assessment (by BPI-SF questionnaire). Exploratory objectives were to assess the association between ARv7 splicing variants (in CTCs samples) and treatment response/resistance. For CTC and ARv7 detection, we used the Adna test Prostate Cancer Panel. **Results:** From March 2017 through January 2021, 68 pts were enrolled at 6 Italian centres. One pt never started treatment because of withdrawal of consent. Median age was 70 years (IQR 65- 78). All pts presented with visceral disease at baseline: 27, 6, 55 pts presented with lung, liver and lymphnodes lesions, respectively. 26 pts presented with only one metastatic site, 22 pts with two, while the remaining part with multiple sites. 15 pts received a previous treatment with docetaxel in the mCRPC phase. The median follow-up was 10 mo. The median time on treatment was 8 mo. At mo 3, 24 pts presented a stable disease, 1 pt achieved a confirmed CR and 20 pts a PR for a 3 mo-DCR of 67% (45/67). Discontinuations due to adverse-events, disease-related death, or disease progression occurred in 6%, 7%, and 40% of pts, respectively. So far, only 26 patients were evaluated for baseline CTC and ARv7. Interestingly, 75% of patients experiencing a progression at month 3 were classified as ARv7 positive at baseline. **Conclusions:** The study met its primary endpoint showing enzalutamide is an active treatment option for men with mCRPC and visceral disease in both pre or post-docetaxel setting. CTCs status combined with ARv7 detection could be useful to personalize treatments. Clinical trial information: NCT03103724. Research Sponsor: Astellas.

5053 **Poster Session**

Immunogenic priming with ^{177}Lu-PSMA-617 plus pembrolizumab in metastatic castration resistant prostate cancer (mCRPC): A phase 1b study. *First Author: Rahul Raj Aggarwal, University of California, San Francisco, San Francisco, CA*

Background: Immune checkpoint inhibitors have limited single agent activity in microsatellite-stable mCRPC. ^{177}Lu-PSMA-617 (Lu) is a PSMA-targeting radioligand therapy that has demonstrated promising anti-tumor activity. We sought to determine whether a single dose of Lu can induce an immunogenic priming effect to improve outcomes of men with mCRPC subsequently treated with pembrolizumab (P). **Methods:** We undertook a phase 1b, single arm trial enrolling chemotherapy-naïve mCRPC patients (pts) with progression (PD) on at least one prior androgen signaling inhibitor (NCT03805594). Pts were required to have $\geq$ 3 PSMA-avid lesions on ^{68}Ga-PSMA-11 PET and measurable disease by RECIST 1.1 criteria. No genomic selection was undertaken. Pts were enrolled sequentially on one of three schedules: A) Single dose of Lu (7.4 GBq) followed by initiation of P (200 mg IV q 3 weeks) 28 days later; B) Lu x 1 dose given concomitantly with first P administration; C) Lu x 1 dose given on C2D1 following initiation of P on C1D1. Pts were treated with P until confirmed radiographic or clinical PD. The primary endpoint was safety; key secondary endpoints included PSA response, objective response rate by RECIST 1.1 criteria (ORR), median duration of response (DOR), and radiographic progression-free survival (rPFS). **Results:** 18 pts were enrolled, 6 per schedule. The median age was 64 (range 51 – 80) and 44% of pts had visceral metastases. The median baseline number of PSMA-avid metastatic lesions was 20 (range 6 – 50+). Six pts (33%) had progressed on prior abiraterone, 4 (22%) on enzalutamide, and 8 (44%) on both. There were no dose-limiting toxicities and one Grade $\geq$ 3 treatment-related adverse event (AE) (inflammatory arthritis, schedule B). There were no grade $\geq$ 3 hematologic AEs. The ORR was 8/18 (44%) and median DOR has not been reached (range 1.9+ – 15.9+ months). Four pts (2 on schedule A, 1 on schedule B, 1 on schedule C) with durable partial responses remain on study treatment for 5.4+, 8.9+, 9.2+, and 17.8+ months, respectively. The median rPFS was 6.5 months (95% CI: 2.5 – 9.8). PSA30, PSA50, and PSA90 response rates were 44%, 28%, and 17%, respectively. Fourteen pts (78%), including all durable responders, had somatic genomic data available. One (7%) harbored a DNA repair mutation (*BRCA1*, non-responder), none were MSI-high, and all carried low tumor mutational burden ($\leq$ 5 mutations/MB). Single cell sequencing of the immune microenvironment from paired metastatic tumor biopsies is underway. **Conclusions:** ^{177}Lu-PSMA-617 as a priming dose followed by pembrolizumab was well tolerated and leads to durable responses in a subset of mCRPC without high mutational burden or microsatellite instability, suggesting a possible immunogenic priming effect of radioligand therapy. Further evaluation of the combination is ongoing in a phase 2 study. Clinical trial information: NCT03805594. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Philanthropic gift - Gene and Ethel Daly.

5054 **Poster Session**

Using real-world outcomes to evaluate the predictive power of tissue-assessed genomic biomarkers for taxane versus novel hormonal therapy (NHT) outcomes in metastatic castration-resistant prostate cancer (mCRPC). *First Author: Ryon Graf, Foundation Medicine, Cambridge, MA*

Background: No established genomic biomarkers exist for guiding treatment decisions between novel hormonal therapy (NHT) vs taxane chemotherapy in mCRPC. However, specific alterations in *AR* have been associated to decreased responsiveness to NHT in this setting. Leveraging routine comprehensive genomic profiling (CGP) testing of mCRPC tissue samples, we hypothesized that patients (pts) with *AR* amplification (*AR*amp) would have better outcomes on taxanes over NHT. **Methods:** Pts were selected from Flatiron Health (FH)-Foundation Medicine (FMI) clinico-genomic database (CGDB), a nationwide deidentified electronic health record database linked to CGP. Data originated from approximately 280 US cancer clinics (~800 sites). CGP results (including analysis of *AR* and 15 other genomic biomarkers) were obtained from mCRPC tumor tissue collected up to 180 days before or 30 days after initiation of new systemic therapy between 1/1/11 - 6/30/20, and linked to PSA response, time to next therapy (TTNT) and overall survival (OS). Multivariable treatment interaction models were adjusted for drug assignment imbalances (line of therapy, prior NHT or taxane use, PSA, alkaline phosphatase, hemoglobin, albumin, years to CRPC, biopsy site) using inverse probability of treatment weighting via propensity scores. **Results:** Among 5754 evaluable mCRPC lines of therapy, 180 receiving NHT and 179 receiving taxanes met inclusion criteria, 359 total from 308 unique patients. Pts with *AR*amp vs no *AR*amp on NHT had worse PSA response (median +57.3% vs. -31.4%, p = 0.002), TTNT (HR: 2.03, p $<$ 0.001), and OS (HR: 2.28, p $<$ 0.001), but had no difference in outcomes on taxanes. Multivariable interaction Cox models found *AR*amp independently associated to better TTNT on taxanes vs. NHT (HR: 0.48, p = 0.010), similar to pts with *RB1* alterations (HR: 0.46, p = 0.027). Consistent treatment interactions were seen with OS for *AR*amp (HR: 0.53, p = 0.025) and *RB1* (HR: 0.32, p = 0.024). While *CDK12* was not predictive, it independently associated with worse OS overall (HR: 2.25, p = 0.0011). In the 55 pts who received NHT followed by taxane immediately after, *AR*amp pre-NHT was associated with better TTNT on the subsequent taxane than on the initial NHT (HR: 0.40, p = 0.028). Of these, 33 had PSA responses evaluable, and *AR*amp pre-NHT was significantly associated with better PSA decline on the subsequent taxane, despite disadvantage of first progressing on NHT (OR: 10.9, p = 0.021). **Conclusions:** Genomic biomarkers routinely identified with CGP such as *AR*amp may aid in identifying mCRPC pts who are to obtain greater benefit from taxane chemotherapy instead of NHT. Prospective efforts are needed to further validate the utility of CGP for assisting treatment decisions for mCRPC patients. Research Sponsor: Foundation Medicine.

5055 **Poster Session**

Long-term adverse events (AE) in patients with metastatic castration-resistant prostate cancer (mCRPC) receiving prostate-specific membrane antigen (PSMA)-based targeted radionuclide therapy (TRT). *First Author: Michael Sun, Weill Cornell Medicine, New York, NY*

Background: PSMA-TRT is a promising investigational treatment for patients with mCRPC. Expected short-term toxicities associated with PSMA-TRT include dose-dependent myelosuppression and xerostomia. However, there is a lack of information regarding long-term effects of PSMA-TRT on marrow, renal, and liver function. Additionally, potential organ dose limits for radiation are derived from studies of external beam radiation, which may not be applicable to TRT. **Methods:** Men treated on prospective clinical trials of PSMA-TRT, from 2003 through 2020 with at least six months of follow-up were included. Variables included treatment, co-morbidities, baseline and most recent renal, liver, and marrow function, along with respective short-term ($<$ 6 months) and long-term toxicities. AEs were graded using CTCAE version 5 and attribution was assessed with most recent clinical follow up. Multivariable logistic regression was used to control for type of TRT, comorbidities, and subsequent therapies. **Results:** 71 (59.7%) patients who received 177Lu-J591, 30 (25.2%) 177Lu-PSMA-617, 11 (9.2%) 225Ac-J591, and 7 (5.9%) 90Y-J591 were included, with median follow up 18 months (range 6-133). Long-term (most recent) laboratory values and AEs are summarized in the table. A majority of AEs were attributed to alternate etiologies. 5 of 14 cases of grade (Gr) $\geq$2 creatinine increase, 3 of 36 cases of Gr $\geq$2 platelets, 2 of 14 cases of Gr $\geq$2 bilirubin, 1 of 15 cases of Gr $\geq$2 AST increase, and 1 of 5 cases of Gr $\geq$2 ALT increase were deemed possibly related to PSMA-TRT. Only two Gr $\geq$3 AEs were attributed to possibly being related to PSMA-TRT: one case of Gr 4 creatinine elevation and one case of Gr 3 ALT elevation. On multivariable analysis, alpha-TRT was associated with hepatic AEs (OR 4.38, p = 0.047), and there was a trend towards higher Charlson Comorbidity scores associating with hematologic AEs (OR 1.27, p = 0.095). **Conclusions:** This is the largest analysis to-date of long-term AEs in patients who have received PSMA-TRT. Long-term effects on renal, liver, and marrow function are infrequent. Research Sponsor: Weill Cornell Medicine, Other Foundation, Other Government Agency, U.S. National Institutes of Health.

Category	Median (IQR)	Total AE (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Alternate cause (%)
Creatinine	0.92 (0.8, 1.33)	36 (30.2)	22 (18.5)	8 (6.7)	4 (3.4)	2 (1.7)	18/36 (50)
AST	36 (24, 57)	65 (54.6)	50 (42)	9 (7.6)	4 (3.4)	2 (1.7)	34/65 (52)
ALT	23 (15, 32)	19 (16)	14 (11.8)	1 (0.8)	2 (1.7)	2 (1.7)	11/19 (58)
Total bilirubin	0.6 (0.5, 1)	21 (17.6)	7 (5.9)	9 (7.6)	3 (2.5)	2 (1.7)	17/21 (81)
WBC	5.5 (3.7, 7.6)	21 (17.6)	0	10 (8.4)	5 (4.2)	6 (5.0)	21/21 (100)
Platelets	136 (60, 202)	68 (57.1)	32 (26.9)	10 (8.4)	13 (10.9)	13 (10.9)	49/68 (72)

5056 **Poster Session**

VERU-111, an oral cytoskeleton disruptor, to treat men with metastatic castration-resistant prostate cancer (mCRPC) who failed an androgen receptor targeting agent. *First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: VERU-111 is an oral cytoskeletal disruptor that disrupts microtubules supporting the cytoskeleton and has no affinity for multidrug resistance proteins. A phase 1b/2 clinical study has been conducted to establish the maximum tolerated dose (MTD) and evaluate the preliminary efficacy in men with mCRPC also resistant to androgen receptor targeting agents. **Methods:** In the phase 1b component of the study, a 3+3 design with escalating oral dosing of 4.5 mg to 81 mg (7 days on drug/14 days off per 21-day cycle) was utilized. The schedule was also expanded to continuous dosing/cycle. The phase 2 portion utilized 63 mg daily dosing to evaluate efficacy in approximately 40 taxane-naïve men with mCRPC that have failed at least one androgen receptor targeting agent. **Results:** In the phase 1b portion of the study, 30 taxane-naïve men with mCRPC and a median age of 76 (61-92) were enrolled. 8 had received prior enzalutamide, 12 abiraterone and 10 both. 8 men had bone mets, 5 lymph node, 5 mixed and 1 had soft tissue metastases at study entry. The MTD of VERU-111 is 72mg (3/11 men had grade 3 diarrhea) and the recommended phase 2 dose is 63mg. Grade 3 diarrhea was not observed at doses $\leq$ 63mg per day and the most common non-dose limiting AEs were mild to moderate nausea, vomiting, diarrhea, and fatigue, with no observed neurotoxicity or neutropenia. Efficacy was assessed by PSA and bone/CT scans. In men treated for $\geq$ 4 continuous 21-day cycles, 6/10 (60%) had PSA declines, 4(40%) men had $\geq$ 30% declines and 2(20%) $\geq$ 50% declines compared to their 21-day cycle baseline PSA. Median PFS is currently 12 months (6-23+ months) with 3 patients continuing on study, 2 of which have been on study for approximately 2 years. In patients receiving at least a single dose of $\geq$ 63 mg daily (n=19), objective tumor responses were seen in 3 men (16%). The median rPFS in these patients is currently 12.4 months. In the phase 2 portion of the study, 55% of the patients had bone only metastases, 11% had nodal only, 32% had mixed bone and nodal disease and 3% had visceral disease at study entry. 6/32 (19%) were previously treated with abiraterone alone, 12/32 (38%) with enzalutamide alone, and 14/32 (44%) had abiraterone in combination with enzalutamide, proxalutamide or apalutamide. The phase 2 portion of the study is ongoing and objective tumor responses have been observed including a CR and PRs and PSA decreases >50%. Patients have been on study as long as 9 months. **Conclusions:** This phase 1b/2 clinical trial, demonstrates that oral daily dosing of VERU-111 has a favorable safety profile and that chronic dosing is feasible. The recommended phase 2 dose of 63mg daily has significant durable antitumor activity. These data support a potential prominent role of VERU 111 for the treatment of men with mCRPC who previously failed an androgen receptor targeting agent and prior to the administration of intravenous chemotherapy. Clinical trial information: NCT03752099. Research Sponsor: Veru Inc.

5057 **Poster Session**

Radiographic progression-free survival as a surrogate endpoint of overall survival in men with metastatic castrate-resistant prostate cancer. *First Author: Susan Halabi, Duke University Medical Center, Durham, NC*

Background: Radiographic progression-free survival (rPFS) is commonly used as a co-primary endpoint in randomized clinical trials in men with metastatic castrate-resistant prostate cancer (mCRPC). However, rPFS has not been established as a valid surrogate endpoint of overall survival (OS) in men with mCRPC. Here, we hypothesized that rPFS is a reliable surrogate for OS in mCRPC. We also explored whether PFS is a valid surrogate endpoint of OS at the aggregate trial level. **Methods:** We performed a systematic search of the literature encompassing the period January 2004-December 2020 using PubMed and clinical trials.gov to identify completed phase III trials in mCRPC post-docetaxel. Eligible trials had to be randomized phase III therapeutic trials that reported OS, PFS or rPFS. OS was measured from the date of random assignment to date of death from any cause or date of last follow-up. rPFS was defined as the time from random assignment to date of disease progression on CT and/or Tc bone scan per trial definition or death from any cause, whichever occurred first. PFS included PSA progression as a component of the composite endpoint. Trial level surrogacy was evaluated by fitting linear regression on the treatment effect of rPFS (or PFS) and OS (in other words, the weighted linear regression of the log(hazard ratio) of OS on the log(hazard ratio) of rPFS). It was pre-specified that rPFS would be considered a valid surrogate for OS if R^2 was 0·7 or higher. **Results:** We identified 33 in men with mCRPC post docetaxel approval. We assessed the association between PFS and OS in 29,456 patients from 30 trials. Overall, a moderate correlation was observed at the trial level between OS and PFS (R^2 = 0.46, 95 %CI = 0.20-0.68) in these trials. In 18 trials with 16,818 mCRPC patients where rPFS was considered as a key endpoint, a moderate correlation between the treatment effects on rPFS and OS was observed at the trial level (R^2= 0.65, 95% CI = 0.23-0.87). **Conclusions:** This meta-analysis demonstrates moderate correlation between treatment effects of rPFS and OS in patients with mCRPC. However, rPFS did not meet the pre-specified surrogacy threshold of 0.7. Clinical trial information: several. Research Sponsor: None.

5058 **Poster Session**

Differences in the tumor genomic landscape between African Americans (AA) and Caucasians (CA) advanced prostate cancer (aPC) patients (pts) by comprehensive genomic profiling (CGP) of cell-free DNA (cfDNA). *First Author: Pedro C. Barata, Tulane Cancer Center, New Orleans, LA*

Background: Emerging data suggest differences in the tumor genomic profile of AA compared with CA men with aPC. We hypothesized that there will be significant differences in the tumor genomic landscape between AA and Ca pts as detected by cfDNA CGP. **Methods:** Pts with aPC and available cfDNA CGP by the Guardant (G360) 73 gene panel were included. In addition, G360 74 gene panel was used to identify CDK12 mutation (not detected in 73 gene panel) in an independent cohort of aPC pts. Barnard's test was used to evaluate the association between genetic mutation and gene. Genomic landscape was also compared by a Bayesian Network (BN) machine learning approach. **Results:** A total of 552 pts (125 AA, 427 CA) tested by G360 73 gene panel were included. Multiple genomic aberrations were enriched in AA patients (Table). In the independent cohort of 261 aPC patients (AA=106 pts, CA=155 pts) tested by G360 74 gene panel, *CDK12* mutation was significant enriched in AA pts. (9.4% vs. 1.9%, p=0.006). Machine learning analysis supported these results, and will be presented at the meeting. **Conclusions:** These hypothesis generating data suggest significant differences in the tumor genomic profile between AA and CA pts with aPC. Identification of molecular drivers of tumor progression enriched in AA pts may allow development of tailored systemic therapy for these men, and decrease disparities in disease related outcomes. Data need external validation. PB,RR,MAB contributed equally to this work. Research Sponsor: None.

Affected Gene	AA (N=125)	Ca (N=427)	p-value
AR	73 (58.4%)	131 (30.7%)	0.0000
MYC	31 (24.8%)	46 (10.8%)	0.0003
ERBB2	7 (5.6%)	4 (0.9%)	0.0018
BRCA 1	4 (3.2%)	1 (0.2%)	0.0055
FGFR1	20 (16.0%)	3 (7.5%)	0.0055
CDK6	27 (21.6%)	50 (11.7%)	0.0059
EGFR	26 (20.8%)	50 (11.7%)	0.0168
GATA3	2 (1.6%)	0 (0%)	0.0168
FGFR2	4 (3.2%)	2 (0.5%)	0.0173

Legend: AA – African American; Ca – Caucasians.

5059 **Poster Session**

First results from a randomized phase II study of cabazitaxel (CBZ) versus an androgen receptor targeted agent (ARTA) in patients with poor-prognosis castration-resistant prostate cancer (mCRPC). *First Author: Kim van der Zande, Netherlands Cancer Insitute, Amsterdam, Netherlands*

Background: In the OSTRICh trial, poor-prognosis mCRPC patients were randomized between CBZ and ARTA, following progression on docetaxel (DOC) treatment. **Methods:** The OSTRICh trial is an open label, multicenter, phase IIb study. Patients with poor-prognosis mCRPC (visceral metastases AND/OR < 12 months responsive to androgen deprivation AND/OR progressing during or within 6 months after DOC completion), were randomized 1:1 between CBZ (25 mg/m^2 IV Q3W and prednisone 2 d 5 mg PO) and ARTA (daily abiraterone 1000 mg and prednisone 2 d 5 mg PO OR enzalutamide 160 mg PO). Life prolonging therapy between DOC and randomization was not allowed. Primary endpoint was to establish the Clinical Benefit Rate (no radiotherapy, no ECOG PS increase $\geq$2, no change of therapy AND no radiological progression) at 12 weeks (CBR) in the study arms, while formal comparison of the CBR was a secondary endpoint. A Fisher Exact test was used to assess differences in rates and a log rank test to assess differences in progression free and overall survival. All time to event endpoints were estimated with the Kaplan-Meier method and censored at last follow-up. **Results:** A total of 106 patients were randomized, 53 in each arm. Baseline median age was 70 (IQR 67-75) years and PSA 79.4 (IQR 29.0 - 160) ng/ml. ECOG PS score was 0/1 in 99 (93%) and 2 in 7 (7%) patients. Al patients fulfilled the criteria for poor-prognosis disease. Thirty-six (34%) patients received DOC in the metastatic hormone sensitive stage, while 41 (39%) previously received ARTA. Twenty-six of 43 evaluable patients in the CBZ arm had clinical benefit at 12 weeks (CBR: 60%, 95% CI: 44%-75%) and 20 of 39 (CBR: 51%, 95% CI: 35%-68%) in the ARTA arm (p = 0.50). At 12 weeks, 30 of 34 (88%, 95% CI: 73% - 97%) patients in the CBZ arm and 24 of 36 (67%, 95% CI: 49% - 81%) patients in the ARTA arm had no radiological progression (p = 0.046). After a median follow-up of 16.4 months (95% CI: 13.6–27.8), a serum PSA decrease $\geq$50% from baseline was established in 12 (23%, 95% CI: 12% - 36%) and 26 (49%, 95% CI: 35% - 63%)(p = 0.008) patients treated with CBZ and ARTA, respectively. Median radiological progression free survival (rPFS) was 6.0 months (95%CI: 4.11-14.5) in the CBZ arm and 5.8 months (95% CI: 5.22-10.2) months in the ARTA arm (p = 0.5), while median overall survival (OS) was 15.3 months (95%CI 9.49-22.4) and 13.8 months (95%CI 11.7-16.4) in CBZ and ARTA treated patients, respectively (p = 0.8). Grade $\geq$3 adverse events (AEs) occurred in 15 (29%) and 8 (15%) of patients treated with CBZ and ARTA, respectively. **Conclusions:** No significant difference in CBR was established between CBZ and ARTA treated patients. However, at 12 weeks significantly more CBZ treated patients had no radiological progression, while $\geq$50% PSA response rates were higher in ARTA treated patients. Clinical trial information: NCT03295565. Research Sponsor: Sanofi.

5060 **Poster Session**

TROP-2 co-expression with androgen receptor splice variants as a new therapeutic target in prostate cancer. *First Author: Charlotte Stahlfeld, University of Wisconsin Carbone Cancer Center, Madison, WI*

Background: Tumor-associated calcium signal transducer 2 (TROP-2, *TACSTD2*) is a transmembrane glycoprotein that is highly expressed in many epithelial cancers. Overexpression of TROP-2 is postulated to mediate cancer cell growth, invasion, and is associated with more aggressive disease. TROP-2 has emerged as a therapeutic target for antibody-drug conjugates in clinical trials including sacituzumab govitecan and DS-1062. Here, we evaluated the expression of TROP-2 in tumor biopsies and circulating tumor cells (CTCs) in men with metastatic castration resistant prostate cancer (mCRPC) to evaluate TROP-2 as a clinically relevant target. **Methods:** RNA-seq data from the SU2C-PCF database and PROMOTE clinical trial (NCT#01953640) was assessed for *TACSTD2* and androgen receptor (AR) splice variant (*AR_V7/AR_V9*) expression. Prostate cancer ChIP-seq data was analyzed to identify binding of the AR to the TROP-2 promoter. EpCAM and TROP-2 captured CTCs were isolated from patients with mCRPC using the VERSA (Versatile Exclusion-based Rare Sample Analysis) platform and assessed for splice variant, neuroendocrine (NE), and AR-regulated gene signatures, in addition to CTC enumeration and TROP-2 protein expression. **Results:** TROP-2 expression was detectable in 90% of patients, in both bone and visceral metastatic biopsies (SUC2-PCF). Although TROP-2 low biopsies were infrequent (10%), 58% of these samples showed high levels of NE markers, as compared with 5% in all other patients. In the PROMOTE study, elevated TROP-2 gene expression was significantly higher in biopsies with high *AR_V7* expression than in those with low ($p = 0.04$) or negative ($p < .01$) *AR_V7* expression. ChIP-seq data demonstrated binding of AR at the TROP-2 promoter as well as at a potential enhancer site upstream, suggesting that TROP-2 expression can be regulated by AR activity. Splice variants and NE gene signatures were expressed in CTCs captured with both EpCAM and TROP-2, although markedly different gene expression profiles between EpCAM and TROP-2 CTCs were observed in a subset of patients with neuroendocrine prostate cancer. Detection of *AR_V7* from TROP-2 CTCs corresponded to shorter overall survival in 20 patients with mCRPC. TROP-2 protein expression was identified on EpCAM captured CTCs, although patients exhibited a wide degree of both intra- and inter-patient heterogeneity. **Conclusions:** Our findings demonstrate that TROP-2 is highly expressed in mCRPC, and is reduced in a subset of patient tumors expressing neuroendocrine markers. In the PROMOTE clinical trial with abiraterone acetate, TROP-2 AR variant expression correlated with increased TROP-2 expression. Binding of the AR to the TROP-2 promoter and potential enhancer was observed in prostate cancer cell lines and biopsies. These results indicate TROP-2 is a high value a biomarker and therapeutic target mCRPC. Research Sponsor: Prostate Cancer Foundation, Other Government Agency, U.S. National Institutes of Health.

5061 **Poster Session**

The national impact of the COVID-19 pandemic on U.S. prostate cancer community care. *First Author: Matthew R. Cooperberg, University of California-San Francisco, San Francisco, CA*

Background: We used data from a specialty-wide, community-based urology registry to determine trends in outpatient prostate cancer (PCa) care during the COVID-19 pandemic. **Methods:** 3,165 (~ 25%) of US urology providers, representing 48 states and territories, participate in the American Urological Association Quality (AQUA) Registry, which collects data via automated extraction from electronic health record systems. We analyzed trends in PCa care delivery from 156 practices contributing data in 2019 and 2020. Risk stratification was based on prostate-specific antigen (PSA) at diagnosis, biopsy Gleason, and clinical T-stage, and we used a natural language processing algorithm to determine Gleason and T-stage from unstructured clinical notes. The primary outcome was mean weekly visit volume by PCa patients per practice (visits defined as all MD and mid-level visits, telehealth and face-to-face), and we compared each week in 2020 through week 44 (November 1) to the corresponding week in 2019. **Results:** There were 267,691 PCa patients in AQUA who received care between 2019 and 2020. From mid-March to early November, 2020 (week 10 – week 44) the magnitude of the decline and recovery varied by risk stratum, with the steepest drops for low-risk PCa (Table). For 2020, overall mean visits per day (averaged weekly) were similar to 2019 for the first 9 weeks (~25). Visits declined to week 14 (18.19; a 31% drop from 2019), recovered to 2019 levels by week 23, and declined steadily to 11.89 (a 58% drop from 2019) as of week 44, the cut off of this analysis. **Conclusions:** Access to care for men with PCa was sharply curtailed by the COVID-19 pandemic, and while the impact was less for men with high-risk disease compared to those with low-risk disease, visits even for high-risk individuals were down nearly one-third and continued to fall through November. This study provides real-world evidence on the magnitude of decline in PCa care across risk groups. The impact of this decline on cancer outcomes should be followed closely. Research Sponsor: Verana Health.

Mean visits per day, averaged over the week.

Risk Stratum	Number of Patients	Baseline (week 10)	Nadir	% Drop from Baseline	Nadir Week	Recovery peak	% Recovery from Nadir 1	Week of Nadir 2	Nadir 2	% of baseline at Nadir 2
Overall	297,691	25.56	18.03	29.44%	14	25.97	105.45%	44	11.89	46.52%
High	37422	6.31	5.24	17.01%	13	6.45	112.99%	41	4.31	68.30%
Mediate	80840	9.68	7.36	23.99%	14	10.04	115.24%	44	5.65	58.37%
Low	44949	6.57	4.49	31.65%	14	7.04	122.27%	44	3.62	55.10%
Unknown	134480	11.39	8.03	29.53%	15	11.79	111.68%	44	5.56	48.81%

5062 **Poster Session**

Genomic landscape of *MSH6*-mutated clinically advanced castrate-resistant prostate cancer (mCRPC). *First Author: Gennady Bratslavsky, SUNY Upstate University Hospital, Bethesda, MD*

Background: Loss-of-function genomic alterations (GAs) in *MSH6* have been associated with a unique subtype of hypermutated mCRPC that is often microsatellite stable (MSS) and may occur in either a sporadic or familial Lynch Syndrome-like clinical setting. **Methods:** 5,617 mCRPC cases were sequenced to evaluate all classes of GA using a hybrid capture-based FDA-approved comprehensive genomic profiling (CGP) assay. Tumor mutational burden (TMB) was determined on 0.8 Mb of sequenced DNA and microsatellite instability high (MSI-High) was determined on 95 loci. MSI-low status was not assessed. **Results:** 78 (1.4%) mCRPC were *MSH6*^{mut} (Table). *MSH6*^{mut} mCRPC included 73.1% short variant mutations, 23.1% biallelic deletions, 2.6% genomic rearrangements, and 1.3% multiple GAs/sample. Co-mutation of *MSH2* was found in 28% of *MSH6*^{mut} cases vs. 2% in *MSH6*^{wt} cases ($P < .0001$) and was most frequently caused by biallelic co-deletion of both genes (73% of co-mutated cases). MSI-High status was present in 46% of *MSH6*^{mut} mCRPC, which was significantly greater than the 2% seen in *MSH6*^{wt} cases ($P < .0001$). An MMR single nucleotide mutational signature was observed in 65% of *MSH6*^{mut} cases, compared to 3% *MSH6*^{wt} cases ($P < .0001$). Among *MSH6*^{mut} cases with neither MSI-High nor MMR mutational signature, 87% did not have biallelic loss of *MSH6* or any other MMR gene, confirming that monoallelic pathogenic mutations are insufficient to cause the MMR-D phenotype. For subjects whose variants could be classified, 45% (19/42) of pathogenic *MSH6* alleles were germline; of these, 58% (11/19) had neither MSI-High nor an MMR single nucleotide signature. *MSH6*^{mut} cases had fewer *TMPRSS2:ERG* fusions ($P = .01$), but harbored significantly higher frequencies of GAs in *AR* ($P = .0002$), *ATM* ($P = .04$), *PIK3CA* ($P = .0003$), *APC* ($P = .005$), *ERBB2* ($P = .001$), and *CDK6* ($p = .046$), likely at least partially attributable to the higher TMB in *MSH6*^{mut} cases ($P < .0001$). **Conclusions:** *MSH6*^{mut} mCRPC is a unique disease that often features a hypermutated genomic signature, although only 46% of cases exhibited MSI-high status. This complex phenotype highlights the potential utility of multiple rather than single biomarkers to understand tumor biology and determine patients who may benefit from immunotherapy. Research Sponsor: Foundation Medicine Inc.

	MSH6^{mut} mCRPC	MSH6^{wt} mCRPC	P Value
Number of Cases	78	5539	
Median age (range) years	69 (44-89+)	67 (38-89+)	NS
GAs/tumor	11.3	3.9	< .0001
MSH2	28%	2%	< .0001
TMPRSS2:ERG	19%	33%	= .01
AR	32%	15%	= .0002
TP53	46%	42%	NS
PTEN	39%	31%	NS
BRCA1	6%	1%	= .001
BRCA2	9%	9%	NS
ATM	12%	6%	= .04
RAD21	10%	11%	NS
PIK3CA	17%	7%	= .003
RB1	6%	6%	NS
APC	19%	9%	= .005
BRAF	3%	4%	NS
ERBB2	6%	1%	= .001
CDK12	12%	6%	NS
CDK6	3%	1%	= .046
MSI High	32/69 (46%)	2%	< .0001
MMR Signature	65%	3%	< .0001
Median TMB	21.3	2.5	< .0001
Mean TMB	69.7	3.6	< .0001
TMB ≥10 mt/Mb	67%	4%	< .0001
TMB ≥20 mt/Mb	52%	2%	< .0001
PD-L1 Low Positive	2/20 (10%)	155/1,683 (9%)	NS
PD-L1 High Positive	0/20 (0%)	15/1,683 (1%)	NS

5063 **Poster Session**

Association of ATM mutations in metastatic prostate cancer with differential genomic alteration profiles from homologous recombination deficient and proficient tumors. *First Author: Charles J. Ryan, Division of Hematology, Oncology and Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN*

Background: ATM mutations, one of a family of DNA repair defects prevalent in prostate cancer, have been included in a list of actionable mutations for PARP inhibitor (PARPi) therapeutic trials. Despite preclinical evidence, PARPi have shown minimal clinical activity in ATM mutant prostate cancer (ATMmPCa). The present analysis explores co-occurring genomic alterations that may drive outcomes of metastatic PCa (mPCa) patients with tumors harboring ATM mutations and provide clues for understanding therapy resistance and potential targets. **Methods:** This study included molecular profiling analysis of 1375 cases of mPCa. Tumors were analyzed using next-generation sequencing (NGS), whole transcriptome sequencing (WTS), and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ). dMMR/MSI-H status was determined by IHC, NGS, and fragment analysis and tumor mutational burden (TMB) was calculated based on somatic nonsynonymous missense mutations. We performed differential gene expression analysis of HR-associated transcripts such as ATR, PARP1-3, RAD50, RAD51A/B/C/D and RAD54. Significance was determined using the χ^2 test and Benjamini-Hochberg method. **Results:** Fifty-nine (4.2%) cases harbored pathogenic ATM mutations, 84 (6.2%) harbored BRCA2 mutations. 1018 tumors (74%) were deemed homologous recombination proficient (HRP) and 155 tumors (11.3%) were HR Deficient (HRD); harboring one or more mutation in HR-related genes excluding ATM and BRCA2. The mutation rate of TP53 was significantly lower in ATMmPCa (12.0%) compared to BRCA2mPCa (35%), HRD (35%) and HRP (46.6%) tumors. ATMmPCa showed higher rates of SMAD2 (3.7%/1%) and FLCN (5.2%/0.3%) alterations compared to HRP cases. PARP1 and RAD51D gene expression was reduced in ATMmPCa compared to HRP ($p < 0.05$) and BRCA2mPCa ($p < 0.05$) tumors, respectively. No differences in gene expression levels were detected for ATR, PARP2, PARP3, RAD50, and RAD54. Chromosomal segments demonstrating differential CNA in ATMmPCa vs HRP, HRD, or BRCA2mPCa included FGF19, FGF4, PTPN11, ALDH2, DAXX, BCL7A, CCND1, BMPR1A and MEF2B (Q-value < 0.05 determined by χ^2). The most common CNA in ATMmPCa was CCND1, present in approximately 13% (7/55) of cases. Compared to BRCA2mPCa and HRD cases, ATMmPCa cases are less likely to display markers of immunotherapy response such as dMMR/MSI-H or TMB ≥10 mutations/MB. **Conclusions:** ATMmPCa demonstrated several differences in co-occurring alterations compared to BRCA2mPCa, HRD and HRP mPCa. ATMmPCa tumors were less likely to harbor alterations in TP53 compared to BRCA2, HRD or HRP tumors. CNA in ATMmPCa occurred in 9 genes across distinct mPCa molecular subtypes and were enriched for those associated with the 11q13 amplicon harboring Cyclin D1. The FGF and PTPN11 related pathways are potentially targetable pathways in ATMmPC and may merit further study. Research Sponsor: None.

5064 **Poster Session**

PSMA-PET/CT Registry for Recurrent Prostate Cancer (PREP): Initial findings from a single center. *First Author: Anil Kapoor, McMaster University Hamilton, Hamilton, ON, Canada*

Background: Several lesion-targeted therapies exist for locally recurrent or limited stage metastatic prostate cancer (PCa) post-radiotherapy (RT) and radical prostatectomy (RP). However, detection of disease sites is limited using conventional imaging (CI) including computed tomography (CT) and bone scan. Prostate specific membrane antigen (PSMA) targeting PET radiopharmaceuticals like [18F]DCFPyL may help detect disease not seen on CI. Our objective was to assess the ability of PSMA targeted PET/CT to detect sites of disease recurrence and impact on patient management. **Methods:** This multi-center prospective registry study included six Ontario centers. Eligible patients in 1 of 7 clinical cohorts (Table) were identified and approved by Cancer Care Ontario (CCO) to have restaging with PSMA targeted PET/CT. Referring physicians were asked to complete a form indicating whether a change in management strategy would occur based on the PET/CT results. At 6 months post-PET/CT, actual patient management will be confirmed via provincial registries. These interim results are from a single center. **Results:** 253 patients were enrolled and had a PSMA targeted PET/CT. At baseline, median age was 71 years (range 50-102 years) and median PSA was 2.7 ng/mL (range 0.04-134.0 ng/mL). The majority of patients (n=59; 23.3%) were in cohort 2 (biochemical failure post-RP). In patients with negative CI, PSMA targeted PET/CT detected disease sites in 68.5% (170/248), resulting in a change in management for 67.8% (137/202) overall and 72.1% and 64.3% post-RT and post-RP, respectively. **Conclusions:** PSMA targeted PET/CT detected occult lesions on CI in the majority of patients enrolled, leading to a high rate of change in management. Our institutional results are in keeping with preliminary results reported for the provincial cohort. Clinical trial information: NCT03718260. Research Sponsor: Cancer Care Ontario.

Change in management post- PSMA PET/CT and median (range) PSA by cohort allocation.

Cohort	N (%)	Change in management n (%)*	Median PSA ng/mL (range)
1. Post RP node + disease or persistently detectable PSA	4 (1.6)	2 (50%)	2.0 (.22-4.1)
2. BF post-RP	59 (23.3)	28 (47.5)	.27 (.11-9.7)
3. BF post-RP followed by adjuvant or salvage prostate bed RT	52 (20.6)	29 (55.8)	1.5 (.11-32.7)
4. BF post-RP or RT while on hormone therapy	43 (17)	27 (62.8)	3.5 (.04-42.6)
5. BF post-RP following lesion-directed treatment of oligometastatic disease	7 (2.8)	3 (42.9)	3.5 (1.2-8.0)
6. BF post primary RT	51 (20.2)	31 (60.8)	4.9 (.18-31.5)
7. PET access cohort (independent adjudication process determines PSMA PET/CT could provide clinically meaningful information)	37 (14.6)	17 (45.9)	6.4 (.13-134.0)
Missing data	0 (0)	51 (20)	
Total (%)	253	137/202 (67.8)	2.7 (.04-134.0)

*Note: Total N=253. Missing data (n=51) for change in management variable, so the data reflect the n (%) out of 202 patients.
PSA=prostate specific antigen; BF=biochemical failure; RP=radical prostatectomy; RT=radiotherapy

5065 **Poster Session**

Single-lesion PSMA protein expression and response to Lu-177 PSMA therapy in patients with castration-resistant prostate cancer. *First Author: Judith Stangl-Kremser, Department of Urology, Michigan Medicine, Ann Arbor, MI*

Background: The recent introduction of Lu-177 PSMA for the treatment of castration-resistant prostate cancer (CRPC) has been met with much excitement. Initial reports of clinical response are promising, despite known inter- and intra-patient molecular heterogeneity. In this study, we examined the utility of PSMA protein expression in metastatic tumor tissues as a predictor of lesion-specific response to Lu-177 PSMA therapy in men with CRPC. **Methods:** Between 2015-2020, 19 patients with metastases at multiple sites underwent metastatic lesion biopsy, Ga-68 PSMA PET imaging, and subsequent treatment with three cycles of Lu-177 PSMA. A monoclonal anti-PSMA antibody (EPITOMICS (USA), 1:50) was used to semi-quantitatively assess PSMA protein expression in the biopsy specimen. The histoscore (range 0-300) was derived from intensity and extent of the immunohistochemistry staining and was determined by experienced genitourinary pathologists. Imaging evaluation was performed according to the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) criteria. We assessed the association of the PSMA protein expression in metastatic tumor tissues and the lesion-specific response to Lu-177 PSMA therapy. **Results:** In 12 patients with biopsy specimens available for staining, PSMA expression correlated with enhancement (SUV_{max}) of the biopsy site on Ga-68 PSMA PET imaging ($r_s = 0.63$). Of the nine patients with repeat imaging after Lu-177 PSMA therapy, five (55.6%) had a lesion-specific response at the site of biopsy. PSMA expression on immunohistochemistry was unable to accurately predict lesion-specific response in univariable analysis (p = 0.81, 95% CI 94.6-76.6). Among the five men with a lesion-specific response, three (60%) experienced overall progression based on PERCIST. There was no association between lesion-specific response and overall progression (p = 0.64). **Conclusions:** In patients with multiple metastases, PSMA protein expression from a single site biopsy was not predictive of site-specific Lu-177 PSMA response based on PERCIST. Additional studies are necessary to further interrogate the clinical consequence of PSMA expression heterogeneity in metastatic sites as well as the mechanisms underpinning resistance to Lu-177 PSMA in patients with CRPC. Research Sponsor: None.

5066 **Poster Session**

Interim PSMA PET/CT for response evaluation during LuPSMA treatment in mCRPC (INTERIM PET): An explorative, multicenter study. *First Author: Andrei Gafita, Ahmanson Translational Theranostics Division, University of California, Los Angeles, CA*

Background: The aim of this analysis was to evaluate the prognostic value of interim PSMA PET/CT in men with metastatic castration-resistant prostate cancer (mCRPC) treated with ^{177}Lu-PSMA and to develop a novel framework for Response Evaluation Criteria In PSMA-imaging (RECIP). **Methods:** This was an explorative, multicenter, retrospective study; 124 men with mCRPC who underwent ^{177}Lu-PSMA treatment and received PSMA-PET/CT at baseline (bPET) and at interim after two cycles of treatment (iPET) met the eligibility criteria and were included in this analysis. The primary endpoint was overall survival (OS). Pairs of bPET and iPET were interpreted by three independent readers for appearance of new lesions. Whole-body tumor lesions were segmented using qPSMA software and total PSMA-positive tumor volume (PSMA-VOL) was obtained. Changes in PSMA-VOL on iPET relative to bPET were calculated. After being tested separately for associations with OS, appearance of new lesions and changes in PSMA-VOL were combined to develop RECIP. **Results:** The median OS was 13.5 months (95%CI, 11.6-15.4). Appearance of at least one new lesion on iPET was observed in 73 (59%) patients and was associated with poor OS (hazard ratio [HR] 2.23; 95%CI, 1.51-3.28; $P < .001$). Based on the current data, RECIP were defined as: partial response (PSMA-PR) as a decline ≥20% in PSMA-VOL and no appearance of new lesions; progressive disease (PSMA-PD) as an increase ≥20% in PSMA-VOL and appearance of new lesions; stable disease (PSMA-SD) was defined as any condition but not PSMA-PR or PSMA-PD. The OS of men with PSMA-PD (n = 41) was significantly worse compared to men with PSMA-SD (n = 47; HR 2.52; 95%CI, 1.61–3.93; $P < .001$) and PSMA-PR (n = 36; HR 4.16; 95%CI, 2.54–6.78; $P < .001$). PSMA-SD was associated with significantly worse OS compared to PSMA-PR (HR 1.65; 95%CI, 1.02–2.65; $P = .039$). The time dependent C-index of associations with OS for response according to RECIP was 0.68 (95%CI, 0.63-0.72). **Conclusions:** Interim staging using PSMA-PET/CT and response classification by RECIP is prognostic for survival of men with mCRPC treated with ^{177}Lu-PSMA. Validation of these findings in clinical trials is warranted. Research Sponsor: None.

5067 **Poster Session**

Impact of androgen deprivation therapy on mortality of prostate cancer patients with COVID-19: A propensity score-based analysis. *First Author: Mateus Bringel Oliveira Duarte, Universidade Estadual de Campinas, Campinas, Brazil*

Background: Previous studies suggested that androgen deprivation therapy (ADT) may reduce severe acute respiratory syndrome coronavirus 2 (SARS-COV2) infectivity. However, it is unknown whether there is an association between ADT and a higher survival in prostate cancer patients with COVID-19. **Methods:** We performed a retrospective analysis of prostate cancer (PC) patients hospitalized to treat COVID-19 in Brazil's public health system. We compared patients with the active use of ADT versus those with non-active ADT, past use. We constructed propensity score models of patients in active versus non-active use of ADT. All variables were used to derive propensity score estimation, and for the outcome analysis we performed a multivariate backward elimination process to select variables to add to the propensity score model. **Results:** We analyzed 109 PC patients with COVID-19 that presented past or current use of ADT. In total, 52.8% of our patients were less than 75 years old, 44.0% (48/109) were in active ADT, and most were using a GnRH analog (73%, 35/48). Also, 63.3% of our cohort died from COVID-19. ADT active use were protective factor in our logistic regression model (OR 0.28, 95% CI 0.12–0.66, P = 0.0036). We noticed a significant imbalance in the propensity score of patients in active and those in non-active ADT. Then, when we performed a propensity score-based inverse weight double robust estimation model, we observed that ADT remained statistically associated with improved overall survival (average treatment effect [ATE] -0.26, 95% CI -0.45 to -0.08, P = 0.0058). **Conclusions:** The active use of ADT was associated with a reduced risk of death in patients with COVID-19. Research Sponsor: FAPESP - Fundação de Amparo a pesquisa do estado de São Paulo.

5068 **Poster Session**

Health-related quality of life (HRQoL) and patient-reported outcomes at final analysis of the TITAN study of apalutamide (APA) versus placebo (PBO) in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) receiving androgen deprivation therapy (ADT).

First Author: Neeraj Agarwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: The phase 3 TITAN study evaluated APA vs PBO in pts with mCSPC receiving ADT. At primary analysis with 22.7 mo median follow-up, APA significantly improved overall survival (OS) and radiographic progression-free survival vs PBO (Chi *NEJM* 2019) while preserving HRQoL (Agarwal *Lancet Oncol* 2019). The study was unblinded; pts on PBO were allowed to cross over to APA. At final analysis with 44 mo median follow-up, APA significantly improved OS vs PBO, reducing risk of death by 35% despite crossover (Chi ASCO GU 2021). We evaluated HRQoL and treatment bother at final analysis. **Methods:** mCSPC pts (N = 1052) were randomized 1:1 to APA (240 mg QD; n = 525) or PBO (n = 527). All pts received ADT. Patient-reported outcomes were assessed using Brief Pain Inventory-Short Form (BPI-SF) and Functional Assessment of Cancer Therapy-Prostate (FACT-P). BPI was completed for 7d consecutively (Days -6 to 1 of each 28-d cycle [C]) through end of treatment (EOT). FACT-P was completed at baseline (BL), C2-C7, then every other C through EOT. Mean scores were reported by treatment group and over time. Time to deterioration on BPI and FACT-P scores was calculated by Kaplan-Meier methods and compared between groups by fitting proportional hazards regression models. **Results:** Of eligible pts per C, > 62% completed BPI through C32 and > 50% completed FACT-P through C31. Pts were relatively asymptomatic with good BL HRQoL: on 0-10 worst pain severity scale (BPI), median scores were 1.1 (APA) and 1.0 (PBO); on 0-156 HRQoL scale (FACT-P total; higher score = better HRQoL), median scores were 113.0 (APA) and 113.3 (PBO). Low BL BPI scores remained stable over time in both groups. On average, favorable BL FACT-P scores did not notably worsen over time in APA or PBO groups. There were no significant differences between groups in median time to deterioration in any BPI or FACT-P scores (Table). At each C at least 86% (APA) and 85% (PBO) of pts were either "not at all" or "a little bit" bothered by side effects. At BL, 76% (APA) and 72% (PBO) had favorable energy levels (reporting lack of energy "not at all" or "a little bit"). Energy levels remained stable or improved at each C for > 78% (APA) and > 71% (PBO) of pts. **Conclusions:** In the final analysis of TITAN, survival benefit with addition of APA to ADT was achieved without significant patient-reported side effect burden or reduced HRQoL compared with PBO in pts with mCSPC. Clinical trial information: NCT02489318. Research Sponsor: Janssen Research & Development.

Median time to deterioration, months	APA	PBO	p Value
BPI worst pain	19.3	12.0	0.17
BPI pain interference[a]	NE	NE	0.32
FACT-P total	9.0	9.2	0.76
FACT-P physical wellbeing	5.6	11.0	0.62
FACT-P emotional wellbeing	12.9	10.2	0.20
FACT-P functional wellbeing	4.6	5.7	0.65
FACT-P social/family wellbeing	5.6	6.5	0.60

[a]25th percentile pain interference: APA, 9.2; PBO, 6.2.
NE, not estimable.

5069 **Poster Session**

Association of androgen receptor signature and *RB1*, *PTEN*, *TP53* gene expression with clinical outcome in metastatic hormone-sensitive prostate cancer treated with docetaxel and androgen deprivation therapy.

First Author: Laura Ferrer-Mileo, Department of Medical Oncology, Hospital Clínic of Barcelona, Barcelona, Spain

Background: Androgen deprivation therapy (ADT) with docetaxel or new antiandrogens has demonstrated a survival benefit in metastatic hormone-sensitive prostate cancer (mHSPC). However, treatment selection for individual patients (pts) remains a challenge. We propose that *TMPRSS2-ERG* and cell plasticity [neuroendocrine (NE), epithelial to mesenchymal transition (EMT)], immune-related, androgen receptor (AR) and tumor suppressor genes (TSG) (*RB1*, *PTEN* and *TP53*) expression signatures may predict clinical outcome in mHSPC pts treated with ADT+docetaxel. **Methods:** This is a multicenter retrospective biomarker study performed in mHSPC pts treated with ADT+-docetaxel. A customized panel of 184 genes was designed and tested in total mRNA from FFPE tumor samples by nCounter platform (Nanostring Technologies). Expression levels were correlated with castration resistance-free survival (CRPC-FS) (primary endpoint) and overall survival (OS) by Kaplan Meier and multivariate Cox modeling. A predictive modeling approach was performed with Bujar R package to develop a signature able to predict CRPC-FS. R (v.3.6.3) software was used for statistical analyses. **Results:** 136 pts were included, and 120 of them were eligible. Median age was 66.9 years (range 46.3-83.6). Gleason score was ≥ 8 in 80.8% of pts; 87.5% and 20.8% of pts had bone and visceral metastases, respectively. Median follow-up was 30.7 months (m) (range 5.5-70.6). 76 pts (63.3%) developed castration-resistant prostate cancer (CRPC). Median time to CRPC was 20 m (range 16.9-23.1) and median OS was not reached. High AR-signature expression independently correlated with longer CRPC-FS (HR 0.4, 95% CI 0.2-0.7, p = 0.003). Considering AR-signature individual gene expression, *ARV7* was independently associated with shorter CRPC-FS (HR 1.7, 95% CI 1.2-2.4, p = 0.003). Low expression of all TSG (*PTEN*, *RB1* and *TP53*) independently correlated with shorter CRPC-FS (HR 0.3, 95% CI 0.2-0.7, p = 0.003) and OS (HR 0.2, 95% CI 0.1-0.5, p < 0.001). Similarly, low expression of 2 out of the 3 TSG genes or only *RB1* plus *PTEN* were also independently associated with shorter CRPC-FS (HR 0.5, 95% CI 0.3-0.9, p = 0.015; HR 0.4, 95% CI 0.2-0.7, p = 0.003, respectively) and OS (HR 0.4, 95% CI 0.2-0.9, p = 0.027; HR 0.2, 95% CI 0.1-0.6, p = 0.001, respectively). *TMPRSS2-ERG* expression, NE, EMT and immune-related signatures were not associated with clinical outcome. Bujar analysis defined a 17-gene signature (including *ARV7*, *RB1*, *PTEN*, *BRCA2* and *ATM)* that was able to discriminate pts at different risk of developing early CRPC. **Conclusions:** High AR-signature expression correlates with a longer CRPC-FS while *ARV7* expression is associated with shorter CRPC-FS. Low expression of TSG is associated with an aggressive clinical evolution in mHSPC pts treated with ADT+taxanes. Research Sponsor: Funded by a grant from Janssen- Pharmaceuticals, number 212082PCR4056, Other Government Agency, CERCA Programme/Generalitat de Catalunya.

5071 **Poster Session**

The efficacy of enzalutamide (ENZA) plus androgen deprivation therapy (ADT) on bone oligometastatic hormone-sensitive prostate cancer: A post hoc analysis of ARCHES.

First Author: Andrew J. Armstrong, Duke Cancer Institute Center for Prostate & Urologic Cancers, Duke University, Durham, NC

Background: In ARCHES (NCT02677896), ENZA + ADT reduced the risk of radiographic progression and improved secondary clinical outcomes in patients with metastatic hormone-sensitive prostate cancer (mHSPC) with variable patterns of disease spread over placebo (PBO) + ADT. This *post hoc* analysis aimed to evaluate the efficacy of ENZA + ADT in patients with bone oligometastatic mHSPC compared to polymetastatic mHSPC in ARCHES. **Methods:** Patients with mHSPC (n = 1150) were randomized 1:1 to ENZA (160 mg/day) + ADT or PBO + ADT, stratified by disease volume and prior docetaxel chemotherapy. This *post hoc* analysis included patients with bone metastases only, categorized as oligometastatic (1–≤5 metastases) or as polymetastatic (≥6 metastases) based on central review at screening. Efficacy outcomes were compared across treatment arms. **Results:** Of the ARCHES population with bone metastases (n = 512), the largest subgroup included patients with ≤5 metastases (ENZA + ADT, n = 160; PBO + ADT, n = 136). Baseline characteristics were generally comparable between treatment arms and across subgroups. When compared to PBO + ADT, ENZA + ADT improved rPFS and secondary endpoints in patients with ≤5 metastases (Table). Similar results were observed across other oligometastatic subgroups (1–≤4) as well as in polymetastatic disease (≥6). The safety profile of ENZA + ADT versus PBO + ADT was similar across subgroups and consistent with previous findings. **Conclusions:** This *post hoc* analysis demonstrates that ENZA + ADT provides clinical benefit across bone oligometastatic as well as polymetastatic mHSPC, supporting the utility of ENZA irrespective of metastatic burden in the ARCHES study. Clinical trial information: NCT02677896. Research Sponsor: This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide. Medical writing and editorial assistance were provided by Folabomi Oladosu, PhD, and Jane Beck, MA, from Complete HealthVizion, funded by the study sponsors.

***Post hoc* analysis of oligometastatic and polymetastatic disease.[a]**

Endpoint, HR (95% CI)[b]	1 (n = 53[c]; n = 44[d])	≤2 (n = 87[c]; n = 76[d])	≤3 (n = 120[c]; n = 103[d])	≤4 (n = 142[c]; n = 117[d])	≤5 (n = 160[c]; n = 136[d])	≥6 (n = 107[c]; n = 109[d])
rPFS[e]	0.17 (0.02, 1.48)	0.24 (0.07, 0.87)	0.21 (0.08, 0.56)	0.16 (0.06, 0.42)	0.22 (0.10, 0.47)	0.35 (0.22, 0.57)
Time to PSA progression	0.14 (0.03, 0.63)	0.09 (0.02, 0.40)	0.16 (0.06, 0.41)	0.12 (0.05, 0.31)	0.11 (0.04, 0.28)	0.13 (0.06, 0.27)
Time to castration resistance	0.13 (0.03, 0.60)	0.15 (0.05, 0.44)	0.17 (0.07, 0.38)	0.15 (0.07, 0.33)	0.17 (0.09, 0.34)	0.27 (0.17, 0.43)
Time to initiation of new antineoplastic therapy	0.40 (0.10, 1.60)	0.45(0.16, 1.31)	0.40 (0.17, 0.94)	0.33 (0.14, 0.75)	0.29 (0.13, 0.66)	0.29 (0.16, 0.51)

[a]Oligometastatic mHSPC was defined as 1–≤5 bone metastases; polymetastatic mHSPC was defined as ≥6 bone metastases; [b]HR < 1 favors ENZA + ADT; HR > 1 favors PBO + ADT; [c]Number of patients in subgroup who received ENZA + ADT; [d]Number of patients in subgroup who received PBO + ADT; [e]Assessed by independent central review, or death, within 24 weeks of treatment discontinuation. CI = confidence interval; HR = hazard ratio; PSA = prostate-specific antigen.

5072 **Poster Session**

Real-world first-line (1L) treatment patterns in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) in a U.S. health insurance database.

First Author: Umang Swami, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT

Background: Over the past 6 years, intensification of androgen deprivation therapy (ADT) with docetaxel (DOC) and novel hormonal therapies (NHT) [abiraterone, enzalutamide, and apalutamide], has been shown to improve survival outcomes in men with mCSPC. This study assessed the real-world utilization of effective combination therapies as 1L treatment in insured pts in the U.S. with mCSPC. **Methods:** This retrospective study used the Optum health insurance claims database, which includes pt claims data from both commercially insured and Medicare Advantage populations. Eligible pts were adult men with ≥1 claim with a metastatic International Classification of Diseases diagnostic code (first claim was index date) within 90 days (d) prior to, or any time after, a prostate cancer diagnosis between January 2014 and June 2019. Pts with evidence of systemic anticancer therapy during the 1-year pre-index baseline period were excluded, unless the first drug claim occurred within 90 d prior to the diagnosis of metastatic disease. The 1L treatments were identified as any treatment for mCSPC within 90 d pre-index, plus any other treatment received within 180 d of the first, and were grouped by regimen: ADT only; ADT + first-generation antiandrogens (AA); ADT + DOC; ADT + NHT; and ADT + NHT + DOC. **Results:** Of 4221 men with mCSPC, 2364 (56.0%) received ADT only; 892 (21.1%) ADT + AA; 577 (13.7%) ADT + NHT; 348 (8.2%) ADT + DOC; and 40 (0.9%) ADT + NHT + DOC. Pts who received ADT + DOC or ADT + DOC + NHT were generally younger than the other treatment groups (Table). By 2019, use of ADT only and ADT + AA had declined, while the use of ADT + NHT and ADT + NHT + DOC had increased (Table). However, in 2018 and 2019, the majority of men with mCSPC still received either ADT alone, or ADT + AA, including those with visceral metastases (Table). Survival analysis across treatment cohorts is ongoing. **Conclusions:** Despite level 1 evidence demonstrating improved survival with intensified treatment (ADT + DOC or NHT), this study shows its underutilization in pts with mCSPC. This is evident even in those with more aggressive disease (visceral metastases) as recently as 2019. These data highlight that a minority of pts with mCSPC received optimal life-prolonging therapies in a commercially insured and Medicare Advantage U.S. population. Further studies are needed to identify the reasons for this underutilization of intensified treatments. Research Sponsor: This study was funded by Astellas Pharma Inc. and Pfizer Inc., the co-developers of enzalutamide. Medical writing was provided by Bioscript and editorial assistance was provided by Complete HealthVizion, funded by the study sponsors.

Pt age and 1L mCSPC treatment over time.

	ADT only (n = 2364)	ADT + AA (n = 892)	ADT + NHT (n = 577)	ADT + DOC (n = 348)	ADT + DOC + NHT (n = 40)
Median age, years (range)	75.0 (41–89)	76.0 (48–89)	73.0 (41–89)	68.0 (43–88)	65.5 (36–84)
Treatment by first metastatic date, %					
2014–2015 (n = 998)	60.6	28.1	2.4	8.5	0.4
2016–2017 (n = 1491)	58.0	23.5	8.9	8.6	0.9
2018 (n = 1118)	51.1	14.9	25.1	7.8	1.1
2019 (n = 614)	52.6	15.3	22.6	7.6	1.8
Any visceral metastases (2018–2019, n = 221), %	54.7	18.6	16.7	8.6	1.3

5073 **Poster Session**

Real-world utilization of advanced therapies and racial disparity among patients with metastatic castration-sensitive prostate cancer (mCSPC): A Medicare database analysis. *First Author: Stephen J. Freedland, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: Several randomized controlled trials have shown that adding docetaxel or novel hormonal therapy (NHT) to androgen deprivation therapy (ADT) improves survival in mCSPC patients. This study aimed to evaluate the real-world utilization of advanced therapies over time and to provide data on utilization patterns among racial minorities that are often under-represented in clinical trials. **Methods:** This was a retrospective analysis of a Medicare database (Jan 2009-Dec 2018). Adult men with ≥1 claim for prostate cancer (PC) who initiated ADT (index date) within 90 days prior to or any time after a metastasis diagnosis were included. The first-line (1L) treatment was grouped by PC drugs prescribed within 30 days prior to and 120 days after the index date, in 4 categories: ADT alone, ADT + first-generation anti-androgen (AA; ≥90 days to avoid capturing AA for flare control), ADT + docetaxel, and ADT + NHT (abiraterone, apalutamide, and enzalutamide). The 1L treatment distributions were described over time and stratified by race. **Results:** A total of 35,195 patients with mCSPC were included in the study, with a mean (SD) age of 76.5 (7.9) years. 11.8% were Black, 5.3% Hispanic, and 78.5% White. 76.4% received ADT alone as 1L treatment, 14.3% ADT + AA, 4.8% ADT + docetaxel, and 4.5% ADT + NHT. While the proportion of patients treated with ADT alone and ADT + AA slowly decreased over time, the utilization of ADT + docetaxel increased since 2015 and the utilization of ADT + NHT increased since 2017 (Table). After the emergence of NHTs for treatment of mCSPC in 2017, treatment intensification with ADT + NHT was numerically lower for Black than White patients. Data from before 2017 also suggest a similar lower use of ADT + AA in Black patients (Table). Survival analysis across treatment cohorts and race are ongoing. **Conclusions:** In this large and nationally representative sample of mCSPC patients, less than one-third of patients received treatment intensification by 2018, possibly due to patient/disease characteristics, provider awareness or therapeutic inertia, or cost. Importantly, the data showed less frequent treatment intensification in Black vs White patients. Further study is required to elucidate underlying reasons for this disparity. Research Sponsor: Pfizer and Astellas Pharma.

	Index year: 2010-2014			Index year:2015-2016			Index year:2017			Index year:2018		
	White, non-Hispanic N = 11,560	Black N = 1,910	Hispanic N = 956	White, non-Hispanic N = 7,801	Black N = 1,155	Hispanic N = 439	White, non-Hispanic N = 4,732	Black N = 624	Hispanic N = 624	White, non-Hispanic N = 3,537	Black N = 447	Hispanic N = 194
ADT alone	80.3%	86.9%	80.0%	74.9%	80.0%	75.2%	72.9%	70.8%	74.7%	68.2%	68.0%	62.4%
ADT + AA	16.4%	10.5%	17.6%	14.7%	11.3%	16.2%	12.0%	14.9%	12.5%	10.1%	16.3%	19.6%
ADT + docetaxel	2.1%	1.5%	<1.5%	8.6%	7.2%	6.2%	5.9%	5.1%	4.0%	5.3%	4.7%	<5.7%
ADT + NHT	1.1%	1.1%	<1.2%	1.8%	1.5%	2.5%	9.2%	9.1%	8.8%	16.5%	11.0%	15.5%-16.5%

5074 **Poster Session**

Real-world treatment patterns among patients diagnosed with metastatic castration-sensitive prostate cancer (mCSPC) in community oncology settings. *First Author: Daniel J. George, Duke Cancer Institute Center for Prostate and Urologic Cancers, Duke University, Durham, NC*

Background: Androgen deprivation therapy (ADT) served as standard of care for mCSPC for decades. Combining ADT with docetaxel (DOC) starting in 2015 or with novel hormonal therapies (NHT) starting in 2017 has demonstrated improved survival compared to ADT alone. This study examined the impact of new evidence on treatment selection for mCSPC patients in real-world oncology practice. **Methods:** Electronic medical record (EMR) data from a network of U.S.-based oncology practices in the ConcertAI Oncology Dataset were used to retrospectively evaluate treatment patterns in mCSPC patients who initiated first-line (1L) therapy between 2014–2019. We estimated the proportion of mCSPC patients receiving each 1L regimen, duration of therapy until initiation of next regimen, and trends in 1L regimen. Treatment patterns were studied in the overall population and by race/ethnicity. Anti-androgen (AA) use for <90 days was not included. **Results:** A total of 858 mCSPC patients were included (70% White, 16% Black, 3% Hispanic, and 11% other race/unknown). Median age at mCSPC diagnosis was 69 years, and 63% presented with *de novo* metastases. The most common mCSPC 1L regimens were ADT + older AA (26.3%, mainly bicalutamide), ADT monotherapy (20.5%), ADT + NHT ± AA (19.2%), and ADT + DOC ± AA (16.4%). The remaining 17.5% received a variety of other therapies, including AA monotherapy (5.9%) or NHT ± AA (5.5%). NHT included abiraterone, apalutamide, and enzalutamide. ADT + NHT ± AA treatment increased each year, while ADT + DOC ± AA treatment peaked in 2017 and then decreased (Table). By contrast, ADT + AA was the most common therapy in 2014 but declined every year. Median duration until initiation of a subsequent regimen was 14.3 months for ADT + NHT ± AA and 10.8 months for ADT + DOC ± AA. Differences in 1L treatment patterns across White and Black patients were not statistically significant in unadjusted analyses. **Conclusions:** Even in 2019, over half of mCSPC patients treated in real-world settings did not receive 1L therapy now known to significantly improve survival (ADT + NHT or ADT + DOC) over ADT alone. Those who did, received shorter durations of treatment than observed in registrational trials. However, we found no initial evidence of racial disparities in treatment. The disconnect between trial evidence and real-world practice could be due to patient/disease characteristics, cost/access issues, or provider awareness. A better understanding of these contributing factors is worthy of further study. Research Sponsor: Pfizer and Astellas Pharma.

Initiation of 1L treatment following mCSPC diagnosis (%).

mCSPC 1L regimen	Median duration to next regimen (months)	2014	2015	2016	2017	2018	2019
ADT + AA	14.3	42.6%	31.9%	31.7%	20.1%	19.8%	16.5%
ADT	8.9	20.4%	19.8%	22.0%	21.5%	15.8%	26.6%
ADT + NHT ± AA	14.3	10.2%	11.2%	14.6%	19.2%	27.7%	34.2%
ADT + DOC ± AA	10.8	8.3%	19.8%	14.6%	22.0%	17.0%	10.1%
Other treatment	n/a	18.5%	17.2%	17.1%	17.3%	19.8%	12.7%

5075 **Poster Session**

Impact of age on efficacy and safety of relugolix: A subgroup analysis from the randomized, phase 3 hero study versus leuprolide in men with advanced prostate cancer. *First Author: Michael Cookson, University of Oklahoma Health Sciences Center, Stephenson Cancer Center, Oklahoma City, OK*

Background: In the phase 3 HERO study, the oral GnRH receptor antagonist relugolix demonstrated sustained testosterone suppression superior to that of leuprolide and a comparative 54% decrease in risk of major adverse cardiovascular events. Relugolix was recently approved for use in the US for the treatment of adult patients with advanced prostate cancer. Here, we further characterize the impact of age on the use of relugolix in advanced prostate cancer from the HERO study. **Methods:** The HERO study was a randomized, open-label, parallel group study evaluating relugolix in men with advanced prostate cancer. Overall, 934 men with advanced prostate cancer underwent 2:1 randomization to receive relugolix 120 mg orally once daily after a single loading dose of 360 mg or leuprolide 3-month injections for 48 weeks. Subgroups analyzed by age were <65 years or ≥65 years and ≤75 years or >75 years. Assessments analyzed included sustained testosterone suppression to castrate levels (<50 ng/dL) from day 29 through 48 weeks, early and profound (<20 ng/dL) castration rates, prostate-specific antigen (PSA) levels, and safety. Testosterone recovery (≥280 ng/dL) was evaluated in 184 patients who enrolled in the testosterone recovery substudy. **Results:** Of the 930 patients (relugolix:622;leuprolide:308) that received study drug in the HERO study, 173 (18.6%) were <65 years and 757 (81.4%) were ≥65 years of age, while 664 (71.4%) were ≤75 years and 266 (28.6%) were >75 years of age. Across all age subgroups, point estimates for sustained castration rates through 48 weeks for relugolix patients were consistent with the overall estimate of relugolix sustained castration rate observed in the overall population. Differences in sustained castrations rates at week 48 between relugolix and leuprolide groups were similar regardless of the age subgroup (table). The likelihood of testosterone recovery at 90 days after completion of treatment was higher in the relugolix group versus the leuprolide group in all age subgroups: <65 (79.1% vs 16.7%), ≥65 (48.6% vs 0%), ≤75 (60.0% vs 4.0%),and >75 years (40.7% vs 0%). No clinically relevant differences were noted in the incidence or types of adverse events within treatment groups in all the age subgroups analyzed. **Conclusions:** In this subgroup analysis of the HERO study, relugolix was effective regardless of age, and the benefit/risk profile remained favorable for relugolix compared with leuprolide, consistent with the overall population. Testosterone recovery was higher in the relugolix group than the leuprolide group for all age subgroups analyzed, with higher rates of recovery in younger versus older men. Clinical trial information: NCT03085095. Research Sponsor: Myovant Sciences GmbH, in collaboration with Pfizer, Inc.

Castration rates.

	Differences Between Relugolix and Leuprolide Groups
<65 years	6.8% (95% CI: -4.3%, 17.9%)
≥65 years	8.2% (95% CI: 4.2%, 12.2%)
≤75 years	6.3% (95% CI: 1.7%, 10.8%)
>75 years	12.1% (95% CI: 5.0%, 19.2%)

5076 **Poster Session**

Proliferation index and survival in men with prostate cancer starting long-term androgen deprivation therapy in the STAMPEDE clinical trial. *First Author: Larissa Mendes, University College London Cancer Institute, London, United Kingdom*

Background: Treatment intensification with docetaxel or abiraterone improved survival for advanced prostate cancer starting androgen deprivation therapy (ADT) in the Systemic Therapy in Advancing or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE, NCT00268476) trial. However, survival and time-to-progression is highly variable on ADT, introducing the risk of unnecessary toxicity from additional treatments for some patients. Here we test the prognostic association of proliferation index using Ki67 scores in the control arm of the STAMPEDE population of high-risk localised (M0) and metastatic (M1) prostate cancer. **Methods:** Pre-ADT diagnostic needle biopsies were obtained from 517 men randomized in STAMPEDE arm A between 2006 and 2015. These were assessed for proliferation using an analytically optimised Ki67 immunohistochemistry assay. Ki67 was tested for associations with baseline clinico-pathological variables (Grade group, pre-ADT serum PSA and imaging metastatic burden) in univariable linear-regression models, and for associations with survival outcomes in multivariable Cox-regression models adjusted for these and additional confounding variables. Primary outcome measure was overall survival, secondary outcomes were prostate cancer-specific, failure-free, progression-free and metastatic progression-free survival. **Results:** Ki67 was available for 475 patients who received ADT only for at least 2 years ± radiotherapy. Of 202 M0, 74 were node positive. Of 273 M1, 116, 127 and 30 were respectively low, high and unknown radiological M1 volume. Ki67 score associated with higher Gleason ($p=7.15x10^{-11}$) and presence of extra-pelvic metastases ($p=1.41x10^{-8}$). Increasing Ki67 scores showed a strong linear association with poorer overall survival, with an estimated 2% increase in the hazard of death per percentage increase in the score (adjusted HR=1.02, 95% CI 1.01-1.02; $p=1.04x10^{-5}$). There was also strong evidence that Ki67 associated positively with all secondary outcomes, including prostate cancer-specific survival (adjusted $p=5.50x10^{-6}$) and metastatic progression-free survival (adjusted $p=3.50x10^{-9}$). **Conclusions:** Ki67 immunoscore is strongly prognostic in clinically advanced prostate cancer independent of Gleason score and the other clinicopathological variables tested in this study. Ki67 is a clinically scalable assay that could improve selection for treatment intensification and provide a tool for screening patients most likely to benefit from further molecular investigation. Research Sponsor: Prostate Cancer UK.

5077 **Poster Session**

Correlation of baseline circulating tumor cells (CTC) and associated genomic profile with survival outcomes in patients (pts) with metastatic castration-sensitive prostate cancer (mCSPC) in a real-world cohort. *First Author: Umang Swami, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: We recently published, in the context of SWOG1216 trial in pts with mCSPC, that higher baseline CTC level were associated with inferior survival outcomes (Goldkorn. Agarwal, CCR, 2021). Here in, we validate these findings in a real world population of mCSPC and interrogate tumor genomic profile with respect to the CTC level. **Methods:** Eligibility criteria: new mCSPC receiving ADT without or with intensification (docetaxel or novel hormonal therapy) and enumeration of baseline CTCs by FDA cleared Cell Search CTC assay. Gene alterations were determined by comprehensive genomic profiling (CGP) of tumor tissue (Foundation Medicine). CTC counts were categorized as 0, 1-4 and ≥5/7.5 ml. Relationships between CTC counts and number (no.) of genes altered and individual gene alterations were assessed via Kruskal-Wallis and chi-squared tests, respectively. Relationships between progression-free survival (PFS), overall survival (OS) and individual mutations were assessed via log-rank tests. Relationships between CTC counts, PFS and OS were assessed by Cox proportional hazards models, both unadjusted and adjusted for multiple variables (Table). **Results:** Overall 103 pts were eligible. Median age: 67 yrs, Gleason score: 9, PSA at ADT initiation: 41 ng/mL. 67 (65%) pts had de-novo metastatic disease and 44 (43%) pts underwent ADT intensification therapy. Pts with greater CTC counts tended to have greater no. of altered genes (p=0.017), greater no. of total alterations (p=0.017) and higher rate of TP53 mutations (p=0.036). In univariate analyses (UVA) and multivariable analyses (MVA), both CTC counts and no. of genes altered were strongly associated with both PFS and OS (Table). CGP of tumors with respect to CTC counts will be presented in meeting. **Conclusions:** Herein, we validate our previous findings from SWOG1216 trial of association of higher CTC level with inferior survival outcomes in a real world mCSPC cohort. The CTC enriched population is associated with a distinct tumor genomic landscape, which may guide further drug development in this pt population at the highest risk of progression and/or death. Research Sponsor: None.

Estimates of association presented as hazard ratio (p-value).

Variable at ADT initiation	PFS UVA	PFS MVA	OS UVA	OS MVA
Age	0.93 (0.62)	0.59 (0.04)	1.21 (0.42)	0.92 (0.80)
Gleason score	1.24 (0.14)	1.51 (0.05)	1.53 (0.11)	1.69 (0.13)
PSA	1.14 (0.02)	1.23 (0.01)	0.99 (0.93)	1.06 (0.67)
De-novo metastatic disease	1.22 (0.44)	0.66 (0.35)	1.41 (0.45)	0.79 (0.74)
ADT intensification (yes/no)	0.65 (0.10)	0.54 (0.08)	1.86 (0.14)	2.17 (0.17)
Volume (high/ low)	1.67 (0.05)	1.58 (0.20)	1.68 (0.24)	0.97 (0.95)
No. of genes altered	1.17 (0.07)	1.33 (0.03)	1.55 (0.001)	1.65 (0.005)
1-4 CTC (Ref 0)	1.50 (0.19)	2.43 (0.04)	1.87 (0.28)	1.79 (0.41)
≥5 CTC (Ref 0)	3.53 (<0.001)	4.52 (0.001)	4.55 (0.003)	3.59 (0.06)

5078 **Poster Session**

Diagnostic performance of Gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging in early-relapsed prostate cancer: Phase 3, prospective, multicenter study (IAEA-PSMA study). *First Author: Juliano J Cerci, Quanta-Diagnóstico e Terapia, Curitiba, Brazil*

Background: Biochemical recurrence (BCR) is a clinical challenge in prostate cancer (PCa) patients with impact on defintion of subsequent therapies. The use of positron emission tomography (PET) with prostate-specific membrane antigen (PSMA) presents better accuracy than standard imaging practice. This phase3, prospective, multicentric, international study evaluates the diagnostic performance and clinical impact of PSMA-PET/CT in evaluating BCR in PCa. **Methods:** Patients with PCa who have undergone primary definitive treatment and with rising PSA were recruited in the study. Overall 17 centers from 15 countries (Azerbaijan, Brazil, Colombia, India, Israel, Italy, Jordan, Lebanon, Malaysia, Mexico, Pakistan, Poland, South Africa, Turkey, and Uruguay) were involved. Images and data were centrally reviewed; data were collected for PSMA site of findings, positivity rate, defined as the percentage of patients with a positive 68Ga-PSMA PET/CT taking into account the composite standard: pathology, correlative imaging, PSA response, with at least 6 mo. clinical follow-up, and impact on patient management by determining changes in the treating physician's documented clinical plans before and after 68Ga-PSMA PET/CT. **Results:** Were enrolled 1198 patients and presented final data from 1004 patients. 68Ga-PSMA PET/CT was positive in 654/1004 patients (65.1%); lesions were identified as: prostate/prostatic bed only in 13.7% cases; pelvic lymph nodes only 20.5%, and with any metastatic disease in 27.0%. There was a correlation between PSMA-PET/CT positivity and Gleason score ($p<0.001$): detection rate was 371/613 (60.5%) in patients with Gleason 7, 130/196 (66.3%) in Gleason 8, 140/180 (77.8%) in Gleason 9 and 13/15 (86.7%) in Gleason 10. There was also significant correlation between lesions identification and PSA values ($p<0.001$): detection rate was 21/41 (51.2%) for PSA <0.2, 84/188 (44.7%) for PSA between 0.2-0.5, 124/232 (53.4%) for PSA 0.5-1.0, 158/235 (67.2%) for PSA ≥1 and <2, 171/206 (83.0%) for PSA ≥2 and <4, and 96/102 (94,1%) in PSA 4 to 10. Also, treatment was modified based on PSMA results in 56.8% of patients. The 68Ga-PSMA PET/CT positivity was consistent and not statistically different among the countries. **Conclusions:** This is the largest multicenter trial on 68Ga-PSMA PET/CT detected local and metastatic recurrence in most men with BCR. 68Ga-PSMA PET/CT results changed the recommended treatment approaches in the majority of patients. This study confirms the reliability of PSMA PET in BC and the worldwide feasibility of such approach. Research Sponsor: International Atomic Energy Agency - IAEA.

5079 **Poster Session**

Darolutamide (DARO) tolerability from extended follow up and treatment response in the phase 3 ARAMIS trial. *First Author: Karim Fizazi, Institut Gustave Roussy and University of Paris Saclay, Villejuif, France*

Background: Patients (pts) with nonmetastatic castration-resistant prostate cancer (nmCRPC) need therapy that prolongs survival with little added toxicity, thus preserving quality of life. The second-generation androgen receptor inhibitors (ARIs) including DARO, apalutamide, and enzalutamide offer durable survival in nmCRPC but differences exist in AE profiles (eg, fatigue, falls, fractures, rash, mental impairment, and hypertension) that can limit daily activities. These AEs may require dose modifications and limit pts' willingness to continue treatment, with an adverse impact on efficacy. DARO is a structurally distinct ARI that significantly extended metastasis-free survival and overall survival (OS) vs placebo (PBO) in ARAMIS (NCT02200614), with minimal AE risk. We report tolerability from extended follow-up and treatment response analyses from ARAMIS. **Methods:** Pts with nmCRPC (N=1509) were randomized 2:1 to DARO or PBO with androgen deprivation therapy. The ARAMIS trial was unblinded at the primary analysis, after which all pts could receive open-label (OL) DARO. Tolerability was assessed every 16 weeks. Pharmacodynamic modeling investigated the association between treatment response (maximum prostate-specific antigen [PSA] decline from baseline) and OS at 2 years using a Cox proportional hazards model. **Results:** As shown in the table, DARO remained well tolerated over the double-blind (DB) and OL periods: 98.8% of pts on DARO received the full planned dose and almost all pts with dose modifications were able to resume and re-establish the planned dose (DARO 89.6% vs PBO 89.7%). Discontinuation of DARO due to AEs increased slightly from the DB period (9.0%) to the DB+OL period (10.5%). Pharmacodynamic modeling showed that longer OS was positively associated with maximum PSA decline in DARO-treated pts. **Conclusions:** DARO remained well tolerated with extended treatment at the recommended dose of 600 mg twice daily. Almost all pts with nmCRPC were able to receive the full planned dose, increasing the likelihood of clinical benefit from effective disease control (PSA decline) and prolonged survival. Tolerability of different ARIs in the real world should be assessed. Clinical trial information: NCT02200614. Research Sponsor: Bayer AG, Pharmaceutical/Biotech Company.

	DARO DB (n=954)	PBO DB (n=554)	DARO DB+OL (n=954)	PBO crossover to DARO OL (n=170)
Median (range) time on treatment, mo	18.5 (0–48)	11.6 (0–45)	25.8 (0–59)	11.0 (1–12)
Mean % planned dose received	98.8	99.3	98.8	99.7
Treatment discontinuation, %[a]	38.0	69.3	51.1	13.5
Due to Disease progression	12.5	25.3	12.6	0
AEs	9.0	8.7	10.6	4.7
Dose modifications				
Patients, n (%)	158 (16.6)	58 (10.5)	183 (19.2)	12 (7.1)
Pts with dose modification who re-escalated to full dose, %[b]	89.9	89.7	89.6	83.3

[a]Includes 1 additional randomized but untreated pt in the DARO DB/DB+OL cohorts. [b]Denominator is pts with dose modifications.

5080 **Poster Session**

A phase II randomized controlled trial of exercise on biochemical progression in men with prostate cancer on active surveillance. *First Author: Dong-Woo Kang, University of Alberta, Edmonton, AB, Canada*

Background: Men with prostate cancer (PCa) undergoing active surveillance (AS) are at increased risks of cardiovascular death and disease progression. Any intervention that can address these issues during AS would be highly beneficial. Clinical and preclinical studies have demonstrated the benefits of exercise to improve cardiovascular health in cancer patients and suggested the potential role of exercise in suppressing PCa progression in men with PCa undergoing AS. Therefore, the purpose of this study was to investigate the effects of exercise on cardiorespiratory fitness and biochemical progress of PCa in men with PCa on AS. **Methods:** The Exercise During Active Surveillance for Prostate Cancer (ERASE) Trial was a single-centre, two-armed, randomized controlled trial in Edmonton, Canada. 52 men with localized PCa who were undergoing AS were randomized to high-intensity interval training (HIIT; n = 26) or usual care (UC; n = 26). The HIIT group performed thrice-weekly, supervised, aerobic HIIT on a treadmill at 85-95% of peak cardiorespiratory fitness (VO_{2peak}) for 12 weeks. The primary outcome was VO_{2peak}, and the secondary and exploratory outcomes included biochemical progression of PCa (prostate-specific antigen [PSA]), PSA kinetics, and growth of prostate cancer cell line LNCaP. **Results:** 46/52 participants (88%) completed the postintervention VO_{2peak} assessment and adherence to HIIT was 96%. Compared to UC, HIIT significantly improved VO_{2peak} (adjusted between-group mean difference, 1.6 $ml \cdot kg^{-1} \cdot min^{-1}$; 95% confidence interval [CI], 0.3 to 2.9; p= 0.014). HIIT also significantly reduced PSA level (adjusted between-group mean difference, -1.1 ug/L; 95% CI, -2.1 to 0.0; p= 0.043) and PSA velocity (p= 0.040), and suppressed LNCaP cell growth (p =0.024). No significant differences were found in PSA doubling time (p= 0.10) and testosterone (p= 0.24). **Conclusions:** The ERASE Trial is the first randomized controlled trial to demonstrate the impact of HIIT exercise for improving physical fitness and inhibiting biochemical progression of PCa in men with localized PCa on AS. Our findings suggest that supervised aerobic HIIT may be a promising intervention in this clinical setting. Larger-scale randomized controlled trials are warranted to determine if improvements in physical fitness and PCa-related markers translate into improved long-term clinical outcomes in these men such as disease progression, receipt of radical treatments, posttreatment complications, and survival. Clinical trial information: NCT03203460. Research Sponsor: Canadian Institutes of Health Research (No. 389507), Other Foundation.

5081 **Poster Session**

Active surveillance of postradical prostatectomy biochemical recurrence: Long-term assessment of outcomes. *First Author: Tom Edward Ahlering, University of California, Irvine, Orange, CA*

Background: Biochemical recurrence (BCR) following radical prostatectomy (RP) is an unreliable predictor of distant metastatic progression/prostate cancer death, resulting in potential complications & expenses of overtreatment. Little has been published on management decisions & outcomes of active surveillance (AS). We characterize our long term experience with AS following post-RP BCR without radiation/androgen deprivation therapy. **Methods:** From June 2002 - September 2019, 1865 men underwent RP. 406 experienced BCR; of these, 138 (34%) were observed without treatment intervention. BCR defined as PSA>0.2 ng/dl, x2. PSAs checked every 1-3 months and entered into a PSADT graph. Men were considered to be formally AS after 3+ years of increasing DT following RP. Men with decreasing DT were treated and censored. **Results:** The table depicts demographics of the AS patients; median follow-up was 7.3 years (IQR: 4.6-10.6) post-RP. Of patients on AS, average age was 63.7 +/- 7.2 years and 86%, 48%, 40%, 51% and 14% were GG 1 through 5, respectively. Current DT of AS patients averages 20 months, with 0% PCSM. Only 10% of patients with decreasing DT began treatment after average 4 years following BCR. **Conclusions:** Of 406 patients experiencing post-RP BCR, 34% of patients are effectively managed with AS, with 0% PCSM across all GG. Presently 69 (50%) AS men have been under observation for 7.3 to 18 years. This suggests that significant portion of patients display benign recurrence, characterized by increasing DT following BCR and can be managed safely with observation alone. Research Sponsor: None.

AS demographics by GGG.

GGG	1	2	3	4	5	Total	
	Count (%)						
N, all	503 (27.0%)	758 (40.6%)	340 (18.2%)	82 (4.4%)	182 (9.8%)	1865 (100%)	
N, BCR	21 (4.2%)	83 (10.9%)	111 (32.6%)	39 (47.6%)	115 (63.2%)	406 (21.8%)	
N, AS	18 (85.7%)	40 (48.2%)	44 (39.6%)	20 (51.3%)	16 (13.9%)	138 (7.4%)	
AS	Mean (SD)						p value
Age, yrs	61.2 (7.1)	61.8 (7.2)	64.0 (7.5)	66.5 (6.2)	67.3 (5.7)	63.7 (7.2)	0.015
Pre-PSA, ng/mL	6.2 (3.3)	8.8 (6.9)	7.5 (4.8)	8.5 (3.8)	12.4 (8.7)	8.4 (5.9)	0.024
SHIM	20.3 (6.9)	21.2 (4.9)	19.9 (8.1)	17.4 (8.5)	18.2 (7.0)	19.8 (7.1)	0.343
BMI	29.0 (4.9)	26.5 (3.7)	26.7 (3.6)	26.7 (3.7)	28.1 (3.9)	27.1 (3.9)	0.167
Time to Death, yrs	8.2 (2.7)	3.5 (NA)	6.8 (3.0)	5.2 (3.0)	NA	6.6 (2.8)	
Current PSAdt, mos	7.8 (55.1)	24.6 (25.2)	23.3 (32.1)	18.1 (24.2)	17.6 (17.0)	20.3 (32.1)	0.406
Follow Up, yrs	9.8 (3.8)	8.7 (4.3)	7.0 (3.4)	4.4 (3.3)	6.1 (4.9)	7.4 (4.2)	< 0.001
median (range)	8.8 (3.7-15.3)	8.1 (1.3-18.0)	5.8 (1.0-13.7)	3.3 (0.2-13.9)	5.7 (0.2-16.8)	7.3 (0.2-18.0)	
	Count (%)						p value
Margins	4 (22.2%)	10 (25.0%)	15 (34.1%)	3 (15.0%)	8 (50.0%)	40 (29.0%)	0.159
p-stage							0.002
pT2	15 (83.3%)	21 (52.5%)	17 (38.6%)	5 (25.0%)	5 (31.2%)	63 (45.7%)	
pT3/T4	3 (16.7%)	19 (47.5%)	27 (61.4%)	15 (75.0%)	11 (68.8%)	75 (54.3%)	
PCSM	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Dead	3 (16.7%)	1 (2.5%)	5 (11.4%)	2 (10.0%)	0 (0.0%)	11 (8.0%)	0.225

5084 **Poster Session**

The somatic mutation landscape of germline *CHEK2*-altered prostate cancer. *First Author: Emily Nizialek, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: The intersection between germline and somatic genomics is an evolving field in which germline mutations may predispose to unique patterns of subsequent somatic mutations in cancer. Germline mutations in *CHEK2*, involved in cell cycle regulation and DNA damage response, are associated with an increased risk of prostate cancer (PCa), while somatic-only *CHEK2* alterations in PCa are rare. The association of germline *CHEK2* (g*CHEK2*)-altered PCa with somatic mutations is unknown, and may inform hypotheses about the etiology of these cancers. **Methods:** Germline DNA sequencing of 1,042 consecutive PCa patients (pts) from the public SignalDB database (www.signaldb.org) was analyzed for prevalence of pathogenic g*CHEK2* mutations and was compared to individuals from the general population estimated by the ExAC database (containing 53,105 germline exomes). A separate cohort of 33 PCa pts from Johns Hopkins (JH) with known g*CHEK2* mutations and available somatic tumor DNA sequencing (from primary prostatic tissue) was used to assess the association of g*CHEK2* mutations with somatic mutations in genes that are recurrently altered in PCa (*TP53*, *RB1*, *PTEN*, *ATM*, *BRCA1/2*, and *CDK12*); the prevalence of these somatic alterations was compared to those in 333 unselected PCa pts from the TCGA cohort. Somatic biallelic inactivation of *CHEK2* was analyzed in a subset of pts. After uncovering a potential link between g*CHEK2* and somatic *CDK12* mutations, we studied a cohort of 69 pts with somatic *CDK12* mutations where germline data were also available. **Results:** 28 of 1,042 (2.7%) PCa pts from SignalDB had a pathogenic g*CHEK2* mutation, compared to a population prevalence (in ExAC) of 1.4% (750 of 53,105) (RR 1.9, 95%CI 1.3–2.8, $P<$ 0.001). Strikingly, only 23.8% of pts from SignalDB with g*CHEK2* mutations had biallelic inactivation in the tumor. Furthermore, none of the 33 g*CHEK2* pts from the JH cohort had evidence of somatic LOH. There were no differences in mutation prevalences involving *TP53*, *RB1*, *PTEN*, *ATM*, and *BRCA1/2* between g*CHEK2*-altered and non-altered PCa pts. Unexpectedly, 5 of 33 (15%) g*CHEK2*-altered pts from the JH cohort had a somatic *CDK12* mutation, compared to only 3 of 333 *CDK12* mutations (1%) in unselected PCa pts from the TCGA cohort (RR 16.8, 95%CI 4.2–67, $P<$ 0.001). Conversely, 11 of 69 (16%) pts with a somatic *CDK12* mutation harbored a pathogenic g*CHEK2* mutation, compared to 28 of 1,042 (2.7%) unselected PCa pts from SignalDB (RR 5.9, 95%CI 3.1–11.4, $P<$ 0.001). **Conclusions:** Prostate cancers from g*CHEK2*-altered pts are infrequently characterized by biallelic *CHEK2* inactivation and may be enriched for somatic *CDK12* mutations, suggesting a unique mechanism of carcinogenesis that is different from g*BRCA2*-altered pts. Conversely, somatic *CDK12*-mutated cancers may be enriched for g*CHEK2* mutations. The co-occurrence of *CHEK2* and *CDK12* mutations suggests a synergistic role in promoting cancer growth. Research Sponsor: None.

TPS5085 **Poster Session**

The Courage study: A first-in-human phase 1 study of the CBP/p300 inhibitor FT-7051 in men with metastatic castration-resistant prostate cancer. *First Author: Andrew J. Armstrong, Duke Cancer Institute Center for Prostate & Urologic Cancers, Duke University, Durham, NC*

Background: Prostate cancer is the second leading cause of cancer-related death among men in the U.S., largely due to metastatic disease that progresses despite hormonal therapy (tx). The role for androgen receptor (AR) signaling in prostate cancer and hormone tx resistance is well-established. CBP/p300 are essential co-activators of AR-mediated transcription. FT-7051 is an oral, potent, and selective inhibitor of CBP/p300 with activity in preclinical models of prostate cancer including models resistant to currently used AR inhibitors like enzalutamide. The Courage Study (NCT04575766) is a first-in-human, multicenter, phase 1, open-label study examining the safety, pharmacokinetics (PK), preliminary anti-tumor activity, and pharmacodynamics (PD) of FT-7051 for the treatment of men with metastatic castration-resistant prostate cancer (mCRPC) who have progressed despite prior tx and have been treated with at least one approved androgen receptor pathway inhibitor. The study will enroll up to 45 men with mCRPC at ~8-15 US sites. **Methods:** The study employs a Bayesian optimal interval (BOIN) design with an accelerated titration. Patients (pts) will initially be enrolled in a dose level cohort size of 1 until a Grade 2 or higher toxicity occurs that is considered related to FT-7051 or the highest dose level is reached. Upon completion of the accelerated titration phase, subsequent cohorts will enroll 3-5 pts. *Treatment:* FT-7051 capsules will be administered on a 28 d cycle (21 d on / 7 d off) with Dose Levels -1 to 7 assigned per protocol using the BOIN design. *Key inclusion criteria*: Diagnosis of mCRPC with either adenocarcinoma or mixed histology AND rising PSA; previously failed at least one approved androgen receptor pathway inhibitor; ≥ 18 yrs of age; prior taxane chemotherapy permitted. *Key exclusion criteria*: Previous solid organ transplant, prior anticancer tx including prior tx with small molecules within 4 wks of first dose of study treatment, prior radiation tx within 4 wks prior to initiation of study treatment, prior androgen antagonist tx within 2 wks, prior radium-223 tx within 6 wks. *Endpoints*: Primary endpoints are to define the recommended phase 2 monotherapy dose of FT-7051 through assessments of DLTs, SAEs, clinically relevant AEs, and clinically relevant safety laboratory values. Key secondary endpoints include: PSA at 12 wks, time to PSA progression, time to radiographic progression, overall response rate, and plasma PK parameters. PD assessments of CBP/p300 inhibition in surrogate tissue, biomarker assessments in CTCs (AR, AR-v7), and peripheral blood are included. *Duration*: Pts will remain on study treatment until they are deemed to be no longer clinically benefiting (NLCB) by the treating Investigator or until unacceptable toxicity. Pt may be followed for survival for up to 24 months from last dose of study treatment. The first pt was dosed January 2021. Clinical trial information: NCT04575766. Research Sponsor: Forma Therapeutics, Inc.

TPS5086 **Poster Session**

CYCLONE 1: A phase 2 study of abemaciclib in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with a novel hormonal agent and taxane-based chemotherapy. *First Author: Neeraj Agarwal, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: In cancer cells, the cyclin-dependent kinases 4 and 6 (CDK4 & 6)/retinoblastoma protein (Rb) pathway is commonly altered, resulting in uncontrolled cell cycle entry and proliferation. CDK4 & 6 inhibitors represent a major advance in the management of hormone receptor-positive (HR+), human epidermal growth factor receptor 2-negative (HER2-) advanced or metastatic breast cancer (ABC or MBC, respectively). Abemaciclib is an oral selective inhibitor of CDK4 & 6 administered on a continuous dosing schedule, approved in combination with endocrine therapy for HR+, HER2- ABC or MBC. In addition, abemaciclib is also approved by the FDA as monotherapy for HR+, HER2- ABC or MBC following endocrine therapy and prior chemotherapy in the metastatic setting. Similar to the estrogen receptor signaling pathway in breast cancer cells, there is evidence that the androgen receptor axis activates CDK4 & 6 to sustain prostate cancer cell proliferation and survival. Preclinical studies in prostate cancer cell lines and xenograft models showed that abemaciclib exhibits single agent activity by inducing cell cycle arrest and tumor growth inhibition. Clinical activity of abemaciclib in combination with abiraterone and prednisone is investigated in a randomized phase 2 study in the first-line mCRPC setting (CYCLONE 2, NCT03706365). Despite recent advances, management of heavily pretreated mCRPC remains a major clinical challenge. Herein, we hypothesize that mCRPC patients whose disease progressed after novel hormonal agents (NHA) and taxane therapies may derive therapeutic benefit from single agent abemaciclib. **Methods:** CYCLONE 1 is a phase 2, single-arm, multicenter study to assess the safety and efficacy of abemaciclib monotherapy in 40 patients with mCRPC progressing after ≥1 NHA and 2 taxane regimens. Patients will be enrolled at time of prostate specific antigen (PSA) or radiographic progression per PCWG3 criteria and have at least 1 measurable lesion per RECIST 1.1. Metastatic tumor tissue (fresh biopsy or archival material <12 weeks) is required at baseline for biomarker analysis. Patients will receive abemaciclib 200 mg twice daily until unacceptable adverse events or disease progression. The primary objective is investigator-assessed objective response rate (ORR). Key secondary objectives include safety, radiographic progression-free survival, overall survival, PSA response rate, time to PSA progression, time to symptomatic progression, Ki-67 expression, patient-reported outcomes, and pharmacokinetics. Assuming an ORR of 15%, the study has over 73% power to observe a response rate of at least 12.5%. Accrual began in January 2021. Clinical trial information: NCT04408924. Research Sponsor: Eli Lilly and Company Ltd.

TPS5087 **Poster Session**

Study evaluating metastatic castrate resistant prostate cancer (mCRPC) treatment using ^{177}Lu-PNT2002 PSMA therapy after second-line hormonal treatment (SPLASH). *First Author: Kim N. Chi, BC Cancer Agency-Vancouver Centre, Vancouver, BC, Canada*

Background: Treatment options with minimal toxicity and novel mechanisms of action are urgently needed to improve clinical outcomes from mCRPC. Prostate-specific membrane antigen (PSMA)-targeted radioligand therapy (RLT) represents a new treatment for patients with PSMA-avid mCRPC. ^{177}Lu-PNT2002 (also known as [Lu-177]-PSMA-I&T) is a PSMA-targeting agent and studies have shown demonstrable promising initial data. This trial seeks to prospectively evaluate the efficacy of ^{177}Lu-PNT2002 for men with progressive mCRPC after androgen receptor axis-targeted (ARAT) therapy. **Methods:** This is a multi-center, open-label, phase III study. All patients must be at least 18 years of age, have documented progressive mCRPC at time of screening, high PSMA expression by PSMA PET/CT per blinded independent central review (BICR), chemotherapy naïve for CRPC and unfit or unwilling to receive chemotherapy. The study will commence with a 25-patient dosimetry lead-in. In the dosimetry phase, patients will receive up to four cycles of ^{177}Lu-PNT2002 at 6.8 GBq every 8 weeks. In the randomization phase, approximately 390 patients will be randomized in a 2:1 ratio to receive ^{177}Lu-PNT2002 (Arm A) versus enzalutamide or abiraterone (with prednisone or dexamethasone) (Arm B). Patients randomized to Arm B have an option to crossover to ^{177}Lu-PNT2002 treatment after BICR-assessed radiologic progression. The primary endpoint is Radiological progression-free survival (rPFS) assessed by BICR using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG3) (bone) criteria. Key secondary endpoints include objective response rate, duration of response, PSA response, and overall survival. The study is powered at 90% to test the alternative hypothesis of a hazard ratio (HR) $\leq$ 0.66 at an α of 0.025. ClinicalTrials.gov identifier: NCT04647526. Clinical trial information: NCT04647526. Research Sponsor: POINT Biopharma Inc.

TPS5088 **Poster Session**

Safety and efficacy of AMG 160, a half-life extended BiTE immune therapy targeting prostate-specific membrane antigen (PSMA), and other therapies for metastatic castration-resistant prostate cancer (mCRPC). *First Author: Sumit Kumar Subudhi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Lesions in mCRPC are typically immunologically cold. AMG 160 binds to PSMA on cancer cells and CD3 on T cells, leading to T-cell infiltration, activation, expansion, and tumor cell killing. In a first-in-human study, AMG 160 has demonstrated a manageable safety profile with preliminary efficacy in heavily pretreated patients. Enzalutamide and abiraterone are novel hormonal therapies (NHTs) that improve survival in mCRPC and may enhance T-cell responses, but resistance occurs. Combination therapy with AMG 160 may help overcome hormonal therapy resistance and broaden use for earlier line mCRPC. Preclinical data have demonstrated enhanced activity when AMG 404, an anti-PD-1 that can overcome T-cell exhaustion, and AMG 160 are combined. The safety and efficacy of AMG 160 combinations will be evaluated. **Methods:** NCT04631601 will enroll ~100 men with histologically or cytologically confirmed adenocarcinoma of the prostate. The protocol consists of 3 subprotocols. Subprotocols A and B are phase 1b, multicenter, open-label studies; subprotocol C is a phase 1b/2 study. Therapeutic combinations include AMG 160 + enzalutamide (A), AMG 160 + abiraterone (B), and AMG 160 + AMG 404 vs AMG 404 monotherapy (C). Patients who received prior PSMA radionuclide therapy may be eligible. Patients must not have received prior PSMAxCD3 bispecific therapy, prior taxane treatment (unless approved by the sponsor) across subprotocols, and prior NHT specific to the subprotocol. In subprotocol C, patients must have progressive disease on an NHT to be eligible. Patients with CNS metastases, leptomeningeal disease, or active autoimmune disease will be excluded. AMG 160 will be administered intravenously (IV). Dexamethasone (or other corticosteroids) will be administered before AMG 160 administration in cycle 1 and possibly subsequent cycles. Enzalutamide or abiraterone will be administered per label. AMG 404 will be administered IV. Primary objectives are to evaluate safety and tolerability and determine the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D) of AMG 160 combinations. Subprotocol C will also evaluate the preliminary antitumor activity of AMG 404 monotherapy. Secondary objectives are to assess preliminary antitumor activity and characterize pharmacokinetics. MTD/RP2D will be established in the dose-escalation phase, and the safety and tolerability of the MTD/RP2D will be confirmed in the expansion phase. Evaluation of preliminary antitumor activity will be based on RECIST 1.1 with Prostate Cancer Working Group 3 modifications, prostate-specific antigen (PSA) response, circulating tumor cell response, progression-free survival (radiographic, PSA, clinical), overall survival, and ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT imaging. The study is currently recruiting patients. Clinical trial information: NCT04631601. Research Sponsor: Amgen Inc.

TPS5089 **Poster Session**

TALAPRO-2: A phase 3 randomized study of enzalutamide (ENZA) plus talazoparib (TALA) versus placebo in patients with new metastatic castration-resistant prostate cancer (mCRPC). *First Author: Neeraj Agarwal, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: TALA blocks poly(ADP-ribose) polymerase (PARP) activity and traps PARP on single-strand DNA breaks, preventing DNA damage repair (DDR) and causing death of cells with DDR alterations (eg, *BRCA1/2*).[a] TALA is approved in multiple countries as monotherapy for germline *BRCA1/2*-mutated human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer. Olaparib and rucaparib are PARP inhibitors approved for use in mCRPC. ENZA is an androgen receptor (AR) inhibitor and an established therapy for mCRPC. As PARP activity has been shown to support AR function, inhibition of PARP is expected to increase sensitivity to AR-directed therapies. In addition, AR blockade downregulates homologous recombination repair gene transcription, which induces a "*BRCA*ness" phenotype. A proof-of-concept study combining olaparib and abiraterone (abi) in pts with mCRPC demonstrated improved median radiographic progression-free survival (rPFS) vs placebo plus abi (13.8 vs 8.2 months) and a tolerable safety profile. Therefore, ENZA may be efficacious regardless of DDR alterations. TALAPRO-2 (NCT03395197) is a Phase 3, 2-part study evaluating the efficacy, safety, pharmacokinetics, and patient-reported outcomes (PROs) of TALA plus ENZA in pts with mCRPC with or without DDR alterations. **Methods:** Enrollment goal is 1037 patients (pts; 19 pts, part 1 dose-finding [completed]; 1018 pts, part 2 placebo-controlled [ongoing; accrual completed in unselected cohort]). Key eligibility criteria: age $\geq$18 years; asymptomatic/mildly symptomatic mCRPC; ECOG performance status $\leq$1; metastatic disease (no brain metastases); and no prior life-prolonging systemic therapy for nonmetastatic CRPC or mCRPC. Prior therapies (excluding novel AR inhibitors) in the castration-sensitive (CSPC) setting are allowed. ADT must continue throughout the study. The randomized double-blind portion (part 2) will evaluate safety, efficacy, and PROs of TALA (0.5 mg once daily [QD]) + ENZA (160 mg QD) vs placebo + ENZA (160 mg QD). Pts are stratified by prior novel hormonal therapy or docetaxel for CSPC or mCSPC (yes or no) and DDR alteration status (deficient vs nondeficient/unknown). The primary endpoint is rPFS, defined as time to progression in soft tissue per RECIST v.1.1 or in bone per PCWG3 criteria by independent central review or death. The key secondary endpoint is overall survival. Efficacy is assessed radiographically every 8 weeks up to Week 25 and every 8–12 weeks thereafter. rPFS will be compared between the two arms by a one-sided stratified log-rank test. Pt recruitment is ongoing at 223 sites in 26 countries, including 32 states across the US, and Europe, Israel, South America, South Africa, and Asia-Pacific region. [a]DDR alterations are defined as known/likely pathogenic variants or homozygous deletions. Clinical trial information: NCT03395197. Research Sponsor: Pfizer Inc, Pharmaceutical/Biotech Company.

TPS5090 **Poster Session**

A phase 1/2a, open-label, multicenter study of intramuscular (IM) abiraterone decanoate (PRL-02) depot in patients with advanced prostate cancer (NCT04729114). *First Author: Tim Warneke, Propella Therapeutics, Inc., Pittsboro, NC*

Background: PRL-02 is a long-acting IM formulation of a lipophilic abiraterone prodrug being developed for the treatment of patients with metastatic castration-sensitive (mCSPC) and metastatic castration-resistant prostate cancer (mCRPC). In nonclinical models, PRL-02 has a longer effective half-life and duration of action compared to oral abiraterone acetate (AA), due to slow release of the prodrug into circulation. PRL-02 is expected to provide greater abiraterone bioavailability and less variability in pharmacokinetics than oral AA. Based upon results in non-human primate models, PRL-02 should provide efficacy (e.g., testosterone [T] suppression) comparable to oral AA, but with lower abiraterone peak plasma concentrations and overall exposures, potentially leading to a superior therapeutic index and safety profile. The current trial is a phase 1/2a, open-label, dose escalation and subsequent dose expansion study of PRL-02 in men with metastatic prostate cancer. Study Objectives: The primary objective of this study is to determine a recommended phase 2 dose (RP2D) of PRL-02 that provides adequate T suppression up to 84 days. The secondary objectives of this study include the evaluation of safety and tolerability, the pharmacokinetic profile following IM administration and the pharmacodynamic effects of PRL-02. **Methods:** The phase 1 portion (Dose Escalation) is a standard 3+3 design intended to identify a RP2D that adequately suppresses T up to 84 days. The phase 2a portion (Dose Expansion) will confirm the safety, tolerability and pharmacodynamic effects of the RP2D. Main inclusion criteria are orchiectomy or ongoing GnRH analogue therapy for at least 3 months and a screening T level $<$50 ng/dL but $>$2 ng/dL. Prior treatment with abiraterone (or any other CYP17 inhibitor) and current treatment with enzalutamide or any other AR blocking agents are excluded. Patients will undergo scheduled periodic assessments of T levels. Patients may remain on study unless their T is $>$1 ng/dL on two sequential determinations starting on Day 28 through Day 77 of the first dosing cycle. In phase 1, three patients will initially be enrolled at each dose. The starting dose is 180 mg (i.e., 1.0 mL of PRL-02) and dose escalation will proceed with a modified Fibonacci sequence. If none of the patients in a cohort experience a dose-limiting toxicity (DLT), the dose will be escalated in the next cohort of 3 patients. A DLT is defined as a drug-related Grade 3 or higher toxicity on the Common Terminology Criteria for Adverse Events v5.0, or meets drug-induced liver injury criteria, occurring during the first 28 days following the first dose. In phase 2a, 12 mCSPC and 12 mCRPC patients will be enrolled to receive up to 4 cycles of PRL-02 at the RP2D. The results of this phase 1/2a study will be presented at a future ASCO conference. Clinical trial information: NCT04729114. Research Sponsor: Propella Therapeutics.

TPS5091 **Poster Session**

A phase III trial of docetaxel versus docetaxel and radium-223 (Ra-223) in patients with metastatic castration-resistant prostate cancer (mCRPC): DORA. *First Author: Michael J. Morris, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Ra-223, a bone-targeted alpha therapy, prolongs survival in patients (pts) with symptomatic mCRPC to bone. Docetaxel targets microtubule trafficking improving survival in the mCRPC and metastatic hormone-sensitive settings. We hypothesized that simultaneously targeting the tumor and bone compartment yields superior outcomes than targeting either alone. We previously determined the dose and schedule of co-administering Ra-223 + docetaxel in a randomized phase I/IIa trial. The combination appeared to have improved declines in prostate specific antigen (PSA) and bone markers, delayed PSA progression, and was better tolerated (with adjusted dose/schedule) relative to standard docetaxel alone. We are now conducting a phase III study to determine the clinical benefit of the regimen. **Methods:** Randomization (1:1) of 738 men with mCRPC to docetaxel or docetaxel + Ra-223 is planned with a projected hazard ratio for treatment effect (15 vs 20 months median survival) of 0.75. Pts with ≥2 bone lesions and progression by Prostate Cancer Working Group 3 criteria are eligible. Other key inclusion criteria are an Eastern Cooperative Oncology Group performance status of 0–1 and normal organ function. Key exclusion criteria are: use of anticancer therapy ≤4 weeks (wks) before randomization and use of bone-seeking radiopharmaceuticals or chemotherapy in the castration-resistant setting, and bulky visceral metastases (≥3 lung and/or liver or a lesion ≥2 cm in the previous 8 wks). Subjects receive docetaxel 75 mg/m^2 IV q3w for 10 doses or docetaxel 60 mg/m^2 IV q3w for 10 doses + Ra-223 55 kBq/kg IV q6w for 6 doses. The primary endpoint is overall survival. Secondary and exploratory endpoints include: radiographic progression-free survival, symptomatic skeletal event-free survival, safety, markers of bone metabolism, alterations in circulating tumor cells and DNA, detection of androgen-receptor splice variant 7, changes in automated bone scan index (aBSI), and assessment of patient-reported outcome instruments (FACT-P, Brief Pain Inventory, Brief Fatigue Inventory). The study is open at 32 sites in the US and Netherlands and has 170 subjects enrolled. The study is sponsored by Memorial Sloan Kettering Cancer Center, and managed by the Prostate Cancer Clinical Trials Consortium. Clinical trial information: NCT03574571. Research Sponsor: Bayer Pharmaceuticals.

TPS5092 **Poster Session**

TNB585.001: A multicenter, phase 1, open-label, dose-escalation and expansion study of tnb-585, a bispecific T-cell engager targeting PSMA in subjects with metastatic castrate resistant prostate cancer. *First Author: Ben Buelow, TeneoBio, Inc., Menlo Park, CA*

Background: Prostate cancer (CaP) is the most common cancer in US men. Disseminated CaP invariably progresses to metastatic castrate-resistant prostate cancer (mCRPC). Current treatment options for mCRPC usually lead to therapeutic resistance, and novel therapies are urgently needed. PSMA is a prostate-specific antigen over-expressed on most mCRPC. Antibodies against PSMA have been used to create T-cell engaging bispecific Abs (TCEs) and chimeric antigen receptor T cells, but all such approaches to date induce frequent/severe cytokine release syndrome (CRS). We combined a high-affinity αPSMA moiety with a low-activating αCD3 binder to create TNB-585; in preclinical studies, TNB-585 showed equivalent anti-tumor efficacy but much reduced cytokine secretion compared to PSMA-targeted TCEs with a strongly activating αCD3 domain. TNB-585 also has a full length silenced Fc domain, conferring a 3-week half-life. A phase 1 study investigating the safety, pharmacokinetics (PK), anti-drug antibodies (ADA) and preliminary activity of TNB-585 in patients with mCRPC is ongoing and described. **Methods:** TNB585.001 (NCT04740034) is an open-label, multi-center study of TNB-585 in patients with mCRPC. The study is divided into escalation (Arm A, N=24) and expansion (Arm B, N=30) arms. Subjects who have received 2 or more prior lines of therapy are eligible. Prior exposure to PSMA-targeted therapy is permitted, as are well-controlled HBV, HCV, and HIV infection; subjects with secondary malignancies that do not interfere with the study may also be enrolled. Other key inclusion/exclusion criteria include EGFR of > 30ml/min and ECOG ≤ 2. TNB-585 is administered as an intravenous infusion every 3 weeks. Subjects must be admitted for 48 hours after their 1st dose; TNB-585 is given on an outpatient basis thereafter. Dose escalation is proceeding in Arm A via single patient cohorts until the onset of toxicity or activity; thereafter subjects enroll using a BOIN design. Arm B will start once the maximum tolerated dose (MTD) / recommended phase 2 dose (RP2D) has been selected. Subjects will be treated until progression or unacceptable toxicity. In Arm A, occurrence of dose limiting toxicities (DLTs) will drive identification of the MTD (or RP2D) based on the BOIN escalation and de-escalation boundaries (λe of 0.236 and a λd of 0.358). In Arm B accrual will be suspended if more than 33% of subjects experience a DLT event. Adverse events (AEs), laboratory profiles, and vital signs will be assessed throughout the study. AEs are graded according to the NCI CTCAE, version 5.0. The activity endpoints (per PCWG3/RECIST1.1) include overall response rate, PSA50, PSA30, CTC counts, progression free survival and overall survival. The relationship between PSMA expression (via PSMA-PET) and activity will be assessed. Clinical trial information: NCT04740034. Research Sponsor: Teneobio, Inc.

TPS5093 **Poster Session**

Radium-223 (Ra-223) versus novel antihormone therapy (NAH) for progressive metastatic castration-resistant prostate cancer (mCRPC) after 1 line of NAH: RADIANT, an international phase 4, randomized, open-label study. *First Author: Karim Fizazi, Institut Gustave Roussy and University of Paris Saclay, Villejuif, France*

Background: Men with mCRPC often receive sequential NAH (abiraterone and enzalutamide) despite reported cross-resistance, indicating a need for further life-prolonging options for progressive disease after prior NAH. Ra-223 is a targeted alpha therapy approved for mCRPC with symptomatic bone metastases based on the phase 3 ALSYMPCA study, in which it demonstrated significantly increased overall survival (OS), reduced symptomatic skeletal event (SSE) risk, improved quality of life, and reduced treatment-emergent adverse event rates vs placebo. As life-prolonging therapy is increasingly used in hormone-sensitive settings, this study has been designed to assess Ra-223 outcomes in patients with mCRPC that progressed after prior treatment with NAH and docetaxel for metastatic hormone-sensitive prostate cancer (mHSPC) or mCRPC. **Methods:** This study is conducted in accordance with the Declaration of Helsinki, international ethical and good clinical practice guidelines, and local laws and regulations, with institutional review board/ethics committee approval at each site and written informed consent from patients before participation. This trial is registered with EudraCT: 2019-000476-42. Participants must be ≥18 years old, with an Eastern Cooperative Oncology Group performance status of 0/1; they must have mCRPC that progressed on/after ≥3 months of NAH for mHSPC or mCRPC and ≥2 cycles of docetaxel unless they refused or were ineligible, with ≥2 bone metastases on bone scan, no visceral metastases, and a worst pain score ≥1 on the Brief Pain Inventory-Short Form. Patients are randomized 1:1 to Ra-223 or NAH: Ra-223 55 kBq/kg intravenously every 4 weeks for 6 cycles or until disease progression, death, or withdrawal of consent if earlier; or abiraterone 1000 mg + prednisone 10 mg daily (if prior enzalutamide) or enzalutamide 160 mg daily (if prior abiraterone) until disease progression, death, or withdrawal of consent. NAH dosing may be modified to manage adverse events. Patients must use luteinizing hormone-releasing hormone analogs, if not surgically castrated, and bone health agents (bisphosphonates or denosumab) throughout the study. The primary endpoint is OS. Secondary endpoints are time to first SSE, radiologic progression-free survival, time to pain progression, adverse events, fracture incidence, and time to deterioration in quality of life (FACT-P total score). Using a test with a two-sided alpha of 0.05, 90% power, and randomization ratio of 1:1, approximately 508 events are required to detect a 33% increase in OS with Ra-223 vs NAH, assuming a median OS of 10 months with NAH. The expected study duration is 55 months, with a target of 696 patients to be randomized. The first patient was enrolled on November 9, 2020; 5 patients have been randomized and 2 have started treatment to date. Clinical trial information: 2019-000476-42. Research Sponsor: Bayer AG.

TPS5094 **Poster Session**

Phase I study of CCW702, a bispecific small molecule-antibody conjugate targeting PSMA and CD3 in patients with metastatic castration-resistant prostate cancer (mCRPC). *First Author: Mark Christopher Markowski, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: CCW702 is a novel bispecific antibody comprised of a small molecule imaging agent ligand (DUPA) with specificity for prostate specific membrane antigen (PSMA) conjugated to an anti-CD3 antibody via an unnatural amino acid. This format has the structure of an antibody drug conjugate with the activity of a CD3-engaging bispecific antibody. The design of CCW702 was leveraged to optimize the structure and function of T cell redirected cytotoxicity against PSMA-positive prostate cancer tumors in preclinical development. **Methods:** This is a first-in-human, open-label, multicenter phase 1 study evaluating the safety and tolerability of CCW702 when administered via subcutaneous (SC) injection in men with mCPRC. This study will be conducted in two parts: Part I, a dose escalation to determine the maximum tolerated dose (MTD) and recommended phase 2 dose (R2PD); Part II, a dose expansion to determine efficacy at the R2PD. Safety, pharmacokinetics (PK), pharmacodynamics (PD), immunogenicity, and preliminary efficacy will be evaluated. Efficacy will be assessed by change in circulating tumor cells (CTC), PSA_{50} response rate, and objective tumor response by RECIST v1.1. Key biomarkers include characterization of CTC, T cell phenotyping in peripheral blood, chemokines and cytokines over time, and evaluation of available tumor biopsies by IHC. Key inclusion criteria include men age ≥ 18 years with histologically or cytologically confirmed adenocarcinoma who, in the metastatic setting, have progressed on at least one novel AR-targeted therapy. Up to 1 prior chemotherapy regimen is allowed. This study will enroll 20-30 patients in Part 1 and approximately 40 patients in Part 2. The study opened in December 2019 and is currently enrolling in the dose escalation phase. Clinical trial information: NCT04077021. Research Sponsor: Wellcome Trust.

TPS5095 **Poster Session**

Open label phase II trial of cabozantinib (cabo) in patients with metastatic castrate resistant prostate cancer (mCRPC) and known amplifications or activating mutations in gene targets who have received prior anti-androgen therapy. *First Author: Jones T. Nauseef, NewYork-Presbyterian Hospital/ Weill Cornell Medical Center, New York, NY*

Background: Despite a variety of therapy classes extending survival in mCRPC – and excepting select population eligible for PARP inhibitors – no molecularly selected drugs are FDA approved in mCRPC. Previously, cabo, an inhibitor of multiple tyrosine kinases (*e.g.* MET, VEGFRs 1-3, RET, KIT, TRKB, FLT-3, AXL, TIE-2), was evaluated in phase III trials (COMET-1, COMET-2) in mCRPC. Despite initial promising results, particularly in bone scan responses and rPFS benefit, further application of cabo in mCRPC was halted after improvement in OS was not observed. It is unclear why prolonged rPFS in COMET-1 (vs. prednisone) did not translate into improved OS. Previous failures may reflect inclusion of relatively cabo-insensitive tumors due to an unselected population with regard to presumed cabo activity. Given that mCRPC specimens from our precision medicine cohort have increased expression of target genes *MET* and *KIT*, and qualifying genomic alterations (amplifications, activating mutations) are reported in ~15% of a publicly-available mCRPC cohort, we developed this rationally-designed study. We predict a molecularly-defined mCRPC cohort will identify the population that most benefits from cabo therapy, as reflected by prolonged rPFS and OS, and more frequent PSA declines and CTC conversions. **Methods:** We have activated a phase II non-randomized, open label trial designed to evaluate treatment response and survival of patients with mCRPC who harbor evidence of increased signaling of the targets of cabo. Study population will have progressed on an ARSI; prior taxane therapy in castration-sensitive PC or CRPC (beyond 12 mos) will be eligible. Molecular eligibility: DNA (tumor or cfDNA) evidence of amplification or activating mutation in selected targets of cabo. Alternatively, IHC confirming high expression (2 or 3+) via CLIA-approved assay is allowed. Overexpression via RNAseq, validated by CLIA-approved IHC, is permitted. All patients will receive 40 mg/d of cabo, with dose-reductions allowed (to 20 mg/d, then 20 mg EOD). Repeat biopsy after 3 weeks on treatment is mandated. Primary endpoint is rPFS. Using median of 5.6 mos (COMET-1) to guide our H_0 (50% rPFS rate at 6 mo), the H_1 is $\geq$75% rPFS at 6 mo. Sample size (30) provides 90% power with one-sided alpha of 0.05 via chi-square test. Secondary endpoints include PSA decline by PCWG3, objective radiographic response proportion, OS, and CTC response rate. Exploratory studies will include serial evaluation of cfDNA (via PCF-SELECT); immune tumor microenvironment response via on-treatment biopsy and collection of plasma for circulating immune markers; and exploration of baseline and on-treatment tumor genomic alterations. This trial is multicentered via the Prostate Cancer Clinical Trials Consortium (PCCTC c20-254). Clinical trial information: NCT04631744. Research Sponsor: Exelixis, Conquer Cancer Foundation of the American Society of Clinical Oncology.

TPS5096 **Poster Session**

A phase I/II study of bintrafusp alfa and NHS-IL12 in combination with docetaxel in adults with metastatic castration sensitive (mCSPC) and castration-resistant prostate cancer (mCRPC). *First Author: Mohammad O. Atiq, National Cancer Institute, Bethesda, MD*

Background: Immune checkpoint inhibition is successful in a small subpopulation of men with prostate cancer. This could be related to barriers to immune response in the tumor microenvironment. Immunocytokines present an opportunity to specifically target the pleiotropic tumor microenvironment impacting immune cells beyond T-cells. NHS-IL12 is an immunocytokine that carries IL-12 (shown to impact natural killer and myeloid cells) and binds to necrotic tissue with exposed histones. Phase 1 studies have indicated immune and even PSA responses in prostate cancer to NHS-IL12 (Strauss J, CCR 2019). Preclinical data has demonstrated synergy with docetaxel, which is standard therapy in both mCSPC and mCRPC. Further synergy has been shown with a novel first-in-class bifunctional fusion protein (bintrafusp alfa) composed of the extracellular domain of human TGF-β receptor II (TGFβRII), which effectively functions to sequester or "trap" all three TGF-β isoforms (Lind H, JITC 2020), fused to a monoclonal antibody against PD-L1. This study will examine the potential of a novel combination of chemotherapy, checkpoint inhibition, and immunocytokines in metastatic prostate cancer. **Methods:** The study will evaluate safety of NHS-IL12 with docetaxel at escalating doses followed by the addition of bintrafusp alfa in all metastatic patients. Once safety of the combination is established, patients will enroll in 2 cohorts with either mCSPC or mCRPC. Eligible patients include mCSPC ($\leq$134 days of starting ADT) and mCRPC (must have been previously treated with abiraterone or enzalutamide), with good performance status (ECOG of $\leq$ 2). Patients with brain metastases or who are immunocompromised are excluded. For mCSPC, the primary endpoint will evaluate the increase in the proportion of patients who have a PSA less than 0.2 ng/mL 7 months after the start of ADT, which is based on the prognostic value of PSA less than 0.2 ng/mL at 7 months in mCSPC (Harshman L, JCO 2017). The secondary endpoint is biochemical and radiographic time to progression. The primary endpoint for the mCRPC patients will evaluate progression free survival with secondary endpoints examining the percentage of patients with a 50% PSA decline from baseline and radiographic response rates per RECIST. Exploratory analysis will analyze changes in immune cell subsets after treatment as well as immune status of the tumor microenvironment. Clinical trial information: NCT04633252. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS5097 **Poster Session**

Identifying androgen receptor (AR) and genomic characteristics that define populations of patients with mHSPC who benefit from early PARP inhibition therapy with talazoparib. *First Author: Saro Kasparian, City of Hope, Duarte, CA*

Background: A minority of men with mCRPC, those with DNA repair mutations, can benefit from PARP inhibitor therapy. In addition to DNA repair, PARP is used by cancer cells to interact with other cellular mechanisms including androgen receptors (AR). The next generation PARP inhibitor talazoparib can, in addition to inhibiting DNA repair, trap PARP, preventing it from carrying out its other functions. As progression in mHSPC is based on AR escape mechanisms, we predict that early exposure to PARP inhibition will delay progression. In addition, AR characteristics and function vary by ethnic populations. AR expression is inversely related with the number of polymorphic CAG repeats. As African American (AfrAm) men commonly have shorter CAG repeats in their AR, they may experience different response duration, but have been under-represented in clinical trials. Furthermore, CAG repeats may be associated with greater signaling through pathways such as wnt and Myc, which is associated with aggressive disease. Thus, studying intensified up-front therapy in a diverse prostate cancer population is a critical unmet need. **Methods:** 70 subjects will be treated with ADT + abiraterone + talazoparib. Outreach by our Division of Health Equities and accrual at community satellites located near diverse populations will be enlisted to accrue a target of 30% African American. Talazoparib will be dosed at 1mg daily (0.75 mg in renal insufficiency). LHRH and abiraterone formulations will be left to physician's choice. PSA and safety labs will be checked every 4 weeks for the first 12 weeks. Imaging will be performed every 12 weeks for the first year then every 24 weeks if PSA is decreasing, or 12 weeks if rising. Data safety monitoring for toxicity after every 10 subjects have been accrued. Diversity of accrual will be evaluated after 30 subjects are enrolled; amendments will be made if the diversity goal is not achieved. Tissue genomics and ctDNA will be measured at baseline; ctDNA will be repeated after 4 weeks and at castration resistance. Endpoints: Primary: PSA nadir at 7 months has been found to be associated with overall survival and is achieved by 55% of men with mHSPC with ADT + abiraterone. With 70 subjects there is 97% power to confirm improved nadir rate of 75%, and 83% power to determine a nadir rate $>$70%. Secondary endpoints include objective response by RECIST 1.1 for subjects with measurable disease. radiographic progression free survival. Correlative objectives include comparing outcomes in subsets of men with high vs low number of AR CAG repeats, men with genomic alterations, and the change in ctDNA alteration fractions from baseline to 4 weeks and at progression. Progress: The trial is open to accrual as of Feb 2021. Sponsor: Pfizer/ Prostate Cancer Foundation RFP Clinical trial information: NCT04734730. Research Sponsor: Pfizer.

TPS5098 **Poster Session**

Phase III study of local or systemic therapy INtensification DIrected by PET in prostate CAncer patients with post-prostaTEctomy biochemical recurrence (INDICATE): ECOG-ACRIN EA8191. *First Author: Neha Vapiwala, University of Pennsylvania, Philadelphia, PA*

Background: Radiation therapy (RT) to the prostate bed and pelvic nodes with short-term androgen deprivation therapy (STAD) is considered a standard of care (SOC) salvage therapy (ST) paradigm for prostate cancer (PC) patients (pts) with post-prostatectomy (RP) biochemical recurrence (BCR). Fluciclovine-PET/CT imaging is FDA-approved in this setting, with improved accuracy for detection of metastases not identified with conventional imaging (CIM). Given PET's greater sensitivity and specificity, its findings are increasingly but variably applied to justify modification or omission of SOC therapies without high-level evidence of clinical benefit. PET may help identify candidates for local or systemic treatment intensification of the otherwise non-tailored SOC approach. Improved systemic control and disease detection with molecular imaging have led to increasing use of focally ablative metastasis-directed RT, to delay or enhance systemic therapy through increased local control. There is also interest in earlier use of systemic therapy; apalutamide (Apa) is a nonsteroidal antiandrogen with established efficacy in improving overall and radiographic progression-free survival (PFS) for non-metastatic castration-resistant and metastatic castration-sensitive PC. This study will evaluate whether pts with PET-detected lesions benefit from such local or systemic treatment intensification approaches. **Methods:** PC pts with post-RP BCR (PSA$>$0.5ng/mL; $>$0.2ng/mL if within 12 mos of RP) and no metastases on CIM who are candidates for SOC ST (RT to prostate bed and pelvic nodes with STAD) are eligible. Prior to study registration, pts undergo SOC baseline PET (^{18}F-fluciclovine but PSMA radiotracers permitted pending commercial availability). Based on institutional clinical interpretation of the SOC PET, pts will be placed in Cohort 1 (PET-negative) or 2 (PET-positive for extra-pelvic metastases). Cohort 1 will be randomized to SOC ST +/- Apa for 6 months and Cohort 2 will be randomized to SOC ST and Apa +/- metastasis-directed RT to PET-positive lesions. The primary endpoint is PFS, defined as time from randomization to radiographic progression on CIM, symptomatic disease or death. Primary objectives are to evaluate whether addition of Apa to SOC ST and addition of metastasis-directed RT to SOC ST and Apa could prolong PFS in Cohorts 1 and 2, respectively. For Cohort 1, 480 pts will be randomized with 85% power to distinguish 5-year PFS rate of 90% (Apa arm) vs. 80% (SOC arm) using one-sided stratified log-rank test with type I error of 0.025. For Cohort 2, 324 pts will be randomized with 85% power to distinguish 5-year PFS rate of 76.5% in the experimental arm from 61.5% in the control arm. Secondary endpoints include overall and event-free survival, toxicity, and PET progression. Clinical trial information: NCT04423211. Research Sponsor: U.S. National Institutes of Health.

TPS5099 **Poster Session**

The fluciclovine (FACBC) PET/CT site-directed therapy of oligometastatic prostate cancer (Flu-BLAST-PC) trial. *First Author: Risa Liang Wong, University of Washington, Seattle, WA*

Background: Patients with biochemical recurrence (BCR) after local definitive therapy for prostate cancer (PC) represent the largest group of patients alive with PC in the United States. For patients with BCR after both radical prostatectomy and radiation, no further definitive treatment options currently exist as standard of care. FACBC PET/CT is a next-generation imaging modality approved in 2016 for suspected PC recurrence based on elevated PSA levels following prior treatment. FACBC PET/CT allows for earlier detection at lower PSA levels of oligometastatic PC in patients who would otherwise be considered as having micro-metastatic disease. FACBC PET/CT may provide potential targets for site-directed therapy; however, it is unknown whether this approach leads to improvement in clinically relevant outcomes. **Methods:** Flu-BLAST-PC (ClinicalTrials.gov Identifier: NCT0417543) is a prospective, interventional study enrolling men with PC and BCR who have previously undergone both radical prostatectomy and adjuvant or salvage radiation to the prostatic fossa, with PSA $\geq$0.5 to $<$ 10 ng/mL, PSA doubling time $>$ 3 to $<$ 18 months, and no radiographically detectable metastases by conventional CT and bone scan imaging. Enrolled patients undergo FACBC PET/CT imaging, and those with no PC metastases detected (Group 1) undergo observation with repeat FACBC PET/CT performed at PSA thresholds of $>$ 2 and $>$ 5 ng/mL, with eligibility for the trial ending at PSA $\geq$10 ng/mL if FACBC PET/CT remains negative. Those with 1-3 PC regions (defined as radiation fields) detected on FACBC PET/CT (Group 2) undergo site-directed therapy with surgery (e.g. lymphadenectomy) and/or radiation, as well as six months of systemic treatment with androgen deprivation therapy (ADT) and abiraterone acetate with prednisone. Patients with $\geq$4 PC regions detected on FACBC PET/CT (Group 3) undergo six months of ADT and abiraterone acetate with prednisone without any site-directed therapy. Patients initially in Group 1 who subsequently have PC metastases detected on repeat FACBC PET/CT imaging per protocol join Group 2 or Group 3 based on the number of PC regions involved. Given the long anticipated survival of patients with PC and BCR, the primary endpoint of the study is undetectable PSA ($<$ 0.2 ng/mL) rate in Group 2 at two years beyond study treatment, with secondary endpoints including the same outcome measure for Group 3, undetectable PSA rate two years after testosterone recovery from ADT in Groups 2 and 3, time to re-initiation of ADT, overall survival, and safety and tolerability. Assuming a null hypothesis of 15% undetectable PSA rate for patients with BCR two years after completing ADT and alternative hypothesis of improvement to 40% in Group 2, planned enrollment is 65 patients in Group 2. This will provide 90% power at the two-sided significance level of 0.05. Five patients have enrolled to date. Clinical trial information: NCT0417543. Research Sponsor: Institute for Prostate Cancer Research, Pharmaceutical/Biotech Company.

TPS5100 **Poster Session**

Phase 1b study of AMG 757, a half-life extended bispecific T-cell engager (HLE BiTEimmune-oncology therapy) targeting DLL3, in de novo or treatment emergent neuroendocrine prostate cancer (NEPC). *First Author: Rahul Raj Aggarwal, Univ of California San Francisco, S San Francisco, CA*

Background: NEPC is an aggressive cancer with poor prognosis. No standard treatment approach for NEPC exists and it remains an unmet need. NEPC is usually treatment-emergent, characterized by histological transformation from adenocarcinoma to a high-grade neuroendocrine tumor (NET), and may develop in 15%–20% of patients (pts) treated with standard prostate adenocarcinoma therapies, including novel hormonal therapies. The inhibitory Notch ligand, Delta-like ligand 3 (DLL3), is highly expressed on the surface of cancer cells, including NEPC cells, making it an attractive and a promising therapeutic target. AMG 757 is an HLE BiTE immuno-oncology therapy designed to redirect cytotoxic T cells to tumor cells by binding DLL3 on cancer cells and CD3 on T cells, resulting in T cell activation and expansion and T cell-dependent killing of tumor cells. AMG 757 showed in vitro activity in DLL3-expressing NETs, including NEPC. Preliminary results of an on-going first-in-human study suggest AMG 757 is safe and effective in pts with small cell lung cancer (NCT03319940), which prompted its study in NEPC. **Methods:** NCT04702737 is an open-label, phase 1b study evaluating AMG 757 infusion in pts with metastatic de novo or treatment-emergent NEPC, consisting of dose exploration and then dose expansion. Key eligibility criteria include adults ($\geq$18 y) with NEPC whose disease progressed/recurred after $\geq$1 treatment course including a platinum-based regimen for de novo NEPC or an androgen signaling inhibitor, measurable disease per modified RECIST 1.1 per Prostate Cancer Working Group 3 modifications, ECOG performance status $\leq$2, life expectancy $>$ 3 mo, adequate organ function, and no untreated/symptomatic brain metastases. Primary objectives are to evaluate safety and tolerability and determine the maximum tolerated dose or recommended phase 2 dose of AMG 757. Secondary objectives are to evaluate antitumor activity (ie, objective response, duration of response, progression-free survival, overall response) and characterize pharmacokinetics. The starting dose for dose exploration will be based on the dose deemed safe and tolerable in the ongoing trial of AMG 757 in SCLC. The study is open to enrollment. Clinical trial information: NCT04702737. Research Sponsor: Amgen Inc.

5500 **Oral Abstract Session**

Efficacy and safety results from neopembrov study, a randomized phase II trial of neoadjuvant chemotherapy (CT) with or without pembrolizumab (P) followed by interval debulking surgery and standard systemic therapy ± P for advanced high-grade serous carcinoma (HGSC): A GINECO study. *First Author: Isabelle Laure Ray-Coquard, Centre Léon Bérard, University Claude Bernard, Lyon, France*

Background: To investigate whether adding Pembrolizumab (P) to neoadjuvant carboplatin-paclitaxel chemotherapy (CP) may increase the optimal debulking rate, assessed by Complete Resection Rate (CRR) after Interval Debulking Surgery (IDS) in patients (pts) with initially unresectable International Federation of Gynecology and Obstetrics (FIGO) stage IIIC/IV ovarian, tubal or peritoneal HGSC. **Methods**: Multicenter, open-label, non-comparative randomized phase II trial. Pts were randomized (2:1) to receive 4 cycles of CP ± P before IDS. After IDS, all patients received post-operative chemotherapy (2 to 4 cycles) and optional bevacizumab for 15 months in total ± P as maintenance therapy for up to 2 years. Randomization was stratified on center, FIGO stage, Bev planned after IDS and disease volume (<5cm/>5cm). Primary endpoint was the centrally reviewed CRR at IDS. 60 pts were planned in the CP+P arm (A'Hern's single-stage design P0=50%, P1=70%). Safety (particularly due to P addition), surgical morbidity, ORR, PFS and OS were secondary endpoints. **Results**: 91 pts were randomized from 02/18 to 04/19 with a median Peritoneal Cancer Index at 24 (range 7-39). 80 pts (88%) received Bev in combination with CP followed by bev ± P in maintenance. In the CP+P group (n=61), 58 (95%) pts had IDS and 78% achieved complete resection. The CRR in this group was 74%, statistically superior to the pre-defined hypothesis. In the CP group, CRR was 70% (29/30 pts underwent IDS). Complete resection after strictly 4 cycles of CP±P was obtained for 41 pts (71%) and 17 (58%) pts in CP+P and CP group, respectively (sensitivity analysis). For CP+P group, numerically higher ORRs were observed before IDS compared to CP group (76% vs 61%). Grade ≥3 adverse events (AE) occurred in 75% of the CP+P group and 67% in the CP group: mainly blood and lymphatic, gastrointestinal and vascular disorders. Postoperative AE (mainly infectious, vascular and gastrointestinal) occurred in 20% and 13% of the pts in CP+P and CP arm, respectively. No difference in the number of fatal events between the two arms: 2 in the experimental arm vs 1 in the control arm. Progression free survival rate at 18 months was 61% (95CI% [47-73]) and 57% (95CI% [37-72]) in CP+P and CP arm, respectively. **Conclusions:** P may be safely added to preoperative treatment in pts deemed non-optimally resectable. The primary objective was met with an improved CRR on CP+P arm. The CRR in the control group was higher than expected. Survival data and translational research including PDL1 status are ongoing to better define P as treatment option in this setting. Clinical trial information: 2016-004-163-39. Clinical trial information: NCT03275506. Research Sponsor: MSD, Fondation ARC.

5501 **Oral Abstract Session**

Optimal treatment duration of bevacizumab (BEV) combined with carboplatin and paclitaxel in patients (pts) with primary epithelial ovarian (EOC), fallopian tube (FTC) or peritoneal cancer (PPC): A multicenter open-label randomized 2-arm phase 3 ENGOT/GCIG trial of the AGO Study Group, GINECO, and NSGO (AGO-OVAR 17/BOOST, GINECO OV118, ENGOT Ov-15, NCT01462890). *First Author: Jacobus Pfisterer, AGO Study Group & Gynecologic Oncology Center, Kiel, Germany*

Background: GOG-0218 established the addition of BEV 15 mg/kg every 3 weeks (q3w) for 15 months to standard front-line chemotherapy for advanced ovarian cancer, but the optimal BEV duration remained unknown. We report primary results from a randomized phase 3 trial designed to address this question. **Methods:** Eligible pts with FIGO stage IIB–IV EOC, FTC, or PPC and ECOG PS ≤2 underwent primary cytoreductive surgery followed by 6 cycles of chemotherapy (paclitaxel 175 mg/m^2 + carboplatin AUC 5 q3w) and BEV (15 mg/kg q3w). Pts were randomized to receive BEV for either 15 months (standard arm BEV15) or 30 months (experimental arm BEV30), stratified by FIGO stage/residual tumor (stage IIB–IIIC/no residual tumor vs stage IIB–IIIC/residual tumor or stage IV). The primary endpoint was investigator-assessed progression-free survival (PFS) according to RECIST v1.1. Secondary endpoints were overall survival (OS), objective response rate, quality of life, safety, and tolerability. The trial was designed with 80.2% power to detect a hazard ratio (HR) of 0.66 favoring BEV30 (2-sided log-rank test, 5% significance level, 10% dropout rate) after 697 PFS events. The trial was funded by F. Hoffmann-La Roche Ltd., performed according to ENGOT model A. **Results:** From Nov 2011 to Aug 2013, 927 women (83% with EOC) from 161 centers were randomized. Baseline characteristics were balanced between arms; median age was 61 years, 96% had ECOG PS 0/1, 58% had no residual tumor, and 77% had high-grade serous histology. Serious adverse events of special interest for BEV occurred in 51/448 pts (11%) vs 61/442 pts (14%) receiving BEV15 vs BEV30, respectively: hypertension (2.7%/4.5%), thromboembolic event (2.2%/3.2%), fistula (3.1%/1.1%), gastrointestinal perforation (0.2%/0.9%), proteinuria (0.7%/1.4%), hemorrhage (0.2%/0.9%), and myocardial infarction (0%/1.1%). Efficacy is shown in the table. **Conclusions:** Longer treatment with BEV for up to 30 months improves neither PFS nor OS in pts with primary EOC, FTC, or PPC. Therefore BEV treatment duration of 15 months remains standard of care. Clinical trial information: NCT01462890. Research Sponsor: F. Hoffmann-La Roche Ltd., Basel, Switzerland.

Endpoint	BEV15 (n = 464)	BEV30 (n = 463)	p-value
PFS events, n (%)	333 (72)	340 (73)	
Median PFS, months (95% CI)	24.2 (22.2–26.5)	26.0 (23.7–29.7)	
PFS HR (95% CI)	0.99 (0.85–1.15)		p = 0.90
Restricted mean PFS (95% CI)*	39.5 (36.3–42.7)	39.3 (36.2–42.4)	p = 0.92
OS events, n (%)	257 (55)	275 (59)	
Median OS, months (95% CI)	54.3 (51.0–64.6)	60.0 (54.0–68.6)	
OS HR (95% CI)	1.04 (0.87–1.23)		p = 0.68
Restricted mean OS (95% CI)*	60.4 (57.2–63.6)	60.8 (57.8–63.8)	p = 0.87

*Performed because of evidence of nonproportional hazards, restricted at the time point of the last observed event (BEV15/BEV30).

5502 **Oral Abstract Session**

Maintenance vigil immunotherapy in newly diagnosed advanced ovarian cancer: Efficacy assessment of homologous recombination proficient (HRP) patients in the phase IIb VITAL trial. *First Author: Rodney Paul Rocconi, University of South Alabama, Mobile, AL*

Background: In the VITAL (NCT02346747) trial, maintenance therapy with Vigil, an autologous tumor cell vaccine transfected with a DNA plasmid encoding GMCSF and bi-shRNA-furin for TGFβ expression control, following frontline platinum-based chemotherapy led to a recurrence-free survival (RFS) benefit in patients with advanced high-grade ovarian cancer (HR=0.69, 90% CI 0.44–1.07, p=0.078) and significantly in *BRCA*-wt patients (HR=0.51, 90% CI 0.30-0.88, p=0.020) (Rocconi et al. *Lancet Oncol.* 2020). Here we report post-hoc HR deficiency (HRD) subgroup analysis and identification of an additional molecular subgroup sensitive to Vigil therapy involving STRING analysis. **Methods:** This double-blind, placebo-controlled, Phase 2b study randomized 92 patients with newly diagnosed stage III/IV ovarian cancer with a complete clinical response (CR) to frontline surgery and chemotherapy. Patients received 1 x 10e7 cells/ml of Vigil or placebo intradermally once a month for up to 12 doses or disease progression. RFS was the primary endpoint assessed by blinded independent central review. HRD status was determined according to the Myriad Genetics myChoice CDx assay (HRD score < 42 for proficient). Using tumor annotated DNA polymorphism data, a protein-protein interaction network was constructed using the STRING database. Properties of this network including topological distance and the identification of hub genes were used to predict a target molecular population sensitive to Vigil. **Results:** In the per-protocol population (PP, n=91), 62 BRCA-wt patients were tested for HRD status. Forty-five patients were HR proficient (HRP) and 17 patients were HR deficient (HRD). No HRP patients in the Vigil group reported treatment related Grade 3 or higher adverse events. From the time of study randomization median RFS was improved with Vigil (n=25) in HRP patients compared to placebo (n=20) (Table 1). Similarly, overall survival (OS) benefit was observed in the Vigil group compared to placebo (Table 1). Improved RFS was demonstrated for a subset of patients with STRING predicted molecular profile. **Conclusions:** Vigil immunotherapy as frontline maintenance in Stage III/IV ovarian cancer is well tolerated and showed clinical benefit in both *BRCA*-wt and HRP molecular profile patients. Results suggest a unique molecular network that enhances sensitivity to Vigil therapy. Clinical trial information: NCT02346747. Research Sponsor: Gradalis, Inc.

	HRP (n=45)	
Endpoint	Vigil (n=25)	Placebo (n=20)
Recurrence-Free Survival (RFS)		
Median (mo.)	10.6	5.7
95% CI (mo.)	5.9-NA	5.6-14.9
HR (90%CI)	0.386 (0.199-0.750), p=0.007	
Overall Survival (OS)		
Median (mo.)	NR	26.9
95% CI (mo.)	28.7-NA	17.1-NA
HR (90%CI)	0.342 (0.141-0.832), p=0.019	

5503 **Oral Abstract Session**

Phase 3, randomized, single-dose, open-label study to investigate the safety and efficacy of pafolacianine sodium injection (OTL38) for intraoperative imaging of folate receptor positive ovarian cancer. *First Author: Janos Laszlo Tanyi, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: Pafolacianine sodium is under investigation as an adjunct to visual inspection and palpation by providing intra-operative imaging of folate receptor positive (FR+) ovarian cancer. Since complete resection (R0) is the strongest predictor of overall survival, methods to enhance detection of lesions are expected to benefit patient outcomes. **Methods:** For this phase 3, randomized, multicenter, single dose, open-label pivotal trial (NCT03180307), patients with ovarian cancer who were scheduled to undergo cytoreductive surgery were recruited from 11 sites in the US and Netherlands from March 2018 through April 2020. The study objectives were to confirm efficacy and safety of pafolacianine sodium (0.025 mg/kg i.v., ≥1 h prior to imaging) in combination with intraoperative near-infrared fluorescence (NIRF) imaging to detect additional lesions not detected by palpation and normal white light alone. **Results:** Pafolacianine sodium was administered to 150 total patients (safety analysis set); 109 patients comprised the full analysis set for efficacy analyses. Patients had primarily serous adenocarcinoma (n = 72; 68.6%) and advanced stage disease (n = 83; 76.1%). In 33% of patients (36 of 109), NIRF imaging with pafolacianine sodium identified additional lesions that were not planned for resection and were not detected by normal white light and palpation ($P < 0.001$, 95% CI [0.243, 0.427]). Among patients who underwent interval debulking surgery, the rate was higher, at 39.7% of patients (23 of 58; 95% CI [0.270, 0.534]). At the individual lesion level, the accuracy of pafolacianine sodium with NIRF to detect ovarian cancer is reflected by sensitivity of 83% (95% CI [73.9, 89.4]) and a false positive rate of 32.7% (95% CI [25.6, 40.7]). Investigators reported achieving complete resection (R0) in 62.4% (68 of 109) of patients. Drug-related adverse events (AEs) were reported by 30% of patients (45 out of 150). The most frequently reported drug-related AEs were nausea (18.0%), vomiting (5.3%), and abdominal pain (4.7%). Infusion reactions at the time of the procedure were mostly (96%) mild or moderate in severity; 89% resolved within 24 hours of onset. No drug-related serious AEs or deaths were reported. **Conclusions:** This phase 3 trial of pafolacianine sodium with NIRF imaging met its primary endpoint, intraoperatively identifying additional cancer not planned for resection in a statistically significant number of patients. Therefore, pafolacianine sodium may offer a novel real-time adjunct to current surgical imaging practice in ovarian cancer surgery. Clinical trial information: NCT03180307. Research Sponsor: On Target Laboratory.

5504 **Oral Abstract Session**

Mirvetuximab soravtansine, a folate receptor alpha (FRα)-targeting antibody-drug conjugate (ADC), in combination with bevacizumab in patients (pts) with platinum-agnostic ovarian cancer: Final analysis. *First Author: David M. O'Malley, The Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus, OH*

Background: Mirvetuximab soravtansine (MIRV) is an ADC comprising a FRα-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. As part of the Phase 1b FORWARD II trial (NCT02606305), the combination of MIRV with bevacizumab (BEV) was evaluated in pts with FRα-positive (medium/high expression; ≥50%/ ≥75% of cells with PS2+ staining intensity), platinum agnostic ovarian cancer, defined as pts with either platinum resistant (PROC) (recurrence within 6 months after last platinum dose) or platinum sensitive (PSOC)responded to the last platinum therapy and did not progress within 6 months) for whom a non-platinum based doublet would be appropriate. **Methods:** Pts received MIRV (6 mg/kg; adjusted ideal body weight) and BEV (15 mg/kg) on Day 1 of a 21-day cycle. Responses were assessed by investigator according to RECIST 1.1 and adverse events (AEs) evaluated by CTCAE v4.03. **Results:** In total, 60 pts received the combination, with a median age of 60 years, a median of 2 prior lines of systemic therapy (range 1-4) and a median follow-up of 17.5 months. The cohort included 32 pts (53%) with PROC disease and 28 (47%) with PSOC disease. Objective responses were seen in 28 of 60 pts for a confirmed overall response rate (ORR) of 47% (95% CI, 34, 60), median duration of response (mDOR) of 9.7 months (95% CI 6.7, 12.9), and median progression free survival (mPFS) of 8.3 months (95% CI 5.6, 10.6). In pts with high FRα expression (n=33), the confirmed ORR was 64% (95% CI 45, 80), mDOR of 11.8 months (95% CI 6.7, 13.7), and mPFS of 10.6 months (95% CI 8.3, 13.3); efficacy results in PROC and PSOC subsets of pts with high FRα expression are shown in the table below. The most common treatment related AEs (all grade, grade 3+) were diarrhea (68%, 2%), blurred vision (63%, 2%), fatigue (58%, 7%), and nausea (57%, 0%). The most common treatment related grade 3 and 4 AEs were neutropenia and hypertension, (12%, 3% and 13%, 0%, respectively); all other grade 3+ events occurred in ≤ 10% of pts. **Conclusions:** The combination of MIRV with BEV demonstrates impressive anti-tumor activity with durable responses and favorable tolerability in high FRα recurrent ovarian cancer. These results build on data previously reported for MIRV/BEV in PROC patients (*Gyn Oncology* O'Malley, et al 2020), suggesting that MIRV has the potential to be a preferred partner for BEV in patients with high FRα recurrent ovarian cancer regardless of platinum sensitivity. Clinical trial information: NCT02606305. Research Sponsor: ImmunoGen.

Efficacy Results.

	All pts	High FRα	PROC High FRα	PSOC High FRα
N	60	33	17	16
Confirmed ORR (95% CI)	47% (34, 60)	64% (45, 80)	59% (33, 82)	69% (41, 89)
mDOR months (95% CI)	9.7 (6.7, 12.9)	11.8 (6.7, 13.7)	9.4 (4.0, NR)	12.9 (6.5, 15.7)
mPFS months (95% CI)	8.3 (5.6, 10.6)	10.6 (8.3, 13.3)	10.1 (5.6, 12.9)	13.3 (8.3, 18.3)

5505 **Oral Abstract Session**

EFFORT: EFFicacy Of adavosertib in parp ResisTance: A randomized two-arm non-comparative phase II study of adavosertib with or without olaparib in women with PARP-resistant ovarian cancer. *First Author: Shannon Neville Westin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Wee1 phosphorylates and inhibits cyclin-dependent kinases 1 and 2 and is involved in regulation of the intra-S and G2/M cell cycle checkpoint arrest for premitotic DNA repair. The Wee1 inhibitor, adavosertib, has demonstrated activity alone and in combination with olaparib in PARP inhibitor (PARPi)-resistant preclinical models. We sought to evaluate efficacy of adavosertib (A) with or without olaparib (O) in a phase II noncomparative study of recurrent PARPi-resistant ovarian cancer. **Methods:** Women with recurrent ovarian, fallopian tube or primary peritoneal cancer with documented progressive disease on a PARPi were eligible. All patients (pts) had measurable disease and adequate end organ function. On the A arm, pts received A 300mg PO daily on days 1-5 and 8-12 of a 21-day cycle. On the A/O arm, pts received A 150mg PO BID on days 1-3 and 8-10 and O 200mg PO BID on days 1-21 of a 21-day cycle. Primary endpoint was objective response per RECIST 1.1 and was assessed every 2 cycles. Clinical benefit rate (CBR) was defined as proportion of pts with objective response or stable disease > 16 weeks. Progression free survival (PFS) was assessed using the Kaplan Meier method and calculated from date of treatment initiation to earliest date of progression, death, or last visit. **Results:** 116 pts were screened with 80 pts enrolled and randomized (A: n=39, A/O: n=41). Median age was 60 years (range 36-76) and the majority of pts had platinum resistant disease (64%) and high grade serous histology (98%). Pts received a median of 4 prior therapies (range 1-11) and 48% had germline or somatic *BRCA* mutations. There were 35 pts evaluable for response in each arm. Table demonstrates efficacy data. On the A arm, Grade 3/4 toxicities occurred in 51% of pts, most commonly neutropenia (13%), thrombocytopenia (10%), and diarrhea (8%). 28 (72%) pts required at least one dose interruption and 20 (51%) required dose reduction. On the A/O arm, Grade 3/4 toxicities occurred in 76% of pts, most commonly thrombocytopenia (20%), neutropenia (15%), diarrhea (12%), fatigue (12%), and anemia (10%). 36 (88%) of pts required at least one dose interruption, 29 (71%) required dose reduction, and 4 (10%) did not restart due to toxicity. **Conclusions:** A given alone and in combination with O demonstrated efficacy in pts with PARPi-resistant ovarian cancer. Although grade 3 and 4 toxicities were observed on both arms, these were generally manageable with supportive care, dose interruptions and dose reductions as needed. Additional translational analyses are ongoing to clarify which pts received clinical benefit. Clinical trial information: NCT03579316. Research Sponsor: AstraZeneca, U.S. National Institutes of Health.

Endpoint	A arm n=35	A/O arm n=35
ORR (90% CI)	23% (12–38)	29% (16–44)
Duration of response, months (95% CI)	5.5 (2.8–NE)	6.4 (2.8–14.6)
CBR (90% CI)	63% (48–76)	89% (76–96)
Median PFS, months (90%CI)	5.5 (3.9–6.9)	6.8 (4.3–8.3)

5506 **Oral Abstract Session**

Intensive versus minimalist follow-up in patients treated for endometrial cancer: A multicentric randomized controlled trial (The TOTEM study—NCT00916708). *First Author: Paolo Zola, Departement of surgical sciences University of Turin, Turin, Italy*

Background: Intensive follow-up in cancer patients, which absorbs a lot of health system resources and can be a source of increased stress for patients, are often proposed on the assumption that an early recognition of relapse will translate in better outcomes. In endometrial cancer few randomized controlled trials were conducted to assess the role of a reduced number of the scheduled visits and of different settings of the follow-up, but did not investigate the contribution of routine serum, cytological or imaging follow-up investigations in improving overall survival or quality of life. The TOTEM study was planned to compare an intensive (INT) vs minimalist (MIN) 5- year follow-up regimen in endometrial cancer patients in terms of overall survival (OS). **Methods:** Patients surgically treated for endometrial cancer, in complete clinical remission confirmed by imaging, FIGO stage I-IV, were stratified by center and in low (LoR) or high (HiR) risk of recurrence and then randomized to INT or MIN hospital-based follow-up regimens. The main study hypothesis was to demonstrate an improvement from 75% to 80% (expected hazard ratio, HR = 0.78) of the 5-year OS with the INT regimen. Secondary objectives were to compare relapse free survival (RFS), health-related quality of life (HRQL) assessed at baseline, at 6 and 12 months and then yearly (with the SF-12 Physical and Mental Health Summary Scale) and costs. **Results:** 1884 patients were randomized in 42 centers between 2008 and 2018, and 1847 patients were available for the final analysis (60% LoR). Compliance with the follow-up scheduled visits was 75.3%, similar between INT (74.7%) and MIN (75.9%) arms, whereas the mean number of recorded exams (laboratory or imaging) was markedly higher in the INT than in the MIN arms (9.7 vs 2.9, $p < 0.0001$). After a median follow-up of 66 months, the overall 5-year OS was 91.3%, 90.6% in the INT and 91.9% in the MIN arms, respectively (HR = 1.12, 95%CI 0.85-1.48, p = 0.429). Comparing the INT vs MIN arms, the 5-year OS were 94.1% and 96.8% (HR = 1.48, 0.92-2.37, p = 0.104) in the LoR and 85.3% and 84.7% (HR = 0.96, 0.68-1.36, p = 0.814) in the HiR group. No relevant differences emerged in RFS between INT and MIN regimens, (HR = 1.13, 0.87-1.48, p = 0.365). At the time of the relapse most women were asymptomatic (146/228, 64.0%), with a tendency of higher proportions in the INT than in the MIN arm, both in the LoR group (78.8% vs 61.1%, p = 0.070) and in the HiR one (64% vs 60%, p = 0.754). HRQL was available only for a subgroup of patients (50% at baseline) and did not differ between arms. **Conclusions:** Intensive follow-up in endometrial cancer treated patients showed a weak and uncertain advantage in detecting earlier asymptomatic relapses but did not improve OS, even in HiR patients, nor influenced HRQL. Frequent routine use of imaging and laboratory exams in these patients should be discouraged. Clinical trial information: NCT00916708. Research Sponsor: Rete Oncologica Piemonte e Valle d'Aosta.

5507 **Oral Abstract Session**

Victoria: A multicentric, randomized, open-label, phase I/II of mTOR inhibitor (VISTUSERTIB) combined with anastrozole in patients with hormone receptor-positive advanced/metastatic endometrial cancer—A CLIPP program INCA in collaboration with GINECO group. *First Author: Pierre-Etienne Heudel, Centre Léon Bérard, Lyon, France*

Background: Endometrial carcinoma is generally hormone dependent and aromatase inhibitors are used in routine practice before or after 1st line chemotherapy (CT) for HR positive patients. Deregulation of the Pi3K-Akt-mTOR signaling pathway is observed in many tumor types including endometroid carcinoma driven oncogenesis and hormonal resistance. Vistusertib (V) is a small-molecule ATP competitive inhibitor of both mTORC1 and mTORC2 complexes. **Methods:** Adult patients (pts) with recurrent oestrogen or progesterone (ER and/or PR) positive advanced/metastatic endometrial carcinoma, one previous line of chemotherapy (CT) allowed, with ECOG PS 0/1, were randomised (2:1, stratification according to prior CT line: 0 vs 1) to receive V (125 mg bid/2 days/week, orally) + Anastrozole (A, 1 mg/d, orally) or A alone. Treatments were given until progression, intolerable toxicity or patient willingness. Following a safety run in phase, a Simon's 2-stage design was employed to explore the 8-week progression free rate (PFR-8W) according to central review (p1: 60%, p0: 40%, type I error rate of 5%, power of 80%). At the end of Stage II, if ≥24/46 evaluable pts are progression free at 8w in Arm A+V, the combination will be considered of interest for further investigation. Overall response rate (ORR) by RECIST v1.1, safety and progression-free survival (PFS) were key secondary endpoints. **Results:** Out of 75 patients (pts) enrolled, 73 were randomised and treated (Arm V+A: 49; Arm A: 24; median age: 69.5 y [36.8; 87.8]), BMI ≥30 kg/m^2: 45%). PS ECOG was 0 (48%) and 44% of randomised pts were chemotherapy naïve; 12% previously received hormonal therapy. At the end of the safety run-in, no major safety concerns were reported. At the end of Simon' Stage II, centrally assessed PFR-8W was 67.3% (33/49 [95% CI unilateral: 54.7; -]) for A + V arm and 39.1% (9/23 [[95% CI unilateral: 22.2; -[) for arm A. Median PFS was 5.2 months (95% CI: 3.4-8.9) and 1.9 months (95% CI: 1.6-8.9) for A+V and A arms, respectively. One complete response and 11 partial responses (PR) were observed (ORR: 24.5 % (CI 95% [13.3 – 38/9%]) in the combination arm and 4 PR in arm A (ORR: 17.4% [CI 95%: 5-38.8%]). Fatigue, lymphopenia, hyperglycaemia and diarrhoea were the main (≥10%) Grade ≥2 adverse events related to V. Overall survival and translational research are ongoing. **Conclusions:** The A+V combination demonstrated clinically and meaningful improvement in 8w-PFR and median PFS with manageable toxicity. PI3K pathway remains a key target for new therapies in endometrial cancer and translational research must help to better select pts benefiting from these targeted therapies. Clinical trial information: NCT02730923. Research Sponsor: French NCI (INCA) and Fondation ARC.

5508 **Oral Abstract Session**

Pertuzumab plus trastuzumab (P+T) in patients (Pts) with uterine cancer (UC) with *ERBB2 or ERBB3* amplification, overexpression or mutation: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *First Author: Hussein Moustapha Ali-Ahmad, Michigan Cancer Research Consortium, Lansing, MI*

Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of UC pts with *ERBB2 or ERBB3* amplification, overexpression or mutation treated with P+T are reported. **Methods:** Eligible pts had advanced UC, no standard treatment options, measurable disease, ECOG PS 0-2, and adequate organ function. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts matched to P+T had UC with *ERBB2 or ERBB3* amplification or overexpression or a pre-specified *ERBB2* mutation. Recommended dosing was P at an initial dose of 840 mg intravenously (IV) over 60 minutes (m), then 420 mg IV over 30-60 m every 3 weeks (wks), and T at an initial dose of 8 mg/kg IV over 90 m, then 6 mg/kg IV over 30-60 m every 3 wks until disease progression. Simon 2-stage design tested the null disease control (DC) - defined as partial (PR), complete response (CR) or stable disease at 16+ weeks (SD 16+) - rate of 15% vs. 35% (power = 0.85; $\alpha = 0.10$). If $\geq$2 of 10 pts in stage 1 have DC, 18 more pts are enrolled. If $\geq$7 of 28 pts have DC, the null DC rate is rejected. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. **Results:** Twenty-eight female pts were enrolled from August 2017 to November 2019; all pts were evaluable for efficacy and toxicity. Demographics and outcomes are summarized in Table. Twenty-two pts had tumors with *ERBB2* amplification (21) or overexpression (1); 4 tumors had *ERBB2* mutations; 1 tumor had *ERBB3* amplification; 1 tumor had both an *ERBB2* amplification and mutation. Two PR and 7 SD16+ were observed in pts with *ERBB2* amplification, and 1 SD16+ was observed in a pt with *ERBB2* V842I mutation only (no amplification) for DC and objective response (OR) rates of 37% (95% CI, 21% to 50%) and 7.1% (95% CI, 0.8% to 24%), respectively. One pt experienced grade 3 muscle weakness at least possibly related to P+T. **Conclusions:** P+T demonstrated evidence of anti-tumor activity in heavily pre-treated UC pts with *ERBB2* amplification or certain mutations. Additional study is warranted to confirm the efficacy of P+T in this pt population. Clinical trial information: NCT02693535. Research Sponsor: Genentech.

Demographics and efficacy outcomes (N=28).

Median age, yrs (range)	**69 (44, 90+)**
ECOG PS, %	
0	32
1	57
2	11
Prior systemic regimens, %	
1-2	43
≥3	57
DC rate, % (OR or SD16+) (95% CI)	37 (21, 50)
OR rate, % (95% CI)	7.1 (0.8, 24)
Median PFS, wks (95% CI)	28.1 (15.3, 40.1)
1 year OS, % (95% CI)	53.4 (36.7, 77.8)

5509 **Clinical Science Symposium**

Evaluation of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in cervical cancer: Data from phase 1 and phase 2 studies. *First Author: Julius Strauss, Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: The accelerated FDA approval of pembrolizumab validated the efficacy of anti–PD-(L)1 therapy for pts with recurrent/metastatic cervical cancer; however, the objective response rate (ORR) with pembrolizumab was 14.3% in pts with PD-L1 expressing tumors. HPV infection is implicated in $>$ 95% of cervical cancers and is linked to upregulation of TGF-β signaling. Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. We report pooled safety and efficacy in pts with immune checkpoint inhibitor–naive, recurrent/metastatic cervical cancer treated with bintrafusp alfa in phase 1 (INTR@PID 001; NCT02517398) and phase 2 (study 012; NCT03427411) studies. **Methods:** Pts with pretreated, immune checkpoint inhibitor–naive, recurrent/metastatic cervical cancer received bintrafusp alfa 0.3-30 mg/kg (phase 1 dose escalation) or 1200 mg Q2W (phase 1 expansion/phase 2) until progressive disease, unacceptable toxicity, or withdrawal. Treatment past progression was allowed. Primary endpoints were safety for the dose-escalation part of the phase 1 study and best overall response per RECIST 1.1 for the expansion part of phase 1 and phase 2 studies. Secondary endpoints for the expansion part of the phase 1 and 2 studies included safety. **Results:** As of May 15, 2020 (phase 1) and December 22, 2020 (phase 2), 39 pts had received bintrafusp alfa for a median duration of 2.8 months (range, 0.5-19.3). The median follow-up to data cutoff was 35.0 months and 24.1 months for the phase 1 and phase 2 studies, respectively. All pts had received prior anticancer therapy; 16 pts (41.0%) had received $\geq$3 prior anticancer regimens. There were 2 complete responses and 9 partial responses (PRs; ORR per RECIST 1.1, 28.2%). Median duration of response was 11.7 months (range, 1.4-41.2), and 5 pts (45.5%) had ongoing responses (duration 1.5-41.2 months). An additional delayed PR was observed (duration 23.7 months). Reponses occurred irrespective of tumor histology or prior bevacizumab or radiation treatment. Median overall survival (mOS) was 13.4 months (95% CI, 5.5 to not reached); 24-month OS rate was 33.2%. Any-grade treatment-related adverse events (TRAEs) occurred in 33 pts (84.6%). Grade 3 TRAEs occurred in 8 pts (20.5%; anemia, colitis, gastroparesis, upper gastrointestinal hemorrhage, keratoacanthoma, cystitis noninfective, hematuria, pneumonitis, rash macular [n = 1 each]); 1 patient (2.6%) had a grade 4 TRAE (asymptomatic hypokalemia related to the above grade 3 gastroparesis). No treatment-related deaths occurred. **Conclusions:** Bintrafusp alfa had a manageable safety profile and demonstrated clinical activity in pts with heavily pretreated, immune checkpoint inhibitor–naive recurrent/metastatic cervical cancer. Clinical trial information: NCT02517398, NCT03427411. Research Sponsor: Merck KGaA, Darmstadt, Germany, and GlaxoSmithKline.

5510 **Clinical Science Symposium**

Clinical activity and safety of simlukafusp alfa, an engineered interleukin-2 variant targeted to fibroblast activation protein-α, combined with atezolizumab in patients with recurrent or metastatic cervical cancer. *First Author: Antoine Italiano, Early Phase Trials Unit, Institut Bergonié, Bordeaux, France*

Background: Simlukafusp alfa (SIM; FAP-IL2v) comprises an interleukin-2 variant (IL-2v) moiety and an antibody against fibroblast activation protein-α (FAP). The binding of SIM to FAP, expressed on cancer-associated fibroblasts, accounts for retention and accumulation in malignant lesions. The engineered IL-2v moiety has an abolished binding to IL-2Rα while the affinity to IL-2R$\beta\gamma$ is retained, resulting in activation of immune effector CD8 T and NK cells, but not of regulatory T cells, and therefore may augment activity of PD-(L)1 inhibitors. **Methods:** The clinical activity and safety of the SIM and atezolizumab (ATZ) combination in patients with recurrent or metastatic (R/M) cervical squamous cell carcinoma (SCC) were evaluated in a phase 2 basket study (NCT03386721). Patients (pts) were treated with SIM 10 mg IV and ATZ 1200 mg IV once every 3 weeks. The primary endpoint was objective response rate (ORR) by RECIST v1.1 assessed by investigators. Secondary endpoints were: disease control rate (DCR), duration of response (DoR), progression free survival (PFS). **Results:** 47 Pts with ECOG $\geq$1 and median age of 53 years (range: 25-69) were enrolled. All pts were checkpoint inhibitor naïve and 40 (85%) had $\geq$ 1 previous lines of therapy in the metastatic setting. The median number of cycles was 6 (range: 1-29). The ORR was 27% (90% CI: 18, 39) and DCR was 71% (90% CI: 58, 80) in 44 response-evaluable patients: 2 (5%) had complete response, 10 (23%) partial response, and 19 (43%) stable disease. Responses were observed across PD-L1 subgroups (SP142 assay, IC/TC cut-off $\geq$ 1%) with 8/22 and 4/18 responders in PD-L1$^+$ and PD-L1$^-$ patients, respectively. Responses were durable, the median DoR was 13.3 months (95% CI: 7.6, 14.7). PFS probability at 6 months was 0.4 (95% CI: 0.27, 0.59). The most common adverse events (AE) (reported in $>$ 30% patients), irrespective of relatedness to treatment and severity, were pyrexia (74.5%), anemia (48.9%), asthenia (48.9%), AST increased (44.7%), nausea (42.6%), ALT increased (42.6%), vomiting (36.2%) and diarrhea (31.9%). Grade 3 and 4 AEs related to SIM were observed in 63.8 % and 29.8 % of pts, respectively, while serious AEs (SAE) related to SIM were reported in 40.4%. The most common SAEs (reported in $>$ 5% pts) irrespective of relatedness to treatment were infusion related reaction (14.9%), pyrexia (6.4%) and hydronephrosis (6.4%). One Grade 5 event occurred, which was unrelated to treatment. **Conclusions:** SIM in combination with ATZ demonstrated an acceptable safety profile in pts with R/M cervical SCC. The anti-tumor activity compares favorably to the approved PD-1 inhibitors in this setting and supports further exploration of IL-2v and checkpoint inhibition in this patient population of high unmet medical need. Clinical trial information: NCT03386721. Research Sponsor: Roche.

5511 **Clinical Science Symposium**

Efficacy and safety results of GX-188E, a therapeutic DNA vaccine, combined with pembrolizumab administration in patients with HPV 16- and/or 18- positive advanced cervical cancer: Phase II interim analysis results (KEYNOTE-567). *First Author: Jong Sup Park, Genexine, Inc., Seongnam, South Korea*

Background: Pembrolizumab was approved for the treatment of recurrent or metastatic cervical cancer, based on 14.3% of objective response rate (ORR) in patients with PD-L1 expression (CPS$\geq$1). GX-188E vaccination has been shown to induce human papillomavirus (HPV) E6- and E7-specific T-cell responses. We aimed to investigate whether a combination of GX-188E (Tirvalimogene teraplasmid) therapeutic DNA vaccine plus pembrolizumab showed antitumor activity against recurrent or advanced cervical cancer. **Methods:** In this open-label, single-arm, phase 2 trial, patients with recurrent or advanced cervical cancer, who were aged over 18 years with ECOG PS of 0 or 1, HPV-16 or HPV-18 and histologically confirmed positive cervical cancer, and who had progressed after standard-of-care therapy were recruited from nine hospitals in South Korea. Patients received intramuscular 2 mg GX-188E at weeks 1, 2, 4, 7, 13, 19, and optional dose at week 46, and intravenous pembrolizumab 200 mg every 3 weeks for up to 2 years or until disease progression. The primary endpoint was the Best Overall Response Rate assessed by the investigator using RECIST version 1.1. **Results:** To date, a total of 52 patients have been enrolled and received at least one study treatment, and this interim analysis was performed after obtaining at least one post-baseline tumor assessment data from 48 patients. Median age was 52 (range, 27-79) years and 46.2% had ECOG PS 1. At the data cutoff date on January 11, 2021, median follow-up duration was 6.2 months (range; 1.7- 24.2 months). According to investigator evaluation, 15 (31.3%) of 48 patients achieved best overall response; 5 (10.4 %) patients had a complete response (CR) and 10 (20.8 %) had a partial response (PR). Especially, this combination treatment showed higher response rate, 48.0 %, in patients with PD-L1 positive, HPV-16 and squamous cell carcinoma. Median PFS was 4.1 months (range; 1.3-24.2) and median OS was 16.7 months (range; 1.7-24.2). In this clinical trial with cervical cancer patients, GX-188E in combination with pembrolizumab has shown an improved median PFS and OS than the monotherapy of pembrolizumab (KEYNOTE-158). 17 (32.7%) of 52 patients had treatment-related adverse events of any grade and two (3.8%) had grade 3 or 4 treatment-related adverse events; increased aspartate aminotransferase or alanine aminotransferase. No treatment-related deaths were reported. **Conclusions:** GX-188E vaccine combined with pembrolizumab in recurrent/advanced cervical cancer was safe and tolerable, and showed an enhanced clinical response rate compared with pembrolizumab alone in particular in patients with PD-L1 positive, HPV-16 and squamous cell carcinoma. The combination therapy could represent a new potential treatment option for this patient population. Clinical trial information: NCT03444376. Research Sponsor: National Onco Venture, Pharmaceutical/Biotech Company.

5512 **Clinical Science Symposium**

Phase IIa study of BVAC-C in HPV type 16 or 18 positive recurrent cervical carcinoma. *First Author: Chel Hun Choi, Samsung Medical Center, Seoul, South Korea*

Background: BVAC-C is a B cell- and monocyte-based immunotherapeutic vaccine transfected with recombinant HPV E6/E7, which was well tolerated in HPV positive recurrent cervical carcinoma in phase I study (J Clin Med . 2020 Jan 5;9(1):147). This phase IIa study sought to determine the antitumor activity of BVAC-C. **Methods:** Twenty-one patients with HPV 16 or 18 positive recurrent cervical cancer who had experienced recurrence after one prior platinum-based combination chemotherapy were enrolled. They were allocated to 3 arms; Arm 1, BVAC-C injection at 0, 4, 8 weeks ($1x10^8$ cells/dose); Arm 2, BVAC-C injection at 0, 4, 8, 12 weeks ($5x10^7$ cells/dose); Arm 3, BVAC-C injection at 0, 4, 8, 12 weeks ($5x10^7$ cells/dose) with topotecan at 2, 6, 10, 14 weeks (0.75 mg/m2 for 3 days). **Results:** The overall response rate was 21% (Arm 1: 29% (2/7), Arm 2: 25% (1/4), Arm 3 : 0 % (0/3)) among the evaluable patients (N = 14), and the median duration of response was 18 months (range, 9 – 26 months). The disease control rate was 43% (Arm 1: 29% (2/7), Arm 2: 50% (2/4), Arm 3 : 67 % (2/3)) and the median duration of stable disease were 12 months (range, 6 - 26 months). The median progression-free survival in all patients was 4 months (95% CI, 2 to Infinite months). Immune responses of patients after vaccination were shown to be correlated with clinical responses of them. Consistent with Phase I study, all evaluated patients showed not only inflammatory cytokine responses (IFN-γ or TNF-α), which might be mediated by the activation of natural killer cells and natural killer T cells, but also potent E6/E7-specific T cell responses upon vaccinations. **Conclusions:** BVAC-C demonstrated a durable antitumor activity with an immune response in HPV 16- or 18-positive recurrent cervical carcinoma patients who failed 1st line platinum based chemotherapy. Clinical trial information: NCT02866006. Research Sponsor: Cellid.

5513 **Poster Discussion Session**

Evaluation of a RAD51 functional assay in advanced ovarian cancer, a GINECO/GINEGEPS study. *First Author: Felix Blanc-Durand, Institut Gustave Roussy, Villejuif, France*

Background: Homologous recombination deficiency (HRD), defined as *BRCA1/2* mutation (*BRCA*mut)or high genomic instability, is currently used to identify patients (pts) with epithelial ovarian cancer (EOC) most likely to benefit from PARP inhibitors. While these genomic tests are useful, they are imperfect: some *BRCA*m EOC demonstrate primary PARPi resistance and some HR-proficient benefit. Another approach to evaluate HRD is to measure the capacity of tumor cells to recruit nuclear RAD51 foci during S/G2 phase in the presence of double strand DNA damage using multiplexed immunofluorescence (IF) for RAD51, geminin (GMN) and yH2AX. We aimed to describe for the 1st time HRD using this RAD51 functional assay in EOC and correlate RAD51 status to platinum response and *BRCA*mut. **Methods:** Tumor samples and clinical data were collected prospectively from pts in the randomized CHIVA trial of neoadjuvant platinum chemotherapy +/- nintedanib. IF for RAD51, GMN, and DAPI was performed on a 3uM slide from FFPE blocks, where feasible, yH2AX was positively scored on a consecutive slide. Tumors were considered RAD51-deficient if $<$ 10% of gem+ tumor cells (TC) had $>$ 5 RAD51+ foci. *BRCA*mut were identified by NGS. **Results:** 155 baseline chemotherapy naïve EOC samples were available. All were advanced stage (IIIC/IV), 75% were G3, 7% G2, 2% G1, and 16% grade UK. A contributive RAD51 result was obtained for 90% (139/155) of samples. Contributive NGS results were available for 130 samples. Overall, yH2AX scores were high (median % TC+: 86%, IQR: 56%-100%) confirming the presence of significant basal DNA damage in high grade EOC. Only 8 samples were yH2AX-low, including two of the three G1 tumors. In contrast, 55% (76/155) of samples were considered RAD51-deficient (score $<$ 10%). With regard to outcome, pts with RAD51-deficient tumors had significantly higher overall response rates to neoadjuvant platinum (68% vs 37%, p = 0.04) and significantly longer median progression-free survival (HR 0.50, IC95% 0.25-0.98, p = 0.02). Considering BRCA status, 15% of tumors harbored a deleterious *BRCA*mut and 67% of these were RAD51-deficient. Importantly among *BRCA*mut EOC, the RAD51-proficient tumors had significantly poorer response to neoadjuvant chemotherapy (RR = 17% vs 75%, p = 0.02). **Conclusions:** We evaluated a novel functional assay of HR functionality in advanced EOC. The assay requires minimal tissue and yields contributive results in 90% of cases. Overall, EOC demonstrate high levels of basal DNA damage, yet 55% fail to recruit RAD51 foci during S/G2 cell cycle phase. These RAD51-deficient EOC have improved outcome after neoadjuvant platinum. Conversely, the RAD51 assay also identified a small subset of RAD51-high *BRCA*mut tumors with poor platinum response. Whether this RAD51 functional assay may also predict PARP inhibitor benefit is currently being investigated. Research Sponsor: ERAPerMed European Grant, Arcagy Gineco.

5514 **Poster Discussion Session**

Progression-free survival (PFS) and second PFS (PFS2) by disease stage in patients (pts) with homologous recombination deficiency (HRD)-positive newly diagnosed advanced ovarian cancer receiving bevacizumab (bev) with olaparib/placebo maintenance in the phase III PAOLA-1/ENGOT-ov25 trial. *First Author: Patricia Pautier, Institut Gustave Roussy, and GINECO, Villejuif, France*

Background: In the Phase III PAOLA-1/ENGOT-ov25 trial (NCT02477644), the addition of maintenance olaparib to bev in pts with newly diagnosed advanced high-grade ovarian cancer (HGOC) resulted in a significant PFS benefit, particularly in HRD-positive (HRD+) pts (hazard ratio [HR] 0.33; 95% CI 0.25–0.45) (Ray-Coquard *et al.NEJM* 2019). We explored efficacy in HRD+ pts by disease stage. **Methods:** Pts with newly diagnosed, FIGO stage III–IV HGOC in response after platinum-based chemotherapy + bev received bev (15 mg/kg q3w for 15 months [mo]) + either olaparib (300 mg bid for 24 mo) or placebo (pbo). This exploratory analysis evaluated PFS (data cut-off [DCO]: Mar 22 2019) and PFS2 (DCO: Mar 22 2020) in HRD+ pts (tumor *BRCA1/BRCA2* mutation [tBRCAm] or genomic instability score [Myriad myChoice HRD Plus] ≥42) by FIGO stage. **Results:** 387/806 randomized pts (48%) were HRD+; 272/387 (70%) had stage III disease and 115/387 (30%) had stage IV disease. 153 (56%) HRD+ stage III pts and 61 (53%) HRD+ stage IV pts had a tBRCAm. Among HRD+ stage III pts, 172 (63%) had upfront surgery (51/172 [30%] had residual disease) and 90 (33%) had interval surgery (19/90 [21%] had residual disease); 52 (45%) HRD+ stage IV pts had upfront surgery (34/52 [65%] had residual disease) and 55 (48%) had interval surgery (18/55 [33%] had residual disease). Median follow-up for PFS and PFS2 was respectively 24.8 and 37.2 mo in HRD+ stage III pts and 24.0 and 37.0 mo in HRD+ stage IV pts. Median PFS, PFS2 and HRs are in the Table. Among HRD+ stage III pts, 36-mo PFS2 (olaparib + bev vs pbo + bev) was 74% vs 60%; among HRD+ stage IV pts, 53% vs 30%. Among HRD+ stage III pts with no residual disease after upfront surgery, HR (95% CI) for PFS was 0.15 (0.07–0.30) and for PFS2 was 0.22 (0.06–0.67). Among HRD+ stage III pts with residual disease after upfront surgery or who received neoadjuvant chemotherapy, or HRD+ stage IV pts, HR (95% CI) for PFS was 0.38 (0.27–0.53) and PFS2 was 0.68 (0.46–1.03). **Conclusions:** In the PAOLA-1 study, maintenance olaparib + bev provided a PFS and PFS2 benefit over pbo + bev in HRD+ pts, irrespective of FIGO stage and residual disease after upfront surgery. Clinical trial information: NCT02477644. Research Sponsor: AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

PFS and PFS2 by FIGO stage in HRD+ pts in PAOLA-1.

	Olaparib + bev	Pbo + bev	HR (95% CI)
Median PFS, mo (95% CI)			
Stage III	39.3 (36.0–NE) (n=182)	19.9 (17.7–23.4) (n=90)	0.32 (0.22–0.47)
Stage IV	25.1 (22.0–37.2) (n=73)	12.8 (10.4–15.8) (n=42)	0.32 (0.20–0.52)
Median PFS2, mo (95% CI)			**HR (95% CI)**
Stage III	NE (50.3–NE) (n=182)	43.0 (35.3–NE) (n=90)	0.57 (0.38–0.87)
Stage IV	37.8 (29.7–NE) (n=73)	25.6 (22.6–35.2) (n=42)	0.56 (0.35–0.91)

NE, not estimable.

5515 **Poster Discussion Session**

Olaparib treatment (Tx) in patients (pts) with platinum-sensitive relapsed ovarian cancer (PSR OC) by BRCA mutation (BRCAm) and homologous recombination deficiency (HRD) status: Overall survival (OS) results from the phase II LIGHT study. *First Author: Cara Amanda Mathews, Program in Women's Oncology, Department of Obstetrics and Gynecology, Women and Infants Hospital, Brown University, Providence, RI*

Background: LIGHT (NCT02983799) evaluated olaparib Tx in pts with PSR OC in cohorts with known BRCAm and HRD status. We report the final OS analyses. **Methods:** We conducted anopen-label, non-randomized, multicenter study of pts with PSR OC and ≥1 prior line of platinum-based chemotherapy (CTx). Pts were assigned to one of 4 cohorts: germline (g) BRCAm; somatic (s) BRCAm; HRD +ve (non-BRCAm); and HRD -ve. Genomic instability score (GIS) and gBRCAm status were determined by Myriad myChoice and BRACAnalysis CDx tests, respectively. HRD +ve tumors were defined by a GIS ≥42. Pts received olaparib Tx (starting dose 300 mg bid) until disease progression or unacceptable toxicity. OS was a secondary endpoint and was analyzed at 12 months (mo) after the primary analysis and 18 mo after the last pt was enrolled. Safety was assessed in pts who received ≥1 dose. **Results:** Data cut-off (DCO) was Aug 27, 2020. Of 272 enrolled pts, 271 received olaparib; of these, 270 had measurable disease at baseline and were included in efficacy analyses (Table). At DCO, 40% of pts had died (maturity) with a median follow-up in censored pts of 26.3 mo. Kaplan–Meier 18-mo OS rates were 86%, 88%, 79%, and 60% in the gBRCAm, sBRCAm, HRD +ve (non-BRCAm), and HRD -ve cohorts, respectively. Platinum-based CTx was the most common first subsequent Tx and was received by 39% pts after olaparib discontinuation. At DCO, the median duration of Tx was 7.4 mo and 244 pts had discontinued treatment, mainly due to disease progression (72%); 5% discontinued due to treatment-emergent adverse events (TEAEs). The only TEAE leading to discontinuation in >1 pt was nausea (2 pts). Serious TEAEs were reported in 25% of pts. The most common serious TEAE was small intestinal obstruction (6%). Three adverse events of special interest occurred, each in 1 pt (<1%): acute myeloid leukemia (post discontinuation), pneumonitis, and pulmonary fibrosis. **Conclusions:** In the final OS analysis, 18-mo OS ranged from 60–88% across the 4 cohorts. Consistent with the primary analysis, the 18-mo OS rate was highest in the BRCAm cohorts (similar OS in g and sBRCAm); among pts without a BRCAm, 18-mo OS was highest in the HRD +ve cohort. No new safety signals were observed compared with the primary analysis and with prior olaparib studies. Clinical trial information: NCT02983799. Research Sponsor: AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

OS and subsequent Tx summary.

	gBRCAm (n=75)	sBRCAm (n=25)	HRD +ve (non-BRCAm) (n=68)	HRD -ve (n=89)	Overall (N=270)*
Deaths, n (%)	20 (27)	5 (20)	24 (35)	51 (57)	107 (40)
Alive at 18 mo (%) (95% CI)	86.4 (76.2–92.4)	88.0 (67.3–96.0)	78.6 (66.6–86.8)	59.6 (48.6–68.9)	74.3 (68.5–79.1)
Received subsequent Tx, n (%)	27 (36)	8 (32)	38 (56)	50 (56)	128 (47)
Platinum-based CTx as first subsequent Tx, n (%)	21 (28)	8 (32)	31 (46)	41 (46)	106 (39)

5516 **Poster Discussion Session**

Combination of PARP and ATR inhibitors (olaparib and ceralasertib) shows clinical activity in acquired PARP inhibitor-resistant recurrent ovarian cancer. *First Author: Stephanie L. Wethington, Johns Hopkins University, Baltimore, MD*

Background: Following multiple blockbuster studies demonstrating long-term progression free and overall survival benefits with poly(ADP-ribose)polymerase inhibitors (PARPi), they have become an integral component of high grade serous ovarian cancer (HGSOC) treatment. Unfortunately, tumors ultimately acquire resistance and thus therapies that overcome PARPi-resistance are urgently needed. Preclinical studies show the addition of ataxia telangiectasia and Rad3-related kinase inhibitors (ATRi) to PARPi overcome PARPi-resistance. We present results of an investigator-initiated study of the combination PARPi (olaparib) and ATRi (ceralasertib) in patients who were on a PARPi and experienced disease progression. **Methods:** We conducted a non-randomized trial (NCT03462342) in platinum sensitive HGSOC immediately following prior PARPi treatment of a 28 day cycle of olaparib 300mg orally twice daily and ceralasertib 160mg orally once daily on days 1-7. Eligibility required a germline or somatic BRCA1/2 mutation, other homologous recombination deficient (HRD) mutation, or positive HRD score (>42 on Myriad My Choice). Clinical benefit from prior PARPi was required (> 12 months on treatment for 1st line maintenance, > 6 months for ≥2nd line maintenance, or treatment of recurrence with response by CA-125 or imaging). No intervening treatment between the PARPi and enrollment was permitted. The primary objectives were safety and objective response rate (ORR). **Results:** Thirteen patients (pt) of median age 60 years (range 43-78) were enrolled. 9 pt (69%) had germline *BRCA* mutations, 3 (23%) somatic *BRCA* mutations and 1 (8%) a positive HRD score. Median time on prior PARPi was 13 months (range 4-60). Prior PARPi indication was 1st line maintenance in 8% (n = 1), 2nd line maintenance in 38% (n = 5) and recurrence in 54% (n = 7). Nine pt (69%) had received olaparib prior to enrollment. The time from prior PARPi to cycle 1, day 1 was 34 days (range 22-311). The ORR was 46% (n = 6); all 6 demonstrating a PR. Pt received a median of 8 (range 3-23) cycles of olaparib and ceralasertib. 4 pt remain on study (4-14 months). 4 pt (31%) experienced grade 3 toxicity: 23% (n = 3) thrombocytopenia, 16% (n = 2) anemia, and 16% (n = 2) neutropenia. There were no grade 4/5 toxicities. There were 4 dose reductions (3 olaparib, 1 ceralasertib). No pt discontinued treatment due to toxicity. **Conclusions:** The combination of olaparib and ceralasertib is well tolerated and shows clinical activity in in a cohort of patients with recurrent HRD HGSOC who have progressed on prior PARPi thus warranting further investigation. This study is the first to suggest the potential of ATR inhibitors to overcome PARPi resistance in an HRD patient population. Molecular profiling studies are underway to identify potential biomarkers associated with response to guide future clinical trial design. Clinical trial information: NCT03462342. Research Sponsor: Astrazeneca, Other Government Agency.

5517 **Poster Discussion Session**

Subgroup analysis of rucaparib versus chemotherapy as treatment for BRCA-mutated, advanced, relapsed ovarian carcinoma: Effect of platinum sensitivity in the randomized, phase 3 study ARIEL4. *First Author: Amit M. Oza, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: In ARIEL4 (NCT02855944), rucaparib significantly improved the primary endpoint of progression-free survival (PFS) vs chemotherapy (CT) in patients with advanced, relapsed ovarian carcinoma (OC) harboring a deleterious *BRCA1/2* (BRCA) mutation (median PFS 7.4 [95% CI 7.3–9.1] vs 5.7 [5.5–7.3] months; hazard ratio (HR) 0.64 [95% CI 0.49–0.84]; *P*=0.001). This prespecified exploratory analysis investigated the effect of platinum sensitivity on the efficacy of rucaparib vs CT in ARIEL4. **Methods:** Patients were randomized 2:1 to oral rucaparib 600 mg twice daily or CT and stratified based on progression-free interval (≥1 to <6 months = platinum resistant; ≥6 to <12 months = partially platinum sensitive; ≥12 months = fully platinum sensitive). In the CT group, patients with platinum-resistant or partially platinum-sensitive disease received weekly paclitaxel 60–80 mg/m^2; patients with fully platinum-sensitive disease received investigator's choice of platinum-based CT (single-agent carboplatin or cisplatin, or platinum doublet). Patients could crossover from CT to rucaparib following radiologic disease progression. Efficacy endpoints were explored in patients with a confirmed BRCA mutation (patients with a reversion mutation were excluded), based on the randomization strata of platinum sensitivity. **Results:** The visit cutoff date was September 30, 2020. PFS and objective response rates (ORR) per RECIST v1.1 for rucaparib vs CT across subgroups are presented in the Table. The most common treatment-emergent adverse events in the rucaparib group were anemia/decreased hemoglobin (platinum-resistant patients: rucaparib 47% vs CT 40%; partially platinum-sensitive patients: 63% vs 27%; fully platinum-sensitive patients: 58% vs 20%) and nausea (52% vs 21%; 51% vs 23%; 60% vs 68%). In the intent-to-treat population, 74/116 (64%) patients in the CT group crossed over to receive rucaparib: 39/59 (66%) with platinum-resistant, 25/31 (81%) with partially platinum-sensitive, and 10/26 (38%) with fully platinum-sensitive disease. **Conclusions:** Results from this exploratory subgroup analysis suggest that rucaparib is a reasonable treatment option for heavily pretreated patients across all platinum sensitivity subgroups. Safety was consistent with prior rucaparib studies. Clinical trial information: NCT02855944. Research Sponsor: Clovis Oncology, Inc.

	Platinum resistant		Partially platinum sensitive		Fully platinum sensitive	
	Rucaparib (n=110)	CT (n=51)	Rucaparib (n=62)	CT (n=28)	Rucaparib (n=48)	CT (n=26)
Median PFS, months (95% CI)	6.4 (5.5–7.4)	5.7 (3.7–7.3)	8.0 (7.0–11.0)	5.5 (2.0–5.6)	12.9 (9.2–14.8)	9.6 (7.5–15.4)
	HR 0.782 (95% CI 0.542–1.127)		HR 0.397 (95% CI 0.242–0.650)		HR 0.689 (95% CI 0.368–1.292)	
ORR, n/N (% [95% CI])	25/107 (23 [16–33])	13/48 (27 [15–42])	32/60 (53 [40–66])	5/25 (20 [7–41])	28/44 (64 [48–78])	13/23 (57 [34–77])

5518 **Poster Discussion Session**

Niraparib efficacy and safety in patients with *BRCA* mutated (*BRCA*m) ovarian cancer: Results from three phase 3 niraparib trials. *First Author: Antonio Gonzalez Martin, Grupo Español de Investigación en Cáncer de Ovario (GEICO) and Medical Oncology Department, Clínica Universidad de Navarra, Madrid, Spain*

Background: Niraparib has been approved for the maintenance treatment of patients with advanced ovarian, fallopian tube, or primary peritoneal cancer after front-line chemotherapy (CT) and in the recurrent setting. Here, we summarize niraparib efficacy and safety in patients with *BRCA*m OC across three phase 3 trials: PRIMA/ENGOT-OV26/GOG-3012 (PRIMA; NCT02655016), ENGOT-OV16/NOVA (NOVA; NCT01847274), and NORA (NCT03705156). **Methods:** Patients enrolled in the PRIMA trial had newly diagnosed advanced ovarian, fallopian tube, or primary peritoneal cancer. All patients had stage III or IV high-grade serous or endometrioid tumors and had a complete or partial response to their first-line platinum-based CT treatment. Subgroup analysis by tumor *BRCA*m status was prespecified. Patients enrolled in the NOVA and NORA studies had platinum-sensitive, high-grade serous ovarian, fallopian tube, or primary peritoneal cancer. Patients had already received at least 2 lines of platinum-based CT regimens. In both studies, subgroup analysis by germline *BRCA*m status was prespecified. The primary endpoint in all trials was progression-free survival (PFS) by blinded independent central review. **Results:** The *BRCA*m populations from each trial are as follows: 223 (148 *BRCA1*m and 75 *BRCA2*m) from the PRIMA trial, 203 (128 *BRCA*1m, 69 *BRCA*2m, and 13 *BRCA*1/2m) from the NOVA trial, and 100 (78 *BRCA*1m, 21 *BRCA*2m, and 1 *BRCA*1/2m) from the NORA trial. PFS results are shown in the Table. Across the 3 trials, the most common treatment-emergent adverse events were thrombocytopenia, anemia, neutropenia, and hypertension. **Conclusions:** Patients with *BRCA*m OC derived a significant PFS benefit from niraparib maintenance treatment across all 3 trials. No new safety signals were identified. Clinical trial information: NCT02655016, NCT01847274, NCT03705156. Research Sponsor: GlaxoSmithKline, Pharmaceutical/Biotech Company.

Trial	n	Niraparib mPFS, months	Placebo mPFS, months	HR (95% CI)
PRIMA				
***BRCA*m**	223	22.1	10.9	0.40 (0.270.62)
FSD	144	22.1	11.1	0.44 (0.260.73)
ISD	79	14.8	10.9	0.29 (0.130.67)
BRCA1	148	19.6	8.4	0.39 (0.230.66)
BRCA2	75	NR	13.6	0.35 (0.150.84)
NOVA				
g*BRCA*m	203	21.0	5.5	0.27 (0.170.41)
BRCA1	128	12.9	5.8	0.39 (0.230.66)
BRCA2	69	NR	5.4	0.12 (0.050.33)
NORA[a]				
g*BRCA*m	100	NR	5.5	0.22 (0.120.39)

[a]*BRCA1* and *BRCA2* data are not currently available.
FSD, fixed starting dose; g*BRCA*m, germline *BRCA* mutated; HR, hazard ratio; ISD, individualized starting dose; mPFS, median progression-free survival; NR, not reached.

5519 **Poster Discussion Session**

Molecular results and potential biomarkers identified from MILO/ENGOT-ov11 phase 3 study of binimetinib versus physicians choice of chemotherapy (PCC) in recurrent low-grade serous ovarian cancer (LGSOC). *First Author: Rachel N. Grisham, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Lower responses to chemotherapy and the unique molecular profile of LGSO led to the adoption of MEK-inhibitors for this disease. Updated analysis from the MILO/ENGOT-ov11 phase III study of binimetinib vs PCC in recurrent LGSOC showed response rate of 24% in those treated with binimetinib (JCO, 2020; NCT01849874). Here we present results of the post-hoc tumor tissue biomarker analysis performed with MILO/ENGOT-ov11. **Methods:** Mutational/copy number analysis was performed via Foundation Medicine on archival tissue obtained prior to randomization. Unbiased univariate analysis was used to test association between mutation status and outcomes in binimetinib and PCC treated patients. Outcomes examined were progression free survival (PFS), binary response by local RECIST 1.1 (complete or partial response [CR/PR] vs. stable [SD] or progressive disease [PD]), and ordinal response. Kaplan-Meier was used to estimate PFS. Cox regression, binary logistic regression, and ordinal logistic regression were used to examine relationship between mutation status and outcomes. **Results:** MILO/ENGOT-OV11 enrolled 341 patients from June, 2013 to April, 2016. Patients were randomized 2:1 to binimetinib or PCC. Based on January 1, 2020 data cut-off the data is as-is, amongst those patients treated with binimetinib with molecular results available, PFS data is available for 144 and response rate (RR) data for 135. There were 47 mutations detected in ≥5% of patients, most commonly *KRAS* (33%). Patients harboring a *KRAS* mutation had 3.4 times the odds of responding to treatment with binimetinib as patients without *KRAS* mutation (95% CI 1.57,7.67; p-value 0.002). There was no difference in effect of *KRAS* G12V mutation vs other *KRAS* mutation on PFS (PFS HR 1.06; 95% CI:0.53, 2.12; p value 0.9). In the 135 patients with binimetinib RR data, other MAPK mutations were identified as follows; *NRAS* in 11(8.1%), *BRAFV600E* in 8(5.9%), *RAF1* in 2 (1.5%), *NF1* in 7 (5.2%). In patients with MAPK mutation (as defined above) the RR was 41% vs 13% in those without MAPK mutation. PFS was significantly better in patients treated with binimetinib harboring MAPK mutation vs those without (HR 0.5; 95% CI 0.31, 0.79; p = 0.003). In patients treated with PCC there was a nonsignificant trend towards improved PFS in those with MAPK mutation vs those without (HR 0.82; 95% CI 0.43,1.59; p = 0.6). A test for interaction between treatment and MAPK pathway was not significant by Cox regression model (p = 0.32). **Conclusions:** While this hypothesis generating analysis is limited by multiple testing, higher response rates and longer PFS were seen in those patients with LGSOC treated with binimetinib who harbored MAPK mutations, most commonly in *KRAS*. Somatic tumor testing should be routinely performed in patients with recurrent LGSOC to aid in clinical decision making. Clinical trial information: NCT01849874. Research Sponsor: Array Biopharma/Pfizer.

5520 **Poster Discussion Session**

An umbrella study of biomarker-driven targeted therapy in patients with platinum-resistant recurrent ovarian cancer (KGOG 3045, AMBITION). *First Author: JUNG-YUN LEE, Institute of Women's Life Medical Science, Yonsei University College of Medicine, Seoul, South Korea*

Background: Heavily treated platinum-resistant ovarian cancer remains a therapeutic challenge. Although standard therapy includes non-platinum single agent chemotherapy (CT), prognoses are very poor in this setting. Anticancer therapies based on molecular biomarkers have improved dramatically. We report data from an umbrella study of biomarker-driven targeted therapy (olaparib, O; cediranib, C; durvalumab, D; tremelimumab, T) in platinum-resistant recurrent ovarian cancer (NCT03699449). **Methods:** Patients with platinum-resistant ovarian cancer with ≥ two lines of prior chemotherapy and ECOG 0/1 were eligible for this study. In the screening phase, archival tumor samples were tested for HRD and PD-L1 status. Treatment arms were allocated according to the test results. For HRD+ patients, we tested the synergistic effects of O with other agents: patients were randomly allocated to arm 1, O+C (O 200mg bid + C 30mg qd); or arm 2, O+D (O 300mg bid + D 1500mg q4w). For HRD- patients, we tested the role of biomarker-driven immunotherapy according to PD-L1 expression: arm 3, D+CT (D 1500mg q4w + PLD or topotecan or weekly paclitaxel [6 cycles]) in patients with high PD-L1 expression; arm 4, D+T75+CT (D 1500mg q4w + T 75mg q4w [4 doses] + PLD or topotecan or weekly paclitaxel [4 cycles]) in patients with low PD-L1 expression; or arm 5, D+T300+CT (D 1500mg q4w + T 300mg [1 dose] + weekly paclitaxel [60mg/m^2 D1,8,15 q4w for 4 cycles]) in patients with low PD-L1 expression. Recruitment to arm 5 was initiated after completion in arm 4. The primary endpoint was objective response rates (ORR) according to RECIST 1.1. **Results:** Between Dec 2018 and Oct 2020, 70 patients were allocated to treatment as follows: arm 1 (n = 16), arm 2 (n = 14), arm 3 (n = 5), arm 4 (n = 18), and arm 5 (n = 17). Median age was 57 years (range 34-77) and median prior lines of treatment was 3 (range: 2-10). Among all patients, the ORR was 35.7% (25/70, 95% CI: 24.6%-48.0%); complete response was observed in two patients. The ORRs (95% CI) for each treatment arm were shown (Table). Treatment-related grade 3/4 adverse events were reported in 37.5%, 35.7%, 20%, 66.7%, and 35.3% of patients in each treatment arm, respectively. No treatment-related adverse events (TRAEs) leading to discontinuation of treatment and no grade 5 TRAEs were observed. **Conclusions:** This is the first biomarker-driven umbrella study conducted in patients with platinum-resistant recurrent ovarian cancer. This umbrella study provides preliminary evidence on the clinical benefit of biomarker-driven targeted therapy. All regimens were manageable, without unexpected toxicities. Clinical trial information: NCT03699449. Research Sponsor: Severance Hospital Research Fund for clinical excellence, Pharmaceutical/Biotech Company.

	Drug	Biomarker	ORR, % (95% CI)
Arm 1 (N = 16)	O+C	HRD+	50 (24.7-75.4)
Arm 2 (N = 14)	O+D	HRD+	35.7 (12.8-64.9)
Arm 3 (N = 5)	D+CT	HRD- & PD-L1+	20 (0.5-71.6)
Arm 4 (N = 18)	D+T75+CT	HRD- & PD-L1-	33.3 (13.3-59.0)
Arm 5 (N = 17)	D+T300+CT	HRD- & PD-L1-	29.4 (10.3-56.0)

5521 **Poster Discussion Session**

Dendritic cell vaccine (DCVAC) combined with chemotherapy (CMT) in patients with newly diagnosed epithelial ovarian carcinoma (EOC) after primary debulking surgery (PDS): Biomarker exploratory analysis of a phase 2, open-label, randomized, multicenter trial. *First Author: Lukas Rob, Third Faculty of Medicine, Charles University and University Hospital Kralovske Vinohrady, Prague, Czech Republic*

Background: Most patients with EOC relapse despite PDS and CMT. Autologous DCVAC can present tumor antigens to elicit a durable immune response. We hypothesized that adding DCVAC to CMT stimulates antitumor immunity and improves clinical outcomes. **Methods:** Key eligibility criteria were FIGO stage III EOC (serous, endometrioid, or mucinous), post-PDS with < 1 cm maximal residuum, no prior systemic therapy, and ECOG 0-2. In part 1, patients were randomized up to 6 weeks after PDS, 1:1:1, into arm A (A; DCVAC concomitant with CMT), arm B (B; DCVAC sequential after CMT), and arm C (C; CMT). Patients were stratified by tumor residuum (0 or < 1 cm). CMT consisted of 6 cycles of carboplatin (AUC 5-7) and paclitaxel (175 mg/m^2). Patients in A and B received up to 10 doses of DCVAC (1×10^7 DCs/dose). The primary endpoint was radiologically assessed progression-free survival (PFS). The key secondary endpoint was overall survival (OS). Results presented refer to a protocol-defined modified intention-to-treat population (mITT) including patients who received ≥1 CMT dose in C or ≥1 DCVAC dose in A and B. **Results:** Between November 2013 and March 2016, 99 patients were randomized. At the final analysis, the mITT included 31 patients in A, 29 patients in B, and 30 patients in C. Key baseline characteristics and DCVAC exposure were comparable across treatment arms. Median PFS was 20.3 months in A, not reached in B, and 21.4 months in C, with corresponding HRs (95% CI) compared to C of 0.98 (0.48-2.00) in A and 0.39 (0.16-0.96) in B. The PFS benefit in B was statistically significant (p = 0.034) This was supported by a non-significant trend in OS in A and B. Median OS was not reached in any arm at the time of median follow-up of 66 months (34% of events). Patients with low CD8+ T-cell counts (CD8^{Lo}) in tumor samples in A and B had significantly improved clinical outcomes compared to patients in C with CD8^{Lo}: median PFS gain of 6 months (19 vs 13 months) and a more robust OS gain (median not reached vs 31 months), with minimal difference between A and B. This effect could not be attributed to statistical differences in high CD8+ T-cell counts (CD8^{Hi}) density patients. These findings indicated the best clinical outcome in DCVAC patients with immunologically "cold" tumors in both DCVAC arms. DCVAC showed a good safety profile with only 8 DCVAC-related adverse events (Grade 1-2). **Conclusions:** DCVAC improved PFS and OS outcomes in patients with newly diagnosed EOC, predominantly in patients with immunologically "cold" tumors, thus representing a promising treatment option in this patient population. Clinical trial information: NCT02107937. Research Sponsor: SOTIO a.s.

5522 **Poster Discussion Session**

Pembrolizumab in combination with bevacizumab and pegylated liposomal doxorubicin in patients with platinum-resistant epithelial ovarian cancer. *First Author: Judith Michels, Gustave Roussy Comprehensive Cancer Center, Villejuif, France*

Background: There is a medical unmet need for effective treatments in platinum resistant ovarian cancer patients. We assessed the safety and efficacy of a combination of pembrolizumab with bevacizumab and pegylated liposomal doxorubicin (PLD). **Methods:** This is an open-label phase 1b trial in patients ECOG 0 or 1 with platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal cancer. The safety of the dual combinations of pembrolizumab with bevacizumab or with PLD were previously evaluated in 6 patients respectively. In the absence of dose limiting toxicities (DLT) the triple combination was evaluated at a maximum tolerated dose (MTD)-1 for PLD in 3 patients and in the absence of DLT at MTD. The sample size was calculated according to the modified toxicity probability interval design. The primary evaluation criteria was the safety, the secondary endpoint was the outcome. Pharmacokinetics of the flat dose of bevacizumab will be evaluated. **Results:** 22 patients were enrolled from September 2019 until June 2020 in six French centers. 3 initial patients have been treated at 20mg/m^2 of PLD (MTD-1) and 19 patients were treated at the dose of 30mg/m^2 of PLD (MTD) combined with 200mg of pembrolizumab until progression, unacceptable toxicity, or withdrawal of consent and 400mg of bevacizumab for a total of six cycles. The patients' characteristics are reported in the table. No DLT occurred. Grade 3 palmar-plantar erythrodysesthesia were reported in 4 patients. The recommended phase II dose of PLD was 30mg/m^2 in combination with pembrolizumab and bevacizumab. For patients treated at MTD, the overall response rate was 32% (6 partial responses) with 74% of clinical benefit with a durable response in 10 patients (53%). Median number of cycles was 7.5 (2 to not reached). Two patients are still on treatment. Correlative studies are ongoing. **Conclusions:** The combination was well tolerated and demonstrated clinical benefit in 74% platinum resistant ovarian cancer patients with durable response (>6 months) in 53% of patients. Clinical trial information: NCT03596281. Research Sponsor: MSD, Other Foundation.

Characteristics	n (%)
Age	
median	70
range	47-77
Origin of cancer, ovary	22 (100)
Histology at diagnosis	
Serous high grade	19 (86)
Clear cell	2 (9)
other	1 (5)
BRCA mutations	
BRCA1[1]	3 (14)
BRCA2[2]	1 (5)
no	15 (68)
Prior antiangiogenic therapy	18 (82)
Prior treatment with PARP inhibitors	9 (41)
Prior chemotherapy regimens	
1-2	12 (54)
>2	9 (41)
Platinum-free interval at first relapse <6 months	9 (41)

[1]Two germline and one somatic, [2]One somatic., MSD, Other Foundation.

5523 **Poster Discussion Session**

A phase II evaluation of pembrolizumab in recurrent microsatellite instability-high (MSI-H) endometrial cancer patients with Lynch-like versus *MLH*-1 methylated characteristics (NCT02899793). *First Author: Dana M Roque, Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD*

Background: Microsatellite instability (MSI-H) is a biomarker for response to immune-checkpoint inhibitors (ICIs); however, these neoplasms are heterogenous including Lynch (germline), Lynch-like (somatic) and sporadic (*MLH1*-methylated) tumors. Whether mechanisms underlying MSI alter responses to ICIs is unclear. We report data from a phase II pilot study (NCT02899793) of pembrolizumab in recurrent MSI-H endometrial cancer (EC) patients and potential mechanisms of primary/secondary ICI resistance. **Methods:** Patients with measurable, MSI-H EC confirmed by immunohistochemistry and polymerase chain reaction were evaluated by next-generation sequencing and received pembrolizumab 200 mg intravenously every 3 weeks for up to 2 years. The primary end point was objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. **Results:** Twenty-five patients (24 evaluable) were treated. Six (25%) patients harbored Lynch/Lynch-like tumors while 18 (75%) had sporadic EC. Tumor mutational burden (TMB) was higher in Lynch-like (median 2939, IQR:867-5108) versus sporadic tumors (median 604, IQR:411-798) (P= 0.0076). Median follow-up was 25.8 months with an ORR of 58% (95% CI, 36.6-77.9%). ORR was 100% in Lynch/Lynch-like patients but only 44% in sporadic patients (P= 0.024). The 3-year progression-free (PFS) and overall survival (OS) proportions were 100% versus 30% (P= 0.017) and 100% versus 43% (P= 0.043), respectively. Grade 3/4 treatment-related adverse events (6.8%) occurred in 12 patients. Defective antigen processing/presentation and deranged induction in interferon responses served as mechanisms of resistance in sporadic MSI-H EC. **Conclusions:** Our study demonstrated prognostic significance of Lynch-like versus sporadic MSI-H EC on ORR, PFS and OS when treated with pembrolizumab. Clinical studies evaluating separate subtypes of MSI-H EC treated with ICIs are warranted. Clinical trial information: NCT02899793. Research Sponsor: Merck.

5524 **Poster Discussion Session**

Anlotinib plus sintilimab in patients with recurrent advanced cervical cancer: A prospective, multicenter, single-arm, phase II clinical trial. *First Author: Qin Xu, Fujian Cancer Hospital, Fuzhou, China*

Background: It is difficult for patients with recurrent advanced cervical cancer to obtain clinical benefits after the failure of standard chemotherapy. However, anti-angiogenic therapy combined with immune checkpoint inhibitors have become a promising strategy for advanced cervical cancer. Anlotinib is a novel multi-target tyrosine kinase inhibitor, inhibiting tumour angiogenesis and proliferative signalling. Sintilimab is a fully humanized, high-affinity monoclonal antibody against programmed cell death-1 (PD-1). This phase II, single-arm study (ChiCTR1900023015) aims to evaluate the efficacy and safety of anlotinib plus sintilimab in patients with recurrent advanced cervical cancer. **Methods:** Patients who have received at least once platinum-based chemotherapy, histopathologically confirmed recurrent advanced cervical cancer (including squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma), more than 1% PD-L1 expression, ECOG 0-1 were considered eligible for enrollment. Anlotinib was taken orally (10mg mg qd, d1-14, 21 days per cycle), and sintilimab was administered intravenously (200mg once every 3 weeks). The treatment was continued until disease progression, death or intolerant toxicity. The primary endpoint was objective response rate (ORR) and the secondary endpoints included disease control rate (DCR), progression free survival (PFS), overall survival (OS) and safety. **Results:** Between September 2019 and February 2021, 42 patients with a median age of 52 years (range:47-58), FIGO histopathological stage I (11.9%), II (31.0%), III (33.3%), IV (9.5%) and undiagnosed (14.3%) were enrolled. 39 of these patients were evaluable. In the efficacy-evaluable population (n = 39), the therapeutic evaluation showed that 2 and 20 patients achieved complete response and partial response respectively, yielding the ORR of 56.4% (22/39, 95% CI:40.2 to 71.5). The DCR was 94.9% (37/39, 95% CI:80.7 to 98.8). The median response time was 1.6 months. The median PFS was not reached. The most common adverse events (AEs) were grade 1 or 2, which included hypothyroidism (33.3%), hypertension (23.8%), AST (21.4%), diarrhea (19.0%), ALT (16.7%), hand-foot syndrome(14.3%), hypertriglyceridemia (14.3%) and anemia (11.9%). The grade 3 AEs were hypertension (4.8%), hyponatremia (4.8%), immune pneumonia (2.4%) and immune myocarditis (2.4%). No higher AEs and treatment-related death were observed. **Conclusions:** Anlotinib plus sintilimab showed a promising efficacy with a favorable toxicity profile for patients with recurrent advanced cervical cancer. We will report more data in the future. Clinical trial information: ChiCTR1900023015. Research Sponsor: None.

5525 **Poster Session**

Parametrial evaluation in cervical cancer by magnetic resonance imaging and clinical examination: Analysis of data from the prospective Leipzig School MMR study. *First Author: Benjamin Wolf, University of Leipzig Medical Center, Department of Gynecology, Leipzig, Germany*

Parametrial evaluation in cervical cancer by magnetic resonance imaging and clinical examination **Background:** In cervical cancer patients, assessment of parametrial tumor extension is important for staging and treatment planning. The 2019 cervical cancer guideline published by the Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) for the first time includes recommendations for usage of magnetic resonance imaging (MRI) in this setting. However, valid data regarding the accuracy of this method, especially in patients with advanced disease, are sparce. The objective of this investigation was to compare the accuracy of parametrial assessment in cervical cancer patients using MRI and clinical examination under general anesthesia. **Methods:** A retrospective cohort study based on data from the prospective monocentric observational Leipzig School Mesometrial Resection study was conducted. Cervical cancer patients staged FIGO IB1 to FIGO IVA who underwent primary surgery between 1999 and 2017 were included. Data from pathological specimen of these patients was compared to the MRI findings and the results from clinical examination under general anesthesia. The gynecological oncologist had access to the MR images during clinical assessment. We calculated sensitivities, specificities, and predictive values for both examination methods. We performed logistic regression modelling to determine factors influencing the accuracy of either method. **Results:** 400 women were included. Pathologically proven parametrial tumor invasion was present in 165 (41%) patients. Examination under anesthesia augmented by intraoperative display of MR images exhibited a higher accuracy (83%) as compared to MRI alone (76%; McNemar's odds ratio = 2.0, 95%CI 1.25 – 3.27, $p = 0.003$). While accuracy was not affected by tumor size in clinical examination, MRI was associated with a significant drop in accuracy in tumors $\geq$ 2.5 cm (univariable logistic regression, OR for a correct diagnosis compared to smaller tumors 0.22, $p < 0.001$). This association remained significant in a multivariable model. There was also a significant decrease in specificity when evaluating parametrial invasion by MRI in tumors $\geq$ 2.5 cm in diameter ($p < 0.0001$). Body mass index had no influence on performance of either method. Accuracy was significantly higher when test results were concordant (OR 7.5 and 6.0 on univariable and multivariable regression modelling, respectively, $p < 0.0001$ in both cases). **Conclusions:** Clinical evaluation of the parametrium by pelvic examination under anesthesia in conjunction with intraoperative presentation of MR images leads to more accurate staging in cervical cancer patients as compared to magnetic resonance imaging alone. Clinical examination should therefore remain an integral part of parametrial assessment in cervical cancer patients. Research Sponsor: None.

5526 **Poster Session**

Discovery and validation of novel methylated DNA markers of cervical cancer. *First Author: Jamie Nadine Bakkum-Gamez, Mayo Clinic, Rochester, MN*

Background: HR-HPV DNA testing, with or without cervical cytology, provides excellent sensitivity for detection of cervical cancer (CC) and its precursors; negative test results indicate that risk of disease is extremely low and enable women to undergo reduced screening with safety. However, management of women who screen positive remains challenging as many will prove to have self-limited HR-HPV infections. DNA methylation is an early event in carcinogenesis that could enhance CC screening specificity. **Methods:** For discovery, DNA from 70 FFPE CC (36 squamous, 34 adenocarcinoma) tissues that were reviewed microscopically, 18 fresh frozen benign cervicovaginal (BCV) tissues collected at the time of benign hysterectomy, and 18 buffy coats from cancer-free women underwent reduced representation bisulfite sequencing (RRBS) to identify MDMs associated with CC. Candidate MDM selection was based on area under the receiver operating characteristic curve (AUC) discrimination, methylation fold change, and low background methylation among benign controls. Candidate MDMs were re-tested using methylation-specific PCR (MSP) to confirm performance. Blinded biological validation was performed using MSP on DNA extracted from independent FFPE CC (38 squamous, 43 adenocarcinoma) and BCV (40) tissues. The performance of CC MDMs was also tested in DNA extracted from cervical dysplasia (36 adenocarcinoma in situ (AIS), 32 cervical intraepithelial neoplasia (CIN) 2/3, 11 CIN 1) FFPE tissues. **Results:** From RRBS discovery and technical validation via MSP, 30 candidate MDMs showed marked methylation fold changes (10 to >1000) across both CC histologies compared to BCV tissue from cancer-free women. Each of the 30 MDMs highly discriminated CC from BCV tissue with 9 MDMs having an AUC >0.90 (Table). CC MDMs also highly discriminated AIS from BCV but did not perform well in CIN 2/3 and CIN 1 (Table). **Conclusions:** Whole methylome sequencing, stringent filtering criteria, and biological validation have yielded outstanding candidate MDMs for CC that highly discriminate CC from BCV, notably with high specificity. Performance in cervical dysplasias varied with higher positivity rates in AIS than in CIN 2/3 and CIN 1. Translation to testing these novel MDMs in lower genital tract biospecimens and the addition of HR-HPV to the CC panel are warranted. Research Sponsor: The V Foundation, Mayo Clinic Transform the Practice Grant.

Top MDMs	AUC (95% CI) (CC v. BCV)	Positivity Rates at 92.5% Specificity Cutoff in Controls CC AIS CIN 2/3 CIN 1			
1	0.97 (0.94 - 1)	0.94	0.72	0.66	0.64
2	0.97 (0.93 - 1)	0.9	0.72	0.41	0.64
3	0.95 (0.91 - 1)	0.9	0.69	0.34	0.45
4	0.95 (0.91 - 0.99)	0.88	0.72	0.25	0.27
5	0.95 (0.9 - 0.99)	0.88	0.72	0.25	0.45
6	0.94 (0.9 - 0.99)	0.91	0.69	0.34	0.18
7	0.92 (0.86 - 0.98)	0.8	0.56	0.22	0.27
8	0.91 (0.86 - 0.97)	0.85	0.64	0.31	0.27
9	0.91 (0.85 - 0.97)	0.85	0.67	0.38	0.27

5527 **Poster Session**

A phase II trial of bevacizumab and rucaparib in recurrent carcinoma of the cervix or endometrium. *First Author: Camille Catherine Jackson, Stephenson Cancer Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: Treatment options for patients with recurrent cervical and endometrial cancer remain limited. Even with optimum care, median survival has stalled at 12-17 months. The PARP inhibitor rucaparib has demonstrated activity in both *BRCA* wild-type and mutant cancers. Furthermore, preclinical studies suggest a synergistic effect of PARP inhibitors and antiangiogenic agents. We hypothesized that the combination of rucaparib and the VEGF inhibitor bevacizumab would yield a clinically-significant anti-cancer effect in patients with persistent or recurrent cervical or endometrial carcinoma. **Methods:** NCT03476798 is a phase II trial of adults with histologically-documented carcinoma of the cervix or endometrium. Patients with evaluable lesions who had undergone at least one prior line of systemic therapy, had adequate performance status and organ function, with a life expectancy of at least three months were eligible. Biopsies were obtained prior to treatment initiation for assessment of baseline tumor biomarkers, including *ARID1A* mutation status. Each cycle comprised 21 days. Rucaparib was administered orally at 600 mg, twice daily. Bevacizumab was administered by IV at 15 mg/kg on day 1 of each cycle. The primary objective was to estimate the proportion of patients with persistent or recurrent cervical or endometrial cancer who survive progression-free for at least six months (PFS6). Kaplan-Meier analysis was used to estimate progression-free survival. **Results:** There were 28 evaluable patients; six had cervical and 22 had endometrial cancer. Median age was 60.5 years (range, 30-74). Self-reported patient races were White (82.1%), Black (10.7%), and Native American (7.1%). Self-identified Hispanic or Latina patients comprised 3.6% of the cohort. Twenty-two of 28 patients had progressive disease by six months [survival distribution function estimate = 0.214 (lower CI, 0.087; upper CI, 0.378)]. Of the six patients who achieved PFS6, one had cervical and five had endometrial cancer. Six patients had a mutation in the *ARID1A* gene and those patients achieved PFS6 at a rate of 66.7%. **Conclusions:** The study hypothesis was evaluated in a two-stage design, and the interim analysis occurred once 28 evaluable patients were enrolled. In order to move on to the second stage, at least seven patients needed to remain progression-free at six months, but only six did. Thus, the study was ended after the interim analysis. The combination of rucaparib and bevacizumab did not provide the expected clinical benefit in this cohort of patients, but may warrant further exploration in patients with *ARID1A* mutations. Clinical trial information: NCT03476798. Research Sponsor: Clovis Oncology.

5528 **Poster Session**

Defective mismatch repair associated mutational signatures, a prognostic and predictive biomarker in endometrial cancer. *First Author: Yifan Emily Chang, Yale School of Medicine, New Haven, CT*

Background: Mismatch repair (MMR) deficiency is the distinguishing molecular feature of a significant portion of endometrial cancers (UCEC), and tumors with MMR deficiency have been identified as candidates for immune checkpoint blockade therapy. We studied MMR deficiency in UCEC using defective mismatch repair associated mutational signatures (MMRd-ams). **Methods:** WES-derived somatic mutation data of 531 UCEC samples from TCGA Pan-Cancer Atlas were analyzed. COSMIC mutational signatures for each sample were calculated using the R package *deconstructSigs*. MMRd-ams were correlated with clinical and molecular features for 507 TCGA samples (cBioPortal). Samples were divided into High MMRd-ams (n = 192) and Low MMRd-ams (n = 315) groups by the average of the representative MMRd-ams (0.2396). Fractions of tumor immune infiltrates were derived from CIBERSORT. **Results:** A significantly higher percentage of patients (47/192, 24.5%) in the High MMRd group had somatic putative driver mutations in at least 1 of the MMR genes (*MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, PMS2* and *EPCAM*), compared with patients in the Low MMRd group (37/315, 11.8%, $p = 0.0003$). 15% (54/359) of tumors in the non-MSI subtypes expressed significant MMRd-ams and were categorized in the High MMRd-ams group. Patients in the High MMRd-ams group had longer progression-free survival (PFS) ($p = 0.0457$, log-rank). Analysis of the inferred composition of tumor immune infiltrates revealed that the High MMRd-ams group had significantly higher fraction of CD8+ T cells ($p < 0.0001$), higher fraction of T follicular helper cells ($p < 0.0001$) and lower fraction of M2 macrophages ($p < 0.001$). Tumors in the High MMRd-ams group also displayed higher mRNA expression levels of immune checkpoint genes: *PDCD1* ($p = 0.0013$), and *CTLA4* ($p = 0.0016$). **Conclusions:** MMRd-ams may be a prognostic and predictive biomarker with significant clinical impact. High MMRd-ams patients prognostically demonstrated longer PFS. Predictively, high MMRd-ams was associated with increased tumor immune infiltrates and elevated expression levels of *CTLA4* and *PDCD1,* known immune checkpoint genes exploitable by immune checkpoint therapies. MMRd-ams importantly characterized a subset of patients that were non-MSI but fit the MMR deficient phenotype by mutational signature. Together these findings open an avenue for recognizing and treating a previously unidentifiable group of patients. Research Sponsor: None.

5529 **Poster Session**

Differentiated activity profile for the PD-1 inhibitor balstilimab. *First Author: Cailin Joyce, Agenus Inc., Lexington, MA*

Background: The development and clinical application of immune checkpoint inhibitors has transformed the therapeutic landscape for cancer treatment in recent years. Balstilimab (AGEN2034) is a fully human, monoclonal IgG4 antibody that binds with high affinity to programmed death 1 (PD-1), thus preventing the interaction between this receptor and its ligands programmed death ligand 1 and 2 (PD-L1, PD-L2). Emerging evidence suggests that balstilimab exhibits a differentiated activity profile compared to currently approved anti-PD-1 agents, including pembrolizumab and nivolumab. **Methods:** Balstilimab as monotherapy was evaluated in a large phase 2 study in patients (pts) with recurrent/metastatic cervical cancer who had relapsed after a platinum-based treatment regimen for advanced disease. Pts were dosed at 3 mg/kg once every 2 weeks for up to 24 months and antitumor activity was assessed using RECIST v1.1. The tumor cell killing activity of balstilimab was evaluated preclinically in a human co-culture system of (1) primary T cells engineered to recognize NY-ESO-1 and (2) NY-ESO-1$^+$ cancer cell lines, including PD-L1 and/or PD-L2-deficient engineered lines. The co-culture system was maintained for ~ two weeks to drive partial T cell exhaustion; a state where cytotoxicity is compromised but recoverable with PD-1 blockade. Cytotoxicity of these partially exhausted T cells was quantified against PD-L1/L2 double positive, single positive, or double negative cancer cells in the presence or absence of PD-(L)1 antibodies. **Results:** In the second-line treatment setting for pts with advanced cervical cancer, balstilimab showed a numerically higher objective response rate (ORR) in subjects with PD-L1$^+$, squamous cell carcinoma (SCC) tumors (21%, 95% CI, 12.7-32.6%) than those reported for pembrolizumab. Unlike pembrolizumab, balstilimab showed activity in PD-L1(-) pts, and irrespective of tumor histology (ORR 7.9%, 95% CI, 2.7-20.8%). Despite lower overall PD-L1 positivity compared to SCC (41.7 v 72.9%), an ORR of 12.5% (95% CI, 5.9-24.7%) was observed in the subset of pts with a poorer prognosis, those with cervical adenocarcinoma. Concordant with clinical observations, balstilimab demonstrated superior rescue of antigen-specific T cell cytotoxicity *in vitro* relative to pembrolizumab, nivolumab, or atezolizumab. Balstilimab also induced cytotoxicity against PD-L1 and/or PD-L2 deficient target cancer cells. **Conclusions:** Taken together, these data suggest functional differentiation of balstilimab from other PD-1 inhibitors with potentially important implications for extending the therapeutic reach of anti-PD-1 therapy. Investigation of the underlying mechanistic basis for these findings is ongoing. Clinical trial information: NCT03104699. Research Sponsor: Agenus Inc.

5530 **Poster Session**

Differential benefit from fractionated dose-dense first-line chemotherapy for epithelial ovarian cancer (EOC) according to KELIM-evaluated tumor primary chemosensitivity: Exploratory analyses of ICON-8 trial. *First Author: Benoit You, Institut de Cancérologie des Hospices Civils de Lyon (IC-HCL), CITOHL, EMR UCBL/HCL 3738, Lyon, GINECO & GINEGEPS, Lyon, France*

Background: ICON8 phase III trial did not show improvement in PFS or OS with first-line weekly dose-dense chemotherapy in EOC. This analysis evaluated the impact of tumor intrinsic primary chemosensitivity (assessed with modeled CA-125 ELIMination rate constant K (KELIM) based on the CA-125 kinetics during the first 100 days of chemo), on survival by treatment arms. **Methods:** Retrospective analysis of ICON8 where EOC patients were treated with chemo (Arm 1, standard (std) carboplatin AUC5-6 & paclitaxel 175mg/m2 q3weeks; Arm 2, carboplatin AUC 5-6 q3weeks and weekly paclitaxel 80 mg/m2; or Arm 3, weekly carboplatin AUC 2 & paclitaxel 80 mg/m2; ratio1:1:1) and debulking primary surgery (immediate (IPS), or delayed (DPS)). The association between standardized KELIM (dichotomized as favorable ≥ 1, or unfavorable < 1) and efficacy of treatment arms and surgery completeness was assessed univariate & multivariate analyses. **Results:** Of 1,566 enrolled patients, KELIM was calculated in 1,004 with ≥ 3 CA-125 available values. KELIM did not differ by treatment arm. Irrespective of surgical strategy, both KELIM and surgery completeness were significant prognostic factors, but treatment arms were not. In 354 IPS patients, 225 had unfavorable KELIM (63%). Weekly dose-dense carboplatin-paclitaxel (Arm 3) (compared to std chemo-Arm 1) was associated with improved survival in unfavorable KELIM patients (PFS:19.6 vs 11.0 months, HR 0.80 [0.54-1.17]; OS : 53.7 vs 40.1 months, HR 0.75 [0.50-1.14]), and worse survival in those with favorable KELIM (PFS: 26.7 vs 48.2 months, HR 1.27 [0.72-2.22]; OS: NR vs 69.2 months, HR 1.05 [0.53-2.06]). Maximum benefit was seen in highest-risk diseases (unfavorable KELIM + incomplete IPS; n = 116; PFS: 17.0 vs 7.4 months, HR 0.49 [0.29-0.82]; OS: 42.6 vs 27.0 months, HR 0.56 [0.33-0.96]). In 611 patients treated with neo-adjuvant chemo +/- DPS (279 unfavorable KELIM, 46%), the same trend for higher survival benefit from dose-dense carboplatin-paclitaxel was found in those with unfavorable KELIM (PFS: 10.8 vs 7.4 months, HR 0.84 [0.63-1.13]; OS: 26.4 vs 23.5 months, HR 0.80 [0.60-1.08]), and reversely. The higher KELIM, the higher the likelihood of complete surgery (OR 4.82 [3.21-7.37]). The prognostic impact of the surgery completeness was greater in unfavorable KELIM patients. **Conclusions:** In ICON8 trial, both the tumor primary chemosensitivity (by KELIM) and completeness of debulking surgery were major drivers of the prognosis & survival. Dose-dense fractionated chemotherapy in 1st-line setting may be beneficial for patients with lower tumor chemosensitivity, whilst it might be detrimental in those with highly chemosensitive disease. The greatest OS benefit (HR 0.56) from dose-dense chemotherapy was seen in highest-risk diseases (unfavorable KELIM and incomplete IPS). Research Sponsor: None.

5531 **Poster Session**

An international, multicenter, real-world analysis of epithelial ovarian cancer treatment and outcomes. *First Author: Geoff Hall, Leeds Cancer Centre, Leeds Teaching Hospitals Trust, Leeds, United Kingdom*

Background: Few major studies have examined and compared the management and outcomes of patients from diagnosis to death between countries. We have established an international collaboration across Europe and South Korea to compare treatment and outcomes in Epithelial Ovarian Cancer (EOC). **Methods:** Patients diagnosed with EOC between January 2012 and December 2018 (age $\geq$18), were included for analysis. Data from medical records from five European and a single South Korean treatment centre were extracted, standardised to a common data model and analysed at each centre using a common script developed in R. Time to each progression/recurrence event (defined as time to next treatment) and overall survival have been estimated using Kaplan Meier methodology and outcomes stratified by categories of interest. Changes in the use of anti-cancer therapies over time and the incidence of BRCA mutations and incidence/timing of second breast cancers have also been examined. **Results:** A total cohort of 2925 patients was identified with a median age at each centre of 53 to 67 years. Advanced disease (FIGO stage III - IV) (range 57% to 84%) and high-grade serous morphology (38% to 70%) were most common at each centre. The timing of surgery (primary, interval debulking or delayed) and the proportion of patients undergoing surgery varied with stage. Patients with stage I disease where most likely to undergo surgery (range 73% to 100%) and stage IV the least (range 39% to 84%). Median overall survival for high grade serous cancers ranged from 1.9 to 4.9 years, and for the whole cohort from 2.1 to 5.5 years. Median time to next treatment at first relapse for the whole cohort ranged from 14 to 22 months. Second breast cancers were noted in 6 to 17% of patients and the majority of these occurred before the diagnosis of EOC at a median time of 96 to 118 months prior to diagnosis of EOC. Additional data on treatment pathways, BRCA status and outcomes by line of therapy for each centre will be presented. **Conclusions:** Preliminary analysis of results across this network suggests a variation in patient populations between sites and substantial differences in both treatments and outcomes. The establishment of a common data model and the use of a common analytic script between sites across six different countries allows for detailed exploration of the factors influencing differences in patient management and treatment outcomes in ovarian cancer patients. Research Sponsor: IQVIA.

5532 **Poster Session**

Metronomic cyclophosphamide and bevacizumab for the treatment of recurrent gynecologic carcinosarcoma: A multi-institution, retrospective study. *First Author: Sara Bouberhan, Massachusetts General Hospital, Boston, MA*

Background: The recent findings from the GOG 261 trial established carboplatin and paclitaxel as the standard first-line therapy for advanced gynecologic carcinosarcoma (GCS). Response rates to alternative regimens are limited, and the optimal chemotherapy for later line treatment of gynecologic carcinosarcoma has not yet been determined. The objective of this retrospective study is to report clinical response to treatment regimens for patients with GCS treated at 2 large academic referral comprehensive cancer centers. **Methods:** This multi-institution, retrospective analysis identified patients with recurrent GCS treated between January 1, 2015 and August 1, 2020 at the Massachusetts General Hospital and the University of Alabama O'Neal Comprehensive Cancer Center. All eligible patients received platinum/taxane as their first-line treatment regimen and were subsequently treated for recurrent disease. Subsequent treatment strategies were investigated. Objective responses were determined based on the clinical radiologist's interpretation. Time on treatment (TOT) and treatment toxicity were identified for each subject. Given the small number of patients in this series, descriptive statistics were employed. **Results:** 29 patients met inclusion criteria. 15 patients had recurrent uterine carcinosarcoma, and 14 patients had recurrent ovarian carcinosarcoma. The most commonly used treatment regimens were: liposomal doxorubicin (PLD)/bevacizumab (ORR: 13%; Range TOT: 2-7 months), metronomic oral cyclophosphamide (MOC)/bevacizumab (ORR: 17%; Range TOT: 1-18 months), weekly paclitaxel/bevacizumab (ORR 60%; Range TOT: 3-18.5 months), liposomal doxorubicin (PLD) (ORR: 0%; Range TOT: 1-3 months), and weekly paclitaxel (ORR: 33%; Range TOT: 4.5-5.5). All regimens were generally well tolerated, and only 3 patients discontinued treatment due to toxicity concerns. **Conclusions:** In summary, in our cohort of gynecologic carcinosarcoma patients, the most active regimen (defined by mean TOT) was paclitaxel/bevacizumab, but prolonged TOT was also observed in the patients treated with MOC/bevacizumab. Given the rarity and aggressive nature of this tumor, further studies into optimal second line chemo (and beyond) are warranted; although, the combination of MOC/bevacizumab should be considered given the tolerability and the duration of treatment in this patient population. Research Sponsor: None.

5533 **Poster Session**

Anlotinib plus pemetrexed as a further treatment for patients with platinum-resistant ovarian cancer: A single-arm, open-label, phase II study. *First Author: Jueming Chen, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Non-platinum chemotherapy is widely used in platinum-resistant recurrent ovarian cancer treatment but with limited efficacy. Combing chemotherapy with angiogenic inhibitors is a new therapeutic choice. Anlotinib is a novel tyrosine kinase inhibitor targeting multiple receptors involved in tumor proliferation, vasculature, and tumor microenvironment. The study aimed to further assess the efficacy and safety of anlotinib combined with pemetrexed in platinum-resistant ovarian cancer. **Methods:** Patients who had received at least two different chemotherapy regimens (including the first line platinum-based regimen), with histologically proven recurrent platinum-resistant or platinum-refractory epithelial ovarian cancer (including salpingocarcinoma and peritoneal carcinoma), ECOG 0-2, were considered eligible for enrollment to receive six 21-days cycles of anlotinib (12 mg QD from day 1 to 14; 21 days per cycle) orally plus pemetrexed intravenously (0.5 g/m^2 on day 1; 21 days per cycle). Subsequent maintenance treatment was anlotinib monotherapy (12 mg QD from day 1 to 14; 21 days per cycle) till disease progression or intolerant toxicity. The primary endpoint was objective response rate (ORR), and the secondary endpoints included disease control rate (DCR), progression-free survival (PFS) and safety. **Results:** As of Jan 2021, 27 patients were enrolled. The median number of chemotherapy was 4 (range, 2-10) and 51.9% (14/27) of patients had ever received antiangiogenic therapy. The ORR was 36.4% (partial response (PR) in 8 patients; 95% CI, 17.2-59.3). The DCR was 100.0% (PR in 8 patients and stable disease (SD) in 14 patients; 95% CI, 73.5-100). The median time of the first response was 1.6 months (range, 1.3-4.4). The median PFS was 9.3 months (95% CI, NE-NE). Furthermore, the ORR of patients with and without prior antiangiogenic therapy was 16.7% (95%CI, 2.1-48.4) and 60.0% (95%CI, 26.2-87.8) respectively (P = 0.074). Any grades of adverse events (AEs) were observed in 92.6% (25/27) of patients, containing allergic eruption (33.3%), hand-foot syndrome (29.6%), hypertension (25.9%), and fatigue (25.9%). The grade 3-4 adverse events were only observed in 5 patients, including 1 with grade 3 proteinuria, 1 with grade 3 ascites, 1 with grade 3 fatigue, 1 with grade 3 edema limbs and 1 with grade 4 anemia. **Conclusions:** The treatment of anlotinib plus pemetrexed showed a promising antitumor activity with tolerable toxicity for patients in platinum-resistant and refractory ovarian cancer. Clinical trial information: ChiCTR2000029654. Research Sponsor: Beijing Medical and Health Found.

5534 **Poster Session**

Efficacy of niraparib maintenance therapy in Chinese women with platinum-sensitive recurrent ovarian cancer with and without secondary cytoreductive surgery: Results from the NORA trial. *First Author: Lingying Wu, National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: NORA is the first, phase III, randomized controlled trial (RCT) that demonstrated individualized starting dose regimen of niraparib, which significantly improved PFS in Chinese patients with platinum-sensitive recurrent ovarian cancer (PSROC). This sub-group analysis evaluated the efficacy of niraparib maintenance therapy with and without secondary cytoreductive surgery (SCS) in PSROC. **Methods:** The NORA phase III RCT included adult (≥18 years) Chinese women with PSROC who were randomized in a 2:1 ratio to receive oral niraparib (n = 177) or matched placebo (n = 88). This retrospective subgroup analysis was based on the progression-free survival (PFS) of niraparib maintenance therapy in these two groups of patients with PSROC, patients with SCS, and patients without SCS. The PFS was assessed by blinded independent central review. The Kaplan-Meier (KM) estimator and log-rank test were performed to calculate the median PFS time. **Results:** Of the 265 evaluable patients, 69 (26.0%) patients received the SCS (niraparib, n = 48; placebo, n = 21), and 196 (74.0%) patients were without SCS (niraparib, n = 129; placebo, n = 67). Among patients with and without SCS, baseline characteristics for BRCA mutation were 26.1% vs 41.8%, complete response to last platinum-based chemotherapy were 68.1% vs 43.9%, time (6-12 months) to progression after penultimate therapy were 23.2% vs 34.7%, respectively. Treatment with niraparib led to a significant reduction of risk to disease progression compared with placebo in patients with SCS (Hazard ratio [95% CI]: 0.32 [0.13–0.78]; P = 0.0102) and without SCS (0.34 [0.23–0.50]; P< 0.001). Moreover, in the subgroups of patients who received SCS, niraparib maintenance therapy had a significantly longer PFS compared with placebo (Median [95% CI]: not reached [18.33 – not estimable] vs 5.75 months [3.68 – not estimable]; P = 0.0102). This trend was also similar in the subgroup of patients who did not receive SCS (Median [95% CI]: 10.28 months [7.49 – 18.37] vs 4.90 months [3.71 – 5.52]; P < 0.0001). **Conclusions:** The results from this retrospective sub-group analysis revealed that niraparib maintenance therapy provided significant clinical efficacy in patients with PSROC, irrespective of SCS. Clinical trial information: NCT03705156. Research Sponsor: Zai Lab, Other Foundation.

5535 **Poster Session**

Safety assessment of niraparib individualized starting dose in patients with platinum-sensitive recurrent ovarian cancer: A randomized, double-blind, placebo-controlled, phase III NORA trial. *First Author: Jing Wang, Hunan Cancer Hospital, The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China*

Background: To present the safety profile of niraparib maintenance therapy in patients with platinum-sensitive recurrent ovarian cancer (PSROC) included in the NORA trial. **Methods:** The double-blind, randomized, placebo-controlled, multicenter, phase III NORA trial (NCT03705156) included adult (≥18 years) Chinese women with PSROC who received ≥2 prior lines of platinum-based chemotherapy. Post ≤8 weeks of the last chemotherapy, patients were randomized (2:1) to receive oral niraparib (300 mg/day or 200 mg/day for patients with bodyweight <77 kg or platelet count <150 × 10^3/μL) or matched placebo. The primary endpoint was progression free survival, reported previously. Safety was assessed in terms of treatment emergent adverse events (TEAEs) related to hematologic toxicity (anemia/platelet count decreased and neutrophil count decreased) and non-hematologic toxicity (nausea/vomiting/constipation/insomnia/palpitations/hypertension). Adverse events (AEs) were graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The data cutoff was February 1, 2020. **Results:** Of 265 patients included, the first 16 patients were given oral niraparib or matched placebo at a fixed starting dose of 300mg while 249 patients received individualized starting dose of niraparib (n = 166) or matched placebo (n = 83) based on baseline bodyweight and platelet count. The incidence of any TEAEs and grade ≥3 TEAEs was 100% and 50.8%, respectively in niraparib group, while 95.5% and 19.3%, respectively in placebo. Incidence of all grades of hematologic toxicity, gastrointestinal adverse events (nausea, constipation and vomiting), insomnia, palpitation and hypertension were highest in the first month after treatment with a gradual decrease in the further months. The median time to onset of grade ≥3 anemia, decreased neutrophil count and decreased platelet count were 87, 28, and 22 days, respectively, in the niraparib group. In niraparib group, any TEAEs that lead to dose reduction was observed in 59.9% of patients. Only 2 (1.1%) patients discontinued the treatment due to platelet count decreased and no patients discontinued niraparib treatment due to anemia or neutrophil count decreased. Overall, only 4% of patients in the niraparib group and 5.7% in the placebo group discontinued the treatment due to TEAEs. **Conclusions:** The lower incidence of TEAEs and the discontinuation rates indicate improved safety profile of niraparib with individualized starting dose in PSROC. Clinical trial information: NCT03705156. Research Sponsor: Zai Lab, Other Foundation.

5536 **Poster Session**

Association of homologous recombination deficiency in ovarian cancer with neoantigen load and expression of immune checkpoints. *First Author: Kathleen Fenerty, Department of Medicine, UCLA, Los Angeles, CA*

Background: Immune checkpoint blockade (ICB) is being explored as a treatment option in ovarian cancer, but objective response rates for single agent ICB are modest at around 10-15%. Validated biomarkers are needed to predict which patients will respond to ICB. BRCA mutations and homologous recombination deficiency (HRD) status are the only validated integral biomarkers in ovarian cancer. HRD tumors exhibit defective DNA repair mechanisms that promote increased mutational burden, which we postulate may correlate with higher neoantigen load and increased expression of targetable immune checkpoints. **Methods:** The Cancer Genome Atlas (TCGA) ovarian cancer dataset was evaluated and previously published, well annotated samples were obtained for HRD status. HLA type was determined with OptiType. Nonsynonymous mutations were annotated with Ensembl VEP. pVAC-Seq using NetMHCpan algorithm predicted neoepitopes 9 amino acids in length for MHC class I, reporting only those with a predicted IC50 less than 500 nM. Immune checkpoint gene expression counts were normalized with TCGAbiolinks. Correlation between HRD status and neoantigen load was assessed by Wilcoxon test. After log2 transformation, Wilcoxon tests evaluated for association between HRD status and expression of immune checkpoints. The relationship between HRD status and PD-L1 protein abundance with reverse phase protein array was measured. **Results:** Data from 154 HRD positive and 198 HRD negative tumors were analyzed. HRD positive status correlated with higher neoantigen load ($p = 0.038$) and increased expression of the immune checkpoints CTLA4 ($p = 0.024$), TIGIT ($p = 0.027$), and PVR ($p = 0.002$), but not PD-L1 ($p = 0.238$), LAG3 ($p = 0.583$), HVEM ($p = 0.805$), GAL9 ($p = 0.750$), NECTIN2 ($p = 0.874$), VSIG3 ($p = 0.438$), PSGL1 ($p = 0.205$) or VISTA ($p = 0.531$). TIM3 ($p = 0.064$) and B7H3 ($p = 0.052$) both demonstrated a trend towards increased expression in HRD tumors. Interestingly, HRD status showed a negative association with PVRIG ($p = 0.028$). There was no association between PD-L1 protein abundance and HRD status. **Conclusions:** HRD positive ovarian tumors demonstrate higher neoantigen load than HRD negative tumors, as well as increased expression of certain immune checkpoints. This supports the hypothesis that increased neoantigen load leads to compensatory induction of immune checkpoints, and suggests that HRD status may predict response to ICB, particularly to drugs that target CTLA4, TIGIT, PVR, TIM3 and B7H4. Research Sponsor: None.

5537 **Poster Session**

Clinical and molecular characteristics of ARIEL3 patients who derived exceptional benefit from rucaparib maintenance treatment for high-grade ovarian cancer (HGOC). *First Author: Tanya Kwan, Clovis Oncology, Inc., Boulder, CO*

Background: ARIEL3 is a placebo-controlled randomized trial of the PARP inhibitor (PARPi) rucaparib as maintenance treatment in HGOC patients (pts) who responded to the latest line of platinum therapy (NCT01968213). Rucaparib improved progression-free survival (PFS) across all predefined subgroups. Here, we present an exploratory analysis of clinical and molecular characteristics associated with exceptional benefit from rucaparib. **Methods:** Pts were randomized 2:1 to receive rucaparib 600 mg BID or placebo. At the data cutoff of Dec 31, 2019, 33/375 (9%) and 1/189 (0.5%) pts were still ongoing and receiving rucaparib or placebo, respectively. Molecular features (genomic alterations, *BRCA1* promoter methylation) and baseline clinical characteristics were compared between pts who derived exceptional benefit (PFS ≥2 yrs), and those with disease progression on first scan (≈12 wks; the short-term [ST] subgroup) within each treatment arm. **Results:** Of 564 pts, 83 (15%) showed exceptional benefit: 79/375 (21%) in the rucaparib arm and 4/189 (2%) in the placebo arm. Within the rucaparib arm, exceptional benefit pts had more favorable clinical prognostic factors at baseline compared with the ST subgroup (Table). While BRCA mutations were enriched in the rucaparib exceptional benefit subgroup, 34/79 (43%) of these pts were BRCA wild type. Among other biomarkers, *RAD51C/D* mutations were associated with exceptional benefit; low genome-wide loss of heterozygosity was enriched within the ST subgroup; and high *BRCA1* methylation was present at similar fractions. Trends were similar in the placebo arm (Table). **Conclusions:** Exceptional benefit in ARIEL3 was more common in, but not exclusive to, pts with favorable clinical characteristics and known mechanisms of PARPi sensitivity. Our results suggest that rucaparib can deliver exceptional benefit to a diverse set of HGOC pts. Clinical trial information: NCT01968213. Research Sponsor: Clovis Oncology, Inc.

	Rucaparib			Placebo		
Baseline characteristics	**Exceptional benefitn = 79**	**ST subgroup n = 64**	**Odds ratio (95% CI)**	**Exceptional benefit n = 4**	**ST subgroup n = 62**	**Odds ratio (95% CI)**
No measurable disease	58 (73%)	26 (41%)	4.0 (2.0–8.0)[a]	3 (75%)	33 (53%)	2.6 (0.4–35.3)
Complete response to latest platinum	31 (39%)	13 (20%)	2.5 (1.2–5.3)[a]	1 (25%)	11 (18%)	1.5 (0.1–11.2)
Penultimate platinum-free interval > 12 mo	55 (70%)	30 (47%)	2.6 (1.3–5.2)[a]	4 (100%)	29 (47%)	NA
BRCA mutation	45 (57%)	12 (19%)	5.7 (2.6–12.6)[a]	3 (75%)	25 (40%)	4.4 (0.6–59.0)
BRCAwt/LOH-high	19 (24%)	19 (30%)	0.8 (0.4–1.6)	0	14 (23%)	NA
BRCAwt/LOH-low	8 (10%)	28 (44%)	0.14 (0.1–0.4)[a]	1 (25%)	16 (26%)	1.0 (0.1–6.8)
BRCAwt + *RAD51C/D* mutation[b]	6 (8%)	0	NA	0	0	NA
BRCAwt + high *BRCA1* promoter methylation[c]	6/25 (24%)	7/47 (15%)	1.8 (0.5–6.0)	0/1	5/29 (17%)	NA

BRCAwt, BRCA wild type; LOH, loss of heterozygosity; ST, short-term; NA, not applicable.
[a]Significant result; [b]$P = 0.033$ (Fisher's exact test); [c]In samples with known methylation status.

5538 **Poster Session**

LIO-1: Lucitanib + nivolumab in patients with advanced solid tumors—Updated phase 1b results and initial experience in phase 2 ovarian cancer cohort. *First Author: Erika P. Hamilton, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: The phase (Ph) 1b part of LIO-1 (NCT04042116; ENGOT-GYN3/AGO/LIO) assessed the oral antiangiogenic, multikinase inhibitor lucitanib + immune checkpoint inhibitor nivolumab, confirming the recommended Ph2 dose (RP2D) of lucitanib as 6 mg QD + nivolumab (480 mg IV every 28 days). To maximize lucitanib exposure and potential clinical benefit of the combination, individualized lucitanib dose titration is being explored in a Ph2 part, across 4 recurrent gynecologic malignancies (endometrial, cervical, ovarian, and ovarian/endometrial clear-cell cancers) using a Simon 2-stage design. We present updated Ph1b data and describe initial experience for the first 24 patients (pts) enrolled in the Ph2 ovarian cancer (OC) cohort. **Methods:** In Ph1b, pts with advanced, metastatic solid tumors received lucitanib at 6, 8, and 10 mg QD + nivolumab (in a 4+3 dose escalation). In the Ph2 OC cohort, pts with recurrent high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer (excluding clear-cell histology) with ≥2 prior chemotherapy regimens (including ≥1 platinum doublet) received the combination at RP2D; lucitanib dose was escalated from 6 mg to 8 mg and then to 10 mg QD for pts who met safety-based titration criteria. Visit cutoff was Feb 1, 2021. **Results:** In the Ph1b part (N = 17), median treatment duration was 109 days (range 14–505+). There has been 1 confirmed complete response (CR; anal cancer) and 1 confirmed partial response (PR; cervical cancer) per RECIST v1.1 with durations of 7.1 and 12.8 months, respectively. Ten pts had stable disease (SD), 3 had progressive disease, and 2 were nonevaluable; 3 pts remain on treatment. Overall disease control rate (CR + PR + SD ≥16 wk) was 47.1%. One dose-limiting toxicity (DLT; grade [G] 3 proteinuria) was observed in a pt receiving lucitanib 6 mg, leading to lucitanib discontinuation; no DLTs were seen at 8 or 10 mg. G ≥3 treatment-emergent adverse events (TEAEs) reported in ≥2 pts included hypertension (HTN; n = 4), fatigue (n = 2), and proteinuria (n = 2). Of the first 24 pts enrolled in the Ph2 OC cohort, 13 (54%) remain on treatment (median duration 59 [2–167+] days). Most frequent any-grade TEAEs were HTN (n = 10), fatigue (n = 8), nausea (n = 7), and proteinuria (n = 6). The only G ≥3 TEAE experienced in ≥2 pts was HTN (n = 4); 1 pt discontinued due to G4 HTN/G2 angina pectoris and 1 pt to G2 colonic perforation. To date, 21 pts have completed ≥1 cycle; 11 met safety-based dose-titration criteria, 10 of whom escalated to the 8 mg lucitanib dose. Of these, 5 pts subsequently escalated to 10 mg. One pt required dose reduction from 6 mg to 4 mg lucitanib. **Conclusions:** Ph1b data suggest that lucitanib + nivolumab has promising signs of antitumor activity. A safety-based dose-titration strategy appears feasible with manageable toxicity, based on experience from the Ph2 OC cohort to date; efficacy data from this cohort will also be presented. Clinical trial information: NCT04042116. Research Sponsor: Clovis Oncology, Inc.

5539 **Poster Session**

Underutilization of germline BRCA testing in commercially-insured women diagnosed with ovarian cancer. *First Author: Stephanie Cham, Brigham and Women's Hospital, Boston, MA*

Background: Germline BRCA (gBRCA) testing has prognostic, therapeutic, and familial implications for patients with ovarian cancer. Since 2010, national guidelines have recommended universal genetic testing, but few data are available about rates and timeliness of testing or factors associated with testing. **Methods:** We examined rates of gBRCA testing and the time from index procedure to testing among commercially-insured women aged 18 to 64 with claims for ovarian, fallopian tube, or primary peritoneal cancers cancer who received cytoreductive surgery and chemotherapy between 2008-2018. We used logistic regression to assess patient-, clinician-, and practice-level characteristics associated with testing. **Results:** Overall, the rate of g*BRCA* testing was 33.9%, increasing from 14.7% in 2008 to 46.4% in 2018; the median time to testing decreased from 280.0 to 72.5 days. Patients who were tested were younger than those who were not (mean [SD] 54.7 [9.9] years vs. 58.1 [11.8] years, $P<.001$) and had fewer comorbidities (Charlson score ≥2: 3.7% vs. 9.5%, P=0.01). There were no differences in testing rates by US region, rurality of practice location, or medical vs. gynecologic oncology providers. However, testing rates were higher in academic and NCI-designated cancer centers (36.2% and 32.5%, respectively), compared with community practices (25.5%; $P<0.001$) (Table). In adjusted analyses, lower test rates were associated with older age (aOR=0.97, 95%CI=0.96-0.98), more medical comorbidities (Charlson score ≥2: aOR=0.77, 95%CI=0.61-0.97), and community practices vs. NCI cancer centers (aOR=0.64, 95%CI=0.46-0.88). **Conclusions:** While the rates and time to testing for gBRCA in patients with new diagnoses of ovarian cancer have improved over time, testing remains underutilized, even among well-insured populations. Future studies should examine barriers to timely genetic testing and identify scalable strategies for increasing testing in women with ovarian cancer, particularly for women treated in community practices. Research Sponsor: None.

Provider and practice level characteristics associated with germline BRCA testing.

Total (N=3603)	**Proportion patients tested (%)**	**Proportion with timely *BRCA* testing (%)**	**Median time from diagnosis to testing, days (IQR)**
Provider type			
Gynecologic oncologist (N=1336, 37.1%)	37.8	63.6	113 + 344 (42-302)
Medical oncologist (N=1534, 42.6%)	34.2	72.1	87 + 321 (34-207)
General OB/GYN (N = 505, 14.0%)	25.2	66.9	111 + 272 (44-111)
Other (N = 228, 6.3%)	28.1	68.8	97 + 358 (47-217)
Practice type			
NCI Cancer Center (N=593, 16.5%)	32.5	68.2	112 + 326 (42-218)
Academic (N = 177, 4.9%)	36.2	68.8	98 + 240 (53-304)
Community (N = 2833, 78.6%)	25.5	67.7	100 + 335 (36-251)

5540 **Poster Session**

Postoperative adjuvant dose-dense chemotherapy with bevacizumab and maintenance bevacizumab after neoadjuvant chemotherapy for advanced ovarian cancer: A phase II AGOG/TGOG trial. *First Author: Wei-Chun Chen, Chang Gung Memorial Hospital of Linkou Main Branch, Taoyuan, Taiwan*

Background: The objective of this study is to evaluate the safety and efficacy of adding bevacizumab to dose-dense adjuvant chemotherapy with bevacizumab maintenance after neoadjuvant chemotherapy (NAC) and interval debulking surgery (IDS) for stage III/IV ovarian, tubal, and primary peritoneal cancer. **Methods:**This phase II clinical trial using Simon's minimax two-stage design was conducted. At the first stage, 13 subjects were enrolled, and the trial would proceed to second stage if ≤3 subjects discontinued treatment for study-defined significant adverse events (AEs). Patients with stage III/IV ovarian, tubal, and primary peritoneal cancer deemed not feasible for primary cytoreductive surgery were enrolled after 3 to 4 cycles of NAC and IDS without disease progression. NAC could be either weekly paclitaxel (80mg/m^2) (dose-dense) plus 3-weekly carboplatin (AUC5-6) or 3-weekly conventional schedule. After IDS, postoperative dose-dense adjuvant chemotherapy for 3 cycles at least (best to 6 cycles), and 3-weekly bevacizumab 15mg/kg was given since postoperative cycle 2. Further 3-weekly maintenance bevacizumab 15mg/kg was given intravenously for 17 cycles. **Results:** Of the 22 enrolled subjects, 13 (59.1%) had no gross lesion after IDS. Of the 13 subjects enrolled on the 1st stage, one study-defined significant AE occurred, therefore the trial proceeded to the 2nd stage (n = 9). The median progression-free survival (PFS) was 22.1 months (95% confidence interval [CI], 13.7 – 30.5), and the median overall survival (OS) was 49.2 months (95% CI, 33.8 – 64.6). Peritoneal Cancer Index score at entering abdomen during IDS was significant for PFS (>12 vs ≤ 12: p = 0.003). One of the 22 subjects did not receive any study treatment. In the safety analysis (n = 21), grade 3/4 AEs included thrombocytopenia of 38.1%, neutropenia 71.4%, and anemia 28.6%. Study-defined significant AEs of bowel perforation, poor-healing wound, and hypertension were found in 1 case each, respectively. **Conclusions:** This phase II trial demonstrated adding bevacizumab to dose-dense adjuvant chemotherapy with bevacizumab maintenance after NAC was feasible with tolerable toxicity and comparable PFS/OS as compared to other studies using bevacizumab in the NAC phase or dose-dense scheduling throughout. Clinical trial information: NCT02022917. Research Sponsor: Ministry of Health and Welfare, Taiwan, Other Foundation.

5541 **Poster Session**

Patient self-reporting of tolerability using PRO-CTCAE: A randomized double-blind placebo controlled phase II trial comparing gemcitabine in combination with adavosertib or placebo in women with platinum resistant epithelial ovarian cancer. *First Author: Ainhoa Madariaga, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: A 4 month improvement in OS was demonstrated when Wee1 inhibitor adavosertib (Ad) and gemcitabine (G; arm A) was compared to G and placebo (P; arm B) in a phase 2 trial in recurrent ovarian cancer (NCT02151292). The patient reported outcome version of the CTCAE (PRO-CTCAE) was used to capture self-report of the frequency, severity and/or interference (scored 0-4; higher scores indicating worse symptomatic adverse events [syAEs]). **Methods:** Ad/P was given orally on D1-2, D8-9, D15-16 with G D1, D8, D15 in a 28-day cycle. English speaking pts in 2 centres completed PRO-CTCAE items electronically in clinic at baseline, D1 and D15 of each cycle and off treatment. An exploratory objective was to characterize syAEs in the first 3 months of therapy. We calculated 12-week area under the curve (AUC12w) as a measure of syAE over time and incremental AUC12w (iAUC12w) for adjustment to baseline syAEs and compared arms A and B using an independent samples t-test. We assessed proportion of scores 3-4 at 6 time-points and compared them using Fisher's Exact Test at each survey. **Results:** 51 pts were enrolled and completed ≥1 survey, 47 were evaluable for primary outcome (arm A: 28, B: 19). ECOG status was ≤1 in 44/47 pts. Median number of cycles of therapy were 5 (1-16) in arm A, and 2 (1-16) in B. Survey completion rates were high (arm A 93%, B 95%). Mean AUC12w fatigue severity (A 152 [standard error 9] vs B 112 [10]; p = 0.005) and interference (A 144 [11] vs 98 [15]; p = 0.018), diarrhea frequency (A 70 [12] vs B 33 [9]; p = 0.014), mucositis (A 23 [6] vs B 6 [3]; p = 0.012) and difficulty swallowing severity (A 10 [3] vs B 2 [2]; p = 0.023) were higher in arm A (any grade). There were no statistically significant between-arm differences in abdominal pain, bloating, nausea, vomiting and anxiety. The iAUC12w was significantly higher in arm A vs B for difficulty swallowing severity (A 10.1 [3] vs B -2.7 [4.7]; p = 0.02), mucositis severity (A 19.9 [6.6] vs B -3.1 [6.9]; p = 0.02) and fatigue severity (A 35.2 [8.2] vs B -3.1 [9.8]; p = 0.005). Proportions with high scores (3-4) were only significantly higher at C1D15 for fatigue severity in arm A (A 55% vs B 19%, p = 0.044). No significant differences were seen in other 3-4 scores per survey time. **Conclusions:** This is the first study evaluating pts self-reported toxicity with adavosertib in a randomized setting, allowing pts self-evaluation of toxicity in the context of improved PFS and OS. Greater fatigue, diarrhea, mucositis and difficulty swallowing were experienced by pts receiving adavosertib and gemcitabine, but score 3-4 reached significance on C1D15 fatigue only. No significant differences were detected in syAE profile for nausea, vomiting, abdominal pain, bloating and anxiety. This approach allows objective assessment of pts perception of toxicity with complex therapy. Clinical trial information: NCT02151292. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Other Government Agency, Pharmaceutical/Biotech Company.

5542 **Poster Session**

A phase I study of mirvetuximab soravtansine (MIRV) and gemcitabine (G) in patients (Pts) with selected frα-positive solid tumors: Results in the ovarian cancer (EC) cohort. *First Author: Mihaela C. Cristea, City of Hope, Duarte, CA*

Background: Mirvetuximab soravtansine (MIRV) is an ADC comprising a FRα-binding antibody, cleavable linker, and the maytansinoid DM4, a potent tubulin-targeting agent. MIRV has promising single agent activity in FRα-positive medium/high expression epithelial ovarian cancer (EOC), at 6 mg/kg, based on adjusted ideal body weight (AIBW) IV every (q) 21 days. This study evaluated MIRV and G in recurrent EOC, endometrial and triple negative breast cancer. The recommended phase 2 dose (RP2D) was established at MIRV 6 mg/kg AIBW IV, day 1 and G 800 mg/m2 IV, d1, 8 q21 days (J Clin Oncol 37, 2019, Abs. #3009). Here we report the results from the EOC cohort. **Methods:** Patients (pts) with FRα-positive platinum resistant EOC with ≤4 prior chemotherapy (CT) regimens, were eligible. FRα positivity was initially defined as ≥ 25% of cells with PS2+ staining intensity (low to high FRα expression) and was subsequently revised to require medium/high FRα expression (≥50%/ ≥75% of cells with PS2+ staining intensity). **Results:** From 10/2017 to 12/2020, 113 EOC pts underwent FRα screening, with 74 FRα-positive results. Thirty total EOC pts (with median 3 prior lines of therapy) were treated; 8 pts during dose escalation and 22 EOC pts at the RP2D (all evaluable for response). Fifteen (50%) pts had high FRα, 10 pts (33%) medium FRα, and 5 pts (17%) low FRα expression. Eleven (36%) of the 30 EOC pts achieved a partial response (PR), 15 pts (50%) had SD and 4 pts (13%) progressed. Among the 11 responders, 5 pts had high FRα, 4 pts medium FRα and 2 pts low FRα expression. Non-heme clinically significant adverse events (AEs) included: G2 sensory neuropathy (4 pts) G3 diarrhea (3 pts), G3 fatigue (2 pts), G3 pneumonitis (2 pts), and 1 pt with G5 respiratory failure (secondary to pneumonia but drug-induced pneumonitis could not be ruled out). **Conclusions:** MIRV in combination with G has promising clinical activity in late line platinum resistant FRα-positive EOC, with best responses observed in high FRα expression. The regimen is well tolerated with expected AEs based on the known toxicities of each agent. This study was approved and funded by the National Comprehensive Cancer Network (NCCN) Oncology Research Program from general research support provided by ImmunoGen Corp and Cancer Center Support Grant P30CA033572. Clinical trial information: NCT02996825. Research Sponsor: NCCN.

5543 **Poster Session**

The correlation between BRCA status and surgical cytoreduction in high-grade serous ovarian carcinoma. *First Author: Rachel Soyoun Kim, University of Toronto Division of Gynecologic Oncology, Princess Margaret Cancer Centre/University Health Network/Sinai Health Systems, Toronto, ON, Canada*

Background: High grade serous ovarian cancers (HGSC) with BRCA mutation are biologically unique, with distinct molecular and clinical behaviour from sporadic cases. It is unclear if these biological differences translate to favorable outcomes at the time of primary cytoreductive surgery (PCS). The aim of this study is to compare the amount of residual disease following PCS in BRCA-mutated (BRCAm) and wildtype (BRCAwt) HGSC, and to assess whether BRCA status is an independent predictor of residual disease. **Methods:** We conducted a retrospective analysis of patients with HGSC with known germline and somatic BRCA mutation status, treated with PCS from 2000 to 2017. We compared the cytoreduction outcomes between the BRCAm and the BRCAwt cohorts and built a predictive model to assess whether BRCA status was associated with amount of residual disease at the time of PCS. **Results:** Of 355 women, 144 harbored germline or somatic BRCA mutations (41%) and 211 were BRCAwt (59%). BRCAm women tended to be younger (54 vs. 59; $p < 0.001$), but there were no differences between the two groups in stage, disease burden at presentation, surgical complexity score, length of surgery, or perioperative complications. The BRCAm group had a higher rate of complete cytoreduction to no residual disease (0mm) [75% vs. 54%], and a lower rate of optimal cytoreduction (1-9mm) [16% vs. 34%] or suboptimal cytoreduction (≥10mm) [9% vs. 12%] ($p < 0.001$). In our predictive model, after accounting for length of surgery, CA-125 level, stage, disease scores and surgical complexity scores, BRCAm status was predictive of complete cytoreduction to 0mm residual disease (OR 4.78; 95% CI 2.32-9.85; $p < 0.001$). **Conclusions:** BRCA status is predictive of complete cytoreduction at time of PCS in HGSC. Timely availability of BRCA testing is paramount as it may aid in the therapeutic decision making between PCS or neoadjuvant chemotherapy in women with newly diagnosed HGSC. Research Sponsor: None.

5544 **Poster Session**

Nanoanalysis of plasma volatile organic compounds using novel DNA-decorated carbon nanotube vapor sensors to noninvasively distinguish ovarian and pancreatic cancer from benign and control samples.

First Author: A. T. Charlie Johnson, University of Pennsylvania Department of Physics & Astronomy, Philadelphia, PA

Background: All cells release volatile organic compounds (VOCs) which emanate from body fluids. Our previous preliminary proof of concept study demonstrated that VOCs released from tissue and plasma from ovarian cancer patients are distinct from those released from samples of patients with benign tumors and controls. We seek to create a sensitive and specific, high-throughput screening test for cancer based on analysis of VOCs using novel nanosensors, first targeting cancers with limited clinical screening modalities. In this study we use these sensors to distinguish vapor characteristics in plasma samples from patients with ovarian and pancreatic cancer from benign specimens and controls. **Methods:** VOCs emanating from .5 mL of thawed, previously banked plasma samples from 93 total individuals were analyzed using a 10-channel nanoelectronic olfaction ("e-nose") system based on single-stranded DNA-decorated single-walled carbon nanotube (DNA-NT) vapor sensors. Analysis was performed on samples from 20 patients with ovarian cancer, 20 with benign ovarian tumors and 20 age-matched women as well as 13 patients with pancreatic cancer, 10 patients with benign pancreatic disease, and 10 age- and sex-matched controls. All ovarian cancer patients and comparators were non-smokers, while 1 pancreatic patient and 1 corresponding control were current smokers. The sample set included cancer patients with both early- and late-stage disease. All cancer specimens were obtained proximal to initial diagnosis and prior to initiation of therapy. With a test time of approximately 20 minutes per sample, the array output for each individual sample creates a vector in a 10-dimensional sensor space. The ability of the nanosensor array to discriminate between malignant, benign, and healthy groups was investigated using linear discriminant analysis (LDA), support vector machine (SVM), *k*-nearest neighbors (KNN), and random forest classification algorithms. Each algorithm was trained and tested according to leave-one-out and repeated stratified *k*-fold cross-validation methods. **Results:** Compared to their corresponding benign and control specimens, the DNA-NT sensor array was able to discriminate the VOCs from ovarian cancer with 95% accuracy and pancreatic cancer with 90% accuracy. Plasma samples from patients with early-stage ovarian and pancreatic cancers were correctly identified by the algorithms. **Conclusions:** Nano-enabled DNA coated vapor sensors were able to distinguish the VOC pattern between cancer, benign and control samples in both ovarian and pancreatic cancer. We provide strong evidence that ovarian and pancreatic cancer alters the VOC pattern emanating from plasma. Our results provide optimism that a diagnostic approach based on vapor detection of ovarian and pancreatic cancer is achievable. Research Sponsor: Klyberg Foundation.

5545 **Poster Session**

Olaparib maintenance monotherapy for non-germline BRCA1/2-mutated (non-gBRCAm) platinum-sensitive relapsed ovarian cancer (PSR OC) patients (pts): Phase IIIb OPINION primary analysis.

First Author: Andres Poveda, Initia Oncology, Valencia, Spain

Background: In the Phase II Study 19 trial (NCT00753545; Ledermann *et al Lancet Oncol* 2014), maintenance olaparib improved progression-free survival (PFS) vs placebo in PSR OC pts, including non-BRCAm pts. A significant PFS benefit was also seen with maintenance olaparib vs placebo in gBRCAm PSR OC pts in the Phase III SOLO2 trial (NCT01874353; Pujade-Lauraine *et alLancet Oncol* 2017). To investigate olaparib maintenance monotherapy in non-gBRCAm PSR OC pts who had received ≥2 prior lines of platinum-based chemotherapy (PBC), we performed the Phase IIIb, single-arm, OPINION study (NCT03402841). **Methods:** Pts had high-grade serous or endometrioid OC and were in complete response (CR) or partial response (PR) to PBC. Pts received maintenance olaparib (tablets; 300 mg bid) until disease progression or unacceptable toxicity. The primary endpoint was investigator-assessed PFS (modified RECIST v1.1). Secondary endpoints included PFS by homologous recombination deficiency (HRD) and somatic BRCA mutation (sBRCAm) status determined by central Myriad tumor and germline testing; and time to first subsequent treatment (TFST). The primary analysis was planned for 18 months (mo) after the last patient was enrolled. **Results:** 279 pts were enrolled from 17 countries (mean age: 64 years); 253 pts (90.7%) were confirmed non-gBRCAm. At data cut-off (Oct 2, 2020), median PFS was 9.2 mo (95% CI 7.6–10.9), with 210 PFS events (75.3% maturity). 65.3%, 38.5% and 24.3% of pts were progression-free (PF) at 6, 12 and 18 mo, respectively. The Table shows PFS in key subgroups. Median TFST was 13.9 mo (95% CI 11.5–16.4). Median exposure to olaparib was 9.4 mo (range 0.0–31.9). Grade ≥3 treatment-emergent adverse events (TEAEs) occurred in 29.0% of pts and serious TEAEs in 19.7% of pts. TEAEs led to dose interruption, dose reduction and treatment discontinuation in 47.0%, 22.6% and 7.5% of pts, respectively. **Conclusions:** Our findings support the use of olaparib maintenance therapy in non-gBRCAm PSR OC pts, consistent with our interim analysis and previous trials in this setting. Clinical trial information: NCT03402841. Research Sponsor: AstraZeneca and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	Subgroup	Events, n (%)	Median PFS, mo (95% CI)	PF at 18 mo, % (95% CI)
Myriad HRD/BRCAm status	HRD+ve* including sBRCAm, n=121	80 (66)	11.1 (9.2–14.6)	36.3 (27.6–45.1)
	HRD+ve excluding sBRCAm, n=94			
	sBRCAm, n=27			
	HRD-ve, n=115	67 (71	9.7 (8.1–13.6)	32.5 (23.1–42.3)
		13 (48)	16.4 (12.8–NE)	49.3 (28.9–66.7)
		96 (83)	7.3 (5.5–9.0)	11.3 (5.9–18.6)
Prior platinum regimens	2, n=165	127 (77)	9.2 (7.4–11.1)	23.7 (17.2–30.7)
	>2, n=114	83 (73)	9.0 (7.2–10.9)	25.3 (17.5–33.9)
Response to last PBC	CR/NED, n=92	60 (65)	13.7 (9.3–16.4)	36.3 (26.3–46.4)
	PR, n=184	147 (80)	7.4 (5.6–9.1)	18.7 (13.2–25.0)
Enrollment age	<65, n=132	100 (76)	9.2 (7.8–12.8)	26.2 (18.9–34.2)
	≥65, n=147	110 (75)	9.0 (7.2–10.8)	22.6 (15.9–30.1)

*Genomic instability score ≥42 NE, not evaluable; NED, no evidence of disease.

5546 **Poster Session**

Feasibility of an adapted schedule of carboplatin plus paclitaxel in elderly women with advanced ovarian cancer: A retrospective cohort.

First Author: Benjamin Nicaise, Department of Medical Oncology, European Georges-Pompidou Hospital, APHP. Centre, France; Paris University, Faculty of Medicine, Paris, France

Background: The EWOC-1 trial compared Carboplatin monotherapy (C mono) to two different Carboplatin + Paclitaxel (CP) regimens (weekly or 3-weekly) in vulnerable elderly patients treated for advanced ovarian cancers (OC). This study was closed prematurely because of a worse outcome in the C mono group. Both CP regimens were equivalent in terms of feasibility and efficacy with different toxicity profiles. Optimal CP regimen in elderly patient is still unknown. Here we propose a study of another adapted regimen of CP (aCP) performed in elderly patients in our institution. **Methods:** We retrospectively analyzed OC patients ≥ 70 years who received a Carboplatin AUC 4-5 d1q3week + Paclitaxel 80 mg/m^2 d1-d8 q3week regimen between 2015 and 2019. Primary endpoint was treatment feasibility according to the EWOC-1 standard: completion of 6 courses of chemotherapy without early stopping for disease progression, death or unacceptable toxicity (adverse event (AE) related to chemotherapy or treatment procedure leading either to early treatment stopping, to an unplanned hospital admission or to death or to a dose delay lasting more than 14 days or more than 2 dose reductions). **Results:** We identified 36 pts with a median age of 79 years (table). All patient but one had an ONCODAGE-G8 score ≤ 14, 30.6% of patients had a comorbidity Charlson's index > 4 and 52.5% had an albumin rate < 35 g/L. The feasibility endpoint was met in 58.3% of patients (IC95% = [25.6; 57.8]). Main causes of treatment failure (TF) were early discontinuation because of toxicity in 6 patients (16.7%) and progressive disease in 3 patients (8.33%). Median PFS was 35.3 months (IC95% = [22.7; NR]) and median OS was 62.1 months (IC95% = [31.4.0; NR]). The most frequent AE were asthenia (all grades = 94.4%, grade 3-4 = 13.9%), anemia (all grades = 94.4%, grade 3-4 = 27.8%), neutropenia (all grades = 66.7%, grade 3-4 = 38.9%) and neuropathy sensory (all grades = 61.1%, no grade 3-4). Non high-grade-serous histological type and a poor Charlson's score were associated with a higher rate of TF (100% and 63.6%, respectively). **Conclusions:** These results are consistent with the findings of the EWOC-1 trial in both CP regimens and suggest that aCP could be non-inferior with an acceptable toxicity profile. Further prospective and comparative studies are mandatory to confirm this trend and to better identify predictive factors of TF in OC elderly patients. Research Sponsor: None.

	N = 36 pts
Age, median [CI 95%]	
FIGO Stage, N (%)	79 [78; 80]
Recurrence	8 (22.2)
IIIA	4 (11.2)
IIIC	16 (44.4)
IV	12 (30)
Histologic type, N (%)	
High grade serous	30 (83.3)
Other	6 (16.7)
Post-operative residue, N (%)	
CCO	24 (66.7)
Non CCO	1 (2.8)
No surgery	11 (30.5)
ECOG PS, N (%)	
0	7 (19.4)
1	20 (55.6)
2	9 (22.5)
Comorbidity Charlson score, N (%)	
0-4	25 (69.4)
> 4	11 (30.6)
G8 ONCODAGE score	
> 14	1 (2.8)
≤ 14	25 (69.4)
missing	10 (27.8)
Cognitive or thymic impairment	
Yes	14 (39)
No	22 (61)
Lymphocytes (/mm^3)	
< 1000	8 (22.2)
> 1000	28 (77.8)

5547 **Poster Session**

Stage I Sertoli-Leydig cell tumors: An interim report from the International PPB/*DICER1* & OTST Registry.

First Author: Alexander Nelson, University of Minnesota Medical School, Minneapolis, MN

Background: Sertoli-Leydig cell tumors (SLCT) are rare ovarian sex cord-stromal tumors which occur primarily in adolescents and young adults and are associated with *DICER1* pathogenic variants. **Methods:** Informed consent for participation in the International PPB/*DICER1* or OTST Registry was obtained. When available, pathology was centrally reviewed. Staging was evaluated by Registry review using the International Federation of Gynecology and Obstetrics (FIGO) classification system. **Results:** Eighty-three patients with stage I SLCT were enrolled. Median age at diagnosis was 15 (range 1-60) years. Most (57/83) patients had germline *DICER1* testing; 35/57 (61%) had germline pathogenic variants. Fifty-six patients had Ia and 27 had Ic SLCT. The distribution of patients receiving chemo based on histology and stage is displayed in Table. One patient with poorly differentiated stage Ia SLCT with sarcomatous elements and no chemo at diagnosis recurred 6 months after surgery and died of disease. Three patients with local diagnosis of stage Ia SLCT, with data unavailable for Registry confirmation of stage, developed a subsequent SLCT 33 to 74 months after diagnosis; of these, 2 died, and 1 remains in treatment for recurrence. Available records and molecular testing in these 3 cases have not provided a distinction between recurrent and metachronous disease. Excluding the latter 3 patients, 3-year overall survival was 97.3% for stage Ia SLCT. Six patients with stage Ic SLCT recurred (Stage Ic1=5 and Stage Ic2=1) with a median time to recurrence of 25 (range 3-53) months. In stage Ic1, 18% (2/11) recurred after upfront chemo compared to 33% (3/9) after surgery alone. Of the 5 patients with stage Ic1 disease that recurred, 4 had intermediate and 1 had poorly differentiated SLCT. One patient had sarcomatous elements and 2 received upfront chemo. Two of the 5 patients are alive, neither received upfront chemo. One patient with poorly differentiated stage Ic2 SLCT with sarcomatous elements and no upfront chemo recurred and died of disease. Three-year event free and overall survival were 86.9 and 88.6% for stage Ic SLCT. Four patients had metachronous SLCT in the contralateral ovary confirmed by clinical review or somatic testing at a median time from diagnosis of 33 (range 28-104) months. All 4 have germline pathogenic variants and no evidence of disease at last follow-up. **Conclusions:** Individuals with early stage SLCT generally fare well, however, ongoing surveillance for recurrence and metachronous disease is indicated. Novel therapies are needed to address recurrent SLCT. Research Sponsor: Pine Tree Apple Tennis Classic Fund and Children's Internal Research Funding.

Patients receiving chemo based on stage and differentiation.

Stage (#)	# Chemo/ # Well Diff (%)	# Chemo/ # Intermediate Diff (%)	# Chemo/ # Poorly Diff (%)	# Chemo/ # No Mention of Diff (%)
Ia (56)	0/3 (0%)	6/39 (15%)	6/12 (50%)	0/2 (0%)
Ic1 (20)	0/1 (0%)	8/14 (57%)	2/3 (66%)	1/2 (50%)
Ic2 (5)	-	3/3 (100%)	0/2 (0%)	-
Ic3 (1)	-	-	1/1 (100%)	-
Ic NOS (1)	-	1/1 (100%)	-	-

5548 **Poster Session**

Circulating tumor DNA as a noninvasive marker of resectability in ovarian carcinomas. *First Author: Roxane Mari, Department of Medical Oncology, Institut Paoli Calmettes, Marseille, France*

Background: Ovarian cancer is the leading cause of death by gynecological cancer. Complete surgery remains one of the main prognostic factors. Laparoscopic exploration is mandatory to assess surgical resectability at diagnosis or after neoadjuvant chemotherapy. However, there is no clinical or biological marker that can correctly predict resectability and may be able to avoid a second laparoscopic exploration for initially unresectable diseases. Our aim was to assess circulating tumor DNA (ctDNA) value as a predictive non-invasive marker of evolution towards resectability for patients with epithelial ovarian cancer receiving first-line chemotherapy. **Methods:** We explored in this work one of the secondary objectives of the CIDOC study (NCT03302884). CIDOC is a multicenter prospective study aiming to explore ctDNA value as early marker of disease relapse after first-line treatment for epithelial ovarian cancer. Patients with mucinous histology or early stages not requiring chemotherapy are excluded. Plasma samples are collected at diagnosis, during neoadjuvant chemotherapy, and during follow-up. After DNA extraction, panel-based next generation sequencing is performed on both tumor samples and germline DNA, and somatic mutations of interest are selected for ctDNA monitoring. ctDNA analyses are conducted using droplet digital PCR (BioRad QX200) by measuring the variant allele fraction (VAF) of previously identified mutations. **Results:** This intermediary analysis has included 47 patients diagnosed between March 2017 and December 2019. Median age was 69 years old (48 – 84). Most of the patients had advanced disease (89.4% stage FIGO III or IV), serous histology (94.8%), and high grade tumor (92.3%). Most of the patients underwent complete interval cytoreductive surgery (76.3% vs 17.4% complete upfront surgery). Most of the tumors had *TP53* mutations (85.1%), following by alterations involving DNA repair genes (38.3%). Median cell-free DNA concentration at baseline was 0.38 ng/µL (0 – 12.8). ctDNA was identified in 92.1% of patients at baseline with a median VAF of 1.84% (0 – 42.52%). ctDNA VAF was correlated to the peritoneal dissemination (p= 0.039) assessed with the peritoneal cancer index. ctDNA clearance after preoperative chemotherapy tended to be correlated to achievement of complete interval surgery for patients receiving neoadjuvant chemotherapy (p= 0.108). **Conclusions:** ctDNA may be a promising non-invasive marker to assess peritoneal cancer spreading and to predict surgical resectability after neoadjuvant chemotherapy. If confirmed in larger populations, this may enable to avoid additional surgical explorations for patients who remain ctDNA positive after chemotherapy. Clinical trial information: NCT03302884. Research Sponsor: AstraZeneca.

5549 **Poster Session**

Health-related quality of life (QoL) in platinum-resistant ovarian cancer patients treated with olaparib and pegylated liposomal doxorubicin (PLD), a multicenter single-arm phase II clinical trial (ROLANDO, GEICO-1601). *First Author: José Alejandro Perez-Fidalgo, Department of Medical Oncology, Hospital Clínico Universitario de Valencia, Valencia, Spain*

Background: The prognosis for patients with platinum-resistant/refractory ovarian cancer (PROC) is poor, and the aim of treatment is focused primarily on symptom control and maintenance of QoL. The objective of this study was to assess the impact on QoL of the combination of pegylated liposomal doxorubicin (PLD) with olaparib (OLA) in PROC patients (pts). **Methods:** ROLANDO is a single arm phase II trial that enrolled pts with high-grade serous or endometrioid and at least one previous PROC recurrence (between 28 days - 6 months after last platinum). Up to 4 previous lines (up to 5 in *BRCA*-mut) were allowed. Pts received 6 cycles of PLD 40 mg/m2 intravenously every 28 days + OLA 300 mg b.i.d. followed by OLA 300 mg b.i.d. monotherapy until progression or unacceptable toxicity. QoL was measured by European Organization for Research and Treatment of Cancer QLQ C30 questionnaire evaluating functional status, and symptom intensity and QLQ OV-28 ovarian cancer specific module, both filled out by pts every 4 months (mo) regardless of disease progression. Questionnaire compliance was reported as percentage of the initial number of pts. Changes between baseline and subsequent visits (Wilcoxon rank test) were evaluated. P values < 0.05 were considered significant. **Results:** From 2017 to 2020, 31 pts were recruited. Median age was 57 y.o., ECOG 0/1: 32.3%/67.7%. Median of prior lines was 2 (range 1-5) and pts were on study treatment for a median of 5 mo (range 1.4-19.5) for OLA and 5 cycles (range 2 - 6) for PLD. QoL information was available at baseline for 30 (97%) pts and decayed to 22 (71%), 13 (42%), 6 (19%) and 4 (13%) pts at 4, 8, 12, and 16 mo respectively. Global health status measured by QLQ C30 and QLQ OV-28 scores was maintained throughout all time points with no significant differences. Significant transient improvement was seen in social functioning after 12 mo ($p = 0.013$). Nausea-vomiting ($p = 0.02$), hair loss ($p = 0.012$) and constipation ($p = 0.037$) showed a significant increase at 4 mo overlapping with PLD administration, and returned to baseline levels afterwards. This was in line with the reported adverse reactions frequency of nausea (58.1%) and vomiting (45.2%). Dyspnea showed a transient significant increase at 12 mo ($p = 0.012$), whereas insomnia ($p = 0.038$) and attitude towards disease ($p = 0.007$) improved at 16 mo. Symptoms such as appetite and constipation did not change after 12 mo. Most functional scales (physical, role, emotional, cognitive, body, sexuality) and symptom scales (fatigue, pain, appetite loss, diarrhoea, neurologic, hormonal and economic burden) had no statistically significant changes. **Conclusions:** Pts treated with OLA+PLD combination reported no signs of clinically relevant deterioration of QoL while on treatment. All QoL items changes were transient in no more than 1 time-point. Clinical trial information: NCT03161132. Research Sponsor: AstraZeneca.

5550 **Poster Session**

Phase 1 dose-escalation study of STRO-002, an antifolate receptor alpha (FRα) antibody drug conjugate (ADC), in patients with advanced, progressive platinum-resistant/refractory epithelial ovarian cancer (EOC). *First Author: R. Wendel Naumann, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: STRO-002-GM1 is a Phase 1, open-label study in patients (pts) with advanced, platinum resistant or refractory EOC. STRO-002 is a novel FRα-targeting ADC with a precise DAR of 4 using site-specific conjugation technology to circumvent limitations of current ADCs. STRO-002 induces immunogenic cell death and contains the tubulin-targeting 3-aminophenyl hemiasterlin warhead SC209, a potent cytotoxin that is a weak substrate for P-gp. **Methods:** STRO-002 is given IV on Day 1 of each 21-day cycle until disease progression. Ocular exams are performed at baseline and every other cycle. Prophylactic corticosteroid eyedrops are not administered. FRα expression was not required for eligibility and retrospective analysis of FRα expression in archival tumor tissue is ongoing. **Results:** Enrollment has been completed with 39 pts treated at 9 dose levels (0.5 to 6.4 mg/kg). Data cut-off is Jan 30, 2021. Median age was 61 years (range 48-79). Median number of prior systemic therapies was 6 (range 2-11). 86% of treatment emergent adverse events (AEs) were Grade 1-2. The most common treatment related Grade 3 and 4 AEs were reversible neutrophil count decreased (36%) and neutropenia (33%), Grade 3 arthralgia (12.8%) and neuropathy (7.7%). Two pts developed neutropenic fever that resolved with antibiotic therapy. 34 pts were treated at clinically active doses ($\geq$ 2.9 mg/kg) and 31/34 are evaluable for RECIST 1.1 response. Objective responses were seen in 10/31 pts - 1 CR, 4 confirmed PR, and 5 unconfirmed PR (imaging studies under review in 1 pt with uPR). Disease control rate (CR+PR+SD) is 74% at $\geq$ 12 weeks and 61% at $\geq$ 16 weeks. 5 pts remain on treatment with 3 ongoing at $>$ 74 weeks. FRα-expression results are available in 14 pts treated at $\geq$ 2.9 mg/kg with 50% low, 21% medium and 29% high FRα-expressing tumors per PS2+ scoring algorithm. 12/13 pts with H-scores of $\geq$ 105 achieved disease control with PR or SD. Maximum plasma concentrations of STRO-002 were achieved at the end of the 1 hour infusion and exposure increased in an apparent dose proportionate/linear manner. **Conclusions:** STRO-002 is a novel FRα-targeting ADC with an encouraging emerging safety and efficacy profile in heavily pretreated relapsed/refractory EOC. No ocular toxicity signals have been observed. Durable responses and anti-tumor activity have been demonstrated across a broad range of FRα expression levels in evaluable pts treated at $\geq$ 2.9 mg/kg. 48% (15/31) of pts were on treatment without disease progression for $\geq$ 24 weeks and 13% (4/31) remain on treatment for over a year, suggesting that STRO-002 is well tolerated in long-term responding patients. A randomized expansion cohort comparing STRO-002 at 4.3 mg/kg vs 5.2 mg/kg dose levels in less heavily pretreated EOC pts is ongoing. Clinical trial information: NCT03748186. Research Sponsor: Sutro Biopharma.

5551 **Poster Session**

Serum-based assay for adnexal mass risk of ovarian malignancy. *First Author: Daniel Ure, Aspira Women's Health, Trumbull, CT*

Background: A Deep learning neural network was developed to assess ovarian cancer risk in women presenting with adnexal mass into risk categories. The algorithm shows potential to improve on the performance of CA-125 as the standard biomarker to monitor women as a clinical management metric to trace increased risk of malignancy. **Methods:** Serum specimens from an enriched biobank (N = 2688) were collected during previous clinical studies from women presenting with an adnexal mass at risk of ovarian cancer. Protein biomarker data from these specimens were used to develop a novel neural network for binary stratification of ovarian cancer risk assessment. These specimens were divided between training and testing data sets using 5-fold cross validation during training. A randomized, separate sample set was withheld from use in training and testing the algorithm for independent validation purposes. As algorithm inputs seven biomarkers are used in the network: cancer antigen 125, human epididymis protein, beta-2 microglobulin, apolipoprotein A-1, transferrin, transthyretin, and follicle stimulating hormone. In addition to these biomarkers, the patient's age and menopausal status are used. Menopause was defined as the absence of menses for $\geq$12 months. The algorithm uses supervised learning with known histopathology diagnoses as the labels for training. The algorithm is a classification deep feedforward neural network. The neural network is regularized using node dropout to reduce overfitting. The final layer of the neural network has two nodes and uses the softmax function to assign a binary classification of low or high-risk of malignancy. **Results:** Algorithm performance metrics are also shown comparing predicted results from the algorithm to the known malignancy diagnoses. The performance metrics are also compared below to the standard of care biomarker test, cancer antigen 125 (CA125), reporting increased sensitivity by 26.1%, and failure to reject the null hypothesis of equivalent specificity. **Conclusions:** The algorithm detected 91% of malignancies in the independent validation data. This high sensitivity in malignancy detection paired with the failure to reject the null hypothesis of equivalent specificity (Pearson's chi-squared test p-value of 0.281) and negative predictive value (NPV) suggest the algorithm could be used two-fold. First, surgical referral to gynecological oncologists for women classified in the high-risk cohort. The second as a goal with future clinical validation, is that women with a low risk of malignancy might be able to delay surgery and enter into a serial monitoring clinical management care pathway. Research Sponsor: None.

	Neural Network	CA125
Malignancy detection rate	21/23 (91.3%)	15/23 (65.2%)
Count of malignancies not detected	2	4
Count of false positives	64	52
Positive predictive value	21/84 (25.0%)	15/67 (22.4%)
Specificity	509/573 (89.0%)	521/573 (90.9%)
Negative predictive value	509/511 (99.6%)	521/529 (98.5%)

5552 **Poster Session**

Disparities in ovarian cancer treatment and overall survival according to race: An update. *First Author: Deanna Huffman, Allegheny Health Network, Pittsburgh, PA*

Background: It has long been identified that black women with ovarian cancer have worse overall survival when compared to white women. Disparities in the adherence to NCCN guideline-directed treatment and socioeconomic characteristics may be responsible for the differences in these outcomes. **Methods:** A retrospective review of National Cancer Database (NCDB) was performed to identify patients diagnosed with ovarian cancer from 2012-2016. We defined adherence to NCCN (National Comprehensive Cancer Network) guidelines as having stage and year-appropriate chemotherapy and surgery. Differences in guideline adherence, socioeconomic characteristics and survival outcomes were assessed. **Results:** In total, 32,163 were identified meeting the study criteria; 27,744 identified their race as "white" and 2,204 identified their race as "black". Characteristics associated with higher likelihood of black race were advanced stage of disease- stage III (OR = 1.1869, CI = 1.03-1.37) or stage IV disease (OR = 1.4495, CI = 1.23-1.70) and treatment in a comprehensive (OR = 1.5757, CI = 1.16-2.15) or academic (OR = 2.3023, CI = 1.70-3.12) treatment facility. Variables associated with a lower likelihood of black race were higher education level (OR for high school degree $<$ 6.5 % = 0.2501, CI = 0.21-0.30) and higher median household income (OR for income $>$ $63,333 = 0.4218, CI = 0.36-0.49). Whether the care received was adherent to NCCN guidelines did not seem to be associated with black race (OR for adherence = 1.0021, CI = 0.89-1.13). 5-year overall survival for patients who received adherent care was 58% for white patients vs. 49% for black patients. Among those who didn't receive adherent care, the outcomes were 49% among white patients vs. 38% among black patients. **Conclusions:** Overall survival remains worse for black patients, regardless of whether their care adhered to NCCN guidelines as defined by our study. This suggests that while receipt of care that is not adherent to NCCN guidelines seems to be negatively associated with overall survival, we must consider and evaluate other socioeconomic, environmental and system factors that are contributing to this continued survival discrepancy in women being treated for ovarian cancer. Research Sponsor: None.

5553 **Poster Session**

Next generation sequencing in ovarian cancer patients: Does personalized medicine improve oncological outcomes? *First Author: Tamar Safra, Sackler Faculty of Medicine, Tel Aviv, Israel*

Background: Ovarian cancer (OC) is the second most common gynecologic malignancy and the most common cause of gynecologic cancer mortality in the United States. Homologous recombination deficiency (HRD), including the *BRCA* mutations, are found in 50% of OC tumors. Next generation sequencing (NGS) provides understanding the underlying molecular and genetic patterns to improve OC treatment. This study examines the prognostic and predictive biomarkers identified with NGS in hopes to improve OC patients outcomes. **Methods:** The patient cohort included 890 consecutive OC patients treated between 2002 and 2020,at the Tel-Aviv Medical Center. We retrospectively evaluated patients with histopathologically confirmed OC. Cox models were used to analyze the clinical impact of various mutations and biomarkers among OC patients with and without FoundationOne CDx NGS testing, by assessing overall survival (OS), progression free survival (PFS), and physicians' timing preferences for referral to NGS testing. **Results:** Among the 890 OC patients, 103 (11.57%) completed NGS molecular testing. The median OS among patients with and without NGS testing, adjusted for age, stage and recurrence status, was 73.36 and 68.50 months, respectively (P = .02). The median PFS was 17.23 and 17.43 months, respectively (P = .77). We also evaluated physicians' preferences regarding timing of molecular profiling, upon diagnosis, after first recurrence and at advanced line of treatment in 31.95%, 36.08% and 26.8% of practitioners, respectively. Of the patients who completed NGS, 48 (52.75%) harbored actionable mutations, and 21 patients (43.75%) received matched targeted therapy. Forty-five patients were microsatellite stable (MSS) (45%), 55 with undetermined status (55%) and 0 patients with MSI-H. Forty-one (71.93%) patients had low ($<$ 5) tumor mutation burden status (TMB), 16 (28.07%) intermediate (5-15) and none with high ($>$ 15) TMB. There was no noticeable survival difference when comparing low with intermediate TMB (P = 0.3). Loss of heterozygosity (LOH) was a significant prognostic biomarker. Patients with high LOH (hLOH $>$ = 16%) had longer OS compared to low LOH (ILOH $<$ 16%), 99.02 vs. 50.23 months, respectively (P $<$ .005). Patients with hLOH and BRCA mutations (BRCA+) had longer OS compared to hLOH/BRCA WT (BRCA-), ILOH/BRCA+, and ILOH/BRCA-, with an unreached median OS of 91.5 vs. 60.48 vs. 45.21 months, respectively (P = .005). **Conclusions:** Our work demonstrates the clinical benefit of NGS personalized medicine as a cornerstone of future treatment strategies in OC. Our study suggests an OS benefit among the NGS tested cohort. We identified LOH as a prognostic biomarker. Prospective studies evaluating larger cohorts are necessary to generate a more extensive evaluation of additional prognostic and predictive biomarkers among OC patients. Research Sponsor: None.

5554 **Poster Session**

Symptom identification and management in epithelial ovarian cancer. *First Author: Ashley Deanelle Hickman, Mayo Clinic Department of Internal Medicine, Rochester, MN*

Background: A better understanding regarding the burden of treatment side effects in patients with gynecological malignancies could help guide symptom interventions and oncologic therapy decision-making. We aim to inform understanding of symptom burden in epithelial ovarian cancer (EOC) by analyzing patient-reported symptom data from patients treated for this condition over a 16-month period. **Methods:** Patients receiving medical oncology care at Mayo Clinic Rochester and at Midwest Mayo Clinic Health System community sites have received symptom-focused surveys prior to each medical oncology visit since March 28, 2019 through the Enhanced Electronic Health Record Facilitated Cancer Symptom Control Study (E2C2). These surveys, administered either through the electronic medical record portal or on a clinic tablet prior to each oncology office visit, no more frequently than every 2 weeks, include six linear analogue scales measuring sleep disturbance, pain, anxiety, emotional distress, and fatigue (SPADE), as well as physical dysfunction on a scale of 0 (none) to 10 (as bad as you can imagine). Scores of 0-3 were considered mild symptoms, 4-6 moderate symptoms, and 7-10 severe symptoms. We collected survey results from March 28, 2019 to July 20, 2020 for patients with EOC and reviewed the number of surveys per patient in addition to the average symptom scores. **Results:** From March 2019 to July 2020, for patients with EOC, there were 2974 encounter-based surveys from 762 patients. The number of surveys completed by each patient ranged from 1-20. The following number of patients returned the correlating number of surveys: 1 survey:240 patients; 2 surveys:145; 3 surveys:79; 4 surveys:56; 5 surveys:58; 6 surveys:45; 7 surveys:38; 8 surveys:27; 9 surveys:22; ≥10 surveys:52. The average score from all surveys for each symptom was: 2.41 for sleep disturbance, 2.03 for pain, 2.32 for anxiety, 1.97 for emotional distress, 3.26 for fatigue, and 2.50 for physical dysfunction. Please see the table for the proportion of surveys that reported symptoms as mild, moderate, or severe. **Conclusions:** Fatigue and physical dysfunction were reported most frequently in patients with EOC, while emotional distress and pain were reported least frequently. 20% of surveys reported moderate to severe emotional distress, while 40% reported moderate to severe fatigue. A targeted approach to symptom management is needed for patients undergoing EOC evaluation and treatment. Our next steps in this analysis include an assessment of potential predictors of greater symptom burden (e.g., specific treatments, age, and other clinical and sociodemographic characteristics). Clinical trial information: NCT03892967. Research Sponsor: U.S. National Institutes of Health.

	Sleep Disturbance	Pain	Anxiety	Emotional Distress	Fatigue	Physical Dysfunction
Mild (0-3)	71.8%	77.9%	74.9%	79.6%	60.0%	69.4%
Moderate (4-6)	20.5%	16.3%	18.7%	15.5%	27.8%	22.7%
Severe (7-10)	7.7%	5.8%	6.4%	4.9%	12.2%	7.9%

5555 **Poster Session**

Association of the Khorana Score with development of venous thromboembolism in ovarian cancer. *First Author: Ellen Marcus, Albert Einstein College of Medicine and Montefiore Medical Center Department of Obstetrics, Gynecology & Women's Health, Bronx, NY*

Background: The Khorana score is a previously validated method to identify patients at high risk of VTE during chemotherapy who would potentially benefit from thromboprophylaxis. The objectives of our study were to evaluate risk factors and timing associated with VTE in a large cohort of ovarian cancer patients and to assess the predictive ability of the Khorana score in this population. **Methods:** After IRB approval, a retrospective analysis was performed of all patients with ovarian cancer in the Albert Einstein Tumor Registry who received treatment between 2000 and 2020. Demographic, clinical, surgical and histologic data and information regarding timing of VTE were abstracted from the medical record. Khorana scores were retrospectively calculated for all patients who received chemotherapy based on their pre-chemotherapy laboratory indices. Bivariate analysis and multivariable logistic regression were used to examine the association between Khorana score and VTE. **Results:** A total of 472 patients were included over a median follow-up time of 33.7 (13.3, 61.1) months of whom 142 (31%) underwent diagnostic imaging to rule out VTE. A total of 62 patients (15%) were diagnosed with VTE with a median time from presentation to VTE of 8.7 (2.7, 30.3) months. Individual covariates which were significantly associated with VTE included stage III-IV disease, epithelial histology, open surgery, radical tumor debulking, and presence of residual disease after surgery. Of the 254 patients who received chemotherapy for their disease, 36 (14%) developed VTE within 3 weeks of receiving chemotherapy. Patients with Khorana scores of 2 (OR 1.73 95% CI 0.88-3.42) or 3 (OR 0.89 95% CI 0.33-2.44) were not significantly more likely to develop VTE during chemotherapy compared to patients with a score of 1. However, patients with a score of 4 were 6.74 times more likely to develop a VTE during chemotherapy (95% CI 1.39 - 32.73). Overall, a Khorana score of 2 or higher conferred no significant increased risk of developing VTE during chemotherapy than a score of 1 (OR 1.61 95% CI 0.85- 3.02). In a multivariable model, the Khorana score was not significantly associated with risk of VTE and a Khorana score of 2 or higher could explain only 0.86% of the variability in predicting VTE. The only variables significantly associated with VTE after adjustment were stage III-IV disease and hyperlipidemia. **Conclusions:** Patients with ovarian cancer are at high risk of developing VTE many months after diagnosis and initiation of chemotherapy. Current ASCO and SGO guidelines recommend thromboprophylaxis for those initiating chemotherapy with a Khorana score of 2 or higher, however our study found that these patients are not at increased risk compared to those with a score of 1. Future models should be developed and validated in large population-based cohorts to determine if there is a more accurate strategy to identify women with ovarian cancer who are at risk for VTE. Research Sponsor: None.

5556 **Poster Session**

Does aggressive surgery only benefit patients with less advanced ovarian cancer? *First Author: Shinichi Tate, Departments of Reproductive Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan*

Background: The recent SCORPION trial showed that aggressive primary debulking surgery (PDS) did not improve survival outcomes in patients with advanced ovarian cancer and was associated with a high incidence of perioperative morbidity. We compared survival outcomes and morbidity between patients who underwent highly aggressive and less aggressive surgery at our hospital; patients with high tumor loads were treated with neoadjuvant chemotherapy (NACT), followed by aggressive surgery. **Methods:** This retrospective study included 209 patients with a surgical complexity score (SCS) ≥8, who underwent aggressive surgery between January 2008 and December 2018. PDS, followed by chemotherapy was performed in this study, and NACT followed by interval debulking surgery (IDS) was performed in patients with excessively high tumor loads, a poor general condition, or unresectable lesions in whom PDS was contraindicated. Based on the median SCS, patients were categorized into highly aggressive surgery and less aggressive surgery groups, and we performed an intergroup comparison of progression-free survival (PFS), overall survival (OS), and perioperative morbidity. **Results:** The median SCS was 13 in all cohorts. The less aggressive surgery group (SCS $<$ 13) and the highly aggressive surgery group (SCS≥13) included 83 and 126 patients, respectively. The peritoneal cancer index in the highly aggressive surgery group was higher than that in the less aggressive surgery group (20 vs. 9). Notably, 52 patients (63%) underwent PDS in the less aggressive surgery group, and 104 patients (83%) underwent IDS after NACT in the highly aggressive surgery group. No intergroup difference was observed in patients without any residual disease (less aggressive surgery group: 74 patients [89%] vs. highly aggressive surgery group: 118 patients [94%], p = 0.245). The median PFS in the less- and highly aggressive surgery groups was 32 months (95% confidence interval [CI] 24–45) and 31 months (95% CI 27–34) (log-rank test, p = 0.622; Wilcoxon test, p = 0.926), respectively. The median OS in the less- and highly aggressive surgery groups was 99 months (95% CI 59–not reached) and 75 months (95% CI 56–106) (log-rank test, p = 0.390; Wilcoxon test, p = 0.799), respectively. Severe perioperative complications (Clavien-Dindo grade ≥IIIb) occurred in 4 patients (4.8%) and 8 patients (6.4%) in the less- and highly aggressive surgery groups, respectively (p = 0.767). **Conclusions:** Aggressive surgery benefits both patients with less advanced and advanced ovarian cancer. Selection of the optimal timing of debulking surgery may lead to better survival outcomes without an increase in perioperative morbidity in patients with high tumor loads, who undergo highly aggressive surgery. Research Sponsor: None.

5557 **Poster Session**

Anlotinib in combination with TQB2450 in patients with recurrent ovarian cancer (ACTION): A multicenter, single-arm, open-label, phase Ib trial. *First Author: Chunyan Lan, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Combination of antiangiogenic therapy and immune checkpoint inhibitor therapy is reported as an effective antitumor strategy. TQB2450 is a humanized IgG1 monoclonal antibody against programmed death-ligand 1 (PD-L1). We aimed to assess the activity and safety of TQB2450 plus the antiangiogenic multi-target tyrosine kinase inhibitor anlotinib in patients with recurrent advanced ovarian cancer. **Methods:** The study with ClinicalTrials.gov identifier NCT04236362 is an open-label, multicohort, and multicenter phase Ib trial evaluating the efficacy and safety of anlotinib combined with TQB2450 in patients with advanced gynecologic cancer. The present study (ACTION study) reports the ovarian cancer cohort. We enrolled patients aged 18–70 years with platinum-resistant or platinum-refractory epithelial ovarian cancer, fallopian tube cancer, or primary peritoneal cancer, an Eastern Cooperative Oncology Group performance status of 0 or 1, and measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST). Eligible patients received anlotinib 12 mg per day orally on days 1 to 14 and TQB2450 1200 mg intravenously on day 1, every three weeks. Treatment continued until disease progression, unacceptable toxicity, and withdrawal of consent. The primary endpoint was objective response rate (ORR) assessed by investigators according to RECIST version 1.1. Secondary endpoints included progression-free survival (PFS), duration of response (DOR), overall survival (OS) and safety. **Results:** Between 21 Feb 2020 and 15 Jan 2021, 33 patients with a median age of 55 years (range, 26-71) were enrolled and received study treatment. Patients had received at least once platinum-based chemotherapy, and the median number of previous chemotherapy lines was 3 (range, 1–6). 30.3% patients had bevacizumab therapy before enrollment. At data cutoff (15 Jan 2021), the median follow-up was 5.1 months (range, 0.1–10.8). In the 25 efficacy-evaluable patients, 13 of them achieved partial response, yielding the ORR of 52.0% (95% CI, 30.4%–71.6%). The median PFS was 6.7 months (95% CI, 4.5 months to not reached). The median duration of response and the median OS were not reached. The treatment-related grade 3 or 4 adverse events (AEs) occurred in 54.5% patients, and the most common ones were palmar-plantar erythrodysesthesia syndrome (21.2%) and hypertension (18.2%). The most potential immune-related AEs included grade 1 to 2 hypothyroidism (24.2%) and fatigue (9.1%). No treatment-related death was recorded. **Conclusions:** Anlotinib plus TQB2450 showed encouraging antitumor activity and tolerable toxicity in patients with recurrent advanced ovarian cancer. Clinical trial information: NCT04236362. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

5558 **Poster Session**

Improving the prediction of surgical outcome at secondary cytoreduction in patients with ovarian cancer: Results from retrospective part of HELP-ER study NOGGO TR2/ENGOT OV47-TR. *First Author: Ioana Braicu, North-Eastern German Society of Gynecological Oncology (NOGGO) and Department of Gynecology with Center for Oncological Surgery, Charité–University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany*

Background: Complete resection at secondary cytoreductive surgery is associated with prolonged progression free and overall survival for patients with relapsed ovarian cancer. Secondary cytoreductive surgery has no impact on survival rates, if macroscopically tumor clearance cannot be achieved. Therefore, in order to avoid unnecessary perioperative morbidity and mortality, selection of patients who will undergo secondary tumor debulking is crucial. This study aims to improve upon the contemporary Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) score by including additional clinical variables like circulating HE4 and CA125 levels to predict surgical outcome at secondary cytoreduction. **Methods:** A total of 90 patients underwent secondary cytoreductive surgery and were retrospectively assigned a positive AGO score. Of those patients, 62 (68.9%) achieved optimal surgical outcome at secondary debulking with 28 (31.1%) patients retaining residual tumor mass ($>$ 0mm). Utilizing clinical variables including circulating HE4 and CA125 levels, we implemented a machine learning workflow to predict suboptimal surgical outcome in patients despite a positive AGO score. **Results:** We elucidated significantly lower levels of circulating HE4 (p = 0.0038) in patients with optimal surgical outcome compared to patients that retain macroscopic residual tumor at secondary cytoreductive surgery. Moreover, machine learning algorithms trained on clinical variables (e.g. serum HE4 level, serum CA125 level, age, Risk of Ovarian Malignancy Algorithmus (ROMA) score and occurrence of peritoneal carcinomatosis) achieved a mean area under the curve (AUC) of 78.4% based on 100 consecutive executions with randomized training and test sets. **Conclusions:** The application of machine learning allows to further improve the prediction of patients with high likelihood of achieving optimal surgical outcome at secondary cytoreduction. In turn, it might identify patients that would benefit from amplified treatment efforts. However, machine learning relies on large amounts of data to account for biological and clinical variation and produce predictions of sufficient/adequate quality. Given this limitation, we would validate this data within the prospective multicentric cohort of patients collected within NOGGO/ENGOT HELP_ER Trial. Research Sponsor: Roche Diagnostics.

5560 **Poster Session**

Real-life data of niraparib maintenance treatment in patients with recurrent platinum-sensitive ovarian cancer. *First Author: Bente Vilming, Oslo University Hospital, Oslo, Norway*

Background: PARP (poly adenosine diphosphate [ADP]–ribose polymerase) inhibitors are the new standard for maintenance treatment in platinum sensitive recurrent ovarian cancer (PSROC), independent of germline (g-BRCA) or somatic *BRCA* mutation status. Real-life data after the introduction of new anti-neoplastic agents are needed to evaluate whether the benefit observed in phase III trials can be translated into clinical practice. The aim of this study was to provide real-life data on efficacy and safety of niraparib in non-gBRCA PSROC. **Methods:** This retrospective multi-center cohort study included patients with PSROC who were enrolled in a national individual patient access program in Norway. Efficacy and safety data were collected from the patients´electronic medical records. The primary outcome was time from start of niraparib treatment to first subsequent treatment (TFST). Secondary endpoints included prevalence of dose interruption and -reduction, as well as adverse events. **Results:** The study included 106 patients with median age of 64 years (range 38-81). After median follow up of 15.3 months (95% CI 12.1-18.5), 71 patients (67%) had progressed, 64 (60%) had started a new line of treatment, and 25 (24%) had died. 25 (24%) patients were still receiving niraparib. Median duration of niraparib treatment was 7.6 months (0.4 to 27.3 months). Median TFST was 11.7 months (95% CI 9.2 -14.2). Patients with elevated CA125 after chemotherapy prior to start of niraparib had shorter progression-free survival (PFS) compared to patients with complete serological response (6.5 months (95% CI 5.7 – 7.3) vs 12 months (95% CI 6.2 – 17.9, ($p < 0.001$)). Grade 3-4 hematologic and non-hematologic events occurred in 25% and 17% of the patients, respectively. The most common grade 3/4 hematologic events were anemia (15%), thrombocytopenia (11%) and neutropenia (8%). Adverse events led to dose interruption in 38% and dose reduction in 44% of the patients. Patients with individualized dosing based on baseline weight and platelet counts had fewer dose reductions ($p < 0.001$) and -interruptions (p = 0.042) than patients whose dose was not adjusted to those baseline values. **Conclusions:** In a real-life setting, niraparib maintenance treatment in patients with non-gBRCA PSROC showed efficacy comparable with the published phase III data and an acceptable safety profile. Individualized dosing at start of treatment minimized adverse events. The prolonged PFS in patients with CA125 normalization after last chemotherapy, suggests that these patients in particular benefit from maintenance treatment but warrants confirmation in a larger sample. Research Sponsor: GSK.

Characteristics		(n, %)
gBRCA status	Non-mutated	96 (91%)
Previous lines of chemotherapy	2	73 (69%)
	≥3	33 (31%)
Response of chemotherapy preceding niraparib[2]	CR	14 (13%)
	PR	80 (75%)
	SD	7 (7%)
	Non-evaluable[3]	5 (5%)
CA125 level prior to start of niraparib	≤35 kU/L	63 (59%)
	> 35 kU/L	43 (41%)

5561 **Poster Session**

Role of CD10 expression in endometriosis-associated mesenchymal stem cells on the progression of endometriosis-associated carcinoma. *First Author: Huda Atiya, University of Pittsburgh, Pittsburgh, PA*

Background: Endometriosis-associated carcinomas (EACs) such as ovarian clear cell cancer (OCCC) are rare, aggressive, chemo-resistant malignancies. While endometriosis is a known chronic inflammatory condition, the molecular mechanisms for the malignant transformation of endometriosis is unknown. Mesenchymal stem cells (MSC) are a critical component of the ovarian cancer microenvironment. Cancer cells reprogram MSCs to form carcinoma-associated MSCs (CAMSCs), which promote cancer growth, chemotherapy resistance, and metastases. MSCs are also found within the endometriotic microenvironment. CD10, a surface protein expressed by endometrial stromal cells, is also expressed on endometriosis-associated MSCs (enMSCs). Preliminary data demonstrate CD10 expression is lost in a subset of enMSCs and this loss is correlated with the acquisition of tumor-promoting properties. We hypothesized that the CD10 negative subset of enMSCs behave similarly to CAMSCs and support the growth of OCCC. **Methods:** EnMSCs were isolated from primary human benign endometriosis deposits involving the ovary or fallopian tubes. Flow cytometry was used to measure surface CD10 expression. We investigated the role of low CD10 enMSCs versus high CD10 enMSCs on OCCC tumor cell growth, chemotherapy resistance and stem-like cell properties in vitro and tumor cell engraftment, growth, and metastases in vivo. Luciferase-expressing OCCC cells were (1) used alone, (2) mixed with low CD10 enMSCs, or (3) mixed with high CD10 enMSCs and injected orthotopically into the ovarian bursa of NSG mice. In vivo imaging system was used to follow tumor progression and metastasis. **Results:** Our results demonstrated that enMSCs have variable CD10 expression. EnMSCs with low CD10 expression significantly enhanced OCCC proliferation, resistance to cisplatin, and sphere formation compared to OCCC alone. In contrast, high CD10 expressing enMSCs significantly reduce OCCC proliferation and sphere formation. Interestingly, low CD10 enMSCs selectively enhanced OCCC cell growth and had no effect on high grade serious ovarian cancer cell growth. Moreover, a reduction of CD10 expression was observed over time when high CD10 enMSCs were co-cultured with OCCC cells. Our results also showed enhanced tumor engraftment when OCCC cells were co-injected with low CD10 enMSCs to 100% one week post-injection, compared to 40% with OCCC and high CD10 enMSCs and 60% with OCCC alone. Further, mice co-injected with low CD10 enMSCs demonstrated increased metastasis and decreased survival compared to mice co-injected with high CD10 enMSCs. **Conclusions:** Our results indicate there is a sub population of enMSCs, marked by decreased CD10 expression, which selectively enhances OCCC growth. This highlights the existence of a tumor-promoting stromal cell within endometriosis which may be critical to the formation and propagation of EACs. Research Sponsor: Magee Women's Cancer Research and Education Funding Committee.

5563 **Poster Session**

Outcomes of ovarian cancer patients treated with platinum or non-platinum based chemotherapy after PARP inhibitor maintenance. *First Author: Ralynn Brann, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: PARP inhibitors (PARPi) are approved for maintenance treatment of platinum sensitive ovarian cancers either after front-line therapy or after treatment for recurrence. Current recommendations include retreatment with platinum-based chemotherapy (PC) after progression on maintenance PARPi. There exists a theoretical concern that progression of disease (POD) on PARPi is indicative of the development of platinum resistance due to similar DNA targets of platinum chemotherapy and PARPi. Our objective was to evaluate the response to subsequent chemotherapy in patients who progressed on PARPi maintenance. **Methods:** All patients with ovarian, fallopian tube, or primary peritoneal cancer treated with PARPi treatment from 2017 to 2021 at two academic tertiary care centers were retrospectively identified. Patients were assessed for treatment time on PARPi, time to POD on PARPi (PFS), type of chemotherapy regimen following PARPi maintenance, and time to disease progression on subsequent therapy following PARPi (PFS2). Comparative statistical analyses were performed with appropriate two-sided statistical tests. Time to progression on chemotherapy after PARPi was calculated using the Kaplan-Meier method. **Results:** A total of 83 ovarian cancer patients treated with PARPi were identified, and of these, 61 (73.5%) were treated with PARPi in the maintenance setting. Among the patients treated with PARPi maintenance, 22 (36.1%) remain on treatment. 19 (31.1%) patients were started on PARPi maintenance after front-line chemotherapy. While on PARPi maintenance, 63.9% discontinued PARPi, the majority due to POD, and 26.2% due to patient intolerance of side effects. Following POD, 21/29 (72.4%) received subsequent PC and 8/29 (27.6%) received non-platinum based chemotherapy (NPC). Treatment time, PFS, and PFS2 are listed in Table. Of the patients who received PC, 14/21 (66.7%) had a PFS2 of over six months and 5/21 (23.8%) had a PFS2 of over 12 months. Of the patients who received NPC, 7/8 (87.5%) had a PFS2 of over six months and 2/8 (25.0%) had a PFS2 of over 12 months. **Conclusions:** Following POD on PARPi, patients responded to both PC and NPC. Time to progression on subsequent chemotherapy after treatment with PARPi does not differ significantly between PC and NPC regimens. Many patients continue to see benefit from PC after PARPi maintenance. Retreatment with PC following POD on PARPi maintenance should still be considered. Research Sponsor: None.

Time outcome (months)	PC after POD on PARPi maintenance	NPC after POD on PARPi maintenance
Median treatment time	9.0 (1.0-31.0)	5.5 (1.0-8.0)
Median PFS	14.4 (1.0-60.0)	5.5 (1.0-8.0)
Median PFS2	7.0 (0.0-23.0)	8.5 (2.0-40.0)

5564 **Poster Session**

Patient care and clinical trials in gynecological oncology: Implications of the COVID-19 pandemic. *First Author: Sara Nasser, North-Eastern German Society of Gynecological Oncology (NOGGO) and Department of Gynecology with Center for Oncological Surgery, Charité–University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany*

Background: This is a prospective international Survey to evaluate the impact of the COVID-19 Pandemic on the management of patients with gynecological malignancies from the multidisciplinary physicians' perspective, with particular focus on clincial infrastructures, and trial participation. **Methods:** The anonymous online survey consisted of 53 COVID-related questions. It was sent to all healthcare professionals in gynaecological oncology centres across Europe and the Pan-Arabian region from April 2020 to October 2020. All healthcare professionals treating women with gynecological cancers were able to participate in the survey. **Results:** A total of 243 answers were collected from 30 different countries. The majority (73%) of participants were gynecological oncologists from university hospitals(71%) with at least an Intensive care unit with cardiopulmonary support available at their institutions. Most institutions continued to perform elective surgeries only for oncological cases (98%). Patients had to wait on average 2 weeks longer for their surgery appointments compared to previous years(range 0-12 weeks). Cases that were prioritised for surgical intervention across all tumors (Ovarian, Endometrium, Cervical) were early stage disease (74%), primary situation (61%), and good ECOG status (63%). The radicality of surgery did not change in the majority of cases (78%) across all tumor types. During the pandemic, only 38% of clinicians stated they would start a new clinical trial. 45% stated the pandemic has negatively impacted the financial structure and support for clinical trials. 79% do not routinely screen patients included in trials for SARS CoV2. Overall, approx. 20% of clinicians did not feel well informed regarding clinical pathways for COVID-19 patients throughout the pandemic. The majority preferred regular updates and training via Webinars (75%), followed by tumorboards and interdisciplinary conferences (45%). 30% of clinicians stated that they are currently experiencing difficulties in providing adequate medical care due to staff shortage. **Conclusions:** Despite well-established guidelines for patient care and performing clinical trials in gynecological oncology, the COVID-19 pandemic has impacted clinical research, and financial structures. Longer waiting times for operative interventions, less support for clinical trials and concerns regarding provision of adequate medical care and triaging patients are very real. This survey underlines the necessity for building robust emergency algorithms tailored to gynecological oncology patients in the future. Research Sponsor: None.

5565 **Poster Session**

Selinexor in combination with weekly paclitaxel in patients with advanced or metastatic solid tumors: Results of an open label, single-center, multiarm phase 1b study. *First Author: Shannon Neville Westin, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Selinexor is a first-in-class novel, oral potent selective inhibitor of nuclear export (SINE) which blocks Exportin-1 (XPO1) leading to nuclear accumulation and activation of tumor suppressor proteins and prevention of translation of proto-oncogenes. Weekly paclitaxel is a standard chemotherapy regimen used in various tumor types. Preclinical models show that selinexor with paclitaxel exerts antitumor activity against multiple solid tumors. Our objective was to determine the maximum tolerated dose (MTD) and recommended phase II dose (RP2D) of selinexor and weekly paclitaxel. **Methods:** This was an open label, single-center, multi-arm phase 1b study utilizing a "3 + 3" design and a "basket type" expansion. Selinexor (twice weekly orally) and weekly paclitaxel (80mg IV 2 week on, 1 week off) was employed as one of 13 parallel arms. Two dose levels (DL) of selinexor were explored: DL1 selinexor 60mg; DL2 selinexor 80mg. Patients (pts) with advanced or metastatic solid tumors were eligible if they had adequate bone marrow and organ function. There was no limit on prior lines of therapy. Efficacy was evaluated using RECIST 1.1. Progression free survival (PFS) was defined as time from treatment until disease progression or death. **Results:** Of 35 pts treated, all were evaluable for toxicity, and 31 (88%) were evaluable for response. Pt diagnoses included ovarian (n = 28), breast (n = 4), prostate (n = 2), and cervical (n = 1) cancer. Pts had a median of four prior therapies (range 1-10), and 47% had a prior taxane. All pts with ovarian cancer had platinum resistant/refractory disease; high grade serous histology was most common. There were no DLTs and DL1 was chosen as the RP2D given its long term tolerability. 97% of pts had at least one treatment-emergent adverse event (TEAE) and the most common TEAEs were anemia (74%), nausea (57%), fatigue (51%), leukopenia (51%), neutropenia (49%), thrombocytopenia (46%), and vomiting (31%). The most prevalent grade $\geq$ 3 TEAE were neutropenia (46%), anemia (31%), leukopenia (17%), and fatigue (9 %). Partial responses (PR) were noted in 4 pts (13%); 10 pts (32%) achieved stable disease for $>$ 4 months for a clinical benefit rate (CBR) of 45%. 16 pts (47%) had prior exposure to a taxane, including 1 pt who achieved PR. Among 24 evaluable pts with ovarian cancer, response rate was 17%, CBR was 58%, and PFS was 6.83 months (95% CI 3.73, not reached (NR)). Median duration of clinical benefit in ovarian cancer was 7.57 months (95% CI: 4.43, NR). **Conclusions:** Oral selinexor in combination with weekly paclitaxel demonstrated promising clinical activity with manageable toxicity, and further evaluation with once weekly selinexor is warranted. This combination should be considered for further exploration in a randomized study, especially in ovarian malignancies. Clinical trial information: NCT02419495. Research Sponsor: Karyopharm, U.S. National Institutes of Health.

5566 **Poster Session**

Phase 1b study of GAS6/AXL inhibitor (AVB-500) in recurrent, platinum-resistant ovarian carcinoma. *First Author: Katherine Cynthia Fuh, Washington University in St. Louis, St. Louis, MO*

Background: AVB-500 is a first-in-class Fc fusion protein that binds the GAS6 ligand thereby inhibiting AXL signaling. Both GAS6 and AXL are highly expressed in high-grade serous ovarian cancer (HSGOC). This study evaluated safety, tolerability, and preliminary efficacy of AVB-500 in combination with pegylated liposomal doxorubicin (PLD) and paclitaxel (Pac) and determine the recommended Phase 2 dose (RP2D). **Methods:** Patients were enrolled in escalating dose cohorts of AVB-500 10mg/kg to 20mg/kg q2 weeks in combination with weekly Pac 80mg/m^2 D1, 8, 15 q28 days or PLD 40mg/m^2 D1 q28 days and assess for safety, pharmacokinetics, pharmacodynamics, and response by investigator, via RECIST v1.1. **Results:** A total of 53 patients with platinum-resistant HGSOC (PROC) were enrolled. A total of 23 patients received Pac + AVB-500 and 30 patients received PLD + AVB-500. Grade 3 or 4 treatment-related adverse events were observed in 4/23 (17%) and 2/30 (7%) PAC and PLD, respectively. No patients discontinued therapy due to an adverse event. Most events were related to known chemotherapy side effects. RP2D was identified as 15mg/kg. Confirmed overall response rate (ORR) with Pac+AVB-500 was 35% (8/23) including 2 CRs and 11% (3/28) in the PLD+AVB-500 subgroup. ORR was 19% (3/16) in patients with platinum free interval (PFI) of $<$ 3 months versus (vs) 23% (8/35) in patients with PFI of 3-6 months. ORR was 11% (2/18) in patients with 1 prior treatment vs 27% (9/33) in patients with 2-3 prior lines of therapy. ORR in patients without prior bevacizumab was 33% (9/27) vs 8% (2/24) in those with prior bevacizumab. Patients treated with Pac combination and whose AVB-500 trough levels were above the minimal efficacious concentration (MEC) of 13.8mg/L achieved the greatest benefit with ORR, median PFS, and median OS of 43% (6/14), 3.9 months, and 17.8 months vs 22% (2/9), 2.8 months, and 8.7 months observed in those whose trough was below the MEC. Among the Pac treated subgroup, the ORR was 47% (13% CR) vs 0% for those with sAXL/GAS6 ratios $>$ 0.773 compared to ratios $<$0.773. 67% of patients had baseline sAXL/GAS6 $>$ 0.773. **Conclusions:** AVB-500 is a novel Fc fusion protein that binds the GAS6 ligand and inhibits AXL signaling. AVB-500 was well-tolerated in combination with Pac or PLD. This Ph1b trial suggested a higher ORR in the Pac treated subgroup, with C1D15 trough levels $>$ 13.8mg/L (most consistently achieved at the 15mg/kg dose level). Exploratory analyses suggested that improved ORR may be observed in patients who have not been exposed to bevacizumab. The serum sAXL/GAS6 ratio may be a potential biomarker of pathway activation and identify patients who most benefit from Pac+AVB-500. The ORR in patients with PFI $<$ 3 months or who had $>$ 1 line of prior therapy were similar to those with 3-6 months PFI or $\leq$1 lines of therapy. Further development of AVB-500 15 mg/kg q2 weeks in combination with Pac is warranted in PROC. Clinical trial information: NCT03639246. Research Sponsor: Aravive, Inc.

5567 **Poster Session**

Assessment of predictive biomarker prevalence in molecularly defined adult-type ovarian granulosa cell tumors. *First Author: Robert Tyler Hillman, MD Anderson Cancer Center, Houston, TX*

Background: The FDA has separately approved pembrolizumab for all advanced solid tumors with either microsatellite instability or high tumor mutational burden ($\geq$10 mutations per megabase), and homologous recombination deficiency is an established biomarker for response to poly ADP ribose polymerase inhibitors in epithelial ovarian cancer. The detection of these predictive biomarkers in adult-type ovarian granulosa cell tumors could identify novel treatment strategies in this rare disease. The primary objective of this study was to determine the prevalence of established predictive biomarkers among molecularly defined adult-type ovarian granulosa cell tumors. **Methods:** With institutional review board approval, we performed a cross-sectional study examining de-identified FoundationOne companion diagnostic molecular profiles for 423 women with molecularly defined (FOXL2 c.C402G positive) adult type ovarian granulosa cell tumors. The dataset was comprised of coding variants for up to 406 genes as well as genomic signatures including microsatellite instability, tumor mutational burden, and genome wide loss of heterozygosity. PD-L1 expression by immunohistochemistry was also available for a subset of tumors. Descriptive statistics were used for comparison between groups and all statistical tests were two-sided. **Results:** Women in this cohort had a mean age of 57 years (range 24-87) at the time of sample submission for molecular profiling. The median tumor mutational burden was 1.3 mutations per megabase [mut/Mb] (range 0-8.8 mut/Mb). TP53-mutated aGCT had a higher tumor mutation burden than TP53 non-mutated tumors (median 2.4 mut/Mb, 95% CI 1.7-3.0 mut/Mb vs median 1.3 mut/Mb, 95% CI 1.5-1.9 mut/Mb; P=.02). All 384 tumors with available microsatellite instability testing were microsatellite stable. Sixty-seven tumors had PD-L1 expression measured and of these 94% (63/67) were negative with the remainder "low positive." No tumors were positive for genome wide loss of heterozygosity. Apart from FOXL2 c.C402G, the most frequent short variants were TERT promoter mutations (-124C$>$T: 190/423, 45.0%; -146C$>$T: 39/423, 9.2%). Other frequently observed variants included truncating mutations in KMT2D/MLL2 (71/423, 16.8%), pathogenic TP53 mutations (35/423, 8.3%), CDKN2A/B deletions (43/423, 10.2%), and activating PIK3CA mutations (23/423, 5.4%). **Conclusions:** No women with molecularly defined adult-type ovarian granulosa cell tumors in this large cross-sectional study would be eligible for FDA-approved pembrolizumab based on either microsatellite instability or high tumor mutational burden. No tumors exhibited evidence of homologous recombination deficiency and molecularly targetable mutations were rare. The development of novel precision treatment options remains a critical unmet need for this rare disease. Research Sponsor: Cancer Prevention and Research Institute of Texas (CPRIT).

5568 **Poster Session**

Correlation of HRD status with clinical and survival outcomes in patients with advanced-stage ovarian cancer. *First Author: Travis T. Sims, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Nearly 50% of patients with high grade ovarian cancer (HGOC) harbor a germline or somatic mutation in BRCA1/BRCA2 or have tumors characterized by homologous recombination deficiency (HRD). HRD is associated with response to poly(ADP-ribose) polymerase inhibitors (PARPi) in HGOC. Although PARPi show great promise, there is interest in investigating how HRD status affects outcomes and can be used to objectively tailor other treatment strategies. We aimed to compare clinical and survival outcomes in HGOC stratified by HRD status. **Methods:** We performed a retrospective analysis of all advanced HGOC from April 2013 to June 2019. Patients were included if germline BRCA and HRD status was known. Clinical outcomes were analyzed and stratified by (1) germline BRCA+ (2) germline BRCA - and somatic BRCA/HRD+, or (3) BRCA-/HRD-. Progression free (PFS) and overall survival (OS) were estimated using Kaplan-Meier methods stratified by HRD status and modeled via Cox proportional hazards regression. **Results:** 1271 patients with advanced HGOC presented during the study period of which 187 met inclusion criteria. 106 patients had germline BRCA mutation, 26 somatic BRCA/HRD+, and 55 BRCA/HRD-. Patients who had HRD- tumor had older median age at diagnosis (63 vs. 54 and 60 years, p$<$0.001), white race (89% vs. 74% and 68%), non-serous histology (20% vs. 6% and 0%, p=0.04), required more NACT chemotherapy cycles (4 vs. 3 and 3 cycles, p=0.03), and less complete gross resection (R0) at tumor reductive surgery (TRS) (60% vs. 83% and 77%, p=0.02). Patients who had BRCA/HRD- tumor had worse PFS (14.9 months) compared to germline BRCA+ (23.5 months) or somatic BRCA/HRD+ (20.2 months, p$<$0.001). Patients with BRCA/HRD- disease also had worse OS (42.3 months) compared to germline BRCA+ (68.8 months) or somatic BRCA/HRD+ (69.2 months). Multivariate analysis for PFS revealed that age (HR 1.02, 95% CI 1.00-1.04), p=0.01), stage (HR 5.7, 95% CI 1.39-23.4, p=0.02), R0 resection at TRS (HR 0.41, 95% CI 0.21-0.83, p=0.01), and BRCA/HRD-status (HR 1.63, 95% CI 1.07-2.48, p=0.02) were significant factors impacting PFS. Multivariate analysis for OS revealed that age (HR 1.07, 95% CI 1.03-1.10, p$<$0.001) and R0 resection at TRS (HR 0.19, 95% CI 0.08-0.44, p$<$0.001) were significant factors impacting OS. **Conclusions:** Germline BRCA-mutant, somatic BRCA/HRD+ HGOC was associated with improved PFS and OS regardless of primary TRS or NACT. BRCA-/HRD- was a negative prognostic factor for survival in HGOC. Research Sponsor: MD Anderson Cancer Moonshot, U.S. National Institutes of Health.

5569 **Poster Session**

Final results of phase 1 evaluation of the safety and clinical activity of sapanisertib in combination with serabelisib and paclitaxel in patients with advanced ovarian, endometrial, or breast cancer. *First Author: David Starks, Avera Cancer Institute, Sioux Falls, SD*

Background: Evidence suggests that activation of the PI3K/AKT/mTOR pathway by paclitaxel may play a role in the development of taxane resistance. Conversely, PI3K inhibitors have been shown to sensitize tumors to the effects of paclitaxel. Therefore, the link between taxane resistance and activation of the PI3K/AKT/mTOR signaling pathway suggests inhibition of this pathway in combination with antimitotic drugs like paclitaxel may improve treatment outcomes in many malignancies. To further investigate this hypothesis we combined the TORC 1/2 inhibitor sapanisertib (TAK-228), the PI3Kα isoform inhibitor serabelisib (TAK-117), and paclitaxel in a phase I trial of heavily pretreated patients to determine the safety, efficacy, and RP2D. **Methods:** This is an open label, cohort study of sapanisertib (TAK-228) and serabelisib (TAK-117) given on days 2-4, 9-11, 16-18, and 23-25 with paclitaxel on days 1, 8, and 15 of a 28-day cycle. A traditional 3+3 dose escalation design with a maximum of 5 dosing cohorts was used. All 5 cohorts plus an expansion cohort are presented. **Results:** Enrollment has been completed and the overall results are summarized. Nineteen patients were enrolled; the majority were heavily pretreated with the average number of prior regimens exceeding 4. Based upon ITT, the ORR is 37%. The ORR is 47% in patients that completed at least 3 cycles. The clinical benefit rate is 73% and the PFS currently stands at approximately 11 months. Two patients with endometrioid endometrial adenocarcinoma achieved a complete response. All patients received comprehensive genomic profiling and 7 patients received prior mTOR inhibitor. Overall, the combination was well tolerated, except by patients in cohort 5. One DLT occurred in the last patient enrolled. The most common non-laboratory AEs were nausea (6%), fatigue (5%), and mucositis (5%). There were 45 (9%) grade 3 or 4 events, and the most common were decreased WBC and non-febrile neutropenia. Hyperglycemia was common in patients with a history of diabetes mellitus. **Conclusions:** Overall, the combination of sapanisertib, serabelisib, and paclitaxel was safe and efficacious throughout the first 4 cohorts. There were few serious adverse events, and most side effects were managed with routine supportive care interventions. Preliminary clinical results appear very promising, especially for patients with PI3K/AKT/mTOR pathway mutations. The positive effects of the combination were routinely seen in the lowest dosing cohorts and clinical benefit was even seen in patients that had previously failed everolimus or temsirolimus. All patients were either resistant or refractory to paclitaxel at time of enrollment, so further exploration of this combination to elucidate the mechanism of benefit is warranted. Clinical trial information: NCT03154294. Research Sponsor: Takeda.

5570 **Poster Session**

Health-related quality of life (HRQoL) in advanced endometrial cancer (aEC) patients (pts) treated with lenvatinib plus pembrolizumab or treatment of physician's choice (TPC). *First Author: Domenica Lorusso, Gynecologic Oncology Unit, Fondazione Policlinico Universitario A. Gemelli IRCCS and Scientific Directorate, Rome, Italy*

Background: In Study 309/KEYNOTE-775, lenvatinib + pembrolizumab (L+P) demonstrated significant and clinically meaningful improvement in OS, PFS, and ORR compared with TPC in aEC pts following prior platinum-based systemic therapy. Given the medical complexity/age of EC pts, QoL analyses are critical, but often under-reported. We present results of pt-reported HRQoL for Study 309/KEYNOTE-775. **Methods:** Pts were randomized 1:1 to receive lenvatinib 20 mg QD PO + pembrolizumab 200 mg IV Q3W (n=411) or TPC (n=416; doxorubicin 60 mg/m^2 IV Q3W or paclitaxel 80 mg/m^2 IV QW, 3 wks on/1 wk off). Pt-reported HRQoL was assessed at cycle 1 day 1, day 1 of each subsequent cycle and at time of discontinuation using EORTC QLQ-C30, its EC module QLQ-EN24, and EQ-5D-5L in treated pts who had ≥1 HRQoL assessment available. Higher scores indicate better functioning/QoL (EORTC QLQ-C30, EQ-5D-5L) or worse symptom severity (QLQ-EN24). Changes in EORTC QLQ-C30 global health status (GHS)/QoL was a secondary endpoint. This was analyzed from baseline to the latest timepoint at which overall completion was ≥60% and overall compliance was ≥80%, using constrained longitudinal data analysis; other HRQoL analyses were exploratory. **Results:** Completion and compliance rates of EORTC QLQ-C30 were >95% in both groups at baseline. Primary analysis was conducted at wk 12 as completion rate was 80% for L+P and 62% for TPC; compliance rate was 93% for L+P and 87% for TPC. Baseline GHS/QoL scores were similar between the L+P group and TPC group: mean (SD) of 65.74 (21.87) vs 65.69 (22.71), respectively. Over 12 wks of follow-up, pts in both groups had slight decreases in GHS/QoL. Similar decreases were observed for pts receiving L+P vs TPC: -5.97 (95% CI: -8.36, -3.58) vs -6.98 (95% CI: -9.63, -4.33). The between-group difference in least-squares (LS) mean score change from baseline to wk 12 for L+P vs TPC was 1.01 points (95% CI: -2.28, 4.31). Over time, QoL scores were generally similar across treatments. Results were similar for other HRQoL endpoints (Table). **Conclusions:** No significant differences were observed in HRQoL scores between treatment groups. With no standard treatment approach following failure of platinum-based therapy, these data along with previously reported efficacy and safety findings from Study 309/KEYNOTE-775 further support that L+P has an overall favorable benefit/risk profile compared to chemotherapy. Clinical trial information: NCT03517449. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	Change from baseline to wk 12 LS mean (95% CI)		Difference in LS means L+P vs TPC (95% CI)
	L+P	TPC	
EORTC QLQ-C30: GHS/QoL	-5.97 (-8.36, -3.58)	-6.98 (-9.63, -4.33)	1.01 (-2.28, 4.31)
Physical functioning	-9.19 (-11.24, -7.14)	-9.10 (-11.37, -6.83)	-0.09 (-3.08, 2.90)
EORTC EN24Urological symptoms	-1.62 (-3.56, 0.31)	0.66 (-1.47, 2.79)	-2.29 (-5.03, 0.45)
EQ-5DVAS	-4.44 (-6.43, -2.46)	-6.79 (-8.98, -4.60)	2.35 (-0.44, 5.14)
Database cutoff: 26 Oct 2020			

5571 **Poster Session**

Race-related disparities in patterns of uterine cancer recurrence. *First Author: Camilla Dagum, Montefiore Med Ctr-Albert Einstein College of Medcn, Bronx, NY*

Background: Racial disparities in uterine cancer outcomes are present, as Black patients with uterine cancer have markedly higher mortality when compared with White patients. Potential etiologies of this discrepancy have been investigated, including implicit bias, histopathologic factors and stage at presentation, molecular and genetic factors, and socioeconomic factors. The purpose of this study is to explore if non-White patients with uterine cancer are more likely to experience distant cancer recurrence compared to White patients. **Methods:** A single-institution retrospective cohort study was performed examining all patients diagnosed with uterine cancer from 2006-2016. Data regarding patient demographics, medical co-morbidities, histology, stage, treatment course, and disease recurrence were abstracted from the medical record. Race was categorized based on how a patient was registered in the medical record. The primary outcome was location of recurrence, with local recurrence defined as vaginal/cuff recurrence and distant recurrence representing nodal, intraperitoneal, or distant recurrence. A multivariable regression model was built in a backwards stepwise fashion to examine the association of individual covariates with distant recurrence as opposed to vaginal recurrence. **Results:** A total of 1205 patients with uterine cancer were included for analysis. Three hundred eighteen (26.5%) patients were White, 472 (39.2%) Black, 319 (26.5%) Hispanic, 91 (7.6%) Asian, and 4 (0.3%) other. A total of 223 (18.5%) patients experienced disease recurrence. Black women experienced a statistically significant increased risk of recurrence compared with non-Black women [OR 1.99 (95% CI 1.37-2.88), $p < 0.01$]. Additionally, Black patients were significantly more likely to experience nodal, intra-peritoneal and distant recurrences relative to White patients ($p < 0.01$). When adjusting for covariates including race, histology, grade, stage and adjuvant treatment, non-White race [OR 3.87 (95% CI (1.42-10.54), $p < 0.01$] was associated with significant increase in risk of distal recurrence. **Conclusions:** The findings of this study suggest that non-White race is potentially contributory to distant recurrence of uterine cancer, even when accounting for histopathologic differences, stage at presentation, and other traditional covariates. These findings suggest that the disparate outcomes experienced by non-White patients are likely multi-factorial in nature and highlight the need for efforts focused on optimizing treatment and improving outcomes of non-White women with uterine cancer. Research Sponsor: None.

Site of disease recurrence for patients diagnosed with recurrent disease, stratified by race (N = 223).

Race	Vaginal (N = 36)	Pelvic nodes (N = 8)	Para-aortic nodes (N = 14)	Intra-peritoneal (N = 63)	Distant (N = 102)	P- Value
White	15 (41.7)	1 (12.5)	3 (21.4)	17 (27.0)	11 (10.8)	< 0.01
Non-white	21 (58.3)	7 (87.5)	11 (78.6)	46 (73.0)	91 (89.2)	

5574 **Poster Session**

Phase II trial assessing niraparib with or without dostarlimab (anti-PD-1) in recurrent endometrial carcinoma. *First Author: Ainhoa Madariaga, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada*

Background: Treatment options in recurrent endometrial carcinoma (EC) are limited. Endometrioid EC shows alterations in PTEN, a possible biomarker of response to PARP inhibitors (PARPi). Similarly, homologous recombination deficiency (HRd), a biomarker of response to PARPi in ovarian cancer, is associated with serous EC harbouring *TP53* mutations. Preclinical EC models have shown synergy between combining a PARPi and immune checkpoint inhibitor (ICI). **Methods:** A pilot multi-centre, non-randomized, phase II trial enrolled patients (pts) with recurrent serous or endometrioid EC in two consecutive cohorts (NCT03016338). In the first cohort (C1) pts received niraparib 200 or 300 mg qd, based on baseline body weight and platelet count, in 4 week (w) cycles. In the second cohort (C2) niraparib was given with dostarlimab 500 mg q 3 w for 4 cycles, followed by 1000 mg q 6 w thereafter. There was no limit on prior lines of therapy. Prior ICI was not allowed in C2. Primary endpoint was clinical benefit rate (CBR; complete, partial response or stable disease ≥16w). Secondary endpoints included toxicity assessment and ORR. CT scans were performed q 8 w. Potential biomarkers were assessed in archival tissue by IHC (PTEN, p53, MMR, PDL-1 [threshold 1%]) and a NGS panel (including *TP53*, *PTEN*, *POLE* and other HRd genes). Tumour mutational burden-high (TMBh) was defined as top 20% mutation load. **Results:** In C1, 25 pts were enrolled (23 evaluable for response). Median age was 69 years old, 64% had serous EC, 72% were platinum resistant (PlatR) and median prior therapies was 2 (range 1-4). Median number of cycles was 3. The CBR was 20% (95% CI: 9-39) and median clinical benefit (CB) duration was 5.3 (1.8-7.2) months. The ORR was 1/23 (4%; 0-20). Related grade (g) ≥3 AEs ≥10% were anemia (24%), fatigue (16%) and thrombocytopenia (16%). In C2, 22 pts were enrolled (all evaluable) and two continue on-treatment. Median age was 64 years old, 46% had serous EC, 68% were PlatR and median prior therapies was 2 (1-6). Three pts had MMR deficient (MMRd) tumors (14%) and one pt a *POLE* mutation (5%). Median number of cycles was 3. The CBR was 31.8% (16-53) and median CB duration was 6.8 months (3.7-9.5). The ORR was 3/22 (14%; 3-35), out of the three responders one had MMRd and one a *POLE* mutation. Related g≥3 AEs ≥10% were anemia (27%) and neutropenia (14%). No significant correlation was detected between CB and IHC markers (PTEN, p53, MMR, PDL-1), or NGS (*PTEN*, *TP53*, HRd TMBh) in C1 and C2. **Conclusions:** Niraparib as single agent for treatment in a PlatR enriched recurrent EC population showed modest activity with clinical benefit rate at 16w of 20%. The combination of niraparib and dostarlimab showed a clinical benefit rate at 16w of 31.8% in a predominantly PlatR recurrent EC. PTEN loss by IHC or NGS, and alterations in HRd genes did not correlate with clinical benefit. Clinical trial information: NCT03016338. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

5575 **Poster Session**

Evaluating the role of aromatase inhibitors (AIs) in the treatment of endometrial stromal sarcomas (ESS). *First Author: Fionnuala Crowley, Mount Sinai Morningside and West, New York, NY*

Background: Endometrial stromal sarcomas (ESS) account for < 20% of uterine sarcomas. They usually express estrogen and progesterone receptors (ER/PR) and are considered hormone sensitive. Due to the rarity of these tumors, large clinical trials studying optimal treatment have not been possible. This study represents the largest retrospective study of ESS treated with AI. **Methods:** The clinicopathological variables and outcomes of patients (pts) with pathologically confirmed low grade ESS treated with AI at our institution between 1998-2020 were recorded. **Results:** 48 pts with ESS treated with AI were identified. They had a median age of 54 years (range 23-84) and BMI of 27 (range 20-50). 79% were white. 6 (12%), 9 (19%), 14 (29%) and 19 pts (40%) had stage 1,2,3,4 ESS, respectively. 37 (77%) were ER+/PR+; 2 (4%) ER+/PR- and 9 pts (19%) had unknown ER/PR status. All pts were postmenopausal at AI initiation. 12 pts (25%) had a synchronous cancer (5 of these had breast cancer {3 of the 5 presented post tamoxifen}). 23 pts (48%) received megestrol acetate and 25 (52%) an AI as first line hormonal manipulation. During their disease course, 35 pts (73%) received letrozole, 21 (44%) anastrozole and 19 (39.6%) exemestane. 22 pts (46%) were treated with more than one AI. 28 pts (58%) reported side-effects; arthralgia (33%) being the most common. 10 pts (21%) discontinued AI due to toxicity; 12 pts (25%) switched AI for toxicity (with improved tolerance in 67% of these pts). Among the 24 pts (50%) with measurable disease there were 2 partial responses (objective response rate of 8.3%). 1-year disease control rate (DCR) was (79%) for all pts and 58% in stage 4 disease. Median PFS for 1st line AI was 161.6 months (95% CI 48.5 to 274.7). **Conclusions:** This study represents the largest study of AI use in ESS to date. We found the ORR to be more modest than previously reported. The majority of pts had prolonged stable disease with a DCR of 58% even in stage 4 disease. Pts who progress on one AI may benefit from trial of a 2nd AI. A phase 2 study of interruption versus maintenance AI in locally advanced/metastatic ESS is currently underway (NCT03624244). Research Sponsor: U.S. National Institutes of Health.

5576 **Poster Session**

Open-label, multicenter, phase 1b/2 study of rebastinib in combination with paclitaxel to assess safety and efficacy in patients with advanced or metastatic endometrial cancer. *First Author: Filip Janku, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Rebastinib is a first-in-class investigational, orally administered, potent and selective switch-control kinase inhibitor of tunica interna endothelial cell kinase (TIE2). This is a 2-part open-label, multicenter Phase 1b/2 study of rebastinib in combination with paclitaxel. Here we provide updated results (ASCO 2020) from the fully enrolled endometrial cancer (EC) cohort of the study. **Methods:** Part 2 of the study has five disease-specific cohorts (EC, platinum-resistant ovarian cancer, gynecological carcinosarcoma, TNBC and inflammatory breast cancer). Patients were treated at the RP2D and evaluated for efficacy (RECIST v1.1) and safety (CTCAE v5.0). **Results:** As of Jan 8, 2021, 38 EC patients were enrolled (median age of 66 years); 42% were of grade 2/3 endometroid histological subtype. All patients received at least 1 prior line of paclitaxel in combination with carboplatin and 79% of patients received ≥3 prior anti-cancer regimens. Sixteen of 38 patients were initially treated with a starting dose of rebastinib 100 mg BID, 11 of which dose reduced to 50 mg BID, and 22 patients were treated with a starting dose of rebastinib 50 mg BID, in combination with paclitaxel 80 mg/m^2 IV weekly (days 1, 8, 15 of 28-day cycle). In 33 evaluable patients with median follow-up of 5.9 months, the ORR was 33% and clinical benefit rate at 8 and 16 weeks was 70% and 55%, respectively, including 11 PRs (8 confirmed) and 12 SDs. Treatment-emergent adverse events (> 20% of patients; mostly ≤ grade 2) included fatigue (n = 18), constipation, peripheral edema (each at n = 16), peripheral sensory neuropathy, nausea (each at n = 15), dyspnea (n = 13), alopecia, hypokalemia (each at n = 11), diarrhea, hypomagnesemia (each at n = 10), dry mouth, dysgeusia (each at n = 9), arthralgia, hypertension, dehydration, GERD and muscular weakness (each at n = 8). Serious adverse events (SAE) at least possibly related to rebastinib included muscular weakness (n = 2 at 100 mg BID, n = 1 at 50 mg BID), nausea (n = 2), acute myocardial infarction, atrial flutter, dehydration, non-infective encephalitis, peritonsillitis, and stress cardiomyopathy (each at n = 1) and were resolved after dose interruption. **Conclusions:** The updated results of rebastinib at 50 mg BID in combination with paclitaxel showed encouraging preliminary anti-tumor activity and an acceptable safety profile in heavily pretreated EC patients, and supports further development in patients with EC (NCT03601897). Clinical trial information: NCT03601897. Research Sponsor: Deciphera Pharmaceuticals, LLC.

5577 **Poster Session**

High prevalence of actionable germline variants in unselected endometrial cancer (EC) patients. *First Author: Monica Levine, The Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus, OH*

Background: The use of upfront germline genetic testing for cancer patients to identify hereditary syndromes and to aid in treatment decision making has increased dramatically. Recent evidence suggests that such testing should be considered for all solid tumors. In EC, mismatch repair deficiency (MMRd) has emerged as an important molecular marker for treatment with checkpoint inhibitors. MMRd is the hallmark of Lynch syndrome (LS), the most common hereditary cause of EC. Therefore, identifying LS not only affords opportunities for cancer prevention but also for making treatment decisions for women who already have EC. Although tumor-based screening is highly effective, some LS diagnoses will be missed. Upfront multi-gene panel testing (MGPT) for EC has been evaluated as an alternative approach to identifying LS with the potential to simultaneously find actionable germline variants in other cancer susceptibility genes (CSGs). Our objective was to determine the frequency and types of actionable germline variants in a large, unselected group of women with EC. **Methods:** Prospective germline MGPT for 47 CSGs was performed for 961 unselected EC cases. Patients diagnosed from 2017-2020 were enrolled at nine different institutions. Clinicopathologic data were abstracted from patients' records. **Results:** 101 likely pathogenic (LP) or pathogenic variants (PV) were identified in 98 women (10.2%). LP/PVs in LS genes were most common: 29 LS cases were identified (3.02%, 95% CI 2.1 - 4.3%). MGPT found 9 cases (one-third of LS cases) that were not identified by tumor screening: 6 were from institutions that do not perform tumor screening and 3 had normal immunohistochemistry. There were 72 LP/PVs found in 17 different CSGs. 21 patients (2.1%) had LP/PVs in high penetrance CSGs other than the LS genes, 19 of which were in genes associated with breast and/or ovarian cancer (4 in *BRCA1*, 6 in *BRCA2*, 6 in *BRIP1*, 2 in *PALB2*, 1 in *RAD51C*). *BRCA1/2* PVs (1.04% of the study population, 95% CI 0.6 - 1.9%) were significantly more frequent in women with type II cancers than the rest of the cohort (P = .005, HR 2.00, 95% CI 1.16 - 4.75). 21 additional LP/PVs were found in moderate risk CSGs (*ATM, CHEK2, NBN, NF1*). **Conclusions:** Upfront MGPT in an unselected EC population improved LS diagnosis and identified an additional 2% of patients with LP/PVs in highly penetrant CSGs. The enrichment of germline BRCA1/2 PVs in type II cancers is consistent with prior reports that non-endometrioid tumors are frequently deficient in homologous recombination. Germline BRCA mutation is a known predictive biomarker in ovarian cancer and an attractive therapeutic target in EC. Knowing germline status at the time of diagnosis facilitates further delineation of germline/phenotype associations, and it defines a genetic syndrome allowing for cancer prevention. Upfront MGPT in EC provides clinically impactful information and should be adopted into routine clinical care. Clinical trial information: NCT03460483. Research Sponsor: The Ohio State University Comprehensive Cancer Center-James Statewide Cancer Impact Award.

5578 **Poster Session**

Trends in the incidence of endometrial cancer among young women in the United States, 2001 to 2017. *First Author: Fangjian Guo, University of Texas Medical Branch at Galveston, Galveston, TX*

Background: Endometrial cancer at this time is predominantly being looked at as a disease of postmenopausal population. Increased obesity has been identified as an important risk factor for endometrial cancer. An overall increase incidence of endometrial hyperplasia and endometrial carcinoma in obese premenopausal women has been reported. A close examination of the relationship between trends in endometrial cancer incidence and obesity prevalence in young women will provide important information for prevention and early screening of the disease and its precursors. This study was to assess current trends in endometrial cancer incidence in women ages 20-29 and 30-39 years in relationship to obesity in the US. **Methods:** We used data on US adult women 20-39 years old from the National Program for Cancer Registries and Surveillance, Epidemiology, and End Results Incidence–U.S. Cancer Statistics 2001–2017 database. This database covered essentially all young female population between 2001 and 2017 in the US (Puerto Rico not included). Incidence was age adjusted to the 2020 U.S. standard population. We also examined the trends in obesity prevalence among females 18-34 years old using data from the National Health and Nutrition Examination Survey (NHANES) III and NHANES 1999-2014. **Results:** There were 24,446 cases of endometrial cancer among young adult women aged 20-39 years during 2001-2017. Endometrial cancer incidence increased from 0.6 per 100,000 in 2001 to 1.2 per 100,000 in 2017 (APC 3.6, 95% CI 2.9-4.4) among young women 20-29 years old, and increased from 4.6 per 100,000 in 2001 to 7.5 per 100,000 in 2017 (APC 3.0, 95% CI 2.7-3.3) among women 30-39 years old. Obesity prevalence also increased significantly from 1988-2014 among females 18-34 years old. Incidence of endometrial cancer and obesity prevalence were both higher in Hispanics than in other racial/ethnic groups. **Conclusions:** The significant increasing incidence in endometrial cancer among young adult women is in accordance with the concurrent increasing prevalence in obesity in young girls and women in the US. This indicates that endometrial cancer screening might need to be considered at much earlier age among patients with abnormal bleeding and certain ethnic populations. Research Sponsor: U.S. National Institutes of Health.

5579 **Poster Session**

Exploring molecular profiles and survival in hormone receptor-positive uterine serous carcinoma. *First Author: Amaranta Craig, Fox Chase Cancer Center, Philadelphia, PA*

Background: Hormone receptor (HR) positivity has been reported as a good prognostic indicator in endometrial cancer. This study investigated estrogen receptor (ER) and progesterone receptor (PR) positivity as indicators of platinum response and improved survival in uterine serous carcinoma (USC), and determined differences in molecular profiles between these tumors and hormone receptor negative tumors. **Methods:** Tumor profiling was done with immunohistochemistry (IHC), next generation sequencing (NGS), and whole transcriptome sequencing (WTS). PD-L1 expression was determined by IHC using SP-142 (cut-off >1%). Microsatellite instability (MSI) status was evaluated with IHC and NGS, and tumor mutational burden (TMB) by totaling somatic mutations per tumor (high if > 10 mutations/ MB). Immune-cell fraction was determined with QuantiSeq. We used insurance claims data to calculate Kaplan-Meier estimates for overall survival (OS). Statistical significance was determined with chi-square and Wilcoxon rank sum test and adjusted for multiple comparisons. **Results:** 2806 USC tumors were available for molecular profiling with 717 HR+/966 HR-, 1559 ER+/1059 ER- and 805 PR+/1809 PR-. Median OS for HR+ patients was longer than patients who were HR- regardless of treatment (1152 v 797 days; hazard ratio 0.68, 95% CI 0.58-0.80, p < 0.01). This OS benefit of HR positivity remained for patients receiving platinum therapy (1134 v 889 days; hazard ratio 0.75, 95% CI 0.58-0.98, p < 0.01). HR+ status trended towards improved OS in those treated with hormone therapy (407 vs 771 days, hazard ratio 0.78, 95% CI 0.59-1.02, p = 0.07). In addition to increased androgen receptor expression (54.2 vs 6.2%, p = < 0.001), PTEN mutations were more common in the HR+ group (10.3 vs 5.1%, p = 0.016). This resulted in in more frequent alterations of the PI3K pathway when compared to HR- tumors 64.5 vs 52.2%, p = < 0.001). PD-L1, TMB, and MSI status were similar between the two cohorts. Checkpoint inhibitor gene expression was notable for higher IDO expression in the HR+ group, but lower CD80, CD86, HAVCR2, IFNG, and PDC1 expression. The immune micro-environment was notable for less B-cells and M1 macrophages, but more M2 macrophages. Breaking the ER and PR positive cohort down to individual expression of each gene resulted in similar OS and molecular findings. **Conclusions:** HR positivity is associated with improved survival in allcomers with USC and those treated with platinum therapy, and there was a trend to improved OS with hormone therapy. More data is needed to determine if HR status is a prognostic marker for IO treatment response. This cohort had a distinct molecular profile compared to HR- tumors. Research Sponsor: None.

5580 **Poster Session**

HER2 in uterine serous carcinoma: Testing platforms and implications for targeted therapy. *First Author: Tenley Klc, University of Minnesota Physician's Oncology Clinic-Masonic Cancer Clinic, Minneapolis, MN*

Background: HER2 is an emerging prognostic and therapeutic target in uterine serous carcinoma (USC). Testing algorithms and platforms in breast and gastric cancers are well studied and validated, but optimal HER2 testing in uterine cancer is not yet established. We aimed to assess the concordance of chromogenic in situ hybridization (CISH), immunohistochemistry (IHC), and next generation sequencing (NGS) platforms to aid in the development of USC specific testing guidelines. We also evaluated the rate of downstream mutations that may affect response to HER2 directed therapy. **Methods:** A total of 2,192 USC tumors were analyzed using NGS (NextSeq, 592 Genes and WES, NovaSEQ), a subset of 1,423 tumors were also tested by IHC and CISH (Caris Life Sciences, Phoenix, AZ). HER2 positivity through IHC (4B5, Ventana) and CISH (INFORM DUAL HER2 ISH Assay, Ventana) was determined based on 2007 and 2018 ASCO/CAP HER2 breast cancer guidelines. PD-L1 expression was tested by IHC using SP142 (Spring Biosciences) (positive cut-off >1%). Microsatellite instability (MSI) was tested by fragment analysis (FA), IHC and NGS. Tumor mutational burden (TMB) was measured by totaling somatic mutations per tumor (TMB-high cut-off > 10 mutations per Mb). Statistical significance was determined using chi-square. **Results:** Rates of HER2 positivity were comparable using the 2018 and 2007 breast cancer guidelines (19.5% vs 17.5%; p=0.25). Based on 2018 guidelines, the concordance between IHC and CISH was 98.9%. Specifically, 229/1423 patients (16%) were IHC+/CISH+, 5 patients (0.4%) were IHC+/CISH- and 11 patients (0.8%) were IHC-/CISH+ (Table). Common pathway alterations in HER2+ USC include TP53, RTK RAS, PI3K, NOTCH, chromatin remodeling and cell cycle genes. Single gene alterations in HER2+ tumors that may implicate HER2 therapy resistance (based on pathway analyses in other tumor types) included PI3K (36%), KRAS (2.6%), and PTEN (2.1%). HER2+ tumors had low immunotherapy biomarker profiles (0.3% MSI-H, 0.8% TMB, 17.1% PD-L1). **Conclusions:** High concordance rates were observed between CISH and IHC. Ultimately these testing platforms need to be validated by response to HER2 targeted therapies in order to develop USC specific HER2 testing guidelines. Research Sponsor: None.

Concordance of IHC and CISH in determining HER2 positivity by 2007 and 2018 breast cancer guidelines.

ASCO/CAP Guidelines (Breast Cancer)	IHC+/ CISH+	IHC-/ CISH-	IHC+/ CISH-	IHC-/ CISH+	Concordance (%)	Sensitivity (%)	Specificity (%)	PPV (%)
2007	164	1160	2	8	99.3	98.8	99.3	95.3
2018	229	1178	5	11	98.9	97.9	99.1	95.4

5581 **Poster Session**

Treatment patterns and outcomes among patients with microsatellite stable (MSS) advanced endometrial cancer in the United States: Endometrial Cancer Health Outcomes (ECHO) retrospective chart review Study. *First Author: Shelby Corman, Pharmerit-an OPEN Health Company, Bethesda, MD*

Background: Traditional platinum-based systemic chemotherapy continue to be the SOC for aEC in the first line. Phase 2 clinical trials of chemotherapy (GOG 129 series) and some targeted therapies (229 series) for second line advanced endometrial cancer (aEC) have proved disappointing. Recently the treatment landscape for aEC patients has significantly changed with newer targeted therapies focusing on the microsatellite instability (MSI) status of endometrial tumors. The objective of the ECHO study was to describe real-world treatment patterns and outcomes in non-MSI-high or DNA mismatch repair proficient (pMMR) aEC patients in clinical practice in the United States (US) prior to 2019. **Methods:** The ECHO study is a multicenter, retrospective chart review study in women diagnosed with aEC in the US. Data were obtained from medical records of adult women (≥18 years) diagnosed with advanced or inoperable aEC (stages III or IV) with known MSI status, who had received at least one prior systemic therapy and progressed between July 1, 2016 – June 30, 2019. De-identified patient data extracted by treating oncologists included patient demographics, clinical and treatment characteristics, and clinical outcomes. Kaplan-Meier analyses were performed to estimate real-world progression-free survival (rwPFS) and overall survival (OS). **Results:** A total of 124 non-MSI-high or pMMR aEC patients who had progression following first line therapy were included in this interim analysis. Average age was 63 years, 62.9% White/Caucasian, 16.9% Hispanic/Latino, and 86% had ECOG ≤1. Metastases were observed in 70% of patients at diagnosis, with the most common metastatic sites being lung (47.6%), liver (32.3%), and distant lymph nodes (29%). As 2nd line therapy, 69% of patients received mono or combination chemotherapy (primarily with doxorubicin), 13% hormonal therapy, and 18% targeted therapy ± chemotherapy. Median duration of 2nd line therapy was 4 months. The majority (86.3%) discontinued 2nd line therapy , with disease progression the most common reason (66.4%). A quarter (26.6%) of patients initiated an additional line of therapy. Median rwPFS from initiation of 2nd line therapy was 5 months (95% confidence interval [CI]: 4-9). Median OS from initiation of 2nd line therapy was 12 months (95%CI: 9-18). Estimated OS rates from initiation of 2nd line therapy at 6, 12, and 24 months were 66%, 47%, and 30%, respectively. **Conclusions:** In this retrospective, chart review study, patients with non-MSI-high/pMMR aEC in the US who failed at least one systemic therapy had poor prognosis on subsequent therapies. There continues to be a significant unmet need in this group of women. Novel therapies are needed that delay progression and/or improve overall survival and further research is indicated to explore this. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and Eisai Inc.

5582 **Poster Session**

Molecular determinants of response to immune-oncology therapy in uterine carcinosarcoma. *First Author: Annelise M. Wilhite, University of South Alabama, Mobile, AL*

Background: Uterine carcinosarcoma (UCS) is subtype of endometrial cancer (EC) with aggressive behavior and poor prognosis. UCS has not traditionally been included in EC clinical trials and treatment options are limited. Immune-oncology (IO) therapy has shown promise UCS, but it is unknown which patients benefit most. We sought to identify immunogenic markers in UCS and explore treatment response to IO therapy. **Methods:** Tumor samples were analyzed using Nex-Gen sequencing of the DNA (NextSeq, 592 genes or NovaSeq, whole exome sequencing) and RNA (NovaSeq, whole transcriptome sequencing) and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ).PD-L1 IHC used SP-142 (cut-off >1%). MSI was tested by FA, IHC and NGS. TMB was measured by totaling somatic mutations per tumor (high > 10 mutations per MB). Immune cell fraction was calculated by QuantiSeq. Overall survival (OS) information was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patient cohorts. Statistical significance was determined using chi-square and Wilcoxon rank sum test and p values adjusted for multiple comparisons (q) to be <0.05. **Results:** A total of 1,144 UCS tumors underwent comprehensive tumor profiling. 68.4% of samples were obtained from primary tumors and 31.6% from metastatic sites. 21.6% of tumors expressed PD-L1, 8.5% were TMB-H and 6.8% were MSI-H/MMRd. UCS patients treated with IO had longer median overall survival than those not treated with IO (months: 31.2 vs 19.4; HR(95% CI): 0.39 (0.17-0.76) p=0.005). Median OS was also increased for dMMR/MSI-H (OS not yet reached vs 18.9 months); HR(95% CI): 0.56 (0.36-0.92) p=0.019) and TMB-H (OS not yet reached vs 18.9 months); HR(95% CI): 0.62 (0.38-0.99) p=0.047). More patients are needed to determine if these markers predict response to IO therapy. The most common mutations in UCS led to pathway dysregulation in the PI3K, RAS, chromatin remodeling, HR, and WNT pathways. dMMR/MSI-H tumors have distinct molecular profiles compared to MSS tumors (table). Additionally, dMMR/MSI-H tumors had higher TMB (96.9% vs 2.2%, q<0.01) and increased frequency of PDL-1 (23.6% vs 13.8%; q=0.04). Immune checkpoint genes were more often expressed in MSI-H tumors, though this was non-significant except for IFNG (4.66-fold increase; q=0.01). **Conclusions:** IO therapy is associated with improved survival in USC. MSI and TMB are markers of improved OS in patients with UCS. MSI tumors have a distinct molecular profile compared to MSS tumors, and they appear to be more immunogenic, which could contribute to the improved survival seen in patients who received IO therapy. Research Sponsor: None.

Gene	MSS (% mut)	MSI-H (%mut)	q-value
TP53	86.5	43.6	<0.01
ARID1A	36.6	91.1	<0.01
PIK3CA	28.7	54.4	<0.01
PTEN	14.4	86.0	<0.01
PIK3R1	10.2	30.6	<0.01
RB1	5.27	23.1	<0.01
NF1	4.56	22.5	0.01
KMT2D	4.50	48.0	<0.01
KMT2C	4.27	22.7	<0.01

5583 **Poster Session**

Anlotinib plus sintilimab in patients with recurrent advanced endometrial cancer: A prospective open-label, single-arm, phase II clinical trial. *First Author: Wei Wei, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Department of Gynecologic Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Endometrial cancer is one of the most common gynecologic malignancies in the world. however, the effects of systemic chemotherapy are limited. The combination of targeted therapy with immunotherapy is a new research field in the treatment of malignant tumors. Anlotinib is a novel tyrosine kinase inhibitor with highly selective inhibition effects on multi-targets, especially on vascular endothelial growth factor receptor, Platelet-derived growth factor receptor and Fibroblast growth factor receptor. Sintilimab is a highly selective, fully humanized, monoclonal antibody, which blocks the interaction between Programmed death 1 and its ligands. This research aimed to evaluate the efficacy and safety of the combination of anotinib and sintilimab in patients with recurrent advanced endometrial cancer. **Methods:** Patients who received at least one platinum-based systemic chemotherapy, had an Eastern Cooperative Oncology Group performance status of 0 or 1 were considered eligible for enrollment. Sintilimab was administered intravenously (200mg， q3w); anlotinib was taken orally (12mg qd, d1-14, 21 days per cycle). The treatment was continued until disease progression, death or intolerant toxicity. The primary endpoint was objective response rate (ORR) and the secondary endpoints included duration of response, disease control rate (DCR), progression-free survival (PFS), overall survival and safety. **Results:** From November 2019 to to September 2020, 23 patients with a median age of 56 years (range: 37-70), FIGO stage IA (21.7%), IB (8.7%), II (4.4%), IIIA (13.1%)， IIIC (30.4%), IVB (21.7%) were enrolled. Among these participants, 22 patients were evaluable. The therapeutic evaluation showed the incidence of complete response, partial response, stable disease and progression disease was 13.6%, 63.7%, 13.6% and 9.1% respectively, yielding the ORR of 77.3% (95%CI: 58.3%-96.3%) and the DCR of 91.7% (95%CI: 79.8%-100%). ≥1 and ＜ 1 Combined Positive Score of PD-L1 expression were observed in 66.7% (14/21) and 33.3% (7/21) patients respectively, and the ORR was 92.9% (95%CI: 77.4%-100%) and 57.1% (95%CI: 18.4%-90.1%) in the two groups. The median time of the first response was 1.5 months (range, 0.7-12.8). The median PFS was not reached. Most of the occurring adverse events (AEs) were grade 1 or 2. Grade 3 AEs included ileus (4.3%), immune myocarditis (4.3%) immune peritonitis (4.3%), hand-foot syndrome (8.7%), neutropenia (4.3%), neutrophils decrease (4.3%), and hypertension (4.3%); Grade 4 AE was lymphocytosis (4.3%). Neither unexpected safety signals nor treatment-related death occurred. **Conclusions:** Anlotinib plus sintilimab showed a promising antitumor activity with a favorable toxicity profile for patients with recurrent advanced endometrial cancer. We will report more data in the future. Clinical trial information: NCT04157491. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd., Pharmaceutical/Biotech Company.

5584 **Poster Session**

Tumor-associated immune cells and progression-free survival in advanced endometrial cancer (EC), results from the PHAEDRA trial (ANZGOG 1601). *First Author: Deborah Smith, Mater Research Institute, The University of Queensland, Brisbane, QLD, Australia*

Background: Activity of durvalumab in patients with deficient mismatch repair (dMMR) advanced endometrial carcinoma (EC) was confirmed in the PHAEDRA trial (ANZGOG 1601). This study investigated the association between immune biomarkers and clinical outcomes in PHAEDRA. **Methods:** Formalin-fixed paraffin embedded sections immunohistochemically stained for PD-L1 using the Ventana platform, were with matched H&E slides scored independently by two pathologists according to the Ventana PD-L1 (SP263) algorithm for urothelial carcinoma (UC). Immune biomarkers assessed were PD-L1 staining of tumor cells (TCP) and immune cells (IC), and presence of tumor-associated immune cells (ICP). **Results:** Sixty-seven of the 71 patients had sufficient tumor for PD-L1 testing. AUC were 0.667, 0.726 and 0.644 for TCP, ICP and IC, respectively for predicting tumor response. Optimal cutpoints were TCP≥1%, ICP≥10% and IC≥35%. ICP≥10% achieved the highest sensitivity (53%) and specificity (82%) of the individual cutpoints. The optimal cutpoint algorithm was able to identify patients who would not respond, (sensitivity 88%, negative predictive value 92%), but had low specificity (48%) and positive predictive value (37%). Differences in PFS were found using ICP≥10% (logrank p = 0.01), compared to TCP (p = 0.25), IC (p = 0.48) and the UC algorithm (p = 0.08) (Figure 1). PFS was shorter in patients with pMMR than dMMR after adjusting for ICP (HR 2.99, 95%CI: 1.61-5.57, $p < 0.001$). Adjustment for MMR reduced the prognostic significance of ICP≥10% for PFS (HR 0.59, 95% CI: 0.28-1.23, p = 0.16). For OS, differences were seen for the UC algorithm (p = 0.02), but not ICP (p = 0.07), TCP (p = 0.18) or IC (p = 0.23). Similarly to PFS, adjustment for MMR reduced the prognostic significance of the UC algorithm for OS (HR: 0.53, 95% CI: 0.25-1.12, p = 0.10). **Conclusions:** In this exploratory analysis, ICP was more closely associated with tumor response and PFS than TCP or IC. ICP alone was better than the UC algorithm for predicting PFS. The optimum cutpoint algorithm was promising for identifying non-responders, but requires external validation. Clinical trial information: ACTRN12617000106336. Research Sponsor: Astra Zeneca.

5585 **Poster Session**

Computational features of TIL architecture are differentially prognostic of uterine cancer between African and Caucasian American women. *First Author: Sepideh Azarianpour Esfahani, Case Western Reserve University, Cleveland Heights, OH*

Background: Although the vast majority of endometrial cancer (EC) is early-stage and thus, curable by surgery, chemotherapy, and radiotherapy (with at least 85% 5-year OS), a fraction of them are aggressive neoplasms such as high-grade or deeply invasive lesions and thus exhibit poor prognosis. African American (AA) women are disproportionately affected by high-grade EC and have 80% higher mortality rate compared with Caucasian American (CA) women. In this work, we evaluated the prognostic ability of computational measurements of architecture of tumor-infiltrating lymphocytes (ArcTIL) from H&E slide images for EC. We also investigated the presence of morphologic differences in terms of ArcTIL features between AA and CA women and whether ArcTIL based population-specific models were more prognostic of OS in AA women compared to a population-agnostic model. **Methods:** The study included digitized H&E tissue slides from 445 post-surgery EC patients from TCGA, with further chemotherapy, or radiotherapy, including only the AA and CA patients, patients without reported race or from other populations were excluded. The dataset was divided into discovery (D1, n = 300), and a validation set (D2, n = 145), while ensuring population balance between two splits (D1(AA) = 65, D1(CA) = 235, D2(AA) = 37, D2(CA) = 108). A machine learning approach was employed to identify tumor regions, and tumor-associated stroma on the diagnostic slides and then used to automatically identify TILs within these compartments. Graph network theory based computational algorithms were used to capture 85 quantitative descriptors of the architectural patterns of intratumoral and stromal TILs. A multivariable Cox regression model (MCRM) was used to create population specific-prognostic models (M_{AA}, M_{CA}) and a population-agnostic model (M_{AA+CA})) to predict OS. All 3 models were evaluated on D2(AA), D2(CA), and D2. **Results:** M_{AA} identified 4 prognostic features relating to interaction of TIL clusters with cancer nuclei in stromal compartment and was prognostic of OS on D2(AA) (see Table) but not prognostic in D2(CA) nor D2(AA+CA). M_{CA} and M_{AA+CA} identified respectively 7 and 6 prognostic features relating to interaction of TIL clusters with cancer nuclei (both in the epithelial and stromal regions) and were prognostic of OS on D2(CA) and D2, but not prognostic in D2(AA). **Conclusions:** Our findings suggest an important role of stromal TIL architecture in prognosticating OS in AA women with EC, while epithelial TIL features were more prognostic in CA women. These findings need to be validated in larger, multi-site validation sets. Research Sponsor: U.S. National Institutes of Health, US Department of Veterans Affairs, US Department of Defense.

	M_AA			M_AA+CA			M_CA		
	HR	CI	P	HR	CI	P	HR	CI	P
D2(AA)	6.16	1.55-24.45	0.01	0.91	0.23-3.62	0.9	1.40	0.36-5.52	0.6
D2	2.12	0.94-4.77	0.07	3.99	1.62-9.78	0.03	2.38	1.07-5.31	0.03
D2(CA)	1.93	0.71-5.24	0.2	7.34	2.12-25.47	0.02	3.47	1.24-9.77	0.02

5586 **Poster Session**

Lurbinectedin (LUR) in combination with Irinotecan (IRI) in patients (pts) with advanced endometrial carcinoma. *First Author: Alejandro Falcon Gonzalez, Hospital Universitario Virgen del Rocio, Seville, Spain*

Background: LUR is a new agent that exerts antitumor activity through inhibition of trans-activated transcription and modulation of tumor microenvironment. Preclinical synergism/additivity in combination with IRI has been reported, thus prompting the conduct of this trial. This synergism had been evaluated and recently reported in patients with Small Cell Lung Cancer, with encouraging results (Ponce et al. WCLC, 2020). **Methods:** Phase I trial to evaluate escalating doses of LUR on Day (D) 1 plus a fixed dose of IRI 75 mg/m^2 on D1 and D8 every 3 weeks (q3w) in pts with advanced solid tumors, enrolled following a standard 3+3 dose escalation design. Phase II to expand in selected indications at the Recommended Dose (RD). In this abstract, the cohort of patients with endometrial carcinoma treated at the RD is presented. **Results:** 21 pts (all female) with endometrial carcinoma were treated at the RD (LUR 2 mg/m2 + IRI 75 mg/m2 + G-CSF); 57% had ECOG PS=1; median age was 64 years (range 34-74); subtype of tumour was split: 67% (14 pts) endometroid, 33% non-endometroid (3 pts serouspapilar, 3 pts clear-cell and 1 pt undifferentiated); median of 2 prior lines (range, 1−7) per pt. Common G1/2 toxicities were nausea, vomiting, fatigue, diarrhea and anorexia; G3/4 hematological toxicities comprised neutropenia (33%), thrombocytopenia (5%) and anemia (38%). Two episodes of febrile neutropenia occurred (9.5%). G3/4 non hematological toxicities consisted of diarrhea (24%), asthenia (19%), nausea (14%) and vomiting (5%), all were transient and manageable. 1 patient (5%) discontinued treatment due to toxicity drug-related (generalized muscular weakness), but no treatment-related deaths were reported. Objective RECIST responses were documented in 4/21 evaluable pts (19%). With 6 pts censored for progression, median PFS was 4.4 months (95% CI 2.1-9.6 months), and PFS at 6 months was 40.4%. The clinical benefit rate (% of pts with Complete Response (CR), Partial Response (PR) or Stable Disease > 4 months) was 43%, and the Disease Control Rate (% of pts with CR, PR or SD) 81%. 3/21 pts (14%) have been more than 12 months on treatment so far. **Conclusions:** The combination of Lurbinectedin and Irinotecan is active in heavily pretreated patients with endometrial carcinoma. The combination was well-tolerated and consistent with the known safety profile for this combination. Myelosuppression, diarrhea, nausea and asthenia were predictable and manageable. Updated results of this cohort will be presented at the meeting. Clinical trial information: NCT02611024. Research Sponsor: PharmaMar SA, CDTI.

5587 **Poster Session**

Exploring molecular profiles of uterine carcinosarcoma with alterations in the chromatin remodeling pathway. *First Author: Annelise M. Wilhite, University of South Alabama, Mobile, AL*

Background: In a preliminary data analysis to identify prognostic molecular biomarkers in uterine carcinosarcoma (UCS), we found that alterations in KMT2C, a gene involved in the chromatin remodeling pathway, correlated with improved survival. We sought to explore relevant biomarkers of KMT2C-mutated (KMT2C-mut) tumors compared to wildtype (KMT2C-wt) tumors. **Methods:** Tumor samples were analyzed using next generation sequencing (NGS) of the DNA (NextSeq, 592 genes or NovaSeq, whole exome sequencing) and RNA (NovaSeq, whole transcriptome sequencing) and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ).PD-L1 IHC used SP-142 (cut-off >1%). Microsatelite instability (MSI) was tested by FA, IHC and NGS. TMB was measured by totaling somatic mutations per tumor (high > 10 mutations per MB). Immune cell fraction was calculated by QuantiSeq. Overall survival (OS) information was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patient cohorts. Statistical significance was determined using chi-square and Wilcoxon rank sum test and p values adjusted for multiple comparisons (q) to be <0.05. **Results:** Molecular analysis was performed on 1,144 UCS tumors. 7.7% were found to be KMT2C-mut. Patients with pathogenic alterations in KMT2C had longer median OS than patients without (OS not yet reached vs 19.0 months HR(95% CI): 0.37(0.19-0.72) p< 0.01). The most common mutations in KMT2C-mut tumors are shown in Table and resulted in more frequent dysregulation in the following pathways compared to KMT2C-wt tumors: chromatin remodeling (100% vs 28%; q<0.01), WNT (39% vs 12%; q=0.01), base/nucleotide excision repair (29% vs 5%; q<0.01), homologous recombination (26% vs 6%; q=0.02), DNA damage sensors (23% vs 4%; q=0.02) and Fanconi anemia (13% vs 1%; q=0.04). KMT2C-mut tumors were more frequently MSI-H (32% vs 6%; q<0.01) and TMB-H (42% vs 5%; q<0.01). Among MSS tumors, KMT2C-mut tumors had increased mutations in JAK1 and POLE (q<0.01) and higher frequency of TMB-H (24% vs 1%; q<0.01) than KMT2C-wt tumors. Additionally, MSS patients with KMT2C-mut had longer OS than patients with KMT2C-wt tumors (OS not yet reached vs 18.9 months; HR(95% CI): 0.33(0.15-0.75) p< 0.01). **Conclusions:** Mutations in KMT2C correlate with improved OS in UCS. KMT2C-mut tumors have distinct molecular profiles from wild type tumors. They exhibit greater immunogenicity, including more frequent MSI-H and TMB-H. This suggests a potential role for Immune-oncology (IO) therapy. Further study of the impact of IO therapies in the cohort is warranted as this may contribute to the improved survival of these patients. Research Sponsor: None.

Gene mutation	Mut	WT	q
PTEN	48.4%	21.6%	0.05
FBXW7	43.3%	17.9%	0.05
JAK1	35.5%	3.6%	<0.01
KMT2D	32.1%	6.9%	0.02
RB1	29.1%	7.1%	0.12
NF1	28.6%	6.5%	0.18
POLE	25.8%	1.0%	<0.01
DICER1	19.4%	2.0%	0.02
ATM	16.1%	1.0%	0.01
MAP3K1	13.8%	0.6%	0.03

5588 **Poster Session**

Association of the presence of estrogen and progesterone receptors in uterine carcinosarcoma with improved survival and increased immunogenicity. *First Author: Nathaniel L. Jones, University of South Alabama, Mobile, AL*

Background: Recent data has shed light on molecular profiles of uterine carcinosarcoma (UCS), but few have correlated molecular profiles with prognosis. In a preliminary data analysis, we found that hormone receptors (HR)—estrogen receptor (ER) and progesterone receptor (PR)—expression was associated with improved OS. Here, we investigate the molecular profile differences between ER+/- and PR +/- tumors. **Methods:** Tumor samples were analyzed using Next-Generation sequencing of DNA (NextSeq, 592 genes or NovaSeq, whole exome sequencing) and RNA (NovaSeq, whole transcriptome sequencing) and immunohistochemistry (IHC) at the Caris Life Sciences Laboratory (Phoenix, AZ).ER and PR tested by IHC on whole tumor (cut-off: +1, 10%). PD-L1 IHC used SP-142 (cut-off >1%). MSI was tested by FA, IHC an NGS. TMB was measured by totaling somatic mutations per tumor (high > 10 mutations per MB). Immune cell fraction was calculated by QuantiSeq. Overall survival (OS) information was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined cohorts. Statistical significance was determined by chi-square and Wilcoxon rank sum test and p-values adjusted for multiple comparisons (q) to be <0.05. **Results:** 1,144 UCS tumors were included. (ER+, n=261; PR+, n=197; HR+ (ER+ and PR+), n=168). Median OS for patients with hormone receptor (HR)+ tumors was significantly longer than for patients with HR- tumors (months: 34.8 vs 17.4; HR(95% CI): 0.67 (0.53-0.84), p<0.01). This remained significant for ER (29.4 vs 17.3) and PR (25.3 vs 18.7) individually. ER+ tumors had fewer alterations in the TP53 pathway (71.4% vs 82.1%) in the WNT (19.5% vs 5.8%) pathway than ER- tumors (q<0.05). PR+ tumors had similar findings in the TP53 and WNT pathways, and also more alterations in the DNA damage sensor pathway. Both ER+ and PR+ UCS tumors had significantly increased MSI-H (ER: 10.9% vs 5.5%, PR: 12.9% vs 5.5%) and TMB-H (ER: 16.8% vs 6.0%; PR: 19.5% vs 6.1%) (all q<0.05) compared to ER- and PR- tumors. They also had increased T-reg cells in their immune micro-environment and increased expression of the immune checkpoint gene IDO1 (q<0.05; Table). **Conclusions:** HR+ tumors have distinct molecular profiles from HR- tumors. ER+ and PR+ UCS tumors appear more immunogenic with more frequent MSI-H status, TMB-H, increased infiltrating regulatory T-cells and IDO1 expression, suggesting possible benefit with immune-oncology (IO) therapy. This may contribute to the observed improved OS, but more data are needed to determine if HR status is a marker of response to IO therapy. Research Sponsor: None.

Immune-related markers in USCs.

Gene	ER+	ER-	Q	PR+	PR-	Q
dMMR/MSI-H (%)	5.5	10.9	0.02	5.51	12.9	<0.01
TMB-H (%)	6.0	16.8	<0.01	6.08	19.5	<0.01
PD-L1 (%)	20.6	24.8	0.17	21.9	20.6	0.69
T-regs (median cell fraction, %)	1.2	0.6	<0.01	1.2	0.6	0.01
IDO1 (median TPM)	6.8	3.0	<0.01	6.2	3.2	0.03

5589 **Poster Session**

Use of Khorana score to predict VTE in patients undergoing chemotherapy for uterine cancer. *First Author: Vincent Wagner, The Ohio State University Wexner Medical Center and James Cancer Hospital, Columbus, OH*

Background: Gynecologic cancers are associated with a high risk of venous thromboembolism (VTE). The Khorana score is a clinically-validated tool to assess risk of VTE in cancer patients (using disease site, BMI and blood counts). Recent ASCO clinical practice guidelines have recommended patients with a Khorana score of 2 or greater be offered pharmacologic thromboprophylaxis during systemic chemotherapy. For women with uterine cancer, the utility of the Khorana score is still unknown. **Methods:** A retrospective cohort study was performed from January 2016 to January 2020. All patients with uterine cancer were screened. Patients receiving chemotherapy, both neoadjuvant (NACT) and adjuvant (ACT), were included. VTE was evaluated for 12 months following the first cycle of chemotherapy. The Khorana score was calculated for each patient using both a high risk score of ≥2 and ≥3 and the patients were stratified based on NACT vs ACT. Logistic regression and chi-square were used to evaluate the prognostic utility of the Khorana score as well as other clinico-pathologic criteria on development of VTE. **Results:** A total of 265 patients were included. The majority of patients were obese (160, 60.4%) and 60 years or older (188, 70.9%). The most common histology was endometrioid (107, 40.4%) followed by serous (71, 26.8%) and the majority were advanced-stage (169, 63.8%). Most women underwent hysterectomy during treatment (243, 91.7%) followed by ACT (228, 86.0%). 14% (37) had NACT. 24 patients developed VTE (9.1%), which was higher, but not statistically different, with NACT vs ACT (13.5% vs 8.3%, p = 0.35). Demographics including age, race and BMI nor pathologic data including histology, grade or stage significantly correlated with development of VTE. Similarly, treatment factors including undergoing hysterectomy and radiation treatment were not statistically significant in regards to VTE. The proportion of patients with high Khorana score (both ≥2 and ≥3) was similar between groups. In the whole cohort, high Khorana score (defined either as ≥2 or ≥3) did not significantly predict VTE; however, the model using ≥3 was more predictive (OR 1.154, 95%CI 0.402-2.907, p = 0.7326). In the NACT cohort, neither model was predictive of VTE (both with OR < 1). In the ACT group, Khorana ≥3 was a better prediction model, but was still not statistically significant (OR 1.557, 95%CI 0.480-4.343, p = 0.4213). **Conclusions:** Although validated in other cancer types, the Khorana score was found to be a poor predictor of VTE in this population. A defined high risk Khorana score of ≥3 (per the original validation study) better predicted VTE than a score of ≥2 (per guidelines). Independent of the Khorana score, demographic and pathologic data were poor predictors of VTE. At this time, use of the Khorana score to guide routine thromboprophylaxis in patients undergoing chemotherapy for uterine cancer should be used with caution. Research Sponsor: None.

5590 **Poster Session**

Immune-response markers and actual response to immune-oncology therapy in uterine serous carcinoma. *First Author: Nathaniel L. Jones, University of South Alabama, Mobile, AL*

Background: Uterine serous carcinoma (USC) is an aggressive subtype of endometrial cancer with poor prognosis and limited treatment options. Immune-oncology (IO) agents have shown promise USC, however data is limited regarding which patients benefit most from IO therapy. In other malignancies, PD-L1, MSI-H status and high TMB have been predictive of IO response. We sought to characterize the immune profiles of USC and investigate treatment response to IO therapy. **Methods:** Tumor samples were analyzed using Nex-Gen sequencing of the DNA (NextSeq, 592 genes or NovaSeq, whole exome sequencing) and RNA (NovaSeq, whole transcriptome sequencing) and immunohistochemistry (IHC) (Caris Life Sciences, Phoenix, AZ).PD-L1 IHC used SP-142 (cut-off >1%). MSI was tested by FA, IHC and NGS. TMB was measured by totaling somatic mutations per tumor (high > 10 mutations per MB). Immune cell fraction was calculated by QuantiSeq. Real-world overall survival (OS) information was obtained from insurance claims data and Kaplan-Meier estimates were calculated for molecularly defined patient cohorts. Statistical significance was determined using chi-square and Wilcoxon rank sum test and p values adjusted for multiple comparisons (q) to be < 0.05. **Results:** Molecular analysis was performed on 2,806 USC tumors. The median age was 67 years. 65.3% were from primary tumors, 34.7% from metastatic sites. In total, 92 patients were treated with IO therapy and had a significantly longer median survival than those not treated with IO (months: 59.6 vs 31.2; HR(95% CI): 0.38(0.24-0.61) p < 0.001), resulting in a survival advantage of 867 days. PD-L1 expression was present in 19.1% of cases, but only 2.3% of tumors were MSI-H and 4.2% were TMB-H. Patients with these markers trended toward a better median survival, but this was not significant; PD-L1 (months: 34.4 vs 31.2; HR(95% CI): 0.90 (0.74-1.1), MSI-H (OS not yet reached vs 31.6 months; HR(95% CI): 0.69(0.38-1.25) and TMB-H (months: 36.4 vs 31.6; HR(95% CI): 0.84(0.50-1.39). Regarding the immune microenvironment, the most common infiltrating immune cells were M2 Macrophages (5.35%), B cells (4.71%), myeloid dendritic cells (3.45%), NK cells (2.94%) and regulatory T cells (1.59%). There were few CD8 T cells and non-regulatory CD4 T cells. **Conclusions:** IO therapy was associated with a median survival benefit of more than 2 years in USC. We did not identify any prognostic markers of IO-therapy response. MSI-H and TMB-H are rare in USC, but PD-L1 is present in nearly 20% of cases. Notably these markers did predict a significant survival benefit, which has important clinical implications. Further study is warranted. Research Sponsor: None.

5591 **Poster Session**

Metabolic and bariatric surgery among endometrial cancer survivors: Are we missing an opportunity to help? *First Author: Justin Gray, UB MD Surgery, Buffalo, NY*

Background: Multiple studies have delineated a clear link between the estrogenic effects of obesity and the incidence of endometrial cancer (EC). Obese EC patients are less likely to receive guideline-recommended surgical treatment (ST) relying instead on chemotherapy and radiation therapy. Furthermore, EC patients are more likely to die from obesity-related complications than from cancer-related causes. Several small-scale studies have demonstrated that metabolic and bariatric surgery (MBS) could offer EC patients fast, safe and effective weight loss, which provides an opportunity to improve survival. This is the first population-based study that examines uptake and outcomes of MBS among EC survivors in New York State (NYS). **Methods:** This study was based on the all-payer longitudinal data from the NYS's Statewide Planning and Research Cooperative System and included inpatient and ambulatory surgeries performed between 2006 and 2012. Using ICD and CPT diagnostic and procedure codes, we identified patients diagnosed with EC for the first time, and we further examined whether they received ST within one year of their initial EC diagnosis. We followed EC patients with ST for 4 years to examine the rates of MBS, and we assessed long-term patient outcomes through 2019. We conducted bivariate and multivariate analyses to evaluate all-cause mortality and identify risk factors for poor surgical outcomes and readmissions. **Results:** Among 24,950 EC patients (2006-2012), 16,156 (65%) of them underwent ST within 1 year of EC diagnosis. Compared to those who did not receive ST, patients who underwent ST were younger, less likely to be White and more likely to be from urban counties, had private insurance, diagnosed with diabetes and hypertension, and had lower Elixhauser scores for readmission and mortality ($p < 0.01$ for all). Within 4 years following ST, 136 (0.8%) EC patients underwent MBS. Those who underwent MBS were younger ($p < 0.01$), predominantly white, privately insured, morbidly obese ($p < 0.01$) and diabetic ($p = 0.01$) compared to those who did not undergo MBS. **Conclusions:** Despite having higher risk of mortality from obesity-related complications such as diabetes and cardiovascular disease, the proportion of EC patients obtaining MBS (0.8%) was similar to that seen among the US population eligible for MBS (1.0%). More research is needed to understand barriers to MBS among eligible women with EC. Research Sponsor: Empire Clinical Research Investigator Program (ECRIP).

5592 **Poster Session**

Photodynamic therapy for preinvasive vaginal cancer. *First Author: Viktoria A. Ivanova, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Photodynamic therapy (PDT) is an effective method for the treatment of various cancers resulting in apoptosis, autophagy and ischemic necrosis of irradiated tissues. The purpose of the study was to analyze the efficacy of PDT for pre-invasive vaginal cancer treatment. **Methods:** PDT results were studied in 20 patients aged 32-65 years with verified pre-invasive vaginal cancer. All patients received PDT with the Latus diode laser and Photolon or Photolan photosensitizers. The effect was evaluated with extended colposcopy. The criteria for efficiency included normalization of the colposcopic picture and the absence of atypical cells. The sizes of the irradiation fields varied from 1.5 to 2 cm, the number of fields - from 1 to 4, the power density - from 0.1 to 0.17 W/cm2, the light dose - from 40 to 100 J/cm2. The duration of a PDT session varied from 10 to 30 min, depending on the number of irradiation fields. The irradiation field necessarily included an area of normal tissue 3-5 mm surrounding the lesion. 4 to 6 sessions were required to restore the normal layer of stratified squamous epithelium. The antitumor efficacy of PDT was evaluated based on the results of visual observation of changes in the area of the treated pathological foci and information on the presence or absence of clinical symptoms of the disease 1 and 3 months after the treatment (WHO criteria). **Results:** Complete regression was registered in 100% of patients after 3 months. Repeated courses of PDT were required in cases with a wide spread of pathological foci and the impossibility of their simultaneous irradiation. At follow-up after 1 month, 3 of 20 patients (15%) showed local foci of atypical changes in the epithelium managed with repeated PDT courses. In 6 months, stable remission of the disease clinical symptoms in the treated pathological foci was registered. The results of the cytological study performed 3 months after PDT were normal in 100% patients; no negative changes were registered 6 and 12 months after PDT. **Conclusions:** The results of PDT in the treatment of patients with pre-invasive vaginal cancer demonstrated its high therapeutic efficacy and a minimal number of adverse reactions, which allows recommending PDT in the treatment of pre-invasive vaginal cancer. Research Sponsor: None.

5593 **Poster Session**

Does time to completion of radiation treatment in locally advanced vulvar cancer impact survival? *First Author: Nancy T. Nguyen, University of California Davis, Department of Obstetrics Gynecology, Division of Gynecologic Oncology, Sacramento, CA*

Background: Although well established in cervical cancer, it is unclear whether time from initiation to completion of radiation therapy for vulvar cancer affects survival outcomes. We seek to assess if completion of radiation, either alone (RT) or as concurrent chemoradiation (CRT), within a planned timeframe in locally advanced squamous cell vulvar cancer impacts overall survival (OS). **Methods:** Women 18 years or older with FIGO stage II to IVA vulvar cancer who received external beam RT or CRT as part of their initial treatment course were identified from the National Cancer Database from 2004-2017. Patients with non-squamous cell carcinoma histology or who received systemic cytotoxic therapies as primary treatment were excluded. Patients who received less than 20 fractions of radiation were also excluded. Time to radiation completion was the number of days from the initiation to completion of radiation. The delay of radiation completion was calculated as the difference between the actual time to radiation completion and predicted duration of radiation. Types of treatment (RT and CRT) were both stratified into groups based on the delay of radiation completion, less than 7 days or greater than 7 days. Chi-square, Fisher Exact ANOVA and Kruskal-Wallis tests were used for analysis. Kaplan-Meier curves with log-rank tests were fit for univariate time-to-event analysis. Multivariable Cox proportional hazard models were fit to assess effects after controlling for confounding. **Results:** There were 2378 patients identified for analysis (n = 856 RT and n = 1522 CRT). Median age was 67 (IQR 56-78) and the CRT group was younger ($p < 0.0001$) than the RT group. The majority were white (88.35%) with advanced FIGO stage III or IVA (72.29 %) disease. Median dose of total radiation was 5720 cGy (IQR 5040-6300) with higher doses observed in the greater than 7 days delay group versus less than 7 days, ($p < 0.0001$). Median follow up was 27.2 (IQR 11.8-57.9) months. For both cohorts, completion of treatment with delay less than 7 days resulted in significant improvement in median survival when compared to treatment completion delay of more than 7 days: RT (Median OS 34.9 versus 21.6 months, $p < 0.01$) and CRT (58 versus 41.3 months, $p < 0.01$). On multivariate subset analysis, both completion of CRT and RT were associated with improved OS when treatment was completed with less than 7 days delay vs greater than 7 days delay, CRT (HR 0.869 [95%CI 0.758-0.997]), RT (HR 0.820 [95%CI 0.698-0.964]). Advanced FIGO stage IVA was associated with the greatest increase in hazard of death, (HR 1.758 [95%CI 1.516-2.039]), compared to FIGO stage II. **Conclusions:** Completion of radiation with less than 7 days delay is associated with improved overall survival, which is independent of concurrent chemotherapy. These findings suggest that strategies to minimize delays in radiation treatment are crucial in treating locally advanced vulvar cancer. Research Sponsor: University of California Davis Department of Obstetrics and Gynecology.

5594 **Poster Session**

Potential impact of HPV vaccine on incidence of high-grade vulvar, vaginal, and anal precancers among females and males aged 15 to 39 years, United States 2000 to 2017. *First Author: Mona Saraiya, CDC/NCCDPHP/DCPC, Atlanta, GA*

Background: Since introduction of HPV vaccine, cervical precancers have decreased, but the vaccine's impact on non-cervical anogenital precancers is unknown. These precancers are identified opportunistically and are not routinely collected in most cancer registries. **Methods:** We examined high-grade vulvar (VIN3), vaginal (VAIN3), and anal (AIN3) precancers among persons aged 15-39 years using 2000-2017 data from select cancer registries covering 27.8% of the U.S. population. Incidence trends were evaluated with Joinpoint regression. **Results:** VIN3 rates declined 21% per year post-HPV vaccination introduction among women. VAIN3 rates declined 19.1% per year among women aged 15-29 years, also post-HPV vaccination introduction. Compared to the pre-vaccination period when AIN3 rates were increasing, AIN3 rates were stable among women aged 15-29 years and among men aged 30-39 years. **Conclusions:** Decreases in rates of VIN3 and VAIN3 after HPV vaccine introduction among younger age groups were similar to declines observed in cervical precancers, suggesting HPV vaccine impact. Research Sponsor: Funding support for the primary author was received from Oak Ridge Institute for Science and Education, an asset of the United States Department of Energy.

TPS5595 **Poster Session**

AdvanTIG-202: A phase 2 study investigating anti-TIGIT monoclonal antibody ociperlimab plus anti-PD-1 monoclonal antibody tislelizumab in patients with previously treated recurrent or metastatic cervical cancer. *First Author: Lingying Wu, Cancer Hospital, Chinese Academy of Medical Sciences, Beijing, China*

Background: Women with recurrent/metastatic cervical cancer represent a poor prognostic group with high unmet clinical needs. T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domains (TIGIT) is a co-inhibitory, immune checkpoint receptor expressed on immune cells and upregulated on T-cells and natural killer cells in multiple solid tumors, inhibiting anticancer immune responses. Ociperlimab (BGB-A1217) is a novel, humanized, monoclonal antibody that binds TIGIT with high specificity and affinity, blocking the interaction with its ligands on tumor cells. Tislelizumab is an anti-PD-1 antibody engineered to minimize binding to FcγR on macrophages to abrogate antibody-dependent phagocytosis, a mechanism of T-cell clearance and potential resistance to anti-PD-1 therapy. Preclinical and clinical studies suggest that dual targeting with anti-TIGIT and anti-PD-1 antibodies produces synergistic immune cell activation and enhanced antitumor activity. **Methods:** AdvanTIG-202 is a Phase 2, randomized, multicenter, open-label study (NCT04693234). Approximately 167 pts with cervical squamous cell or adenosquamous carcinoma or adenocarcinoma, recruited from 100 centers, whose disease progressed on or after ≥ 1 prior line of chemotherapy for recurrent/metastatic disease will be included in this 2-Part study. In Part 1, approximately 80 pts will be randomized (1:1) to either ociperlimab 900 mg intravenously (IV) in combination with tislelizumab 200 mg IV every 3 weeks (Q3W) (Arm 1), or tislelizumab monotherapy 200 mg IV Q3W (Arm 2), until disease progression, unacceptable toxicity, or withdrawal of consent. In Part 2, Arm 1 will be expanded by approximately 87 additional pts whose tumors are evaluable for PD-L1 expression. The primary endpoint is overall response rate (ORR) (RECIST v1.1) assessed by Independent Review Committee (IRC) in Arm 1. Secondary endpoints are investigator-assessed ORR in Arm 2, IRC-assessed and investigator-assessed ORR in Arm 1, IRC-assessed and investigator-assessed duration of response, progression-free survival, time to response, disease control rate, clinical benefit rate and overall survival, cancer-specific health-related quality of life (HRQoL), safety, pharmacokinetics and immunogenicity in Arms 1 and 2. Exploratory endpoints are generic HRQoL and the association of biomarkers with patient prognosis, response or resistance. Clinical trial information: NCT04693234. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Jessica Jones, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by BeiGene, Ltd.

TPS5596 **Poster Session**

Tisotumab vedotin versus investigator's choice chemotherapy in second- or third-line recurrent or metastatic cervical cancer (innovaTV 301/ENGOT-cx12/GOG 3057, trial in progress). *First Author: Ignace Vergote, Belgium and Luxembourg Gynaecological Oncology Group (BCOG), University of Leuven, Leuven Cancer Institute, Leuven, Belgium*

Background: Doublet chemotherapy (paclitaxel plus either platinum or topotecan) with bevacizumab (if eligible) is recommended for first-line treatment of recurrent (not amenable to curative therapy) or metastatic cervical cancer (r/mCC; Tewari 2014). In the second-line setting, there are limited data for currently available treatment options. Tisotumab vedotin (TV) is an investigational antibody-drug conjugate (ADC) composed of a tissue factor (TF)-directed human monoclonal antibody covalently linked to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable linker. TV is directed to cells expressing TF and releases MMAE upon internalization, resulting in cell cycle arrest and apoptotic cell death. TV has anti-tumor activity on multiple tumor types and kills tumor cells by direct cytotoxicity, bystander cytotoxicity, antibody-dependent cellular cytotoxicity, antibody-dependent cellular phagocytosis , and in a manner consistent with immunogenic cell death. In a recent phase 2 pivotal trial (innovaTV 204), TV demonstrated a clinically meaningful objective response rate (ORR) of 24% and median duration of response (DOR) of 8.3 months, as well as a manageable and tolerable safety profile with most adverse events being mild to moderate, in r/mCC patients with disease progression on or after chemotherapy. These findings support further investigation of TV in patients with r/mCC who progress on available first-line treatment options. **Methods:** The innovaTV 301 trial (NCT04697628) is a global, randomized, open-label, phase 3 clinical trial evaluating the efficacy and safety of TV in patients with previously treated r/mCC. Eligible patients must be ≥18 years, have r/mCC, and have experienced disease progression after receiving 1-2 prior lines of therapy (either standard of care systemic chemotherapy doublet or platinum-based therapy [if eligible; paclitaxel+cisplatin+bevacizumab, paclitaxel+carboplatin+bevacizumab, or paclitaxel+topotecan/nogitecan+bevacizumab]). Approximately 482 patients will be randomized 1:1 to receive 21-day cycles of either TV (2.0 mg/kg IV once every 3 weeks) or investigator's choice of chemotherapy: topotecan (1 or 1.25 mg/m^2 IV; Day 1 [D1] to D5 of each cycle), vinorelbine (30 mg/m^2 IV; D1 and D8 of each cycle), gemcitabine (1000 mg/m^2 IV; D1 and D8 of each cycle), irinotecan (100 or 125 mg/m^2 IV; weekly for 28days, then every 42 days), or pemetrexed (500 mg/m^2 IV, D1 of each cycle). The primary endpoint of this trial is overall survival. Key secondary endpoints are progression-free survival, ORR, time to response, DOR, safety, and quality of life outcomes. The study is currently enrolling and will have sites open in the US, EU, Japan, Latin America, Taiwan, Singapore, and South Korea. Clinical trial information: NCT04697628. Research Sponsor: Seagen Inc.

TPS5597 **Poster Session**

Immunotherapy in combination with PARP inhibition in advanced cervical cancer patients functionally competent or deficient for the Fanconi anemia repair pathway. *First Author: John Paul Diaz, Miami Cancer Institute Baptist Health South Florida, Miami, FL*

Background: Immunotherapy has improved outcomes for patients with recurrent or metastatic cervical cancer whose tumors express PD-L1. Pembrolizumab (PEM), a monoclonal antibody that binds to programmed cell death 1 (PD 1) receptor, inhibits interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). It is approved for the treatment of recurrent or metastatic cervical cancer. Despite promising results, new strategies are being developed to improve immunotherapy responses. This includes DNA-damaging agents that have the potential to enhance the response to immunotherapy by promoting neo-antigen release, increasing tumor mutational burden, and enhancing PD-L1 expression. Poly-ADP-ribose polymerase (PARP) inhibitors, such as olaparib, have shown synergy with immunotherapy in preclinical and early clinical studies. PARP-based therapy is based on the inhibition of single-strand DNA repair, leading to DNA damage and increased tumor mutational burden. As a result, the tumor becomes a more attractive target for immunotherapy. Based on this, we are investigating the interplay between homologous recombination (HR) repair deficiency, another mechanism of DNA repair, and solid tumor response to ICI. Our approach uses an all-inclusive functional immunofluorescence assay of the Fanconi Anemia triple-staining immunofluorescence (FATSI) we developed and can be performed in paraffin-embedded tumors. **Methods:** This is a phase II open-label single center trial evaluating the role of PEM and olaparib in patients with metastatic cervical cancer who have progressed on first-line standard of care chemotherapy. FATSI will be performed in all patients. We hypothesize that FATSI negative tumors will be associated with improved responses. Other eligibility criteria include measurable disease by imaging, 18 years of age or older, and no previous exposure to ICI or PARP inhibitor. The primary objective is to evaluate the immune-related objective response rate (iORR) achieved in patients with FA Repair Pathway functionally competent and functionally deficient tumors. Secondary objectives include 20-week progression free survival and overall survival. Other exploratory objectives include evaluation of the mutation load and markers of neo-antigenicity, T cell receptor clonotype analyses (before and after treatment), and alterations in HR repair genes. We will utilize a two-stage phase II design to detect an iORR ≥ 20% in the whole population tested vs. the null hypothesis that the true iORR ≤5%, represents a response by chance alone or other infrequent unknown mechanisms. An interim analysis requires at least 2 of the first 20 evaluable patients enrolled have an objective response. If this occurs, we will accrue 28 additional patients to total 48. Enrollment is ongoing and two patients are currently on treatment. Clinical trial information: NCT04483544. Research Sponsor: Florida Department of Health, Pharmaceutical/Biotech Company.

TPS5598 **Poster Session**

ENGOT-ov54/Swiss-GO-2/MATAO including LOGOS (Low-Grade Ovarian cancer Sub-study): MAintenance Therapy with Aromatase inhibitor in epithelial Ovarian cancer—A randomized, double-blinded, placebo-controlled, multicenter phase III Trial. *First Author: Viola A. Heinzelmann-Schwarz, Swiss GO and University Hospital Basel, Basel, Switzerland*

Background: The prognosis of advanced epithelial ovarian cancer (OC) is poor with a relapse rate of 75% at 5 years. Some 80% of OC express estrogen receptor (ER). This is the first trial that wants to capitalize on this and prospectively evaluates letrozole, a potent aromatase inhibitor, as initial maintenance treatment for high and low grade OC. **Methods:** Eligible pts have primary OC, FIGO Stage II-IV with low or high grade serous or endometrioid histology, with (interval) debulking surgery, ECOG-status 0-2, Positivity (≥ 1%) for ER expression, and at least 4 cycles of platinum-based chemotherapy (neoadjuvant allowed). Pts are allowed to undergo concurrent maintenance treatment with bevacizumab and PARP inhibitors. Extensive quality of life (QoL) questionnaires via an App and physical activity measurements by a tracking device as well as G8 geriatric score, ESGO surgery questionnaire, and Charleson Comorbidity Index are routinely assessed. Primary objective is to evaluate the efficacy of letrozole maintenance therapy after standard surgical and chemotherapy treatment as measured by Progression Free Survival (PFS) compared to no maintenance therapy (placebo). Primary outcome is PFS, defined as time from date of first letrozole/placebo administration until date of progression or death by any cause. Stratification for high and low grade histologies and ER measurement is performed via a digital centralized pathology review process. Final analysis will be performed for the whole cohort and for the subgroup of low grade ovarian cancers (LOGOS subprotocol). Secondary objectives and outcomes are overall survival (OS), quality adjusted progression free survival (QAPFS), time to first subsequent treatment (TFST), quality adjusted time without symptoms (TWiST), and health related QoL. Study is designed as international, randomized (1:1 ratio), two-arm, multi-centric, double-blinded, placebo-controlled superiority phase III trial. In total, 528 pts will be randomly assigned to letrozole or placebo for 5 yrs or until unacceptable toxicity, progression of underlying disease, or study discontinuation. Final analysis is planned after 5 years without interval analysis and follow-up is collected for up to 10yr and for the low-grade cohort for up to 12yr. Clinical trial information: NCT04111978. Research Sponsor: Swiss GO Trial Group.

TPS5599 **Poster Session**

Clinical trial in progress: Pivotal study of VB-111 combined with paclitaxel versus paclitaxel for treatment of platinum-resistant ovarian cancer (OVAL, VB-111-701/GOG-3018). *First Author: Rebecca Christian Arend, University of Alabama at Birmingham, Birmingham, AL*

Background: Ofranergene obadenovec (VB-111) is a targeted anti-cancer gene therapy with a dual mechanism of action that includes a broad antiangiogenic effect and induction of a tumor directed immune response. A phase II trial in patients with platinum resistant ovarian cancer showed that VB-111 in combination with weekly paclitaxel was well tolerated and associated with a CA-125 Objective Response Rate (ORR) of 58% with a trend for improved survival. The favorable outcomes were associated with induction of an immunotherapeutic effect of tumor infiltration with CD-8 T cells. Based on these observations, a phase III study was initiated in collaboration with the GOG Foundation, Inc. **Methods:** Study NCT03398655 is an international, randomized, double-blind, placebo-controlled, phase III study. Eligible patients have recurrent platinum-resistant epithelial ovarian cancer with measurable disease (RECIST 1.1), and may have been previously treated with up to 5 prior lines of therapy. Patient are randomized 1:1 to receive VB-111 (1x10^{13} VPs) with weekly paclitaxel (80mg/m^2), or weekly paclitaxel with placebo. Randomization is stratified by number of prior treatment lines, prior antiangiogenic therapy and platinum refractory disease status. The efficacy endpoints are OS, PFS and ORR by RECIST 1.1 and by CA-125 (GCIG criteria). A pre-planned interim analysis was performed by the DSMC in the first 60 patients evaluable for CA-125 response. The analysis met the pre-defined criteria of a CA-125 ORR (GCIG) in the treatment arm at least 10% higher than in the control arm. Study enrolment is ongoing and over 220 patients were enrolled in the US, EU, and Israel. Enrolment of the full sample size of 400 patients is expected to complete by the end of 2021. Clinical trial information: NCT03398655. Research Sponsor: VBL therapeutics.

TPS5600 **Poster Session**

Trial in progress: A phase 1, multicenter, open-label, dose-exploration and dose-expansion study evaluating the safety, tolerability, pharmacokinetics, and efficacy of AMG650 in subjects with advanced solid tumors. *First Author: Ramaswamy Govindan, Washington University School of Medicine, St. Louis, MO*

Background: KIF18A is a mitotic kinesin motor protein that regulates chromosome positioning during cell division and is overexpressed in a subset of human cancers. *TP53* mutant unstable aneuploid cancer cells with chromosomal instability (CIN) features are dependent on KIF18A motor activity to prevent lethal multipolar cell division. Preclinical data demonstrate that treatment with AMG 650; an oral, first in class, selective small molecule inhibitor of KIF18A may be safe and tolerable. We are conducting a first-in-human phase 1 study with AMG 650 in adult subjects with locally advanced or metastatic solid tumors with *TP53MUT*, triple negative breast cancer (TNBC), high grade serous ovarian cancer (HGSOC) or serous like endometrial cancers and other solid tumors. **Methods:** In this phase 1, multicentric, dose escalation and dose expansion study we evaluate the safety and tolerability of AMG 650 monotherapy in patients with advanced/metastatic solid tumors (NCT04293094). The main objective is to determine the maximum tolerated dose (MTD) and/or recommended phase 2 dose (RP2D) based on emerging safety, efficacy, and pharmacodynamics (PD) data prior to reaching the MTD. Key inclusion criteria include the presence of measurable disease and diagnosis of advanced/metastatic triple negative breast cancer (TNBC), high-grade serous ovarian cancer (HGSOC), serous-like endometrial cancer or other solid tumors with documented TP53 mutations. In the dose expansion phase, participants with locally advanced or metastatic TNBC or HGSOC will be treated with the preliminary RP2D identified from the dose exploration part of the study. Primary endpoints include the incidence of Dose Limiting Toxicities (DLTs),Treatment-Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Treatment-related Adverse Events and the evaluation of the number of participants who experience a clinically significant change from baseline in vital signs, electrocardiogram and laboratory tests parameters. Secondary endpoints include Objective Response Rate, Duration of Response, Progression-free Survival, Clinical Benefit Rate, Time to Response, Time to Progression, Overall Survival (OS), Maximum Plasma Concentration (Cmax) of AMG 650, Time to Maximum Plasma Concentration (Tmax) of AMG 650 as well as Area Under the Plasma Concentration-time Curve (AUC) Over the Dosing Interval for AMG 650. Continuous monitoring of toxicity is conducted. The study began enrolling pts in March 2020 and is ongoing. For more information, please contact Amgen Medical Information: medinfo@amgen.com Clinical trial information: NCT04293094. Research Sponsor: Amgen inc.

TPS5601 **Poster Session**

A randomized phase III, two-arm trial of paclitaxel, carboplatin, and maintenance letrozole versus letrozole monotherapy in patients with stage II-IV, primary low-grade serous carcinoma of the ovary or peritoneum. *First Author: Amanda Nickles Fader, The Johns Hopkins Hospital, Baltimore, MD*

Background: Low-grade serous carcinoma of the ovary or peritoneum (LGSOC) is a rare subtype of epithelial carcinoma. Differences in epidemiology, pathogenesis, disease presentation, and clinical outcomes have been characterized between women diagnosed with LGSOC and those with the p53-driven high-grade serous carcinoma (HGSOC). Ultimately, patients with LGSOC should be treated differently than those with HGSOC. Several studies suggest that LGSOC is relatively chemoresistant and that most tumors robustly express estrogen and progesterone receptors. Recently, retrospective reports suggest that utilization of the aromatase inhibitor, letrozole, as monotherapy or in addition to platinum/taxane-based chemotherapy in those with primary advanced-stage LGSOC results in preliminarily promising survival outcomes. **Methods:** This study is a two-arm, randomized, open-label, Phase III clinical trial. The primary objective is to assess whether letrozole monotherapy (2.5 mg po daily) is non-inferior to carboplatin (AUC 5-6) and paclitaxel (175 mg/m^2) followed by letrozole maintenance therapy with respect to progression free survival in women with primary, Stage II-IV LGSOC who have undergone an attempt at maximal surgical cytoreduction. Secondary endpoints include incidence of adverse events, objective response rate in those with measurable disease after surgery, response duration, overall survival, and adherence to letrozole maintenance therapy. Study subjects must have undergone a bilateral salpingo-oophorectomy, and p53 IHC testing of tumors is required to rule out those with aberrant p53 expression commonly observed in HGSOC tumors. Study strata include residual disease status and country of enrollment. Four hundred and fifty patients will be enrolled in the United States, Canada and South Korea through the NRG Oncology trials network. Correlative aims include analyzing the association of ER/PR tumoral expression with aromatase inhibitor therapy response and determining ESR1 mutational status in those who develop letrozole resistance. The study includes two interim analyses; at 20% information time, a futility analysis will be conducted, and at 40% information time, both efficacy and futility will be assessed. This is one of the first randomized trials performed in women with primary, advanced LGSOC, and the study is open with 71 patients enrolled at the time of abstract submission. Clinical trial information: NCT04095364. Research Sponsor: U.S. National Institutes of Health.

TPS5602 **Poster Session**

A phase I/II, multicenter, open-label study of REGN5668 (mucin [MUC]16 x CD28 bispecific antibody [bsAb]) with cemiplimab (programmed death [PD]-1 Ab) or REGN4018 (MUC16 x CD3 bsAb) in recurrent ovarian cancer (rOVCA). *First Author: Ira Seth Winer, Wayne State University/Karmanos Cancer Center, Detroit, MI*

Background: There is a high unmet need in rOVCA treatment, with 14,000 deaths/year in the US and a 30%–40% 5-year overall survival rate in patients (pts) with advanced disease. REGN5668 and REGN4018 are human IgG4-based bsAbs that bridge ovarian MUC16+ tumor cells to CD28 and CD3, respectively, on T-cells to stimulate cytotoxicity. Cemiplimab is a human monoclonal Ab that blocks PD-1 binding to PD-ligand(L)1 and PD-L2. REGN5668 demonstrated increased preclinical anti-tumor activity with PD-1 inhibition or REGN4018 relative to each monotherapy. A Phase I/II study of REGN4018 alone or with cemiplimab is ongoing. **Methods:** This first-in-human study (NCT04590326) will assess safety, tolerability, pharmacokinetics, and preliminary anti-tumor activity of REGN5668 with cemiplimab (Module 1) or REGN4018 (Module 2) in pts with rOVCA. Key inclusion criteria include histologically confirmed diagnosis of advanced epithelial ovarian (except carcinosarcoma), fallopian tube, or primary peritoneal cancer; serum CA-125 level $\geq$2x upper normal limit; $\geq$1 prior-line of platinum-based therapy; prior treatment with or intolerance to available standard-of-care therapy. Exclusion criteria include recent biologic therapy ($<$ 5 half-lives or 28 days, whichever is longer, except $<$ 3 half-lives for bevacizumab or other nonimmunomodulatory Abs with half-lives $>$ 7 days); approved conventional therapy (except biologics or immunotherapy) $<$ 3 weeks (wks) or investigational agents $<$ 4 wks prior to first study dose; and anti–PD-L1 therapy $<$ 5 half-lives prior to first study dose. This two-phase study includes dose escalation (a 4+3 design modified from 3+3) and expansion phases. In Module 1, $\leq$84 pts will receive 3–4 wks of REGN5668 monotherapy lead-in at assigned intravenous (IV) weekly (QW) dose levels, followed by REGN5668 QW combined with cemiplimab IV every 3 wks. In Module 2, $\leq$106 pts will receive 4–5 wks of REGN4018 QW IV lead-in, followed by REGN4018 full QW dose combined with REGN5668 at initial and full assigned QW doses. In expansion, REGN5668+cemiplimab and REGN5668+REGN4018 combination regimens will each recruit 20 pts in stage 1 and 30 pts in stage 2 using a Simon two-stage design. In escalation, primary endpoints are dose-limiting toxicities, serious and treatment-emergent adverse events (TEAEs), deaths, laboratory abnormalities (Grade $\geq$3), concentrations of REGN5668 in serum alone and in each combination regimen; key secondary endpoint is objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. In expansion, primary endpoint is ORR by RECIST 1.1 for each combination; key secondary endpoints are TEAEs, serious AEs, deaths. Key exploratory endpoints are correlation between clinical efficacy endpoints and baseline protein expression levels of MUC16 and PD-L1. Clinical trial information: NCT04590326. Research Sponsor: Regeneron Pharmaceutical, Inc.

TPS5603 **Poster Session**

ENGOT-ov60/GOG3052/RAMP 201: A phase 2 study of VS-6766 (dual RAF/MEK inhibitor) alone and in combination with defactinib (FAK inhibitor) in recurrent low-grade serous ovarian cancer (LGSOC). *First Author: Susana N. Banerjee, The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research, London, United Kingdom*

Background: VS-6766 is a unique small molecule inhibitor that blocks MEK kinase activity and RAF phosphorylation of MEK. This mechanism of blockade has been shown to limit compensatory MEK activation, thereby potentially enhancing efficacy of MEK inhibition. Defactinib, (VS-6063), an orally active small molecule, is a potent adenosine 5'-triphosphate (ATP) competitive, reversible inhibitor of focal adhesion kinase (FAK). Defactinib has shown synergistic activity with BRAF and MEK inhibitors in both in vitro and in vivo solid tumor models. Prior molecularly unselected studies with single agent MEK inhibitors have shown response rates up to 26% in recurrent LGSOC. A third of patients with recurrent LGSOC harbor somatic KRAS mutations. FAK inhibition has been shown to induce tumor regression when combined with RAF, MEK or RAF/MEK inhibitors in in vivo models of KRAS mutant ovarian cancer. The combination of VS-6766 and defactinib is currently being evaluated in the ongoing Investigator Sponsored FRAME study (NCT03875820). In this proof of concept study, durable objective responses have been reported in recurrent LGSOC patients, particularly those with KRAS mutations including patients who have had a prior MEK inhibitor (Banerji et al AACR 2020). Based on preclinical studies demonstrating efficacy of both VS-6766 and the VS-6766/defactinib combination and preliminary results of the FRAME study, the phase II ENGOT-ov60/GOG3052 has been developed in recurrent LGSOC. **Methods:** This is a Phase II, adaptive, two-part, multicenter, parallel cohort, randomized, open label study designed to evaluate the efficacy and safety of VS-6766 versus VS-6766 in combination with defactinib (NCT04625270). The study will be conducted in two parts. Part A will determine the optimal regimen based on confirmed overall response rate (independent radiology review) in KRAS-mutated LGSOC. Part B will determine the efficacy of the optimal regimen identified in Part A in KRAS-mutated and KRAS wild-type LGSOC. The minimum expected enrollment is 52 subjects with KRAS-mutated tumors (32 subjects in Part A and 20 in Part B) and 36 with KRAS wild-type tumors in Part B. Patients will be randomized to receive VS-6766 (4.0 mg PO, twice weekly 3 weeks on, 1 week off) or VS6766 with defactinib (VS-6766 3.2 mg PO, twice weekly + defactinib 200 mg PO BID 3 weeks on, 1 week off) till progression. Key inclusion criteria include histologically confirmed LGSOC, presence of KRAS mutation (Part A), prior systemic therapy for metastatic disease and up to 1 prior line of MEK/RAF inhibitor therapy permitted. This international study is open to enrollment. Clinical trial information: NCT04625270. Research Sponsor: Verastem.

TPS5604 **Poster Session**

ROCSAN trial (GINECO-EN203b/ENGOT-EN8): A multicentric randomized phase II/III evaluating dostarlimab in combination with niraparib versus niraparib alone compared to chemotherapy in the treatment of endometrial/ovarian carcinosarcoma after at least one line of platinum based chemotherapy. *First Author: Isabelle Laure Ray-Coquard, Centre Léon Bérard and University Claude Bernard Lyon 1 and GINECO, Lyon, France*

Background: Gynecological carcinosarcomas (CS) are rare and highly aggressive tumors with a 5-year overall survival (OS) < 10%. After initial treatment majority of patients (pts) relapse and receive diverse chemotherapies (CT) producing modest benefits. The median PFS in relapse after platinum based CT is less than 4 months and median OS less than 1 year. New innovative strategies are urgently needed. Since CS showed high DNA damage response activity and potentially a high tumor mutation load resulting in neo-antigens, a synergy between PARPi and anti-PD1 is expected. **Methods:** ROCSAN is a multicentric, randomized, open-label, integrated Phase II/III study. In the Phase II, 63 pts with recurrent or progressing endometrial or ovarian CS after at least a first line of platinum-based CT will be randomized (2:2:1) to receive either niraparib in monotherapy, niraparib in combination with dostarlimab or standard CT (paclitaxel, doxorubicine, gemcitabine, topotecan). Stratification factors include the number of previous CT lines (1 vs 2-3), FIGO stage at diagnosis (I-II vs III-IV), CS localisation (ovarian vs endometrial), and performance status (0-1 vs 2). The primary objective of the Phase II is to select the best experimental strategy between niraparib and dostarlimab/niraparib combination based on Response Rate at 4 months (RR-4M by RECIST1.1). A single stage design with a 10% unacceptable RR-4M and a 30% targeted RR-4M was used to determine Phase II sample size, assuming a 10% one sided alpha for each comparison and more than 90% power. A pick-the-winner selection design could be used in case of promising efficacy in each experimental arm. At the interim analysis, an Independent Data Monitoring Committee will make recommendation for the selection of the optimal experimental arm. The Steering committee could then support to continue enrolment for the international Phase III which is calibrated to detect an improvement in median OS from 7 months (Standard CT) to 11.7 months (best experimental arm). Assuming a 5% alpha level and 80% power, 133 additional pts could be randomized (2:1). Secondary endpoints include safety, PFS, PFS2, TTST, ORR, duration of response, patient report outcomes (assessed via EORTC QLQ-C30 OV28, HADS, PRO-CTCAE). A translational program supported by European Community is associated to the clinical study to identify predictive biomarkers of response/resistance to study treatments, to correlate with immune environment, a special focus on genetic instability and the EMT process will be included. Trial is currently recruiting only in France for the phase II part, the first pt was randomized in July 2020. Clinical trial information: NCT 03651206. Research Sponsor: GSK, European Community.

TPS5605 **Poster Session**

A phase 3, randomized, double-blind, adaptive, placebo/paclitaxel-controlled study of AVB-S6-500 in combination with paclitaxel in patients with platinum-resistant recurrent ovarian cancer (GOG-3059/ENGOT OV-66/AVB500-OC-004). *First Author: Katherine Cynthia Fuh, Washington University in St. Louis, St. Louis, MO*

Background: The AXL receptor and its activating ligand, GAS6, are important drivers of metastasis and therapeutic resistance in human cancers. This signaling axis represents an attractive target for therapeutic intervention, but the strong picomolar binding affinity between endogenous GAS6 and AXL and the promiscuity of small molecule AXL inhibitors have presented a barrier to specific and potent inhibition of AXL. AVB-S6-500 is a highly sensitive and specific inhibitor of AXL, with ~200-fold higher affinity than wild-type (WT) AXL. AVB-S6-500 binds GAS6, the sole ligand of AXL, inhibiting its interaction with AXL thereby dramatically reducing AXL signaled invasion and migration of highly metastatic cells in vitro and inhibiting metastatic disease in nonclinical models of aggressive human cancers. A Phase 1b study in platinum resistant ovarian cancer showed no dose limiting toxicities and established a recommended Phase 2 dose of 15mg/kg administered every 2 weeks. Longer progression free survival (PFS) and overall survival (OS) times were observed in patients who had not been previously treated with bevacizumab. Furthermore, retrospective analyses demonstrated that serum soluble AXL to GAS6 ratio may identify patients more likely to respond to this therapy. **Methods:** Patients with high grade serous, platinum resistant ovarian cancer, who have received no more than 4 prior therapy regimens will be randomized 1:1 to AVB-500 + PAC or PAC + placebo. Patients will be stratified by recurrence after last platinum regimen (<3, 3-6 months), prior lines (1-2, 3-4), and prior bevacizumab (yes, no). The primary endpoint is PFS by RECIST v 1.1 as assessed by the investigator, with OS a key secondary endpoint. The study design is adaptive; with two interim analyses addressing conditional power in the bevacizumab treated subset, and in a serum soluble AXL, GAS6 biomarker subset, respectively, with interim results used to define the final target population. Simulations confirm a nominal one-sided type 1 error below 0.025, and show >90% statistical power for PFS under the following assumptions of PFS medians. Study recruitment began in Q1. Clinical trial information: NCT04729608. Research Sponsor: Aravive, Inc.

TPS5606 **Poster Session**

FLORA-5: Front-line chemoimmunotherapy (Paclitaxel-Carboplatin-Oregovomab [PCO] versus chemotherapy (Paclitaxel-Carboplatin-Placebo [PCP]) in patients with advanced epithelial ovarian cancer (EOC)—Phase III double-blind placebo controlled multinational study. *First Author: Angeles Alvarez Secord, Duke Cancer Institute, Duke University Medical Center, Durham, NC*

Background: Oregovomab binds tumor-associated CA125 rendering the target antigen CA125 more immunogenic or "neoantigen-like" through altered and enhanced antigen processing and presentation to specific T cells. This phenomenon is hypothesized to bypass tumor-associated immune suppression when administered in combination with chemotherapy. In a randomized phase II study, immunization with oregovomab in a schedule-dependent combination with paclitaxel and carboplatin induced tumor immunity and demonstrated significant improvement in PFS (median (months) 41.8 PCO vs 12.3 PCP, HR 0.44 p = 0.0027, and OS median N.E. PCO vs 43.2 PCP HR 0.34 (p = 0.0077)) in patients with previously untreated EOC. The FLORA-5, the definitive confirmatory global registration trial, is currently recruiting patients in the front-line setting. **Methods:** The study is a phase 3, multicenter, double-blind, placebo-controlled clinical trial. Optimally debulked patients with FIGO III/IV EOC and serum CA125 > 50 U/ml receiving adjuvant (Cohort 1) or neoadjuvant (Cohort 2) chemotherapy will be randomized post-surgery to paclitaxel and carboplatin with or without oregovomab. Patients with germline BRCA1/2 mutations will be excluded. Chemotherapy will be administered every 3 weeks in both cohorts. Oregovomab/placebo is administered simultaneously at cycles 1, 3, and 5 of chemotherapy with a single maintenance dose at 12 weeks following cycle 5 in Cohort 1. Neoadjuvant patients (Cohort 2) will be administered oregovomab/placebo post interval debulking surgery at cycles 4 and 6 with maintenance doses at 6- and 18-weeks following cycle 6. No other post front-line maintenance therapy is permitted. The primary objective is PFS determined by RECIST 1.1 criteria. Cohort 1 will recruit 372 patients with a 90% power to detect a difference with an alpha of 0.025 and a hazard ratio of 0.65 when 252 PFS events have been observed. Cohort 2 will be analyzed separately recruiting 232 patients with a 90% power to detect a difference with an alpha of 0.025 and a hazard ratio of 0.60 when 165 PFS events have been observed. An interim analysis for futility will be performed. Secondary objectives include OS, frequency and severity of adverse events, and quality of life. Exploratory objectives include iRECIST, TFST, TSST, PFS2, and evaluation of potential biomarkers. The study is actively enrolling in the US with 9 patients enrolled at time of submission. Centers in Europe, South America and Asia are expected to begin accruing shortly. Clinical trial information: NCT04498117. Research Sponsor: Oncoquest.

TPS5607 **Poster Session**

Uplift (ENGOT-ov67): A pivotal cohort to evaluate XMT-1536 (upifitamab rilsodotin), a NaPi2b-directed antibody drug conjugate for platinum-resistant ovarian cancer. *First Author: Debra L. Richardson, Stephenson Cancer Center at the University of Oklahoma Health Sciences Center, Oklahoma City, OK*

Background: XMT-1536 (upifitamab rilsodotin), is a first-in-class Dolaflexin ADC targeting NaPi2b, a sodium-dependent phosphate transport protein, broadly expressed in solid tumors such as serous epithelial ovarian cancer (OC) and non-small cell lung adenocarcinoma. XMT-1536 uses the Dolaflexin platform to deliver approximately 10 DolaLock auristatin payload molecules per antibody and is being evaluated in a Phase I study (NCT03319628). Observation of preliminary antitumor activity was reported in the ovarian cancer expansion cohort, including in patients previously treated with bevacizumab and PARPi (Tolcher et al, ASCO 2019; Richardson et al, ASCO 2019; Hamilton et al, ESMO 2020). Updated data on the OC cohort included 31 patients with higher NaPi2b expression as of December 2020 (Mersana Therapeutics, 2021). In these patients, the ORR was 32% and the DCR was 74%. Complete responses were observed in 2 patients with platinum-resistant ovarian cancer, both of whom had received prior treatment with bevacizumab and PARP inhibitors. Platinum resistant ovarian cancer remains a serious unmet medical need as treatment options are limited and response rates to these treatments are low. Based on the favorable safety and efficacy profile of XMT-1536, UPLIFT was designed as a Phase 2 single-arm registrational cohort of patients with platinum resistant ovarian cancer as part of the ongoing Phase I FIH dose escalation and expansion study to accelerate development and provide a streamlined pathway to regulatory review. **Methods:** The UPLIFT cohort is enrolling patients with platinum resistant high grade serous ovarian, fallopian tube and primary peritoneal cancer with up to 4 prior lines of therapy. The RP2D of XMT-1536 was determined to be 43 mg/m^2 administered intravenously every 4 weeks (q4w) and will be the dose evaluated in the UPLIFT cohort. UPLIFT will enroll approximately 180 patients with platinum-resistant advanced ovarian cancer to obtain approximately 100 patients with higher NaPi2b expression. Prior bevacizumab is required for those patients with 1 or 2 prior lines of therapy. Tumor samples (fresh or archived) will be collected prior to enrollment for retrospective tumor tissue evaluation of NaPi2b expression. The primary objective is assessment of confirmed objective response rate to XMT-1536 as assessed by Investigator in patients with higher NaPi2b expression. Secondary endpoints include confirmed objective response rate regardless of NaPi2b expression, duration of response, and adverse events. Correlative aims include assessing blood and tissue biomarkers for association with clinical benefit. This study is being conducted in collaboration with ENGOT and GOG. Patients will be enrolled globally. Clinical trial information: NCT03319628. Research Sponsor: Mersana Therapeutics.

TPS5608 **Poster Session**

ENGOT-en11/GOG-3053/KEYNOTE-B21: Phase 3 study of pembrolizumab or placebo in combination with adjuvant chemotherapy with/without radiotherapy in patients with newly diagnosed high-risk endometrial cancer. *First Author: Toon Van Gorp, UZ Leuven, Leuven, Belgium*

Background: Pembrolizumab, a selective humanized anti–PD-1 monoclonal antibody, has demonstrated activity in patients with previously treated mismatch repair (MMR) deficient (dMMR; 57.1% ORR as monotherapy and 63.6% ORR as combination therapy with lenvatinib) and MMR proficient (pMMR; 36.2% ORR as combination therapy with lenvatinib) endometrial cancer (EC). ENGOT-en11/GOG-3053/KEYNOTE-B21 is a phase 3, randomized, double-blind study of pembrolizumab or placebo in combination with adjuvant chemotherapy with/without radiotherapy in patients with EC. **Methods:** Eligible patients are ≥18 years old with newly diagnosed, histologically confirmed high-risk (stage I/II non-endometrioid, stage III/IVa, p53 abnormality) EC (carcinoma or carcinosarcoma) following surgery with curative intent with no evidence of disease post-operatively or on imaging, and without prior systemic therapy/radiotherapy. In total, ~990 patients are randomized to receive pembrolizumab 200 mg or placebo Q3W for 6 cycles + chemotherapy (carboplatin area under the curve [AUC] 5 or 6 + paclitaxel 175 mg/m^2 Q3W or carboplatin AUC 2 or 2.7 + paclitaxel 60 mg/m^2 QW) in stage 1. Patients receive pembrolizumab 400 mg or placebo Q6W for 6 cycles in stage 2 per their treatment assignment. At the investigator's discretion, radiotherapy (external beam radiotherapy [EBRT] and/or brachytherapy) ± radiosensitizing cisplatin 50 mg/m^2 (days 1 and 29) may be administered after completion of chemotherapy. Randomization is stratified by MMR status (pMMR vs dMMR) and, within pMMR, by planned radiation therapy (cisplatin-EBRT vs EBRT vs no EBRT), histology (endometrioid vs non-endometrioid), and International Federation of Gynecology and Obstetrics (FIGO) surgical stage (I/II vs III/IVA). Dual primary endpoints are disease-free survival (DFS; per investigator assessment) and overall survival (OS), both estimated by the Kaplan-Meier method, with a stratified log-rank test to assess treatment differences and a Cox proportional hazard model with Efron's method of tie handling to assess the magnitude of treatment differences. Secondary endpoints include DFS (per blinded independent central review), DFS (per investigator assessment) and OS by biomarker status (PD-L1 and tumor mutational burden), safety (per National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0) and quality of life (per European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and Endometrial Cancer Module [EORTC QLQ-EN24]). The study began enrollment in December 2020. Clinical trial information: NCT04634877. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS5609 **Poster Session**

A phase 2, two-stage study of avelumab and axitinib in patients with mismatch repair proficient (MMR-P) recurrent or persistent endometrial cancer (EC). *First Author: Elizabeth Katherine Lee, Dana-Farber Cancer Institute, Boston, MA*

Background: Despite significant strides in understanding the molecular pathogenesis of EC, there remain few effective therapies for recurrent disease. Deeper insight into the roles of disordered tumor vasculature and HIF1α- and VEGF-mediated immunosuppressive effects on myeloid-derived suppressor cells, T-cells, and PD-L1 expression contributed to the development of new targeted regimens. Activity of pembrolizumab and lenvatinib was demonstrated in a phase 2 trial in MMR-P EC (NCT02501096). By inhibiting VEGF receptor (VEGFR) and PD-L1 signaling, immunologically "cold" tumors may become inflamed. However, there are concerns regarding the toxicity of pembrolizumab/lenvatinib and alternatives are sought. The combination of the anti-PD-L1 antibody avelumab with axitinib, an inhibitor of VEGFR 1-3 and PDGFR with more potent IC_{50} inhibitory activity than lenvatinib, has also shown synergistic activity and is FDA approved as first line treatment for patients with renal cell cancer. We therefore hypothesized that this combination would be well tolerated and efficacious in recurrent MMR-P EC. **Methods:** This is an investigator-initiated, phase 2, two-stage single cohort trial evaluating avelumab with axitinib in recurrent or persistent EC. Participants must have MMR-P EC of any histology and have received at least one chemotherapeutic regimen, with no upper limit on the number of prior lines received. Prior use of immune checkpoint (IC) inhibitors is excluded. Treatment consists of avelumab 800mg IV every 2 weeks and axitinib 5mg orally twice daily. Co-primary endpoints are progression-free survival at 6 months (PFS6) and objective response rate by RECIST 1.1. Translational objectives include characterization of tumor-infiltrating lymphocytes, infiltrating myeloid cells, expression of IC markers, and whole exome sequencing to evaluate mutations in genes related to DNA repair and immunologic response. This is a two-stage design in the method of Sill et al, with 16 participants anticipated in stage 1 and 19 participants in stage 2, for a total of 35 participants. Accrual is ongoing. Clinical trial information: NCT02912572. Research Sponsor: Pfizer.

TPS5610 **Poster Session**

SIENDO/ENGOT-EN5/GOG-3055: A randomized phase 3 trial of maintenance selinexor versus placebo after combination platinum-based chemotherapy in advanced or recurrent endometrial cancer. *First Author: Ignace Vergote, Belgium and Luxembourg Gynaecological Oncology Group (BCOG), University of Leuven, Leuven Cancer Institute, Leuven, Belgium*

Background: Endometrial cancer (EC) is the most common gynecologic malignancy. Options for advanced or recurrent EC following platinum-based therapy and/or radiotherapy are limited and prognosis remains poor. Selinexor is a novel, oral selective inhibitor of nuclear export (SINE) which forces nuclear retention and activation of tumor suppressor proteins. Selinexor in combination with low dose dexamethasone is approved for relapsed/refractory multiple myeloma. In addition, selinexor monotherapy has demonstrated broad activity in other hematologic malignancies and solid tumors. In a phase 2 study, 50 mg/m^2 (~80 mg) selinexor administered twice weekly demonstrated a disease control rate (SD ≥ 12 weeks or a PR) of 35% with 2 confirmed partial responses among 23 heavily pretreated EC patients); similar results were observed in 60 pts with platinum resistant or refractory ovarian cancer (median 5 prior regimens, ORR 8%, DCR 30%) (Vergote I et al. Gynecol Oncol 2020). In the absence of approved maintenance therapies, we conducted this study to evaluate the efficacy of selinexor compared with placebo as maintenance therapy in patients with advanced or recurrent EC following platinum-based chemotherapy. **Methods:** This is a multicenter, double-blind, placebo-controlled, randomized phase 3 study in patients in partial (PR) or complete remission (CR) after completing at least 12 weeks of taxane-platinum combination therapy for primary Stage IV disease and recurrent disease (i.e., relapse after primary therapy for early stage disease including surgery and/or adjuvant therapy). A total of 248 patients will be enrolled at 80 sites in Europe, North America, and Israel. Patients will be randomized in a 2:1 ratio to either maintenance therapy with 80 mg oral selinexor once weekly or placebo. Stratification factors include primary Stage IV versus first recurrence at the time of taxane-platinum therapy and disease status after chemotherapy (PR vs CR). Treatment will continue until disease progression. The primary endpoint is progression free survival (PFS) per RECIST v1.1. Secondary endpoints include disease-specific survival, overall survival, time to first subsequent therapy, time to second subsequent therapy, PFS on subsequent therapy and safety and tolerability. The study is currently open and enrolling patients. Clinical trial information: NCT03555422. Research Sponsor: Karyopharm Therapeutics Inc.

TPS5611 **Poster Session**

A phase 2, two-stage study of mirvetuximab soravtansine (IMGN853) in combination with pembrolizumab in patients with microsatellite stable (MSS) endometrial cancer (EC). *First Author: Rebecca L. Porter, Dana Farber Cancer Institute, Boston, MA*

Background: Folate receptor-alpha (FRα) is expressed on endometrial cancer (EC) cells and is associated with poor prognosis. Mirvetuximab soravtansine (ImmunoGen), an antibody drug conjugate (ADC) comprising a FRα-binding antibody, cleavable linker, and the tubulin-disrupting maytansinoid DM4, showed tolerability and single agent activity in a Phase 1 study with dose expansion in FRα+ advanced/recurrent EC (NCT01609556) and also when combined with chemotherapy, bevacizumab as well as pembrolizumab (NCT02606305). In addition to having direct target-mediated cytotoxicity, ADCs also stimulate the local tumor immune microenvironment. Mirvetuximab soravtansine has been shown to activate monocytes and promote phagocytosis of mirvetuximab-treated FRα-positive tumor cells through a mechanism of Fc-FcγR interaction. Further, the combination of ADCs with immune checkpoint inhibitors (ICI) can overcome primary resistance to immunotherapy in murine models. Given the low response of MSS endometrial cancers to PD-1 blockade, we hypothesized that addition of mirvetuximab may enhance response of these tumors to immunotherapy. **Methods:** This is a Phase 2, single cohort study of mirvetuximab soravtansine with pembrolizumab in recurrent or persistent EC. Patients must have advanced or recurrent MSS serous endometrial cancer with at least 1 and up to 3 prior lines of therapy. Confirmation of FRα expression (with PS2+ staining intensity in ≥ 50% of cells, performed centrally at Ventana Medical Systems, Inc) is required. Prior receipt of ICI is excluded. Patients will receive the combination of mirvetuximab soravtansine 6 mg/kg AIBW IV and pembrolizumab 200 mg IV administered every 21 days. The co-primary endpoint is progression-free survival at 6 months (PFS6) and objective response rate (ORR) by RECIST 1.1. Translational objectives include assessment of tumor infiltrating lymphocytes (TILs), expression of immune checkpoint markers, and whole exome sequencing (WES) for DNA repair pathway mutations, neoantigens, and polymorphisms in immunologically relevant genes. Statistical considerations are for a Simon two-stage optimal design with 16 patients in Stage 1 and 19 patients in Stage 2, to a total of 35. Prespecified activity for the first stage of accrual was met, and second stage accrual began November 2020. Clinical trial information: NCT03835819. Research Sponsor: ImmunoGen, Merck.

TPS5612 **Poster Session**

ADAGIO: A phase IIb, open-label, single-arm, multicenter study assessing the efficacy and safety of adavosertib (AZD1775) as treatment for recurrent or persistent uterine serous carcinoma. *First Author: Joyce F. Liu, Dana-Farber Cancer Institute, Boston, MA*

Background: There is a high unmet medical need for therapies treating uterine serous carcinoma (USC), an aggressive type of endometrial carcinoma with an increased likelihood of recurrence and limited therapeutic options. 5-year overall survival (OS) for USC is estimated to be 35–50% for women with stage I–II disease and 0–15% for women with stage III–IV disease (Acharya *et al. Lancet Oncol* 2005). USC exhibits high rates of mutation in *TP53* ($>$ 90% of cases), as well as mutations or amplifications in other cell-cycle regulators or oncogenes, including *CCNE1*, *FBXW7*, *MYC*, *RB1*, and *KRAS*/*NRAS* (Zhao *et al. PNAS* 2013; Levine DA *et al. Nature* 2013), which may contribute to increased replication stress and susceptibility to inhibition of the tyrosine kinase WEE1. WEE1 inhibition is expected to release a tumor cell from DNA-damage-induced arrest at the G2/M boundary, so that unrepaired DNA damage may be taken into mitosis, leading to cell death. A Phase II study of the WEE1 inhibitor adavosertib in 34 women with recurrent or persistent USC reported an objective response rate (ORR) of 29.4% and a median duration of response (DoR) of 9.0 months; further correlative analysis and a translational biopsy cohort are planned (Liu *et al. J Clin Oncol* 2020). This Phase IIb study, ADAGIO, a single-arm, multicenter, global study (NCT04590248), aims to expand on these findings and will evaluate the efficacy and safety of adavosertib in women with recurrent or persistent USC who have previously received platinum-based chemotherapy. **Methods:** Women aged $\geq$18 years with histologically confirmed recurrent or persistent USC who have previously received at least one platinum-based chemotherapy regimen for the management of USC and have evidence of measurable disease according to RECIST v1.1 are eligible for this study. Participants with carcinosarcomas are not eligible. Prior receipt of immune checkpoint inhibitors, vascular endothelial growth factor inhibitors and human epidermal growth factor receptor 2 targeted therapy is permitted, with no restriction on the number of prior lines of systemic therapy a participant may have previously received. Approximately 120 eligible participants will receive oral adavosertib 300 mg qd on days 1–5 and 8–12 of a 21-day treatment cycle until disease progression, unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. The primary outcome measure is ORR, defined as the percentage of patients with measurable disease at baseline who have a confirmed complete or partial response, as determined by blinded independent central review (RECIST v1.1 assessment every 6 weeks for the first 48 weeks, then every 9 weeks). Secondary outcome measures include DoR, depth of response, progression-free survival, OS, disease control rate, biomarkers, safety, tolerability, and pharmacokinetics. Clinical trial information: NCT04590248. Research Sponsor: AstraZeneca.

6000 **Oral Abstract Session**

Camrelizumab versus placebo combined with gemcitabine and cisplatin for recurrent or metastatic nasopharyngeal carcinoma: A randomized, double-blind, phase 3 trial. *First Author: Li Zhang, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Camrelizumab plus gemcitabine and cisplatin (GP) showed promising preliminary anticancer activity as first line (1L) therapy in patients (pts) with recurrent or metastatic nasopharyngeal carcinoma (R/M NPC) in a phase 1 trial (*W Fang et al; Lancet Oncol 2018*). Here, we compared the efficacy and safety of camrelizumab with placebo plus GP as 1L therapy for pts with R/M NPC in a phase 3 trial. **Methods:** Eligible pts with previously untreated R/M NPC were randomized (1:1) to receive either camrelizumab (200 mg on day 1) plus gemcitabine (1000 mg/m^2 on days 1, 8) and cisplatin (80 mg/m^2 on day 1) or placebo plus the same chemotherapy regimens intravenously Q3W for a maximum of 6 cycles, followed by maintenance therapy with camrelizumab or placebo. The primary end point was progression-free survival (PFS) per independent review committee (IRC). Secondary end points included investigator-assessed PFS, objective response rate (ORR), disease control rate (DCR), duration of response (DOR), overall survival (OS) and tolerability. This trial is registered with ClinicalTrials.gov, number NCT03707509. **Results:** From Nov 2018 to Nov 2019, 263 pts from 28 centers were randomized to camrelizumab plus GP (n = 134, camrelizumab arm) or placebo plus GP (n = 129, placebo arm). At data cutoff on Dec 31, 2020 (67.7% maturity), 178 IRC-assessed PFS events occurred, and the median follow-up was 15.6 months (range 1.3-25.5). The median PFS per IRC was 10.8 months (95% CI 8.5-13.6) in the camrelizumab arm and 6.9 (95% CI 5.9-7.9) in the placebo arm (HR 0.51 [95% CI 0.37-0.69]; one-sided $P < 0.0001$). Investigator-assessed PFS showed similar results. IRC-assessed ORR was 88.1% (95% CI 81.3-93.0) in the camrelizumab arm and 80.6% (95% CI 72.7-87.1) in the placebo arm, with a median DOR of 9.9 (95% CI 7.7-12.5) and 5.7 months (95% CI 5.2-6.9; HR 0.48 [95% CI 0.34-0.68]), respectively. The DCR was 96.3% (95% CI 91.5-98.8) in the camrelizumab arm and 94.6% (95% CI 89.1-97.8) in the placebo arm. 18-month PFS rate was 34.8% (95% CI 25.7-44.1) vs 12.7% (95% CI 6.8-20.5), respectively. OS benefit was observed in the camrelizumab arm vs placebo arm (median not reached vs 22.6 months; HR 0.67 [95% CI 0.41-1.11]). Grade ≥3 treatment-related adverse events (TRAEs) occurred in 93% of pts in the camrelizumab arm and 90% in the placebo arm. The most common grade ≥3 TRAEs were decreased white blood cell count (66% vs 70%), decreased neutrophil count (64% vs 65%), decreased platelet count (40% vs 40%), and anemia (39% vs 43%). None of the differences were statistically significant. The safety profile was as expected, with no new signals observed. **Conclusions:** Addition of camrelizumab to GP significantly prolonged PFS as 1L therapy for R/M NPC, with a manageable safety profile. These data suggest that first line treatment with camrelizumab plus GP could be a standard of care for R/M NPC. Clinical trial information: NCT03707509. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

6001 **Oral Abstract Session**

Cabozantinib versus placebo in patients with radioiodine-refractory differentiated thyroid cancer who have progressed after prior VEGFR-targeted therapy: Results from the phase 3 COSMIC-311 trial. *First Author: Marcia S. Brose, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Cabozantinib (C), an inhibitor of VEGFR2, MET, AXL, and RET, showed clinical activity in patients (pts) with radioiodine (RAI)-refractory differentiated thyroid cancer (DTC) in phase 1/2 studies (Cabanillas 2017; Brose 2018). This phase 3 study (NCT03690388) evaluated the efficacy and safety of C vs placebo (P) in pts with RAI-refractory DTC who had progressed during/after prior VEGFR-targeted therapy for whom there is no standard of care. **Methods:** In this double-blind, phase 3 trial, pts were randomized 2:1 to receive C (60 mg QD) or P, stratified by prior lenvatinib treatment (L; yes, no) and age (≤65, > 65 yr). Pts with RAI-refractory DTC must have received L or sorafenib for DTC and progressed during or following treatment with ≤ 2 prior VEGFR inhibitors. Pts randomized to P could cross over to open-label C upon disease progression per blinded independent radiology committee (BIRC). The primary endpoints were objective response rate (ORR) in the first 100 randomized pts and progression-free survival (PFS) in all randomized pts. PFS and ORR were assessed by BIRC per RECIST v1.1. The study was designed to detect an ORR for C vs P (2-sided $\alpha = 0.01$) and a hazard ratio (HR) for PFS of 0.61 (90% power, 2-sided $\alpha = 0.04$). A prespecified interim PFS analysis was planned for the ITT population at the time of the primary ORR analysis. **Results:** As of 19 Aug 2020,125 vs 62 pts had been randomized to the C and P arms, respectively; median age was 66 yr, 55% were female and 63% received prior L. Median (m) follow-up was 6.2 months (mo). At the planned interim analysis, the trial met the primary endpoint of PFS with C demonstrating significant improvement over P (HR 0.22, 96% CI 0.13–0.36; p < 0.0001). mPFS was not reached for C vs 1.9 mo for P; PFS benefit was observed in all prespecified subgroups including prior L (yes, HR 0.26; no, HR 0.11) and age (≤65 yr, HR 0.16; > 65 yr, HR 0.31). ORR was 15% for C vs 0% for P (p = 0.0281) but did not meet the prespecified criteria for statistical significance (p < 0.01). A favorable OS trend was observed for C vs P (HR 0.54, 95% CI 0.27–1.11). Treatment-emergent adverse events (AEs) of any grade with higher occurrences in the C vs P arm included diarrhea (51% vs 3%), hand-foot skin reaction (46% vs 0%), hypertension (28% vs 5%), fatigue (27% vs 8%), and nausea (24% vs 2%); grade 3/4 AEs were experienced by 57% of pts with C vs 26% with P. Dose reductions due to any grade AEs occurred in 57% of pts with C vs 5% with P. Treatment discontinuations due to AEs not related to disease progression occurred in 5% of pts with C vs 0% with P. No treatment-related deaths occurred in either arm. **Conclusions:** C showed a clinically and statistically significant improvement in PFS over P in pts with RAI-refractory DTC after prior VEGFR-targeted therapy with no unexpected toxicities. C may represent a new standard of care in pts with previously treated DTC. Clinical trial information: NCT03690388. Research Sponsor: Exelixis.

6002 **Oral Abstract Session**

A phase II trial cohort of nivolumab plus ipilimumab in patients (Pts) with recurrent/metastatic salivary gland cancers (R/M SGCs). *First Author: Bharat Burman, Tufts Univ. School of Medcn., Washington, DC*

Background: R/M SGCs are a diverse group of malignant neoplasms arising from the major or minor salivary glands and have no standard treatment. The impact of combining PD-1/CTLA-4 checkpoint blockade in R/M SGCs is unknown. **Methods:** In a Simon's two-stage minimax phase II trial, pts with progressive R/M SGCs (any histology except adenoid cystic carcinoma (ACC)) were enrolled and treated with nivolumab 3 mg/kg every 2 weeks plus ipilimumab 1 mg/kg every 6 weeks (1 cycle = 6 weeks). Imaging, using RECIST v1.1 response assessment, was scheduled to be performed approximately every 12 weeks. The primary endpoint was best overall response (BOR = complete response [CR]+partial response [PR]) per RECIST v1.1. To detect a difference between an unacceptable BOR of 5% and a desirable BOR of 20% (one-sided type I error of 10%, power of 90%), at least 1 in the first 18 pts required an observed response. At least 4 responses of 32 total pts were needed to meet the primary endpoint. Treatment beyond progression of disease (PD) was allowed at the discretion of the investigator. A second cohort of pts with ACC was analyzed and reported separately. **Results:** From 7/25/2017-7/16/2020, 32 pts were enrolled and evaluable for the primary endpoint. There was 3 confirmed PRs in the first 18 pts, therefore enrollment of the second stage continued. BOR rate was 16% (5/32). Seven pts never reached a first disease assessment and were classified as non-responders: 5 due to clinical PD, 1 due to toxicity, and 1 pt withdrew. Four pts discontinued the trial for toxicities: pancytopenia (1), blurry vision (1), cardiomyopathy/hyperglycemia (1), and neutropenic sepsis (1), and mucositis (1). The 5 confirmed responders had regressions ranging from -66% to -100% in target lesions, with a duration of therapy ranging from 15.7 to 29.5 months (treatment ongoing for one as of 2/6/20). **Conclusions:** This cohort met its primary endpoint, and the responses observed were dramatic and durable. Paired biopsy and peripheral blood samples will be analyzed to elucidate insights into mechanisms of response and resistance to dual checkpoint blockade. Clinical trial information: NCT03172624. Research Sponsor: U.S. National Institutes of Health, Geoffrey Beene Cancer Research Center, Cycle for Survival, and the Overman Fund.

6003 **Oral Abstract Session**

Metronomic capecitabine as adjuvant therapy in locoregionally advanced nasopharyngeal carcinoma: A phase 3, multicenter, randomized controlled trial. *First Author: Jun Ma, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Patients suffering from locoregionally advanced nasopharyngeal carcinoma (NPC) commonly develop disease recurrence, despite a high rate of complete clinical remission after standard of care (concurrent cisplatin-radiotherapy, with or without induction chemotherapy). The benefit of additional adjuvant chemotherapy remains unclear. **Methods:** Patients with high-risk locoregionally advanced NPC (stage III to IVA, excluding T3-4N0 and T3N1), and with no locoregional disease or distant metastasis after definitive chemoradiotherapy, were eligible. They were randomly assigned (1:1) within 12 to 16 weeks after the last radiation dose to receive either capecitabine at a dose of 650 mg/m^2 twice daily for 1 year (metronomic capecitabine group) or observation (standard-therapy group). The primary end point was recurrence-free survival (RFS). The calculated sample size was 201 per group, with an 80% power (two-sided α 0.05) to detect a target hazard ratio (HR) of 0.52. **Results:** A total of 406 patients underwent randomization, comprising 204 in the metronomic capecitabine group and 202 in the standard-therapy group. After a median follow-up of 36 months (corresponding to 43 months when calculated from the start of standard therapy), the estimated 3-year RFS was 85.9% in the metronomic capecitabine group, as compared with 76.5% in the standard-therapy group (intention-to-treat population; HR 0.51, 95% confidence interval 0.32–0.81; $P = 0.003$). The incidence of grade 3 adverse events was 17.4% in the metronomic capecitabine group and 5.5% in the standard-therapy group; hand-foot syndrome was the most common adverse event related to capecitabine (9.0%). One grade 4 neutropenia occurred in the metronomic capecitabine group. Neither group sufferd from treatment-related deaths. During treatment, there was no clinically meaningful deterioration of health-related quality of life associated with the use of metronomic adjuvant capecitabine. **Conclusions:** The addition of metronomic capecitabine as adjuvant therapy to chemoradiotherapy significantly improved RFS in locoregionally advanced NPC, with a manageable safety profile and no compromise to quality of life. Clinical trial information: NCT02958111. Research Sponsor: Sun Yat-sen University Clinical Research 5010 Program, Pharmaceutical/Biotech Company.

	Metronomic capecitabine (%)	Standard therapy (%)	
Intention-to-treat population	n = 204	n = 202	P value
3-yr recurrence-free survival	85.9	76.5	0.003
3-yr overall survival	93.6	89.6	0.03
3-yr distant recurrence-free survival	90.5	82.1	0.008
3-yr locoregional recurrence-free survival	92.6	88.2	0.05
Safety population	n = 201	n = 200	
Completed the 1-year treatment period	74.1	–	
Any grade 3 adverse events	17.4	5.5	
Any grade 4 adverse events	0.5	0	

6005 **Oral Abstract Session**

Adjuvant capecitabine in locoregionally advanced nasopharyngeal carcinoma: A multicenter randomized controlled phase III trial. *First Author: Jingjing Miao, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China*

Background: We conducted a multicenter, randomized controlled phase III clinical trial (NCT02143388) to investigate the efficacy and toxicity of adjuvant capecitabine (AC) in addition to concurrent cisplatin and radiotherapy (CCRT) compared to CCRT alone in high-risk locoregionally advanced nasopharyngeal carcinoma (LANPC) patients. **Methods:** Eligibility criteria included AJCC/UICC 7th ed TNM stage III-IVb and one of the following features: T3-4N2 or T1-4N3 or pre-treatment plasma EBV DNA concentration of >20,000 copy/ml or gross primary tumor volume (GTVnx) of >30 cm^3 or a maximum standard uptake value (SUVmax) of >10.0 by ^{18}FDG PET-CT within the primary tumor or multiple neck node metastases, with any larger than 4 cm. All patients were randomly assigned in a 1:1 ratio to receive CCRT (3-weekly cisplatin at 100 mg/m^2 for 2-3 cycles) followed by AC (1000 mg/m^2 bi-daily for 14 days every 21-day cycle for 8 cycles), or CCRT alone. The prescribed radiation doses were 68-72 Gy/30-32 fractions to the PTVnx, 60-68 Gy/30-32 fractions to PTVnd, 60-64Gy/30-32 fractions to $PTV_{high\text{-}risk}$, 54-58Gy/30-32 fractions to $PTV_{low\text{-}risk}$. Primary end point was failure-free survival (FFS). **Results:** Between Mar 2014 to Jul 2018, 180 patients were recruited (90 patients in CCRT+AC arm and 90 in CCRT alone arm). All patients completed RT and ≥2 cycles of concurrent cisplatin in both treatment arms (cumulative dose intensities for cisplatin were 200 mg/m^2 in both arms). 85 (94.4%) patients went on to receive AC, with 71 (78.9%) patients completing 8 cycles; 19 (22.4%) patients had dose reduction of AC. With a median follow-up of 44.8 mo, the 3-y FFS was significantly superior in the CCRT+AC arm than the CCRT arm for the intention-to-treat cohort (87.7% *vs* 73.3%; HR: 0.52 [95% CI: 0.29-0.77], $P = 0.037$). 3-year overall, distant metastasis-free and locoregional relapse-free survival were 92.6% *vs* 88.9% (HR [95% CI]: 0.66 [0.28-1.59]), 88.8% vs. 81.1% (HR: 0.67 [0.33-1.33]) and 91.5% *vs* 80.0% (HR: 0.50 [0.25-1.00]), respectively. Incidences of G3-4 acute toxicities were 57.8% (52 of 90) in CCRT+AC arm and 51.1% (46 of 90) in CCRT alone arm, with a higher incidence of hand foot syndrome (3.5% *vs* 0%), xerostomia (11.1% *vs* 3.3%), mucositis (23.3% *vs* 16.7%), and anemia (5.6% *vs* 2.2%) in the CCRT+AC arm. G3-4 late toxicities occurred in 13.3% (12 of 90) and 9.0% (8 of 89), respectively. **Conclusions:** The addition of capecitabine to CCRT conferred a superior disease control than CCRT alone in high-risk LANPC. Survivals in ITT and PP set. Clinical trial information: NCT02143388. Research Sponsor: National Natural Science Foundation of China [No. 81872469 and 82073330]; Wu Jieping Medical Foundation [No. 320.6750.19089 and 320.6750.17108]; Sun Yat-sen University Cancer Center 308 Program.

		ITT		PP	
Variable		CCRT+AC (N = 90)	CCRT alone (N = 90)	CCRT+AC (N = 71)	CCRT alone (N = 90)
FFS	Failure or death, N (%)	15 (16.7)	27 (30.0)	8 (11.3)	27 (30.0)
OS	3-y FFS, %	87.7	73.3	92.9	73.3
	Death, N (%)	8 (8.9)	12 (13.3)	3 (4.2)	12 (13.3)
DMFS	3-y OS, %	92.6	88.9	98.6	88.9
	Distant metastasis or death, N (%)	13 (14.4)	19 (21.1)	6 (8.5)	19 (21.1)
	3-y DMFS, %	88.8	81.1	94.3	81.1

6006 **Oral Abstract Session**

Association of pathological response to neoadjuvant pembrolizumab with tumor PD-L1 expression and high disease-free survival (DFS) in patients with resectable, local-regionally advanced, head and neck squamous cell carcinoma (HNSCC). *First Author: Trisha Michel Wise-Draper, University of Cincinnati Cancer Center, Cincinnati, OH*

Background: Patients with resected HNSCC, with high-risk (positive margins, extracapsular spread [ECE]) or intermediate-risk pathological features have an estimated 1-year DFS of 65% and 69%, respectively. Immune checkpoint blockade improved survival of patients with recurrent/metastatic HNSCC, and preclinical models indicate radiotherapy (RT) synergizes with anti-PD-1. Therefore, we administered the PD-1 inhibitor pembrolizumab (pembro) pre- and post-surgery with adjuvant RT +/- cisplatin in patients with resectable, locoregionally advanced (clinical T3/4 and/or ≥2 nodal metastases) HNSCC (NCT02641093). **Methods:** Eligible patients received pembro (200 mg I.V. x 1) 1-3 weeks before resection. Adjuvant pembro (q3 wks x 6 doses) was administered with RT (60-66Gy) with or without weekly cisplatin (40mg/m2 X 6) for patients with high-risk and intermediate-risk features, respectively. The primary endpoint was 1-year DFS estimated by Kaplan Meier curves. Safety was evaluated by CTCAE v5.0. Pathological response (PR) to neoadjuvant pembro was evaluated by comparing pre- and post-surgical tumor specimens for treatment effect (TE), defined as tumor necrosis and/or histiocytic inflammation and giant cell reaction to keratinaceous debris. PR was classified as no (NPR, < 20%), partial (PPR, ≥20% and < 90%) and major (MPR, ≥90%). Tumor PD-L1 immunohistochemistry was performed with 22c3 antibody and reported as combined positive score (CPS). **Results:** Ninety-two patients were enrolled. Seventy-six patients received adjuvant pembro and were evaluable for DFS. Patient characteristics included: median age 58 (range 27 – 80) years; 32% female; 88% oral cavity, 8% larynx, and 3% human papillomavirus negative oropharynx; 86% clinical T3/4 and 65% ≥2N; 49 (53%) high-risk (positive margins, 45%; ECE, 78%); 64% (44/69 available) had PD-L1 CPS ≥1. At a median follow-up of 20 months, 1-year DFS was 67% (95%CI 0.52-0.85) in the high-risk group and 93% (95%CI 0.84-1) in the intermediate-risk group. Among 80 patients evaluable for PR, TE scoring resulted in 48 NPR, 26 PPR and 6 MPR. Patients with PPR/MPR had significantly improved 1-year DFS when compared with those with NPR (100% versus 68%, p = 0.01; HR = 0.23). PD-L1 CPS ≥ 1 was not independently associated with 1-year DFS, but was highly associated with MPR/PPR (p = 0.0007). PPR/MPR in PD-L1 CPS < 1, ≥1 and ≥20, were estimated as 20, 55 and 90%, respectively. Grade ≥ 3 adverse events occurred in 62% patients with most common including dysphagia (15%), neutropenia (15%), skin/wound infections (10%), and mucositis (9%). **Conclusions:** PR to neoadjuvant pembro is associated with PD-L1 CPS≥1 and high DFS in patients with resectable, local-regionally advanced, HNSCC. Clinical trial information: NCT02641093. Research Sponsor: Merck & Co., Startup funds, internal pilot grants.

6007 **Oral Abstract Session**

Primary results of the phase II CheckRad-CD8 trial: First-line treatment of locally advanced head and neck squamous cell carcinoma (HNSCC) with double checkpoint blockade and radiotherapy dependent on intratumoral CD8+ T-cell infiltration. *First Author: Markus Hecht, Department of Radiation Oncology, Universitatsklinikum Erlangen, Friedrich-Alexander-Universitat Erlangen-Nürnberg, Erlangen, Germany*

Background: Inhibition of the PD-1/PD-L1 pathway is efficient in recurrent/metastatic HNSCC. Targeting the immune checkpoint CTLA-4 may be synergistic to radiotherapy. This trial studies feasibility and efficacy of combined PD-L1/CTLA-4 blockade concomitant to induction chemotherapy and radiotherapy. **Methods:** Patients with previously untreated stage III-IVB (AJCC 8th edition) HNSCC were eligible for this multicenter phase II trial. Treatment consisted of a single cycle of cisplatin 30mg/m^2 d1-3, docetaxel 75mg/m^2 d1, durvalumab 1500mg fix dose d5 and tremelimumab 75mg fix dose d5. Patients with at least 20% increase of intratumoral CD8+ immune cell density or pathological complete response (pCR) in the re-biopsy (performed on d22-26) entered radioimmunotherapy (RIT) up to a total dose of 70Gy. Patients received further three cycles of durvalumab/tremelimumab (q4w, two concomitant and one subsequent) followed by eight cycles of durvalumab mono (q4w). Primary endpoint was a feasibility rate of patients entering RIT to receive treatment until at least cycle 6 of immunotherapy of ≥80% (i.e. dose limiting toxicity/DLT ≤20%; exclusion of patients with other reasons than DLT for treatment discontinuation; feasibility unacceptable if ≤65%). The calculated sample size was 57 patients to enter RIT. Main secondary endpoints were progression-free survival (PFS) and overall survival (OS). **Results:** Between Sep 2018 and Mai 2020, 80 patients were enrolled (one excluded). Median age was 60 years, 33 patients (42%) were current smokers, 43 patients (54%) had oropharyngeal tumors (53% p16 positive), 44 patients (56%) were stage IV. Median follow up was 12.5 months. After induction chemo-immunotherapy 41 patients had pCR and 31 an intratumoral CD8+ immune cell increase. Of 60 patients entering RIT (primary endpoint cohort), 10 received DLT and 4 discontinued for other reasons. The feasibility rate of the RIT cohort until cycle 6 was 82%, meeting the primary endpoint of ≥80% (95% confidence interval (CI), one-sided (lower boundary): 72%). The RIT cohort had a PFS rate at 1 year of 79% (CI 69-90%) and at 2 years of 73% (CI 61-87%) and an OS rate at 1 year of 89% (CI 81-98%) and at 2 years of 86% (CI 77-97%). The entire study cohort had a PFS rate at 1 year of 75% (CI 65-85%) and at 2 years of 68% (CI 58-81%) and an OS rate at 1 year of 86% (CI 78-95%) and at 2 years of 80% (CI 70-91%). Toxicity (treatment-related or un-related) ≥grade 3 appeared in 75 patients (95%) and mainly consisted of dysphagia (53%), leucopenia (48%) and infections (29%). DLT mainly consisted of hepatitis (10%). **Conclusions:** The trial met the primary endpoint feasibility. CD8+ T cell-based pathological patient selection after induction therapy identifies patients with promising PFS rates after chemotherapy-free RIT. Clinical trial information: nct03426657. Research Sponsor: AstraZeneca.

6008 **Oral Abstract Session**

Enhanced pathologic tumor response with two cycles of neoadjuvant pembrolizumab in surgically resectable, locally advanced HPV-negative head and neck squamous cell carcinoma (HNSCC). *First Author: Ravindra Uppaluri, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: We reported that one cycle of neoadjuvant pembrolizumab induced pathologic tumor response in >10% (pTR-any) and in >50% (pTR-2) of the resection bed in 44% and 22% of patients (pts) with surgically resectable HPV-negative, Stage III/IV HNSCC (*Clin Cancer Res* 2020). We hypothesized that two cycles of neoadjuvant pembrolizumab would induce pTR-2 in 50% of pts. Increasing the pathologic response rate may favorably impact clinical outcomes. **Methods:** Multi-institutional phase 2 trial where pts with locally advanced, HPV-negative HNSCC received two cycles of pembrolizumab (200 mg), given 42 and 21 days prior to surgery. Resected tumor was analyzed by two independent pathologists for pTR (tumor necrosis and/or giant cell/histiocytic reaction to keratinous debris) in the resection bed (primary tumor and/or lymph nodes). Additional definitions: pTR-1 (>10-49%) and major pathologic response (> 90%). The primary endpoint was pTR-2. A sample size of 26 pts was needed to detect a significantly higher pTR-2 rate of 50%, with 80% power using a one-sided alpha level of 0.05. Pts were followed for serious adverse events (AEs) for 30 days after surgery and for AEs of clinical interest for 90 days following the last dose of pembrolizumab. Pts underwent baseline blood collection and tumor biopsies to match with blood and surgical specimens obtained post-pembrolizumab. Planned correlatives included PD-L1 expression, immune function, and molecular signatures of activation in the pre- and post-treatment blood and tumor tissue. **Results:** Characteristics of 29 enrolled and treated pts were median age 62 (30-82) yrs, smoking history 62% (18 pts); clinical stage T_2 (n = 6), T_3 (n = 5), T_4 (n = 18) and $N_{0/1}$ (n = 17), N_2 (n = 12). All treated patients received two cycles of neoadjuvant pembrolizumab, which was tolerated well with only one (3%) grade 3 AE (rash) and no grade 4 AEs. The primary endpoint was evaluable in 25 pts, and not evaluable in 4 pts (one pt withdrew before surgery and in three pts, pTR review was pending). pTR-2 occurred in 44% (11 of 25 pts), and 4 (16%) of these pts had a major pathologic response including 1 (4%) pathologic CR at the primary site. **Conclusions:** Two (vs one) cycles of neoadjuvant pembrolizumab resulted in a two-fold increase in the frequency of pTR-2 (44% vs 22%). These data imply that the frequency of pTR to neoadjuvant pembrolizumab can be improved by increasing the number of cycles and the treatment interval. Clinical trial information: NCT02296684. Research Sponsor: Merck Inc.

6010 **Poster Discussion Session**

Updated report of a phase II randomized trial of transoral surgical resection followed by low-dose or standard postoperative therapy in resectable p16+ locally advanced oropharynx cancer: A trial of the ECOG-ACRIN cancer research group (E3311). *First Author: Robert L. Ferris, University of Pittsburgh Medical Center and University of Pittsburgh Cancer Institute, Pittsburgh, PA*

Background: Definitive or postoperative chemoradiation (CRT) is highly curative for human papillomavirus-associated (HPV+) oropharynx cancer (OPC) but induces significant toxicity. As a potential deintensification strategy, we studied primary transoral surgery (TOS) and, in intermediate pathologic risk patients, reduced dose postoperative RT (PORT). **Methods:** E3311 is a phase II trial with randomization to reduced- or standard-dose PORT for resected stage III-IVa (AJCC7) intermediate pathologic risk HPV+ OPC, stratified by smoking history. Primary endpoints have been reported; we now present updated 3-year PFS and patient-reported outcomes (PRO), including head and neck-cancer specific quality of life (FACT-H&N) and swallowing perception and performance (MDADI). **Results:** Of 519 enrolled patients, 495 underwent TOS. The primary oncologic endpoint was 2-year PFS for 50 Gy (Arm B) or 60Gy (Arm C). Among 360 eligible and treated patients (ETP), Arm A (observation, N = 38) enrolled 11%, Arms B (N = 100) or C (N = 109) randomized 58%, and Arm D (66Gy + weekly cisplatin, N = 113) enrolled 31%. With 35.1 months median follow-up, 3-year PFS Kaplan-Meier estimate is 96.9% (90% CI [91.9%, 100%]) for Arm A; 94.9% (90% CI [91.3%, 98.6%]) for Arm B; 93.5% (90% CI [89.4%, 97.9%]) for Arm C; and 90.7% (90% CI [86.2%, 95.4%]) for Arm D. Recurrences and death without recurrence were 4 and 1 in Arm B, and 5 and one in Arm C. Smokers ($>$ 10 pack-years) did not have worse 3-year PFS in Arms B or C. Treatment arm distribution and outcome for ineligible patients who started adjuvant therapy mirrored the 360 ETP. A comparison combining arms B/C versus arm D in the proportion of patients stable/improved in FACT-H&N total score, from baseline to 6 months post-treatment as a pre-specified endpoint, was 56% vs. 38% (p value = 0.011, one-sided Fisher's exact test); however, underlying differences in treatment and risk may be confounding. An exploratory comparison between Arms B and C revealed improvement in FACT H&N (63% in Arm B vs. 49% in Arm C had a stable/improved score, p-value = 0.056). **Conclusions:** Primary TOS and reduced PORT retained outstanding oncologic outcome at 35 months follow up, with favorable QOL and functional outcomes, in intermediate risk HPV+ OPC. Clinical trial information: NCT 01898494. Research Sponsor: U10CA180820, U10CA180794, UG1CA189953, UG1CA232760, UG1CA233184, UG1CA233196, UG1CA233247, UG1CA233329, UG1CA233331, UG1CA233337, U10CA180863, Canadian Cancer Society #704970.

6011 **Poster Discussion Session**

Nivolumab, nabpaclitaxel, and carboplatin followed by risk/response adaptive de-escalated locoregional therapy for HPV-associated oropharyngeal cancer: OPTIMA II trial. *First Author: Ari Rosenberg, University of Chicago, Chicago, IL*

Background: Despite the success of anti-PD-1 in recurrent/metastatic head and neck cancer, incorporation in the curative setting with induction therapy has yet to be investigated. Favorable prognosis of human papillomavirus associated (HPV+) oropharyngeal cancer (OPC) has led to interest in treatment de-escalation. OPTIMA 2 evaluated nivolumab (nivo) with nab-paclitaxel and carboplatin followed by risk/response adaptive de-intensified treatment for locoregionally advanced HPV+ OPC. We report the primary analysis and outcomes. **Methods:** OPTIMA 2 enrolled locoregionally advanced HPV+ OPC. Nivo, nab-paclitaxel, and carboplatin were administered for 3 cycles. High-risk (HR) included any of the following: T4, N2c-N3 (AJCC 7th edition), $>$ 20 pack year smoking history, non-HPV16 subtype; All others were low-risk (LR). Arm A included LR with $\geq$50% post-induction shrinkage by RECIST received single-modality de-escalation with low-dose radiation (RT) alone (50 Gy) or transoral robotic surgery (TORS). Arm B included HR with $\geq$50% shrinkage or LR with $<$50% received intermediate-dose chemoradiation (CRT) to 45-50Gy. Arm C included all others and received regular dose CRT to 70-75Gy. Adjuvant nivo was administered for 6 months. The primary endpoint was deep response rate (DRR) $\geq$50% shrinkage to induction therapy. **Results:** From September 2017 until March 2020, 73 patients (pts) were eligible and started treatment. One pt died during induction. The DRR following induction was 70.8% (95% CI 60.3%, 81.3%). Median follow-up 23.1 months. Median age 61 (range 39-85), T4 12.3%, N2c/N3 19.2%, LR 47.9%, and HR 52.1%. De-escalated treatment was administered in 84.9%. Arm A N = 28, Arm B N = 34, and Arm C N = 10. 2-year progression free survival (PFS) for full cohort was 90.4% (95% CI = 79.3%, 95.7%). 2-year PFS for Arms A, B, and C were 96.3%, 85.8%, and 100.0% respectively. 2-year overall survival (OS) for full cohort was 93.3% (95% CI = 82.4%, 97.5%). 2-year OS for Arm A, B, and C were 96.0%, 91.9%, and 100.0% respectively. Among TORS (N = 9), pathologic complete response (pCR) rate was 66.7%. G-tube rates in Arms A, B, and C were 7.1%, 44.1%, and 75.0% respectively (p = 0.0001). Grade 4 toxicity in arms A, B, and C, were observed in 7.1%, 8.8%, and 10.0% of pts respectively. There were 3 local failures and no distant failures. **Conclusions:** Nivo/nab-paclitaxel/carboplatin followed by risk/response adaptive de-escalated treatment in locoregionally advanced HPV+ OPC demonstrates excellent survival outcomes with reduced toxicity and enteral feeding rates, including high risk disease. Induction chemoimmunotherapy demonstrates a high rate of deep clinical response and represents a promising de-escalation approach that incorporates anti-PD1 in the definitive setting. High pCR rate was observed following nivo/nab-paclitaxel/carboplatin. Clinical trial information: NCT03107182. Research Sponsor: Bristol Myers Squibb.

6012 **Poster Discussion Session**

Randomized trial of radiotherapy with weekly cisplatin or cetuximab in low risk HPV associated oropharyngeal cancer (TROG 12.01): A Trans-Tasman Radiation Oncology Group study. *First Author: Danny Rischin, Department of Medical Oncology, Peter MacCallum Cancer Centre and the Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Australia*

Background: The excellent prognosis of patients with low risk HPV associated oropharyngeal squamous cell carcinoma has led to concerns about overtreatment and excessive toxicity with radiotherapy and cisplatin, leading to interest in de-intensification trials. We investigated whether cetuximab, an EGFR targeting antibody, when combined with radiotherapy would result in a decrease in symptom burden and toxicity with similar efficacy when compared to weekly cisplatin. **Methods:** TROG 12.01, a randomised, multicentre trial involving 15 sites in Australia and New Zealand enrolled patients with HPV associated oropharyngeal squamous cell carcinoma, AJCC 7th edition Stage III (excluding T1-2N1) or stage IV (excluding T4 and/or N3 and/or N2b-c if smoking history $>$10 pack years and/or distant metastases). Patients were randomised (1:1) to receive radiotherapy (70Gy in 35 fractions) with either weekly cisplatin, 7 doses of 40mg/m^2 or cetuximab, loading dose of 400mg/m^2 followed by 7 weekly doses of 250 mg/m^2. The primary outcome was symptom severity assessed by the MD Anderson Symptom Inventory Head and Neck Symptom Severity Scale from baseline to 13 weeks post completion of radiotherapy using the area under the time-severity curve (AUC). Sample size was 170 evaluable patients to provide at least 90% power to detect an effect size of 0.5, using a 2-sided test at 0.05 level of significance. Trial was registered on ClinicalTrials.gov: NCT01855451. **Results:** Between 17th June 2013 and 7th June 2018, 189 patients were enrolled and 182 were evaluable, with 92 on cisplatin arm and 90 on cetuximab included in the main analysis. The median follow-up was 4.1 years (0.4 - 5.3). Analyses were performed in all eligible randomised patients that commenced treatment (modified intention-to-treat population). There was no difference in the primary endpoint of symptom severity; difference in AUC cetuximab – cisplatin was 0.05 (95%CI: -0.19, 0.30), p= 0.66. The T-score (mean number of $>$ grade 3 acute adverse events) was 4.35 (SD 2.48) in the cisplatin arm and 3.82 (SD 1.8) in the cetuximab arm, p= 0.108. The 3 -year failure-free survival rates were 93% (95% CI: 86-97%) in the cisplatin arm and 80% (95% CI: 70-87%) in the cetuximab arm (hazard ratio = 3.0 (95% CI: 1.2-7.7); p=0.015. The increase in failures in the cetuximab arm was evenly split between distant and locoregional failures. **Conclusions:** For patients with low risk HPV associated oropharyngeal cancer, radiotherapy and cetuximab had inferior failure-free survival without improvement in symptom burden or toxicity compared to radiotherapy and weekly cisplatin. Radiotherapy and cisplatin remains the standard of care. Clinical trial information: NCT01855451. Research Sponsor: National Health and Medical Research Council (Project Grant 1047673), Pharmaceutical/Biotech Company.

6014 **Poster Discussion Session**

TRYHARD, a randomized phase II trial (RTOG Foundation 3501) of concurrent accelerated radiation plus cisplatin (cis) with or without lapatinib (Lap) for stage III- IV Non-HPV head and neck carcinoma (HNC). *First Author: Stuart J. Wong, Medical College of Wisconsin, Milwaukee, WI*

Background: Chemoradiation (CRT) with cis or anti-EGFR Ab has been shown to improve survival of patients with stage III-IV HNC. Since Lap, a dual EGFR and HER2 inhibitor, has shown effectiveness with CRT in a pilot non-HPV HNC cohort, the RTOG Foundation launched a phase II trial to test the hypothesis that adding Lap to the RT-cis for frontline therapy of stage III-IV Non-HPV HNC improves progression-free survival (PFS). **Methods:** Patients with stage III-IV carcinoma of the oropharynx (p16-negative), larynx, and hypopharynx, having Zubrod performance of 0-1, and meeting predefined blood chemistry criteria were enrolled after providing consent. Patients were randomized (1:1) to 70 Gy (6 weeks) + 2 cycles of CDDP (q3 weeks) plus either Lap (1500 mg daily, Arm A) or placebo (Arm B) starting 1 week prior to RT and concurrent with RT and for 3 months post RT. PFS was the primary endpoint. The protocol specified 69 PFS events (142 patients) for the final analysis based on HR = 0.65, 80% power, 1-sided alpha 0.20, and one interim efficacy and futility analysis at 50% information. PFS rates between arms for all randomized patients were compared by 1-sided log-rank test (1-sided alpha 0.1803). Overall survival (OS) was a secondary endpoint. **Results:** From 10/'12 to 04/'17, 142 patients were enrolled, of whom 127 were randomized, 63 to Arm A and 64 to Arm B. Arms A vs B, respectively, were similar in baseline patient characteristics, radiation delivery, completing $\geq$ 70 Gy (85.7% vs. 82.8%) and cisplatin delivery, completing 200 (±5%) mg/m^2 (65.1% vs 70.3%), but dissimilar in Lap/placebo delivery (median dose, 87000 mg vs. 125250 mg). Median follow-up was 4.1 years for surviving patients. The final analysis suggests no improvement in PFS of adding Lap to CRT (HR [A/B]: 0.91, 95% confidence interval CI 0.56-1.46; *P*= 0.34; 2-year rates: 50.6%, CI 37.5-63.7% vs. 56.2% CI 43.0-69.4%), or in OS (HR: 1.06, CI 0.61-1.86; P = 0.58; 2-year rates: 71.8% CI 60.1-83.5% vs. 76% CI 64.5-87.4%), death within 30 days of therapy (3.3% vs. 3.4%), and overall treatment-related grade 3-5 adverse event rate (86.7% vs. 84.7%). Grade 3-4 mucositis rates on Arm A and Arm B were 21.7% vs. 23.7%, all grade dysphagia and rash rates were 43.3% vs. 59.3%, and 13.3% vs. 6.8%, respectively. **Conclusions:** The addition of Lap to the radiation-cisplatin platform did not improve progression-free or overall survival in unselected non-HPV HN. Thus, dual EGFR, HER-2 inhibition does not appear to enhance the effects of chemoradiation. Although we showed that accrual to a non-HPV HN specific trial is feasible, new strategies must be investigated to improve the outcome for this poor prognosis HN population. Research Sponsor: Novartis.

6015 **Poster Discussion Session**

Randomized phase II trial of ficlatuzumab with or without cetuximab in pan-refractory, advanced head and neck squamous cell carcinoma (HNSCC). *First Author: Julie E. Bauman, Department of Medicine, Division of Hematology/Oncology, University of Arizona Cancer Center, Tucson, AZ*

Background: Cetuximab (C), an anti-EGFR monoclonal antibody (mAb), is approved for advanced HNSCC but benefits a minority. Crosstalk between the EGFR and hepatocyte growth factor (HGF)/cMet pathways is a known resistance mechanism. HGF is also immunosuppressive within the tumor microenvironment. A Phase I study confirmed the safety of C and ficlatuzumab (F), an IgG1 anti-HGF mAb, with preliminary efficacy and biomarker data suggesting that dual pathway inhibition may overcome tumor-intrinsic or immune cetuximab resistance. **Methods:** The primary objective of this phase II randomized, non-comparative trial was to evaluate the efficacy of F (20 mg/kg every 2 wks), with or without C (500 mg/m^2 every 2 wks), in pan-refractory, advanced HNSCC. Eligibility criteria included recurrent/metastatic HNSCC, performance status (PS) 0-1, C resistance (defined as progression on or within 6 months of exposure), and resistance to or ineligibility for platinum and anti-PD1 mAb. Randomization was stratified by HPV status and center. The primary endpoint was median progression-free survival (mPFS). An arm was deemed worthy of further study if the lower bound of the 90% 1-sided confidence interval (CI) excluded the historical control of 2 months. Secondary objectives included overall response rate (ORR) in the overall and HPV-stratified populations. A Bayesian continuous monitoring rule for futility was applied. **Results:** 60 patients were randomized and 58 treated between Jan 2018 and Dec 2020 (27 to F; 33 to FC). Baseline characteristics were balanced across major prognostic variables including age, PS, HPV status, platinum resistance, and PD1 mAb exposure. Median time since prior cetuximab was 3.5 months (range 0-48 months). Grade ≥3 adverse events attributed to F included: pneumonitis (2); edema (3); diarrhea (1); LFT elevation (1); rash (2); electrolyte abnormality (2). The Table presents efficacy data. The F arm stopped for futility after 26 evaluable subjects accrued. The FC arm completed accrual and met the primary endpoint; 32 evaluable subjects had mPFS of 3.6 months (lower bound 90% 1-sided CI: 2.3 months) and ORR of 19% (6/32). All responses were in HPV- subjects, including 2 complete (CR) and 4 partial responses (PR) to the FC combination and 1 PR to F monotherapy. The mPFS and ORR for the HPV- population (n = 16) on FC were 3.8 months and 38% (6/16). Mechanistic signaling and immune biomarkers are under analysis. **Conclusions:** The well-tolerated FC combination met the primary PFS endpoint in pan-refractory, advanced HNSCC with notable activity in HPV- HNSCC, warranting phase III investigation. Clinical trial information: NCT03422536. Research Sponsor: Aveo, U.S. National Institutes of Health.

	F (n = 26)	FC (n = 32)
Total Population		
ORR[a]	1PR/26 (4%)	2PR + 4CR/32 (19%)
mPFS[b]	1.8 (1.7)	3.6 (2.3)
HPV+		
ORR	0/10 (0%)	0/16 (0%)
mPFS	NE[c]	2.3 (1.9)
HPV-		
ORR	1PR/16 (6%)	2CR + 4PR/16 (38%)
mPFS	NE	3.8 (2.9)

[a]ORR: PR+CR/n
[b]mPFS: Months (lower bound of 90% 1-sided CI)
[c]NE = not evaluated

6016 **Poster Discussion Session**

Phase II trial of soluble EphB4-albumin in combination with PD-1 antibody (pembrolizumab) in relapsed/refractory head neck squamous cell carcinoma. *First Author: Alexandra Jackovich, University of Southern California, Los Angeles, CA*

Background: EphB4 receptor tyrosine kinase and its ligand EphrinB2 are highly induced in head neck squamous cell carcinoma (HN SCC) tumor cells and vessels, particularly in HPV negative tumors. Each are predictors for poor survival with worse prognosis when both are induced. EphB4 provides tumor cell survival and EphrinB2 inhibits immune cell invasion. Soluble EphB4-Alb blocks bidirectional signaling, enhances immune cell recruitment alone and when combined with PD-1 antibody. **Methods**: A phase II trial of sEphB4-Alb combined with pembrolizumab accrued HN SCC patients after failure of one or more prior regimens. IHC positivity for p16 was used as a surrogate for HPV infection. Treatment regimen was sEphB4-Alb 10 mg/kg weekly IV infusion with pembrolizumab 200 mg IV infusion every three weeks. Study endpoints were toxicity, overall response rates (ORR) and overall survival (OS). Response to therapy was based on RECIST 1.1 criteria. Patient tumor samples were collected at baseline with a 2nd biopsy at week 8 on therapy, for tissue analysis of PD-L1, EphrinB2 and other biomarkers. **Results**: Twenty-four patients were accrued to the phase II trial combination of sEphB4-Alb and pembrolizumab. Age, sex, prior treatment, HPV status, and response data are summarized in the table below. The most common toxicity was hypertension with 8 patients experiencing grade 3 HTN. No grade 4 or above toxicities were observed. Among HPV negative cases, partial and complete responses were observed in 6 of 14 patients (43%) with complete response (CR) observed in 3 of 6 responders. Additionally, rapid response was observed in 3 of 14 HPV negative patients. Response was associated with increase in immune markers on 2nd biopsy. Median overall and progression-free survival in all patients was 12.6 months and 8.6 months, respectively. **Conclusions:** 1. sEphB4-Alb was well tolerated in combination with PD-1 antibody. 2. sEphB4-Alb was associated with increased immune response to tumor, when combined with PD-1 antibody. 3. sEphB4-Alb appears to have substantial activity (including complete remission) when combined with PD-1 antibody in relapsed/refractory HPV negative HN SCC. Clinical trial information: NCT03049618. Research Sponsor: Merck.

	sEphB4-Alb + PD-1 Ab N = 24
Age – median (range)	61 (31–79)
Male sex – no. (%)	19 (79)
Median prior regimens – no. (range)	1 (0–2)
Prior cetuximab – no. (%)	5 (21)
Response rates – no. (%)	
ORR	6 (25)
CR	3 (12)
HPV neg. – no. (%)	14 (58)
HPV neg. ORR (%)	6 (43)
HPV pos. – no. (%)	10 (42)
HPV pos. ORR (%)	0

6017 **Poster Discussion Session**

Efficacy of concurrent cetuximab (CTX) and nivolumab (NIVO) in previously untreated recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). *First Author: Christine H. Chung, Moffit Cancer Center, Tampa, FL*

Background: Current standard of care for patients (pts) with previously untreated R/M HNSCC that are incurable is either pembrolizumab (pembro) with/without chemotherapy depending on the Programmed Death-Ligand 1 (PD-L1) combined positive score (CPS). We evaluated the combination of CTX and NIVO for its efficacy. **Methods:** Pts were treated with CTX 500 mg/m2 IV on Day (D) -14 as a lead-in followed by CTX 500 mg/m2 IV and NIVO 240 mg/m2 IV on D1 and D15 every 28-D cycle (C). Pts with CTX infusion reaction or who did not receive C1D1 for any reason were non-evaluable and replaced. NIVO dose reduction was not allowed. **Results**: Fifty-four evaluable pts were analyzed. Median age was 62 (42-85). ECOG performance status at baseline was 0 (20, 37%), 1 (30, 56%), and 2 (4, 7%). Primary sites were oral cavity 19 (35%), oropharynx 22 (41%), hypopharynx 3 (6%), larynx 9 (17%), and unknown primary 1 (2%). p16 status is positive 22 (41%), negative 29 (54%), and unknown 3 (6%). PD-L1 CPS is <1 in 6 (11%), >1 in 26 (48%), and unknown 22 (41%). Median follow up time for overall survival (OS) was 12.2 months. The most common grade 3 treatment-related adverse events (TRAEs) occurring in ≥2 pts were hypomagnesemia 2 (4%), hypophosphatemia 2 (4%), fatigue 4 (7%), and rash-acneiform 4 (7%). The only grade 4 TRAEs were hypomagnesemia in 1 (2%) and CTX infusion reaction in 1 (2%). The most common grade 3 immune-related adverse event (IRAE) occurring in ≥2 was fatigue 2 (4%). No grade 4 IRAEs is observed. Median progression-free survival (PFS) and OS were 7.8 and 14.5 months, while 1-year PFS and 1-year OS were 39% and 61%, respectively. There were no statistically significant differences in either PFS and OS based on tumor p16 or PD-L1 status. **Conclusions**: The clinical trial met its primary endpoint of 1-year OS. Our data indicate the combination of CTX and NIVO is safe and effective in pts with previously untreated incurable R/M HNSCC. Clinical trial information: NCT03370276. Research Sponsor: Lilly, Florida Health Department.

6018 **Poster Discussion Session**

A randomized phase II trial of diffusion-weighted MR imaging-guided radiotherapy plus chemotherapy versus standard chemoradiotherapy in locoregional advanced nasopharyngeal carcinoma. *First Author: Feng Liu, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China*

Background: We hypothesized that diffusion-weighted MR imaging (DWI) guided dose-painting radiotherapy (DP-RT) was associated with improved tumor control and survival compared with standard CT-based radiotherapy in locoregionally advanced nasopharyngeal carcinoma (NPC). The purpose of this randomized phase II trial was to compare the efficacy and toxicity of DWI guided DP-RT plus chemotherapy versus standard CT-based radiotherapy plus chemotherapy in locoregionally advanced NPC. **Methods:** Two hundred and fifty-six patients with stage III-IVa (8th AJCC) NPC were randomly assigned to receive DWI-guided dose-painting radiotherapy plus chemotherapy (DP-RT group, n = 128) or standard CT-based radiotherapy plus chemotherapy (CT-based RT group, n = 128). Patients in both groups received 3 cycles of induction chemotherapy followed by cisplatin-based concurrent chemoradiotherapy. In DP-RT group, subvolume GTVnx-DWI (gross tumor volume of nasopharynx in DWI) was defined as the areas within the GTVnx (gross tumor volume of nasopharynx) with an apparent diffusion coefficient (ADC) below the mean ADC (ADC $<$ mean). The dose to GTVnx-DWI was escalated to DT 75.2 Gy/32 Fx in patients with T1-2 disease, and DT 77.55 Gy/33 Fx in those with T3-4 disease, in 2.35 Gy per fraction. In CT-based RT group (n = 128), PGTVnx was irradiated at DT 70.4-72.6 Gy/32-33 Fx in 2.2 Gy per fraction. This trial is registered with chictr.org.cn, number ChiCTR1800015779. **Results:** Compared with standard CT-based radiotherapy, DWI-guided DP-RT significantly improved 2-year local recurrence-free survival (LRFS, 100% vs. 95.4%; P = 0.024), distant metastasis-free survival (DMFS, 97.9% vs. 90.6%; P = 0.006), disease free survival (DFS, 93.2% vs. 86.8%; P = 0.021), and overall survival (OS, 100% vs. 95.2%; P = 0.038). No statistically significant differences in acute and late toxic effects were observed. Multivariate analysis showed that dose painting (DWI-guided DP-RT vs CT-based RT without DP) was a significant independent prognostic factor for DMFS and DFS (P = 0.021 and P = 0.020, respectively). **Conclusions:** Diffusion-weighted MR imaging guided dose-painting radiotherapy plus chemotherapy is associated with a considerable survival benefit, without increasing toxicity, as compared with standard CT-based radiotherapy plus chemotherapy, among patients with locoregionally advanced nasopharyngeal carcinoma. Clinical trial information: ChiCTR1800015779. Research Sponsor: Cancer Foundation of China, and China Hunan Provincial Science and Technology Department.

6019 **Poster Discussion Session**

The 30 ROC trial: Precision intra-treatment imaging guiding major radiation reduction in human papillomavirus related oropharyngeal cancer. *First Author: Nancy Y. Lee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Our previously published proof-of-concept trial using functional imaging to select patient with human papillomavirus (HPV) oropharyngeal carcinoma (OPC) for radiation de-escalation showed promising results. Here we report the outcome of a larger validation trial using the same paradigm where select HPV+ OPC patients received a definitive dose of 30Gy concurrently with chemotherapy and were subsequently observed. **Methods:** The trial enrolled patients who had p16+, T0-2, N1-N2c, M0 OPC by AJCC 7th TNM. Patients were required to have resection of the primary site (negative margin not required) or core biopsy of lymph node if unknown primary. In addition to standard positron emission tomography (PET), a pre-radiation dynamic ^{18}F-FMISO (fluoromisonidazole) PET was performed to identify hypoxia in gross nodal disease. Patients with evidence of hypoxia ($>$ 1.2 tumor to muscle standard uptake value on ^{18}F-FMISO) underwent repeat^{18}F-FMISO PET around 2 weeks into radiation. Patients without pre-radiation hypoxia or with resolution of hypoxia on ^{18}F-FMISO PET received 30Gy with 2 cycles of concurrent chemotherapy (cisplatin 100mg/m^2 or carboplatin AUC 1.25 x 4 with 5-fluorouracil 2400 mg/m^2). **Results:** From 11/2/17-1/4/21, 158 HPV+ OPC patients consented and were enrolled on trial. Patient characteristics were as follows: male (90%); ages 36-80 years; T-stage T0(26), T1(77), T2(55); N stage N1(19), N2a(15), N2b(95), N2c(29). Of the 114 patients with pre-treatment hypoxia, 24 had persistent hypoxia and received 70Gy. 128 patients were de-escalated to 30Gy and chemotherapy (86% cisplatin). 6 patients withdrew from trial [3 decided to receive standard of care; 3 refused ^{18}F-FMISO PET]. Acute mucositis rates were 11% grade 0, 59% grade 1, and 30% grade 2, respectively. Acute xerostomia rates were 92% grade 1 and 8% grade 2, respectively. Weight loss was infrequent and only 19% complained of grade 1 and 5% complained of grade 2 weight loss. Six patients experienced grade 3 adverse events (diarrhea (2), syncope (2), vasovagal (1), dysphagia (1)). No patients required PEG tubes. With a median follow-up is 12 months (range: 2 months to 40 months), the 1-year locoregional control, distant metastasis-free overall survival rates were 94%, 100%, and 100%, respectively. Among the 30Gy de-escalated patients, none failed in the primary site. 8 patients had recurrent nodal disease underwent successful salvage surgery of which no additional therapy was given to 4 patients. **Conclusions:** Major de-escalation to 30Gy using patient specific treatment response based on hypoxia resolution resulted in excellent locoregional control with significant toxicity reduction. Updated results along with detailed correlative analysis will be presented. Clinical trial information: NCT03323463. Research Sponsor: U.S. National Institutes of Health, Serra Mucositis Funds.

6020 **Poster Session**

Long-term follow-up of bintrafusp alfa, a bifunctional fusion protein targeting TGF-β and PD-L1, in advanced squamous cell carcinoma of the head and neck (SCCHN). *First Author: Byoung Chul Cho, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Bintrafusp alfa is a first-in-class bifunctional fusion protein composed of the extracellular domain of the TGF-βRII receptor (a TGF-β "trap") fused to a human IgG1 mAb blocking PD-L1. A previous report of an expansion cohort from a phase 1 study (NCT02517398) suggested that bintrafusp alfa had a manageable safety profile and early signs of clinical activity in patients with heavily pretreated, advanced SCCHN after a median follow-up of 86.4 weeks. Here we report long-term efficacy and safety for this cohort. **Methods:** Patients with advanced SCCHN that progressed/recurred after platinum therapy in the recurrent/metastatic setting, or $<$ 6 months after platinum therapy in the locally advanced setting, received bintrafusp alfa 1200 mg every 2 weeks until confirmed progressive disease, unacceptable toxicity, or trial withdrawal. The primary endpoint was confirmed best overall response assessed per RECIST 1.1 assessed by independent review committee (IRC); safety was a secondary endpoint. **Results:** As of May 15, 2020, 32 patients had received bintrafusp alfa for a median of 2.8 months (range, 0.5-29.9 months), no patient remained on treatment, and median follow-up to data cutoff was 41.7 months (range, 39.8-43.5 months). The objective response rate (ORR; 13%) was unchanged since the previous report; median duration of response (DOR) was increased at 21.4 months (95% CI, 5.5 months to not reached [NR]). While the clinical activity of bintrafusp alfa may be improved in patients with HPV-positive tumors (Table), outcomes were generally similar between PD-L1 subgroups ($\geq$1% vs $<$ 1% tumor cells). The overall safety profile was consistent with the previous report for this cohort, without grade 4 nor 5 treatment-related adverse events (TRAEs); no new TRAEs of grade 3 or that led to discontinuation of bintrafusp alfa were reported. **Conclusions:** With a median follow-up of over 3 years in patients with heavily pretreated advanced SCCHN, bintrafusp alfa showed sustained clinical activity and 3-year OS of 24.0%, which compares favorably to historical data. Clinical activity appeared to be greater in patients with HPV-positive tumors than those with HPV-negative tumors. The safety profile was manageable and consistent with earlier analysis. Further investigation of bintrafusp alfa in SCCHN and other HPV-associated cancers is ongoing. Clinical trial information: NCT02517398. Research Sponsor: Merck KGaA, Darmstadt, Germany, and GlaxoSmithKline.

	HPV-positive(n = 11)	HPV-negative (n = 20)	Overall (N = 32)
ORR per IRC (95% CI), %	27.3 (6.0-61.0)	5.0 (0.1-24.9)	12.5 (3.5-29.0)
Median DOR (95% CI), months	18.1 (5.5-24.7)	NR (NR-NR)	21.4 (5.5-NR)
Median progression-free survival (PFS) per IRC (95% CI), months	1.4 (1.2-19.6)	1.4 (1.2-4.0)	1.4 (1.3-4.0)
18-month PFS, %	27.3	17.5	21.3
24-month PFS, %	13.6	11.7	12.8
Median OS (95% CI), months	8.0 (2.9-NR)	9.1 (6.3-24.3)	9.1 (6.6-24.3)
18-month OS, %	45.5	43.0	44.0
24-month OS, %	45.5	30.7	36.0
36-month OS, %	34.1	18.4	24.0

6021 **Poster Session**

The association of skeletal muscle mass and cisplatin pharmacokinetics in head and neck cancer patients: The prospective PLATISMA study. *First Author: Laura Molenaar-Kuijsten, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Locally advanced head and neck squamous cell carcinoma (HNSCC) is commonly treated with cisplatin-based chemoradiotherapy (CRT). Cisplatin is associated with severe toxicity, which negatively affects survival. In recent years, a relationship between low skeletal muscle mass (SMM) and toxicity has been described. This increased toxicity may be related to an altered cisplatin distribution and binding in the fat-free body mass, of which SMM is the largest contributor. This study aims to investigate the association between cisplatin pharmacokinetics and SMM in HNSCC patients. **Methods:** We performed a prospective observational study in HNSCC patients treated with CRT with cisplatin. Patients received standard-of-care chemotherapy with three cycles of cisplatin, at a dose level of 100 mg/m^2 per cycle. Quantitative data on body size descriptors including SMM, measured on computed tomography scans, and cisplatin pharmacokinetics (total and ultrafilterable plasma concentration) were collected, as well as data on toxicity. **Results:** 45 evaluable patients were included in the study. A large proportion of the study population had a low SMM (46.7%). The majority of patients (57.8%) experienced cisplatin dose limiting toxicities. Pharmacokinetic analysis showed a significant relationship between cisplatin pharmacokinetics and the body size descriptors SMM, weight, fat-free mass, and body surface area ($p<$ 0.005). In a simulation, patients with a low SMM were predicted to reach higher bound cisplatin concentrations. The higher concentration of bound cisplatin could be seen as a reflection of the smaller volume of distribution, and could thereby explain the increased toxicity in patients with a low SMM. **Conclusions:** We found an association between cisplatin pharmacokinetics and SMM. Patients with a low SMM were predicted to reach higher bound cisplatin concentrations, which could be an explanation for the increased toxicity in this patient group. Clinical trial information: Trial NL7469 (NTR7711). Research Sponsor: Dutch Cancer Society.

6022 **Poster Session**

Anlotinib in radioiodine-refractory differentiated thyroid carcinoma: A subanalysis based on ALTER01032 study for patients with poor baseline characteristics. *First Author: Yihebali Chi, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Anlotinib (anlo), a multikinase inhibitor, has demonstrated a significant survival benefit in treating locally advanced or metastatic radioiodine-refractory differentiated thyroid carcinoma (RAIR-DTC) with a nearly 4 folds prolongation in median progression-free survival (mPFS) (HR = 0.21, $p < 0.0001$) compared with placebo in a randomized, placebo-controlled phase 2 study (ALTER01032, NCT02586337). Older age, bone metastasis, structural progression within a short time are generally indicated as negative prognostic factors for thyroid cancer. This subanalysis explored the outcomes of patients (pts) enrolled in ALTER01032 study with these poor baseline characteristics. **Methods:** 113 pts were enrolled, 76 in anlo arm and 37 in placbo arm. The primary endpoint is PFS. Pts with older age ($\geq$ 55), bone metastasis or radiographic documented disease progression within 3 months (mo) before enrollment were selected. The PFS and overall survival (OS) for these pts were estimated and compared. Since 64.9% pts in placebo arm received crossover treatment with open label anlo after progression while only 3 pts in anlo arm received post-study treatment, the penitential bias for OS from imbalance of subsequent treatment was adjusted by a two-stage estimation method. **Results:** The results of subanalysis were summarized in the table below. Pts with poor baseline characteristics showed higher risk of progression and death. Significant PFS prolongation was shown across all subgroups in pts received anlo compared with their counterparts who received placebo ($P < 0.05$). In pts with bone metastasis or structural progression within 3 mo, anlo treatment achieved significant OS benefit ($P < 0.05$). Also, in older pts, a trend of OS improvement was observed (HR = 0.85 (95% CI 0.37, 1.97)). Most pts in placebo arm received crossover anlo. After adjustment, a near-significant decrease of death risk was observed in older pts received anlo compared with those received placebo (HR = 0.48 (95% CI 0.20, 1.13)). **Conclusions:** This subanalysis showed anlo effectively improved both PFS and OS of pts with RAIR-DTC who have poor baseline characteristics above. Interestingly, although most pts in placebo arm received crossover anlo, they still have higher risk of death, indicating the importance of earlier treatment for these pts. Clinical trial information: NCT02586337. Research Sponsor: None.

Features	No. of pts (Anlo / Placebo)	mPFS for Anlo (mo)	mPFS for placebo (mo)	HR (95% CI) , P-value	Crossover anlo n (%)	HR (95% CI) for OS, P- value	Adjusted HR for OS (95% CI), P- value
Older age	39/25	29.5	6.9	0.23 (0.12, 0.46), 0.0001	19 (76.0)	0.85 (0.37, 1.97), 0.710	0.48 (0.20, 1.13), 0.0862
Bone metastasis	20/11	36.1	5.6	0.10 (0.03, 0.28), 0.0001	7 (63.6)	0.16 (0.05, 0.51), 0.0005	0.04 (0.00, 0.30) 0.0001
Progression within 3 mo before enrollment	45/23	NR	6.9	0.096 (0.045, 0.206), 0.0001	17 (73.9)	0.35 (0.14, 0.86), 0.017	0.21 (0.08, 0.55), 0.001

6023 **Poster Session**

Toripalimab plus intensity-modulated radiotherapy for recurrent nasopharyngeal carcinoma: An open-label single-arm, phase II trial. *First Author: Mingyuan Chen, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Toripalimab is a humanized immunoglobulin G_4 monoclonal antibody against programmed death 1 (PD-1). We aimed to investigate the efficacy and safety of toripalimab in combination with intensity-modulated radiotherapy (IMRT) for recurrent nasopharyngeal carcinoma (rNPC). **Methods:** We conducted a single-arm, phase II trial with rNPC patients who had biopsy-proven disease and were unsuitable for local surgery. Eligible patients received IMRT in combination with toripalimab administered via intravenous infusion of 240 mg once every 3 weeks for a maximum of seven cycles. The primary endpoint was the objective response rate (ORR). The secondary endpoints included safety profiles, progression-free survival (PFS). **Results:** Between May 2019 and January 2020, a total of 25 rNPC patients were enrolled (18 men [72.0%] and 7 women [28.0%]; median [IQR] age, 49.0 [43.5-52.5] years). With a median (IQR) follow-up duration of 14.6 months (13.1-16.2) months, 19 patients (79.2%) achieved an overall response, and disease control was achieved in 23 (95.8%) patients at 3 months post radiotherapy. The 12-month progression-free survival was 91.8% (95% CI 91.7% - 91.9%). The incidences of acute (grade ≥3) blood triglyceride elevation, creatine phosphokinase elevation, skin reaction, and mucositis were 1 (4.0%), 1 (4.0%), 2 (8.0%), and 1 (4.0%), respectively. The incidences of late severe (grade ≥3) nasopharyngeal wall necrosis, nasal bleeding, and trismus were 28.0%, 12.0%, and 4.0%, respectively. **Conclusions:** Toripalimab combined with IMRT was tolerable and showed promising antitumor activity in rNPC patients. Clinical trial information: NCT03854838. Research Sponsor: the Key-Area Research and Development of Guangdong Province.

6024 **Poster Session**

Afatinib and pembrolizumab for recurrent or metastatic head and neck squamous cell carcinoma (ALPHA Study): A phase II study with biomarker analysis. *First Author: Hsiang-fong Kao, Department of Oncology, National Taiwan University Hospital, Taipei, Taiwan*

Background: Epidermal growth factor receptor (EGFR) pathway inhibition may synergize with anti-PD1 activity by inhibiting macrophage function, increasing antigen presentation, and augmenting T cell responses. Afatinib, an irreversible EGFR tyrosine kinase inhibitor (TKI), has been shown to enhance anti-PD1 activity in in vitro and animal studies. We thus hypothesized that adding afatinib to pembrolizumab may improve the treatment outcomes for patients with recurrent or metastatic head and neck squamous cell carcinoma (HNSCC). **Methods:** The ALPHA study (NCT03695510) is a single-arm, phase II study with a Simon 2-stage design. Patients with platinum-refractory, recurrent, or metastatic HNSCC are eligible for the study. Afatinib (40mg, oral, daily) and pembrolizumab (200mg, every 3 weeks) are administered to eligible patients. The primary endpoint is the objective response rate (ORR). PD-L1 IHC testing (22C3), comprehensive genomic profiling (CGP, Roche Foundation Medicine One CDx), and targeted multiplexed gene expression profiling (Nanostring nCounter PanCancer Immune Profiling Panel) were applied for biomarker analysis. **Results:** From JAN 2019 to MAR 2020, 29 patients were enrolled in the study. Age: mean = 53.4 years old; M/F = 27/2. Tumor type: oral cavity: 19; oropharynx: 6, hypopharynx: 2, larynx: 2. PD-L1 TPS > = 50: 7/29 (24.1%), CPS > = 20: 8/29 (27.6%), TMB > 10: 0/25 (0%). The common treatment-related adverse events (AEs; all grades, grade > = 3) were skin rash (22/29, 4/29), diarrhea (17/29, 3/29), paronychia (13/29, 0/29), mucositis (9/29, 1/29), and weight loss (2/29, 0/29). One patient experienced grade 2 pneumonitis. Twelve patients had partial responses to the treatment (12/29, ORR: 41.4%). The data cut-off date was 11FEB2021. The median progression free survival (PFS) was 4.1 (95% confidence interval [CI], 1.9-6.3) months. The median overall survival (OS) was 8.4 (95% CI, 4.1-10.8) months. Patients with high PD-L1 expression had a higher response rate (TPS > = 50: ORR = 0.71, CPS > = 20: ORR = 0.63). EGFR amplification might also predict a higher response rate (ORR: 3/3, 100%). MTAP loss or mutation may predict a poor response to the treatment (ORR: 0/5, 0%), shorter PFS (HR: 4.21, [95% CI: 1.34-13.24], p = 0.014), and shorter OS (HR: 4.20 [95% CI: 1.32-13.41], p = 0.015). Nine patients underwent paired pre-treatment and post-treatment biopsies for gene expression analysis. The mRNA of HLA-A, HLA-B, CXCL13, CXCL9, and CD8A were elevated in the post-treatment biopsies. Three patients underwent post-progression biopsies for CGP study. One patient had a new MTAP mutation. **Conclusions:** Afatinib can modify tumor microenvironment and increase the clinical response rate in pembrolizumab-based therapy in HNSCC patients. PD-L1, EGFR amplification, and MTAP loss/mutation could be biomarkers for cancer immunotherapy. Clinical trial information: NCT03695510. Research Sponsor: Boehringer Ingelheim, Merck.

6025 **Poster Session**

A phase 2 study of liposomal irinotecan with 5-fluorouracil and leucovorin in squamous cell carcinoma of head and neck or esophagus after prior platinum-based chemotherapy or chemoradiotherapy. *First Author: Li-Yuan Bai, Department of Hematology and Oncology, China Medical University Hospital, Taichung, Taiwan*

Background: Liposomal irinotecan (nal-IRI) + 5-FU/LV has been approved and used in treating patients with metastatic pancreatic cancer after gemcitabine-based therapy through the NAPOLI-1 study result. This phase 2 trial evaluated the activity of NAPOLI-1 regimen in patients with squamous cell carcinoma (SCC) of head and neck (H&N) or esophagus that progressed on or recur after platinum-based chemotherapy or concurrent chemoradiotherapy. **Methods:** Patients with histologically confirmed SCC of H&N or esophagus whose disease progressed while on or progressed/recurred within 6 months after platinum-based chemotherapy or chemoradiotherapy, and unsuitable for further surgical or radiation intervention were eligible. Prior anti-EGFR or anti-PD1/anti-PDL1 treatment was allowed. The regimen consisted of nal-IRI 70 mg/m^2 (irinotecan free base) followed by LV 400 mg/m^2 and 5-FU 2400 mg/m^2, every 2 weeks. A Simon's 2-stage design was used with planned 30 evaluable patients in the first stage and 52 evaluable patients in total. The primary endpoint is objective tumor response. **Results:** From December 2018 to April 2020, 59 subjects were enrolled, including 16 with esophagus cancer and 43 with H&N cancer. Thirty-seven (63%) patients had metastatic disease at enrollment. The mean of treatment cycles were 5 (range, 1-21). Among the total 59 enrolled subjects, 53 subjects (14 esophagus cancer, 39 H&N cancer) were evaluable for objective tumor response. The disease control rate in esophagus cancer was 50% (7 SD, intent-to-treat (ITT) population 43.8%). For H&N patients, 1 CR, 4 PR, and 23 SD resulted in the response rate 12.8% (11.6% in ITT population) and disease control rate 72% (65% in ITT population). The median progression free survival (N = 59) was 2.5 months (esophagus/H&N: 1.5/2.7 months) and the median overall survival was 5.9 months (esophagus/H&N: 4.2/7.3 months). Seventy-eight percent of patients had ≥grade 3 treatment-related adverse events. The most frequent ≥grade 3 toxicities were decreased lymphocyte count (50.8%), decreased neutrophil count (42.4%), and decreased white blood count (33.9%). Only 3 patients (5%) had grade 3 diarrhea during the treatment period. **Conclusions:** This study showed the modest efficacy and manageable toxicity profile of nal-IRI+5-FU/LV in platinum-refractory locally advanced or metastatic H&N or esophagus cancer patients. Clinical benefits including complete tumor response were noted in H&N patients. The role of this regimen in selective patients and the efficacy of combination with immunotherapeutic agents warrant further explorations. Clinical trial information: NCT03712397. Research Sponsor: None.

6026 **Poster Session**

Preliminary results of the efficacy and safety of all-trans retinoic acid combined with low-dose apatinib in the treatment of patients with recurrent/metastatic adenoid cystic carcinoma of the head and neck. *First Author: Lulu Ye, Radiotherapy Division, Department of Oral and Maxillofacial-Head Neck Oncology, Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Background: There is no standard treatment for recurrent/metastatic adenoid cystic carcinoma of the head and neck (R/M ACCHN). Moreover, MYB and/or NOTCH1 mutation can lead to worse prognosis. Currently, anti-angiogenic targeted therapy is a relatively effective treatment option, but the accompanied toxicities may hinder the continuous medication. All-trans retinoic acid (ATRA) induces differentiation and promotes apoptosis, enhancing the cytotoxicity of anti-tumor agents; on the other hand, inhibits c-MYB and/or NOTCH1 expression. Apatinib is an oral tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor receptor 2. We reported the preliminary results of the efficacy and safety of ATRA combined with low-dose apatinib in patients with R/M ACC. **Methods:** In this exploratory study, patients with pathologically or histologically confirmed advanced, R/M ACC with measurable disease were screened. Patients who previously received anti-angiogenic therapy then withdrew due to toxicities could be recruited. ATRA was administered orally at a dose of 20 mg twice a day, and apatinib was administered orally at a dose of 250 mg once a day. The primary endpoint was objective response rate (ORR), as assessed according to the Response Evaluation Criteria In Solid Tumors v1.1. **Results:** Between March 2019 and April 2020, a total of 16 patients were enrolled. The median age was 53 years (range: 35-69), and 7 (44%) patients were male. Four (25%) patients received ATRA plus apatinib as the third-line therapy, while 12 (75%) received as the second-line therapy. Of 16 patients, 3 (19%) achieved partial response and 13 (81%) achieved stable disease (SD), with ORR of 19% and disease control rate of 100%, respectively. Among patients with SD, 12 (75%) showed tumor shrinkage (3%-28%) and 1 (6%) showed minor tumor enlargement (2%). The median follow-up time was 14.5 months (range: 8.1-22.1). Throughout the period, 5 (42%) patients developed disease progression. The 6-month and 12-month progression-free survival rates were 100% and 80%, respectively. Grade 3 adverse events included hand-foot syndrome (1 [6%]) and proteinuria (1 [6%]). No grade ≥4 adverse events occurred. **Conclusions:** ATRA combined with low-dose anti-angiogenic drug apatinib could be a potential treatment option for patients with R/M ACC, including those with pretreated advanced ACC after progression on or intolerance to other therapies. These encouraging results were worth further investigations, and a randomized phase 2 trial in ongoing (the Aplus study, NCT04433169). Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co., Ltd.

6027 **Poster Session**

Mathematical predication models to optimize post-treatment surveillance in HPV-associated oropharyngeal cancer. *First Author: Vivek Nair, University of Chicago Pritzker School of Medicine, Chicago, IL*

Background: In this study we develop post-treatment imaging surveillance schedules for locally advanced oropharyngeal carcinoma (OPC) specific to the unique recurrence patterns of tumor stage and HPV status, using mathematical models. Current post-treatment imaging surveillance recommendations for OPC are not evidence based. The exception is the use of a positron emission tomography (PET) scan at 3 months post-treatment, after which practice across institutions diverge. An optimized and personalized surveillance schedule for OPC patients can minimize costs and diagnostic delays. **Methods:** A Markov multi-state model defining local and distant recurrences was trained using 2159 patients from the National Cancer Database. Patients from 2010-2015 treated at an academic or major cancer center with curative radiotherapy were included. Tumors must have been stage III to IVB (AJCC 7th edition) with known p16/HPV status. Model performance was then successfully externally validated using the 2016 International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S) study. Optimized radiographic surveillance schedules were created using this model, assuming a PET at month 3 and including 0 to 6 additional computed tomography (CT) scans of the neck and chest. Optimization was done for minimization of latency, defined as time between disease recurrence and radiographic discovery. **Results:** Model-selected schedules varied significantly from commonly utilized-surveillance schedules (such as imaging every 3 months within the first year from treatment) and showed lower mean diagnostic latency for every stage and HPV status (shown in Table). In the lowest risk cohort (Stage III HPV+), the optimized schedule had a sensitivity of 65% and latency of 3.1 months. In the highest risk group (Stage IVB HPV-), the optimized schedule had a sensitivity of 76% and latency of 1.9 months. **Conclusions:** Mathematical model optimization for HPV status and stage is feasible and produces non-intuitive results. These results could be used to inform surveillance if payors reimburse for fewer total scans. Across all cohorts, each added CT scan increases surveillance sensitivity and decreases latency. Incorporation of physical exam and direct visualization results into the model are still needed. Future steps include cost effectiveness research and prospective clinical trials. Research Sponsor: None.

Performance of optimized PET+6 additional CT scan surveillance strategies, divided by stage and HPV-status.

Cohort	Optimized Post-PET CT Scan Months	Sensitivity	Latency (months)	Latency (months) for Non-Optimized Post-PET CT Scans at Months 6,9,12,18,24,36
Stage III HPV+	8,13,18,23,28,33	.65	3.1	3.9
Stage III HPV-	6,9,12,15,19,23	.70	1.8	2.6
Stage IVA HPV+	7,11,15,19,23,31	.68	2.9	3.2
Stage IVA HPV-	6,10,14,18,23,30	.71	2.4	2.8
Stage IVB HPV+	6,9,13,18,23,30	.70	2.8	3.3
Stage IVB HPV-	6,9,12,16,20,24	.76	1.9	2.2

6028 **Poster Session**

Results from a phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with PD-L1 unselected metastatic second-line squamous head and neck carcinoma. *First Author: Irene Brana, Vall d'Hebron University Hospital, Vall d'Hebrón Institute of Oncology, Barcelona, Spain*

Background: Eftilagimod alpha (efti) is a soluble LAG-3 protein that binds to a subset of MHC class II molecules to mediate antigen presenting cell (APC) activation and CD8 T-cell activation. The stimulation of the dendritic cell network and subsequent T cell recruitment with efti may lead to stronger anti-tumor responses in combination than observed with pembrolizumab alone. We hereby report results of the 2nd line metastatic squamous head and neck carcinoma (HNSCC) cohort (part C) of phase II trial (NCT03625323). **Methods:** Patients (pts) with HNSCC progressed on or after 1st line platinum-based therapy and unselected for PD-L1 expression were recruited into part C. The study used a Simon's 2-stage design (18 pts planned for stage 1 and 19 for stage 2), with objective response rate (ORR) by iRECIST as the primary endpoint (EP). Secondary EPs include tolerability, disease control rate (DCR), progression free survival (PFS), overall survival (OS), pharmacokinetics, pharmacodynamics and immunogenicity. Efti was administered as 30 mg subcutaneous injection every 2 wks for 8 cycles and then every 3 wks for 9 cycles with pembrolizumab (200 mg intravenous infusion every 3 wks for up to 2 yrs). Imaging was performed every 8 weeks. PD-L1 was assessed centrally (22C3 clone). The study was approved by ethics committees and institutional review boards. **Results:** In total 38 pts were enrolled. The median age was 62 yrs (range 37-84) and 89 % were male. The ECOG PS was 0 and 1 in 34% and 66%, respectively. Primary location at diagnosis was the oral cavity (29%), oropharynx (37%), hypopharynx (18%) and the larynx (16%). All PD-L1 subgroups (CPS $<$ 1 %, $\geq$ 1 to $\leq$19; $\geq$20) were included. All pts were pre-treated with platinum-based chemotherapy. Pts received a median of 3.0 (range 1 – 21) pembrolizumab and 5.0 (range 1-31) efti administrations. Thirty-five (35) pts were evaluated for response (cut-off Jan 2021) with 4 (11 %) pts showing CR, 7 (20 %) pts PR, 3 (9 %) pts SD, 16 (46 %) pts PD with 5 (14 %) pts being not evaluable as per iRECIST. ORR was reported with 31.4 % (95 % CI 16.9 % - 49.3 %) and DCR 40 %Median PFS was 2.1 months and 35 % were progression free at 6 months. Median OS (46 % events) was 12.6 months. There were no adverse reactions leading to treatment discontinuation. The most common ($>$ 10 %) treatment emergent adverse events were cough (18 %), asthenia (16 %), dyspnea (11 %), fatigue (13 %), diarrhea (11 %), hypothyroidism (11%), upper respiratory tract infection (11%) and back pain (11%). **Conclusions:** Efti in combination with pembrolizumab is safe and shows encouraging antitumor activity in platinum pre-treated 2nd line HNSCC patients. Clinical trial information: NCT03625323. Research Sponsor: Immutep S.A.

6029 **Poster Session**

Update on safety and efficacy of a phase 1/2 of SNS-301 added to pembrolizumab in patients with advanced squamous cell carcinoma of the head and neck (SCCHN). *First Author: Alain Patrick Algazi, Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA*

Background: The absence of infiltrating antigen-specific CD8+ T-cells at baseline is associated with low response rates to PD-1 blockade. SCCHN tumors often exclude effector T cells, and 2nd line response rates are low (13-18%). Highly immunogenic, antigen specific antitumor vaccines may expand intratumoral CD8+ T cells, potentially increasing durable response rates to PD-1 blockade. SNS-301 is a first-in-class, bacteriophage-based immune activating agent targeting human aspartate β-hydroxylase (ASPH), a tumor associated antigen overexpressed in multiple tumor types. SNS-301 is a self-adjuvanted vaccine consisting of λ-bacteriophage engineered to express an immunogenic fragment of ASPH fused to the phage gpD coat protein. The study objectives are to evaluate safety, immunogenicity and preliminary efficacy of SNS-301 added to pembrolizumab in patients (pts) not achieving tumor reductions on PD-1 blockade alone. **Methods:** Intradermal SNS-301 was combined with pembrolizumab in pts with locally advanced unresectable (LA) or metastatic/recurrent (met) SCCHN with a best response of stable disease (SD) or unconfirmed progressive disease (uPD) on ongoing PD-1 blockade $>$ 12 weeks. Pts provided pre and on-treatment biopsies to characterize the tumor microenvironment using Nanostring and multiplex immunohistochemistry (mIHC). Blood samples were collected to evaluate B and T cell responses using ELISA/ELISPOT assays. **Results:** As of February 4, 2021, 13 pts were enrolled. Median duration of PD-1 blockade was 48 weeks (range 14-114) at study entry. There were no DLTs & mostly Grade 1-2 unrelated adverse events. Only two related Grade 3 events were reported: rash & dehydration (also a serious adverse event). Ten pts were evaluable for efficacy: 1 pt with PD-L1 negative (neg) disease & SD on pembrolizumab monotherapy achieved a partial response (PR; -52% at 8 months), 4 pts achieved SD & 5 pts had progressive disease. Two of the pts with SD had long-lasting duration (8 & 10 months) of which the latter had PD-L1 neg disease. One pt with uPD at enrollment achieved SD for 4 months. Analyses of pre- & on-treatment biopsies from the PR pt demonstrated an increase in infiltrating CD8+ T cells, PD-L1 expression & PD-1/PD-L1 proximity measures. Nanostring analysis demonstrated increased gene expression signatures for immune cells in the PR pt that was concordant with the mIHC & clinical outcome. **Conclusions:** The combination of SNS-301 and pembrolizumab was well-tolerated and resulted in encouraging clinical efficacy in pts not expected to respond to PD-1 blockade alone. Translational data suggest cellular response to SNS-301 and transformation of a poorly inflamed tumor to an immunologically active tumor in a responding pt (PR). Based on these data, an additional cohort will start enrolling PD-1 blockade naïve pts with LA/met SCHNN in the front-line setting. Clinical trial information: NCT04034225. Research Sponsor: None.

6030 **Poster Session**

Expansion cohort validation of a clinical predictive model for head and neck cancer survival in patients treated with immune checkpoint inhibitors. *First Author: Georgios Laliotis, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: Immune checkpoint inhibitors (ICI) therapy is approved for patients (pts) with recurrent-metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). The majority of pts will die within two years of diagnosis. We have shown that pretreatment clinical characteristics may predict overall survival (OS). Here, we expand our analysis to a total of 201 pts. **Methods:** Between January 15,2016 and April 9, 2020, 201 pts with R/M HNSCC were treated with ICI as first, second line and beyond. Data on p16 status, hemoglobin (Hb), albumin, lactate dehydrogenase (LDH), neutrophil, platelet and lymphocyte count was recorded initially. OS was defined from the start of ICI to death. Progression Free Survival (PFS) was defined from the start of ICI to disease progression (PD) or death. A nomogram was created using the rms package to generate individualized survival prediction. **Results:** 201 pts were analyzed, sex: 154 male (77%), 47 female (23%), median age 61 (IQR: 55-68). ICI drug: pembrolizumab 100 (50%), nivolumab 91 (45%), ipilimumab+-nivolumab 10 (5%). Line of therapy: First: 98 (49%), second and beyond: 103 (51%). Tumor site: oropharynx 84 (42%), oral cavity 45 (22%), others 72 (36%). p16 status: negative 132 (66%), positive 69 (34%). Laboratory values: Median neutrophil count: 4.58 (IQR: 3.43-6.47), Median lymphocyte count: 0.69 (IQR: 0.47-1.08), Median Platelet count: 229 (IQR: 187-300), hemoglobin (Hb) normal/low 101/100 (50%/50%), albumin: normal/low 156/45 (78%/22%), LDH: normal/high 124/77 (62%/38%). Overall response rate: 36 (18%). Median OS: 12 months (CI: 9.4-14.8), median PFS: 4 months (CI: 3.5-5.7). The variables associated with OS were neutrophil count (high) [HR 1.28 (1.08 – 1.51), *p=0.004*], lymphocyte count (high) [HR 0.75 (0.60 – 0.95), *p=0.015*], albumin (low) [HR 2.06 (1.37 – 3.10), *p$<$0.001*], hemoglobin (low) [HR 1.64 (1.14 – 2.35), *p=0.007*], LDH (high) [HR 1.78 (1.23 – 2.56), *p=0.002*] and p16 status (positive) [HR 0.58 (0.39-0.87), *p=0.009*]. Using the prognostic index of the chosen model, we stratified patients into three risk groups at the 33rd and 66th percentile. Median OS in the good risk group was 24 months (CI: 18.5-NR), average risk group 13.8 months (CI: 11-20), poor risk group 2.3 months (CI: 1.7-4.4). The discrimination of the model after internal validation was c-index of 0.72. **Conclusions:** A small percentage of R/M HNSCC pts treated with ICI have good long-term survival outcomes. In a larger cohort, we internally validated the utilization of a simple, inexpensive and widely accessible nomogram based on clinical and laboratory variables which can predict OS in this patient population. Research Sponsor: None.

6031 **Poster Session**

Adjuvant nivolumab following salvage resection in head and neck squamous cell carcinoma patients previously treated with definitive therapy: A single-arm phase II multi-institutional study. *First Author: Jennifer Leddon, University of Cincinnati Medical Center, Cincinnati, OH*

Background: Salvage surgery for locally recurrent head and neck squamous cell carcinoma (rHNSCC) results in local control rates of 33-50% but only 20-40% of patients achieve long-term survival necessitating additional therapy (Haque et al., Oral Oncol. 2019). Many patients are ineligible for re-irradiation and chemotherapy alone after salvage surgeryhas shown no survival benefit. The clinical activity and tolerability of immune checkpoint inhibitors has been demonstrated in metastatic HNSCC, but the benefit after salvage surgery (SS) has not been studied. Here we report the results of a multi-center phase II investigation of nivolumab, a PD-1 inhibitor, after SS in recurrent HNSCC (NCT03355560). **Methods:** HNSCC patients undergoing curative-intent SS were enrolled to receive 6 months of nivolumab beginning 4-11 weeks after surgery. All received radiation with or without chemotherapy as prior definitive therapy and had no other curative treatment options at the time of surgery. Key exclusion criteria included: distant metastatic disease, gross residual disease, or a history of immunodeficiency, autoimmunity, or pneumonitis. The primary endpoint was 2-year disease-free survival (DFS) measured by Kaplan Meier curves. Safety was evaluated by CTCAE v5.0. **Results:** 39 patients were enrolled. Median age was 68 years (range, 49-85). 12/39 (31%) were female. 34/39 (87%) were white. Disease sites included oropharynx 9/39 (23%), oral cavity 14/39 (36%), and larynx 16/39 (41%). P16 status was 26% (+), 48% (-), and 26% (unknown). 17/39 (44%) had high risk pathologic features (positive margins or extranodal spread) at time of SS. 28/39 (72%) patients experienced treatment-related adverse events (TRAE), the most common of which were fatigue (26%), hypothyroidism (10%) and acneiform rash (13%). Grade 3-4 TRAEs were rare, occurring in 3/39 (8%) patients and included diarrhea, oral pain, neck pain, productive cough, stridor, and COPD exacerbation. 3/39 (8%) required treatment discontinuation and there were no grade 5 events. The 2-year DFS was 60% (95%CI 0.39-0.91). 2-year overall survival was 74% (95% CI 0.54-1). In single-cell multiplex cytokine analysis, patients who relapsed following adjuvant nivolumab had a significantly higher proportion of peripheral blood CD8 T cells which displayed a polyfunctional cytokine profile. IFN-γ and Granzyme were the dominant CD8 cytokines in both responders and non-responders, however CD8 expression of MIP1a and TNF-α were significantly higher in patients who ultimately relapsed. **Conclusions:** Nivolumab after salvage surgery in rHNSCC is well tolerated and shows promising antitumor activity in this high-risk patient population with unmet need. Immunotherapy after salvage surgery should be studied in randomized clinical trials. Clinical trial information: NCT03355560. Research Sponsor: BMS.

6032 **Poster Session**

A phase III multicenter randomized clinical trial to compare cisplatin plus fluorouracil with or without docetaxel as the first-line induction chemotherapy for locoregionally advanced nasopharyngeal carcinoma: Long-term outcomes update. *First Author: Wang Fang FangZheng, Zhejiang Cancer Hospital, Hangzhou, China*

Background: A phase III multicenter prospective randomized controlled trial was conducted to compare cisplatin plus 5-fluorourcil with or without docetaxel as first-line induction chemotherapy in the patients with locoregionally advanced nasopharyngeal carcinoma (LANPC). Here, we report on the long-term outcomes and late toxicities of the trial (NCT01536223). **Methods:** Patients with newly diagnosed LANPC, stage III-IV disease, Karnofsky performance score$\geq$70, without metastasis were eligible and randomly assigned 1:1 to TPF versus PF for three cycles. The primary end point was progression-free survival; local control, OS and advent events were important key secondary end points. The Kaplan-Meier method and the log-rank test were used to conduct and compare the survival curves in this study. **Results:** Two hundred ninety-nine patients were enrolled. 276 patients (138 TPF and 138 PF) were evaluable. Baseline characteristics were well-balanced between two groups, and the median age was 48 (range, 18-60 years). The ORR rates after induction chemotherapy and chemoradiotherapy were 90.6% and 9797.8% in TPF group and 87.0% ($P > 0.05$) and 97.8% ($P > 0.05$), respectively. The median follow-up was 99 months. For all patients, the 5- and 8-year OS and PFS were 76.9% and 74.9%, 72.3% and 69.1%, respectively. PF was associated with a similar PFS versus TPF (5-year PFS of 72.4% versus 73.2%, P = .747), and an equivalent OS at 5 years (79.2% and 79.1%, P = 0.519). Treatment-related grade 3 to 4 advent events were less frequent with PF compared with TPF. **Conclusions:** With prolonged follow-up, the survival outcomes in the PF group were not noninferiority to those in the TPF group, but grade 3 to 4 advent events were less frequent. Clinical trial information: NCT01536223. Research Sponsor: None.

6033 **Poster Session**

Effect of neoadjuvant systemic therapy given during window trials on quality metrics in resectable head and neck squamous cell carcinoma. *First Author: Marco A. Mascarella, University of Pittsburgh Medical Center Cancer Center, Pittsburgh, PA*

Background: Quality oncologic care, including negative surgical margin status, adequate lymph node yield and prompt initiation of adjuvant treatment, impacts disease control and overall survival in patients with mucosal head and neck squamous cell carcinoma (HNSCC). The aim of this study was to ascertain the effect of neoadjuvant systemic therapy given during window trials on oncologic quality metrics in patients with delayed definitive surgery for a HNSCC. **Methods:** Treatment-naïve patients with HNSCC participating in one of two window of opportunity clinical trials at UPMC from 2009-2019 were included. Neoadjuvant regimens consisted of one dose of cetuximab (n = 33) or anti-ErbB3 antibody (n = 9) within 28 days of surgery. Sociodemographic, clinical and tumor staging were recorded. The primary outcome was overall oncologic quality, as defined as a composite measure of negative margin status, adequate lymph node yield, completion of adjuvant therapy (if indicated) and time to initiation of adjuvant therapy within 6 weeks of surgery. Secondary outcomes were difference in clinical and pathologic stages and overall survival (OS). **Results:** A total of 42 patients with a mean age of 57.1 ($\pm$10.2) years and median follow-up of 58 months were analyzed. 29 patients had clinical stage IVA disease with 43% (18/42) oral cavity, 36% (15/42) larynx/hypopharynx and 21% (9/42) oropharynx primaries. All patients underwent surgery following neoadjuvant systemic therapy. In 30 patients (71%), all oncologic quality markers were achieved. Pathological downstaging occurred in 21% (9/42) of patients with 4 patients no longer meeting criteria for adjuvant treatment and were observed. 3 patients showed pathological upstaging. The 3-year OS were 76% (95% CI of 63.6-88.4), respectively. Patients with a pathologic downstage migration (64.9%, 95% CI of 49.9-79.8) had higher 5-year OS compared to those without (57.8%, 95% CI of 40.1-76.4, P = 0.046). **Conclusions:** Most patients receiving neoadjuvant systemic therapy on window trials prior to surgery met all oncologic quality markers. Importantly, even with brief window trial therapy pathologic downstaging was achieved and associated with significantly better overall survival. Research Sponsor: None.

6034 **Poster Session**

Phase II trial of combined durvalumab plus tremelimumab with proton therapy to boost the abscopal effect for recurrent or metastatic head and neck squamous cell carcinoma. *First Author: Hana Kim, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: This phase 2 study investigated whether durvalumab plus tremelimumab with proton therapy improves objective response rate (ORR), overall survival (OS), and progression-free survival (PFS) in heavily treated recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) via boosting abscopal effect. **Methods:** Thirty-one patients who have previously received more than one chemotherapy regimen, including at least one platinum-based regimen and have at least two measurable lesions enrolled at Samsung medical center. Patients received durvalumab 1500mg intravenously (IV) in combined with tremelimumab 75 mg IV every four weeks for four cycles followed by durvalumab 1500mg every four weeks. After one cycle of durvalumab and tremelimumab combination, proton therapy was performed with a total dose of 25 Gy in 5-Gy daily fractions to one of the measurable lesions. We assessed the target lesion response outside the radiation field by RECIST criteria 1.1 to evaluate the abscopal effect. **Results:** Between March 2018 and July 2020, 31 patients were enrolled. The median age was 59 years, and median two prior chemotherapy regimens were administered. With 24.8 months of follow-up, the median number of cycles of immunotherapy was three. The ORR was 27.3%, including one complete response and five partial responses. Median OS was 6.4 months (95% CI, 1.0 to 11.8), and median PFS was 2.4 months (95% CI, 0.6 to 4.2). Median duration of response was 15.9 months (range 3.7 – 21.2). Grade 3 or higher adverse events were observed in 6 (27.3%) patients; anemia (n = 1), constipation (n = 1), electrolyte imbalance (n = 2), hyperglycemia (n = 1), pneumonia (n = 1). **Conclusions:** Combination of durvalumab/tremelimuab with proton therapy is well tolerable and shows encouraging anti-tumor efficacy in non-irradiated tumor lesions of heavily treated HNSCC patients. These results suggest that the combination of immunotherapy with proton therapy might enhance the abscopal effect. Clinical trial information: NCT03450967. Research Sponsor: AstraZeneca.

6035 **Poster Session**

Maintenance intervention to improve survival in patients with metastatic nasopharyngeal carcinoma who benefit from first-line treatment: A prospective multicenter randomized controlled clinical study. *First Author: Ying Lu, The Fourth Affiliated Hospital of Guangxi Medical University, Liuzhou, China*

Background: The role of drug maintenance intervention in improving survival outcomes remains controversial.To investigate the safety and effect of Tegafur(S1) maintenance intervention in patients with metastatic nasopharyngeal carcinoma who benefit from the first-line treatment in a multicenter randomized controlled study, and to identify the related biological prognostic factors and guide the individualized treatment choice. **Methods:** Patients with metastatic nasopharyngeal carcinoma in the Fourth Affiliated Hospital of Guangxi Medical University and other cancer centers who met the inclusion criteria were randomly divided into maintenance therapy group: S1 maintenance therapy until disease progression or intolerance; Observation group: follow-up to disease progression. PFS, overall survival (OS) and adverse reactions of S1 maintenance therapy were compared between the two groups. The correlation between EBV-DNA, human serum amyloid A (SAA) and prognosis was evaluated. **Results:** Follow-up was conducted to May 2020, with a median follow-up of 19.8 months (6.1-51.3 months), 183 cases were evaluable (88 cases in S1 maintenance treatment group, 95 cases in observation group). Compared with the observation group, the S1 maintenance treatment group significantly increased patients' median PFS (16.2 months vs. 8.7 months, $P < 0.001$) and median OS (32.1 months vs. 18.2 months, $P < 0.001$). Reduced the risk of poor prognosis for PFS and OS (PFS: HR 0.305, 95%CI 0.211-0.441, < 0.001; OS: HR 0.363, 95%CI 0.238-0.553, $P < 0.001$). In the maintenance treatment group, the median S1 treatment lasted for 14 courses (4-58 courses), and the main adverse reactions were grade 1 skin pigmentation, oral mucositis, hand-foot syndrome, nausea, etc. No grade 4 toxic reaction occurred, and it was well tolerated. Compared with observation patients with negative EBV-DNA, observation patients with positive EBV-DNA had a higher risk of poor prognosis for PFS (HR 1.764, 95%CI 1.078-2.887, P = 0.024). The risk of poor prognosis in patients with positive EBV-NDA was significantly reduced by 61.1% (< 0.001) for PFS and 65.5% (P = 0.001) for OS (P = 0.001). Compared with the observation group with stable SAA expression, S1 maintenance therapy significantly improved the prognosis of patients. Patients with continuous decline in SAA had a 61.9% lower risk of poor prognosis in PFS ($P < 0.001$) and a 60.2% lower risk of poor prognosis in OS (P = 0.007). **Conclusions:** For patients with metastatic nasopharyngeal carcinoma who benefit from first-line treatment, maintenance therapy of S1 can significantly improve the survival prognosis and is well tolerated. Patients with positive EBV-DNA and continuous decline in SAA may benefit more from maintenance intervention. Clinical trial information: ChiCTR-IOR-16007939. Research Sponsor: Guangxi Natural Science Foundation(China)Liuzhou City Science and technology research projects (China).

6036 **Poster Session**

Final analysis of a phase 1b, randomized, multicenter study of talimogene laherparepvec (T-VEC) plus pembrolizumab (pembro) combination for the treatment (Tx) of recurrent/metastatic squamous cell carcinoma of the head and neck (R/M HNSCC): MASTERKEY-232. *First Author: Kevin Joseph Harrington, The Royal Marsden//The Institute of Cancer Research NIHR Biomedical Research Centre, London, United Kingdom*

Background: T-VEC, a genetically modified herpes simplex virus-1, is the first FDA- and EMA-approved oncolytic viral immunotherapy designed to enhance systemic antitumor immune responses. R/M HNSCC is a disease with considerable clinical complexity and poor prognosis. Pembro is a PD-1-specific humanized monoclonal antibody currently approved as first-line Tx for this disease, but there is an unmet need among many patients (pts). To meet this gap, the safety and preliminary efficacy of T-VEC plus pembro in pts with R/M HNSCC was evaluated in a phase 1b study (Harrington et al. *Clin Cancer Res.* 2020). Here, we present results of the final analysis of this study (NCT02626000). **Methods:** Eligible pts (≥18 yrs) had ECOG-PS of 0 or 1; histologically confirmed R/M HNSCC of the oral cavity, oropharynx, hypopharynx, or larynx unsuitable for curative surgical resection or radiotherapy; platinum-refractory and with injectable tumors. Pts with known active CNS metastases and any systemic or local therapy 28 days before enrollment were excluded. T-VEC was injected intralesionally up to 8.0 mL of 10^6 PFU/mL according to lesion sizes on day 1; after 3 weeks, subsequent doses of ≤8.0 mL of 10^8 PFU/mL were given Q3W. Pembro was given intravenously at 200 mg Q3W. Pts were followed-up for 36 mos after the last patient was enrolled in the study. Key endpoints (irRECIST per investigator assessment) were objective response rate (ORR), best overall response (BOR), disease control rate (DCR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), and safety. **Results:** A total of 36 pts (80.6% male) were enrolled and treated: 28 (77.8%) had confirmed PD-L1-positive tumor (CPS ≥1), 5 (13.9%) were HPV-positive, 13 (36.1%) had metastatic disease, and 19 (52.8%) had prior lines of therapy in the R/M setting. At the final analysis, 7 pts (19.4%) completed the study, and 29 (80.6%) discontinued the study due to death. Safety profile was consistent with that at 1-yr analysis (Harrington et al. *Clin Cancer Res.* 2020). Confirmed ORR was seen in 16.7% (95% CI, 6.4–32.8). No patient had a complete response as their BOR, 6 (16.7%) had a partial response, 8 (22.2%) had stable disease, 6 (16.7%) had progressive disease, 6 (16.7%) were unevaluable, and 10 (27.8%) died before the first response assessment. The DCR was 38.9% (95% CI, 23.1–56.5). The median DOR was 45.9 mos (95% CI, 8.5–NE). The median PFS was 3.0 mos (95% CI, 2.0–5.8), and the median OS was 5.8 mos (95% CI, 2.9–11.4). **Conclusions:** The safety results at 3 yrs for T-VEC plus pembro in pts with R/M HNSCC were consistent with those of the 1-yr analysis. Although the response rate was consistent with that observed with pembro alone in historical HNSCC studies, the extended DOR in responding patients warrants further investigation. Clinical trial information: NCT02626000. Research Sponsor: Amgen.

6037 **Poster Session**

Interim analysis of IMMUNEBOOST-HPV: A multicenter, randomized, open label, phase II study evaluating the feasibility, and tolerance of neoadjuvant nivolumab in high-risk HPV driven oropharynx cancer. *First Author: Haitham Mirghani, Hôpital Européen Georges Pompidou HEGP, Paris, France*

Background: Among HPV-positive Oropharyngeal Cancer (OPC) patients (pts), some has a less favorable prognosis (T4, N2/N3, smokers >10 pack-year [p/y]). We assume that neoadjuvant immunotherapy might improve their oncological outcomes, so we tested nivolumab (N) prior to ChemoRadiaTion (CRT). **Methods**: The study population is restricted to HPV positive OPC pts (both p16+ & HPV-DNA+) with advanced disease (T4, N2/N3) or a smoking history >10 p/y. Pts were randomly allocated 1:2 to receive either cisplatin-based CRT (n=20) or 2 cycles of N 240 mg followed by CRT (n=41). The Primary Endpoint (PE) is the rate of pts who can receive Full Treatment in Due Time (FTDT), according to these criteria: a) 2 N infusions on day 1 and on day 14-16 b) CRT started between days 28-37 after the 1st N infusion c) No RT break ≥1 week d) RT dose received >95% of theoretical dose e) Cisplatin dose received ≥200 mg/m^2 To achieve FTDT, all criteria are required in the Experimental Arm (EA) while only criteria c), d), and e) are required in the Control Arm (CA). In the EA, the trial was designed in 2 steps, with FTDT rate of 88% considered as inacceptable versus an alternative of 98%, a type I error of 0.10, and a type 2 error of 0.08. As per protocol, patient accrual was temporarily suspended after inclusion of 19 pts in the EA (1st step) and results were reviewed by an Independent Data Monitoring Committee (IDMC). To resume pts' inclusion, FTDT had to be achieved in 18 pts in the EA. **Results**: From 07/2019 to 09/2020, 30 pts were enrolled including 11 in the CA (demographics are summarized in table). 2 pts in the EA did not reach the PE. For the 1st patient, the cisplatin dose was <200 mg/m^2 due to grade 1 hearing loss and grade 2 tinnitus (1st cycle: 100 mg/m^2, 2nd cycle: 80 mg/m^2, no 3rd cycle). For the 2nd patient, CRT began at D38 due to logistical issues (maintenance of RT devices). As this delay was unrelated to N or to patient's condition, the IDMC considered that the inclusions could resume for the 2nd step. 7 N-related Adverse Events (AE) were reported in 4 pts including 3 serious AE (ankylosing spondylitis flare-up, colitis, diabetic ketoacidosis). **Conclusions**: Neoadjuvant N before CRT seems feasible for the treatment of OPC pts. The trial has reopened to inclusion as recommended by the IDMC. Clinical trial information: NCT03838263. Research Sponsor: Programme Hospitalier de Recherche Clinique en Cancérologie (PHRC-K) financé par le ministère de la Santé (Direction générale de l'offre de soins (DGOS)), Pharmaceutical/Biotech Company.

	CA	EA
Age		
Median	62	58
Min; Max	50-69	36-70
Sex		
Male	10 (91%)	14 (73.7%)
Female	1 (9%)	5 (26.3%)
ECOG		
ECOG 0	11 (100%)	17 (89.5%)
ECOG 1	0	2 (10.5%)
T-stage		
2	2 (18.2%)	5 (26.3%)
3	2(18.2%)	5 (26/3%)
4	7 (63.6%)	9 (47.4%)
N-stage		1 (5.3%)
0	2 (18.2%)	
1	7 (63.6%)	10 (52.6%)
2	2 (18.2%)	6 (31.6%)
3	0	2 (10.5%)
Tobacco consumption		
Non	3 (27.3%)	4 (21.1%)
Former	7 (63.6%)	14 (73.7%)
Current	1 (9.1%)	1 (5.3%)

6038 **Poster Session**

Use of cetuximab added to weekly chemotherapy to improve progression-free survival in patients with recurrent metastatic head and neck squamous cell carcinoma after progression on immune checkpoint inhibitors. *First Author: Majd Issa, Ohio State University-James Cancer Hospital Solove Research Institute, Columbus, OH*

Background: Immune checkpoint inhibitors (ICI) are currently approved in the treatment of patients (pts) with recurrent-metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). The majority of pts will progress on ICI. Little is known regarding the best treatment approach for this patient population. We previously showed that the combination of weekly carboplatin, paclitaxel and cetuximab was associated with reduced risk of grade 3/4 toxicities, which makes it an ideal regimen in this setting. Here; we report the outcomes of pts with R/M HNSCC who were treated with chemotherapy alone vs weekly chemotherapy plus cetuximab after progression on ICI. **Methods:** Between January 15th 2016 and April 9th 2020, 154 pts who progressed on ICI were analyzed. Among these pts, 64 had received subsequent systemic therapy and met the inclusion criteria. Progression Free Survival (PFS) was defined as the time elapsed between initiation of subsequent chemotherapy and tumor progression or death. Overall Survival (OS) was defined as the time elapsed between initiation of subsequent chemotherapy to death. Descriptive statistics and Cox regression were used to explore study variables. **Results:** 64 pts received subsequent chemotherapy after progression on ICI. 28 pts (44%) received a combination of weekly chemotherapy plus cetuximab. This regimen included carboplatin AUC 1.5, paclitaxel 45 mg/m^2, and cetuximab loading dose of 400mg/m^2 followed by weekly dose of 250 mg/m^2. 36 pts (56%) received chemotherapy alone without cetuximab. These regimens included capecitabine, afatinib, and gemcitabine, among others. Sex: 51 males (80%), 13 females (20%), age (median): 61 (IQR: 53-66), tumor site: oropharynx 32 (50%), oral cavity 11 (17%), larynx 8 (12%), other sites 13 (21%). P16 status: negative 36 (56%), positive 28 (44%). Prior ICI drug: pembrolizumab 34 (53%), nivolumab 26 (41%), ipilimumab + nivolumab 4 (6%). Median follow up: 9 months (IQR: 5-13). Overall response rate: weekly chemotherapy plus cetuximab 32%, chemotherapy alone 22% (p = 0.4). Pts who received chemotherapy alone had a median PFS of 3.2 months (CI: 2-5) vs 5.6 months (CI: 4.3-10.1) in the weekly chemotherapy plus cetuximab group. After adjusting for p16 status and prior ICI drug, PFS was improved in the group that received weekly chemotherapy plus cetuximab vs. chemotherapy alone (HR: 0.52; CI: 0.28-0.98; p = 0.042). Median OS was 10 months (CI: 8.5-NR) in the weekly chemotherapy plus cetuximab group vs 8.7 months (CI: 5.7-13.8) in the chemotherapy alone group (HR: 0.84; CI: 0.4-1.8; p = 0.8). **Conclusions:** Pts with R/M HNSCC who progressed on ICI experience longer PFS with the addition of cetuximab to weekly chemotherapy. Further investigation in a larger cohort of pts is needed to fully assess the impact on survival for this treatment combination. Research Sponsor: None.

6039 **Poster Session**

Adjuvant toripalimab or combined with S-1 in recurrent, previously irradiated head and neck squamous cell carcinoma treated with salvage surgery: A phase II clinical trial (The RePASS study). *First Author: Shengjin Dou, Radiotherapy Division, Department of Oral and Maxillofacial-Head Neck Oncology, Shanghai Ninth People's Hospital, College of Stomatology, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Background: The predominant pattern of failure for Head and Neck Squamous Cell Carcinoma (HNSCC) is locoregional disease. Salvage surgery remains the standard of care for operable disease. Re-irradiation after previous full course radiotherapy generally has been considered contraindicated. Since anti-PD-1 antibodies were efficacious and safety in recurrent/metastatic HNSCC, this study aimed to evaluate the efficacy and safety of adjuvant toripalimab (anti-PD-1 antibody) in recurrent, previously irradiated HNSCC treated with salvage surgery. **Methods:** This study was a single-arm, phase II study. Patients with HNSCC occurring in an area of previously irradiated and with at least one high risk factors after salvage surgery (1- positive margin; 2- extranodal extension; 3-rStaging T3-4/N2-3/T2N1) were enrolled. In the Stage I of 12 patients, patients received toripalimab 240mg once every 3 weeks until confirmed disease progression or unacceptable toxicity, for 12 months. In the stage II of 8 patients with PD-L1 CPS≥1, patients received toripalimab combined with S-1, which was given orally at 25 mg/m^2, twice daily, on day 1 to 14, repeated every 21 days for 4-6 cycles. The primary endpoint was 1-year progression-free survival (PFS). We hypothesized a 1-year PFS of at least 56% and assumed a null hypothesis of 34%. A retrospective cohort of 16 patients was compared. **Results:** Between May 2019 and December 2020, 20 patients were enrolled. High-risk factors included ENE (35%), positive margin (25%), T3-4(30%) and T2N+(10%). Seventeen patients have PD-L1 CPS≥1 and 3 patients have CPS < 1. With a median follow-up of 11.2 months, estimated 1-year PFS and overall survival was 57.0% (95% confidence interval, 32%– 77%) and 79.2% (51%–91%). The primary PFS endpoint has exceeded the hypothesis and its median has not been reached. When compared to the retrospective cohort, the PFS was significantly better(p=0.001), even for Stage I patients(Median PFS: 5.1 vs 3.7 months, p=0.03). Stage II patients resulted a better PFS and OS compare to stage I (p=0.02 and p=0.002). For patients with CPS≥1, 1-year PFS and OS was 79.1% (95% confidence interval, 51%–91%) and 91.7%(68%–99%), which were significantly better than patients with CPS < 1 (p=0.001 and p=0.05). Adjuvant Toripalimab or combine with S-1 was well-tolerated with no grade 3-4 toxicity and dose interruption as a result of treatment-related adverse event only occurred in 2 patients. Flow cytometry revealed that patients with short PFS had fewer baseline overall count of B cells(p=0.09). **Conclusions:** Adjuvant Toripalimab or combined with S-1 after salvage surgery is efficacious and safety in recurrent, previously irradiated HNSCC, and a better PFS was observed in patients treated with combined therapy and with CPS≥1. Further randomized trials are warranted. Clinical trial information: NCT04126460. Research Sponsor: Shanghai Junshi Biosciences.

6040 **Poster Session**

Update and external validation of a multivariable prediction model for tube feeding dependency for at least four weeks during chemoradiotherapy for head and neck cancer. *First Author: Anna C. H. Willemsen, Department of Internal Medicine, Division of Medical Oncology; GROW-School of Oncology and Developmental Biology; Department of Respiratory Medicine, NUTRIM School of Nutrition and Translational Research in Metabolism, Maastricht University Medical Center, Maastricht, Netherlands*

Background: Patients who receive chemoradiation or bioradiation (CRT/BRT) for locally advanced head and neck squamous cell carcinoma (LAHNSCC) often experience high toxicity rates, which may interfere with oral intake, leading to (temporary) tube feeding (TF) dependency. International guidelines recommend gastrostomy insertion when the expected use of TF exceeds four weeks. In this study we aimed to update and externally validate a prediction model to identify patients in need for TF for at least four weeks, meeting the international criteria for prophylactic gastrostomy insertion. **Methods**: This retrospective multicenter cohort study was performed in four tertiary referral head and neck cancer centers in the Netherlands. The prediction model was developed using data from the University Medical Center Utrecht and the Netherlands Cancer Institute. The model was externally validated in patients from the Maastricht University Medical Center and Radboud University Medical Center. The primary endpoint was TF, initiated during or within 30 days after completion of CRT/BRT, and administered for at least four weeks. Potential predictors were retrieved from patient medical records and radiotherapy dose-volume parameters were calculated. **Results**: The developmental and validation cohort included 409 and 334 patients respectively. Multivariable analysis showed significant predictive value ($p < 0.05$) for adjusted diet at start of CRT/BRT, percentage weight change prior to treatment initiation, WHO performance status, tumor-site, nodal stage, mean radiation dose to the contralateral parotid gland, and mean radiation dose to the oral cavity. The area under the receiver operating characteristics curve for the updated model was 0.73 and after external validation 0.64. Positive and negative predictive value at 90% cut off were 80.0% and 48.2% respectively. **Conclusions**: This externally validated prediction model to estimate TF-dependency for at least four weeks in LAHNSCC patients performs well. This model, which will be presented, can be used in clinical practice to guide personalized decision making on prophylactic gastrostomy insertion. Research Sponsor: NUTRIM Graduate Programme.

6041 **Poster Session**

Racial and regional differences in incidence of oropharyngeal cancer in the United States during 2001 to 2017. *First Author: Fangjian Guo, University of Texas Medical Branch at Galveston, Galveston, TX*

Background: The incidence of human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma (OPSCC) has been reported to be increasing among both middle-aged and elderly adults in the United States. This study was to assess racial and regional differences in the incidence of OPSCC among adults in the US. **Methods:** We included 271,037 adult patients ≥ 20 years old diagnosed with potentially HPV-related OPSCC from the US Cancer Statistics 2001–2017 database which essentially covered the entire US population. Incidence of OPSCC was age- adjusted to the US standard population. Annual percentage change (APC) in the incidence was assessed across races/ethnicities and regions of residence. **Results:** Among these adults with potentially HPV-related OPSCC from 2001-2017, 5.3% were Hispanics, 83.0% were non-Hispanic Whites, and 9.2% were non-Hispanic Blacks, and 79.1% were male. Incidence of OPSCC increased from 3.9 per 100,000 in 2001 to 4.0 per 100,000 in 2017 (APC 0.43, 95% confidence interval (CI) 0.01, 0.85) in Hispanics, increased from 5.3 per 100,000 in 2001 to 8.6 per 100,000 in 2017 (APC 2.97, 95% confidence interval (CI) 2.71, 3.24) in non-Hispanic Whites, and decreased from 6.3 per 100,000 in 2001 to 5.1 per 100,000 in 2017 (APC -1.27, 95% confidence interval (CI) -1.56, -0.99) in non-Hispanic Blacks. The incidence increased from 5.8 per 100,000 in 2001 to 7.8 per 100,000 in 2017 (APC 1.94, 95% confidence interval (CI) 1.67, 2.21) in the South, increased from 5.0 per 100,000 in 2001 to 7.1 per 100,000 in 2017 (APC 2.13, 95% confidence interval (CI) 1.92, 2.34) in the Northeast, increased from 4.9 per 100,000 in 2001 to 6.3 per 100,000 in 2017 (APC 1.85, 95% confidence interval (CI) 1.53, 2.17) in the West, and increased from 4.9 per 100,000 in 2001 to 7.7 per 100,000 in 2017 (APC 2.79, 95% confidence interval (CI) -2.52, 3.07) in the Midwest. The incidence decreased from 0.9 per 100,000 in 2001 to 0.8 per 100,000 in 2017 (APC -0.81, 95% confidence interval (CI) -1.41, -0.20) among adults 20-44 years old, increased from 9.0 per 100,000 in 2001 to 12.7 per 100,000 in 2017 (APC 2.01, 95% confidence interval (CI) 1.66, 2.36) among adults 45-64 years old, and increased from 10.9 per 100,000 in 2001 to 16.7 per 100,000 in 2017 (APC 2.96, 95% confidence interval (CI) 2.75, 3.16) among adults 65+ years old. **Conclusions:** OPSCC incidence increased across racial/ethnic groups, regions, and age groups from 2001 to 2017, except that the incidence decreased among non-Hispanic Blacks and young people. Underlying causes for the decreasing trend in the incidence of OPSCC among certain groups need further investigation. Research Sponsor: U.S. National Institutes of Health, Center for Interdisciplinary Research in Women's Health, The University of Texas Medical Branch.

6042 **Poster Session**

Efficacy and toxicity of weekly paclitaxel, carboplatin, and cetuximab as induction chemotherapy or in cases of metastases or relapse for head and neck cancer in elderly or frail patients. *First Author: Rebecca Forman, Yale New Haven Hospital, New Haven, CT*

Background: Standard of care treatments for locally advanced and metastatic head and neck squamous cell carcinoma (HNSCC) are not well tolerated, particularly in elderly or frail patients. One combination that has been studied in recent years is paclitaxel, carboplatin and cetuximab (PCC). Studies have shown this regimen yields promising results when used as an induction chemotherapy for locally advanced disease. PCC has also been studied in patients with metastatic or recurrent incurable disease, and has shown good response with tolerable toxicity rates, but there is a relative dearth of evidence surrounding its use. **Methods:** This retrospective observational study utilized EMR data analysis software to generate the cohort of adult patients that received PCC for HNSCC in 2014-2019 as well as demographic data. Chart review was used to gather details about the patients' tumors and clinical course. Modified RECIST response rates (MRRR), progression free survival (PFS) and overall survival (OS) were the primary end points calculated for the metastatic/recurrent group, and percentage of successful inductions (e.g., patients went on to definitive treatment, avoided surgery) and MRRR were used for the induction group. **Results:** There were 80 patients in the cohort. The average age was 65 (range 33-84) and the patients were 81% male. The most common tumor site was the tongue (25 patients), followed by tonsil (15), oropharynx (9), and larynx (7). 13 patients had p16 positive disease. Most patients had Stage IVA (36 patients), followed by IVB (20), and IVC (15); the remainder had stage III or below or unknown stage. The most common reasons patients did not receive cisplatin were performance status (13 patients), hearing loss (11), concern for nephrotoxicity (6) and age (5). 97.5% of patients experienced at least one adverse effect. The most common adverse effect was dermatologic (69%), followed by hematologic (51%), fatigue (41%) and gastrointestinal symptoms (41%). 53 patients (66%) experienced at least one dose interruption due to adverse effects. 11 patients (14%) stopped treatment due to toxicities. 58 patients received PCC for metastatic or recurrent disease. They had received a median of 1 line of systemic treatment prior; 72% had prior radiation, and 26% had prior salvage surgery. The MRRR was 22% (5 patients with complete response, 8 partial response, 15 stable, 27 progression). There was a 7.0 month mean PFS, and 17.3 month mean OS. Of the 22 patients who received PCC as induction, 86% (19) successfully reached their induction endpoint. The MRRR was 64% (8 patients with complete response, 6 partial response). **Conclusions:** PCC is a relatively well-tolerated combination with a very good induction success rate. More research is needed around alternate options for frail and elderly patients with HNSCC. Research Sponsor: None.

6043 **Poster Session**

Palbociclib (P) in patients (pts) with head and neck cancer (HNC) with *CDKN2A* loss or mutation: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *First Author: Evan P. Pisick, Cancer Treatment Centers of America, Zion, IL*

Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of HNC pts with *CDKN2A* loss or mutation treated with P are reported. **Methods:** Eligible pts had advanced HNC, no standard treatment options, measurable disease, ECOG PS 0-2, and adequate organ function. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts received P at 125 mg orally once daily for 21 days, followed by 7 days off until disease progression. Pts matched to P had *CDKN2A* loss or mutation and no *RB*mutations. Simon 2-stage design tested the null disease control (DC) - defined as partial (PR), complete response (CR) or stable disease at 16+ weeks (SD 16+) - rate of 15% vs. 35% (power = 0.85; $\alpha = 0.10$). If ≥2 of 10 pts in stage 1 have DC, 18 more pts are enrolled. If ≥7 of 28 pts have DC, the null DC rate is rejected. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. **Results:** 28 pts (64% male) with HNC with *CDKN2A*loss (20 pts) or mutation (8 pts) were enrolled from June 2016 to Sept 2019. All were eligible for efficacy and toxicity. Demographics and outcomes are summarized in Table. No objective response (OR) and 10 pts with SD16+ (9 with *CDKN2A* loss, 1 with mutation) were observed for a DC rate of 37% (95% CI: 21%, 50%); the null DC rate of 15% was rejected (p=0.005). 14 pts had at least one grade 3-5 adverse or serious adverse event (AE/SAE) at least possibly related to P with the most common being low WBC/platelets. Other grade 3-4 AEs included anemia, fatigue, hypocalcemia, and syncope. There was one pt with grade 5 respiratory failure likely due to extensive lung metastases and aspiration but P-related pneumonitis could not be ruled out. **Conclusions:** Monotherapy P demonstrated modest anti-tumor activity and clinically significant AEs in heavily pretreated pts with HNC with *CDKN2A*loss or mutation. Additional study is warranted to confirm the efficacy of P in pts with HNC with *CDKN2A*loss or mutation. Clinical trial information: NCT02693535. Research Sponsor: Pfizer.

Demographics and efficacy outcomes (N=28).

Median age, yrs (range)	**58 (33, 80)**
ECOG PS, %	
0	25
1	68
2	7
Prior systemic regimens, %	
1-2	25
≥3	75
DC rate, % (OR or SD16+) (95% CI)	37 (21, 50)
OR rate, % (95% CI)	0 (0, 12)
Median PFS, wks (95% CI)	9.4 (8.0, 20.3)
Median OS, wks (95% CI)	42.0 (22.9, 68.1)

6044 **Poster Session**

Capecitabine maintenance therapy after induction chemotherapy in newly diagnosed metastatic nasopharyngeal carcinoma: An open-label, randomized, controlled, phase trial. *First Author: Guo-Ying Liu, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Capecitabine maintenance therapy improves outcomes in various tumor types, but minimal data are available on the effect of capecitabine maintenance therapy in metastatic nasopharyngeal carcinoma (NPC). We aimed to investigate whether capecitabine maintenance therapy would prolong the progression-free survival (PFS) of newly diagnosed metastatic NPC, in comparison to best supportive care (BSC). **Methods:** This was an open-label, randomized, controlled, phase trial. Eligible patients for maintenance randomisation were aged 18-65 years old with newly diagnosed metastatic NPC at the Sun Yat-Sun University Cancer Center (SYSUCC), had completed 4 to 6 cycles of induction chemotherapy as per protocol and had achieved disease control to protocol treatment, including capecitabine. Patients were randomly assigned 1:1 to capecitabine maintenance (oral 1,250 mg/m^2/day on days 1-14 every 21 days) for up to 24 months with BSC or BSC alone. The primary endpoint was PFS. The secondary endpoints included overall survival, duration of response, objective response rate and adverse effects. Analyses were done by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02460419 and is ongoing and no longer recruiting new patients. **Results:** Between May 16th, 2015, and January 9th, 2020, 140 metastatic NPC patients were screened, and 104 eligible patients were randomly assigned to capecitabine maintenance plus BSC (n = 52) or BSC alone (n = 52). After a median follow-up of 33.1 months (IQR, 21.5-50.7 months), median PFS was 35.2 months in the capecitabine maintenance group and 9.1 months in the BSC group (HR: 0.426; 95%CI: 0.248-0.731, P = 0.001). The most commongrade 3 or 4 adverse events during maintenance therapy were hand-foot syndrome (10.0%), nausea/vomiting (6.0%), fatigue (4.0%), and mucositis (4.0%). Totally 37 deaths occurred during follow-up, 14 (26.9%) in the capecitabine maintenance group and 23 (44.2%) in the BSC group. Overall survival data was immature. No deaths in the capecitabine maintenance group were deemed treatment related. **Conclusions:** Capecitabine maintenance significantly improved PFS in patients with newly diagnosed metastatic NPC who achieved disease control after induction chemotherapy compared to BSC and exhibited low grade and manageable toxicities. Clinical trial information: NCT02460419. Research Sponsor: None.

6045 **Poster Session**

Evaluation of radiomics as a predictor of tumor hypoxia and response to anti-PD-1 mab treatment (IO) in recurrent/metastatic HNSCC patients (R/M). *First Author: Dan Paul Zandberg, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: There is a great need for non-invasive predictors of the tumor microenvironment and the efficacy of anti-PD-1 mAb treatment (IO) in R/M HNSCC patients. We previously showed that lower tumor hypoxia was associated with increased efficacy with IO (*Journal of Clinical Oncol*. 38, no. 15_suppl (May 20, 2020) 6546) and now we evaluate the predictive value of radiomics in this same patient cohort. **Methods:** We studied radiomic signatures in a cohort of 36 patients with R/M HNSCC treated with IO. Treatment response was evaluated using RECIST 1.1. Patients were categorized as: Responders (R) ie CR, PR, SD and non-Responders (NR) i.e PD. As per our previous analysis (ref above) hypoxia was evaluated on archival FFPE samples via immunofluorescent imaging and defined by the ratio of percent area (% CAIX) / the mean intensity (Int) of carbonic anhydrase IX in tumor (%CAIX/Int). ImageJ software was used to determine %CAIX and Int. Feature extraction was performed on the pre-immunotherapy baseline CT scans. The lesions were segmented using 3D slicer v4.10.2 to create a volume of interest (VOI) for radiomic texture analysis (TA). A total of 400 features (10 histogram-based and 390 second-order texture features) were calculated from each extracted volume of interest (VOI). Radiomic features were obtained using a feature selection approach based on Least Absolute Shrinkage and Selection Operator (LASSO). Selected features were used to build a classification model, using XGboost, for prediction of tumor response to immunotherapy. Cross-validation was performed using the Leave One Out Cross Validation (LOOCV) approach for the XGBoost method to evaluate the robustness of the estimates and calculated accuracy, sensitivity, specificity and p-value. **Results:** Our patient cohort had a median age of 59, 69% male, 58% smokers. 61% received IO for platinum failure, 39% frontline. Primary site included 39% OC, 22% OPC (38% HPV positive), 17% Larynx, 5% hypopharynx, and 17% other. Radiomics applied to the primary HNSCC tumor highly predicted tumor hypoxia status with a sensitivity, specificity, and accuracy of 78%, 83%, and 81%, respectively, p = 0.0001. To predict response, we applied radiomics to both the primary HNSCC tumor and pathological lymph nodes; radiomics was also able to predict whether a patient would be a responder (N = 8) versus a non-responder (N = 28) to IO based on the pre-immunotherapy baseline CT scan. The sensitivity, specificity, and accuracy were 93%, 88%, and 92%, respectively, p = 0.02. **Conclusions:** Even in a small cohort, radiomics could predict response to IO and tumor hypoxia in R/M HNSCC patients. To our knowledge this is the first evaluation of this kind in this patient population. Further evaluation of radiomics as a predictor of efficacy with IO and the tumor microenvironment is warranted. Research Sponsor: U.S. National Institutes of Health.

6046 **Poster Session**

Refining TNM-8 M1 categories with anatomic subgroups for previously untreated de novo metastatic nasopharyngeal carcinoma. *First Author: Sik-Kwan Chan, Department of Clinical Oncology, The University of Hong Kong, Hong Kong, Hong Kong*

Background: The eighth edition TNM (TNM-8) classified de novo metastatic (metastatic disease at presentation) nasopharyngeal carcinoma (NPC) as M1 without further subdivision. However, survival heterogeneity exists and long-term survival has been observed in a subset of this population. We hypothesize that certain metastatic characteristics could further segregate survival for de novo M1 NPC. **Methods:** Patients with previously untreated de novo M1 NPC prospectively treated in two academic institutions (The University of Hong Kong [n = 69] and Provincial Clinical College of Fujian Medical University [n = 114] between 2007 and 2016 were recruited and re-staged based on TNM-8 in this study. They were randomized in 2:1 ratio to generate a training cohort (n = 120) and validation cohort (n = 63) respectively. Univariable and multivariable analyses (MVA) were performed for the training cohort to identify the anatomic prognostic factors of overall survival (OS). We then performed recursive partitioning analysis (RPA) which incorporated the anatomic prognostic factors identified in multivariable analyses and derived a new set of RPA stage groups (Anatomic-RPA groups) which predicted OS in the training cohort. The significance of Anatomic-RPA groups in the training cohort was then validated in the validation cohort. UVA and MVA were performed again on the validation cohorts to identify significant OS prognosticators. **Results:** The training and the validation cohorts had a median follow-up of 27.2 months and 30.2 months, respectively, with the 3-year OS of 51.6% and 51.1%, respectively. Univariable analysis (UVA) and multivariable analysis (MVA) revealed that co-existing liver and bone metastases was the only factor prognostic of OS. Anatomic-RPA groups based on the anatomic prognostic factors identified in UVA and MVA yielded good segregation (M1a: no co-existing liver and bone metastases and M1b: co-existing both liver and bone metastases; median OS 39.5 and 23.7 months respectively; $P = .004$). RPA for the validation set also confirmed good segregation with co-existing liver and bone metastases (M1a: no co-existing liver and bone metastases and M1b: co-existing liver and bone metastases), with median OS 47.7 and 16.0 months, respectively; $P = .008$). It was also the only prognostic factor in UVA and MVA in the validation cohort. **Conclusions:** Our Anatomic-RPA M1 stage groups with anatomical factors provided better subgroup segregation for de novo M1 NPC. The study results provide a robust justification to refine M1 categories in future editions of TNM staging classification. Research Sponsor: None.

6047 **Poster Session**

Outcomes and prediction of lethal recurrence after transoral robotic surgery for HPV+ head and neck cancer. *First Author: Devraj Basu, The University of Pennsylvania, Philadelphia, PA*

Background: Increasing use of transoral robotic surgery (TORS) for human papilloma virus-related (HPV+) head and neck squamous cell carcinomas (HNSCCs) is likely to impact recurrence patterns and outcomes. Profiling HPV+ HNSCC recurrences after TORS and identifying features predictive of lethal outcome would facilitate tailoring adjuvant therapy and guide surveillance post-therapy. This study uses long term follow-up of patients at the first institution to bring TORS into clinical use to describe the recurrence patterns, distinguish outcomes associated with distinct patterns, and create a risk model for lethal recurrence. **Methods:** This retrospective cohort study at a single academic tertiary center analyzed 634 consecutive, treatment-naïve HPV+ HNSCC patients receiving TORS and neck dissection for clinical features at presentation and pathologic traits identified by surgical resection. The main outcomes were distant metastatic recurrence (DMR) and locoregional recurrence (LRR). Multivariate logistic regression with backward stepwise elimination was used to identify features associated with recurrence. **Results:** 6.5% of patients developed DMR at a median of 12.4 months after surgery and had a 5-year overall survival (OS) of 52.5% (95% CI, 33.9%-68.2%), whereas the 6.2% patients developing LRR alone had 5-year OS of 83.3% (95% CI, 66.2%-92.2%; P = .01). After recurrence, 5-year progression-free survival was 24.7% (95% CI, 11.4%-40.7%) for DMR cases and 85.7% (95% CI, 65.1-94.6%) for cases with LRR alone (P < .001). Comparing recurrent cases to recurrence-free controls showed DMR to be independently associated with positive surgical margins (AOR 5.7; 95% CI, 2.1-15.7) and advanced clinical stage at presentation (AOR 6.5; 95% CI, 1.9-23.0). Positive margins increased DMR risk by 4.2-fold and reduced 5-year disease-free survival (P < .001) in early-stage cases (Table), which comprised 95% of the cohort. By contrast, isolated LRR was associated with failure to receive indicated adjuvant therapy and was usually controllable by salvage therapy. **Conclusions:** Based on the largest single institution cohort reported to date, long term oncologic outcomes for HPV+ HNSCCs after TORS are excellent overall. While DMR is often fatal, LRR is salvageable with durable disease control. In addition to standard staging criteria, positive margins indicate substantially higher risk of DMR but not LRR. A risk model for DMR that incorporates margin status after TORS is relevant for guiding clinical trial design and whole-body surveillance. Research Sponsor: U.S. National Institutes of Health.

Risk model for DMR.

Advanced clinical stage	Positive margin	Total patients (N)	DMR absent (N)	DMR present (N)	Risk DMR (%)	Coefficient in model[a]	Adjusted odds ratio	95% CI	P value
No	No	270	244	26	9.6	-	[reference]	-	-
No	Yes	20	12	8	40.0	1.8	6.3	2.3-16.7	< .001
Yes	No	12	7	5	41.7	1.9	6.7	2.0-22.6	.002
Yes	Yes	0	-	-	-	-	-	-	-

a. Coefficient in logistic regression model. Intercept is -2.2

6048 **Poster Session**

Ultra-sensitive detection and quantification of HPV DNA in the plasma of patients with oropharyngeal squamous cell carcinoma (OPSCC) enrolled in the OPTIMA 2 treatment de-escalation trial. *First Author: Hillary Sloane, Sysmex Inostics, Baltimore, MD*

Background: Human papillomavirus (HPV) infection is a primary factor driving the increasing incidence of OPSCC. As patients with HPV+ OPSCC show significantly improved treatment response and prognosis, there is an urgent need to de-escalate treatment of HPV+ OPSCC that optimizes oncologic control while minimizing treatment-related toxicity. Cell-free HPV DNA (cfHPV-DNA) from plasma specimens represents a promising noninvasive surrogate of disease burden in these patients. To enable cfHPV-DNA analysis as a strategy to monitor response to therapy and guide treatment de-escalation, we developed a highly sensitive assay for HPV16/18 detection and quantification in plasma, based on the SafeSEQ next-generation sequencing (NGS) technology. **Methods:** Longitudinal plasma samples were collected from patients with locoregional HPV+ OPSCC treated on our institutional de-escalation protocol of induction chemoimmunotherapy followed by risk/response stratified de-escalated locoregional therapy, OPTIMA 2 (NCT03107182). Neck CT or MRI was obtained for all patients at baseline and following induction chemoimmunotherapy; radiographic response to induction therapy was assessed per RECIST 1.1 criteria. cfHPV-DNA was quantified in plasma samples collected at baseline and at the end of induction therapy. Changes in cfHPV-DNA levels were correlated with radiographic response. **Results:** The SafeSEQ HPV assay demonstrates high analytical sensitivity, with ability to detect a single copy of HPV DNA. Replicate testing of contrived samples containing HPV 16/18 DNA at defined levels revealed robust quantitative detection across a dynamic range over 5 orders of magnitude. The assay showed a low level of background signal (< 0.04 copies per sample) across 20 healthy donor samples, indicating high specificity. In plasma samples collected at baseline from patients enrolled in OPTIMA 2, cfHPV-DNA was detected at levels ranging from 1 to > 30,000 copies/ml. A high correlation was observed between dynamic changes in patients' cfHPV-DNA levels and radiographic responses following induction therapy. Furthermore, in samples collected longitudinally during induction therapy, changes in cfHPV-DNA levels accurately tracked radiographic responses to therapy. **Conclusions:** We have developed a highly sensitive and specific cfHPV-DNA detection assay based on SafeSEQ NGS technology and have successfully applied it to monitor therapeutic response in HPV+ OPSCC patients. The assay exhibits robust quantitative detection of HPV across a broad range of levels, even when only a few copies are present, enabling high-resolution molecular monitoring. Prospective studies are underway to further evaluate the kinetics of cfHPV-DNA as a predictor of response to therapy in order to more precisely guide the management of patients with HPV+ OPSCC. Research Sponsor: Sysmex.

6049 **Poster Session**

The impact of tumor infiltrating lymphocytes (TILs) on disease progression in human papillomavirus (HPV)-related oropharyngeal squamous cell carcinoma. *First Author: Linda X Yin, Department of Otorhinolaryngology, Mayo Clinic, Rochester, MN*

Background: In the head and neck, human papillomavirus-related oropharyngeal squamous cell carcinoma (HPV(+)OPSCC) has a better prognosis and more tumor infiltrating lymphocytes (TILs) compared to its HPV(-) counterpart. Within HPV(+)OPSCC, the prognostic value of TILs in the primary tumor and in metastatic lymph nodes is not well understood. **Methods:** This is a matched case-control study at a tertiary care center of HPV(+)OPSCC patients who underwent primary surgery between 05/2007–12/2016. Cases developed locoregional recurrence or distant metastases during follow-up, while controls did not during a similar duration of follow-up. Pairs were matched on age, American Joint Committee on Cancer (AJCC) 8th edition pathologic stage, sex, year of surgery, degree of adjuvant treatment, comorbidities, and smoking status. One representative H&E slide of the primary tumor and lymph node (when nodal disease was present) from each patient was independently reviewed by two pathologists (JG, MR) blinded to outcome, for tumor TILs (tTILs) density (defined as % TILs), presence/absence of desmoplastic stroma, and when stroma was present, for stromal TILs (sTILs) density (defined as relative crowding of TILs). The Brandwein-Gensler pattern of invasion (POI) score was used to grade the primary tumor. Interrater agreement was assessed using Cohen's *kappa*. Associations between TILs and time to disease progression were assessed using Cox proportional hazards regression models. **Results:** 41 case-control pairs (N=82) were included in the study: 38 (46%) were AJCC pStage I, 37 (45%) were pStage II, and 7 (9%) were pStage III; 22 (27%) underwent surgery alone, 15 (18%) underwent surgery with adjuvant radiotherapy, and 45 (55%) underwent surgery with adjuvant chemoradiation. Interrater agreement was fair for tTILs density in the primary tumor (k=0.24) and lymph node (k=0.23), moderate for desmoplastic stroma in the primary tumor (k=0.58) and lymph node (k=0.64), moderate for sTILs density in the primary tumor (k=0.58) and lymph node (k=0.48), and fair for the POI score (k=0.17). tTILs density ≥10% (HR 0.35, 95% CI 0.14-0.90, p=0.028) and a moderate/dense sTILs density (HR 0.15, 95% CI 0.04-0.68, p=0.014) in the primary tumor were significantly associated with decreased risk of disease progression. An aggressive POI score of III or IV was significantly associated with increased risk of disease progression (HR 4.00, 95% CI 1.34-11.96, p=0.013). None of the study measures in the lymph node were significantly associated with disease progression. **Conclusions:** In HPV(+)OPSCC, a higher density of tumor and stromal TILs and non-aggressive POI in the primary tumor specimen may indicate a lower risk of disease progression. TILs may serve as a powerful prognostic marker for the adaptive immune response to this disease. Research Sponsor: None.

6050 **Poster Session**

Endostar combined with intensity-modulated radiotherapy in low-risk local advanced nasopharyngeal carcinoma: A phase II, randomized, multicentric clinical trial. *First Author: Min Kang, Department of Radiation Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning, China*

Background: A Phase II, randomized, prospective, multicentric trial was conducted to evaluate the efficacy and safety of Endostar plus radiotherapy in patients with low-risk local advanced nasopharyngeal carcinoma (NPC). This study reported the preliminary results of NCT02237924. **Methods:** From 09/2014 to 08/2016, patients with low-risk local advanced NPC were randomly treated with Endostar plus radiotherapy (ERT group, n=60) and concurrent chemoradiotherapy (CCRT group, n=60). Primary endpoint was the 5-year overall survival (OS) rate. The secondary endpoints were 3-year OS rate, progression free survival (PFS) rate, loco-regional recurrence free survival (LRRFS) rate and distance metastasis free survival (DMFS) rate. **Results:** After a median follow-up of 47 months, 3-year OS rate were 93.2% and 79.3% (p=0.032), 3-year PFS rate were 89.8% and 70.6% (p=0.011), 3-year DMFS rate were 93.2% and 80.7%, in two groups, respectively (P=0.042). 3-year LRRFS rate were 96.6% and 92.0% in two groups, respectively (but P=0.565). For short-term curative effects, CR rate were 71.2% and 60.0% for primary tumor, 74.6%and 63.3%for cervical lymph nodes, in two groups, respectively (P < 0.05). Moreover, the incidences of adverse events were significantly lower in ERT group compared with in CCRT group. The grade 3/4 Hyponatraemia (0 [0%] vs 3 [5%] , p=0·04), the grade 1/2 vomiting (10 [16.7%] vs 52 [86.7%], p=0.000), dry mouth (45 [75.0%] vs 56 [93.3%], p=0.012), leukopenia (22 [36.7%] vs 42 [70.0%], p=0.000) and weight loss (30 [50.0%] vs 45 [75.0%], p=0.005). No patients died of treatment-related causes. **Conclusions:** OS, PFS, and DMFS rates can be improved, adverse events be reduced, with better tolerability, by Endostar plus radiotherapy, when compared to concurrent chemoradiotherapy for local advanced low-risk NPC. Clinical trial information: NCT02237924. Research Sponsor: National Natural Science Foundation of China.

Survival outcomes to treatment.

	Endostar + radiotherapy (n = 60)	Chemo-radiotherapy (n = 60)	Hazard ratio* (95% CI)	P value†
Overall survival				
Deaths	5(8.3%)	13(21.7%)		
patients with 3 years OS	93.2% (86.8-99.6)	79.3% (68.9-89.7)	0.342 (0.122-0.960)	0.032
Progression-free survival				
Failures	7(11.7%)	17(28.3%)		
patients 3 years PFS rate	89.8% (82.2-97.4)	70.6% (58.8-82.4)	0.362 (0.150-0.873)	0.018
Locoregional failure-free survival				
Locoregional failures	3(5.0%)	4(6.7%)		
without locoregional failure at 3 years	96.6% (91.9-99.9)	92.0% (84.4-99.6)	0.651 (0.146-2.911)	0.572
Distant failure-free survival				
Distant failures	4(6.7%)	11(18.3%)		
without distant failures at 3 years	93.2% (86.7-99.7)	80.7% (70.5-90.9)	0.325 (0.103-1.021)	0.042

6051 **Poster Session**

Phase I study of functionalized hafnium oxide nanoparticles (NBTXR3) activated by radiotherapy in cisplatin-ineligible locally advanced HNSCC patients. *First Author: Christophe Le Tourneau, Institut Curie, Saint-Cloud, France*

Background: The non-surgical standard of care (SOC) for the treatment of locally advanced head and neck squamous cell carcinoma (LA HNSCC) patients is concurrent chemoradiation with high dose cisplatin or cetuximab in case of contra-indication to cisplatin. However elderly patients, and those with poor performance status, comorbidities, and/or intolerance, may not benefit from these SOC treatments and represent a high unmet need. New approaches are thus needed to improve clinical outcomes without adding toxicity. NBTXR3, a novel radioenhancer, composed of functionalized hafnium oxide nanoparticles**,** is injected once intratumorally and activated by radiotherapy (RT).NBTXR3 increases the RT energy deposit inside tumor cells and subsequently increases tumor cell death compared to RT alone, while sparing healthy tissues. We present here the results of the dose expansion part of the phase I study evaluating NBTXR3 plus intensity modulated radiation therapy (IMRT) in this population. **Methods:** Patients with stage III-IVA or T3/T4 (AJCC/UICC TNM staging system 8th ed.) HNSCC of the oropharynx or oral cavity, ineligible to cisplatin or cetuximab and amenable for RT, received a single intratumoral injection of NBTXR3 and IMRT (70 Gy in 35 fractions /7 weeks). A classical 3 + 3 dose escalation design has tested four doses of NBTXR3, equivalent to 5, 10, 15, and 22% of baseline theoretical tumor volume. The RP2D established as 22% of baseline tumor volume is further tested in the dose expansion part. The primary endpoints of the dose expansion part are objective response rate (ORR) and complete response rate (CRR) of the primary tumor, by imaging according to RECIST 1.1. Safety is also evaluated. **Results:** As of August 13, 2020, 43 patients have been treated in the phase I dose expansion part. The median age was 70.7 years old (range: 50.7- 89.9), 70% of patients had cardiac disorder risk, 44% had gastrointestinal disorder risk and 44% metabolic and nutrition disorder risk. The median tumor volume was 42.8 mL (range: 1.3 - 222.3). At a median time of 7.8 months after NBTXR3 injection, the ORR of the primary lesion was 83.9% and the CRR 67.7% in the evaluable population for efficacy (N = 31). Three patients (7%) experienced at least one serious adverse event (AE) related to the injection procedure and/or NBTXR3 which represented less than 1% of all reported AEs. RT-related toxicity was as expected with IMRT. Three deaths due to AEs related to RT and other causes were reported. The recruitment is ongoing and updated efficacy and safety results will be presented. **Conclusions:** NBTXR3 intratumoral administration followed by IMRT may represent an option in elderly patients or patients with multiple comorbidities with LA-HNSCC who have limited therapeutic options. NBTXR3 activated by RT showed promising anti-tumor efficacy, supporting further evaluation in a phase III randomized trial. Clinical trial information: NCT01946867. Research Sponsor: Nanobiotix, SA.

6052 **Poster Session**

Inductive camrelizumab and apatinib for patients with locally advanced and resectable oral squamous cell carcinoma: A single-arm trial (Icemelting trial). *First Author: Lai-Ping Zhong, Department of Oral & Maxillofacial-Head & Neck Oncology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

Background: In patients with locally advanced oral squamous cell carcinoma (LAOSCC), major pathologic response (MPR) to induction therapy may translate into improved survival. The induction therapy using chemo-free drugs, such as the combination of anti-PD1 and anti-VEGFR drugs, has not been well issued in LAOSCC. **Methods:** A prospective single arm trial (NCT04393506) has been performed to evaluate the induction therapy of anti-PD1 and anti-VEGFR protocol in LAOSCC patients at clinical stage III and IVA. The patients received three cycles of intravenous Camrelizumab (PD-1 antibody, 200mg) on d1, d15, d29; and oral Apatinib (anti-VEGFR inhibitor, 250mg) daily, initiating on d1, ending on the 5th day before surgery. Radical surgery was planned on d42-d45. Post-operative radiotherapy was planned within 1.5 months after surgery, based on clinical and pathological stage. The primary endpoints were MPR and safety; primary tumors were assessed for the percentage of residual viable tumor that was identified on HE staining, and tumors with no more than 10% viable tumor cells were considered as MPR. This study has been approved by institutional ethics committee at Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. **Results:** From April to December 2020, 21 patients were enrolled in this trial, and one patient withdraw from the trial at the beginning of treatment. The induction therapy was well-tolerated with no grade 3-4 toxicity or serve induction therapy-related AEs. One patient required surgery delay for 7 days due to unexplainable cTnI elevation. One patient put off Camrelizumab for 14 days due to grade 2 thrombocytopenia. One patient suspended Apatinib for 21 days due to grade 2 Hyperbilirubinemia. The induction therapy did not effect on the subsequent standard treatment. MPR rate was 40% (8/20), including 5% (1/20) pCR. Radiological evaluation of response to induction therapy showed 3 PR, 10 SD, 5 PD and 2 NA. Weak correlation was found between pathologic and radiological evaluation on induction therapy. Combined positive score (CPS) of PD-L1 expression in biopsy was evaluated in 19 patients; all 4 patients with CPS$\geq$ 20 had MPR, 3 out of 11 patients with 1$\leq$CPS $<$ 20 had MPR, and 1 out of 4 patients with CPS $<$ 1 had MPR. **Conclusions:** The chemo-free protocol of induction therapy using Camrelizumab and Apatinib is safe and well-tolerated for the patients with LAOSCC. The MPR rate is much higher using the anti-PD1 and anti-VEGFR protocol than the traditional induction chemotherapy protocol in LAOSCC. Clinical trial information: NCT04393506. Research Sponsor: Shanghai Municipal Commission of Health and Family Planning, Program of Shanghai Academic/Technology Research Leader.

6053 **Poster Session**

Neoadjuvant and adjuvant nivolumab and lirilumab in patients with recurrent, resectable squamous cell carcinoma of the head and neck. *First Author: Glenn J. Hanna, Dana-Farber Cancer Institute, Boston, MA*

Background: Locoregional recurrence (LRR) is a major cause of death for patients (pts) with squamous cell carcinoma of the head and neck (SCCHN). With therapy options limited by prior treatment, surgery often represents the best chance for disease control. Emerging data suggests a role for neoadjuvant immunotherapy in upfront resectable SCCHN and the importance of NK cells in the tumor microenvironment. We hypothesized that dual immune checkpoint inhibition (anti-PD-1, nivolumab [N] and anti-KIR, lirilumab [L]) before and after salvage surgery would improve 1-year disease-free survival (DFS). **Methods:** Pts with operable LRR of SCCHN (any HPV or smoking status) with a disease-free interval of $>$ 8 weeks after curative intent therapy were eligible for this phase II trial. Pts received a single dose of pre-op N (240 mg) + L (240 mg) 7-21 days before surgery, followed by 6-cycles of adjuvant N+L on days 1, 15 (N alone) of a 28-day cycle (C) for C1-3; and on day 1 for C4-6. Primary endpoint was 1-year DFS; 37 DFS events among N = 54 pts provided 81% power to detect improvement in 1-year DFS from 57% to 67.5% (one-sided 10% Wald's test). Secondary endpoints: safety, radiologic response (RECIST v1.1) to pre-op N+L, and overall survival (OS). Correlatives included tumor sequencing, PD-L1 status, and immunoprofiling. **Results:** Between 3/15/18 and 5/29/20, N = 29 enrolled (stopped due to expiration of drug supply). Among 28 treated pts, median age: 66, 18% (5/28) women, 83% smokers; primary site: 10 oral cavity, 8 oropharynx (5/8 HPV+), and 10 larynx/hypopharynx. 96% (27/28) had prior HN radiation; 71% (20/28) prior chemotherapy. There were no delays to surgery. Grade 3+ adverse events: 11% (3/28); no deaths from treatment. At time of surgery, 96% (27/28) had stable disease radiologically with 3 showing regression, 4% (1/28) had disease progression. Pathologic response to N+L was observed in 43% (12/28): 4/28 (14%) major (tumor viability, TV $\leq$10%); 8/28 (29%) partial (TV $\leq$50%). PD-L1 CPS at surgery was similar regardless of pathologic response (p = 0.63). 68% (19/28) completed all 6-cycles of adjuvant N+L; N = 1 came off for toxicity. Ten pts (36%) recurred (local = 8, distant = 2). 5/28 (18%) had positive margins, of which 4 (80%) recurred; 4/28 (14%) declined to start adjuvant N+L, of which 3 (75%) later recurred. At median follow-up of 20.2 months, 1-year DFS70% (95%CI, 48-84%) and 1-year OS: 85% (95%CI, 65-94%). Median tumor mutational burden was 4 (range, 1-11). *TP53* was the most frequent alteration (78%, 21/27). CD39 expression by TILs and CD38 expression by circulating CD4/8+ T cells increased after N+L exposure ($p < 0.05$). **Conclusions:** Neoadjuvant and adjuvant N+L was safe and well tolerated. We observed a 43% pathologic response rate prior to salvage surgery, with a favorable 1-year DFS of 70% and 1-year OS $>$ 80% among previously irradiated pts. Further evaluation of this strategy is warranted (NCT03341936). Research Sponsor: Bristol Myers Squibb.

6054 **Poster Session**

Transoral robotic surgery for human papillomavirus-associated oropharynx squamous cell carcinoma: Recurrence and survival in the Veterans Affairs health system. *First Author: Abhishek Kumar, University of California, San Diego, La Jolla, CA*

Background: Most transoral robotic surgery (TORS) literature comes from single and multi-institutional studies at tertiary-care academic intuitions. Long-term outcomes for patients with HPV-mediated oropharyngeal squamous cell carcinoma (HPV-OPSCC) treated with upfront TORS in other hospital settings across the United States are largely unknown. We present long-term recurrence and survival outcomes from a novel Veterans Health Administration (VHA) longitudinal dataset that includes patient-level data. **Methods:** Retrospective analysis of national VHA patients with p16-positive OPSCC diagnosed between January 2010 and December 2016, treated with TORS primary tumor resection with neck dissection. Outcome measures included: Cancer-specific survival (CSS), progression free survival (PFS), overall survival (OS), recurrence, extranodal extension (ENE), positive surgical margin (PSM), and adjuvant therapy regimen. **Results:** One hundred sixty-one patients were included of whom 29 (18%) were low-risk [0-1 metastatic lymph nodes, negative margins]; 45 (28%) intermediate-risk [close surgical margins, 2 to 4 metastatic nodes, LVI or PNI, pathologic T3 or T4 tumor]; and 87 (54%) high-risk [PSM, ENE, and/or $\geq$ 5 metastatic nodes]. ENE was present in 41% of cases and 24% of cases had positive surgical margins. Median follow-up was 5.6 years (95% CI 3.0-9.3). The 5-year CSS rates for low, intermediate, and high-risk groups were: 100%, 90.0% (95% CI 75.4-96.1%), and 88.7% (78.3-94.2%). On univariable analysis, pathologic factors associated with inferior CSS were: pT3-T4 tumor category (HR 3.81, 95% CI 1.31-11; p = 0.01), presence of more than four metastatic lymph nodes (HR 3.41, 95% CI 1.20-11; p = 0.02), and ENE (HR 3.53, 95% CI 1.06-12; p = 0.04). Close or PSM were not associated with CSS (HR 0.67, 95% CI 0.21 – 2.14; p = 0.50). In the low-risk group, 48% avoided adjuvant therapy and although there were five recurrences, none died from cancer. The intermediate-risk group was treated with adjuvant radiation in 64% of cases, and chemoradiation in 29% of cases; and there were five locoregional recurrences and three distant recurrences. Adjuvant chemoradiation was used in 68% of high-risk cases. Of the seven total patients with distant recurrences, six died of their disease. **Conclusions:** Our findings in this national cohort of Veterans with HPV-OPSCC demonstrate that TORS followed by adjuvant therapy yields favorable survival outcomes. Tumor-category, ENE, and more than four nodal metastases were the strongest adverse features in our data, and surgical margins did not have a significant impact on survival. Further investigations with large cohorts and prospective clinical trials are needed to elucidate the true oncologic implications of high-risk features and to identify patients best suited for de-intensified treatment. Research Sponsor: U.S. Department of Defense. Grant Number: W81XWH-17-PCRP-PRA.

6055 **Poster Session**

Survival outcomes in primary head and neck adult sarcoma: A systematic review and meta-analysis. *First Author: Sondos Zayed, Department of Radiation Oncology, London Health Sciences Centre, London, ON, Canada*

Background: Head and neck sarcomas (HNS) are rare entities and confer substantial morbidity and mortality. Yet, the optimal management of HNS remains unclear. This study aimed to describe the epidemiology of HNS and to identify the most favorable treatment approach. **Methods:** We performed a systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, using the PubMed (Medline), EMBASE, and Cochrane Library databases, queried from 1990 until present. Articles in the English language reporting on survival outcomes of adult primary HNS patients treated with curative-intent were included. All estimates were weighted based on sample size. Analysis of variance (ANOVA) and two-sample t-tests were used as appropriate. Meta-analyses were performed using random effects models. This study was registered with PROSPERO, CRD42021220970. **Results:** A total of 3652 articles were identified, with 42 articles reporting on 21228 patients, meeting inclusion criteria. Mean ± SD age was 56.7 ± 14.6 years with 14170 (67.0%) men and 6991 (33.0%) women. The most common locations included skin and soft tissues (n = 12749, 63.3%), bones of skull and face (n = 2256, 11.2%), and oral cavity (n = 1775, 8.8%). The most common histologies included undifferentiated pleomorphic sarcoma (n = 5065, 24.8%), osteosarcoma (n = 2578, 12.6%), Kaposi sarcoma (n = 2316, 11.3%), chondrosarcoma (n = 2141, 10.5%), and hemangiosarcoma (n = 2072, 10.1%). 5459 patients had early stage I-II disease (76.9%) whereas 1643 had late stage III-IV disease (23.1%). Most received surgery alone (n = 10968, 61.0%), 3917 (21.8%) received surgery and radiotherapy (RT), 2173 (12.1%) received definitive RT/chemoradiotherapy (CRT), 811 (4.5%) received surgery and CRT, and 98 (0.5%) received surgery and chemotherapy. Negative margins were achieved in 6081 (76.5%). Mean ± SD follow-up was 55.3 ± 42.8 months. Weighted mean, 2-, 5-, and 10-year overall survival (OS) were 78.5 months, 75.9%, 63.2%, and 54.9% respectively. There was no significant difference in mean OS (P = 0.674) or 5-year OS (P = 0.965) between patients who received surgery alone, multimodality treatment with surgery and RT/CRT, or definitive RT/CRT. Mean ± SD 5-year OS was significantly higher with negative margins (62.7 ± 20.8%) compared with positive margins (22.7 ± 19.1%; P = 0.001). Mean ± SD local recurrence rate (LRR) was 32.0 ± 13.0%. LRRs were 41.8% for definitive RT/CRT, 39.3% for surgery and CRT, 33.6% for surgery alone, 24.7% for surgery and chemotherapy, and 20.1% for surgery and RT (P = 0.126). **Conclusions:** In the largest HNS study to date, negative margins were associated with an improvement in OS. Multimodality treatment did not confer an OS benefit. Definitive RT/CRT may be associated with a higher LRR. Randomized trials are needed to establish the optimal treatment approach for HNS. Research Sponsor: None.

6056 **Poster Session**

A phase II study of PRV111 nanoengineered cisplatin patch as a neoadjuvant therapy for early-stage oral squamous cell carcinoma (OSCC). *First Author: Nishant Agrawal, The University of Chicago, Chicago, IL*

Background: OSCC is a devastating disease causing substantial morbidity and mortality. Despite advancements in the conventional therapeutic approaches, surgical resection often leads to permanent disfigurement, while radiotherapies and systemic platinum-based chemotherapy result in significant toxicities, affecting patient wellbeing and quality of life. Thus, development of novel therapeutic approaches is paramount to improve health outcomes and survival of patients with OSCC. Systemic toxicity is often dose limiting, but could be tentatively reduced by locoregional administration. We have developed PRV111, a nanotechnology based patch for local and regional delivery of highly concentrated potent cisplatin, designed to penetrate tumor tissue, reach and enter regional lymph nodes and avoid systemic circulation. Here we present the results of phase 1/2 CLN-001 trial, designed to improve efficacy and reduce toxicity by neoadjuvant treatment with PRV111. **Methods:** A phase 1/2, single arm, open-label CLN-001 (NCT03502148) study has enrolled 12 patients with confirmed OSCC; unknown nodal involvement, no distant metastasis, and tumor size $\leq$ 4.0 cm. Three weeks prior to surgery, patients were administered 1 cycle of standalone neoadjuvant PRV111, consisting of up to 4 treatment visits (each visit dose: $\leq$12mg of cisplatin, each patch loading dose: 2mg of cisplatin). The primary endpoints were safety, efficacy and tumor reduction in ~ 7 days by greater than 30%. Secondary endpoints included nanoengineered patch consistent and complete adhesion to mucosal surfaces and uniform drug release. Exploratory endpoints included immunogenesis/immunomodulation. **Results:** PRV111 successfully met all clinical primary endpoints, as well as safety and efficacy objectives. It caused over 70% tumor reduction in ~7 days with over 87% response rate across 10 subjects. No dose-limiting toxicities, serious adverse event, or systemic toxicities were reported and no locoregional recurrences were evident in 6 months. PRV111 induced ~15 times increase in tumor infiltrating lymphocytes compared with the initial biopsy. Concentrations of cisplatin found in the tumor and regional lymph nodes were over 300 and 100 times higher respectively as compared with IV cisplatin, with only negligible amount of cisplatin found in the blood. Grade 1 or 2 oral and tongue pain induced by the treatment were the most common adverse events. Furthermore, 97.5% successful patch performance was achieved across 182 patches used in the study. **Conclusions:** Adding neoadjuvent PRV111 to the care for patients with OSCC may improve the surgical outcome and increase event free survival. Given these encouraging results, future studies are needed to establish the application of this non-invasive platform in head and neck SCC and other epithelial cancers, including anal, colorectal, genitourinary, nasal, and skin. Clinical trial information: NCT03502148. Research Sponsor: U.S. National Institutes of Health, Other Government Agency, Pharmaceutical/Biotech Company, U.S. National Institutes of Health.

6057 **Poster Session**

Impact of comprehensive geriatric assesment (CGA) in the treatment decision and outcome of older patients with locally advanced head and neck squamous cell carcinoma (LA-HNSCC). *First Author: Sandra Llop Serna, Institut Català d'Oncologia, Barcelona, Spain*

Background: Up to 24% of patients (pts) newly-diagnosed with LA-HNSCC are 70 years old (yo). NCCN guidelines recommend a geriatric assessment to guide treatment decisions in this pts population. Comprehensive geriatric assessment (CGA) of older HNSCC pts was implemented at our institution in 2018. We evaluated the impact of CGA in treatment decision and outcome and compare it to a control cohort with no CGA treated within the same institution. **Methods:** Retrospective single-institution analysis of two consecutively-treated cohorts of newly-diagnosed elderly LA-HNSCC pts treated at the Catalan Institute of Oncology: a cohort treated based on CGA between 2018-2020; and a control cohort with no CGA treated based on physician criteria following tumor board decision between 2016-2018. Pts demographics and disease characteristics were obtained from our in-site prospective database. Treatment received (standard, adjusted, palliative-intent, best supportive care [BSC]), treatment completion rate (TCR) an overall response rate (ORR) after conservative treatment were collected and compared for both cohorts using chi-square. **Results:** A total of 197 pts were included: CGA cohort =81; Control cohort=96. Baseline characteristics were similar between cohorts (Table). Pts in CGA cohort were classified as fit (F) 35 (34.7%), medium-fit (MF) 51 (50.5%) and unfit (UF) 15 (14.9%) according to CGA results. CGA changed final treatment decision following tumor board in 31 % of the cases. Pts were more likely to receive standard treatment in the CGA cohort when compared control (36 vs 21%; *p = 0.048*), with no differences observed in TCR (84% vs 86%; *p = 0.805*). In pts who underwent conservative treatment, ORR was similar between CGA and control cohort (73.9% vs 66.7 %; *p = 0.082*), respectively. Tumor progression was the major cause of death in both groups. **Conclusions:** Older pts with LA-HNSCC who underwent CGA were more likely to receive standard treatment than those who did not, supporting the relevance of CGA for clinical decision-making in this pt population. No differences were observed in CRR, TCR or death cause. In-deep survival analysis are on-going. Research Sponsor: None.

Cohorts characteristics.

	CGA cohort (n= 81)	Control cohort (n=96)
Median AGE (range)	80 (70-96)	77 (70-92)
Smoking Status: active/former/ never: n (%)	23/ 45/ 32	31/ 40/ 29
Oral Cavity/Oropharynx/Larynx/ Hypopharynx: n (%)	44/ 11/ 29/ 16	33/ 22 /37/ 8
Stage III / IV: n (%)	30 vs 70	21 vs 79
Treatment received: Standard(%) Adjusted(%) Palliative–intend treatment(%) BSC (%)	36: F 55; MF 38; UF 7 53: F 26; MF 63; UF 12 F 0; MF 33; UF 66.7 4: F 0; MF 33; UF 66.7	7:21: 75 PS $\leq$1; 25 PS $\geq$ 2 63: 57 PS $\leq$1; 43 PS $\geq$2 5: 60 PS$\leq$1; 40 PS$\geq$2 11: 10 PS$\leq$1; 90 PS $\geq$2

6058 **Poster Session**

Survival (OS) and progression-free survival (PFS) results after induction chemotherapy (IC) followed by de-escalated chemoradiotherapy (RDCRT) for locally advanced (LA) HPV positive oropharynx cancer (HPVOPC. *First Author: Marshall R. Posner, Hematology and Medical Oncology, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: HPVOPC has a significantly better prognosis and survival than HPV negative cancer resulting in overtreatment with significant acute and late toxicities and mortality. Radiation therapy is the single greatest determinant of toxicity. Studies to support reduction of radiation dose are a high priority. IC improves local regional control, reduces distant metastases, and may support radiotherapy de-escalation. Patients with T4, ECE, and N2c disease have poorer local regional control (LRC) and a higher rate of distant metastases (DM) and may be suitable for this option. **Methods:** Data was combined for the experimental arm of a previously reported Phase 3 trial (12 subjects, NCT01706939) and a continuation Phase 2 trial (20 subjects, NCT02945631). After informed consent subjects who were PCR+ HPVOPC, smoked $<$ 20 py, and were LA or functionally unresectable were treated with Taxotere, cisplatin and reduced 5-fluorouracil (mTPF) for 3 cycles and then assessed for response. Responders were treated with 5600 cGy and weekly carboplatin, and then followed for LRC, DM, PFS, OAS and toxicity. Data was analyzed as of 2/1/21. 85% LRC at 3 years was considered non inferior to standard of care chemoradiotherapy. An acceptable end point was predetermined to be 80% PFS and 85% LRC at 3 years in this LA population. **Results:** 32 subjects were entered and included in the analysis, all responded to IC and had RDCRT. 2 patients with non-HPV16 subtypes were initially entered, treated with IC, responded, and then were taken off study and excluded from the analysis due to non-HPV 16 subtype. They were treated with 7000 cGy and are alive and well. Poor risk factors (ECE, T4, N2c, Non-HPV16 subtype) were present in 72% of 32 subjects; 22 (69%) never smoked. At data cutoff with a median follow up of 50m (21-95m), 28/32 (87.5%) have LRC, 1/32 DM (3.1%), OS is 28/32 (87.5%) and PFS is 27/32 (84.4%). All 5 patients who recurred did so in the first 12m (median 8m); all had 1 or more poor risk factors and 1 is alive with disease 42m post recurrence. 2 year LRC, PFS and OS are 87.4% [95% CI: 69.8%, 95.1%], 84.4% [95% CI: 66.5%, 93.2%] and 90.6% [95% CI: 73.7%, 96.9%] respectively. There was no therapy-related mortality, generally rapid recovery from CRT and minimal long term consequences (to be reported). **Conclusions:** Induction with mTPF followed by RDCRT resulted in excellent LRC, PFS and OS in patients with LA HPV OPC and significant risk factors. These results compare favorably to standard of care and other dose de-escalation trials in high and low risk categories. This treatment paradigm is highly effective in a LA, high risk HPVOPC patients and is a reasonable treatment option to be compared to other de-escalation treatment plans in Phase 3 trials for this higher risk population. Clinical trial information: NCT02945631, NCT01706939. Research Sponsor: None.

6059 **Poster Session**

Prospective manipulation of the gut microbiome with Microbial Ecosystem Therapeutic 4 (MET4) in locoregionally advanced oropharyngeal squamous cell carcinoma (LA-OPSCC) undergoing primary chemoradiation (ROMA2). *First Author: Geoffrey Alan Watson, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Therapeutic manipulation of the gut microbiome in cancer patients (pts) is an area of active investigation. MET4 (NuBiyota) is an oral alternative to fecal transplant consisting of a mixture of human gut bacteria associated with immunotherapy (IO) response. We previously reported variation in IO-responsive taxa across stages in human papilloma virus related (HPV+) LA-OPSCC pts treated with chemoradiotherapy (CRT) (Oliva et al., ASCO 2020). ROMA-2 is the first interventional study evaluating the safety, feasibility and ecological effect of MET4, in combination with definitive CRT in HPV+ LA-OPSCC (NCT03838601). **Methods:** This is an investigator-initiated study of pts with HPV+ LA-OPSCC treated with standard of care CRT. MET4 is administered daily until week 4 of CRT or unacceptable toxicity. Stool samples are collected at baseline, week 4, week 8-10, and 2-months post CRT. Bacterial V4 16S rDNA was extracted from stool and sequenced. Microbiome analyses were conducted in R using DADA2, phyloseq and DESeq2. **Results:** As of February 11 2021, 25 pts have been enrolled. A total of 50 stool samples from the first 14 pts were collected (98% adherence) and analyzed. Baseline cohort characteristics: median age = 62.5 (range, 48-69); Stage I/II/III = 5/1/8; use of antibiotics = 1pt. 3 pts did not complete the 3-week course of MET4 treatment due to non-compliance (n = 1), withdrawal of consent (n = 1) and grade 2 diarrhea (n = 1). Other reported MET4-related adverse events (all grade 1) included bloating (n = 2), flatulence (n = 1) and belching (n = 1). No longitudinal changes in alpha-diversity were seen from baseline through follow up. Administration of MET4 resulted in a transient trend towards increased cumulative MET4 taxa relative abundance (RA) by week 4. Stage III patients demonstrated the lowest MET4 taxa RA at baseline, and the greatest increase in MET4 taxa RA from baseline to week 4. By week 4 the following taxa in all pts were increased compared to baseline: *Eubacterium hallii* (21.71 Log2-Fold change[L2FC], padj < 0.001) and *Parabacteroides johnsonii (*23.67 L2FC, padj $<$ 0.001). An increase in the following taxa was observed by weeks 8-10 compared to baseline: *Akkermansia muciniphilla* (3.75 L2FC, padj = 0.027), *Bacteroides fragilis* (6.73 L2FC, padj = 0.010), *Alistipes onderdonkii* (3.30 L2FC, padj = 0.049) and *Parabacteroides distasonis* (24.43 L2FC, padj < 0.001). **Conclusions:** Manipulation of the gut microbiota in these pts was feasible and safe. MET4-induced ecological changes are heterogenous and vary by taxa. MET4 taxa implicated in IO-response were increased by week 4 and week 8-10. This increase was higher in pts with stage III disease. These data suggest that specific subgroups may benefit from combination IO therapy and may guide pt selection for further interventional clinical trial design. Clinical trial information: NCT03838601. Research Sponsor: Tumor Immunotherapy Program, Princess Margaret Cancer Center.

6060 **Poster Session**

Postoperative PET/CT for detection of early recurrence (ER) after surgery for squamous cell carcinomas (SCC) of the oral cavity (OC). *First Author: Yao Yu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Patients with ER after surgery and prior to postoperative radiation (RT) for SCC of the OC have aggressive biology and poor prognosis. After the introduction of a PET/CT simulator in our department, we incorporated post-operative PET/CT as part of RT planning. We hypothesized PET/CT would improve detection of macroscopic disease before postoperative RT. **Methods:** We reviewed the medical records of patients treated with postoperative radiotherapy between 2005 and 2019 for OC SCC. Clinicopathologic risk factors were recorded. Intermediate risk factors (IRFs) included pT3-4 disease, nodal disease, perineural invasion (PNI), lymphovascular invasion (LVI), and close ($<$ 5mm) surgical margins (SM); extranodal extension (ENE) and positive SM were considered high-risk factors (HRF). Patients were stratified into risk groups based upon the number and type of risk factors: 0-1 IRFs, 2 IRFs, $\geq$3 IRFs, and any HRF. Patients were considered to have ER if they had biopsy confirmed recurrence, or if the imaging or exam was sufficiently suspicious, after discussion with the head and neck team, to warrant treatment to definitive doses of RT (70 Gy). **Results:** Our cohort included 391 patients with SCC of the OCC who were treated with postoperative radiotherapy. 61% of patients were male, 35% had pT3-4 disease, 36% had pN2a-3 disease, 53% had PNI, 20% had LVI, 30% had ENE, and 14% had positive SM. The most common sites were oral tongue (46%), alveolar ridge (18%), and buccal mucosa (13%). 237 (61%) patients underwent postoperative PET/CT planning, and 165 patients (41%) were planned with CT only. Patients screened with post-operative PET/CT were more likely to be diagnosed with ER (46/237, 19.4%) than those simulated with CT only (6/154, 3.9%, $p <$ 0.0001). Among patients simulated with PET/CT, 7%, 9%, 14%, and 35% of patients were diagnosed with ER for patients with 0-1 IRFs, 2 IRFs, $\geq$3 IRFs, and any HRF, respectively. Median follow-up was 4.1 years (95% CI 3.6 – 4.5). Among 52 patients with ER, 24 (49.0%) had local, 41 (83.7%) had regional, and 5 (10.2%) had distant recurrence. 17 (33%) of ER were biopsy proven. For patients with ER, 3-year freedom from locoregional recurrence, distant-metastasis free survival, and overall survival were 45.2% (95% CI 32% - 64%), 55% (95% CI 42% – 72%), and 43% (95% CI 30% - 61%), respectively. For patients without ER, use of postoperative PET/CT was associated with improved disease-free survival (HR 0.68, 95% CI 0.46 – 0.98, p = 0.041) and overall survival (HR 0.59, 95% CI 0.38 – 0.91, p = 0.019). **Conclusions:** Postoperative PET/CT may increase detection ER compared to CT simulation alone and improve risk stratification. Patients with ER are at high risk of locoregional failure, distant metastases, and mortality, despite salvage therapy. A prospective trial is underway at our institution to systemically study the role of PET/CT for detection of ER. Research Sponsor: U.S. National Institutes of Health.

6061 **Poster Session**

Impact of COVID19 pandemic on treatment outcome of locally-advanced head and neck squamous cell carcinoma (LA-HNSCC): IMPACCT study. *First Author: Pau Guillen Sentis, Institut Catala d'Oncologia, Barcelona, Spain*

Background: Treatment (ttm) of cancer patients (pts) was compromised during the first wave of COVID19 pandemic due to collapse of healthcare systems. Standard of care (SOC) for LA-HNSCC pts had to be adapted as operating rooms were temporarily unavailable, and to reduce risk of COVID19 exposure. The IMPACCT study evaluated the outcome of LA-HNSCC pts treated at the Catalan Institute of Oncology during the first semester of 2020 and compared it to a control cohort previously treated in the same institution. **Methods:** Retrospective single institution analysis of two consecutively-treated cohorts of newly-diagnosed HNSCC pts: from January to June of 2020 (CT20) and same period of 2018 and 2019 (CT18-19). Pt demographics and disease characteristics were obtained from our in-site prospective database. Ttm modifications from SOC as per COVID19-contingency protocol in CT20 for LA-HNSCC were collected. Chi-squared was used to compare variables and ttm response between cohorts. One-year recurrence-free survival (1yRFS) and overall survival (1yOS) of LA-HNSCC pts were estimated by Kaplan-Meier method and compared by Log-rank test. **Results:** A total of 306 pts were included: CT20=99; CT18-19=207. Baseline characteristics were balanced between cohorts (Table1). In pts treated with conservative ttm (non-surgical approach), persistence disease was higher in CT20 vs CT18-19 (26 vs. 10% p=0.02). Median follow-up of CT20 and CT18-19 was 6.8 months (IQR 5.1-7.9) and 12.3 (6.7-18.4), respectively. A trend towards lower 1yRFS and 1yOS was observed in CT20 vs CT18-19 (72 vs 83% p=0.06; 80 vs 84% p=0.07), respectively. Within CT20, 37 pts (37%) had one or more ttm modifications: switch from surgery to conservative ttm (n=13); altered radiotherapy fractionation (n=14); reduced cisplatin cumulative dose to 200mg/m2 (n=19); no adjuvant ttm (n=1). Pts who received modified ttm had no differences in 1yRFS vs those who did not (80 vs 66% p=0.31), but higher 1yOS was observed (97 vs 67% p$<$0.01). When stratified by stage, 1yOS difference remained significant in stage III/IVA (100 vs 61% p$<$0.01) but not in I/II (100 vs 77% p=0.28) or IVB (67 vs 50% p=0.54). **Conclusions:** COVID19 pandemic had a negative impact on ttm outcomes and survival in LA-HNSCC pts when compared to our historical cohort. Ttm modifications based on COVID19-contingency protocol did not compromise ttm efficacy in terms of RFS and was associated with better OS in Stage III/IVA. Research Sponsor: None.

Main pts characteristics.

	CT20=99	CT18-19=207	Chi-squared test p-value
Gender: (%) male	74	76	0.79
Age: median (IQR)	66 (57-76)	65 (57-75)	0.26*
Smoking status: (%) active/former/never	50/35/15	52/29/19	0.45
Location: (%) pharynx/larynx/oral cavity	27/29/44	31/36/33	0.12
Stage: (%) I-II/III-IVA/IVB/IVC	33/56/7/4	36/58/3/3	0.51
Treatment received: (%) surgical/conservative/palliative/best supportive care	42/51/3/4	56/38/1/5	0.07

* t-test comparison

6062 **Poster Session**

Quality of life analysis of HPV-positive oropharyngeal cancer patients in a randomized trial of reduced-dose (rdCRT) versus standard (sdCRT) chemoradiotherapy: Five-year follow-up. *First Author: Mai Takahashi, Harvard University T H Chan School of Public Health, Boston, MA*

Background: Human papillomavirus-positive oropharyngeal cancer (HPV OPC) portends a more favorable prognosis compared to HPV-negative cases. To prevent overtreatment, long-term morbidity and deterioration in functionality and quality of life (QoL), multiple studies have focused on de-intensification techniques for HPV OPC treatment. To this end, we prospectively assessed differences in patient reported QoL in locally advanced HPV OPC patients receiving rdCRTversus sdCRT)in a randomized trial using a sequential therapy plan. **Methods:** Patients were enrolled between December 2012 and February 2016; received 3 cycles of induction docetaxel, cisplatin, and 5-FU; and were randomized to sdCRT (70 Gy) or rdCRT (56 Gy) with weekly carboplatin. Patients were followed for Progression Free Survival (PFS), Overall Survival (OS), and changes in QoL as assessed by the MD Anderson Dysphagia Inventory (MDADI), MD Anderson Symptom Inventory (MDASI Head and Neck), Xerostomia Questionnaire (XQ), and the European Organization for Research and Treatment of Cancer Questionnaire (EORTC QLQ-C30) with the head and neck module (EORTC HN). A mixed model ANOVA was used to estimate changes from baseline QoL to that at each follow-up timepoint and to compare the difference in QoL changes between the treatment arms. **Results:** We randomized 20 HPV+ locally advanced (LA) patients (median age: 56.5 yrs) to rdCRT (12 subjects) or sdCRT (8 subjects). 70% had high risk features. At a median follow-up of 81.5 mos, PFS and OS were 87.5% and 83.3% for sdCRT and rdCRT, respectively with a median OS of 76 mos in both arms. One patient in the sdCRT arm developed an HPV negative retromolar trigone squamous cell cancer in the radiation field 7 yrs after therapy. Baseline QoL was identical in the 15 patients who completed the QoL modules. Patients receiving rdCRT hadsignificantly lower declines in QoL scores at 3-6 month follow-up. At 5 yrs, differences in QoL changes all favored the rdCRT arm (Table) and two QoL scales reached statistical significance (P$<$0.05). **Conclusions:** In HPV OPC patients, rdCRT resulted in comparable long-term survival and greater improvement in specific domains of QoL when compared to sdCRT. Our results support the need for a larger, long-term Phase 3 study in LA HPVOPC to assess these two treatments with respect to survival, QoL, and safety. Clinical trial information: NCT02945631. Research Sponsor: None.

Changes in QoL differences at 5 years comparing rdCRT vs sdCRT.

	rdCRT	sdCRT	P-value
MDADI	-0.75 [-14.62, 13.11]	-11.76 [-31.8, 8.27]	0.37
MDASI SI	-0.45 [-2.6, 1.7]	1.36 [-1.73, 4.44]	0.34
MDASI SS	0.06 [-1.22, 1.34]	1.57 [-0.28, 3.42]	0.18
XQ	1.55 [-0.57, 3.68]	4.69 [1.64, 7.75]	0.10
EORTC GHS	11.49 [-4.36, 27.35]	-23.94 [-46.84, -1.05]	0.01
EORTC FS	9.35 [-3.67, 22.36]	-8.16 [-26.92, 10.6]	0.13
EORTC SS	-7.76 [-18.16, 2.64]	15.19 [0.26, 30.12]	0.01
EORTC HN	-7.49 [-16.68, 1.71]	7.90 [-5.34, 21.15]	0.06

6063 **Poster Session**

Evaluating a clinically validated circulating tumor HPV DNA assay in saliva as a proximal biomarker in HPV+ oropharyngeal squamous cell carcinoma. *First Author: Sophie P. Gerndt, Washington University School of Medicine, St. Louis, MO*

Background: HPV genomic DNA in plasma and saliva has been widely studied, however more recently, circulating tumor human papillomavirus DNA (ctHPVDNA) has emerged as a reliable biomarker for surveillance in HPV+ oropharyngeal squamous cell carcinoma (OPSCC). A commercial assay for this biomarker distinguishes tumor-derived viral DNA (tumor-tissue modified viral DNA or TTMV) from other non-cancer associated sources of HPV DNA. The use of this technology has been previously described in plasma, but its utility in saliva is currently unknown. **Methods:** A prospectively collected and banked biospecimen repository was used to identify 46 patients with HPV+ OPSCC with paired pre treatment plasma and saliva samples. All samples were assessed for DNA integrity and TTMV using a clinically validated ddPCR-based assay (NavDx™; Naveris Inc, Natick, MA) to measure TTMV for HPV-16, -18, -31, -33 and -35 from frozen plasma and saliva samples. Retrospective chart review was performed to collect clinical and pathological data. Graphpad was used for statistical analysis. Spearman's r was used to correlate TTMV copies in saliva and plasma. Wilcoxon test was used to compare between sample types. Mann-Whitney test was used for categorical variables. **Results:** TTMV DNA was detectable in 43 of 46 plasma samples and in 44 of 46 saliva samples. One plasma sample failed quality control measures, one of each sample type had undetectable TTMV, and one of each type was indeterminate. Of 41 evaluable patients with paired samples, there were 38 (93%) males, 36 (88%) were stage I-II, 5 (12%) were stage III-IV (AJCC 8th, clinical staging), and 25 (61%) had a history of smoking with a median of 37.5 pack years. TTMV was significantly enriched in saliva compared to plasma ($p<0.0001$), with median copy number 14,139 copies/ml (IQR=193,339.5) and 774.7 copies/ml (IQR=4,826.1), respectively. There was a significant positive correlation between plasma and saliva TTMV levels (r=0.344, p=0.028). There was no difference in overall stage for either specimen type. There was a trend in both sample types toward higher TTMV in patients with a history of smoking. Pack-year history was available for 38 (93%) patients in the final cohort. When grouping by pack-years, plasma TTMV approached significance (p=0.058) while high saliva TTMV was significantly associated with >10 pack-year history (p=0.011). **Conclusions:** This is the first study to demonstrate successful quantification of tumor-tissue modified HPV DNA in saliva. Compared to plasma, pre treatment saliva samples demonstrated significantly higher levels of TTMV. TTMV distinguishes ctHPVDNA from other sources of HPV. These data highlight the potential use of TTMV detection in saliva for early detection of HPV+ OPSCC as well as its potential role in local surveillance after treatment. More research is needed to elucidate the effects of smoking on TTMV levels. Research Sponsor: Naveris Inc.

6064 **Poster Session**

Quantitative immunofluorescence and mRNA analysis of immune-related biomarker groups in matched paired tumor samples from OPHELIA window study in head and neck squamous cell carcinoma (HNSCC). *First Author: Amanda Psyrri, National Kapodistrian University of Athens, Attikon Hospital, Athens, Greece*

Background: Preclinical models suggest that PARP inhibitor-induced DNA damage can promote immune priming through a range of mechanisms including STING pathway activation. PARP inhibition also leads to adaptive upregulation of PD-L1 expression in preclinical models. To understand the distinct effects that different forms of DDR defects may have on tumor immunogenicity we decided to integrate genomic profiling with gene expression profiling and immunohistochemistry (IHC)/fluorescent assessments of PD-L1 expression, CD8 T-cell infiltration, and broad immune infiltrate, in order to define the overlap between DDR and immune-related biomarker groups and to build a deeper understanding of how DNA damage interfaces with antitumor immunity. **Methods:** 39 patients were enrolled in OPHELIA phase II trial in which pts were randomized 3:3:3:1 to Cisplatin (C) 60 mg/m2 on d1 followed by Olaparib (O) 75mg d 1-5 (Arm A), O 300 mg bid for 21-28 days (Arm B), no treatment (ARM C) or D 1500 mg on d1 followed by O 600 mg daily for 21-28 days (Arm D). PD-L1, STING, Ki67 and γ-H2AX were assessed using quantitative immunofluorescence (QIF). The GeneXpert (GX) closed system real-time quantitative reverse transcription polymerase chain reaction (RT-qPCR) was used for quantitative assessment of CD274 (PD-L1), PDCD1LG2 (PD-L2), CD8A, and IRF1 multiplex mRNA panel in pre- and post-treatment samples. **Results:** Ki67 was decreased in 23 out of 29 (79.3%) available samples when assessed by QIF; 13 / 23 had a decrease of at least 25%. $\Delta\gamma$-H2AX did not differ among treatment groups. A significant increase was observed in PD-L1 and PD-L2 mRNA levels after treatment with D-O ($p = 0.023$ and $p = 0.016$, respectively). An increase trend in posttreatment CD8A mRNA was observed in 23 out of 29 cases in the three treatment arms ($p = 0.21$, ARM A; $p = 0.082$, ARM B; $p = 0.16$, ARM D). IRF1 mRNA and STING protein levels were not upregulated after olaparib- based treatment in the available paired treatment samples. **Conclusions:** This window study demonstrated a significant upregulation of PD-L1 mRNA, corresponding to our previous data of increased Combined Positive Score (CPS) in the D-O arm post-treatment. Our findings suggest that addition of D to O leads to PD-L1 upregulation. Dual blockade of PARP and PD-1 can boost immune response and antitumor activity in HNSCC. Clinical trial information: NCT02882308. Research Sponsor: Astrazeneca.

6065 **Poster Session**

Cisplatin and capecitabine induction chemotherapy in nasopharyngeal carcinoma. *First Author: Zhiyuan Xu, Department of Clinical Oncology,The University of Hong Kong-Shenzhen Hospital,Shenzhen,China, Shenzhen, China*

Background: Induction chemotherapy (IC) followed by concurrent chemoradiotherapy (CCRT) is now one of the standard treatment for locally advanced nasopharyngeal carcinoma (LANPC). Cisplatin/fluorouracil is one of the recommended IC regimens. Capecitabine is an oral fluoropyrimidine prodrug with higher concentrations of fluorouracil attained in the tumor cells after enzymatic conversions. We conducted this study to evaluate the feasibility, efficacy and safety of cisplatin and capecitabine (PX) IC followed by CCRT in LANPC. **Methods:** Newly diagnosed patients with LANPC (stage III-IVB according to 7th edition of AJCC/UICC system [TNM-7] and stage III-IVA according to 8th edition [TNM-8) were prospectively recruited from January 2015 to October 2019. They received induction PX (cisplatin: 80mg/m2 on day 1 + capecitabine: 1000mg/m2 twice daily from day 1 to 14 every 3 weeks for 3 cycles) followed by CCRT (cisplatin: 100mg/m2 every 3 weeks for a total of 2-3 cycles concurrent with intensity-modulated radiation therapy [IMRT]). IMRT with doses of 70Gy, 63Gy and 56Gy were delivered to 3 levels of planning target volumes (PTV) (high, intermediate and low risk) respectively and simultaneously in 35 fractions/7 weeks. Tumor response by MRI and CT was evaluated after completion of IC and 16 weeks after completion of CCRT according to RECIST v1.1. All adverse events were graded with NCI CTCAE v4.03. **Results:** One hundred and forty-five patients were recruited. The stage distributions according to TNM-8 were 82(56.6%) and 63(43.3%) for stage III and IVA, respectively. One hundred and thirty-seven patients completed 3 cycles of induction PX and 122 patients completed IMRT with 2 to 3 cycles of concurrent cisplatin. The median (interquartile range, IQR) tumor regression rates after 2-3 cycles of PX at the nasopharynx (NP) and the neck region (NK) were 51.2% (37.3%-66.5%) and 71.8% (56.7%-81.1%), respectively. At 16 weeks after CCRT, only one patient had residual disease. After a median follow-up of 33 months, 20 treatment failures and 8 deaths were observed. The estimated 2-year progression-free survival (PFS) and overall survival (OS) were 89.8% and 97.2%. The rates of grade 3/4 leukopenia, neutropenia, anemia, nausea/vomiting and electrolyte disturbance during IC were 6.2%, 15.9%, 6.9%, 4.1% and 9.0%, respectively. The corresponding rates were 45.1%, 24.6%, 27.5%, 2.8% and 11.3% during CCRT. Only 1 (0.7%) grade 3/4 hand-foot syndrome and 3 (2.1%) grade 3/4 diarrhea during IC were observed. The rates of grade 3/4 mucositis and dermatitis were 31.0% and 12.7%, respectively. There were no treatment-related deaths. **Conclusions:** Induction PX followed by CCRT was effective and well tolerated in patients with LANPC. Clinical trial information: NCT03427359. Research Sponsor: Shenzhen Key Medical Discipline Construction Fund (No. SZXK014) and Shenzhen Science and Technology program (Grant No: KQTD20180411185028798).

6066 **Poster Session**

The SINTART 1 study: A phase II trial of induction chemotherapy (IC), surgery, photon-, proton-and carbon ion-based radiotherapy (RT) integration in locally advanced operable sinonasal epithelial tumors patients (pts). *First Author: Carlo Resteghini, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Sinonasal epithelial tumors are rare diseases with several histotypes and poor prognosis. Multimodal approach including surgery is widely used, although no standard therapy has been established in prospective trials. This study assessed activity and safety of an innovative integration of multimodality treatment - IC, surgery and RT - modulated by histology, molecular profile and response to IC. **Methods:** Pts with untreated, operable squamous cell carcinoma (SCC), p53 wild type intestinal type adenocarcinoma (ITAC), sinonasal undifferentiated and neuroendocrine carcinoma (SNUC, SNEC) were enrolled in a single-arm, phase II, multicenter clinical trial from 2014 to 2018. Pts was treated with up to 5 IC cycles, whose regimen was selected according to histotype, followed either by curative radio-chemotherapy (CRT) (pts with ≥80% reduction of initial tumor volume (TV)) or surgery and adjuvant (C)RT. Photon and/or proton/carbon ion-based RT was employed according to disease site and stage. Primary endpoint was 5 years PFS, secondary endpoints were OS, IC ORR per RECIST 1.1 and safety. **Results:** Out of 39 enrolled pts, 35 pts were evaluable for primary endpoint. Two pts were only considered for safety analyses because definitive diagnosis on surgical specimen did not meet the study entry criteria; other two pts were screening failure due to inoperable disease. Five-year PFS was 38% (95% CI, 21 – 69), with a median PFS of 26 months. Five-year OS was 46% (95% CI, 28 – 75), with a median OS of 36 months. Responses to IC are reported in table. Globally, 15 pts avoided surgery. Overall treatment safety was in line with multimodality intensive head and neck cancer treatments (5% of pts with G3-4 adverse event during IC). One sudden cardiac death was recorded. At a median follow up of 27 months, 5 G3-4 RT related late adverse events have been recorded (1 G3 neurotoxicity, 2 G3 hearing impairment, 2 G3 xerostomia). Three-year PFS - OS for pts achieving PR/CR vs SD/PD to IC were 49.8% - 56.7% vs 43.2% - 53%, respectively. **Conclusions:** Treatment of advanced SNC with histology-driven IC followed by locoregional therapy tailored to response to IC was safe and showed survival rate similar to surgery containing case series. In the first prospective study, a surgery sparing multimodal approach proved feasible and effective in IC responsive pts. Clinical trial information: NCT02099175. Research Sponsor: Supported by Fondazione Regionale per la Ricerca Biomedica.

	all TYPES (35)	%	SCC (13)	SNUC (15)	ITAC (3)	SNEC (4)
IC scheme			TPF*	TPF*	PFL†	EP/AI‡
Response Rate	19	54	7 (54%)	9 (60%)	0	3 (75%)
≥80% TV Reduction	12	34	3	6	0	2
Complete Response	3	9	0	2	0	1
Partial Response	16	45	7	7	0	2
Stable Disease	14	40	6	4	3	1
Progressive Disease	2	6	0	2	0	0

*Docetaxel, cisplatin, 5fluorouracil; †Cisplatin, 5fluorouracil, Leucovorin; ‡ Cisplatin, Etoposide alternated to Doxorubicin; Ifosfamide.

6067 **Poster Session**

Comparative assessment of the eighth and seventh AJCC staging edition prognostic performance of patients with p16 positive oropharynx cancer. *First Author: Felippe Lazar Neto, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The American Joint Committee on Cancer (AJCC) TNM staging system defines the anatomical extent of disease and serves as a guide for treatment and prognosis. The favorable prognosis of p16+ oropharyngeal squamous cell carcinoma (OPSCC) compared to p16 negative counterpart led to major updates in the AJCC 8th edition. Its prognostic performance, however, warrants further validation. **Methods:** We included patients diagnosed with p16+ OPSCC enrolled in a prospective registry (*Stiefel*) at The University of Texas MD Anderson Cancer Center between March 2015 and December 2018. Patients' stage at diagnosis was classified according to the AJCC 7th (AJCC-7) and 8th (AJCC-8) editions. Overall survival (OS) and progression-free survival (PFS) was defined as time from diagnosis to death or to progression or death, respectively. The Kaplan-Meier method was used to calculate 1- and 3-year survival probabilities. Differences between groups were compared using the log-rank test. Prognostic discriminative performance of each staging system was evaluated using Harrel's C-statistic. Survival differences between heavy ($>$ 10 pack-years [PY]) vs. light/never smokers ($\leq$ 10 PY) by AJCC-8 staging groups was assessed with the log-rank test. **Results:** Of 463 patients, the median follow-up was 34.7 months (2.3-169.74). Nearly 90% (N=413) of patients were down-staged from AJCC-7 to AJCC-8 with 69% of patients with IVA disease based on AJCC-7 (N=319) re-staged as stage I (N=196 [42%]), II (N=79 [17%]) or III (44 [10%]) according to AJCC-8. Over 60% (N=279) of patients were staged as I with AJCC-8. Compared to AJCC-7, AJCC-8 had improved prognostic ability (C-statistic, 0.58 for AJCC-7 vs. 0.63 for AJCC-8) and provided better discriminative survival probabilities at 1 and 3-year follow-up (Table). Similar results were observed for PFS. Smoking status did not impact OS when stratified by AJCC-8 staging groups: I, p=0.347; II, p=0.310; and III, p=0.532 for $>$ 10 vs. $\leq$ 10 PY. **Conclusions:** Our cohort validates that the AJCC-8 provides better prognostic discriminative performance when compared to AJCC-7, however, a disproportionate number of patients were classified as stage I. Smoking was not associated with survival within each staging group. Research Sponsor: Stiefel Oropharyngeal Research Fund.

Survival probabilities at 1- and 3-years follow-up according to the AJCC 7th and 8th edition staging systems.

AJCC	Staging	No. Total	No. Events	1-Year (95%CI)	3-Year (95% CI)	Log-rank
7th	I	17	1	100	93.3 (61.3-99.0)	p < 0.001
	II	29	5	89.1 (69.9-964)	85.4 (65.6-94.3)	
	III	54	5	94.3 (83.4-98.1)	90.2 (78.0-95.8)	
	IVA	319	59	92.0 (88.4-94.5)	81.6 (76.5-85.8)	
	IVB	19	7	94.1 (65.0-99.2)	60.1 (30.9-80.1)	
	IVC	25	11	59.4 (37.6-75.8)	50.9 (27.1-70.6)	
8th	I	279	38	93.4 (89.7-95.8)	85.7 (80.6-89.6)	p < 0.001
	II	94	20	91.4 (83.6-95.6)	80.5 (70.4-87.5)	
	III	65	19	90.2 (79.5-95.5)	71.5 (57.4-81.7)	
	IV	25	11	59.4 (37.6-75.8)	50.9 (27.1-70.6)	

6068 **Poster Session**

Pathologic and radiographic responses in a window of opportunity for durvalumab plus metformin trial for squamous cell carcinoma of the head and neck (HNSCC). *First Author: Joseph M. Curry, Department of Otolaryngology, Thomas Jefferson University, Philadelphia, PA*

Background: Durvalumab is a human monoclonal IgG1 antibody directed against programmed death-ligand 1 (PD-L1). PD-1/PD-L1 immune checkpoint inhibition (ICI) shows promise in HNSCC, but durable responses have been seen in only a fraction of patients. Metformin, a biguanide oral anti-hyperglycemic, has shown promise in altering immunity within the tumor microenvironment (TME) towards a stronger anti-tumor distribution of immune cells. We aimed to investigate the combined effect of metformin and durvalumab in patients with HNSCC. **Methods**: This was a single-center prospective phase 1, window of opportunity clinical trial in which previously untreated patients with any stage resectable HNSCC were randomized 3:1 to durvalumab + metformin (Arm A) or durvalumab alone (Arm B) during a four-week period between diagnosis and surgical resection. Six patients were included in a safety lead-in of durvalumab and metformin and an additional 32 patients were randomized. The primary endpoint was immune cell polarization. Here we report pathologic and radiographic effect. Pathologic effect was graded independently by two pathologists. Radiographic effect was evaluated using the immune-related Response Criteria (irRC). **Results**: Thirty-eight patients were enrolled (29 Arm A, 9 Arm B). Three patients withdrew consent prior to intervention (2 Arm A, 1 Arm B) and were excluded from analysis. AJCC 8th edition staging was as follows: Stage I (n = 21), Stage II (n = 2), Stage III (n = 3), Stage IVa (n = 6), Stage IVb (n = 3). Primary tumor sites included the oropharynx (n = 20, all p16+), oral cavity (n = 11), larynx (n = 2), maxillary sinus (n = 1), and unknown (n = 1). Pathologic effect was observed in 55% (18/33) of evaluable patients: 60% in Arm A vs 37.5% in Arm B (p = 0.418). 40% of patients with involved lymph nodes had discordance of pathologic effect at the primary site versus lymph node. Radiographic response based on irRC among 30 evaluable patients included 1 CR, 1 PR, 24 SD, and 4 PD. There was a significant correlation between pathologic effect and radiographic disease control, defined as CR, PR, and SD (p = 0.021), but no correlation when looking only at radiographic responders (p = 0.925). No patients experienced Grade 3–4 treatment or immune-related adverse events or a delay in surgery due to trial participation. All patients remained resectable. **Conclusions**: Our data demonstrate that the study intervention was well-tolerated in HNSCC patients. There was a trend towards an increased proportion of pathologic responders in the group receiving metformin. Additional studies targeting the TME are needed to further elucidate whether synergistic effects between metformin and durvalumab were seen in this patient cohort. Clinical trial information: NCT03618654. Research Sponsor: Astra Zeneca.

6069 **Poster Session**

The efficacy and safety of anlotinib in neoadjuvant treatment in locally advanced thyroid cancer: A single-arm phase II clinical trial. *First Author: Naisi Huang, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Surgery is the primary treatment for locally advanced thyroid cancer (TC). For some locally advanced TC, R0/R1 resection could not be achieved at initial diagnosis and neoadjuvant treatment would be an option. However, there is still little evidence regarding neoadjuvant treatment in locally advanced TC. **Methods:** This single-arm, phase 2 study investigated the efficacy and safety of Anlotinib (12mg orally daily, for two weeks on/on week off) for 2-6 cycles in patients with locally advanced TC in the neoadjuvant setting. Operable patients received surgery after neoadjuvant treatment. The primary endpoint was objective response rate (ORR). **Results:** A total of 13 patients were included and received an average of 3.5 cycles (range: 3-6 cycles) of Anlotinib treatment. 12 cases were papillary thyroid cancer, and 1 was follicular thyroid cancer. The ORR of Anlotinib was 76.9% with 10 partial response (PR), 2 stable disease (SD), and 1 progressive disease (PD). 8 PR and 1 SD patients received surgery after neoadjuvant treatment, of whom 8 had R0/1 resections and 1 had R2 resection. 2 PR patients refused to have surgery and the rest 2 patients were not operable. The R0/1 resection rate for intent to treat population was 61.5% and for per-protocol population was 72.7%. The maximum reduction in sum of tumor diameter was an average of 34.8% (range: 30.9%-45.5%) for PR patients. Most adverse events were grade 1 or 2. Common adverse events of all grade were hypertension (76.9%), hypertriglyceridemia (69.2%), proteinuria (53.8%), TSH increase (53.8%), cholesterol elevation (53.8%) and hand-foot syndrome (38.5%). The majority of adverse events discontinued after the neoadjuvant treatment stopped. **Conclusions:** Anlotinib demonstrated antitumor activity in the neoadjuvant treatment in locally advanced TC and the majority of patients achieved R0/1 resection. Adverse events were consistent with the known Anlotinib adverse event profile. These results suggest that Anlotinib neoadjuvant treatment represents a new option for locally advanced TC. Clinical trial information: NCT04309136. Research Sponsor: CHIA TAI TIANQING PHARMACEUTICAL GROUP CO., LTD.

6070 **Poster Session**

Planned drug holiday in a cohort study exploring the effect of lenvatinib on differentiated thyroid cancer. *First Author: Makoto Tahara, Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan*

Background: Lenvatinib is now available for unresectable radioactive iodine (RAI)-refractory differentiated thyroid cancer (DTC). However, toxicities are considerable and require frequent dose interruption and modification. Recently, planned drug holidays, which are dose interruptions in accordance with the timing of severe or intolerable adverse events, have been proposed to avoid severe adverse events due to lenvatinib (Tahara M.ESMO Open 2018). Our retrospective study demonstrated that progression-free survival (PFS) and overall survival (OS) were significantly longer in patients who used planned drug holidays than those who did not (Matsuyama C et.al, 2020 Annual Meeting of the Japan Association of Endocrine Surgeons). **Methods:** In this prospective observational study, patients with curatively unresectable and progressive RAI-refractory DTC were treated with lenvatinib in a real-world clinical setting. Lenvatinib was administered orally at a dose of 24 mg daily. Dose modification for toxicities were permitted. Primary endpoint was OS, and secondary endpoints were time to treatment failure (TTF), time to failure of strategy (TFS), PFS with clinical progressive disease, response rate, quality of life, safety, and patient reports. This study was registered with UMIN Clinical Trials Registry (UMIN000022243). **Results:** 262 patients were accrued. Of 255 evaluable, 153 were female; median age was 70 (range 27.0-88.0); histology was papillary thyroid carcinoma/follicular thyroid carcinoma/poorly DTC in 204/45/4; previous therapy was surgery/RAI/molecular targeted drug in 246/164/14; reason for initiation of lenvatinib was disease progression/unsuitable for RAI in 241/4. 1-year OS was 85.6% (95%CI: 80.6-89.4%); 1-year TTF rate was 74.9% (95%CI: 69.1-79.8%); 1-year TFS rate was 80.8% (95%CI: 75.4-85.2%); and 1-year PFS rate was 84.4% (95%CI: 79.3-88.4%). Overall response by RECIST was 3 (1.2%) in CR and 151 (61.9%) in PR. Most common grade 3 or 4 toxicities were hypertension (61.4%), hand foot syndrome (10.2%), fatigue (9.1%), anorexia (8.3%) and diarrhea (4.7%). Grade 5 toxicities occurred in 4 patients (fistula, hypoxia, respiratory failure, trachea stenosis). Of 253 patients evaluable for efficacy, 73 used planned drug holidays. TTF, TFS and PFS were significantly longer in patients who used planned drug holiday than those who did not (Table). **Conclusions:** Planned drug holiday for lenvatinib demonstrated significantly better clinical outcomes, including TTF, TFS and PFS, than daily oral administration. These data further support use of a planned drug holiday in RAI-refractory DTC patients receiving lenvatinib. Clinical trial information: 000022243. Research Sponsor: Eisai Co., Ltd.

Planned drug holiday	1-year TTF (95%CI)	1-year TFS (95%CI)	1-year PFS (95%CI)
yes (n = 73)	87.6% (77.6-93.4)	84.9% (74.4-91.3)	94.5% (86.1-97.9)
no (n = 180)	69.8% (62.4-75.9)	65.0% (57.5-71.5)	83.5% (77.2-88.3)
Log-rank test	p = 0.0049	p = 0.0017	p = 0.0190

6071 **Poster Session**

Predictive and prognostic biomarker identification in a large cohort of androgen receptor-positive salivary duct carcinoma patients scheduled for combined androgen blockade. *First Author: Gerben Lassche, Department of Medical Oncology, Radboud University Medical Center, Nijmegen, Netherlands*

Background: Patients suffering from recurrent or metastatic (R/M) salivary duct carcinoma (SDC) are often treated with combined androgen blockade (CAB). This treatment however frequently fails (response rates: 18-53%), resulting in a worse prognosis. Therefore, biomarkers that have prognostic value and can predict treatment response are urgently needed. **Methods:** mRNA from 77 R/M androgen receptor (AR) positive SDC patients treated with leuprorelin acetate combined with bicalutamide was extracted from pre-treatment tumor specimens. AR, Notch, Mitogen-Activated Protein Kinase (MAPK), Transforming Growth Factor beta (TGFβ), Estrogen Receptor (ER), Hedgehog (HH) and the Phosphoinositide 3-Kinase (PI3K) signaling pathway activities were calculated based on expression levels of relevant target genes. Besides this, 5-alpha reductase type 1 (*SRD5A1*) expression and Human Epidermal growth factor Receptor 2 (HER2) status were determined. Clinical benefit was defined as complete or partial response or stable disease $\geq$6 months. **Results:** Of the 7 signaling pathways, AR pathway activity was the best predictor of clinical benefit (AUC 0.67, 95%-CI 0.54-0.80). At a threshold of 47.8, 21% of the patients tested negative, with a negative predictive value of 93%. *SRD5A1* expression outperformed the signaling pathways regarding predictive value (AUC 0.78, 95%-CI 0.67-0.88). Fitting of a multivariable model led to the identification of *SRD5A1*, Notch and TGFβ as most predictive combination (AUC 0.82, 95%-CI 0.72-0.91). AR, Notch, HH and *SRD5A1* were also of prognostic importance regarding progression free survival and *SRD5A1* expression levels also for overall survival (median of 175.0 weeks for high versus 96.7 weeks for low expression). **Conclusions:** Our study revealed predictive and/or prognostic value of AR, HH, Notch and TGFβ signaling activities and *SRD5A1* expression in SDC patients treated with CAB. AR pathway activity can be used for identifying non-responders. Further clinical validation is required before implementation of these biomarkers in clinical practice. The observed role of *SRD5A1* expression in CAB response forms a rational basis for including SRD5A1-inhibitors in the treatment of SDC patients. Research Sponsor: None.

Pathway (mean [range])	Clinical benefit[1]	No clinical benefit[1]	Difference
AR	57.5 [31.7-71.9]	52.2 [29.6-71.9]	p = 0.013
Notch	68.1 [58.8-79.3]	64.0 [39.3-76.0]	p = 0.033
MAPK	63.0 [47.8-73.2]	65.4 [31.0-84.9]	p = 0.089
TGFβ	66.2 [49.2-74.5]	68.1 [57.5-78.5]	p = 0.34
ER	35.3 [11.3-45.3]	32.9 [16.7-44.9]	p = 0.068
HH	25.9 [11.3-38.9]	26.2 [5.7-35.0]	p = 0.59
PI3K	16.7 [6.5-32.9]	16.7 [6.5-28.8]	p = 0.86
***SRD5A1* expression[2]**	0.37 [-1.46-3.67]	1.45 [-1.46-2.39]	p = 0.001

[1]73 samples passed quality check for pathway analysis, 76 for *SRD5A1* expression analysis.
[2]Log transformed value of *SRD5A1* expression normalized to *HPRT1*.

6072 **Poster Session**

Clinical disease course and survival outcomes following disease recurrence in adenoid cystic carcinoma (ACC) with NOTCH signaling pathway activation. *First Author: Brindley Sonal Hapuarachi, Weston Park Hospital, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield, United Kingdom*

Background: ACC is a rare salivary cancer for which effective drug therapies remain lacking. The highest rates of disease recurrence are in patients with NOTCH pathway activation, which is reported in 10-20% of ACC tumors. Novel drugs targeting NOTCH signaling are under investigation in the recurrent and metastatic setting. To understand their clinical utility, there is an urgent need to better characterize the disease course and outcomes following current standard of care treatment from diagnosis and following recurrence. **Methods:** 120 patients with ACC underwent clinical review at a single UK Cancer Centre from 2017-19. Patients were retrospectively assessed for tumor NOTCH pathway activation using next generation sequencing (NGS) targeting *NOTCH1/2/3* genes (n = 98) and/or by immunohistochemistry (IHC) for the NOTCH1 intra-cellular domain (NICD1) (n = 87). To understand the disease course with NOTCH pathway activation, treatment data including surgery, radiotherapy and systemic therapies were extracted and presented as swimmer plots. Kaplan-Meier survival analysis was performed and a difference in survival with/without NOTCH activation was calculated with log rank test. Overall survival (OS) was calculated both from diagnosis and from first confirmed disease recurrence or metastasis, and recurrence free survival (RFS) calculated from diagnosis. **Results:** Of 120 patients, median age was 46 years (22-74 years). 114/120 patients (95%) had confirmed disease recurrence at clinical review. The primary site was major salivary gland in 58/120 (48%), the others were minor salivary. NOTCH1/3 activating somatic mutations were identified in 11% by NGS (11/98) and NICD1 diffuse nuclear staining was seen in 6% by IHC (5/87) for overall NOTCH activation in 11% (13/120). In NOTCH activated ACC, primary site was major salivary gland in 7/13 (54%), and non-pulmonary visceral/bone metastases were present in 6/13 (46%). Consistent with other reports, patients with NOTCH activation (n = 13) had shorter RFS (0.9 vs 3.6 years, p = 0.11) and significantly reduced OS from diagnosis (4.0 vs 16.3 years, $p < 0.0001$). Critically, as therapies targeting NOTCH signaling are being evaluated in recurrent/metastatic ACC, there was significantly reduced OS from time of first confirmed disease recurrence or metastasis (1.5 vs 9.6 years, $p < 0.0001$). This reduction in OS for NOTCH activation following recurrence was seen consistently whether patients were classified using NGS (1.9 vs 9.6 years, p = 0.0009) or NICD1 IHC (0.8 vs 8.5 years, $p < 0.0001$). **Conclusions:** This is the first study to report clinical outcomes for patients with NOTCH pathway activated ACC following disease recurrence. Although ACC is frequently considered an indolent disease, the short survival in this sub-group of ACC patients demonstrates the urgent need to develop effective drug therapies in this setting. Research Sponsor: The Ella Project (The Christie Charity), The Infrastructure Industry Foundation and Syncona Foundation, Pharmaceutical/Biotech Company.

6073 **Poster Session**

Selpercatinib efficacy and safety in patients with *RET*-altered thyroid cancer: A clinical trial update. *First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Selpercatinib, is a first-in-class, highly selective, CNS active and potent RET inhibitor approved in multiple countries for treatment of *RET*-fusion positive lung or thyroid cancers. Reported is an update of efficacy and safety results in *RET*-altered thyroid cancer, with a longer follow up (30 Mar 2020 data cutoff vs 16 Dec 2019) and additional enrolment. **Methods:** Patients (pts) with *RET*-mutant medullary thyroid cancer (MTC) and *RET*-fusion positive thyroid cancer (TC) were enrolled in the global (16 countries, 89 sites) Phase 1/2 LIBRETTO-001 trial (NCT03157128). The primary endpoint was objective response rate (ORR) per RECIST 1.1 by independent review committee (IRC). Secondary endpoints included duration of response (DoR), progression-free survival (PFS), clinical benefit rate (CBR; CR+PR+SD $\geq$16 weeks), and safety. The integrated analysis set (IAS, n = 143) includes efficacy evaluable MTC pts previously treated with cabozantinib and/or vandetanib (cabo/vande). The primary analysis set (PAS), a subset of IAS, is the first 55 enrolled pts. Cabo/vande naïve MTC pts (N = 112) and TC pts with prior systemic treatment (N = 22) were also analyzed. Safety population includes all pts who received $\geq$1 dose of selpercatinib (MTC N = 315; TC N = 42) by data cutoff. **Results:** For MTC patients, the ORR for IAS was 69.2%, in the PAS it was 69.1%, and 71.4% for cabo/vande naïve MTC pts. The ORR for TC pts (n = 22) was 77.3% (see table). Most treatment-emergent adverse events (TEAEs) were low grade; the most common ($\geq$25% of MTC and/or TC pts treated with selpercatinib) were dry mouth, diarrhea, hypertension, fatigue and constipation for both MTC and TC pts, increased ALT/AST, peripheral edema and headache in MTC pts and nausea in TC pts. 4.8% of MTC and TC pts discontinued selpercatinib due to TEAEs but only 1.9% with MTC and none with TC discontinued due to treatment-related adverse events. **Conclusions:** In this updated analysis, selpercatinib continued to show marked and durable antitumor activity in pts with *RET*-altered thyroid cancers. Selpercatinib was well tolerated and no new safety concerns were identified. A global, randomized, phase 3 trial (LIBRETTO-531) evaluating selpercatinib compared to cabo/vande in kinase inhibitor naïve MTC pts is ongoing. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

	PAS (n = 55)	IAS (n = 143)	Cabo/Vande naive (n = 112)	RET-Fusion TC (n = 22)
ORR % (95% CI)	69.1 (55.2, 80.9)	69.2 (61.0, 76.7)	71.4 (62.1, 79.6)	77.3 (54.6, 92.2)
CBR % (95% CI)	92.7 (82.4, 98.0)	90.9 (85.0, 95.1)	93.8 (87.5, 97.5)	100.0 (84.6, 100.0)
DoR, median (95% CI), months	NE (19.1, NE)	NE (19.1, NE)	21.95 (21.9, NE)	18.4 (10.1, NE)
Duration of follow-up median, months	17.45	10.05	9.26	20.27
Rate (%) PFS, > 12 months (95% CI),	82.3 (68.7,90.4)	76.9 (67.9, 83.7)	92.9 (84.5, 96.8)	68.6 (42.7, 84.6)

Clinical benefit rate, CBR; Complete response, CR; Not estimated, NE; Objective response rate, ORR; Partial response, PR; Progressive disease, PD; Stable disease, SD.

6074 **Poster Session**

Efficacy of selpercatinib after prior systemic therapy in patients with *RET* mutant medullary thyroid cancer. *First Author: Lori J. Wirth, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Selpercatinib is a first-in-class, CNS active, highly selective, and potent RET kinase inhibitor which has demonstrated durable antitumor activity in patients (pts) with *RET* altered thyroid cancer and is approved in multiple countries for the treatment of *RET* fusion+ lung or thyroid cancers. As response rates to cancer therapy usually decline on subsequent lines of therapy, the efficacy of selpercatinib was examined in the context of the last prior therapy received before trial enrollment. **Methods:** Pts with *RET* mutant medullary thyroid cancer (MTC) previously treated with multikinase inhibitors (cabozantinib and/or vandetanib) were enrolled in the global LIBRETTO-001 trial (NCT03157128). This post-hoc exploratory intrapatient analysis, based on March 30, 2020 data cutoff date, was performed to compare the retrospective physician-reported objective response rate (ORR) from the last systemic therapy prior to enrollment, as reported in pts case reports, to ORR by independent review committee per RECIST 1.1 with selpercatinib treatment, with each patient serving as his/her own control. **Results:** Efficacy-evaluable pts, 64% male, 90% white with a median age of 58 years, received prior therapy for MTC (n = 143). Pts had a median of 2 (range 1-8) prior systemic regimens. The ORR on selpercatinib (69%) was markedly higher than for the last prior therapy (10%) received before enrollment. ORR improvements with selpercatinib were observed regardless of prior therapy: cabozantinib (66% vs 14%) or vandetanib (71% vs 12%). Fewer pts had progressive disease as their best overall response with selpercatinib (2/143; 1.4%) compared to last prior therapy (33/143; 23.1%). Notably selpercatinib achieved 62% ORR in pts that did not respond to their previous line of therapy prior to enrolment. This shift from non-responder to responder on selpercatinib therapy was consistent regardless of prior cabozantinib or vandetanib treatment, where pts achieved 57% and 61% ORR respectively when subsequently treated with selpercatinib. In contrast, only 3% of patients did not respond to selpercatinib after a previous response to the immediate prior therapy. Similarly, 5% and 2% of patients were non-responders on selpercatinib after a prior response with cabozantinib and vandetanib therapy respectively. **Conclusions:** Prior to selpercatinib, response with previous multikinase therapy was rare. By contrast, selpercatinib demonstrated robust efficacy regardless of response to or specific prior therapy in pts with *RET* mutant MTC. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

6075 **Poster Session**

Phase Ib, international, dose-escalation study to evaluate the safety, pharmacokinetics (PK) and efficacy of ST-617 for the attenuation of oral mucositis (OM) in patients receiving chemoradiation (CRT) for head and neck (H&N) cancer. *First Author: Daniel Osei-Fofie, Oncology Dept, Kimberley Hospital, Kimberley, South Africa*

Background: OM is a common, painful, and costly toxicity associated with cytotoxic regimens used to treat H&N cancers, which may result in radiotherapy treatment interruptions to negatively impact tumor control. There are currently no approved interventions to successfully prevent or delay OM onset among patients being treated with radiation therapy, with or without concomitant chemotherapy (CRT). Oxidative stress is a critical event in OM's pathogenesis. Through its effect on Nrf2, ST-617 has marked anti-oxidative activity/properties. Supportive Therapeutics is developing ST-617, a dithioethione, for the attenuation of OM onset, duration and severity. The objective of this trial was to assess the safety, tolerability, PK, PD and efficacy of ST-617 in patients at high risk of severe OM (SOM). **Methods:** A dose escalation trial in which ST-617 administered as an oral suspension, 1-2 hours before the administration of daily RT fractions was performed at 9 study sites in South Africa and Australia. Eighteen patients with diagnoses of oral or oropharyngeal CA were enrolled (up to 6 pts/dose). Patients received concomitant cisplatin either weekly or tri-weekly. ST-617 was administered 3 days prior to CRT, and then continuing daily until the end of treatment. Safety outcomes, using CTCAE criteria (v 4.03) were used. Dose escalation occurred in the absence of toxicity. OM occurrence and severity were assessed by trained and validated evaluators using WHO, NCI-CTC and RTOG criteria; scores were centrally assigned. The primary efficacy endpoints included the incidence and duration of SOM (WHO grades 3 or 4) vs historical controls. PD tracking measured total ROS/RNS, GSH/GSSG, regulation in plasma and buccal epithelial cells. **Results:** 17 pts completed the 50, 100 and 150mg/day with no safety issues. No early dose limiting toxicity (DLT) or serious Adverse Event linked to ST-617 were observed. AEs observed were mainly nausea which is usually associated with CRT as expected. The 100 mg/day dose has been well tolerated with no grade 4 OM. No CRT dose interruptions or delays due to OM has been observed. Total ROS/RNS levels in plasma and buccal samples show significant decrease with increased ST-617 dosing from 50 to 100 mg/day. **Conclusions:** ST-617 administration was safe at all doses tested. The course and severity of patients treated with ST-617 compared favorably with historical controls. Mechanistic correlation between ROS/RNS levels was seen. A randomized, controlled, double blind trial is planned with the recommended dose of 100mg/day. Clinical trial information: 20180138. Research Sponsor: None.

6076 **Poster Session**

Randomized phase II study of sorafenib with or without everolimus in patients with radioactive iodine refractory Hürthle cell thyroid cancer (HCC) (Alliance A091302/ ITOG 1706). *First Author: Eric Jeffrey Sherman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: HCC is a rare subtype of follicular cell thyroid cancer that has been poorly studied in the past. Recent genomic studies have shown the PI3K/Akt/mTOR pathway is frequently altered in HCC. In addition, a phase II study of sorafenib (S) and everolimus (E) showed promising data in HCC. A study to evaluate this was initiated through Alliance and the International Thyroid Oncology Group. **Methods:** Patients (pts) were randomized to either sorafenib and everolimus (SE) vs. sorafenib alone (S). Inclusion criteria included; (1) diagnosis of HCC (confirmed through central review), no prior S or E, refractory to radioactive iodine, progressive disease by RECIST over prior 14 months. Primary endpoint was a comparison of progression-free survival (PFS) between SE and S using a stratified 1-sided log-rank test with 0.20 significance level and a power of 80%. 28 events were needed at final analysis. Secondary endpoints consisted of overall survival (OS), confirmed response rate (RR), and adverse events. **Results:** 35 pts were randomized from 10/2014 to 9/2019, 34 of which were evaluable for analysis (17-SE; 17-S) because 1 patient cancelled prior to receiving treatment. Median age was 66.5 years and 74% were male. ECOG performance status (PS) was 0 (47%) and PS 1 (53%). 41% had prior systemic treatment for HCC. No significant differences in baseline characteristics were observed between treatment arms. Median follow-up in 22 alive patients was 39.2 months (range: 15.1-64.9). Seven (21%) patients remain on treatment. PFS was significantly improved in the SE arm as compared to the S arm (HR=0.65 (95% CI: 0.26, 1.57); median PFS: SE=24.7 months (95% CI: 6.1-no upper), S=10.9 months (95% CI: 5.5-no upper); stratified 1-sided p=0.1662). OS was similar between the arms (2-sided p=0.4138). Confirmed response rate was similar between arms as well (SE: 18% (3 partial response (PR) vs. S: 24% (3 PR, 1 complete response)); Fisher's exact p=1.00). Grade 3 adverse event (AE) rates (regardless of attribution) were similar between arms (SE: 77% vs. S: 77%; p=1.00). Each arm had 1 patient with at least one grade 4 AE (SE patient: cardiac arrest, tracheal obstruction, encephalopathy; S patient: mucositis oral) and no grade 5 AEs. **Conclusions:** PFS was improved with the addition of E to S in this small randomized multi-institutional phase II study done. Accrual was difficult, but these promising results suggest that this combination should be further studied. Support: U10CA180821, U10CA180882, U24CA196171; https://acknowledgments.alliancefound.org; Novartis/GSK; ClinicalTrials.gov Identifier: NCT02143726. Clinical trial information: NCT02143726. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

6077 **Poster Session**

Radiomics-based prediction of response to multikinase inhibitors in radioiodine-refractory differentiated thyroid cancer patients. *First Author: Valentina Corino, Department of Electronics, Information and Bioengineering (DEIB), Politecnico di Milano, Milan, Italy*

Background: Antiangiogenic tyrosine kinase inhibitors (TKIs) represent the first-line treatment for radioiodine-refractory differentiated thyroid cancer (RR-DTC). Currently, no predictive factors for the activity of these drugs are available. We investigated whether radiomics may have a predictive role in this setting. **Methods**: We retrospectively identified patients (pts) affected by metastatic RR-DTC, treated with TKIs between July 2008 and January 2020 at our Institution, with availability of computed tomography (CT) scans at baseline and after at least 2 courses of TKI. Response to TKIs was evaluated according to RECIST v1.1. Pts with complete or partial response at the first radiological evaluation were considered responders (R), pts with stable or progressive disease non-responders (NR). A dedicated radiologist segmented the target lesions as regions of interest (ROIs). Radiomic features related to multiple categories (shape and size, first order statistics, textural features) were extracted from each ROI and computed using the PyRadiomics library v. 3.0. A semi-supervised form of principal component analysis estimated principal components that were then used for response classification through a k nearest neighbors (kNN) classifier. The quality of the model was assessed through train-validation-test split (55% of the data used as training set, 25% as validation set, 20% as test set), repeated 100 times. Performance of the predictive models was quantified with the mean Area Under the ROC Curve (AUC) obtained in the test set. **Results**: A total of 51 pts with metastatic RR-DTC who had received lenvatinib (n=37), sorafenib (n=4), axitinib (n=3), or vandetanib (n=7) were analyzed. Median age was 64.6 years, with a male prevalence (72.5%). Metastatic sites were lung (84.3%), bone (35.3%), brain (9.9%). Median time from TKI treatment start to the first radiological evaluation was 2.77 months, 24 pts (47%) were R (all partial responses) and 27 (52.9%) NR. In the radiomic analysis, 851 features were computed and 4-19 principal components were selected. Models' performance of prediction of early response to TKIs is presented in Table. For each value of AUC, the corresponding 95% confidence interval is reported in brackets. **Conclusions**: Radiomics predicted the response to TKIs of RR-DTC pts with an accuracy of 71%. Radiomics technique has the potential to enable clinicians to anticipate the probability of response to TKIs at baseline, directing toward the most suitable patient-tailored therapeutic path. Prospective studies may further validate these preliminary findings. Research Sponsor: None.

Early response	Accuracy	TPR	TNR	AUC
Validation set	0.85 ± 0.07	0.83 ± 0.11	0.86 ± 0.09	0.85 (0.83 – 0.86)
Test set	0.71 ± 0.18	0.68 ± 0.26	0.73 ± 0.25	0.71 (0.67 – 0.74)

Legend: TPR = true positive rate; TNR = true negative rate; AUC = area under the curve.

6078 **Poster Session**

A pooled analysis of response to selective RET inhibitors among patients with medullary thyroid cancer with M918T versus non-M918T RET mutations. *First Author: Janice Kim, U.S. Food and Drug Administration, Silver Spring, MD*

Background: Medullary thyroid cancer (MTC) accounts for 1 to 2% of thyroid cancers in the United States; *RET* alterations occur in >95% of hereditary and 50% of sporadic forms. Up to 80% of patients with sporadic MTC have somatic M918T RET mutations, which is associated with poor prognosis (1). The tyrosine kinase inhibitors (TKIs) cabozantinib and vandetanib are approved to treat patients with MTC regardless of *RET* status; however, retrospective analyses have suggested that there may be greater benefit in patients with M918T mutations (1,2). Newly approved therapies selpercatinib and pralsetinib, developed for patients with *RET* mutations, have demonstrated higher response rates than previous first line therapies. In this analysis, we examine the differences in overall response rate (ORR) between patients with MTC with *RET* M918T non-*RET* M918T mutations. **Methods:** An analysis of ORR in patients with MTC with RET M918T mutations with non-M918T mutations was conducted using the efficacy populations used to support the approvals of pralsetinib and selpercatinib using the following groups: Patients who received prior cabozantinib or vandetanib (referred to as "previously treated"). Patients with no prior cabozantinib or vandetanib ("TKI naïve"). All patients regardless of prior therapy. **Results:** Exploratory analysis of ORR of pooled population of Selpercatinib and Pralsetinib in patients with MTC with RET M918T mutations and non-M918T mutations. [1] Prior vandetanib or cabozantinib. [2] No prior vandetanib or cabozantinib. Two groups of patients were analyzed (*RET* M918T mutation and *RET* non-M918T mutation), with subgroups with respect to prior treatment. Among all patients regardless of prior therapy, the ORR was similar between M918T non-M918T groups. Among previously treated patients, the ORR was lower in the M918T group vs. the non-M918T group, while in the TKI naïve group the ORR was higher in the M918T groups vs the non-M918T group although the 95% CIs overlap in both comparisons. **Conclusions:** There were no major differences in ORR among mutational subtypes in patients with MTC treated with *RET* inhibitors, regardless of prior therapy. ORR was similar between patients with M918T and non-M918T mutations. Additional experience in ongoing clinical studies may provide additional data regarding responses across specific mutation types. References: 1.Sherman SI et al "Correlative analyses of RET and RAS mutations in a phase 3 trial of cabozantinib..." Cancer. 2016;122(24):3856-3864. 2.Wells SA Jr et al "Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer..." J Clin Oncol. 2012;30(2):134-41. Research Sponsor: None.

	Previously treated[1] N = 70	TKI naïve[2] N = 64	All Patients N = 134
M918T ORR (95% CI)	61% (49, 73)	75% (63, 85)	68% (59, 76)
	Previously treated[1] N = 40	**TKI naïve[2] N = 53**	**All Patients N = 93**
Non-M918T ORR (95% CI)	70% (53, 83)	66% (52, 78)	68% (57, 77)

6079 **Poster Session**

Trastuzumab deruxtecan (T-DXd) in patients with human epidermal growth factor receptor 2 (HER2)-expressing salivary duct carcinoma: Subgroup analysis of two phase 1 studies. *First Author: Hideaki Bando, Aichi Cancer Center Hospital, Aichi, Japan*

Background: T-DXd is an antibody-drug conjugate composed of an anti-HER2 antibody, cleavable tetrapeptide-based linker, and membrane-permeable topoisomerase I inhibitor payload. T-DXd has been approved for use in the US and Japan for both breast cancer and gastric cancer and has demonstrated safety and efficacy for additional solid tumors indications in the first-in-human (FIH) (J101; NCT02564900) and drug-drug interaction (DDI) (A104; NCT03383692) phase 1 studies. Here we present the combined subgroup analysis for salivary duct carcinoma. **Methods:** Patients (pts) with HER2-expressing salivary duct carcinoma after standard treatment or without any available standard treatment in both the FIH study and DDI study were included in this analysis. HER2 expression at enrollment was defined by IHC and/or amplification by ISH or NGS via local testing. A retrospective analysis of HER2 IHC and ISH of archived samples was conducted after enrollment by central laboratory per ASCO CAP guidelines. Pts with salivary duct carcinoma received T-DXd at 6.4 mg/kg and 5.4 mg/kg IV every 3 weeks in the FIH study and DDI study, respectively. RECIST version 1.1 was used for efficacy assessments by investigators. **Results:** Of 329 pts enrolled in both the FIH (289 pts) and DDI (40 pts) studies, a total of 17 pts with salivary duct carcinoma were pooled in this analysis: 8 pts with T-DXd at 6.4 mg/kg from FIH study and 9 pts with T-DXd at 5.4 mg/kg from DDI study. The sites of primary disease were parotid gland for 6 pts, submandibular gland for 4 pts, sublingual gland for 1 pt, and unknown for 6 pts. As for HER2 status by the central laboratory, 11 pts were IHC3+, 1 pt was IHC2+/ISH- and 5 pts had no available samples. Fourteen pts received HER2 targeted agents as a prior cancer therapy including trastuzumab. At data cutoff (FIH study: 1 Aug 2019; DDI study: 26 Sep 2018), the confirmed overall response rate was 47% (8/17) and the best overall response was PR in 8 pts and SD in 9 pts. Median duration of response and progression-free survival were 12.9 months and 14.1 months, respectively. Treatment-emergent adverse events (TEAEs) occurred in all 17 pts (grade ≥3, 64.7%); most common grade ≥ 3 TEAEs were decreased neutrophil count (8/17, 47.1%), decreased white blood cell count (6/17, 35.3%), anemia (2/17, 11.8%) and decreased platelet count (2/17, 11.8%). Three pts (3/17, 17.6%) had adjudicated drug related interstitial lung disease (Grade 1 for 2 pts and Grade 3 for 1 pt). Of these 17 pts, 7 pts (41.2%) experienced dose interruption and 3 pts (17.6%) experienced dose reduction due to TEAEs. Four pts (23.5%) discontinued treatment due to TEAEs. **Conclusions:** T-DXd showed promising antitumor activity in HER2-expressing salivary duct carcinoma with durable response. The safety profile was generally consistent with previous results in the other solid tumors. Clinical trial information: NCT02564900 and NCT03383692. Research Sponsor: Daiichi Sankyo Co., Ltd., Japan .

6080 **Poster Session**

Patient-reported outcomes (PROs) from a phase II trial of pembrolizumab for HPV-associated papilloma patients with laryngeal, tracheal and/or pulmonary involvement. *First Author: Sara I. Pai, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Recurrent respiratory papillomatosis (RRP) is caused by human papillomavirus (HPV) types 6 & 11. RRP proliferates in the respiratory tract impacting breathing, swallowing, and voice and carries a 1-4% risk of malignant transformation.There is no curative therapy for RRP. Given the tolerized host immune response against HPV, the safety and efficacy of pembrolizumab (pembro) as an alternative treatment for this patient population was evaluated in a phase II clinical trial. Patient reported outcomes (PROs) were assessed during the trial to capture the patient perspective of pembro as an alternative to surgery or in office procedures, both standard of care (SOC). **Methods:** RRP patients who had previously undergone >3 procedures in any year, or with known tracheal or pulmonary involvement prior to study entry were treated with pembro 200mg every 3 weeks. The primary endpoint of the trial was best 'overall response rate' (ORR) measured by an endoscopic-based disease burden score (lower score reflects better 'response') and/or RECIST 1.1, secondary endpoint included PROs. Twenty-one patients were required to assess the primary endpoint. Most of the QoL surveys used Likert scale to assess PROs ('never, sometimes, often, most of the time, always'). The percentage reporting 'never' having an issue with symptom or activity at baseline, 6 months, and at time of ORR (nadir disease burden score) is reported here. **Results:** Twenty-one patients were accrued. Median age (range) was 45 (19-68), 57% (12/21) were male and 67% (14/21) were white. Questionnaire completion rates were 100% at baseline, 90% at 6 months, and 85% at ORR. Improvement in: social interactions (less difficulty with: physical intimacy [38%,56%,65% reporting 'never' at baseline, 6 months, and at ORR respectively]), discussing disease diagnosis [19%,21%,39%]); personal feelings (less depression [14%,32%,33%], less anxiety [5%,16%,22%], less embarrassment [19%,37%,50%]), and work-related absences (less frequently fabricating reasons for work absence due to disease-related treatment [57%,78%,56%] and less utilization of family vacation or FMLA for disease treatment [29%,53%,56%]) were reported. At ORR, 72% (13/18) patients reported that IV infusion was not emotionally burdensome and 78% (14/18) reported it as the preferred treatment relative to their perceived experience with SOC surgery or in office procedures. **Conclusions:** PRO results show consistent benefit in key aspects of the patient experience with pembro over procedure based SOC further supporting its overall clinical benefit in patients with HPV-associated RRP. Clinical trial information: NCT02632344. Research Sponsor: MERCK, Other Government Agency.

6081 **Poster Session**

Molecular profiling and targeted agents in recurrent, metastatic salivary gland tumor (R/M SGT) patients (pts) treated at two academic centers. *First Author: Alberto Hernando-Calvo, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*

Background: Treatment selection based on actionable alterations (AAs) is an appealing strategy for pts with R/M SGT. The GEMS-001 study (NCT02069730) at Princess Margaret Cancer Centre (PM) and the Vall DHebron Institute of Oncology (VHIO) pre-screening program facilitate the identification of AAs for R/M SGT pts and treatment selection. **Methods:** We analyzed R/M SGT treated at PM and VHIO from 2015 to 2020. Clinicopathological features, molecular alterations and treatment modalities were correlated with outcomes. The primary endpoint was overall response rate (ORR) by RECIST 1.1. Clinical benefit rate (CBR) was defined by pts with partial response or stable disease ≥4 months. Clinical actionability of multigene panel testing (NGS) and immunohistochemistry (IHC) were assessed as per institutional molecular tumor boards or investigators. Pts were opportunistically matched to available therapies from each center. **Results:** In total 206 pts were enrolled. On IHC, HER2 overexpression was present in 9%, Androgen Receptor (AR) 33%, Estrogen/Progesterone Receptor (ER/PR) 11% and ALK overexpression 0%. On NGS, PIK3CA mutation (mut) was in 9%, NTRK fusion 6%, NOTCH1-3 mut 5%, HRAS mut 6%, ERBB2/3 alterations (alt) 4% and FGFR1-4 alt 3%. Up to 92 pts (45%) displayed at least 1 AA and 36 pts (18%) had ≥2 AAs. A total of 60 pts (29%) were matched to AAs. Of those matched, median age was 60 years (range 33-84), M:F 21:39, 95% ECOG≤1 with a median number of prior treatment lines 0 (range 0-3), and their AAs included 26 AR, 9 HER2 or ERBB2 overexpression, 9 PIK3CA mut, 3 NTRK fusion, 3 FGFR1-3 alt and 10 other AAs (2 ER/PR overexpression, 2 EGFR mut, 1 c-kit mut, 1 BAP1 mut, 1 Non-V600 BRAF mut, 1 CDKN2A mut, 1 CHEK2 mut and 1 PTCH1 mut). Overall, ORR was 27% for the matched population. See table for outcomes. **Conclusions:** In our cohort, almost one third of the population received therapies matched to AAs. Our results suggest that targeted therapies have promising activity in pts with R/M SGT supporting comprehensive molecular and IHC profiling in treatment determination. Research Sponsor: None.

AA	ORR	CBR
NTRK	100%	100%
HER2	77%	56%
AR	23%	35%
PIK3CA	0%	67%
FGFR	0%	100%
NOTCH	0%	50%
Other	0%	44%

6082 **Poster Session**

Benefits of pembrolizumab in progressive radioactive iodine refractory thyroid cancer: Results of the AcSé Pembrolizumab Study from Unicancer. *First Author: Sophie Leboulleux, Institut Gustave Roussy, Villejuif, France*

Background: AcSé Pembrolizumab is a Phase II, non-randomized parallel arm, open-label, multicentric study from Unicancer investigating the efficacy and safety of pembrolizumab monotherapy in different cohorts of patients with rare cancers (NCT03012620). Here we report the first results of pembrolizumab in the radioactive iodine refractory thyroid cancer cohort. **Methods:** Main inclusion criteria were progressive radioactive iodine refractory (RAIR) thyroid cancer (TC) resistant to standard treatment, age > 18, ECOG PS≤1. Patients received pembrolizumab 200 mg IV as a 30-minute infusion on Day 1 of every 21-day cycle for a maximum of 2 years. The primary endpoint was the confirmed objective response (OR) rate according to RECIST v1.1 by investigator. Secondary endpoints included duration of response, progression-free survival (PFS), overall survival (OS), and safety. **Results:** 43 patients (21 female, mean age 64.8 years; range 40-86) with TC (27 patients with differentiated TC (DTC) [papillary: 7; follicular: 14: oncocytic: 5 poorly differentiated: 1] and 16 patients with anaplastic TC (ATC)) were included from September 2017 to December 2020. The median number of previous systemic treatment lines was 2 (range, 0-7) in DTC and 2.5 (range, 1-4) in ATC. The median number of pembrolizumab cycles was 4 (range, 1-35). The median follow-up was 5.9 months (range: 22 days-22.9 months) for DTC and 2.7 months (range: 3 days-24.4 months) for anaplastic TC. For DTC the best tumor response was partial response (PR) in 3 (11.1%) patients and stable disease (SD) in 5 (18.5%). Median duration of response was 2.5 months (range: 5 days-7.2 months). The median PFS was 2.6 months, the 6-month PFS was 16.9 %. The median OS was 12.7 months with a 6-month OS of 73.3%. For ATC the best tumor response was PR in 3 cases (18.8 %) and SD in 1 case (6.2 %). Median duration of response was 1.6 months (range: 2 days-7.2 months). The median PFS was 2.3 months, the 6-month PFS was 33.8 %. The median OS was 3.6 months with a 6-month OS of 32.9%. Treatment emergent adverse event included 9 Grade 1-2, 20 Grade 3 (3 being considered as related and 17 as not related) and 1 Grade 4 (sepsis, unrelated). Overall, the toxicity profile was similar to that observed in other cancers. **Conclusions:** The response rates observed under pembrolizumab is low in DTC and not negligible in ATC, but with a short duration of response. Clinical trial information: NCT03012620. Research Sponsor: La Ligue Nationale contre le Cancer, Other Government Agency, Pharmaceutical/Biotech Company.

6083 **Poster Session**

***NTRK, RET, BRAF,* and *ALK* fusions in thyroid fine-needle aspirates (FNAs).** *First Author: Lori J. Wirth, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Receptor tyrosine kinase (RTK) fusions may be targeted by small molecule inhibitors to treat various advanced tumors, including thyroid cancer. Clinical trials have studied selective inhibitors of *ALK, BRAF, NTRK* and *RET*, leading to several FDA-approved therapies. The Afirma Genomic Sequencing Classifier (GSC) classifies cytologically indeterminate thyroid nodules as molecularly benign or suspicious. The Xpression Atlas reports 905 genomic variants and 235 fusion pairs on GSC Suspicious, Suspicious for Malignancy (SFM), and Malignant FNA samples at the time of diagnosis. Here we report the prevalence of these fusion genes in real-world clinical practice. **Methods:** We analyzed anonymized data from 50,644 consecutive Bethesda III-VI nodule FNA samples submitted to the Veracyte CLIA laboratory for molecular testing using whole transcriptome RNA sequencing (RNA-Seq). Gene pairs are listed alphabetically. **Results:** 32,080 Bethesda III/IV nodules were classified as GSC Benign and 278 were Parathyroid Classifier positive. No *ALK, BRAF, NTRK1/3,* or *RET* fusions were identified among these samples. Among 16,594 Bethesda III/IV GSC Suspicious FNAs, 3% (n = 529) were positive for *ALK, BRAF, NTRK1/3 or RET* fusions. Among the 1,692 Bethesda V/VI FNAs, the proportion of positive nodules was 8% (n = 135). Among these combined cohorts of Bethesda III/IV GSC Suspicious and Bethesda V/VI, the most common gene fusions observed for each of the 5 studied RTK genes was: *ETV6/NTRK3* (n = 164, 72% of *NTRK3* fusions), *CCDC6/RET* (n = 104, 55% of *RET*), *BRAF/SND1* (n = 32, 20% of *BRAF*), *ALK/STRN* (n = 20, 37% of *ALK*), and *NTRK1/TPM3* (n = 14, 50% of *NTRK1*). *BRAF* showed the highest diversity of fusions, with 80 gene partners. Different gene partners with *RET, ALK, NTRK1,* and *NTRK3* numbered 25, 11, 9, and 5, respectively. **Conclusions:** Whole-transcriptome RNA-seq on small sample thyroid FNA specimens can identify clinically relevant *ALK, BRAF, NTRK,* and *RET* fusions across Bethesda categories. The prevalence ranges from 3% in Bethesda III/IV Afirma GSC Suspicious specimens to 8% among Bethesda V/VI specimens. Future studies need to determine if detection of precision medicine candidates by pre-operative FNA can optimize initial treatment, predict response to treatment, and prioritize selective targeted therapy should systemic treatment be needed. Research Sponsor: Veracyte.

Number and prevalence of selected receptor tyrosine kinase gene fusions among 50,644 thyroid FNA samples by Bethesda category.

RTK gene	AUS/FLUS(III) N = 39464	FN/SFN(IV) N = 9488	SFM(V) N = 837	Malignant(VI) N = 855
ALK	29 (0.07%)	22 (0.23%)	3 (0.36%)	0 (0.00%)
BRAF	88 (0.22%)	47 (0.50%)	15 (1.79%)	13 (1.52%)
NTRK1	16 (0.04%)	8 (0.08%)	2 (0.24%)	2 (0.23%)
NTRK3	126 (0.32%)	67 (0.71%)	21 (2.51%)	15 (1.75%)
RET	86 (0.22%)	40 (0.42%)	40 (4.78%)	24 (2.81%)
Any	345 (0.87%)	184 (1.94%)	81 (9.68%)	54 (6.32%)

AUS/FLUS- atypia or follicular lesion of undetermined, FN/SFN-follicular and Hürthle cell neoplasm or suspicious for same

6084 **Poster Session**

Treatment patterns and systemic therapy outcomes for patients with salivary duct carcinoma and adenocarcinoma NOS. *First Author: Luana Guimarães Sousa, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Salivary duct carcinoma (SDC) and adenocarcinoma, not otherwise specified (Adeno-NOS) are rare and aggressive subtypes of salivary gland cancers. Biomarker studies revealed targetable alterations such as androgen receptor (AR) and HER2 overexpression; nevertheless, chemotherapy (CT) remains the cornerstone treatment of patients (pts) with locally advanced or metastatic disease based on limited efficacy data. We sought to describe the treatment patterns and outcomes of SDC and Adeno-NOS pts. **Methods:** We retrospectively collected clinicopathological, treatment, and outcomes data of SDC or Adeno-NOS pts that were seen at MD Anderson from 1990-2020. AR positivity was defined by IHC staining in ≥ 10% of tumor cells, and HER2 by IHC 2+ or 3+ scores. Overall response rate (ORR) was assessed by an independent radiologist per RECIST v1.1. Recurrence-free survival (RFS) and overall survival (OS) from diagnosis were estimated using log-rank test. A multivariable cox regression model was performed to estimate the hazard-ratio (HR) of risk factors on pts outcomes. **Results:** 200 pts were included, 110 had SDC and 90 Adeno-NOS. Most pts (61%) presented with locoregional disease (stage III-IVB), while 13% had distant metastasis (IVC). AR was positive in 77% of cases, and HER2 in 47%. In the curative setting (N=174), 98% pts underwent surgery and 90% radiotherapy (RT); 15 pts with stage IVA-B disease had aggressive trimodality therapy including surgery, RT, and systemic therapy. Overall, 55% pts recurred. The mRFS and 5-y RFS rate were 24 mos (95%CI, 16-43) and 34.5%, respectively. For pts with IV-A-B stage, trimodality therapy was associated with an improved OS in comparison to surgery and/or RT (39 mos vs NA, p=0.04). In the metastatic setting, 82 pts received ≥1 line of systemic therapy; the preferred 1st line regimen was platinum/taxane with or without trastuzumab (50%). Table summarizes the ORR and mPFS to each therapy line. ORR and PFS was higher for HER2-targeted therapy (1st line: 47% and 11 mos; 2nd line 29% and 6 mos; respectively); only 10 pts received androgen blockage. At a median follow-up of 7.5 y, the mOS was 5 ys and the 5-y OS rate was 50%. In multivariate analysis, higher T and N stages (HR 2.1 and 3.8, p<0.05), and positive margins (HR 2.0, p=0.003) were associated with worse RFS; older age (HR 1.03, p=0.003), and higher TNM stage (HR 1.78, p=0.006) were associated with worse OS. HER2 expression was not prognostic. **Conclusions:** This study validates prognostic factors in SDC and adeno-NOS and is the largest series to report outcomes to palliative systemic therapy per treatment line, providing a benchmark for future studies in these diseases. Aggressive trimodality therapy may improve outcomes of pts with stage IVA-B disease. Research Sponsor: Research funds from Klaus pharma.

Line of tx	Evaluable pts	ORR (%)	mPFS (95%CI), mos
1st	76	26 (34)	5.3 (4-9)
2nd	44	11 (25)	5 (2-7)
3rd	30	7 (23)	4 (3-10)

TPS6085 **Poster Session**

Encorafenib and binimetinib with or without nivolumab in treating patients with metastatic radioiodine refractory BRAF V600 mutant thyroid cancer. *First Author: Matthew H. Taylor, Earle A. Chiles Research Institute, Portland, OR*

Background: Differentiated thyroid cancer is the most common endocrine malignancy and has a high frequency of actionable molecular aberrations including BRAF V600E mutations (45%), RET fusions (10%), and NTRK fusions (< 2%). FDA approved systemic therapies for metastatic radioiodine refractory differentiated thyroid cancer (RR-DTC) include multikinase inhibitors (Lenvatinib and sorafenib), NTRK inhibitors (larotrectinib and entrectinib for NTRK fusion+ cancers), and RET inhibitors (selpercatinib and pralsetinib for RET fusion+ cancers). Previous phase II clinical trials showed clinical efficacy with first and second generation BRAF inhibitors in patients with BRAF mutant RR-DTC. BRAF inhibitors have not yet been FDA approved for treatment of BRAF mutant RR-DTC. Effective therapeutic options for patients with BRAF mutant RR-DTC remains an important unmet clinical need. BRAF mutant thyroid cancers often show elevated expression of PD-L1. Additionally, BRAF inhibition results in increased expression of PD-L1 in thyroid cancer. This clinical trial seeks to evaluate the safety and efficacy of encorafenib plus binimetinib with or without nivolumab in patients with BRAF mutant metastatic RR-DTC. Encorafenib and binimetinib are highly selective and potent oral inhibitors of BRAF and MEK, respectively. Nivolumab is a potent inhibitor of the immune co-inhibitory receptor programmed cell death protein 1 (PD-1). **Methods**: This is a phase II, single institution, open-label, randomized clinical trial evaluating the combinations of (Arm 1) encorafenib 450 mg/day + binimetinib 45 mg twice daily and (Arm 2) encorafenib 450 mg/day + binimetinib 45 mg twice daily + nivolumab 480 mg I.V. every 4 weeks in patients with metastatic BRAF mutant RR-DTC. The trial will enroll 20 patients in each arm and treatment will be given in 28 day cycles for up to 2 years. Eligible patients must have metastatic/unresectable BRAF mutant RR-DTC, an ECOG performance status of 0-1 and adequate bone marrow, liver and kidney function. Patients with CNS metastases are included if the metastases have been treated and remained stable or are asymptomatic and ≤10 mm in diameter. Patients may be systemic therapy naïve or have previously been treated with multikinase inhibitors. Prior therapy with BRAF, MEK or immune checkpoint inhibitors is exclusionary. The primary endpoint is confirmed objective response rate (ORR) determined by RECIST v1.1 with restaging imaging every 12 weeks. Secondary endpoints include progression free survival, overall survival, and safety/tolerability (CTCAE v5.0). Arms 1 and 2 will be evaluated independently and are not powered for direct comparison. The trial design includes continuous toxicity monitoring with a Pocock-type stopping boundary. This clinical trial is in progress and 3 patients have been enrolled. Clinical trial information: NCT04061980. Research Sponsor: Bristol Myers Squibb and Pfizer.

TPS6086 **Poster Session**

Phase II multicenter randomized trial to assess the efficacy and safety of first line nivolumab in combination with paclitaxel in subjects with R/M HNSCC unable for cisplatin-based chemotherapy (NIVOTAX): A TTCC study. *First Author: Lara Iglesias, Hospital Universitario 12 de Octubre, Madrid, Spain*

Background: Nivolumab is the standard of care for patients (pts) with R/M HNSCC in the platinum-refractory setting. Up to 20% of R/M HNSCC pts are ineligible for cisplatin-based CT due to poor performance status and/or comorbidities. ERBITAX (weekly cetuximab + paclitaxel) is a recommended regimen for this patient population according to the Spanish Society of Medical Oncology guidelines. Preclinical data suggests a role for paclitaxel as immuno-modulator, mainly by increasing tumor infiltrating CD8+ (Galluzzi L., et al 2015). NIVOTAX trial aims to evaluate efficacy and safety of nivolumab + paclitaxel vs ERBITAX as first-line treatment for R/M HNSCC pts with platinum-refractory disease or ineligible for platinum-based chemotherapy. **Methods:** NIVOTAX (NCT04282109) is a randomized, open-label, multicenter, phase II trial sponsored by the Spanish Group of Head and Neck Cancer Treatment (TTCC) including R/M HNSCC pts not amenable for curative-intent therapy, previously untreated for R/M disease and not candidates for cisplatin-based chemotherapy. Population is distributed in 3 Groups: 1= Platinum-refractory; 2=Platinum-sensitive but unable to receive cisplatin due to: Karnofsky performance status (KPS) 70% and/or major comorbidities (renal/heart failure, grade ≥2 hearing loss) and/or previous allergic reactions to platinum compounds; 3= Platinum-sensitive but cumulative cisplatin dose received ≥225 mg/m^2 for locally-advanced disease. Pt are stratified according to: KPS (70% vs 80-100%); PD-L1 by Combined Positive Score (CPS ≥1 vs < 1); and HPV positivity (HPV+ oropharynx vs HPV-/non-oropharyngeal). 141 Pt are being randomized 2:1 to NIVOTAX (nivolumab 240 mg q2 weeks + weekly paclitaxel at 80 mg/m^2 up to 12 weeks followed by maintenance nivolumab 480 mg/ q4 weeks) or ERBITAX (weekly 250 mg/m^2 plus paclitaxel 80 mg/m^2 up to 12 weeks followed by maintenance cetuximab 250 mg/m^2 weekly). Both arms will be continued up to a maximum of 24 months. Primary end-point is to evaluate treatment efficacy in terms of 2-year overall survival (2-y OS). It is assumed that 2-y OS in the NIVOTAX arm will be at least 26% (10% gain when compared to the expected 16% 2-y OS rate in this pt population). Secondary objectives include progression free survival (PFS), overall response rate, disease control rate, duration of response, 6m PFS, 5y-OS and safety profile. Response endpoints will be assessed using RECIST 1.1 criteria. As of February 12, 2021, 64 pts have been randomized. Planned safety data review for the first 10 pts treated with NIVOTAX regimen did not show any unexpected AE. Clinical trial information: NCT04282109. Research Sponsor: Bristol-Myers Squibb.

TPS6087 **Poster Session**

The AIM-HN Study: A pivotal study evaluating the efficacy of tipifarnib in patients with recurrent or metastatic head and neck squamous cell carcinoma with *HRAS* mutations. *First Author: Robert I. Haddad, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Head and neck squamous cell carcinoma (HNSCC) accounts for more than 830,000 new cancer cases each year worldwide. The prognosis for recurrent and/or metastatic (R/M) HNSCC patients remains poor with an estimated median overall survival (mOS) of 7-15 months in the first line setting and 5-8 months in the second line setting and beyond. Approximately 4-8% of HNSCC tumors are driven by gain-of-function mutations in the *HRAS* (m*HRAS*) proto-oncogene. Tipifarnib is a potent and selective farnesyltransferase inhibitor that disrupts HRAS function by blocking required protein membrane localization, and subsequent cellular growth and survival. Data from a prior phase 2 study (RUN-HN; NCT02383927) of tipifarnib in R/M m*HRAS* HNSCC patients in the second line plus setting demonstrated encouraging efficacy, with an objective response rate (ORR) of 55% and mOS of 15.4 months for patients with mHRAS variant allele frequency (VAF) $\geq$ 20%, providing support for pursuing a pivotal trial in this patient population. **Methods:** AIM-HN (NCT03719690) is a global, open-label single-arm pivotal study evaluating the efficacy and tolerability of tipifarnib in second line plus R/M m*HRAS* HNSCC patients. The primary objective is to determine the ORR in patients with a m*HRAS* VAF $\geq$ 20% (High VAF population), as assessed using RECIST v1.1 by Independent Review Facility. Key secondary objectives include the ORR for patients of all VAF levels, and the duration of responses for both VAF$\geq$ 20% and all VAF levels. Key inclusion criteria include: histologically confirmed head and neck cancer of squamous histology not amenable to local therapy with curative intent; known tumor missense *HRAS* mutation (with VAF determined and available) detected by Next Generation Sequencing; ECOG performance status of 0-1; measurable disease by RECIST v1.1; and adequate organ function. Key exclusion criteria include: salivary gland, thyroid, (primary) cutaneous squamous or non-squamous histologies; intolerable Grade 2 or $\geq$ Grade 3 neuropathy or unstable neurological symptoms within 4 weeks of Cycle 1 Day 1; or active, uncontrolled infections requiring systemic therapy. Tipifarnib is administered at a dose of 600 mg, orally with a meal twice a day for 7 days in alternating weeks (Days 1-7 and 15-21) of 28-day cycles until discontinuation criteria are met. All patients are being followed for safety through the End of Treatment visit, roughly 30 days after treatment discontinuation or immediately before the administration of another anticancer treatment, whichever occurs first. Upon therapy discontinuation, all patients are being followed approximately every 12 weeks for survival status, and the use of subsequent therapy. The IDMB last reviewed data in October 2020 and recommended the trial continue as planned. AIM-HN is continuing to enroll patients globally. Ho et al, *JCO*, accepted. Clinical trial information: NCT03719690. Research Sponsor: Kura Oncology.

TPS6089 **Poster Session**

CMP-001-007: Open-label, phase 2 study of intratumoral CMP-001 + pembrolizumab in patients with recurrent or metastatic head and neck squamous cell carcinoma. *First Author: Deborah J.L. Wong, University of California Los Angeles, Los Angeles, CA*

Background: PD-1 blockade ± chemotherapy has recently become a primary systemic therapy recommended by NCCN guidelines for patients (pts) with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). However, most pts still do not respond to treatment, indicating a large unmet need for pts with unresectable disease. CMP-001 is a toll-like receptor 9 (TLR9) agonist comprising a CpG-A oligodeoxynucleotide packaged in a virus-like particle that can induce type I interferon secretion from tumor-associated plasmacytoid dendritic cells, promoting a Th1-like chemokine milieu in the tumor microenvironment and inducing an antitumor CD8+ T-cell response. In a phase (ph) 1b study in pts with metastatic melanoma, intratumoral (IT) injection of CMP-001 + intravenous (IV) pembrolizumab (pembro) reversed PD-1 blockade resistance, induced responses in injected and noninjected lesions, and had an acceptable safety profile (Milhem et al, SITC 2020). This combination is therefore being tested in pts with HNSCC. **Methods:** CMP-001-007 (NCT04633278) is an open-label, multicenter, ph 2 study designed to investigate the efficacy and safety of CMP-001 + IV pembro in adult pts with histologically or cytologically confirmed R/M HNSCC considered incurable by local therapies. Eligible pts have undergone a pretreatment tumor biopsy, received no prior systemic therapy in the R/M setting, and have primary tumor locations of oropharynx, oral cavity, hypopharynx, or larynx. In addition, pts must have PD-L1-positive tumors (combined positive score $\geq$1), known tumor human papillomavirus (HPV) status (for oropharyngeal cancer), and measurable disease per RECIST v1.1 with $\geq$1 lesion amenable to IT injection. Pts with primary tumors in the nasopharynx are excluded. Enrolled pts will receive CMP-001 10 mg once weekly for 7 doses and every 3 weeks (Q3W) thereafter. The first dose may be administered subcutaneously or via IT injection, with all subsequent doses administered IT. All pts will also receive pembro 200 mg IV Q3W after the CMP-001 injection. Treatment continues until unacceptable toxicity or disease progression. The primary endpoint is investigator-assessed objective response rate (ORR) per RECIST v1.1. Secondary endpoints include safety, duration of response (DOR), progression-free survival (PFS), overall survival, and effects of HPV infection and PD-L1 expression on ORR, DOR, and PFS. Exploratory endpoints include analyses of baseline and changes from baseline in tumor or serum biomarkers related to TLR9, immune checkpoints, and potential predictors of response, as well as serum concentrations of CXCL10 and CMP-001. Refer to clinicaltrials.gov/ct2/show/NCT04633278 for the most current information on enrolling sites. Clinical trial information: NCT04633278. Research Sponsor: Checkmate Pharmaceuticals.

TPS6090 **Poster Session**

The BURAN study of buparlisib (AN2025) in combination with paclitaxel compared to paclitaxel alone, in patients with recurrent or metastatic head and neck squamous cell carcinoma. *First Author: Denis Soulieres, Centre Hospitalier de l'Université de Montréal, Montréal, QC, Canada*

Background: Buparlisib (AN2025) is a 2,6-dimorpholino pyrimidine derivative oral pan-class I PI3K inhibitor. The PI3K signaling pathway is one of the most frequently altered pathways in HNSCC. A previous randomized, double-blind, placebo-controlled phase II study (BERIL-1)assessed patients with recurrent/metastatic HNSCC after PD on or after platinum-based chemotherapy in the metastatic setting. Patients assigned 1:1 to receive second-line oral buparlisib or placebo, plus intravenous weekly paclitaxel in 28-day cycles. Median PFS 4.6 months buparlisib arm, 3.5 months placebo arm (hazard ratio 0.65 [95% CI: 0.45–0.95], nominal one-sided p=0.011). Median OS 10.4 months buparlisib arm, 6.5 months placebo arm (hazard ratio 0.72 [95% CI: 0.49-1.04], nominal one-sided p=0.041). Best ORR buparlisib arm 39%, placebo arm 14%. Safety in buparlisib arm was manageable and comparable to placebo arm. (Soulieres, Lancet Oncology). Results suggest that buparlisib in combination with paclitaxel could be effective treatment following failure of platinum-based chemotherapy. **Methods:** The treatment algorithm for HNSCC was recently modified with inclusion of anti-PD-1/PD-L1 agents that provide a survival advantage, defining an unmet need after their use. The BURAN study is initiated as a confirmatory study to define activity in this setting. Methods: A multicenter, randomized, open-label phase III trial evaluating efficacy and safety of daily buparlisib (100 mg) in combination with weekly paclitaxel (80 mg/m^2), compared to weekly paclitaxel alone, in patients with refractory, recurrent, or metastatic HNSCC, progressing after prior anti PD-1/anti PDL-1 therapy either as monotherapy or with a platinum-based regimen (in combination or sequence), and no more than two prior lines of treatment. 483 patients will be randomized 2:1, to receive either buparlisib in combination with paclitaxel or paclitaxel alone, stratified according to historical HPV status. Primary Objective: OS of buparlisib in combination with paclitaxel compared to paclitaxel alone. Secondary Objectives: Comparative PFS, ORR, and DoR, by Investigator and Independent Radiological Review Committee. Efficacy in subgroups of patients by randomization strata. Effect on symptoms and health related QOL. Efficacy related to biomarkers, microbiome analysis. Pharmacokinetics (PK) of buparlisib in combination with paclitaxel. Safety Objective: Comparative safety and tolerability. Primary analysis is OS in the ITT population, once 383 events have occurred, to demonstrate a 20% reduction in risk of death. Survival follow-up is to a maximum of five years. Trial opened December 12, 2020; X patients currently enrolled. Clinical Trial registry number: NCT04338399. Clinical trial information: NCT04338399. Research Sponsor: Adlai Nortye USA Inc.

TPS6091 **Poster Session**

TrilynX: A phase 3 trial of xevinapant and concurrent chemoradiation for locally advanced head and neck cancer. *First Author: Jean Bourhis, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland*

Background: Concurrent chemoradiotherapy (CRT) is the standard of care for previously untreated patients with locoregionally advanced squamous cell carcinomas of the head and neck (LA-SCCHN). Xevinapant (Debio 1143) is an orally available antagonist of inhibitor of apoptosis proteins with the potential to enhance the antitumor activity of platinum-based chemotherapy and radiotherapy. The radiosensitizing effect of xevinapant is mediated through caspase activation and TNF, IFNγ, CD8 T cell-dependent pathways. Three-year follow-up results from a randomized Phase 2 study showed significant improvements of xevinapant versus placebo in addition to standard chemoradiation (CRT) for locoregional control (LRC) rate at 18 months, PFS and OS. The addition of xevinapant was well tolerated, manageable and did not jeopardize backbone therapy [1, 2]. **Methods:** TrilynX is a multinational, Phase 3, double-blind, placebo-controlled, randomized clinical study assessing the efficacy of xevinapant in combination with concurrent CRT compared with placebo in combination with CRT for LA-HNSCC. Adult patients with newly diagnosed, pathologically proven, treatment-naive LA-SCCHN will be enrolled. Study population will include hypopharynx, larynx and p16-negative oropharyngeal. Other eligibility criteria: ECOG PS 0 or 1, AST and ALT $\leq$ 3.0 x ULN, total bilirubin $\leq$ 1.5 $\times$ ULN, and eligible for definitive CRT. Approximately 700 eligible patients will be randomly assigned to receive oral xevinapant at 200 mg per day on days 1 to 14 of 3-week cycles or placebo for three cycles in combination with cisplatin (100 mg/m^2, q3w) for three cycles, and concomitant standard fractionation intensity-modulated radiotherapy (70 Gy/7 weeks). The concurrent CRT period will be followed by a monotherapy period consisting of further three cycles of xevinapant or placebo. The primary endpoint is Event Free Survival (EFS) assessed by a Blinded Independent Radiological Committee (BIRC). An interim analysis will occur when 279 EFS events as assessed by the BIRC are observed. The primary analysis will occur once 429 EFS events are observed. TrilynX has ~90% power to detect the expected hazard ratio benefit of 0.73. Secondary end-points include OS, PFS, LRC, ORR, HRQL, and safety. Data driven design, patients will be followed up for a minimum of 60-months. PK sparse sampling is performed to assess exposure-response relationships with efficacy and safety. Biomarkers of response and resistance will be explored. TrilynX started in August 2020 and it is ongoing. References: [1] X. Sun et. al, Lancet Oncol; 21(9): 1173-1187, 2020. [2] J. Bourhis et al., Ann Oncol; 31 (suppl 4): LBA39, 2020. Clinical trial information: NCT04459715. Research Sponsor: Debiopharm Internation SA.

TPS6092 **Poster Session**

First-in-human phase I/II trial of PRGN-2009 vaccine as monotherapy or with bintrafusp alfa in patients with recurrent/metastatic (R/M) human papillomavirus (HPV)-associated cancers (HPVC) and as neoadjuvant/induction therapy in locoregionally advanced (LA) HPV oropharyngeal (OP) and sinonasal (SN) squamous cell cancer (SCC). *First Author: Charalampos S. Floudas, Genitourinary Malignancies Branch, NCI, NIH, Bethesda, MD*

Background: R/M HPVC (cervical, anal, oropharyngeal, etc.) are incurable by current therapies. For newly diagnosed LA HPV-OPSCC standard-of-care (SOC) is radiotherapy ± chemotherapy (C/RT) or surgery ± adjuvant C/RT, with considerable risk of relapse. Newly diagnosed LA SNSCC treatment follows the OPSCC paradigm, and detection of HPV appears to confer improved prognosis. Neoadjuvant PD-1 immune checkpoint blockade (ICB) before surgery may improve RFS and is being evaluated in a multicenter phase III clinical trial (Keynote-689). PRGN-2009 (P) is a novel gorilla adenovirus vaccine containing 35 non-HLA-restricted epitopes of HPV 16 and 18 shown to induce HPV specific responses (preclinical models). Bintrafusp alfa (BA) is a bifunctional fusion protein targeting TGF-β and PD-L1 with promising activity in HPVC. This trial will evaluate the safety and activity of P/ P + BA in patients with previously treated R/M HPVC and as neoadjuvant/induction therapy before SOC surgery or C/RT in newly diagnosed LA HPV-OPSCC and HPV-SNSCC. **Methods:** This is a first-in-human, investigator-initiated, single-center phase I/II trial. Pts with previously treated (incl. ICB) R/M HPVC are eligible for Phase I: P dose escalation arm (3+3 design, 6-12 patients) testing 2 dose levels ($1x10^{11}$, $5x10^{11}$ viral particle units, SC Q2W three times, then Q4W), and combination arm (10 patients) testing P (recommended phase 2 dose (RP2D), same schedule) + BA (1200 mg IV Q2W). Treatment (both arms) will continue until disease progression, unacceptable toxicity, decision to withdraw. Primary endpoint is safety. Secondary endpoints include ORR (RECIST 1.1), PFS, and OS. For Phase II, patients with newly diagnosed stage II/III (AJCC Cancer Staging Manual, 8th ed.) HPV-OPSCC and stage II/III/IVA/IVB HPV-SNSCC planned for SOC C/RT or surgery will be eligible for two treatment arms of 20+2 patients each (sequential): P arm and P + BA, to evaluate the treatment activity. All patients will have pre-treatment biopsy, receive two cycles of the study treatment at the NCI Clinical Center two weeks apart, followed by post-treatment biopsy and SOC treatment (at the referring institution) 4 weeks after the first study treatment. Primary endpoint is post-treatment $\geq$2-fold increase in tumor-infiltrating CD3+ cells. Secondary endpoints include RFS, OS. Exploratory endpoints for both arms include analyses of immune subsets, soluble factors, and HPV-specific immune responses in peripheral blood and tissue where available, and in Phase II sequencing (exome, scRNA), immune spatial profiling with multiplex immunofluorescence, and salivary HPV DNA. Clinical trial registry: NCT04432597. Clinical trial information: NCT04432597. Research Sponsor: U.S. National Institutes of Health.

TPS6093 **Poster Session**

NRG Oncology HN006: Randomized phase II/III trial of sentinel lymph node biopsy versus elective neck dissection for early-stage oral cavity cancer. *First Author: Stephen Yenzen Lai, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Since patients with early-stage oral cavity cancer (OCC; T1-2N0M0; AJCC 8^{th} ed) have a 20-30% rate of occult nodal metastases despite clinical and radiographic assessment, standard of care treatment includes elective neck dissection (END). Many patients have comprehensive surgical management of the regional cervical nodal basin even though the majority of those necks (70-80%) will not contain disease. Assessment of draining first echelon lymph nodes by sentinel lymph node (SLN) biopsy (Bx), a less invasive surgical procedure, may provide an alternative to END, while potentially reducing morbidity and cost. A decisive clinical trial comparing SLN Bx versus END can focus the HNC clinical and research community and resources on establishing the standard of care for management of the neck in early-stage OCC. **Methods:** In order to address the efficacy of SLN Bx in this population, we recently activated an international multi-institutional phase II/III prospective trial randomizing patients to two surgical arms: SLN Bx and END. PET/CT is an integral imaging biomarker in this trial. A node-negative PET/CT study with central read is required before randomization. Patients with a positive PET/CT central result will remain in a registry to compare imaging findings with final neck pathology. Given the current evidence available regarding morbidity for SLN Bx versus END, the phase II will determine if patient-reported neck and shoulder function and related QOL at 6 months after surgery using the Neck Dissection Impairment Index (NDII) shows a signal of superiority of SLN Bx compared to END. A total of 228 randomized patients with negative PET/CT for potential evaluation of shoulder-related morbidity with difference in 6-month NDII scores (minimum important difference ^{3}7.5; one-sided a = 0.10; 90% power) will serve as the "Go/No-Go" decision to move forward into phase III. The phase III portion is a non-inferiority (NI) trial with disease-free survival (DFS) as the primary endpoint (NI margin hazard ratio 1.34 based on a 5% absolute difference in 2-year DFS; one-sided alpha 0.05; 80% power, and an interim look for efficacy at 67% of the events based on an O'Brien-Fleming boundary). The NDII at 6 months after surgery is a hierarchical co-primary endpoint for the phase III. Target accrual of phase III is 618 PET/CT negative patients, including those randomized in phase II (297 DFS events required for the final analysis). In addition to radiotherapy and imaging credentialing, quality assurance will include central pathology review of all negative SLN Bx cases and surgeon credentialing through an education course and SLN Bx and END case review by the surgical co-chairs. A surgical quality assurance working group will review all trial SLN Bx and END outcomes. As of 02/15/21, 7 patients have been screened and 6 of the planned 228 randomized patients in phase II have been enrolled. Clinical trial information: NCT04333537. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS6094 **Poster Session**

Trial in progress: A phase I/II trial of novel MDM2 inhibitor alrizomadlin (APG-115), with or without platinum chemotherapy, in patients with p53 wild-type salivary gland carcinoma. *First Author: Paul Swiecicki, University of Michigan Medical School, Department of Internal Medicine, Division of Hematology/Oncology, Ann Arbor, MI*

Background: Salivary gland carcinoma is a rare tumor that accounts for 6% of all head and neck cancers. This histologically and anatomically heterogeneous malignant tumor type is largely resistant to platinum and other chemotherapies but commonly has wild-type *TP53* based on next-generation sequencing analysis. Alrizomadlin is a novel, orally active, small molecular agent that binds to MDM2, restoring p53 tumor suppressor function and inducing apoptosis in tumor cells retaining wild-type p53. Preliminary clinical evidence suggests promising antitumor activity and a favorable safety profile for alrizomadlin in the treatment of solid tumors (Rasco 2019). **Methods:** This US multicenter open-label trial is evaluating alrizomadlin with or without platinum chemotherapy in adults with histologically documented wild-type *TP53* salivary gland carcinoma, including primary or metastatic lesions, an ECOG performance status 0-1, and a life expectancy of at least 12 weeks. In addition, subjects need to have measurable disease by computed tomography according to RECIST v1.1, with radiographic disease progression within the prior 12 months, high-grade status with or without metastases, and/or not amenable to curative treatment. An initial randomized phase (Part 1) will be followed by a single-arm phase (Part 2). Treatment arms include a cycle length of 21 days, and the study is using a time-to-event continual reassessment method. In Part 1 (42 patient target), patients are randomly allocated (in a 1:2 ratio) to one of two arms: single-agent alrizomadlin at a starting dose of 150 mg (Arm A) or at a starting dose of 150 mg with concomitant IV carboplatin administered at starting AUC = 4.5 (Arm B). Based on overall response rate (ORR; complete or partial response after Cycle 2) and safety profile, the most promising treatment arm will be advanced to Part 2, which has a target enrollment of 20 patients. Study endpoints are (1) dose-limiting toxicity (DLT), which is defined by the rate of drug-related grade $\geq$ 3 adverse events (by NCI CTCAE v5.0) over the first 2 cycles (6 weeks) of study treatment; (2) maximum tolerated dose based on these DLTs; and (3) ORR by RECIST v1.1 observed at up to 12 months. As of January 27, 2021, 11 of 42 patients had been enrolled in Part 1. Internal study identifier APG-115SG101. Clinical trial registration: NCT03781986. Clinical trial information: NCT03781986. Research Sponsor: Ascentage Pharma Group Corp Limited (Hong Kong); University of Michigan NCI Cancer Center Support Grant (P30CA046592), Ann Arbor, MI.

6500 **Oral Abstract Session**

Racial and ethnic disparities among patients with breast cancer and COVID-19. *First Author: Gayathri Nagaraj, Loma Linda University Medical Center, Loma Linda, CA*

Background: Racial/ethnic minorities have disproportionately increased risk of contracting COVID-19 and experiencing severe illness; they also have worse breast cancer (BC) outcomes. COVID-19 outcomes among racial/ethnic minorities with BC are currently unknown. We sought to compare clinicopathologic characteristics and COVID-19 outcomes stratified by race/ethnicity. **Methods:** The COVID-19 and Cancer Consortium registry (NCT04354701) was used to identify patients with invasive BC and laboratory-confirmed SARS-CoV-2 diagnosed in the U.S. between 2020-03-06 and 2021-02-04. The primary analysis was restricted to women who self-identified as non-Hispanic White (NHW), non-Hispanic Black (NHB), or Hispanic (H). Demographic, cancer characteristics, and COVID-19 outcomes were evaluated. COVID-19 outcomes included: hospital admission, intensive care unit (ICU) admission, mechanical ventilation, death within 30 days of COVID-19 diagnosis and death from any cause during follow-up. Descriptive statistics were used to compare clinicopathologic characteristics and Fisher exact tests were used to compare COVID-19 outcomes across the 3 racial/ethnic groups. **Results:** A total of 1133 patients were identified of which 1111 (98%) were women; of which 575 (52%) NHW, 243 (22%) NHB, 183 (16%) H, and 110 (10%) other/unknown. Baseline characteristics differed among racial/ethnic groups. H were younger (median age: NHW 63y; NHB 62y; H 54y) and more likely to be never smokers (NHW 62%; NHB 62%; H 78%). NHB had higher rates of obesity (NHW 40%; NHB 54%; H 46%), diabetes (NHW 16 %; NHB 32%; H 20%) and combined moderate and severe baseline COVID-19 at presentation (NHW 28%; NHB 42%; H 28%). Cancer characteristics are as shown (Table). Significant differences were observed in outcomes across racial/ethnic groups including higher rates of hospital admission (NHW 34%; NHB 49%; H 34%; P <0.001), mechanical ventilation (NHW 3%; NHB 9%; H 5%; P=0.002), 30-day mortality (NHW 6%; NHB 9%; H 4%; P=0.043) and total mortality (NHW 8%; NHB 12%; H 5%; P=0.05) among NHB compared to NHW and H. **Conclusions:** This is the largest study to show significant differences in COVID-19 outcomes by racial/ethnic groups of women with BC. The adverse outcomes in NHB could be due to higher moderate to severe COVID-19 at presentation and preexisting co-morbidities. H did not have worse outcomes despite having more active disease and recent anti-cancer therapy, including with cytotoxic chemotherapy – potentially due to younger age and nonsmoking status. Research Sponsor: U.S. National Institutes of Health.

Total	NHW n = 575	NHB n = 243	H n = 183
ER+	321 (56%)	118 (49%)	78 (43%)
HER2+	114 (20%)	51 (21%)	**54 (30%)**
Triple negative	42 (7%)	**40 (16%)**	**28 (15%)**
Active cancer	144 (25%)	74 (31%)	**88 (48%)**
Anti-cancer treatment within 0-4 weeks	284 (49%)	119 (49%)	**121 (66%)**
Cytotoxic chemotherapy	92 (16%)	56 (23%)	**68 (37%)**
Targeted Therapy	67 (12%)	29 (12%)	38 (21%)
Endocrine Therapy	202 (35%)	71 (29%)	56 (31%)

6501 **Oral Abstract Session**

The impact of the COVID-19 pandemic on stage at diagnosis of breast and colorectal cancers. *First Author: Jade Zhou, UC San Diego Health, San Diego, CA*

Background: Effective cancer screening leads to a substantial increase in the detection of earlier stages of cancer, while decreasing the incidence of later stage cancer diagnoses. Timely screening programs are critical in reducing cancer-related mortality in both breast and colorectal cancer by detecting tumors at an early, curable stage. The COVID-19 pandemic resulted in the postponement or cancellation of many screening procedures, due to both patient fears of exposures within the healthcare system as well as the cancellation of some elective procedures. We sought to identify how the COVID-19 pandemic has impacted the incidence of early and late stage breast and colorectal cancer diagnoses at our institution. **Methods:** We examined staging for all patients presenting to UCSD at first presentation for a new diagnosis of malignancy or second opinion in 2019 and 2020. Treating clinicians determined the stage at presentation for all patients using an AJCC staging module (8^{th} edition) in the electronic medical record (Epic). We compared stage distribution at presentation in 2019 vs 2020, both for cancers overall and for colorectal and breast cancer, because these cancers are frequently detected by screening. **Results:** Total numbers of new patient visits for malignancy were similar in 2019 and 2020 (1894 vs 1915 pts), and stage distribution for all cancer patients was similar (stage I 32% in 2019 vs 29% in 2020; stage IV 26% in both 2019 and 2020). For patients with breast cancer, we saw a lower number of patients presenting with stage I disease (64% in 2019 vs 51% in 2020) and a higher number presenting with stage IV (2% vs 6%). Similar findings were seen in colorectal cancer (stage I: 22% vs 16%; stage IV: 6% vs 18%). **Conclusions:** Since the COVID-19 pandemic, there has been an increase in incidence of late stage presentation of colorectal and breast cancer, corresponding with a decrease in early stage presentation of these cancers at our institution. Cancer screening is integral to cancer prevention and control, specifically in colorectal and breast cancers which are often detected by screening, and the disruption of screening services has had a significant impact on our patients. We plan to continue following these numbers closely, and will present data from the first half of 2021 as it becomes available. Research Sponsor: None.

6502 **Oral Abstract Session**

Medicaid patients more likely to die at home without hospice during the pandemic versus before, exacerbating disparities with commercially insured patients. *First Author: Laura Elizabeth Panattoni, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The COVID-19 pandemic dramatically reduced family access to hospitals and created new barriers to home hospice care, raising concerns about how the pandemic has impacted cancer patients' place of death and end of life home hospice support. Hypothesizing that Medicaid-enrolled cancer patients may be at greater risk of disruptions in end-of-life care compared to commercially insured patients, we examined changes in place of death and home hospice support for Medicaid and Commercial enrollees following the pandemic. **Methods:** We linked WA State cancer registry records with claims from Medicaid and approximately 75% of commercially insured cancer patients in the state. Patients ages 18-64 with solid-tumor malignancies who died March-June 2020 (COVID) were compared to those who died March-June 2017-2019 (Pre-COVID). Place of death was categorized as hospital, home with hospice, and home without hospice; nursing home deaths were excluded. Given our sample size, we examined differences in the likelihood of place of death with Fisher's exact tests and multinomial logistic regressions stratified by payer and by COVID period, controlling for age, gender, race, stage, cancer type, and census tract-level neighborhood deprivation. We report marginal effects. **Results:** In Fisher's exact analyses, Medicaid but not commercial patients were significantly less like to die in hospital and more likely to die at home without hospice during COVID (Table). In pre-post adjusted analysis of Medicaid patients, the probability of dying in the hospital was 12.3% (p=0.03) percentage points lower during the pandemic versus before, while the probability of dying at home without hospice was 11.1% (p=0.04) greater. Place of death did not change significantly pre-post for commercial patients. In addition, Pre-COVID, the probability of dying in the hospital was 10.7% (p=0.03) greater for Medicaid than commercial patients. During COVID, the probability of dying at home without hospice was 15.8% (p=0.04) greater for Medicaid versus commercial patients but lower for women (ME=20.2%; p=0.01) and colorectal versus breast cancer patients (ME=39.2%; p=0.01). **Conclusions:** Following COVID, Medicaid patients place of death shifted from hospital to homes, but without an increase in the use of home hospice services. In contrast, place of death and hospice use among commercial patients did not significantly change. This widening disparity in home deaths without hospice services raises concerns that the pandemic disproportionately worsened end of life experience for low income patients with cancer. Research Sponsor: Fred Hutchinson Cancer Research Center.

	Commercial			Medicaid		
Place of Death	Pre-COVID (N=162)	COVID (N=47)	p-value*	Pre-COVID (N=322)	COVID (N=90)	p-value*
Hospital	36.2%	29.8%		46.5%	35.2%	
Home Hospice	41.7%	51.1%	0.56	31.4%	31.9%	0.03
Home without Hospice	21.5%	19.1%		19.3%	31.9%	

*Fisher's exact.

6503 **Oral Abstract Session**

Association between perceptions of prognosis and end-of-life outcomes for patients with advanced lung and gastrointestinal cancer. *First Author: Carlisle E. W. Topping, Massachusetts General Hospital, Boston, MA*

Background: Many patients with advanced cancer maintain misperceptions of their prognosis and are thus unprepared to make difficult decisions regarding their end-of-life (EOL) care. However, studies examining the associations between patients' perceptions of their prognosis and their EOL outcomes are limited. **Methods:** We conducted a secondary analysis using longitudinal data from a randomized controlled trial of a palliative care intervention for patients with newly diagnosed incurable lung and non-colorectal gastrointestinal cancer. We administered the Prognosis and Treatment Perceptions Questionnaire to assess patients' perceptions of their prognosis at baseline, week-12, and week-24, using the final assessment closest to death. We used multivariate logistic and linear regression models, adjusting for age, gender, marital status, cancer type, and randomization to the palliative care intervention, to examine the associations among patients' perceptions of their prognosis with the following EOL care outcomes abstracted from the electronic health record: 1) hospice utilization and length-of-stay (LOS); 2) hospitalizations in the last 30 days of life; 3) receipt of chemotherapy in the last 30 days of life; and 4) location of death. **Results:** We enrolled 350 patients in the parent trial, of which 80.5% (281/350) died during the study period and were included in this analysis. Overall, 59.4% (164/276) of patients reported that they were terminally ill, and 66.1% (154/233) reported that their cancer was likely curable at the assessment closest to death. In multivariate analyses, patients who reported that their cancer was likely curable were less likely to utilize hospice (OR = 0.25, 95%CI 0.10-0.61, P = 0.002) or die at home (OR = 0.56, 95%CI 0.32-0.98, P = 0.043), and more likely to be hospitalized in the last 30 days of life (OR = 2.28, 95%CI 1.20-4.32, P = 0.011). In contrast, patients' report that they were terminally ill was only associated with lower likelihood of hospitalizations in the last 30 days of life (OR = 0.52, 95%CI 0.29-0.92, P = 0.025). Patients' perceptions of their prognosis were not associated with hospice LOS or chemotherapy administration in the last 30 days of life. **Conclusions:** Patients' perceptions of their prognosis are associated with important EOL outcomes including hospice utilization, hospitalizations at the EOL, and death at home. Interventions are needed to enhance patients' perceptions of their prognosis in order to optimize their EOL care. Research Sponsor: Leukemia & Lymphoma Society, U.S. National Institutes of Health.

6504 **Oral Abstract Session**

Cancer diagnosis and adverse financial events: Evidence from credit reports. *First Author: Veena Shankaran, Hutchinson Institute for Cancer Outcomes Research (HICOR), Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Increasing evidence shows that cancer patients (pts) experience financial hardships after diagnosis. Few studies, however, have used objective financial data to estimate the relative risk of adverse financial events (AFEs) in cancer pts versus individuals without cancer. Using a retrospective case-control design, we investigated whether cancer pts are at increased risk of new AFEs, as measured by their credit reports. **Methods:** Western Washington Surveillance Epidemiology and End Results (SEER) cancer registry (cases) and voter registry (controls) records from 2013 to 2018 were linked to quarterly credit records from TransUnion (2012-2020), one of the 3 largest national credit agencies. Controls were age and sex matched to cases and assigned an index date corresponding to the diagnosis (dx) date of the matched case. Individuals with evidence of any AFE in the credit report closest to index/dx date or did not survive to 24 months were excluded. Cases and controls experiencing any of the following AFEs within 24 months were compared, using two-sample z tests: severe (3rd party collections, charge-offs), more severe (tax liens, delinquent mortgage payments), and most severe (foreclosures, repossessions). Multivariate logistic regression models were used to evaluate the association between cancer dx and AFE, adjusting for age, sex, dx year, and available credit 6 months before the index/dx date. **Results:** A total of 332,825 individuals (84,185 cases and 248,640 controls, mean age 66 (SD 13), 52.7% female) were included. The mean available line of credit in the year before index/dx date was $12,303. AFEs were more common in cases versus controls (Table). After adjusting for age, sex, available credit above or below $12,303, and dx year, cancer dx was significantly associated with any AFE (OR 1.77, 95% CI 1.7-1.85, p<0.0001), severe AFEs (OR 1.94, 95% CI 1.85-2.03, p<0.0001), more severe AFEs (OR 1.23, 95% CI 1.12-1.36, p<0.0001), and most severe AFEs (OR 1.46, 95% CI 1.16-1.86, p=0.0016). Age >65 and higher available baseline credit were associated with decreased risk of any and each category of AFE. **Conclusions**: Within 24 months from dx, significantly higher proportions of cancer pts experienced AFEs relative to controls. Such events on credit reports have serious and long-lasting consequences on financial status. Studies that link clinical and financial data to investigate the impacts of these events on treatment decisions, quality of life, and clinical outcomes are needed. Research Sponsor: Justin Butler Foundation; Texas4000 Foundation.

Adverse financial events.

Outcome	Cancer (N=84,185)	Control (N=248,640)	P-value
Any	4.7%	2.5%	<0.001
Severe	4.1%	2.0%	<0.001
3rd party collections	3.2%	1.3%	<0.001
Charge-offs	1.48%	0.96%	<0.001
More severe	0.72%	0.55%	<0.001
Tax liens	0.06%	0.05%	0.22
Delinquent mortgage payments	0.99%	0.75%	0.035
Most severe	0.13%	0.09%	0.002
Repossessions	0.10%	0.06%	0.0001
Foreclosures	0.03%	0.02%	0.45

6505 **Oral Abstract Session**

Temporal trends in oncology drug revenue among the world's major pharmaceutical companies: A 2010-2019 cohort study. *First Author: Daniel E. Meyers, University of Calgary, Calgary, AB, Canada*

Background: In the past decade there has been a 70% increase in the number of clinical trials for cancer drugs. During this time, there has also been a substantial increase in the price of cancer drugs. It is unclear how these trends have changed the revenue landscape of major pharmaceutical companies. In this study we characterize temporal trends in cancer drug revenue relative to non-cancer drugs. **Methods:** This retrospective cohort study used publicly available global sales data from the 10 pharmaceutical companies with the highest annual revenue in 2019; Abbvie (AB), AstraZeneca (AZ), Bristol Myers Squibb (BMS), GlaxoSmithKline (GSK), Johnson & Johnson (JJ), Merck (M), Novartis (N), Pfizer (P), Roche (R) and Sanofi (S). We quantified the contribution of cancer drugs to net revenue for each company from 2010 – 2019 using consolidated annual financial reports (i.e. 10-K or 20-F forms). Cancer drugs were defined as those with an FDA-approved indication for anti-cancer effect or supportive care. All sales data were converted to USD and adjusted for global inflation. Trends in the percentage of company revenues accounted for by cancer drugs were assessed with the Kendall-Mann test. P-values were adjusted for multiple hypothesis testing using the Benjamini-Hochberg method. **Results:** During 2010-2019, cumulative annual revenue generated from cancer drugs in our cohort of companies (n = 10) increased by 96%, from $52.8 billion to $103.5 billion. The cumulative revenue from non-oncology drugs decreased by 19%, from $342.5 billion to $276.9 billion. The proportion of total revenue generated from cancer drugs grew over time; from 13% in 2010 to 27% in 2019 (p < 0.001). During 2015-2019, annual revenue for the study cohort grew by 12%: from $339.7 billion to $380.4 billion. During this period non-oncology revenues remained stagnant (mean $278.9 billion, range 276.9 – 281.9), while oncology revenues grew by 66%; from $61.4 billion to $103.5 billion. Six companies (AB, AZ, BMS, JJ, N, and P) saw substantial increases in the proportion of revenue attributable to cancer drugs. R had both the highest net revenue ($23.9 billion), and highest proportion of revenue (57%) from cancer drugs in 2010 among the cohort, similar to 2019 ($27.7 billion, 57%; p = 0.37). While not reaching significance over the total study period, M saw increases in oncology revenue from $1.5 billion in 2015 to $12.3 billion in 2019 (4% to 30% of total revenue); driven almost exclusively by sales of Pembrolizumab. **Conclusions:** Amongst the world's largest pharmaceutical companies, sales revenue from cancer drugs have increased by 96% over the past decade, while revenues from non-cancer drugs have decreased by 19%. Revenues from cancer drugs accounted for 27% of company revenues in 2019. Further work is needed to understand if this massive increase in sales revenues has translated into proportional improvements in patient and population outcomes. Research Sponsor: None.

6506 **Oral Abstract Session**

The association of sexual orientation with cancer screening and diagnosis. *First Author: Michael Joseph Herriges, SUNY Upstate Medical University, Syracuse, NY*

Background: Data on heterogeneity in cancer screening and diagnosis rates among sexual minorities (SMs) is lacking. Recent studies have shown SMs are more likely to engage in risky health behavior and have decreased healthcare utilization compared to heterosexual counterparts. However, few studies have examined how sexual orientation (SO) impacts cancer screening and prevalence. We therefore investigated whether SO affects prevalent gender-specific cancer screening and prevalence, including prostate (PCa), breast (BC), and cervical cancer (CC). **Methods:** This was a cross-sectional survey-based US study, including men and women aged 18+ from the Health Information National Trends Survey (HINTS) database (part of the National Cancer Institute's division of cancer control and population sciences) between 2017-2019. The primary endpoint was individual-reported PCa, BC, and CC screening and prevalence rates among heterosexual and SM men and women. Multivariable logistic regression analyses assessed association of various covariates with undergoing screening and diagnosis of these cancers. **Results:** Overall, 4,441 (95.18%) men and 6,333 (96.75%) women reported a SO of heterosexual whereas 167 (3.6%) and 58 (1.2%) men and 105 (1.6%) and 108 (1.6%) women reported a SO of gay and bisexual, respectively. Mean age was higher in the heterosexual group compared to the gay and bisexual groups in both men (57.7 [±16.0] vs. 52.4 [±14.5] and 51.9 [±18.0] years, p = < 0.001) and women (56.2 [±16.7] vs. 49.0 [±17.1] and 40.0 [±14.8] years, p = < 0.001). Homosexuals and bisexuals were less likely to be screened for PCa (30.53% and 27.58% vs 41.27%, p = < 0.001), BC (63.81% and 45.37% vs 80.74%, p = < 0.001), and CC (90.48% and 86.11% vs 95.36%, p = < 0.001) than their heterosexual counterparts. While rates of PCa and BC diagnoses were similar across SO, more homosexual and bisexual women were diagnosed with CC compared to their heterosexual counterparts (4.76% and 3.70% vs 1.85%, p = 0.039). Multivariable logistic regression models showed that SMs were less likely to be screened for cancer with ORs of 0.61 (95% CI 0.39-0.95, p = 0.030) for PCa, 0.52 (95% CI 0.30-0.92, p = 0.025) for BC, and 0.21 (95% CI 0.09-0.46, p = < 0.001) for CC. Although multivariable models did not show that SMs were more likely to be diagnosed with PC, BC, or CC, SMs were more likely to be diagnosed with any cancer with ORs of 1.64 (95% CI 1.06-2.54, p = 0.026) in women only and 1.50 (95% CI 1.11-2.03, p = 0.009) in men and women combined. **Conclusions:** These data suggest that in addition to other established and known specific socio-economic risk factors, SMs may be less likely to undergo screening of prevalent malignancies such as PCa, BC, and CC. This provides more evidence of ongoing healthcare inequality, urging our healthcare system to invest more in cancer screening of this vulnerable population. Research Sponsor: None

6507 **Oral Abstract Session**

Mobile low-dose computerized tomography (LDCT): Three-year follow up of solution for early diagnosis of lung cancer in under-served populations. *First Author: Derek Raghavan, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Randomized trials have proven that screening high-risk patients with LDCT of chest reduces lung cancer mortality compared to screening with chest x-ray. Under-served patients lack access to this test due to geographic and socio-economic factors. We hypothesized that a mobile screening unit would improve access and increase survival in this group, which is most at risk of lung cancer deaths. **Methods:** We installed a BodyTom portable 32 slice low-dose CT scanner (Samsung Inc) into a 35 foot coach (Frazier Inc), reinforced to avoid equipment damage during road travel. It includes waiting area, high speed wireless internet connection for rapid image transfer, and electronic tablets to deliver smoking cessation and health education programs and shared decision-making video aids. We used LUNG RADS approach to lesion classification, yielding high sensitivity and specificity in assessment. All films were reviewed by a central panel. This is certified as a lung cancer screening Center of Excellence by the Lung Cancer Alliance. Protocol was approved by Advarra IRB. Medicare pts excluded as insurance covered them for LDCT, although this reduced potential number of cases diagnosed as this is highest risk population. **Results:** We screened 1200 uninsured or under-insured subjects, mean age 61 years (range 55-64), with average pack year history of 47.8 (30-150); 61% male; 18% Black, 3% Hispanic/Latino; 78% rural. We found 97 pts with LUNG RADS 4 lesions, 30 lung cancers (2.5%), including 15 at stage I-II treated with curative intent; 5 incidental non-lung cancers (renal CA 2, head & neck CA 1, pancreas CA 2); more than 50% with cardiovascular disease or COPD seen on LDCT. Of eligible first-screen subjects (J. Clin. Oncol., 2019, 37, 383S), 440 attended Year 1 repeat LDCT and 161 attended Year 2 LDCT. Only one pt with surgically resected CA lung has relapsed to date. **Conclusions:** Mobile LDCT yields higher screening rate for under-served pts than prior international studies, with strong protocol adherence and paucity of early cancer deaths in high-risk population with traditionally poor compliance. Research Sponsor: Bristol Myers Squibb Foundation; Leon Levine Foundation.

6508 **Oral Abstract Session**

Reducing racial disparities in time to breast cancer diagnosis: Impact of immediate screening mammogram reads during the COVID pandemic. *First Author: Janeiro Achibiri, Massachusetts General Hospital, Boston, MA*

Background: During the COVID-19 pandemic, barriers to access screening mammography along with goals to reduce visits supported immediate reading of screening mammograms. Typically, screening mammograms are reported after patients have left the facility. If imaging is abnormal, then an additional visit is needed for diagnostic imaging, introducing delays and potential disparities.Thus, we implemented an immediate-read screening mammography program and measured its impact on racial/ethnic disparities in time to diagnostic imaging after an abnormal screening mammogram. **Methods:** Responding to the COVID-19 pandemic, we implemented an immediate read screening program in late May 2020. Patients were provided imaging results before discharge and if the exam was abnormal, efforts were made to perform diagnostic imaging during that visit. We identified consecutive screening mammograms performed weekdays 8:00am-4:30pm and Saturdays 9:00am-4:00pm pre-implementation (6/1/19-10/31/19) and post-implementation (6/1/2020-10/31/2020). Exams left unread while awaiting comparison studies, due to technical factors, or for more than 10 days were excluded. Patient demographics and time from screening exam completion to report finalized were obtained from the electronic medical record. Cancer detection rate (CDR), abnormal interpretation rate (AIR), and positive predictive value (PPV) were calculated. Multivariable linear and logistic regression models were used to compare time from screening exam to report, same-day diagnostic imaging, and screening performance metrics pre- and post-implementation overall and by patient subgroups. **Results:** After 963 exams met exclusion criteria, a total of 8,222 pre- and 7,235 post-implementation exams were included. Median time to report finalization decreased from 61minutes (interquartile range [IQR]:24, 152) to 4 minutes (IQR:2, 7) for pre- and post-implementation periods ($p < 0.001$). During the pre-implementation period, non-white patients had lower odds of having same-day diagnostic imaging after an abnormal screening exam (age-adjusted odds ratio: 0.28; 95% CI: 0.10, 0.78 p = 0.015). There was no evidence of this disparity post-implementation. AIR was higher in the pre- versus post-implementation period (6.3% versus 5.0%; $p < 0.001$). There was no evidence of a difference in CDR (5.8 versus 4.2 cancers/1,000 exams) and PPV (9.2% versus 8.4%) for pre- versus post-implementation periods. **Conclusions:** An immediate read screening mammography program reduces racial/ethnic disparities in time to diagnostic imaging after an abnormal screening mammogram, thus promoting equity in access to care. Research Sponsor: None.

	Pre- implementation	Post- implementation
Age-adjusted OR of a Same-Day Diagnostic Exam, Non-White:White	0.28 (95% CI: 0.10, 0.78, p = 0.015)	0.87 (95% CI: 0.48, 1.56, p = 0.637)

6509 **Poster Discussion Session**

Mortality risk for patients undergoing cancer treatment who acquire SARS-CoV-2: ASCO registry. *First Author: Kathryn Finch Mileham, Levine Cancer Institute/Atrium Health, Charlotte, NC*

Background: The ASCO Registry was created to analyze the impact of COVID-19 (COVID) on treatment (Tx) and outcomes of patients (pts) with cancer. **Methods:** The Registry includes pts with 1) a confirmed COVID diagnosis (Dx) and 2) clinically evident cancer receiving Tx/supportive care or resected cancer on adjuvant Tx <12 mos since surgery. Practices report data on cancer Dx and Tx at COVID Dx, COVID symptoms, comorbidities, cancer/COVID Tx, and survival. Kaplan-Meier estimation provided 30- and 90-day mortality rate estimates for pts with COVID Dx before or since 6/1/20 within pt subgroups with 95% confidence intervals (CI). Data submission cutoff for all practices was 10/24/20, except one that was 11/16/20. **Results:** This analysis reports on 453 pts with COVID Dx 3/5/20 to 10/22/20 who were on anticancer drug Tx for regional (9%) or metastatic (53%) solid tumors or hematologic cancers (38%) at COVID Dx. 38 practices entered data: health system-owned 51% of pts, privately-owned 25%, academic 24%. 53% of pts have ≥30 days follow-up or died ≤30 days from COVID Dx. Median age is 64 years; 53% of pts are female; 28% of pts are asymptomatic at COVID Dx. Multiple myeloma was most frequent cancer (17%). All-cause mortality rates (30 and 90 days) increased with pts' age at COVID Dx [Table]. No mortality difference was seen based on sex, race, or comorbidities (hypertension, diabetes, pulmonary disease). Pts with COVID Dx before June 1 had worse survival than pts diagnosed on/after June 1. Pts with B-cell malignancies had higher mortality rates than pts with solid tumors. **Conclusions:** Severity of COVID illness and mortality were greater for patients with COVID Dx pre-June 1 than on/after June 1. Differences on/after June 1 may be attributed to improvements in COVID management, higher COVID testing rates, and more asymptomatic pts diagnosed. Variations in COVID-19 pt populations over time due to these changes should be considered when analyzing and interpreting pandemic data. Cancer pts with advanced age and B-cell cancers are at greatest risk of death but mortality rates for all groups (except those admitted to ICU) improved after 6/1/2020. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

		Pre-June 1 N	Post-June 1 N	Pre-June 1 30-day mortality (95% CI)	Post-June 1 30-day mortality (95% CI)	Pre-June 1 90-day mortality (95% CI)	Post-June 1 90-day mortality (95% CI)
Age	≤70 yrs	127	176	14% (8%, 20%)	5% (1%,10%)	20% (12%, 27%)	18% (2%, 32%)
	> 70 yrs	64	86	23% (12%, 33%)	14% (0%, 22%)	30% (7%, 42%)	19% (4%, 31%)
Race	Black	55	68	17% (6%, 26%)	7% (0%, 15%)	23% (11%, 34%)	14% (0%, 27%)
	White	111	164	19% (11%, 27%)	9% (3%, 15%)	26% (16%, 34%)	23% (0%, 42%)
Cancer Type	Metastatic solid tumor	103	137	14% (6%, 20%)	7% (1%, 13%)	21% (12%, 30%)	18% (2%, 31%)
	B-cell	61	83	28% (16%, 39%)	10% (2%, 18%)	34% (20%, 45%)	24% (1%, 41%)
Hospitalization	No	77	174	3% (0%,6%)	1% (0%, 4%)	5% (0%, 10%)	1% (0%, 4%)
	Yes but not in ICU	75	60	17% (8%, 25%)	5% (0%, 11%)	27% (16%, 38%)	18% (0%, 35%)
	ICU	32	24	53%(31%, 68%)	58% (25%, 77%)	61% (38%, 75%)	84% (22%, 97%)

6510 **Poster Discussion Session**

Real-world patient-reported and clinical outcomes of BNT162b2 mRNA COVID-19 vaccine in patients with cancer. *First Author: Ishwaria Mohan Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Most COVID-19 (C19) vaccine trials excluded patients with active cancer. Here, we report our real-world patient-reported and clinical outcomes of BNT162b2 mRNA C19 vaccine in patients with cancer. **Methods:** Our institutional Data-Driven Determinants for COVID-19 Oncology Discovery Effort (D3CODE) follows a longitudinal observational cohort of pts w cancer getting C19 vaccine. Pts complete a validated PRO tool, MD Anderson Symptom Inventory (MDASI, 13 core, 6 interference plus 17 items of symptoms from prior vaccine trials) pre-dose 1, then daily x 6d, then weekly, then on day of dose 2, then daily x 6d, then weekly x 3w. Demographics, cancer variables, prior immune checkpoint inhibitors (ICI), C19 status pre- & post-vaccine are aggregated via Syntropy platform: Palantir Foundry. Primary outcome is incidence of PRO symptoms bw dose 1 & 2 across AYA 15-39y, mid-age 40-64y & senior 65y+ cohorts. Secondary outcomes include PRO symptom incidence post-dose 2, post-vaccine change in cancer symptoms, post-vaccine symptom severity based on prior ICI, and confirmed C19 > 7 days post-dose 2. First planned 8-wk interim analysis is reported here. **Results:** 6388 pts w cancer (4973 w mets) received a BNT162b2 vaccine dose (4811 both doses, 1577 received one & await dose 2). Overall, median age 64y (range 16-95y); 382 AYAs, 2927 mid-age, 3079 seniors (65-70y n = 1158, 70-79y n = 1521, 80-89y n = 378, 90y+ n = 22). 4099 (64%) are White, 823 (13%) AA, 791 (12%) Hispanic, 441 (7%) Asians. Primary cancers: breast (1397), GU (821), heme (775), thoracic/HN (745), and CRC (385). Prior to dose 1, 1862 had no prior systemic tx while 4526 pts did including 3243 who had only non-IO tx (chemo, targeted tx), 1,283 had immunotherapy including 857 who had ICIs prior to dose 1. *Patient-reported symptoms after C19 Vaccine:* Of 6388 pts, 4714 (74% response rate, median age 67y, range 16-95y) completed 16485 PRO surveys. After 2 doses, seniors reported lower mean scores vs mid-age or AYAs on 22 of 36 symptoms including injection site pain, palpitations, itch, rash, malaise, fevers/chills, arthralgia, myalgia, headache, pain, fatigue, nausea, disturbed sleep, distress ($p < 0.05$). Pts w prior ICIs had higher severity of itch, rash ($p < 0.05$) from baseline after both dose 1 & 2 vs pts without systemic tx. Post dose 1, pts with prior ICI had higher increase in fatigue, malaise, itch, rash, myalgia, anorexia from their baseline vs pts without systemic tx ($p < 0.05$). *C19 Outcomes:* Of 6388 pts, 616 had a C19 test at any time post-dose 1: 23 (0.36%) tested positive of whom 20 (0.3%) were between dose 1 & 2; two (0.031%) were within 7 days post-dose 2, and one patient (0.016%) tested positive 16 days after dose 2, requiring admission. **Conclusions:** This real-world observational cohort demonstrates post-vaccine symptom burden and outcomes in patients with cancer. Second interim analysis is planned at 16 weeks. Research Sponsor: American Cancer Society, the Andrew Sabin Family Foundation, Gabrielle's Angels Foundation, Cancer and Aging Research Group (CARG) R21/R33 Infrastructure Grant, Gabrielle's Angel Foundation For Cancer Research, U.S. National Institutes of Health.

6511 **Poster Discussion Session**

Epidemiology and clinical course of SARS-CoV-2 infection in cancer patients in the Veneto Oncology Network during the first and second pandemic waves. *First Author: Valentina Guarneri, Department of Surgery, Oncology and Gastroenterology, University of Padua, and Division of Medical Oncology 2, Veneto Institute of Oncology IOV-IRCCS, Padua, Italy*

Background: Since the beginning of the COVID-19 outbreak, the Veneto Oncology Network ROV licensed dedicated guidelines for cancer patients care during the pandemic, and developed a regional registry (ROVID) aimed at describing epidemiology and clinical course of SARS-CoV-2 infection in cancer patients. Preliminary data on 170 patients mainly diagnosed during the first pandemic wave have been published (Guarneri V, Eur J Cancer 2021). Here we report the data of additional 270 patients, comparing clinical data and outcomes between first (W1) and second (W2) pandemic waves. **Methods:** All patients with cancer diagnosis and documented SARS-CoV-2 infection are eligible. Data on diagnosis, comorbidities, anticancer treatments, details on SARS-CoV-infection including source of contagion, clinical presentation, hospitalization, treatments and fate of the infection are recorded. **Results:** 440 patients have been enrolled, 196 diagnosed during W1 (until September 2020) and 244 during W2. The most common cancer type was breast cancer (n = 116). Significant differences in clinical characteristics between W1 and W2 were the followings: ECOG PS 0 (34% vs 58%), presence of cardiac comorbidities (30% vs 13%), presence of any co-morbidities (81% vs 62%), smoking habits (23% vs 13%). Patients diagnosed in W1 were less likely on active anticancer therapy (54% vs 73%) at the time of SARS-CoV-2 infection. Distribution per stage, presence of lung metastases, disease setting (curative vs palliative), active treatment discontinuation due to infection were similar between W1 and W2. Patients diagnosed in W1 were more likely symptomatic for SARS-CoV-2 infection (80% vs 67%), and reported more frequently an in-hospital contact as potential source of infection (44% vs 9%). Significantly more patients diagnosed in W1 were hospitalized (76% vs 25%). All-cause mortality rates were 30.6% for patients diagnosed in W1 vs 12% for patients diagnosed in W2 ($p < 0.001$). However, deaths due to SARS-CoV-2 infection were more frequent in patients diagnosed in W2 (86% vs 54%, odds ratio 3.22; 95% CI 1.97-5.279). **Conclusions**: Differences in clinical characteristics between W1 and W2 reflect different pattern of virus circulation. The dramatic reduction of in-hospital contact as a source of infection reflects the efforts put in place to protect this vulnerable population from in-hospital exposure. The lower all-cause mortality rate observed in W2 is in line with the observed less frail population. However, the higher relative risk of death due to SARS-CoV-2 infection observed in W2 reinforces the need to adopt protective measures including vaccination in cancer patients, irrespectively of age, stage, and comorbidities. Research Sponsor: Research Grant from Fondazione CARIPARO.

6512 **Poster Discussion Session**

Association of state Medicaid income eligibility limits and long-term survival after cancer diagnosis in the United States. *First Author: Jingxuan Zhao, American Cancer Society, Atlanta, GA*

Background: Income eligibility limits for Medicaid, the health insurance programs for low-income populations in the United States, vary substantially by state for the non-elderly population. This study examined associations between state Medicaid income eligibility limits and long-term survival among newly diagnosed cancer patients. **Methods:** 1,426,657 adults aged 18-64 years newly diagnosed with 17 common cancers between 2010 to 2013 were identified from the National Cancer Database. States' Medicaid income eligibility limits were categorized as < = 50%, 51%-137%, and > = 138% of Federal Poverty Level (FPL). Survival time was measured from diagnosis date through December 31, 2017, for up to 8 years of follow-up. Multivariable Cox proportional hazard models with age as time scale were used to assess associations of eligibility limits and stage-specific survival, controlling for age group, sex, race/ethnicity, metropolitan statistical area, number of health conditions other than cancer, year of diagnosis, facility type, and the random effect of state of residence. **Results:** Among newly diagnosed cancer patients aged 18-64 years, 22.0%, 43.5%, and 34.5% resided in states with Medicaid income eligibility limits ≤50%, 51%-137%, and ≥138% FPL, respectively. Compared to patients living in states with Medicaid income eligibility limits ≥138% FPL, patients living in states with Medicaid income eligibility limits ≤50% and 51-137% FPL were more likely to have worse survival for most cancers in both early and late stage. The highest hazard ratios (HRs) were observed among patients living in states eligibility limits ≤50% FPL (p trend < 0.05). For example, for early stage female breast cancer patients, the HRs were 1.31 (95% confidence interval [95% CI]: 1.18 – 1.46) and 1.17 (95% CI: 1.06 – 1.30) for patients living in states with Medicaid income eligibility limits ≤50% and 51%-137% compared to those living in states with Medicaid income eligibility limits ≥138% FPL. **Conclusions:** Lower Medicaid income eligibility limits were associated with worse long-term survival within stage, with variation below the Medicaid eligibility threshold as part of the Affordable Care Act. States that have not expanded Medicaid income eligibility limits should expand them to help improve survival among cancer patients. Research Sponsor: None.

6513 **Poster Discussion Session**

Impact of clinical trial enrollment on episode costs in the Oncology Care Model (OCM). *First Author: Garrett Young, OneOncology, Nashville, TN*

Background: Clinical trials are critical for improving outcomes for patients with cancer. However, there is some concern from health insurers that clinical trial participation can increase total cost of care for cancer patients. We investigated the impact of clinical trial participation on total costs paid by Medicare during the OCM program in a large community-based practice. **Methods:** Tennessee Oncology (TO) is a community oncology practice comprising over 90 oncologists across 30 sites of care. We linked TO trial data and electronic medical record data with OCM data for episodes of care from 2016-2018. To assess the impact of trial participation on total cost relative to routine care, we created matched comparator groups for each OCM episode based on cancer type, metastatic status, number of comorbidities, performance status, and age. Patients with breast cancer receiving hormone therapy only were excluded. Absolute and percent cost differences between groups were calculated for episodes that had a comparator group size of five or greater. Differences in total cost for trial episodes were compared to non-trial episodes, and significance was assessed using the Mann–Whitney U test. We also studied the impact of trial participation on receipt of active treatment in the last 14 days of life (TxEOL), hospice use, and hospitalizations. **Results:** During the study period, 8,026 completed OCM episodes met study criteria. Patients were enrolled in a clinical trial for 459 of these episodes. On average, episodes during which patients were on trial cost $5,973 less than matched non-trial episodes (Table), independent of early versus late-phase trial. Most savings resulted from decreased drug costs. There were no differences in rates of TxEOL (15% vs. 14% p=1.0), rates of hospitalizations (31% vs. 30% p=0.54), or hospice use (52% vs. 62% p=0.08) between trial and non-trial episodes. Median difference from comparator group average cost was significantly lower for clinical trial episodes (-18% vs. -6%, p<0.01). **Conclusions**: In the community setting, total costs paid by Medicare for patients participating in clinical trials during OCM episodes were lower than costs for similar patients receiving routine care. Clinical trial participation did not adversely impact end-of-life care or likelihood of hospitalization. These findings suggest that patient participation in clinical trials does not increase total cost of care nor enhance financial risk to payers. Research Sponsor: None.

		Avg. savings per episode ($ in thousands)			
Cancer	Trial episodes	Overall	Drug	Inpatient	Ancillaries	Other
Lung	68	16.9	19.2	-1.4	-0.6	-0.4
Breast	67	13.1	17.5	-0.5	-1.4	-2.5
Multiple Myeloma	64	-1.7	5.6	-1.8	-1.9	-3.6
Small Intestine / Colorectal	61	0.5	-2.4	2.4	-0.5	1.0
Prostate	45	2.8	4.9	-1.5	0.2	-0.7
Lymphoma	37	-8.9	-0.9	-3.2	-2.0	-2.7
Chronic Leukemia	20	5.3	3.4	1.9	-0.9	1.0
Gastro/Esophageal	20	13.0	2.9	2.0	0.5	7.5
All other	77	8.1	9.4	1.5	-1.6	-1.1
Total	459	6.0 k	8.1 k	-0.2 k	-$1.1 k	-0.9 k

6514 **Poster Discussion Session**

A successful model of biosimilar adoption in a community oncology practice. *First Author: Lalan S. Wilfong, Texas Oncology/The US Oncology Network, Dallas, TX*

Background: The emergence of biosimilars creates an opportunity for more cost-effective treatment. Utilization of biologics in cancer care has increased and accounts for 70% of oncologic drug spending growth from 2010 to 2015. Biosimilars can play a vital role in controlling this rapid rise in cost. Practices focused on Value Based Care arrangements, such as the Oncology Care Model, can reduce total cost of care by increasing utilization of biosimilars. The process of interchange is complicated by the designation of each biosimilar which prevents simple interchange. Communication with physicians and the healthcare team along with patient education and consent must be performed. We describe a successful model for therapeutic interchange of brand drugs to biosimilars. **Methods:** Texas Oncology elected to increase utilization of biosimilars in 2020. We collaborated with McKesson Specialty Health to create educational materials for patients and clinical staff. Communication was sent to all personnel about the therapeutic interchange process. A central pharmacy team reviewed all new orders and substituted a biosimilar for brand, unless a payer insisted on origin drug or a biosimilar not in the practice formulary. Additionally, a report was generated weekly of all existing patients who would benefit from switching. The pharmacists, upon consultation with the physician, then substituted a biosimilar for brand drug. Patients were then educated and re-consented. We started with rituximab in 07/2020 followed by bevacizumab in 09/2020 then trastuzumab in 10/2020. **Results:** The table below shows our conversion rate for all administrations. We were able to increase utilization of biosimilars from January of 2020 to December of 2020 from 5% to 80% for Rituximab, 9% to 88% for bevacizumab and 8% to 74% for trastuzumab. Based on average ASP for a 70 kg patient, the potential savings per administration is $550 for bevacizumab, $850 for trastuzumab, and $1400 for rituximab. In one month alone, this project dramatically reduced cost by $4 million or 21% by conversion to these three biosimilars. Additional savings can be realized with the use of biosimilar multi-dose vials vs single dose vials. **Conclusions:** Our comprehensive team approach successfully deploys therapeutic interchange of biosimilars for brand drugs in a community oncology practice which leads to substantial cost savings. This has real implications in controlling the total cost of care. Research Sponsor: None.

Represents all administrations administered during each time period.

Biosimilar Uptake by Month, 2020	Bevacizumab biosimilars	Rituximab biosimilars*	Trastuzumab biosimilars*
January	9%	5%	8%
February	16%	12%	13%
March	19%	16%	14%
April	22%	18%	19%
May	23%	20%	19%
June	26%	24%	23%
July	30%	31%	25%
August	30%	58%	30%
September	36%	67%	32%
October	66%	71%	36%
November	85%	77%	50%
December	88%	80%	74%

*excludes subcutaneous products.

6515 **Poster Discussion Session**

Health outcomes and resource utilization associated with postsurgical opioid use among cancer patients undergoing curative-intent surgery. *First Author: Na Lin, The Center for Health Informatics, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada*

Background: To date, it remains unclear whether new persistent post-surgical opioid use is associated with subsequent opioid overdose, higher mortality and greater consumption of healthcare resources among cancer patients. To fill this gap, a population-based cohort study by applying real-world data has been performed to compare the long-term outcomes and healthcare resource use between new persistent and non-persistent opioid users among cancer patients after curative-intent surgery. **Methods:** This retrospective cohort study included all adult cancer patients with solid tumours who received curative-intent surgery in Alberta between 2011 and 2015, with a follow-up period until December 31, 2019. Patients who had multiple tumors, or had a follow-up < 6 months, or > 30 days of hospitalization were excluded. A new persistent post-surgical opioid user was defined as a patient who was opioid-naïve before surgery (no opioid prescription filled prior to the surgery) and subsequently filled at least one opioid prescription between 60 and 180 days after surgery. The outcomes (opioid overdose and mortality within 3 years) and health resource use (emergency department visits and hospitalization within the first year) after surgery were evaluated by applying multivariable logistic and Cox regressions. **Results:** A total of 19,219 patients received curative-intent surgery with a median follow-up of 47 months, of which 1,530 (8.0%) were identified as postoperative new persistent opioid users. Compared with the non-persistent group, a higher rate of opioid overdose (OR = 1.81, 95% CI: 1.49-2.2) within 3 years of surgery has been observed for new persistent opioid users, who were also associated with a greater likelihood of being hospitalized (OR = 2.52, 95% CI: 2.21-2.87) and visiting an emergency room (OR = 2.0, 95% CI: 1.78-2.24) within the first year after surgery. A higher overall (HR = 1.37, 95% CI: 1.2-1.57) and non-cancer caused mortality (HR = 1.39, 95% CI: 1.18-1.65) has also been detected for new persistent opioid users during the study follow-up period. **Conclusions:** For cancer patients undergoing curative-intent surgery, reducing new persistent opioid use is imperative to improve subsequent outcomes and health resource utilization. Research Sponsor: None.

6516 **Poster Discussion Session**

Disparities in surveillance imaging after breast conserving surgery for primary DCIS. *First Author: Danalyn Byng, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Due to the elevated risk of ipsilateral invasive breast cancer (iIBC) after diagnosis with primary ductal carcinoma in situ (DCIS), professional guidelines recommend surveillance screening within 6-12 months (mo) after completion of initial local treatment and annually thereafter. To characterize adherence to these guidelines, we explored longitudinal patterns of utilization and factors associated with the use of surveillance imaging (mammography, MRI, ultrasound) for women with primary DCIS treated with breast conserving surgery (BCS) ± radiotherapy (RT) within 6 mo of diagnosis. **Methods:** A treatment-stratified random sample of patients diagnosed with screen-detected and biopsy-confirmed DCIS in 2008-15 was selected from 1,330 Commission on Cancer-accredited facilities (up to 20/site) in the US. All imaging exams coded as asymptomatic were collected from 6 mo up to 10 years (yr) post-diagnosis. Time was defined according to 12-mo long surveillance periods. To be included in a given surveillance period, women had to be alive and free of a new breast cancer diagnosis through the end of the period. Women were classified as "consistent" screeners if they had at least one surveillance screen during each period, for the first 5 yr post-treatment or until censoring, whichever occurred first. Repeated measures multivariable logistic regression with generalized estimating equations was used to model receipt of surveillance breast imaging over time. The model included clinical and socioeconomic features. **Results:** The final analytic cohort contained 12,559 women; 8,989 (71.6%) received RT after BCS. Median age was 60 yr (interquartile range: 52-69) and median follow-up was 5.6 yr (95% confidence interval [CI] 5.6-5.7). Among women who received BCS (instead of BCS+RT), 62.5% (79.7%) underwent surveillance imaging within 6-18 mo after diagnosis. 38.7% (54.0%) were categorized as "consistent" screeners. Compared to white women, Black women were less likely to receive surveillance screening after treatment for primary DCIS (odds ratio [OR] 0.85, 95% CI 0.77-0.94). Hispanic ethnicity had a similar association (OR 0.86, 95% CI 0.74-0.99) compared to non-Hispanic ethnicity. Women with private insurance, compared to government insurance, were more likely to receive screening (OR 1.20, 95% CI 1.11-1.30). Prognostic tumor features indicative of a higher risk of subsequent iIBC, including higher grade, presence of comedonecrosis, and hormone receptor-negative DCIS, were not associated with screening uptake. **Conclusions:** Despite guidelines recommending annual surveillance imaging, many women with primary DCIS do not undergo regular imaging after BCS. The findings from this US-based study suggest that disparities in screening uptake are associated with race/ethnicity and insurance status rather than prognostic tumor features. Research Sponsor: PCORI (PCS-1505-30497, CER-1503-29572), Other Foundation, Cancer Research United Kingdom.

6517 **Poster Discussion Session**

Should we routinely screen for frailty prior to gynecologic oncology surgery? Frailty as a potential predictor of adverse postoperative outcomes in elderly patients. *First Author: Sarah J. Mah, McMaster University, Hamilton, ON, Canada*

Background: Frailty is increasingly recognized as an adverse prognostic factor of postoperative morbidity and survival in several surgical disciplines. There is no consensus on routine frailty screening in Gynecologic Oncology. Our goal was to evaluate the predictive role of the National Surgical Quality Improvement Program(NSQIP) comorbidity-based modified Frailty Index-5(mFI-5) in Gynecologic Oncology patients over the age of 70. **Methods:** Elective laparotomies between 01/2016-09/2020 at the Juravinski Hospital in Hamilton, ON were reviewed using prospectively-collected NSQIP data and chart review. Complication severity was assessed by Clavidien-Dindo classification. The primary outcome was rate of 30-day grade III-V complications. Secondary outcomes were: grade II-V complications, myocardial injury, length of stay(LOS), non-home discharge, and non-initiation/non-completion of adjuvant chemotherapy. Logistic regression analysis was performed. Survival analysis and receiver-operator characteristic curves are underway. **Results:** In this cohort of 259 patients, frail patients(mFI-5$\geq$2) were at significantly greater risk of grade III-V complications (OR23.77, 95%CI 9.69-66.26, $p < 0.0001$), grade II-V complications (OR3.8, 95%CI 1.96-7.85, $p = 0.0002$), myocardial injury (OR3.44, 95%CI 1.66-7.05, $p = 0.0009$), LOS$\geq$5-days (OR2.96, 95%CI 1.61-5.52, $p = 0.0006$), non-home discharge (OR7.37, 95%CI 2.81-20.46, $p < 0.0001$), and non-initiation/non-completion of chemotherapy (OR7.34, 95%CI 2.43-23.06, $p = 0.0006$), than non-frail patients on univariate analysis(UVA). On multivariable analysis, frailty remained independently associated with grade II-V complications and grade III-V complications (OR4.64, 95%CI 2.31-9.94, $p < 0.0001$, controlling for stage, operative duration and intraoperative complication, and OR24.49, 95%CI 9.72-70.67, $p < 0.0001$, adjusting for BMI, stage and operative duration, respectively). On UVA, age, surgical complexity score, and smoking were not predictive of complications. Frailty also independently predicted non-home discharge (OR7.37, 95%CI 2.81-20.46, $p < 0.0001$) when adjusting for age. **Conclusions:** Frailty as assessed with mFI-5, independent of age, strongly predicted morbidity and non-home discharge after Gynecologic Oncology surgery. Strategies for perioperative optimization could help address these disparities. mFI-5 is a concise tool that can be used for routine frailty screening and risk stratification. Research Sponsor: None.

6518 **Poster Discussion Session**

National Cancer Institute (NCI) implementation of the American Society of Clinical Oncology (ASCO) and Friends of Cancer Research (Friends) broadening clinical trials eligibility criteria. *First Author: Andrea M. Denicoff, National Cancer Institute, Rockville, MD*

Background: The 2017 ASCO/Friends eligibility criteria guidelines recommend inclusiveness to promote generalizable trial results and clear rationale for necessary exclusion. These guidelines focused on brain metastases, minimum age for enrollment, HIV infection, and organ dysfunction and prior and concurrent malignancies. In September 2018, the NCI Cancer Therapy Evaluation Program (CTEP) implemented modernized protocol template language to operationalize these criteria. We evaluated utilization of the new language among CTEP-sponsored treatment trials. **Methods:** We evaluated protocols first approved by CTEP between 11/01/2018 and 4/30/2020. The most recent approved protocol version was evaluated for consistency with the new template language for brain metastases, HIV infection, prior or concurrent malignancies, minimum age, and cardiac, liver and kidney function. If a particular criterion was not relevant for a trial, it was not included in the analysis. We did not score age in pediatric or adult-specific trials (e.g. prostate). **Results:** 122 trials (71% early and 29% late phase) were identified and included in the analysis. Compliance with the new criteria language ranged from a high of 87.7% for liver function to a low of 11.5% for "new or progressive brain metastases" (table). Modernized criteria language was lacking in nearly 46% of trials in the use of concurrent or prior malignancy criteria and 31% of trials for the cardiac criteria. Of the 87 trials for non-localized disease or non-brain tumor trials, 64.4% did not address brain metastases, leaving it to investigator discretion. Thus, 75.9% of trials could theoretically enroll patients with brain metastases. Only 6 trials were considered relevant for patients < 18 years old; 50% were consistent with the age criterion (not shown in table). **Conclusions:** Implementing ASCO/Friends eligibility criteria requires focused reviews during protocol development to ensure compliance. CTEP is using these findings to continue to improve its protocol review processes to broaden eligibility in clinical trials. Maximizing opportunities for diverse populations to participate in trials is a priority for the National Cancer Institute and CTEP will continue efforts to achieve this goal. Research Sponsor: U.S. National Institutes of Health.

Broadened Eligibility Criteria Category	No. of Analyzable Trials	Modernized Criteria Implemented	Modernized Criteria Not Implemented	Criteria Not Addressed in Eligibility
Liver function	122	87.7% (107)	6.6% (8)	5.7% (7)
Kidney function	122	86.1% (105)	9.0% (11)	4.9% (6)
Cardiac function	122	58.2% (71)	31.1% (38)	10.7% (13)
HIV	122	76.2% (93)	6.6% (8)	17.2% (21)
Prior / Concurrent Cancer	122	34.4% (42)	45.9% (56)	19.7% (24)
Treated/ Stable Brain Metastases	87	50.6% (44)	17.2% (15)	32.2% (28)
New/ Progressive Brain Metastases	87	11.5% (10)	24.1% (21)	64.4% (56)

6519 **Poster Discussion Session**

Racial and ethnic representation trends in United States oncology training programs. *First Author: Conner Lombardi, University of Toledo College of Medicine, Toledo, OH*

Background: Utilizing race and ethnicity data from the Accreditation Council for Graduate Medical Education (ACGME), this study aims to assess representation trends across American Society of Clinical Oncology (ASCO) participant specialties from the past five academic years in order to characterize current needs and effectively address these needs moving forward. **Methods:** Self-reported ethnicity/race data from the ACGME database books were collected from academic years 2015-16 to 2019-2020 for the following oncologic training programs: hematology and medical oncology, medical oncology, gynecologic oncology, pediatric hematology and oncology, radiation oncology, complex general surgical oncology. Summary statistics and chi-square analysis were conducted to compare underrepresented minority (URM) trends across programs. URM groups were cross-referenced with definitions provided by the AAMC and included those who identify as Hispanic, Latino or of Spanish origin, Black or African American, and Native American or Alaskan. **Results:** Over the study period, only 1,250 (9.0%) of 13,853 oncology trainees identified as URM. Chi-square analysis demonstrated no significant change in URM representation in all oncology specialties combined between 2015-16 and 2019-20 (8.9% [95% CI, 7.8%-10.0%] vs. 9.7% [95% CI, 8.7%-10.8%]; P=.31). Between 2015-16 and 2019-20, Hematology and oncology (+1.3%), pediatric hematology and oncology (+0.3%) all demonstrated insignificant increasing trends in representation while radiation oncology (-0.3%), complex general surgical oncology (-4.0%) had statistically insignificant decreasing trends in representation. Gynecologic oncology (+6.0%) demonstrated a significant increasing trend in representation. **Conclusions:** This is the first study to characterize the vast disparities in representation in oncologic training programs in the United States. There is a demonstrated lack of representation across all oncology training programs and a lack of significant improvement over the study period. A multiprong approach is needed to improve diversity and representation across the spectrum of the oncology workforce in the United States. Research Sponsor: None.

6520 **Poster Discussion Session**

Individual and institutional predictors of sexual orientation and gender identity data collection in oncology practice: An ASCO survey.

First Author: Charles Stewart Kamen, University of Rochester Medical Center, Rochester, NY

Background: Most oncology practices do not collect patients' sexual orientation (SO) or gender identity (GI) (SOGI), prohibiting assessment of sexual and gender minority (SGM) patients' cancer disparities and identification of such patients in cancer care or research. Studies report that 90% of SGM patients would disclose their SOGI, while 78% of clinicians believe that patients would not. Preliminary evidence indicates that SOGI disclosure improves health outcomes. Organizations, including ASCO and NIH, have called for routine SOGI data collection, but institutional barriers, e.g. lack of SOGI fields in EMRs, hinder progress. This study aimed to delineate institutional and individual-level factors related to SOGI data collection in oncology. **Methods:** From Oct to Nov 2020, an anonymous 54 item online survey was distributed to ASCO members via direct outreach, listservs and social media. The survey assessed whether respondents' institutions collect SOGI data, factors related to SOGI data collection, respondents' attitudes about SOGI data and SGM patients, and demographics. Simple and multiple logistic regression modeling determined factors associated with respondents' reports of SOGI data collection at their institutions. **Results:** Nearly half of 257 respondents reported their institutions collect SO and GI data (42%, 48%, respectively); over a third reported their institutions did not collect SO or GI data (36%, 34%, respectively); and a fifth were unsure (22%, 18%, respectively). Collection of both SO and GI was associated in unadjusted models with leadership support and having resources for SOGI data collection. SO collection was also associated with type of institution, having an SGM family member, and belief that knowing SO is important for providing quality care. GI collection was associated with the respondent's role, SO, political leaning, past SGM training, and belief that knowing GI is important for providing care. Odds ratios (OR) from adjusted models with 95% confidence intervals (CI) comparing respondents who reported SO or GI collection as "Yes" vs. "No" are reported (comparisons to "Unsure" not presented). Most respondents (79%) felt it was important to know both SO and GI to provide quality care, while 14% felt neither was important. **Conclusions:** Whether or not institutions collect SOGI data is related to many factors. Despite limited statistical power, the same three factors emerged as drivers of data collection: leadership support, resources and individuals' attitudes. These are critical and possibly self-reinforcing elements for collecting SOGI data. Research Sponsor: None.

Results from adjusted logistic regression models for SOGI collection.

Predictor	OR (SO)	95% CI (SO)	OR (GI)	95% CI (GI)
Leadership support	8.01	2.45-26.2	6.02	2.32-15.6
Institutional resources	10.6	4.05-27.7	18.7	5.34-65.3
Importance of knowing patient SO or GI	4.28	1.50-12.2	2.76	1.01-7.51

6521 **Poster Session**

Socioeconomic status variables contribute to the disparities in female triple negative breast cancer outcome in the United States, 2011-2015: A population study based on NCI Surveillance, Epidemiology and End Results (SEER) database.

First Author: Zikun Wang, Indiana University Bloomington School of Public Health, Bloomington, IN

Background: Cancer disparities pertinent to socioeconomic status (SES) still exist in the American healthcare system. How SES variables impact the outcome of triple negative breast cancer (TNBC) needs identification. **Methods:** We enrolled 22,434 women diagnosed with invasive TNBC in 2011 – 2015 from the SEER 18 program. The primary outcome was to identify SES risk factors for TNBC cause specific survival (TNBCCSS)and overall survival (OS) via the Cox Proportional Hazard Regression Model. SES information was collected: race, insurance status, marital status, and percentage of families with incomes below the poverty level and adults with less than high school graduate (<HSG) in a county of the patient's residency; all analyses were also adjusted for clinicopathological characteristics. We categorized rates of poverty and <HSG as quartiles. **Results:** 18,578 (82.8%) women were insured or insured/ no specifics (NS), and 3,360 (15.0%) received Medicaid upon TNBC diagnosis; only 496 (2.2%) patients were uninsured. The TNBCCSS rates of insured, insured/ NS, Medicaid, and uninsured cohorts were 86.6%, 83.6%, 77.4% and 73.2%, respectively. In multivariable adjusted analyses, the TNBC cause specific mortality risk of patients who were uninsured or receiving Medicaid was significantly higher than that of women who were insured (Hazard ratio [HR] = 1.60, 95% confidence interval [CI]: 1.34-1.92 and HR = 1.29, 95% CI: 1.18-1.41, respectively). Women residing in a county with a high poverty rate (the 3rd quartile [rate of 11.1 – <14.3%]) had significantly worse TNBC cause specific mortality risk as compared to women with residency of the lowest poverty rate (HR = 1.25, 95% CI: 1.10-1.41). Single and widowed cohorts had better HR of TNBCCSS compared with the married population (HR = 0.86, 95% CI: 0.79-0.95 and HR = 0.82, 95% CI: 0.73-0.93, respectively). Notably, we observed a synergistic effect among race, insurance status and TNBC OS: black women receiving Medicaid had significantly lower HR compared with their non-Hispanic white counterparts (HR = 0.86, 95% CI: 0.74-0.98). Rate of <HSG was marginally correlated with the TNBCCSS. **Conclusions:** SES variables contribute to the disparities in TNBC survival. TNBC cause specific mortality risk of patients without insurance or with Medicaid at the time of TNBC diagnosis is 60% and 29% higher compared with insured women (Table). Race and insurance status act synergistically upon TNBC OS. Research Sponsor: None.

Results of Multivariable Cox Regression Analysis associating insurance status and TNBC survival.

	TNBCCSS			OS		
	HR	95% CI	*P* value	HR	95% CI	*P* value
Insurance status			<0.0001			<0.0001
Insured	1.00 (Ref.)	(–)		1.00 (Ref.)	(–)	
Uninsured	1.60	1.34-1.92		1.59	1.36-1.86	
Any Medicaid	1.29	1.18-1.41		1.38	1.28-1.48	
Insured/ NS	1.04	0.93-1.15		1.10	1.02-1.19	

6522 **Poster Session**

Investigating tumor molecular profiling as a possible contributor to racial/ethnic disparities in pancreatic cancer.

First Author: Evan Justin Walker, University of California San Francisco, San Francisco, CA

Background: A variety of biologic, socioeconomic, and treatment-related factors may contribute to the racial/ethnic disparities observed in pancreatic ductal adenocarcinoma (PDAC) outcomes. As tumor molecular profiling (TMP) is now recommended for patients (pts) with advanced PDAC to inform treatment selection, we hypothesized that rates of TMP, detection of actionable alterations (AA), and use of molecularly-targeted treatments differ across different racial/ethnic groups and may contribute to disparate outcomes. **Methods:** This retrospective analysis included all Non-Hispanic White (NWH), Asian, Hispanic/Latinx (H/L), and Black/African American (B/AfrAm) pts with PDAC who underwent TMP at UCSF over a 4-yr period. Medical records were reviewed for demographic and disease-specific data. Alterations classified as 'pathogenic' or 'likely pathogenic' in TMP clinical reports were included, and were categorized as 'actionable' if there was clinical or preclinical evidence of benefit from targeted therapy in any cancer. Associations between NHW and other groups were tested with Fishers exact test. **Results:** Between 1/2016-1/2020, 159/727 (22%) pts underwent PDAC TMP. 60 AA were detected in 54 pts. Rates of TMP or AA detection were not associated with racial/ethnic group (Table). Most AA (33/60, 55%) were associated with the Homologous Recombination DNA Damage Repair (HR-DDR) pathway (*ARID1A* n = 15, *ATM* n = 7, and *BRCA1* n = 5). Other common AA included *PIK3CA* alterations (n = 6), *CDK4/6* amplifications (n = 5), *AKT2* amplifications (n = 4) and *KRAS* G12C mutation (n = 4). Molecular targets differed between groups (HR-DDR genes comprised 55% AA in NHW vs 100% in H/L, p = 0.03). Regarding treatment, rates of platinum chemotherapy for HR-DDR gene-altered PDAC differed significantly between groups. Three NHW pts with HR-DDR alterations received a PARP-inhibitor +/- ATR inhibitor. **Conclusions:** To our knowledge, this is the first study to report PDAC TMP rates and therapeutic implications across racial/ethnic groups. Acknowledging the limitations of sample size and what defines AA, we observed no significant differences in rates of testing nor AA detection. Further study is needed to evaluate whether rates of molecularly-informed treatment selection contribute to racial/ethnic disparities in clinical outcomes. As therapeutic advances increase the likelihood of identifying AA, equitable access to both TMP and targeted treatments must be ensured for all pts with PDAC. Research Sponsor: None.

	NHW	Asian	H/L	B/AfrAm
	n = 484	n = 133	n = 75	n = 35
TMP	111 (23%)	27 (20%)	16 (21%)	5 (14%)
	–	p = 0.56	p = 0.88	p = 0.30
Pts with AA	34/111 (31%)	11/27 (41%)	7/16 (44%)	2/5 (40%)
	–	p = 0.36	p = 0.39	p = 0.65
Total AA	n = 38	n = 12	n = 7	n = 3
HR-DDR AA	21 (55%)	5 (42%)	7 (100%)	0 (0%)
	–	p = 0.51	p = 0.03	p = 0.11
HR-DDR AA, Received Platinum	18/21 (86%)	5/5 (100%)	3/7 (43%)	n/a
	–	p = 1.00	p = 0.04	
HR-DDR AA, Received PARP-inhibitor	3/21 (14%)	0/5 (0%)	0/7 (0%)	n/a
	–	p = 1.00	p = 0.55	

6523 **Poster Session**

Racial and ethnic enrollment disparities in acute myeloid leukemia clinical trials.

First Author: Andrew Hantel, Dana-Farber Cancer Institute, Boston, MA

Background: Racial and ethnic disparities in clinical trial enrollment compound inequities in drug development and the delivery of patient-centered care. Despite significant survival disparities in acute myeloid leukemia (AML), enrollment disparities data are limited. **Methods:** We performed a structured search and abstraction of demographic data for all United States (US) AML clinical trials from 2002-2017 listed on clinicaltrials.gov and compared the results to the incidence and demographic distribution of AML using the Surveillance, Epidemiology, and End Results program and 2010 US Census. We calculated enrollment fractions (the number of enrollees divided by the number of incident cases) for the five mutually exclusive race/ethnicity groups of non-Hispanic White (NH-White), Black (NH-Black), Asian/Pacific Islander (NH-Asian/PI), American Indian/Native Alaskan (NH-AI/AN), and Hispanic patients. We compared these using X^2 testing, with NH-White as the comparator, and reported odds ratios with 95% confidence intervals (CI). To assess trends over time, we adjusted enrollment from 2005-2008 for changes in AML incidence and NH-White enrollment for a later period (2011-2014), comparing this expected enrollment fraction to the actual enrollment fraction during that later period. **Results:** Of 223 eligible studies (patient N=17372) on clinicaltrials.gov, 99 (44.4%) reported racial demographics (N=8417; 48.5%) and 68 (30.5%) reported race and ethnicity (N=6554; 37.7%). Enrollment and incidence proportions by race are shown in the table. Among trials reporting race and ethnicity, all groups had lower odds of enrollment compared to NH-White patients (Table). For the 99 trials reporting race data, Black and AI/AN patient enrollment odds were lower (OR 0.60 [95% CI: 0.55, 0.65]; 0.50 [95% CI: 0.33, 0.76]), but Asian/PI enrollment was not (OR 0.91 [95% CI: 0.82, 1.01]). The relative enrollment of NH-Black, NH-Asian/PI, and Hispanic patients declined later in the study period (Table). **Conclusions:** In AML clinical trials performed in the US from 2002-2017, NH-White patients were enrolled at higher rates compared to other racial and ethnic groups; enrollment diversity declined over time. An important first step to reducing enrollment disparities will be to improve the reporting of demographic enrollment data. Research Sponsor: U.S. National Institutes of Health.

	NH-White	NH-Black	NH-AI/AN	NH-Asian/PI	Hispanic
Proportion of Trial Enrollment (%)	79.7	7.3	0.3	3.6	9
Proportion of AML Incidence (%)	74.8	10.1	0.5	4.5	10.1
Overall Enrollment Fraction (%)	3.5	2.4	1.8	2.6	2.9
Odds of Enrollment vs NH-White (95% CI)	Reference	0.68 (0.61, 0.75)	0.31 (0.31, 0.82)	0.75 (0.65, 0.86)	0.83 (0.76, 0.91)
Relative Change in Enrollment, 2005-8 vs 2011-14 (%)[1]	Reference	-19.0	36.6	-18.6	-21.0
Actual vs Expected Enrollment Odds, 2011-14 (95% CI)	0	0.80 (0.67, 0.97)	-2	0.80 (0.64, 0.99)	0.78 (0.65, 0.94)

[1]adjusted for changes in incidence and NH-White enrollment [2]enrollee N too small for X^2testing.

6524 **Poster Session**

Association of electronic-health record (EHR)-derived race with BRCA testing in patients (pts) with breast cancer (BC) with similar genetic ancestry (GA) in a clinicogenomic database (CGDB). *First Author: Yanling Jin, F. Hoffmann-La Roche Ltd., Mississauga, ON, Canada*

Background: Disparities in health outcomes can be affected by biological factors associated with GA and social determinants of health. These factors can be teased apart using GA data from comprehensive genomic profiling (CGP) in pts with cancer. CGDBs that link EHR data with CGP enable the selection of pts with similar GA. Holding GA constant provides an opportunity to directly study the effects of reported race in health disparities. This study evaluated a published racial disparity (BRCA testing rates in African American [AA] vs White pts with BC) in a population with fixed, similar GA. **Methods:** The nationwide (US-based) deidentified Flatiron Health and Foundation Medicine (FMI) BC CGDB (Q3 2020) was used. For each pt, GA fractions from 5 geographic ancestry groups (African [AFR]; Admixed American; East Asian; European [EUR]; South Asian) were derived by FMI using an admixture analysis workflow using genes captured in the CGP assay. To focus on BRCA testing in AA vs White pts and find a sufficient population with similar GA but AA or White race, pts with admixture of both EUR and AFR ancestry were selected. The chosen fractions were: Cohort 1=35%-65% AFR and EUR each; Cohort 2=25%-60% AFR and EUR each; Cohort 3=30%-60% AFR. Cohorts overlap but were chosen to increase sample size. In each cohort, documented BRCA testing prevalence, time from diagnosis to BRCA test date, age at BRCA test and overall survival (OS) were compared between races. Other race (OR) and missing race (MR) were also reported. **Results:** Most pts (4130/6903) in the BC CGDB had ≥75% EUR ancestry; 129 pts had AFR ancestry fractions ≥25% with EUR ancestry >0%. AA pts had the lowest BRCA testing rates (39%, 43%, 44% for Cohorts 1-3, respectively), which were 18%, 10% and 17% lower compared with White pts, respectively (Table). In Cohorts 1-3, AA pts experienced a longer median time between diagnosis and testing (399, 668, 900 days) compared with White pts (93, 667, 106 days). The median age at BRCA test was 16, 9 and 8 years younger in AA pts (49, 47 and 50 years) compared with White pts. Although pts with MR data had the lowest OS compared with the other races within each cohort, the sample size of each arm for all cohorts was too small to make conclusions. **Conclusions:** This study demonstrated that when holding GA constant, racial disparities persist in BRCA testing patterns and outcome in pts with BC from a CGDB. With increasing availability of linked clinical and genomic data, further exploration of disparities in genetically similar cohorts can provide deeper insight for cancer outcomes and health disparities research. Research Sponsor: Genentech, Inc.

Sample size and BRCA testing frequency of EHR-derived race by cohort.

Cohort (n)	AA, n (%)	White, n (%)	OR, n (%)	MR, n (%)
Cohort 1 (58)	36 (39)	7 (57)	10 (60)	5 (40)
Cohort 2 (90)	40 (43)	17 (53)	23 (61)	10 (50)
Cohort 3 (86)	43 (44)	13 (62)	20 (60)	10 (50)

6525 **Poster Session**

Impact of Medicaid expansion on two-year mortality among stage IV breast cancer (BC) patients according to race. *First Author: Catalina Malinowski, MD Anderson Cancer Center, Houston, TX*

Background: Inadequate access to healthcare services is associated with worse outcomes. Disparities in access to cancer care are more frequently seen among racial/ethnic minorities, uninsured patients, and those with low socioeconomic status. A provision in the Affordable Care Act called for expansion of Medicaid eligibility in order to cover more low-income Americans. In this study, we evaluate the impact of Medicaid expansion in 2-year mortality among metastatic BC patients according to race. **Methods:** Women (aged 40-64) diagnosed with metastatic BC (stage IV *de novo*) between 01/01/2010 and 12/31/2015 and residing in states that underwent Medicaid expansion in 01/2014 were identified in the National Cancer Database. For comparison purposes, 2010-2013 was considered the pre-expansion period and 2014-2015 the post-expansion period. We calculated 2-year mortality difference-in-difference (DID) estimates between White and non-White patients using multivariable linear regression models. Results are presented as adjusted differences (in % points) between groups in the pre- and post-expansion periods and as adjusted DID with 95%CI. Covariates included age, comorbidity, BC subtype, insurance type, transfer of care, distance to hospital, region, residence area, education, income quartile, facility type and facility volume. In addition, overall survival (OS) was evaluated in pre- and post-expansion periods via Kaplan-Meier method and Cox proportional hazards models; results are presented as 2-year OS estimates, hazard ratios (HRs), and 95% CIs. **Results:** Among 7,675 patients included, 4,942 were diagnosed in the pre- and 2,733 in the post-expansion period. We observed a reduction in 2-year mortality rates in both groups according to Medicaid expansion. Among Whites 2-year mortality decreased from 42.5% to 38.7% and among non-Whites from 45.4% to 36.4%, resulting in an adjusted DID of -5.2% (95%CI -9.8 to -0.6, p = 0.027). A greater reduction in 2-year mortality was observed among non-Whites in a sub-analysis of patients who resided in the poorest quartile (n = 1372), with an adjusted DID of -14.6% (95%CI -24.8 to -4.4, p = 0.005). In the multivariable Cox model, during the pre-expansion period there was an increased risk of death for non-Whites compared to Whites (HR 1.14, 95% CI 1.03 to 1.26, P = 0.04), however no differences were seen in the post-expansion period between the two groups (HR 0.93, 95% CI 0.80 to 1.07, P = 0.31). **Conclusions:** Medicaid expansion reduced racial disparities by decreasing the 2-year mortality of non-White patients with metastatic breast cancer and reducing the gap when compared to Whites. These results highlight the positive impact of policies aimed at improving equity and increasing access to health care. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

6526 **Poster Session**

Financial toxicity, symptom burden, illness perceptions, and communication confidence in cancer clinical trial participants. *First Author: Subha Perni, Harvard Radiation Oncology Program, Massachusetts General Hospital and Brigham and Women's Hospital/Dana-Farber Cancer Institute, Boston, MA*

Background: Cancer clinical trial (CCT) participants are at high risk for experiencing adverse effects from financial toxicity, yet this remains understudied in the CCT population. We sought to describe associations among patient-reported financial toxicity (financial burden [FB] and trial cost concerns), physical and psychological symptoms, illness perceptions, and communication confidence in CCT participants. **Methods:** From 7/2015-7/2017, we prospectively enrolled CCT participants who expressed interest in financial assistance and a group of patients matched by age, sex, cancer type, specific trial, and trial phase. We assessed FB (burdened by costs of cancer care), trial cost concerns (worried about affording medical costs of a CCT), physical (Edmonton Symptom Assessment Scale [ESAS]) and psychological (Patient Health Questionnaire-4 [PHQ-4]) symptoms, illness perceptions (Brief Illness Perception Questionnaire [BIPQ]), and communication confidence (Perceived Efficacy in Patient-Physician Interactions [PEPPI]). We used regression models to explore sociodemographic associations with FB and trial cost concerns, and to examine associations of FB and trial cost concerns with patients' symptom burden, illness perceptions, and communication confidence, adjusting for age, sex, race, performance status, marital status, and metastatic status. **Results:** Of 198 patients enrolled, 112 (56.6%) reported FB and 82 (41.4%) had trial cost concerns. Patients with FB were younger (OR 0.96, 95% CI 0.94-0.98) and had lower incomes (< $100,000, OR 4.61, 95% CI 2.35-9.01). Patients reporting trial cost concerns also had lower incomes (< $100,000, OR 2.78, 95% CI 1.45-5.29). On adjusted analyses, patients with FB had higher ESAS total (OR 1.03, 95% CI 1.02-1.05), ESAS physical (OR 1.04, 95% CI 1.02-1.07), PHQ-4 depression (OR 1.54, 95% CI 1.22-1.94), and PHQ-4 anxiety (OR 1.30, 95% CI 1.08-1.55) scores, as well as more negative illness perceptions (OR 1.04, 95% CI 1.01-1.07), but no significant difference in communication confidence (OR 0.98, 95% CI 0.93-1.05). Patients reporting trial cost concerns had higher ESAS total (OR 1.03, 95% CI 1.01-1.05), ESAS physical (OR 1.04, 95% CI 1.01-1.06), PHQ-4 depression (OR 1.35, 95% CI 1.10-1.65), and PHQ-4 anxiety (OR 1.27, 95% CI 1.07-1.51) scores, as well as more negative illness perceptions (OR 1.06, 95% CI 1.03-1.10), and lower communication confidence (OR 0.93, 95% CI 0.87-0.99). **Conclusions:** In this study of CCT participants, younger patients with lower incomes were most vulnerable to financial toxicity. Financial toxicity was associated with greater symptom burden, more negative illness perceptions, and lower communication confidence, which underscores the importance of addressing these issues when seeking to alleviate the adverse effects of financial toxicity in CCT participants. Research Sponsor: Lazarex Foundation, Trefler Foundation.

6527 **Poster Session**

Social determinants of health, genetic ancestry, and mortality in ECOG-ACRIN E5103. *First Author: Samilia Obeng-Gyasi, The Ohio State University, Columbus, OH*

Background: Social determinants of health (SDH) and genetic ancestry have been independently implicated in breast cancer presentation, treatment and mortality. However, little is known about the relationship between SDH and genetic ancestry on clinical trial outcomes. The objective of this study is to assess the association between SDH, genetic ancestry and clinical outcomes in patients enrolled in an adjuvant breast cancer clinical trial. **Methods:** ECOG-ACRIN (EA) 5103 randomized patients to receive AC + taxane + bevacizumab or placebo. SDH were operationalized as insurance status at trial registration (individual SES) and neighborhood socioeconomic status (nSES). Insurance categories included: (1) Private, 2) Medicare including private/Medicare, military, 3) Medicaid including Medicaid/Medicare, uninsured, 4) self-pay). The nSES index was calculated using zip codes linked to county level data on occupation, income, poverty, wealth, education and crowding. Genome-wide single-nucleotide polymorphism arrays were used to define African ancestry (AA), European ancestry (EA) and other (OA). Multivariable regression and Cox-Proportional Hazard models (odds ratios (OR) and hazard ratios (HR) with corresponding 95% confidence intervals (CI)) were used to assess associations with chemotherapy completion and overall mortality. Estimates were adjusted for the following clinical covariates: age, tumor size, nodal status, hormone receptor status, and primary surgery at randomization. **Results:** The study cohort included 2453 EA (79.2%), 381 AA (12.2%) and 265 OA (8.6%). Medicaid patients (OR 0.76(0.59-0.99); ref private) and those with AA (OR 0.62(0.49-0.78); ref EA) were less likely to complete chemotherapy. Regarding overall mortality, Medicaid insurance (HR 1.42(1.05-1.92) was associated with a higher mortality than private insurance. Conversely, there was no significant difference in mortality by ancestry (AA HR 1.27 (0.97-1.66); OA HR 0.90 (0.63-1.29): ref EA). Neighborhood socioeconomic status did not appear to be associated with chemotherapy completion or mortality. **Conclusions:** SDH reflective of individual SES, such as insurance, appear to be stronger drivers of trial completion and mortality compared to nSES among patients enrolled in E5103. Moreover, study results suggest an interplay between ancestry and individual proxies for SDH in trial completion. Nevertheless, the relationship between ancestry and lower rates of chemotherapy completion do not appear to translate into higher mortality rates among patients of AA. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

6528 **Poster Session**

Differences by race in patient-reported symptoms during chemotherapy among women with early-stage, hormone receptor-positive breast cancer.

First Author: Xin Hu, Emory University, Rollins School of Public Health, Department of Health Policy and Management, Atlanta, GA

Background: Symptom burden may contribute to racial differences in cancer treatment adherence and survival. Evidence on changes in symptom burden during chemotherapy and whether these differ by race is scarce. We used patient reported outcomes data collected before and after breast cancer chemotherapy initiation to compare symptom burden by race. **Methods:** Using electronic medical records of a large cancer center in the southern region of the US, we identified Black and White women diagnosed with stage I-III, hormone-receptor positive breast cancer from January 2007 to December 2015. A tablet-based platform [ConcertAI] was used to collect patient reported symptoms at the point of care. We included patients with at least one completed symptom report before and during chemotherapy. We focused on two standardized composite scores – physical symptoms and treatment side-effect (mean of 50 and standard deviation of 10), and calculated changes in symptoms using the closest report before chemotherapy and the most severe score reported during chemotherapy. Patients with a 10-point increase were classified as having a clinically meaningful increase in symptom burden. We used Oaxaca-Blinder decomposition to quantify racial differences in symptom burden change explained by baseline characteristics. These included baseline symptom scores, sociodemographic characteristics (age, regional level household income and education, state) and clinical characteristics (cancer stage and primary chemo regimen). **Results:** Among 1,167 included patients, Black women (30%) were younger (52 vs. 55 years old, $p< .001$), more likely to live in areas with lower median household income and less education, and reported most severe scores about 2 weeks later than White women ($p< .05$). They were also more likely to report a 10-point increase in symptom burden for physical (68.5% vs. 61.2%, $p= .017$) and side-effects symptoms score (49.0% vs. 41.4%, $p= .015$). This was driven by larger increases in selected individual symptoms among Black women, such as sweating, itching, and numbness (under physical symptom score), and hair loss and taste change (under side-effect score). Decomposition analyses showed that baseline characteristics (especially primary chemo regimen) explained 79.2% ($p= .002$) and 35.2% ($p= .131$) of the increased probability of Black women reporting a 10-point increase in physical symptom and side-effects scores respectively. **Conclusions:** Black women with early-stage breast cancer were more likely to report a clinically meaningful increase in treatment side-effects and physical symptoms during chemotherapy compared to White women. Differences by race in physical symptoms scores were mostly explained by baseline characteristics. Future studies should examine whether racial differences in symptom burden translate into differences in treatment adherence and mortality. Research Sponsor: U.S. National Institutes of Health.

6529 **Poster Session**

Uptake of immunotherapy in patients with advanced cancer: A population-based study using health administrative data from Ontario, Canada.

First Author: Jacques Raphael, London Regional Cancer Program, Western University, London, ON, Canada

Background: The introduction of immunotherapy (IO) in the treatment of patients with cancer has significantly improved clinical outcomes. Herein we report on IO uptake in Ontario, Canada, a publicly funded healthcare system. **Methods:** We conducted a retrospective cohort study using provincial health administrative data to: 1) assess IO uptake in adult patients with advanced melanoma, bladder, lung, head and neck (HN) and kidney cancers; and 2) identify predictors of IO usage between 2011 (pre-IO funding) and 2019. The datasets were linked using unique encoded identifiers and analyzed at ICES. IO uptake was captured between cancer diagnosis and last follow up and reported as a proportion of the entire cohort and by tumor site and drug type. A competing risk Fine and Gray regression model with death as competing risk was used to identify factors associated with IO use. **Results:** Among 59,510 patients with one of the five advanced cancers of interest, 7,660 (12.9%) received IO. Details of IO uptake are summarized in Table. IO uptake increased yearly from 2011 (2.7%) to 2019 (34.0%). Uptake was highest in melanoma (48.2%) and lowest in HN cancer (5.8%). The most commonly used drugs used were pembrolizumab (41.1%) and nivolumab (40.5%). In adjusted analysis, predictors of lower IO uptake included older age (hazard ratio (HR) 0.953, 95%CI 0.934-0.972 with every additional 10 years), female sex (HR 0.859, 95%CI 0.819-0.9), lower income quintile (HR 0.893, 95%CI 0.83-0.96), history of hospital admission (HR 0.768, 95%CI 0.734-0.805), female oncologist (HR 0.942, 95%CI 0.892-0.995), and *de novo* stage 4 cancer (HR 0.918, 95%CI 0.873-0.966). Predictors of higher IO uptake were low Charlson score (HR 1.118, 95%CI 1.01-1.236) and previous radiation therapy (HR 1.438, 95%CI 1.367-1.512). IO uptake was heterogeneous across cancer centres levels (1 to 4) and regions. **Conclusions:** While the use of IO for advanced cancer has steadily increased over time, uptake is associated with patient and physician characteristics, as well as system level factors. This variation suggests potential inequity in access to these potentially life-prolonging drugs and should be further investigated and addressed. Research Sponsor: Medical Oncology Research Fund (MORF) (University of Western Ontario), type: seed grant for the division of medical oncology.

Immunotherapy uptake by year and tumor site.

IO uptake N= 59,510	Bladder N=3,708	HN N=7,253	Kidney N=3,387	Lung N=41,324	Melanoma N=3,838	Overall Uptake per year
Year 2011	2.9%	1.4%	9.4%	0.7%	25.7%	2.7%
Year 2012	4.5%	3.1%	11.0%	1.7%	37.4%	4.6%
Year 2013	7.2%	3.9%	12.7%	2.5%	36.9%	5.9%
Year 2014	7.3%	3.3%	16.0%	4.7%	48.2%	8.0%
Year 2015	10.2%	3,8%	20.8%	8.7%	50.5%	11.7%
Year 2016	12,8%	5.6%	23.5%	12.9%	56.2%	15.6%
Year 2017	14.6%	10.2%	33.0%	18.2%	57.2%	20.4%
Year 2018	17.8%	12.5%	35.8%	27.6%	62.6%	27.8%
Year 2019	32.0%	11.9%	55.6%	32.3%	67.9%	34.1%
Overall Uptake per site	10.9%	5.8%	23.1%	10.2%	48.2%	12.9%

6530 **Poster Session**

Process redesign and daily management to improve cancer care access at the public healthcare system in Sao Jose dos Campos, Brazil.

First Author: Carlos Frederico Pinto, Instituto de Oncologia do Vale, Sao Jose Dos Campos, Brazil

Background: Cancer is the second leading cause of death in Sao Jose dos Campos (SJC, a mid-sized city with 720,000 hab. in Sao Paulo state, Brazil) and the most relevant budget in tertiary care. The City Healthcare Authority created in October 2018 a team to manage and provide more effective and efficient cancer care and access to the public healthcare system by using process redesign and daily management tools (Previna Project). The aim was to guarantee access to cancer specialist and care up to 60 days form diagnosis, understanding that this can impact in cancer morbidity, mortality, and cost. **Methods:** The Previna was grounded in 4 major actions: (1) process redesign (2) escalated daily management system, (3) improve communication channels to all providers connecting primary care to specialized care, (4) and emergency access. (1) Process Redesign involved connecting and linking access to several providers and eliminating unnecessary steps or repeated orders in the system, it also involved alerts into the system for specific conditions like elevated PSA or CEA; positive fecal occult blood test; BIRADS 4-5 mammogram; abnormal PAP smears; and new screening protocols for prostate and colorectal cancer. (2) Daily Management involved internal daily discussions about capacity and review of system alerts or demands. Weekly discussions on specialized procedures including imaging, biopsies, chemo, radiation or surgery flows; and biweekly meetings with all providers (3 hospitals and 4 specialized practices). (3) Communication channels improvements involved a hotline to access flow managers for primary and secondary care units, specialist's consultancy by phone, and (4) emergency access provided for units with special needs or urgent care requirements. All actions were connected by flow managers using alert systems, visual boards, kanban and similar tools to manage daily progress. **Results:** The access to cancer care and treatment up to 60 days improved from 2017 to 2020 almost two-fold with the Previna (Table). Cancer diagnosis also increased substantially, and it is expected to be related to previous periods underdiagnosed patients. Flow redesign also reduced median time to process Her2, ER and PR for breast cancer from 38 days in 2018 to 9 days in 2019 and 4 days in 2020, positively impacting treatment decisions. The hotline access reviewed and answered 2,389 demands from care providers between 2018 and 2020. Access to Cancer Care for ICD C00 – C97 (excl. C44 and C73) in SJC. **Conclusions**: The combined use of daily management, lean tools and flow redesign in the Previna was able to improve access and anticipate cancer diagnosis in a public healthcare system using simple and low-cost initiatives. Research Sponsor: None.

	2016	2017	2018	2019	2020 (oct)
< 60 days	286 (51,1%)	287 (45,9%)	691 (68,8%)	1039 (72,2%)	644 (84,8%)
> 60 days	274	338	314	401	115
Total	560	625	1005	1440	759

6531 **Poster Session**

Disparities in cancer prevalence in African Americans: A United States population study 2021.

First Author: Ahmad Nader Kassem, Metrohealth Medical Center Case Western Reserve University, Cleveland, OH

Background: African-Americans (AA) have the highest incidence and death rates from cancer and the shortest survival of all racial groups in the USA, as reiterated by the American Cancer Society's Cancer Facts and Figures for AA from 2019. We studied cancer prevalence in AA compared to Caucasians, focusing on patients with above-normal Body Mass Index (BMI). **Methods:** Data was collected from Explorys, IBM, a national database including over 73 million patients. Patients were divided based on age (18-64 and $\geq$ 65 years; for female cancers 18-49 and $\geq$ 50 years), race (Caucasians and AA), and BMI (18.5 - $<$ 25 and $\geq$ 25.0 kg/m^2). The odds ratio (OR) and 95% confidence interval (CI) for multiple cancer rates in AA compared to Caucasians were calculated with P values $<$0.001 considered significant. **Results:** N: Normal BMI EW: Excess weight (Females) C: Caucasian S: Significant NS: Non-significant. **Conclusions**: Our results show a significantly lower than expected prevalence of screenable cancers in AA compared to Caucasians, diverging widely from established incidence rates. The difference was more remarkable in pre-Medicare age ($<$ 65 years) and excess weight patients. These disparities are concerning for a compromised healthcare access contributing to underdiagnosis of cancer or shorter survival among AA in the US. Research Sponsor: None.

Cancer	Age 18-64 N AA total: 1000750 (529350) C total: 5930380 (3646380)	OR (CI) P-Value	Age18-64 EW AA total: 2106560 (1273160) C total: 10013170 (5406650)	OR (CI) P-Value	Age $\geq$ 65 N AA total: 220780 (119270) C total: 2262190 (1386540)	OR (CI) P-Value	Age $\geq$ 65 EW AA total: 538570 (330900) C total: 4829500 (2537140)	OR (CI) P-Value
Prostate	AA: 2290 C: 7970	1.39 [1.33-1.46] S	AA:7300 C:25350	1.59 [1.56-1.63] S	AA:12260 C: 77210	1.37 [1.34-1.4] S	AA:25350 C:177480	1.58 [1.55-1.60] S
Lung	AA: 2590 C: 19780	0.78 [0.74-0.81] S	AA: 3500 C: 27740	0.60 [0.58-0.62] S	AA: 5460 C: 46160	1.21 [1.18-1.25] S	AA: 6730 C: 61390	0.98 [0.96-1.01] NS
Colon	AA: 2970 C: 23970	0.73 [0.71-0.76] S	AA: 6250 C: 42650	0.70 [0.68-0.72] S	AA: 5230 C: 46940	1.14 [1.11-1.18] S	AA: 9510 C: 80640	1.06 [1.04-1.08] S
Bladder	AA: 450 C: 4480	0.60 [0.54-0.66] S	AA: 1020 C: 9820	0.49 [0.46-0.53] S	AA: 1840 C: 28740	0.66 [0.63-0.69] S	AA: 3250 C: 54580	0.53 [0.52-0.55] S
Pancreas	AA: 580 C: 2880 18-49 N AA: 381930 C: 2376980	1.19 [1.09-1.30] S	AA: 900 C: 4000 18-49 EW AA: 798050 C: 3119900	1.07 [0.99.0-1.15] NS	AA: 1280 C: 9500 $\geq$ 50 N AA:226700 C: 2418890	1.38 [1.30-1.46] S	AA: 1580 C: 12060 $\geq$ 50 EW AA: 421050 C: 2826420	1.17 [1.11-1.24] S 0.79 [0.78-0.80] S
Breast	AA: 1960 C: 22860	0.53 [0.51-0.56] S	AA: 4490 C: 32820	0.54 [0.52-0.55] S	AA: 12090 C: 150500	0.86 [0.84-0.88] S	AA: 16680 C: 141870	
Cervix	AA: 480 C: 4320	0.69 [0.63-0.76] S	AA: 1050 C: 6780	0.61 [0.57-0.65] S	AA: 1000 C: 10260	1.04 [0.97-1.11] NS	AA: 1080 W: 9300	0.78 [0.73-0.83] S
Uterus	AA: 510 C: 4730	0.67 [0.61-0.74] S	AA: 1270 C: 8170	0.61 [0.57-0.64] S	AA: 1590 C: 17580	0.97 [0.92-1.02] NS	AA: 2210 W: 20290	0.73 [0.70-0.76] S

6532 **Poster Session**

Association of the Affordable Care Act with survival among adolescents and young adults with lymphomas in California. *First Author: Renata Abrahão, University of California, Davis, Sacramento, CA*

Background: Our recent study showed that the implementation of the Affordable Care Act (ACA) was associated with increased health insurance coverage among adolescents and young adults (AYAs, 15–39 years) diagnosed with lymphomas in California and decreased likelihood of late stage at diagnosis. However, AYAs of Black or Hispanic race/ethnicity (vs Whites) and those living in lower socioeconomic (SES) neighborhoods were at higher risk of presenting with advanced stage. We aimed to determine whether the increased insurance coverage under the ACA was associated with improved survival, and to identify the main predictors of survival among AYAs with lymphomas. **Methods:** We used data from the California Cancer Registry linked to Medicaid enrollment files on AYAs diagnosed with a primary non-Hodgkin (NHL) or Hodgkin (HL) lymphoma during March 2005–September 2010 (pre-ACA), October 2010–December 2013 (early ACA) or 2014–2017 (full ACA). Patients were followed from lymphoma diagnosis until death, loss to follow-up or end of the study (12/31/2018). Health insurance was categorized as continuous Medicaid, discontinuous Medicaid, Medicaid enrollment at diagnosis/uninsured, other public or private. We used multivariable Cox proportional regression to examine the associations between all-cause survival and era of diagnosis, adjusting for sex, age and stage at diagnosis, health insurance, race/ethnicity, neighborhood SES, treatment facility, comorbidities, and marital status. **Results:** Of 11,221 AYAs, 5,878 were diagnosed with NHL and 5,343 with HL. Most patients were male (56%), White (45%), presented with earlier stage (I/II, 56%), and had private insurance (57%). The proportion of AYAs who received initial care at National Cancer Institute-Designated Cancer Centers (NCI-CCs) increased from 24% pre-ACA to 31% after full ACA implementation ($p < 0.001$). AYAs diagnosed in the early (aHR = 0.76, 95% CI 0.67–0.88) and full ACA (aHR = 0.55, 95%CI 0.47–0.64) eras had better survival than those diagnosed pre-ACA. Compared to those with private insurance, survival was worse among patients with no insurance (HR = 2.13, 95% CI 1.83–2.49), discontinuous Medicaid (HR = 2.17, 95% CI 1.83–2.56) and continuous Medicaid (HR = 1.93, 95% CI 1.63–2.29) at diagnosis. Regardless of their insurance, older AYAs, males, unmarried, those with later stage (II–IV), residents in lower SES neighborhoods, and those of Black, Hispanic, Asian/Pacific Islander, and American Indian/Alaskan Native race/ethnicity experienced worse survival. **Conclusions:** Following the ACA implementation in California, AYAs diagnosed with lymphomas experienced increased access to care at NCI-CCs and improved survival. Yet, racial/ethnic and socioeconomic survival disparities persisted. Moving forward, policy actions are required to mitigate structural and social determinants of health disparities in this population. Research Sponsor: Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) .

6533 **Poster Session**

Measuring disparities in quality of oncology care across oncology practices. *First Author: Nancy Lynn Keating, Harvard Medical School, Boston, MA*

Background: Equity is now recognized as an essential aspect of health care quality. Racial inequities in clinical performance diminish overall system performance. We assessed the feasibility and reliability of practice-level measures of racial disparities in chemotherapy-associated emergency department (ED) visits and hospitalizations. **Methods:** Using fee-for-service Medicare data, we identified 1,196,970 Black or White fee-for-service Medicare beneficiaries with cancer receiving chemotherapy in 2016-2019, who were attributed to 5511 oncology practices that treated at least 1 Black and 1 White beneficiary (96.4% of all beneficiaries). We studied two CMS quality measures: chemotherapy associated ED visits and chemotherapy associated hospitalizations. For each outcome, we estimated multi-level models with separate practice-level random intercepts for Black and White patients to quantify practice-level Black-White disparities in adjusted rates of these measures and assess the associations of these rates with the proportion of Black patients in the practice. **Results:** Overall, 108,177 Black and 966,381 White beneficiaries with cancer were treated at 1321 practices with reliable estimates (reliability ≥70%) of Black-White differences in rates of chemotherapy-associated ED visits; 101,411 Black and 915,895 White beneficiaries were treated at 1,012 practices with reliable estimates of chemotherapy-associated hospitalizations. These practices treated 80% or more of all Black and White beneficiaries; 10% of these practices treated 75% of Black beneficiaries. The median adjusted Black-White rate difference across practices was +8.9% [interquartile interval (IQI) +5.0%, +12.8%; 5th, 95th percentile -1.8 to +19.2%] for chemotherapy associated ED visits and +4.4% [IQI +1.3%, +7.7%; 5th, 95th percentile -3.5% to +13.5%] for chemotherapy associated hospitalizations. Chemotherapy-associated ED visit rates were 3.2 percentage points higher for Black vs White patients ($P < .001$) at the practice with the mean % of Black patients, but the difference was smaller in practices with more Black patients (0.4 percentage points less for each 10% increase in Black share, $P < .001$). Chemotherapy-associated hospitalization rates were 0.6 percentage points lower for Black vs White patients ($P = .01$) but did not vary by practice racial composition. **Conclusions:** Using data from more than 1000 practices over 4 years, we calculated reliable estimates of practice-level racial disparities in chemotherapy-associated ED visits and hospitalizations. Practice-level performance for these quality measures was generally lower for Black versus White beneficiaries. Measuring and providing feedback on practice-level Black-White disparities in oncology performance measures may be one effective tool for advancing racial equity in care quality for cancer patients receiving chemotherapy. Research Sponsor: Arnold Ventures.

6534 **Poster Session**

What accounts for the racial disparity in survival from estrogen receptor-positive, axillary node-negative breast cancer in the United States? An analysis of the SEER-Oncotype database. *First Author: Kent Hoskins, University of Illinois at Chicago College of Medicine, Division of Medical Oncology, Chicago, IL*

Background: In a previous analysis of the SEER-Oncotype database (Hoskins, et al. JAMA Oncol, 2021), we reported that among women with estrogen receptor (ER)-positive, axillary node-negative breast cancer (BC), Black women were more likely than non-Hispanic White (White) women to have a high risk Oncotype Recurrence Score (RS), and the adjusted hazard for BC-specific death was 1.5-2.5 times higher for Black than for White women within each RS risk category. In this study we examined the role of health insurance, census tract socioeconomic status and tumor biology in the racial disparity in ER-positive BC mortality among US women. **Methods:** We obtained BC-specific survival data from the SEER-Oncotype database for women diagnosed with first primary, stages I-II, ER-positive, node-negative BC between 1/1/2004 -12/31/2015 who had an Oncotype Recurrence Score (RS) through Genomic Health Laboratory. The racial (Black:White) BC mortality disparity was estimated as a disparity hazard ratio (HR) from a series of Cox proportional hazards models of time to BC death. The baseline model adjusted for SEER registry and age at diagnosis (included in all models). We estimated the disparity HR after controlling for variable domains one at a time, as well as cumulatively in this order: neighborhood SES index (a composite measure including census tract education, income and poverty) and insurance (none, public, private); tumor biology (RS, PR status, tumor grade); tumor size; and treatment (surgery type, initiation of radiation and chemotherapy). **Results:** The analysis included 57,428 White and 6,003 Black women with node-negative, ER-positive BC (median follow-up = 54 months). The total disparity HR for BC death was 1.67 (95% CI: 1.37, 2.02). Tract SES and insurance together accounted for 21% of the disparity HR (adjusted HR 1.52, 95% CI: 1.22, 1.88); most of this was due to differences in insurance status, with tract SES accounting for 7% of the disparity when considered in isolation. Tumor biology (RS, PR status and grade) accounted for 30% of the disparity (adjusted HR = 1.41, 95% CI:1.14, 1.75); together, the domains of social determinants and tumor biology accounted for 50% of the disparity HR (adjusted HR = 1.30, 95% CI: 1.04, 1.62). Tumor size and treatment initiation each explained roughly 10% of the disparity HR when considered in isolation but did not account for any of the disparity once other factors were accounted for. Results obtained from additional methods for mediation analyses, including a method of rescaled coefficients and structural equation modeling (SEM) applied to discrete-time survival analysis will also be presented. **Conclusions:** In this study of node-negative, ER-positive BC, much of the BC survival disparity among US women could be explained by racial differences in measured tumor biology and social determinants of health. Research Sponsor: None.

6535 **Poster Session**

Accessibility of Telehealth services for cancer care at cancer hospital in the United States. *First Author: Victoria A. Marks, Yale School of Medicine, New Haven, CT*

Background: The COVID-19 pandemic has dramatically accelerated the availability of telehealth services for patients with cancer. However, little national cross-sectional data is available to inform potential gaps in access. We aimed to characterize overall access to and trends in telehealth availability for new cancer care patients at hospitals across the United States. **Methods:** We performed a cross sectional secret-shopper study to evaluate the availability of telehealth services for new patients for three major cancer types—colorectal, breast, and skin cancer—at Commission on Cancer accredited hospitals during the period of April to November 2020. American Hospital Association and Center for Medicare and Medicaid Service databases were queried to determine hospital characteristics. We described hospital variation in access to telehealth services using descriptive statistics. Univariable and multivariable logistic regression were used to identify factors associated with telehealth availability. **Results:** Of 334 successfully contacted facilities, 248 (74%) offered new patient telehealth services for at least one cancer type. However, access differed by cancer site: telehealth availability for new patients with skin, colorectal, and breast cancer was 47%, 42%, and 38%, respectively. Of the facilities sampled, 47% offered telehealth for one cancer type, 40% for two cancer types, and 14% for all three cancer types. Rates of any telehealth access among the cancer types ranged from 61% at Community Cancer Programs to 100% at NCI Designated Programs. In multivariable logistic regression, facility type was significantly associated with telehealth access while factors such as bed size, ownership, and volume were not significantly associated. **Conclusions:** Although access to telehealth services for patients with cancer has increased, overall gaps in access remain. Within facility differences in telehealth access imply opportunities to better align services within institutions, though further investigation is warranted as these offerings mature. Research Sponsor: None.

Facility Type	Colorectal, Breast, or Skin OR (95% CI)	ColorectalOR (95% CI)	Breast OR (95% CI)	Skin[a] OR (95% CI)
Community (n = 75)	Ref	Ref	Ref	-
NCI Designated (n = 29)	1	9.1 (2.3, 36.6)**	4.9 (1.1, 21.6)*	-
Integrated Network (n = 36)	2.5 (0.9, 7.0)	2.1 (0.8, 5.3)	1.2 (0.5, 3.1)	-
Academic Comprehensive (n = 44)	1.9 (0.6, 6.1)	1.9 (0.7, 5.3)	1.6 (0.6, 4.7)	-
Comprehensive Community (n = 150)	1.4 (0.7, 2.6)	1.1 (0.6, 2.1)	0.7 (0.4, 1.5)	-

[a]Association between facility type and Medicaid acceptance for skin cancer care did not approach significance ($p < 0.1$) on univariable analysis and was not included in the multivariable model. *$p < 0.05$, **$p < 0.01$

6536 **Poster Session**

Significant decline in cancer diagnostic testing in U.S. CMS population during the COVID-19 pandemic. *First Author: Dave Smart, Diaceutics, Belfast, United Kingdom*

Background: The COVID-19 pandemic has caused >400,000 infection related deaths in the US to January 2021. Actions taken to limit COVID-19 infection and mortality could potentially lead to unintended consequences, precipitating excess mortality due to other causes. One such cause is delayed cancer diagnosis. Significant decreases in presentation for cancer diagnosis at the primary care level have been noted in the UK. This study aimed to look for evidence of a similar effect in the US. **Methods:** CMS claims data from JAN18-JUN20 associated with primary diagnosis across 11 cancers (bladder, breast, cervical, colorectal, endometrial, lung, ovarian, pancreatic, prostate, sarcoma and thyroid) were analyzed for use of surgical pathology (SP), a procedure associated with initial diagnosis, and immunohistochemistry (IHC). Test volumes varied widely by test and cancer so were normalized to enable comparison across indications. This was done by dividing the month-on-month difference for the period JAN19-JUN19 vs JAN20-JUN20 by the median monthly test volume for the period JAN18-DEC19 ("pre-COVID period"). Extent and duration of declines in test rates and number of missing patients as the sum of these declines were then determined. The ratio of IHC to SP testing was taken to determine any decline in likely post-initial diagnosis testing. **Results:** There were significant (>10%) declines in test volumes for SP for all 11 cancers at some time in Q1-Q2 2020. Table. Extent, duration and return to pre-COVID levels for SP testing across 11 cancers Median extent and duration of the decline was 56% (range 41.1%-80.4%) and 2 months (range 1- >4). This equates to 32,192 missing diagnoses across all cancers. SP test volumes for all cancers except lung and breast had returned to around pre-COVID levels by JUN20. There was no significant (>10%) increase in normalized SP test volume after the COVID dip for any cancer. While SP showed decreased test volumes across all cancers at some point during the first half of 2020, test volume ratios of IHC to SP showed increases for most cancers in the same time period. **Conclusions:** These data highlight that the decline in patients presenting to their primary care physicians with suspicion of cancer for diagnostic investigation was linked to COVID-19 prevention strategies. No evidence for increased, "catch up" testing to address presentational/diagnostic backlog was observed. Thus, it is predicted that these patients may subsequently present with a more advanced cancer. Potential excess morbidity, mortality and cost associated with absent or delayed diagnosis should be factored into cancer control programs going forward. Research Sponsor: Diaceutics Inc.

Cancer Type	Colorectal	Cervical	Breast	Prostate	Bladder	Thyroid	Sarcoma	Ovarian	Endometrial	Lung	Pancreas
Dip Max (%)	80.4	76.1	75.9	67.7	66.9	55.7	54.3	49.5	48.1	46.0	41.1
Dip Duration (M)	3	2	>4	2	3	3	3	2	2	>4	1
Pre-COVID test volume restored	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y

6537 **Poster Session**

Racial differences in geriatric assessment (GA) impairments, health-related quality of life (HRQOL), and body composition in older adults with gastrointestinal (GI) malignancies: Results from the Cancer and Aging Resilience Evaluation (CARE) registry. *First Author: Grant Richard Williams, Institute for Cancer Outcomes and Survivorship, University of Alabama at Birmingham, Birmingham, AL*

Background: Despite recent cancer advances, racial disparities in outcomes persist. Our objective was to examine racial differences in GA impairments, HRQOL, and body composition metrics as a novel way to understand outcome disparities in older adults with GI malignancies. **Methods:** The CARE registry at the University of Alabama at Birmingham (UAB) is an ongoing prospective cohort study that consecutively enrolls older adults (≥60y) with GI malignancies. The CARE registry utilizes a patient-reported GA that measures a broad range of aging-related health issues. HRQOL is measured using PROMIS Global-10. Computed-Tomography (CT) images are procured to measure skeletal muscle index (SMI) and skeletal muscle density (SMD) from the L3 cross-section. For this study, we examined the adjusted odds ratio (aOR) for racial differences in GA impairments, HRQOL, sarcopenia (defined as men BMI < 25, SMI ≤43 cm^2/m^2; men BMI ≥25, SMI < 53 cm^2/m^2; women SMI < 41 cm^2/m^2), and myosteatosis (defined as BMI < 25, < 41 Hounsfield Units [HU]; BMI ≥25, < 33 HU), adjusting for age, sex, education, cancer type, cancer stage, and comorbidity. **Results:** We included 448 patients with GI malignancies, with self-reported race as White or Black, a completed GA and available CT imaging +/- 60 days of GA completion. Mean age at enrollment was 70±7.2y, 58% were male and 25% were Black. Primary cancer diagnoses included colorectal cancer (33%), pancreatic cancer (25%), and other GI malignancies (52%). Black participants had lower education (high school or < 54% vs. 38%, $p< 0.01$) and were less likely to be married (55% vs 71%, $p< 0.01$). Black participants reported more limitations in activities of daily living (aOR = 2.0 (95% confidence level [CI] 1.01-3.9, $p= 0.03$) and frailty (aOR = 1.9, 95% CI 1.1-3.3, $p= 0.02$). Similarly, Black participants reported lower HRQOL (physical: β coefficient, -2.7; $p= 0.03$; mental: β coefficient, -2.4; $p= 0.03$). Conversely, Black participants were less likely to have sarcopenia (aOR = 0.5, 95% CI 0.3-0.9, $p= 0.02$) and myosteatosis (aOR = 0.12, 95% CI 0.02-0.8, $p= 0.02$). **Conclusions:** Differences in frailty, HRQOL, and body composition between Black and White participants present the first step towards understanding disparities in cancer outcomes amongst older adults. Research Sponsor: U.S. National Institutes of Health.

6538 **Poster Session**

One size does not fit all: Evaluating disparities in lung cancer screening eligibility amongst Hispanic/LatinX and African Americans. *First Author: Coral Olazagasti, Northwell Health, New Hyde Park, NY*

Background: Lung cancer (LC) is the leading cause of cancer death among Hispanic men. African Americans (AA) have the highest LC mortality rate in the United States (US). We sought to identify the tendencies for screening eligibility amongst Hispanic/LatinX (H/L) and AA prior to their LC diagnosis according to the National Comprehensive Cancer Network (NCCN) and The United States Preventive Service Task Force (USPSTF) guidelines. **Methods:** We conducted an observational study in patients diagnosed with LC from 2016 to 2019. Current and former smokers were included in the analysis. Charts were reviewed for demographics, smoking history, family history, personal history of other malignancy, and prior exposures to assess screening their eligibility prior to LC. The chi-square test was used to examine the association between race and ethnicity with each screening criteria. **Results:** A total of 530 subjects were reviewed, of which 428 were included in the analysis. One hundred and fifty three and 245 subjects were ineligible for NCCN and USPSTF screening criteria prior to their LC diagnosis. Twenty-eight of the subjects failing to meet NCCN criteria identified as AA and 12 as H/L. Forty and 20 of the USPSTF ineligible subjects identified as AA and H/L. There was a significant association between ethnicity and individual screening eligibility, where 52% of H/L met NCCN eligibility compared to 20% of H/L who met USPSTF eligibility (p = 0.0010). There was a significant association between ethnicity and USPSTF criteria (p = 0.0166), as 80% of H/L subjects were screening ineligible under USPSTF criteria compared to 56% of non-Hispanic or other [Table]. **Conclusions:** In our study, H/L had significant lower tendencies of meeting the USPSTF LC screening eligibility criteria than non-H/L or other. Notably, there was a profound association between ethnicity and eligibility of screening criteria, where a proportionally higher number of H/L who were ineligible under USPSTF criteria met NCCN criteria. These findings suggest that leniency in the screening criteria can possibly lead to earlier detection of lung cancer in high-risk individuals. Our study is in line with developing data that minority individuals at high-risk for lung cancer can be missed, mainly if current USPSTF criteria was to be applied. Recently, USPSTF has modify their criteria which may benefit more of these individuals. To improve rates of screening and overall mortality of minorities, organizations should continue to re-evaluate and liberalize their screening guidelines. Research Sponsor: None.

Screening criteria eligibility per race and ethnicity.

	NCCN Eligible			USPSTF Eligible		
	Yes (%)	No (%)	p-value	Yes (%)	No (%)	p-value
Race						
African American	56.9	43.1	**0.206**	38.5	61.5	**0.496**
White, Asian, other	65.6	34.4		43.8	56.2	
Ethnicity						
Hispanic/LatinX	52.0	48.0	**0.201**	20.0	80.0	**0.017**
Non-Hispanic/LatinX	65.0	35.0		44.4	55.6	

6539 **Poster Session**

Insurance status and survival in diffuse large B-cell lymphoma: A National Cancer Database study before and after the Affordable Care Act. *First Author: Antoine N Saliba, Mayo Clinic, Division of Hematology, Rochester, MN*

Background: The impact of insurance status on survival in diffuse large B-cell lymphoma (DLBCL), the most common aggressive lymphoma, has not been evaluated after the implementation of the Affordable Care Act (ACA). The aim of this study is to compare overall survival (OS) in patients across insurance status groups and in the periods before and after the ACA. **Methods:** Adult patients with newly diagnosed DLBCL were identified from the National Cancer Database. The analysis was restricted to patients 64 years of age or younger as most patients 65 years or older are eligible for Medicare under the ACA. The 2004-2017 period was chosen to represent the immunochemotherapy era preceding and following the ACA. Logistic regression was used to explore associations between abstracted variables and insurance status groups. The Kaplan-Meier method and Cox proportional hazards model were used for survival analysis. **Results:** 93,692 adults (age < 64 years) with newly diagnosed DLBCL and known insurance status were identified (41.3% female, median age 54 years [range: 18 – 64], 81.8% White and 12.1% Black). 7,211 (7.7%) patients were uninsured, 64,744 (69.1%) had private insurance, 11,936 (12.7%) had Medicaid, and 9,801 (10.5%) had Medicare. When compared to insured patients (private insurance, Medicaid or Medicare), uninsured patients were more likely to have a median household outcome of < $38,000 [OR 1.93 (95% CI 1.79-2.07)], less likely to receive chemotherapy [OR 0.69 (0.64-0.77)], more likely to be male [OR 1.14 (1.07-1.21)], more likely to be non-White [OR 1.30 (1.20-1.40), and more likely to present with stage III or IV disease [OR 1.24 (1.16-1.32)]. Uninsured patients had an inferior OS [HR 1.21 (95% CI 1.15-1.27)] when compared to insured patients after adjustment for baseline comorbidity (Charlson-Deyo score ≥2), advanced stage, treatment with chemotherapy, and sociodemographic factors including sex, age, race, household income, facility type (academic/community), and location (urban/rural). With a median follow-up time of 14.8 years (95% CI 14.6-not reached), median OS was lower in uninsured patients [13.4 years (12.3-not reached) vs 14.8 years (14.7-not reached); p < 0.0001]. Despite the lack of major changes in DLBCL therapies, a diagnosis after the implementation of the ACA (in 2010 or later) was associated with a superior OS when compared with the outcomes of patients diagnosed in 2010 or earlier [HR 0.93 (95% CI 0.90-0.95)]. Similarly, five-year OS was superior in the insured group [HR 0.93 (95% CI 0.89-0.96)]. **Conclusions:** Uninsured patients with DLBCL and < 64 years old had inferior OS when compared with insured patients, and uninsured status emerged as an independent risk factor for inferior OS. Our data highlight the independent effect of insurance disparities - a potential indicator of variations in access to health care - on survival in DLBCL. Research Sponsor: None.

6540 **Poster Session**

High incidence of concurrent disease states detected during mobile lung cancer screening in an underserved population. *First Author: Daniel R. Carrizosa, Atrium Health Levine Cancer Institute, Charlotte, NC*

Background: Studies such as the National Lung Screening Trial (NLST; N Engl J Med 2011;365:395-409) have shown a survival benefit to low-dose Lung CT screening in high-risk smokers. Levine Cancer Institute (LCI) initiated the first mobile low dose computerized tomographic (LDCT) lung screening program for underserved populations in 2017. In addition to being able to intervene early in the natural history of lung cancer, the project has also shown a previously unreported high incidence of incidental diseases in this population. We characterize these findings in 1198 patients. **Methods:** From May 2017, subjects with criteria eligible for NLST screening were identified and underwent LDCT for lung cancer detection. Patients screened in the program were all uninsured or underinsured, mean age 60.8 years, 18% were African American, 3% Latin-x and 78% were rural with an overall 47.1 mean pack-year smoking history. These patients were screened using a novel mobile LDCT (J Clin Oncol 37, 2019 suppl; abstr 6567) created for this program. By December 2020, 1198 patients completed their first screening. All CT scans were reviewed by two separate radiologists and were reviewed for quality assurance by a separate expert multidisciplinary team. **Results:** Of the 1198 subjects, 84% (1006 subjects) were found by LDCT to have a least one incidental disease. More than half of the subjects (645, 53.8%) had coronary atherosclerosis. Of those, 25% (183) were described to have at least moderate disease with 8% (96) described as severe. Overall, 42% (504) were found to have emphysema and 25% (299) had vascular atherosclerotic disease; 1.8% (22) of those screened had a detected aortic aneurysm. In total, thirty separate disease findings were found (listed from fourth to tenth most common finding: degenerative spine changes [205], cholelithiasis [59], hiatal hernia [52], pericardial effusions [38], fatty liver [32], kidney stone [3]), and cardiomegaly [30]). 3.5% (42) were found to have an undiscovered breast, adrenal, liver or kidney mass that required further workup. **Conclusions:** The number of incidental findings in our mainly rural underserved subject group was very high (84%). 35.5% of patients in the National Lung Screening Trial died from heart disease or respiratory disease. These numbers have not been overtly discussed and our study confirms the number of concerning incidental diseases that can lead to morbidity or mortality. In this high-risk, underserved population of heavy smokers, the opportunity for positive impact on other disease states can be increased by a mobile lung cancer screening program by increasing access to care. Research Sponsor: Bristol Myers Squibb Foundation; Leon Levine Foundation.

6541 **Poster Session**

Racial disparities in second-line (2L) treatment and overall survival among patients (pts) with hormone receptor positive HER2 negative (HR+HER2-) metastatic breast cancer (mBC) treated in routine practice. *First Author: Xiaoliang Wang, Flatiron Health, New York, NY*

Background: In the US, African American (AA) women have similar incidence of breast cancer (BC) as White women, but have 40% higher BC mortality. This disparity results from differences in biological and social determinants of cancer treatment. Previous studies have focused primarily on first-line(1L) treatment, but little is known about racial differences in treatment beyond 1L and the impact these differences may have on outcomes. **Methods:** This analysis utilized data from the nationwide Flatiron Health electronic health record (EHR)-derived de-identified database and included pts with mBC initiating 2L treatment between 2/3/2015-2/29/2020. 2L treatment was caterogized broadly as CDK 4/6 inhibitors (CDKi), endocrine monotherapy, everolimus combination therapy, and chemotherapy and other systemic therapies. Real-world overall survival (rwOS) was defined as time from 2L initiation to death (censored at last EHR activity). Multinomial logistic regression was used to assess the likelihood of 2L treatment between AA and White (reference) pts, adjusted for demographics and clinical factors, including ECOG performance score, 1L treatment and 1L progression. Median rwOS was estimated using the Kaplan-Meier method and adjusted hazard ratios (aHR) were estimated using multivariable Cox proportional hazards models additionally adjusted for 2L treatment. Stratified analysis was conducted by 1L and 2L treatment. **Results:** A total of 389 AA and 2776 White pts were included. Compared to White pts, AA pts were younger (median age: 61 vs 65) and more likely to be under-insured (8% vs 3%), and present with de novo metastatic disease (30% vs 26%). AA pts were also less likely to receive CDKi in 2L (29% vs 35% in White), but this difference was not statistically significant after adjustment (OR = 0.83; 95% CI: 0.62-1.11). Compared to White pts who had a median rwOS of 25.6 months (95% CI: 24.5-27.4), AA pts had a median rwOS of 20.4 months (95% CI: 17.3-24.0). Poorer rwOS among AA pts was observed across all 2L treatment groups. After adjusting for covariates and 2L treatment, the observed rwOS difference was no longer statistically significant. However, in stratified analysis among pts who did not receive 1L CDKi, AA pts had 48% higher hazard of death if they received 2L CDKi (aHR = 1.48; 95% CI: 1.08-2.00), and 49% higher hazard of death if received 2L endocrine monotherapy (aHR = 1.49; 95% CI: 1.15-1.94). In contrast, adjusted rwOS was similar between AA and White pts among those who received 1L CDKi. **Conclusions:** These exploratory findings suggest that AA pts were less likely, partially associated with other factors, to receive CDKi at 2L. In addition, AA pts had worse rwOS than White pts even after receiving 2L CDKi among those who did not receive 1L CDKi. This disparity was not observed among patients who received 1L CDKi. Research Sponsor: This study was sponsored by Flatiron Health, which is an independent subsidiary of the Roche Group.

6542 **Poster Session**

Prostate cancer treatment disparities during the COVID-19 pandemic, lessons from a multi-institutional collaborative. *First Author: Adrien Bernstein, Fox Chase Cancer Center, Philadelphia, PA*

Background: Minority communities have been disproportionately affected by COVID-19, however the impact of the pandemic on prostate cancer (PCa) treatment is unknown. To that end, we sought to determine the racial impact on PCa surgery during the first wave of the COVID-19 pandemic. **Methods:** After receiving institutional review board approval, the Pennsylvania Urologic Regional Collaborative (PURC) database was queried to evaluate practice patterns for Black and White patients with untreated non-metastatic PCa during the initial lockdown of the COVID-19 pandemic (March-May 2020) compared to prior (March-May 2019). PURC is a prospective collaborative, which includes private practice and academic institutions within both urban and rural settings including regional safety-net hospitals. As data entry was likely impacted by the pandemic, we limited our search to only practices that had data entered through June 1, 2020 (5 practice sites). We compared patient and disease characteristics by race using Fisher's exact and Pearson's chi-square to compare categorical variables and Wilcoxon rank sum to evaluate continuous covariates. Patients were stratified by risk factors for severe COVID-19 infection as described by the CDC. We determined the covariate-adjusted impact of year and race on surgery, using logistic regression models with a race*year interaction term. **Results:** 647 men with untreated non-metastatic PCa were identified, 269 during the pandemic and 378 from the year prior. During the pandemic, Black men were significantly less likely to undergo prostatectomy compared to White patients (1.3% v 25.9%;$p < 0.001$), despite similar COVID-19 risk-factors, biopsy Gleason grade group, and comparable surgery rates prior (17.7% vs. 19.1%;$p = 0.75$). White men had lower pre-biopsy PSA (7.2 vs. 8.8 vs. $p = 0.04$) and were older (24.4% vs. 38.2% < 60yr;$p = 0.09$). The regression model demonstrated an 94% decline in odds of surgery(OR = 0.06 95%CI 0.007-0.43;$p = 0.006$) for Black patients and increase odds of surgery for White patients (OR = 1.41 95%CI 0.89-2.21;$p = 0.142$), after adjusting for covariates. Changes in surgical volume varied by site (33% increase to complete shutdown), with sites that experienced the largest reduction in cancer surgery, caring for a greater proportion of Black patients. **Conclusions:** In a large multi-institutional regional collaborative, odds of PCa surgery declined only among Black patients during the initial wave of the COVID-19 pandemic. While localized prostate cancer does not require immediate treatment, the lessons from this study illuminate systemic inequities within healthcare, likely applicable across oncology. Public health efforts are needed to fully recognize the unintended consequence of diversion of cancer resources to the pandemic in order to develop balanced mitigation strategies as viral rates continue to fluctuate. Research Sponsor: PURC is funded by the Health Care Improvement Foundation through practice participation.

6543 **Poster Session**

COVID-19 and exacerbation of screening mammography inequities. *First Author: Gary X. Wang, Massachusetts General Hospital, Boston, MA*

Background: After state-mandated cessation of screening mammography (SM) in Spring 2020 due to COVID-19, centers were urged to resume screening, particularly of patients at increased risk. As our tertiary-care medical center's screening program provides SM at four sites across our metropolitan area, we examined whether sites that historically served more patients from more disadvantaged areas returned slower to pre-COVID volumes. **Methods:** Patient records were linked by ZIP code of residence to ZIP Code Tabulation Area (ZCTA)-level area-based social metrics (ABSMs) from the 2014-2018 American Community Survey. We compared baseline pre-COVID (May-October, 2015-2019) SM population ABSMs between our four imaging sites for: % persons below poverty (≥ vs < 10%), % persons of color (POC) (quintiles: top 2 vs bottom 3), index of racialized economic segregation (quintiles: bottom 2 [more POC low-income households] vs top 3 [more white non-Hispanic (WNH) high-income households]); and race/ethnicity (% WNH vs POC). We modeled weekly SM volumes per screening day by site using Poisson regression and tested for weekly differences at each site, COVID-era (May-October 2020) vs pre-COVID; and tested for monthly differences in SM population composition by logistic regression modeling. **Results:** There were 89,082 pre-COVID and 16,220 COVID-era SM exams. At pre-COVID baselines the four sites differed in population composition by ABSMs and race/ethnicity (all chi-square P values < .001) (Table). The two sites that served more disadvantaged populations (A, B) returned slower to pre-COVID volumes (site-specific weekly screening volume no longer different [$P > .05$] vs pre-COVID) (Table). As a result, compositions of the aggregate SM population across all sites showed a smaller proportion of patients from the most disadvantaged ZCTAs by ABSMs (all P values < .001) before returning to pre-COVID compositions three months after SM resumption. **Conclusions:** SM was slower to return to pre-COVID volumes at imaging sites that historically served lower-income communities of color. As a result, our COVID-era SM population skewed away from patients in disadvantaged ZCTAs. Our findings highlight the need to monitor for emergent disparities in the pandemic era. Future work will focus on understanding causes of inequitable SM engagement across our imaging sites to mitigate care disparities for our most vulnerable patients. Research Sponsor: None.

Composition of patients screened by imaging site, 2015-2019, and time needed to return to pre-COVID screening volumes in the COVID era at each site.

	Zip code tabulation area-level area-based social metrics		Persons of color (POC) in screening population		Time to return to pre-COVID volume
	Poverty rate ≥ 10%		POC, top 2 quintiles (more POC)		Segregation, bottom 2 quintiles (more POC low-income households)
Site A	68.8%	63.5%	46.2%	42.3%	14 weeks
Site B	41.6%	21.8%	15.6%	21.9%	12 weeks
Site C	13.5%	4.3%	3.5%	12.3%	5 weeks
Site D	25.9%	8.5%	7.4%	5.9%	3 weeks

6544 **Poster Session**

Association of parental cancer and school absenteeism, medical financial hardship, healthcare use, and psychological distress among minor children. *First Author: Zhiyuan Zheng, American Cancer Society, Atlanta, GA*

Background: A cancer diagnosis can affect the entire family, including minor children. However, little is known about the association of parental cancer on minor children's school absenteeism, family's financial ability to afford healthcare for children, as well as healthcare use, psychological distress, and behavioral problems. **Methods:** The 2015 to 2018 National Health Interview Survey was used to identify minor children (ages 5-17 years) whose parent(s) reported a cancer history (n = 695, representing 1.2 million children) and children whose parent did not report a cancer history (n = 19,122, representing 35.7 million children). Separate multivariable logistic regressions were used to compare school absenteeism, financial hardship, healthcare use, and psychological distress among children with and without parental cancer history. All analyses adjusted for children's age group (5-11 years, 12-14 years, and 15-17 years), sex, family income as a percentage of the federal poverty line, marital status of their parents, survey year, and region. **Results:** Children of cancer survivors were more likely to receive annual well-child checkups, experience school absenteeism, take prescription medications for more than 3 months, visit hospital emergency rooms, suffer psychological distress, and have behavioral problems than children of parents without a cancer history (Table). **Conclusions:** Parental cancer history is associated with disruption in their minor children's life. The associated psychological distress and physical and emotional health among these children may develop into more severe health issues in adulthood. Special attention to minor children of parents with a cancer history may be required to help prevent development of longer-term physical and mental health problems. Research Sponsor: None.

Adjusted results of measures of impact of parental cancer on minor children.

	Children of cancer survivors				Other children		
	%	95%CI		p	%	95%CI	
Medical financial hardship (unable to afford prescription medicine, mental care, dental care, eyeglasses ≤12 m)	75.9 8.8	71.4 6.2	80.5 11.5	.011 .211	70.0 7.1	69.1 6.6	70.9 7.6
Health problems requiring more than 3 months of prescription medication	23.5	19.4	27.5	<.001	15.4	14.7	16.1
Hospital emergency visit ≤12 m	19.9	16.1	23.7	.028	15.7	15.0	16.4
No well-child checkup ≤12 m	13.0	10.0	16.1	.013	16.9	16.2	17.7
Often worried ≤6 m	31.8	27.3	36.3	.022	26.5	25.7	27.3
Often unhappy, depressed, or tearful ≤6 m	14.7	11.6	17.8	.044	11.5	10.9	12.1
Problems with attention span/completing chores or homework ≤6 m	14.7	11.5	17.9	.020	10.9	10.3	11.5
Difficulties with emotions, concentration, behavior, or getting along with others	31.8	27.2	36.4	<.001	22.4	21.6	23.2

6545 **Poster Session**

Barriers to web-based symptom management systems (web-SyMS). *First Author: Michael J. Hassett, Dana-Farber Cancer Institute, Boston, MA*

Background: Web-SyMS can reduce the burdens of cancer and its treatment. While patients frequently express willingness to use these systems, only a subset actively engages with them. Some patients may lack the tools and confidence needed to benefit from web-SyMS. We sought to characterize these barriers among community-based cancer patients receiving care across six diverse healthcare systems. **Methods:** We surveyed patients receiving chemotherapy at three healthcare systems (Baptist, TN; Maine Medical, ME; Dana-Farber, MA) and patients recovering from cancer-directed surgery at three healthcare systems (West Virginia University, WV; Dartmouth-Hitchcock, NH; Lifespan, RI). Surveys were conducted as part of a pre-implementation analysis of eSyM – an EHR-embedded web-SyMS that collects, tracks, and manages patient reported outcomes during cancer therapy. **Results:** Among 563 respondents, access to tech devices (i.e., tablet, computer, or smartphone) was high: 78% reported access to ≥2 devices and only 5% reported access to no devices. However, confidence using tech devices to accomplish online tasks varied: 45% very confident, 38% somewhat confident, 11% little-no confidence. Compared to medical oncology patients, surgery patients were more likely to report being very confident (57% vs. 31%). There were significant differences based on patients' self-reported tech confidence (Chi-square $P<.05$ for all values in the table). **Conclusions:** Low self-reported tech confidence may identify patients who are at high risk for experiencing the burdens of cancer but may be less likely to benefit from web-SyMS. Addressing this barrier is critical to improving outcomes and addressing disparities. Clinical trial information: NCT03850912. Research Sponsor: U.S. National Institutes of Health.

	Very (n=254)	Somewhat (n=212)	Little or No (n=61)
Not employed (% retired, disabled, other)	38	62	76
Education (% high school or less)	18	25	52
Health literacy (% little-no confidence)	3	11	22
Health numeracy (% little-no confidence)	7	17	32
Go up & down stairs (% much difficulty-unable)	9	11	23
Self-manage symptoms (% little-no confidence)	9	10	20
Easy to ask for help when I don't understand something (% disagree)	8	10	20
Pain interferes with daily activities (% quite a bit-very much)	14	18	26
Average fatigue (% quite a bit-very much)	26	27	38

6546 **Poster Session**

Disparity in telehealth and emergency department use among Medicaid and commercially insured patients receiving systemic therapy for cancer in Washington State following the COVID-19 Pandemic. *First Author: Scott David Ramsey, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Washington was the first US state to experience the COVID-19 pandemic. Transmission risks and patient fears of visiting oncology practices during its onset resulted in rapid adoption of telehealth services. We hypothesized that the pandemic would widen disparities in oncology practice visits between Medicaid and commercially insured patients, resulting higher rates of emergency department (ED) visits during initial treatment. **Methods:** Linking Washington State SEER records with Medicaid and commercial insurance enrollment and claims records, we compared adults age <65 with new solid tumor malignancies who received systemic treatment at academic and community oncology practices. Persons starting therapy March – June 2020 (COVID) were compared with those starting therapy March-June 2017-2019 (Pre-COVID). Poisson regressions were used to evaluate differences in oncology practice office visits and telehealth visits. Logistic regressions were used to evaluate the likelihood of at least one ED admission among patients starting systemic therapy pre- and post-COVID. **Results:** Among patients who met inclusion criteria (652 Commercial, 349 Medicaid), Medicaid enrollees had more advanced disease and more comorbidity versus commercial enrollees. In unadjusted analysis of E&M and telehealth service visit codes, office-based visits fell for both insurance groups (Table) while telehealth service visits (negligible pre-COVID) were higher for commercial versus Medicaid enrollees post-COVID. The proportion of persons with ≥ 1 ED visit during therapy fell for both insurance groups. In Poisson models, Medicaid enrollees had significantly fewer total visits (P=0.001) and fewer telehealth visits ($p<0.001$) compared commercial enrollees during the COVID period. In the logit models, ED visits trended lower for both groups after COVID (OR 0.53 95% CI 0.279 to 1.008). Among Medicaid enrollees, persons ages 40-49 and breast cancer patients were more likely to visit the ED. Among the commercially insured, persons with 2 or more comorbidities were more likely to visit the ED. The pre-post COVID change in likelihood of an ED visit was not significantly different between insurance groups (p=0.355). **Conclusions**: In Washington State, the COVID-19 pandemic created a substantial disparity in access to office-based and telehealth care for low-income patients receiving systemic therapy for new cancers. Reduced oncology practice visits among Medicaid patients did not widen existing disparities in utilization of emergency care. Research Sponsor: U.S. National Institutes of Health.

Average visit days per patient, March- June.

	Commercial Insurance				Medicaid			
Year	Office	Tele- health	Total Oncology Visits	ED Visits	Office	Tele health	Total Oncology Visits	ED Visits
Pre-COVID	5.79	0.00	5.79	14.43%	6.08	0.00	6.08	21.67%
COVID	5.50	0.87	6.37	9.15%	4.68	0.53	5.27	18.35%

6547 **Poster Session**

Disruptions to U.S. medical oncology care during the COVID-19 Pandemic: CancerLinQ Discovery (CLQD) analysis. *First Author: Abdul-Rahman Jazieh, Cincinnati Cancer Advisors, Cincinnati, OH*

Background: The COVID-19 pandemic disrupted all facets of healthcare delivery including cancer care. This study evaluates the disruptions to US medical oncology practice during the pandemic in terms of number and type of patients (pts) encounters to determine the impact on continuity of patient care. **Methods:** We conducted a retrospective cohort analysis using the CLQD electronic health record database, containing data from 2+ million pts from all 50 states. We assessed changes in the monthly proportions of visit encounter types (in-person outpatient [IPOP] and telehealth [TE]) for new and established patients (NP and EP) with an invasive malignancy, benign or in situ neoplasm, or benign hematology diagnosis having an encounter between 1/1/2018 and 9/30/2020. **Results:** 781,945 pts were studied. Median age on 1/1/2018 was 64 years (IQR: 53-73), 38% were female, and 58% had an invasive malignancy. From 12/2019 to 9/2020, total monthly encounters dropped from 157,964 to 90,662. Monthly IPOP visits for NP dropped from 11.2% to 7.9%, an absolute drop of 3.3% and a relative drop of 30%; TE for NP increased by 1.1% (Table). Monthly IPOP visits for EP, as a percentage of all visits, dropped from 94.4% to 86.6% from 12/2019 to 6/2020 but rebounded to 90.4% by 9/2020. Fraction of TE increased substantially during the pandemic period reaching a peak in 6/2020 (13.8% for EP and 1.6% for NP) and decreased in 9/2020 to 9.6% and 1.1% for EP and NP, respectively. Compared to non-Hispanic patients, Hispanic patients had a larger reduction in IPOP and more TE during the study period. Percentage of monthly encounters, by type, from baseline*. **Conclusions:** We observed a reduction in the absolute number and monthly percentage of IPOP encounters during the COVID-19 pandemic. For EP, increases in TE does not fully compensate for reductions in IPOP. The reduction in IPOP NP encounters is particularly concerning since it was not accompanied by a compensatory increase in TE. The reduction in NP is consistent with reported pandemic-associated reductions in cancer screening and suggest a notable delay in cancer diagnoses during the pandemic. Reduction in Hispanic IPOP encounters warrants further evaluation. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

	New IPOP, % (% change from 12/2019)	New TE, % (% change from 12/2019)	Established IPOP, % (% change from 12/2019)	Established TE, % (% change from 12/2019)
Overall, 12/2019 (Baseline)	11.2	0	94.4	0.4
Overall, 06/2020	8.1 (-3.1)	1.6 (+1.6)	86.6 (-7.8)	13.8 (+13.4)
Overall, 09/2020	7.9 (-3.3)	1.1 (+1.1)	90.4 (-4.0)	9.6 (+9.2)
Non-Hispanic, 12/2019	10.8	0	94.7	0.4
Non-Hispanic, 06/2020	7.9 (-2.9)	1.5 (+1.5)	87.2 (-7.5)	13.1 (+12.7)
Non-Hispanic, 09/2020	7.9 (-2.9)	1.1 (+1.1)	90.9 (-3.8)	9.0 (+8.6)
Hispanic, 12/2019	12.9	0	93.9	0.8
Hispanic, 06/2020	7.9 (-5.0)	3.3 (+3.3)	82.5 (-11.4)	21.4 (+20.6)
Hispanic, 09/2020	7.4 (-5.5)	2.3 (+2.3)	87.3 (-6.6)	16.1 (+15.3)

*Row totals may be >100% because patients may have >1 encounter per month.

6548 **Poster Session**

Access to cancer care for Medicaid patients at cancer hospitals in the United States. *First Author: Victoria A. Marks, Yale School of Medicine, New Haven, CT*

Background: As the result of expansions associated with the Affordable Care Act (ACA), one in five Americans are now insured through Medicaid. Despite overall increases, access to care for Medicaid-insured patients with cancer may be limited by facilities due to lower reimbursement and administrative burden. We aimed to directly assess facility-level acceptance of Medicaid patients with a new diagnosis of cancer. **Methods:** We performed a cross-sectional secret shopper study to evaluate access to cancer care for colorectal, breast, urologic, and skin cancer at Commission on Cancer (CoC) accredited hospitals. We studied the relationship between Medicaid access and facility-level characteristics assessed through American Hospital Association and Center for Medicare and Medicaid Service data using univariable statistics and multivariable logistic regression. **Results:** Among 334 CoC facilities contacted, the overall rate of Medicaid acceptance for at least one investigated cancer type was 99% (n = 331). However, we identified hospital-level variation in Medicaid acceptance across cancer types, where Medicaid acceptance for colorectal, breast, urologic, and skin cancer was 90%, 96%, 87%, and 80%, respectively. Of the hospitals that accepted Medicaid, 2% accepted Medicaid for one cancer type, 8% for two, 21% for three, and 68% for all four cancer types. In multivariable logistic regression, odds of Medicaid acceptance were lowest in comprehensive community cancer centers ($p < 0.05$ for colorectal and urologic cancer) and for-profit designated facilities ($p < 0.05$ for urologic and skin cancer) (Table). Hospitals in states with Medicaid expansion were also more likely to accept Medicaid for urologic (OR: 2.5, 95% CI: 1.2-5.2) and breast (OR: 12.8, 95% CI: 2.7-60.2) cancer care. **Conclusions:** Access disparities persist for patients with Medicaid, with acceptance rates differing substantially within and between facilities. Facility-level differences in Medicaid access among CoC facilities are notable given the use of hospital registry data to estimate ACA-related effects. Research Sponsor: None.

Hospital Characteristic		ColorectalOR (95% CI)	UrologicOR (95% CI)	Breast[a]OR (95% CI)	SkinOR (95% CI)
Facility Type	Community (n = 75)	Ref	Ref	Ref	Ref
	NCI Designated (n = 29)	0.2 (0.0, 2.2)	0.4 (0.0, 4.1)	-	1
	Integrated Network (n = 36)	0.4 (0.0, 3.2)	0.6 (0.1, 2.8)	-	0.5 (0.1, 2.0)
	Academic Comprehensive (n = 44)	0.8 (0.1, 10.2)	0.8 (0.1, 6.5)	-	0.9 (0.2, 5.1)
	Comprehensive Community (n = 150)	0.2, (0.0, 0.8)*	0.27 (0.1, 0.8)*	-	0.4 (0.2, 1.0)
Ownership	Government (n = 39)	Ref	Ref	Ref	Ref
	For-profit (n = 38)	0.6 (0.1, 4.3)	0.1 (0.0, 1.0)*	-	0.1, (0.0, 0.7)*
	Nongovernment, Not-for-profit (n = 257)	0.9 (0.2, 4.1)	0.2 (0.0, 1.7)	-	0.4 (0.1, 1.6)

[a] Association between facility type and Medicaid acceptance for breast cancer care did not approach significance ($p < 0.1$) on univariable analysis and was not included in the multivariable model. *$p < 0.05$

6549 **Poster Session**

Disparities in reporting and representation of women, older adults and racial minorities in immune checkpoint inhibitor (ICI) clinical trials. *First Author: Irbaz Bin Riaz, Mayo Clinic, Rochester, MN*

Background: Representation and outcomes of women, older adults, and racial minorities in ICI trials has not been previously described. **Methods:** MEDLINE and Embase were searched to identify ICI RCTs. Data for trial characteristics, proportion of trials reporting race, age and sex as well as the proportion of patients by race, age and sex enrolled in ICI trials was collected. Descriptive statistics were reported for trials reporting minority representation and proportion of included patients by race, age and sex. Disparities in representation were calculated using enrollment incidence disparity (EID) and enrollment incidence ratios (EIR) by comparing trial enrollment against U.S. population-based estimates acquired from the SEER 18 incidence database. The relationship of EID to key trial characteristics were compared using standard parametric and non-parametric statistical tests. Trends in EIR were analyzed using the Joinpoint Regression Analysis software. **Results:** 108 ICI trials from 2009 to 2020 with 48,360 patients were included in this analysis. All RCTs reported sex (101/101). 78 trials reported race (72%), of which only 41 trials (38%) reported data on all 5 U.S. racial categories (Black, White, Asian, Pacific Islander and Native American). Participation of Black patients was reported in 66 trials (61%), White participants in 78 trials (72%), Asians in 69 trials (64%), Native Americans and Pacific Islanders in 41 trials (38%), and Hispanics in 24 trials (22%). Age categories were inconsistently defined, and 80 trials (74%) reported the proportion of patient by age categories. Subgroup analyses of clinical outcomes by race, age and sex were reported in 17 (22%), 62 (79%) and 57 (73%) trials respectively. Women (trial proportion [TP]: 32%; EIR: 0.77), patients aged $\geq$ 65 years (TP: 42%; EIR: 0.74), Black participants (TP: 1.8%; EIR: 0.17) and Hispanic participants (TP: 5.9%; EIR: 0.67) were largely underrepresented, and Asians were overrepresented (TP: 15.9%; EIR: 2.64). Black patients were underrepresented across all cancer types. Similarly, women, older adults ($>$ 65 years of age) and Hispanic patients were consistently underrepresented across cancer types with few exceptions. Representation of older adults increased significantly from 2010-2020 (APC: 2.72), while representation of Black patients decreased significantly from 2009-2020 (APC: -23.37). Black patients were found to be significantly underrepresented in phase III trials ($p = 0.0005$), trials with OS as the primary endpoint ($p = 0.004$), and PD1 inhibitor trials ($p = 0.002$). Hispanics were significantly underrepresented in PD1 inhibitor trials ($p = 0.003$). **Conclusions:** There is both suboptimal reporting about participation and underrepresentation of women, racial minorities (particularly Black patients) and older adults in ICI trials as compared to their cancer incidence. Research Sponsor: None.

6550 **Poster Session**

Racial disparity in uterine cancer treatment and survival: A matter of Black women's lives. *First Author: Alexandrina Balanean, Cardinal Health, Dublin, OH*

Background: Despite similar incidence rates of uterine cancer (UC) in Black and White women, the former have worse prognosis and survival. Absence of denominator correction for UC hysterectomy (prevalence varies within the United States [US] by race/region) may underestimate incidence. The objective of this study is to compare treatment and survival of patients with UC by race in a large, contemporary, population-based study with at least 5 years of follow-up. **Methods:** With the latest available data from the Surveillance, Epidemiology, and End Results database, comparisons between Black and White patients were made using chi-square and Mann-Whitney tests. Cox proportional hazards regression estimated the adjusted risk of mortality by including age at diagnosis, race, US region, tumor histology/stage/grade, and receipt of hysterectomy as covariates. **Results:** A total of 105,036 women (11,028 Black and 94,008 White) newly diagnosed with UC in 2000-2013 and followed through 2018 were identified. Median age at diagnosis was 62 years, and more patients in the South were Black (41% vs 17%, $P<.0001$). Higher rates of type 2 (15% vs 6%), late-stage (44% vs 28%), and high-grade (48% vs 25%) tumors at diagnosis were also found in Black women (all $Ps<.0001$; Table). Compared with White women, Black women had lower 5-year survival rate (18% vs 37%, $P<.0001$), shorter survival (median 49 vs 78 months, $P<.0001$), and higher adjusted mortality risk (hazard ratio [HR]: 1.3, 95% CI: [1.3, 1.4], $P<.0001$). Lack or unknown status of hysterectomy was also associated with higher death risk (HR: 3.6, 95% CI: [3.4, 3.9], $P<.0001$). **Conclusions:** Correcting for hysterectomy attenuates racial disparity in incidence; however, black women have inferior outcomes primarily due to increased aggressive histology, late-stage, and high-grade tumors as well as decreased use of hysterectomy. Underestimation of at-risk populations may be misdirecting cancer control efforts, highlighting the importance of accurate reporting to inform potential treatment adaptations. Next steps are to assess cancer-specific mortality with Fine-Gray competing risk models. Research Sponsor: Cardinal Health.

UC cohort, 2000-2018.

	All (N=105,036)	Black (n=11,028)	White (n=94,008)	*P*-value
Type 2 histology (n, %) * *(N=103,586; n=10,817; n=93,039)*	7,228 (7.0%)	1,635 (15.1%)	5,593 (6.0%)	<.0001
Late-stage (regional, distant) tumor (n, %)	31,460 (30.0%)	4,862 (44.1%)	26,598 (28.3%)	<.0001
High-grade (3, 4) tumor (n, %) * *(N=87,817; n=8,615; n=79,202)*	24,036 (27.4%)	4,136 (48.0%)	19,900 (25.1%)	<.0001
Had hysterectomy (n, %)	92,057 (87.6%)	8,782 (79.6%)	83,275 (88.6%)	<.0001
Died of UC (n, %)	20,906 (19.9%)	4,027 (36.5%)	16,879 (18.0%)	<.0001
Survival, months (median, interquartile range)	75 (40-124)	49 (15-96)	78 (42-127)	<.0001
Adjusted mortality risk (HR [95% CI])				
• Lack/unknown status of hysterectomy	3.6 [3.4, 3.9]	-	-	<.0001
• Black race	-	1.3 [1.3, 1.4]		<.0001

* Non-missing data

6551 **Poster Session**

Comparison of patient-reported impact of COVID19 on cancer care delivery: A prospective, cross-sectional study. *First Author: Emily Hsu, University of Connecticut Health Center, Farmington, CT*

Background: Impact of COVID19 on cancer care delivery and outcomes remains unknown. Few trials have investigated patients' perceived risks and benefits, and cancer care delivery (CCD) alterations related to COVID19. We sought to identify differences on behaviors and social determinants of health in Hispanics and other underrepresented populations (H/UP) compared to the general population (GP). **Methods:** An IRB-approved validated 27-item questionnaire was offered in English and Spanish to all pts. receiving cancer care at participating cancer centers over a 4 month period. Examined variables included demographic information, social risk and behavioral factors, preferred sources of health information, and overall satisfaction with CCD during the pandemic. **Results:** A total of 180 pts were enrolled in the study. Compared to GP, H/UP's perceived risk of COVID19 was higher with 93% vs 87% more likely to cancel or avoid social gatherings and 54% vs 46% more likely to change daily routine. H/UP appeared more concerned with personal and financial safety; if unable to find work/get paid for 2 weeks, 26% H/UP vs 10% GP would struggle to keep up with expenses. 40% H/UP vs 10% GP have concerns on perceived ability to secure food on short term and consider COVID19 a major threat to their health (70% vs 46%) and financial situation (63% vs 35%). H/UP's perceived benefits of protective measures is higher with 81% vs 60% routinely practicing social distancing (SD) and 79% vs 66% in agreement with punitive actions for not following SD. Analysis demonstrated no significant difference by age, gender, level of education, marital status, however Hispanic ethnicity and Spanish as primary language was a statistically significant variable ($p = 0.025$) in perceived risks and satisfaction with CCD. No major differences were noted on sources of health information although more H/UP relied on social media (33% vs 24%). H/UP appeared to be more skeptical about availability and safety of targeted vaccines (40% vs 15%). Satisfaction regarding CCD was comparable (84% vs 86%), although more H/UP perceived CCD alterations (15% vs 10%). Going forward, H/UP would prefer to incorporate virtual visits (VV) when possible (36% vs 25%). **Conclusions:** COVID19-related societal, financial, health and personal fears are increased in H/UP which likely negatively affects quality of life of these at-risk populations. H/UP's trust in SD recommendations is heightened although linguistically and culturally appropriate information may be deficient. H/UP's belief in vaccine availability and safety is comparable to GP, although recent reports suggest deeper fear and emphasize their fear of experimentation. Interventions aimed to decrease these differences could incorporate standard communications with special attention to social media. H/UP would prefer to incorporate VV into their care, although most do not possess appropriate technology to do so. Research Sponsor: None.

6552 **Poster Session**

Effect of income on patient decision-making in localized prostate cancer. *First Author: Xinglei Shen, University of Kansas Cancer Center, Westwood, KS*

Background: Socioeconomic status affects goals of care and treatment choices. We investigated the impact of low household income on diagnosis, goals of care, and treatment choice in patients with localized prostate cancer. **Methods:** The North Carolina Prostate Cancer Comparative Effectiveness & Survivorship Study (NC ProCESS) is a population-based cohort of prostate cancer patients identified at the time of diagnosis, enrolled from 2011-2013, and followed prospectively. Sociodemographic information and decision making factors including goals of care were collected by patient report. Patients were asked to rate the importance of quality of life, cure, burden to friends and family, cost, and effect on daily activity as well as which of these goals was the most important in their treatment decision making. Annual household income was stratified in to 3 levels: < 40K (low), 40-90K (middle),>90K (high). **Results:** Of 1382 patients, 539 (39%), 553 (40%), and 290 (21%) reported low, medium, and high household income. Lower income patients were less college educated, more frequently unemployed, and had higher rates of either no insurance or government sponsored insurances. Low income patients had higher PSA and worse clinical stage at diagnosis. In goals of care, low income patients more frequently rated high importance on burden (78.8% vs 76.0% vs 65.2% p<0.01) and cost of cancer (61.2% vs 38.5% vs 14.5% p<0.01), and factors other than cure as the most important treatment decision factor. While overall treatment rate at 1 year was similar by income group, the type of treatment differed. On multivariate analyses, adjusting for age, race, clinical risk group, employment, insurance, and treatment goal, high income was associated with increased odds of having surgery (OR 1.81, CI 1.16 – 2.81), and reduced odds of having radiation (0.60, CI 0.36-0.99). **Conclusions:** Poor patients with low household income have worse prostate cancer at diagnosis. These patients have different goals of care which impact their choice of treatment. These findings provide novel insight into disparities in diagnosis and outcome in prostate cancer. Research Sponsor: PCORI.

Stage, goals of care and treatment of newly diagnosed prostate cancer patient by income.

	Low Income N= 539	Medium Income N= 553	High Income N=290	P-value
PSA at diagnosis (median, IQR)	6.1 (4.8 – 8.7)	5.4 (4.4 – 7.4)	4.6 (3.8 – 6.3)	< 0.01
Clinical risk group at Diagnosis				
Low	52.7%	60.6%	60.0%	
Favorable intermediate	12.2%	11.2%	17.2%	
Unfavorable intermediate	23.7%	21.5%	15.5%	<0.01
High risk	9.8%	6.2%	6.9%	
Metastatic	1.5%	0.5%	0.3%	
Most Important Goal of Care				
Quality of life	28.8%	29.2%	23.7%	
Cure	54.4%	61.9%	74.3%	
Burden to friends and family	9.3%	5.2%	0.4%	<0.01
Cost	3.3%	1.0%	0.4%	
Effect on daily activity	3.0%	2.1%	1.2%	
Treatment decision at 1 yr				
Any treatment	72.0%	74.1%	73.1%	0.72
Surgery	29.1%	41.2%	52.1%	<0.01
Radiation	25.2%	18.4%	12.1%	<0.01
Brachytherapy	16.0%	15.2%	8.3%	<0.01
Hormonal therapy	10.4%	6.5%	2.4%	<0.01

6553 **Poster Session**

Racial disparities in access to prostate cancer clinical trials: A county-level analysis. *First Author: Aasthaa Bansal, University of Washington, Seattle, WA*

Background: African American men (AAs) have a higher burden of prostate cancer compared to other populations. We sought to determine if they experience disparities in access to prostate cancer clinical trials. **Methods:** We created a county-level database of all U.S. counties by linking together prostate cancer clinical trial data from the Aggregate Analysis of ClincalTrials.gov (AACT) database with county-level socioeconomic, demographic and healthcare facility data derived from several external data sources. Using this data linkage, we examined two specific potential access barriers. First, we investigated the relationship between %AAs in the county and access to NCI designated cancer facilities, adjusting for county population size and other characteristics. Then, among counties with cancer facilities, we investigated the relationship between the %AAs in the county and number of available prostate cancer treatment trials per capita per year. We used logistic and negative binomial regression models, respectively, to address these questions. **Results:** Between 2008 and 2015, 613 prostate cancer trial sites were found among 3,145 U.S. counties. Counties with higher %AAs were less likely to have cancer facilities (adjusted odds ratio = 0.85, 95% CI (0.78, 0.92)). Among counties with cancer facilities, those with higher %AAs had significantly fewer prostate cancer trials per capita per year (rate ratio per 10% increase in %AAs: 0.90, 95% CI (0.83,0.96)), after adjusting for county-level sociodemographic and healthcare system factors. **Conclusions:** Counties with higher proportions of AAs appear to be less likely to have access to NCI designated cancer facilities. Among counties with cancer facilities, those with higher proportions of AAs appear to have fewer available prostate cancer treatment trials per capita per year. Clinical trials in prostate cancer therapy should ensure adequate availability of enrollment sites in regions with high concentrations of AAs. Research Sponsor: U.S. National Institutes of Health.

6554 **Poster Session**

Mediators of racial disparity in the use of prostate MRI. *First Author: Michael S. Leapman, Department of Urology, Yale School of Medicine, New Haven, CT*

Background: Evidence of racial disparity in the use of prostate MRI presents new obstacles to closing recognized gaps in treatment and outcome for black men with prostate cancer. To anticipate strategies for improving equity in cancer care, we examined mediators of racial disparity in the use of prostate MRI surrounding the diagnosis of prostate cancer. **Methods:** We conducted a multiple mediation analysis among patients with localized prostate cancer in the Surveillance, Epidemiology, and End Results (SEER)-Medicare database between January 2008 and December 2015. We assessed claims for prostate MRI within the six-month period preceding or following diagnosis. We first identified candidate clinical and sociodemographic meditators based on their association with both race and prostate MRI, including the Index of Concentrations at the Extremes (ICE), a measure of racialized residential segregation calculated at the zip code or census tract level. We used non-linear Multiple Additive Regression Trees (MART) models to estimate the direct and indirect relative effects of mediators. **Results:** We identified 71,597 eligible patients. Black patients with prostate cancer were less likely (5.3%) to receive a prostate MRI when compared with white patients (7.0%; unadjusted odds ratio 0.75, 95% CI 0.67-0.84, p < 0.001). 33.1% (95% CI 20.6-44.9) of the racial disparity in prostate MRI use was attributable to variation in SEER region, 22.5% (95% CI 13.0-30.2) to residence in a high poverty area, 17.2% to residential segregation (ICE group 17.2%, 95% CI 8.1-27.9%), and 13.2% to dual eligibility for Medicaid (95% CI 8.6-20.2%). Clinical and pathologic factors were not significant mediators. After accounting for the mediators, the direct effects of race accounted for 6.2% of the observed disparity in prostate MRI use. **Conclusions:** Sociodemographic factors including geographic region, and area-level measures of income and residential segregation explain the majority of the observed racial disparity in the use of prostate MRI among older Americans with prostate cancer. The findings underscore that measurable structural factors can be readily identified that underlie racial disparity in access to emerging diagnostic tools for patients with cancer. Research Sponsor: U.S. National Institutes of Health.

6555 **Poster Session**

Examining racial disparities in male breast cancer. *First Author: Elizabeth Shurell Linehan, Division of Breast Surgical Oncology, Kaiser Permanente, San Francisco, CA*

Background: Male breast cancer (MBC) accounts for approximately 1% of all breast cancers. Racial disparities have not been examined in MBC. **Methods:** Within a large, integrated health delivery system, all adult female and male patients who were diagnosed with breast cancer from 01-01-2010 to 12-31-2018 were examined. Bivariate analysis was performed to examine clinical and demographic factors associated with breast cancer-related mortality. We conducted more detailed chart review in the MBC-only group (data period 01-01-2010 to 12-31-2019) to assess the mean time to treatment (from diagnosis to surgery, surgery to chemotherapy, and surgery to radiation) stratified by race using bivariate (t-test, one way ANOVA) analyses. **Results:** 32,848 female breast cancer and 226 MBC patients were evaluated; MBC patients represented 0.63% of all breast cancer patients. Between males and females, there was no statistically significant difference in race, with an overall distribution of 62% White, 19% Asian, 8% Black, and 11% Hispanic. To our knowledge, this is the largest and most racially diverse sample of MBC patients to date. MBC patients at diagnosis were significantly older (p < .0001), more obese (p < 0.0018), and sicker according to the Charlson Comorbidity Index (CCI) (p < 0.0001) compared to female breast cancer patients. Males were more likely to be diagnosed at an advanced stage (19.2%) compared to females (12.5%) (p = 0.0037). With a mean follow up of 5 years, overall mortality was statistically significantly worse in MBC (23.0%) compared to female breast cancer patients (12.0%) (p < 0.0001). Furthermore, breast cancer-related mortality was significantly higher in males (8.1%) than in females (4.5%) (p = 0.0124). In the MBC-only analysis, stage at diagnosis was not influenced by patient race. Asian and White MBC patients had the shortest mean time from diagnosis to surgery (27 and 29 days, respectively), with Hispanic MBC patients experiencing the longest time to surgery (46 days). Black MBC patients experienced the shortest mean time to chemotherapy after surgery (39 days), whereas Asian MBC patients experienced the longest time to chemotherapy (50 days). In survivorship, Black and Asian patients were least likely to undergo screening mammography (33.3%, and 43.3%, respectively), compared to 52% of White and 50% of Hispanic MBC patients. Ultimately, 13% of Asian and 11% of Hispanic MBC patients died of breast cancer, compared to 6.7% of Black and 6.2% of White MBC patients. **Conclusions:** While we found no statistically significant differences in mortality by race among MBC patients, our findings indicate that non-white patients had longer time to treatments, less survivorship screening, and worse disease related mortality than their white counterparts. Future study can elucidate these racial inequalities, enabling more equitable breast cancer treatment among patient subgroups. Research Sponsor: Kaiser Permanente Community Benefit Grant.

6556 **Poster Session**

In-hospital outcomes of CAR T-cell therapy in United States in 2018: A nationwide analysis. *First Author: Manoj P. Rai, Asante Rogue Regional Medical Center, Medford, OR*

Background: CAR T-cell therapy is a type of adoptive cell transfer (ACT). In 2017 CAR T-cell therapy was approved by the Food and Drug Administration (FDA) for management of diffuse large B-cell lymphoma refractory to at least two prior lines of therapy (DLBCL) including primary mediastinal large B-cell lymphoma (PMBCL), and B cell precursor acute lymphoblastic leukemia (ALL) up to 25 years of age that is refractory or in second or later relapse. Since its inception, several patients underwent CAR T-cell therapy but data on real world outcome is limited. In this study we aim to evaluate the in-hospital outcomes of CAR T-cell therapy in the United States in 2018. **Methods:** This is a cross-sectional study using National Inpatient Sample 2018 database. Discharges with the ICD-10-PCS code for CAR T-cell therapy and ICD-10-CM code of ALL, DLBCL or PMBCL were included in the study. We analyzed their in-hospital outcomes (Total discharges, length of stay in days, hospitalization cost, and mortality - number of deaths). We applied the cost to charge ratio to hospitalization charges to estimate the mean hospitalization cost. The weighted sample represents national estimates. **Results:** We identified 785 discharges with CAR T cell therapy and diagnosis of ALL, DLBCL or PMBCL. 155 (19.75 %) were ALL, 620 (78.98%) DLBCL, and 10 (1.27%) PMBCL. Mean length of stay for the study cohort was 23.26 days. Specifically, for ALL mean LOS was 33.67 days, DLBCL 20.76 days, and PMBCL 17 days. Mean hospitalization cost for the study cohort was $285,989, specifically for ALL it was $342,228, DLBCL $274,102, PMBCL $179,431. There were a total of 60 (7.6%) deaths in the study cohort. Diagnosis specific mortality was 20 (12.9%) in ALL, 40 (6.4%) in DLBCL and none in PMBCL. **Conclusions:** Majority of discharges who underwent CAR T-cell therapy were DLBCL followed by ALL and PMBCL. CAR-T Cell hospitalizations have high costs and long length of stays. Mean length of stay was highest in ALL discharges, least in PMBCL. Mean hospitalization cost was higher in DLBCL discharges compared to ALL and was least in PMBCL discharges. The in-hospital mortality with the CAR-T cell therapy appears to be higher than reported in clinical trials, especially for ALL. Research Sponsor: None.

	CAR T-cell therapy (Overall)	CAR T-cell therapy for ALL	CAR T-cell therapy for DLBCL	CAR T-cell therapy for PMBCL
Total number of hospitalizations	785	155 (19.75 %)	620 (78.98%)	10 (1.27%)
Mean length of stay (days)	23.26 (20.15 - 26.37)	33.68 (24.6 - 42.70)	20.76613 (17.62 - 23.91)	17 (14.22 - 19.78)
Mean hospitalization Cost ($)	285,989 (246,781.9 – 325,197)	342,228.3 (241,621.5 - 442,835)	274,101.9 (232,857 – 315,347)	179,431.2 (19,658 – 339,205)
Mortality (n)	60 (7.6%)	20 (12.9%)	40 (6.4%)	0 (0%)

Total number of hospitalizations, mean length of stay, mean hospitalization cost and mortality in discharges with CAR T-cell therapy (overall vs. ALL vs. DLBCL vs. PMBCL).

6557 **Poster Session**

Characteristics of patients hospitalized through the emergency department with an oncology drug-related side effect. *First Author: Elisea Avalos-Reyes, CVS Health, Irving, TX*

Background: Recent advances in oncology treatment present an expanding spectrum of cancer-treatment-related emergencies.Many aspects of healthcare utilization, specifically emergency department (ED) visits, are not well studied in this population. The purpose of this study is to determine (1) what proportion of cancer patients visit the ED with an oncology drug-related side effect and are admitted and (2) what factors impact the probability of inpatient admission among these patients. **Methods:** This study evaluated ED visits by adult patients undergoing active drug treatment for cancer insured by a large commercial and Medicare health plan in the United States between January 1, 2018, and September 30, 2019. Among cancer-related ED visits, logistic regression was used to determine the marginal effect of demographic and clinical characteristics of patients on acute inpatient admission. **Results:** There were 39,921 total ED visits among patients undergoing drug treatment for cancer; of these, 76% presented with an oncology drug-related side-effect. 36% of all ED visits resulted in admission, 5% resulted in an observation stay. After adjusting, age was not a significant predictor of inpatient admission. Being male ($p < 0.01$) and living in urban ($p < 0.01$) or suburban ($p < 0.01$) zip codes significantly increased the likelihood of admission. Patients with colorectal ($p = 0.019$), gastrointestinal ($p < 0.01$), blood ($p < 0.01$), lung ($p < 0.01$), metastatic ($p < 0.01$) cancers, or Hodgkin's lymphoma ($p < 0.01$) had significantly increased risk of admission. Patients with prostate ($p < 0.01$) cancer had a significantly reduced risk of admission. The primary complaint upon presentation to the ED was the most important predictor of inpatient admission; sepsis, pneumonia, medical complications, white cell disorders, metastatic cancer, and fractures were all associated with a significantly higher (all $p < 0.001$) risk of admission. Patients with comorbid heart failure ($p < 0.001$), those taking ulcer medications ($p < 0.01$), or inflammatory bowel disease ($p = 0.03$) had a significantly increased risk of admission. Results were consistent regardless of payer (Medicare or commercial health plan). **Conclusions:** This study identified cancer patients for whom acute inpatient admission from an ED presentation is more likely. Future studies identifying cancer patients who may be at risk of making an ED presentation based on demographic, clinical and disease-related characteristics are needed and may help inform targeted follow up of patients to mitigate potentially avoidable ED presentation and subsequent inpatient admission. Research Sponsor: None.

6558 **Poster Session**

Supportive oncology care at home intervention for patients with pancreatic cancer. *First Author: Ryan David Nipp, Department of Medicine, Division of Hematology & Oncology, Massachusetts General Hospital & Harvard Medical School, Boston, MA*

Background: Patients with pancreatic cancer receiving chemotherapy often experience substantial symptoms and high healthcare utilization. We sought to determine the feasibility of delivering a Supportive Oncology Care at Home intervention designed to address the needs of patients receiving treatment for pancreatic cancer. **Methods:** We prospectively enrolled patients with pancreatic cancer who were participating in a parent trial of neoadjuvant FOLFIRINOX and residing in-state, within 50 miles of our hospital. Patients received the Supportive Oncology Care at Home intervention during neoadjuvant treatment (i.e., up to 4 months). The intervention entailed: 1) remote monitoring of daily patient-reported symptoms, daily vital signs, and weekly body weight; 2) a hospital in the home care model for symptom assessment and management; and 3) structured communication with the oncology team. We defined the intervention as feasible if ≥60% of patients enrolled in the study and ≥60% completed the daily assessments within the first two weeks of enrollment. We tracked numbers of phone calls, emails, and home visits generated by the intervention. We conducted exit interviews with patients, caregivers, and oncology clinicians to assess the acceptability of the intervention. In addition, we compared rates of treatment delays, urgent clinic visits, emergency room (ER) visits, and hospitalizations among those who did (n = 20) and did not (n = 24) receive Supportive Oncology Care at Home from the parent trial. **Results:** From 1/2019-9/2020, we enrolled 80.8% (21/26) of potentially eligible patients. One patient became ineligible following consent due to moving out-of-state, resulting in 20 participants (median age = 67 years [range 55-77]; 60.0% female). Within the first two weeks of enrollment, 65.0% completed all the daily assessments, with participants reporting 96.1% of daily symptoms, 96.1% of daily vital signs, and 92.5% of weekly body weights. Each participant generated an average of 2.22 phone calls (range 0.62-3.77), 2.96 emails (range 1.50-5.88), and 0.15 home visits (range 0-0.69) per week. During exit interviews, > 80% of patients, caregivers, and clinicians found the intervention to be helpful and convenient, and they reported high satisfaction with the communication among patients, clinicians, and the hospital in the home team. Patients receiving the intervention had lower rates of treatment delays (55.0% v 75.0%), urgent clinic visits (10.0% v 25.0%), ER visits or hospitalizations (45.0% v 62.5%), as well as a lower proportion of days spent in urgent clinic, ER, or hospital (2.7% v 7.8%), compared with those not receiving the intervention who were in the same parent trial. **Conclusions**: These findings demonstrate the feasibility and acceptability of a Supportive Oncology Care at Home intervention. Future work will investigate the efficacy of this intervention for decreasing healthcare use and improving patient outcomes. Clinical trial information: NCT03798769. Research Sponsor: Stand Up To Cancer.

6559 **Poster Session**

The impact of HIV infection on overall survival among women with stage IV breast cancer in South Africa. *First Author: Yoanna S Pumpalova, Columbia University Irving Medical Center, New York, NY*

Background: Advanced stage at breast cancer (BC) diagnosis is common in sub-Saharan Africa. In public hospitals across South Africa (SA), 10-15% of women present with metastatic BC, compared to <5% in the U.S., and 20% of new BCs are diagnosed in women living with HIV (WLWH). We evaluated the impact of HIV on overall survival (OS) among women with stage IV BC, which is associated with a poor prognosis in SA. **Methods:** We conducted a prospective cohort study of women diagnosed with stage IV BC between February 2, 2015 and September 18, 2019 at six public hospitals in SA. Baseline characteristics were compared by HIV status and multivariate Cox regression models were used to estimate the effect of HIV on OS. **Results:** Among 550 eligible women, 147 (26.7%) were WLWH. Compared to HIV-negative BC patients, WLWH were younger (median age 45 vs. 60 years, p<0.001), predominantly black (95.9% vs. 77.9%, p<0.001), and more likely to have hormone receptor-negative BC (32.7% vs. 22.6%, p=0.016). HER2 tumor status did not differ by HIV status (25.3% HER2 positive overall), and Ki67 index was not increased among WLWH (57.1% Ki67 > 20 overall). Receipt of systemic anti-cancer therapy did not differ by HIV status (80.9% treated overall) and most women were treated with anthracycline (55.5%). HIV status was not associated with OS (Hazard Ratio (HR)=1.13, 95% confidence interval (CI)=0.89-1.44) (Table). In an exploratory subgroup analysis, WLWH and hormone receptor-negative BC had shorter OS compared to HIV-negative women (1-year OS: 27.1% vs. 48.8%, p=0.003; HR=1.94, 95% CI=1.27-2.94), which was not observed for hormone receptor-positive BC. Results were unchanged when analysis was restricted to black women only. **Conclusions:** HIV status was not associated with worse OS in women with stage IV BC in SA and cannot account for the poor survival in our cohort. Subgroup analysis revealed that WLWH with hormone receptor-negative BC had worse OS; this differential effect of HIV on BC survival by hormone receptor status is a novel finding that warrants further investigation. Research Sponsor: U.S. National Institutes of Health.

Multivariate Cox proportional hazard ratio model of risk factors for mortality in women with stage IV breast cancer in South Africa (2015-2019), stratified by self-identified ethnicity.

	All Women*		Black Women*	
	HR (95% CI)	P-value	HR (95% CI)	P-value
HIV Positive	1.13 (0.89-1.44)	0.32	1.08 (0.84-1.40)	0.55
Age ≥50	1.16 (0.93- 1.46)	0.20	1.20 (0.94-1.53)	0.15
T-stage (T4)	1.60 (1.27-2.02)	**<0.001**	1.56 (1.20-2.01)	**0.001**
Hormone Receptor Negative	1.39 (1.10-1.76)	**0.006**	1.46 (1.13-1.87)	**0.003**
HER2 Positive	1.07 (0.85-1.35)	0.56	1.07 (0.83-1.37)	0.60
Ki67 proliferation index >20%	1.47 (1.18-1.83)	**0.001**	1.51 (1.19-1.93)	**0.001**
Visceral Metastases	1.31 (1.06-1.61)	**0.01**	1.34 (1.07-1.69)	**0.01**
Had surgery	0.50 (0.35-0.72)	**<0.001**	0.44 (0.29-0.67)	**<0.001**
Had chemotherapy	0.12 (0.09-0.16)	**<0.001**	0.12 (0.09-0.17)	**<0.001**

*Adjusted for treatment hospital and performance status.

6560 **Poster Session**

Changes in patient-reported outcomes (PROs) and tumor markers (TMs) to predict treatment response and survival outcomes in patients with metastatic gastrointestinal (GI) cancer. *First Author: Joy X. Jarnagin, Massachusetts General Hospital, Boston, MA*

Background: PROs assessing quality of life (QOL) and symptoms at a single timepoint frequently correlate with clinical outcomes in patients with cancer, yet efforts to understand how longitudinal changes in PROs can predict for treatment outcomes are lacking. In practice, oncologists often use changes in serum TMs (CEA and CA19-9) to monitor patients with GI cancer, and thus we sought to examine associations of 1-month changes in PROs and TMs with treatment response and survival outcomes among patients with advanced GI cancer. **Methods:** We prospectively enrolled patients with metastatic GI cancer prior to initiating chemotherapy at Massachusetts General Hospital from 5/2019-12/2020. At baseline (start of treatment) and 1-month later, we collected PROs (QOL [Functional Assessment of Cancer Therapy General {FACT-G}], physical symptoms [Edmonton Symptom Assessment System {ESAS}], and psychological symptoms [Patient Health Questionnaire-4 {PHQ-4}]) and TMs. We used regression models to examine associations of 1-month changes in PROs and TMs with treatment response (clinical benefit [defined as decreased or stable tumor burden] or progressive disease at the time of first scan) and survival outcomes (progression-free survival [PFS] and overall survival [OS]), adjusted for baseline values of each respective variable. **Results:** We enrolled 159 of 191 patients approached (83.2% enrollment); 134 had 1-month follow-up data (median age = 64 years [range: 28 to 84 years], 64.2% male, 46.3% pancreaticobiliary cancer). For treatment response, 63.4% had clinical benefit and 36.6% had progressive disease at the time of first scan (mean time to first scan = 2.01 months). Changes in PROs (ESAS-Total: OR = 0.97, p = 0.022; ESAS-Physical: OR = 0.96, p = 0.027; PHQ-4 depression: OR = 0.67, p = 0.014; FACT-G: OR = 1.07, p = 0.001), but not TMs (CEA: OR = 1.00, p = 0.836 and CA19-9: OR = 1.00, p = 0.796), were associated with clinical benefit at the time of first scan. Changes in ESAS-Total (HR = 1.03, p = 0.004), ESAS-Physical (HR = 1.03, p = 0.021), PHQ-4 depression (HR = 1.22, p = 0.042), FACT-G (HR = 0.97, p = 0.003), and CEA (HR = 1.00, p = 0.001) were predictors of PFS. Changes in ESAS-Total (HR = 1.03, p = 0.006) and ESAS-Physical (HR = 1.04, p = 0.015) were predictors of OS, but 1-month changes in TMs (CEA: HR = 1.00, p = 0.377 and CA19-9: HR = 1.00, p = 0.367) did not significantly predict for OS. **Conclusions:** We found that 1-month changes in PROs can predict for treatment response and survival outcomes in patients with advanced GI cancers. Notably, 1-month changes in CEA only correlated with PFS, while changes in CA19-9 did not significantly predict treatment response or survival outcomes. These findings highlight the potential for early changes in PROs to predict treatment outcomes while underscoring the need to monitor and address PROs in patients with advanced cancer. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

6561 **Poster Session**

Concomitant infections in patients with cancer and COVID-19: A COVID-19 and Cancer Consortium (CCC19) study. *First Author: Kyle T. Enriquez, Vanderbilt University Medical Center, Nashville, TN*

Background: COVID-19 has been associated with immune modulation that may predispose infected patients to bacterial, viral, or fungal co-infections. Due to critical illness, $>$ 70% of patients with severe COVID-19 receive empiric antibacterial or antifungal therapy, along with standard anti-COVID-19 treatments. However, the frequency of proven or probable secondary infections is $<$ 10%. To our knowledge, there are no studies evaluating co-infections in patients with cancer and COVID-19, a vulnerable group with multiple risk factors for co-infections. We aim to describe the prevalence of bacterial, viral, and fungal co-infections, identify risk factors for coinfection, and investigate the potential impact of co-infections on mortality, in patients with a history of cancer and COVID-19. **Methods:** The CCC19 registry (NCT04354701) includes patients with active or prior hematologic or invasive solid malignancies reported across academic and community sites. We captured bacterial, fungal, or viral co-infections diagnosed within ±2 weeks from diagnosis of COVID-19, identified factors associated with an increased risk of having a co-infection, and evaluated the association of co-infections with 30-day all-cause mortality. **Results:** We examined 6732 patients with a history of cancer and a laboratory-confirmed diagnosis of SARS-CoV-2 reported to CCC19 by 82 sites between March 17, 2020 and February 3, 2021, with complete data on coinfection status. Median age was 65 (interquartile range: 55-75) years with 48% male, 52% non-Hispanic white, 19% non-Hispanic black, and 16% Hispanic. 5448 (81%) had solid tumors and 1466 (22%) had hematologic malignancies. Bacterial infections were reported in 823 patients (12%), including 296 Gram+ and 245 Gram- bacterial events. Documented viral (176 patients, 3%) and fungal (59 patients, 0.9%) co-infections were rare. The risk for co-infections increased with age, and they were more frequent among men, older patients, and those with diabetes, pulmonary or renal comorbid conditions, active progressive cancer, or hematologic malignancies (unadjusted $P<$ 0.01). The frequency of reported co-infections decreased over the study period (divided into quartiles, Mantel-Haenszel $P<$ 0.01). All-cause mortality rates were higher among those with bacterial (24% vs. 10%), viral (22% vs. 12%), and fungal (37% vs. 12%) coinfections compared to those without (unadjusted $P<$ 0.01). **Conclusions:** The frequency of bacterial infections in patients with cancer and COVID-19 is relatively low. Viral and fungal co-infections are uncommon. Co-infections are associated with higher mortality rates. Several patient and tumor factors can be used for risk stratification and guide early empiric antimicrobial agent selection, which may improve clinical outcomes. These data could inform antimicrobial stewardship interventions in this tenuous patient population. Research Sponsor: U.S. National Institutes of Health.

6562 **Poster Session**

Impact of disruptions in breast cancer control due to the COVID-19 pandemic on breast cancer mortality in the United States: Estimates from collaborative simulation modeling. *First Author: Oguzhan Alagoz, University of Wisconsin-Madison, Madison, WI*

Background: The COVID-19 pandemic has disrupted breast cancer control through short-term declines in screening, delays in diagnosis and reduced/delayed treatments. We projected the impact of COVID-19 on future breast cancer mortality. **Methods:** Three established Cancer Intervention and Surveillance Modeling Network (CISNET) models projected the impact of pandemic-related care disruptions on breast cancer mortality between 2020 and 2030 vs. pre-pandemic care patterns. Based on Breast Cancer Surveillance Consortium data, we modeled reductions in mammography screening utilization, delays in symptomatic cancer diagnosis, and reduced use of chemotherapy for women with early-stage disease for the first six months of the pandemic with return to pre-pandemic patterns after that time. Sensitivity analyses were performed to determine the effect of key model parameters, including the duration of the pandemic impact. **Results:** By 2030, the models project 1,297 (model range: 1,054-1,900) cumulative excess deaths related to reduced screening; 1,325 (range: 266-2,628) deaths from delayed diagnosis of symptomatic women, and 207 (range: 146-301) deaths from reduced chemotherapy use for early-stage cancer. Overall, the models predict 2,487 (range 1,713-4,875) excess deaths, representing a 0.56% (range: 0.36%-0.99%) cumulative increase over deaths that would be expected by 2030 in the absence of the pandemic's disruptions. Sensitivity analyses indicated that the impact on mortality would approximately double if the disruptions lasted for a 12-month period. **Conclusions:** The impact of the initial pandemic-related disruptions in breast cancer care will have a small long-term cumulative impact on breast cancer mortality. The impact of the initial pandemic-related disruptions on breast cancer mortality will largely be mitigated by the rapid return to usual care. As the pandemic continues it will be important to monitor trends in care and reassess the mortality impact. Research Sponsor: U.S. National Institutes of Health.

Scenario	Cumulative number of deaths by 2030 Median (range across models)	
No COVID-19 impact	473,903 (444,352-493,595)	
	Excess number of deaths Median (range)	% increase Median (range)
2: Reduced screening (50% of women missed their scheduled screening exams)	1,297 (860-1900)	0.27% (0.19-0.38)
3: Delayed diagnosis (25% of women delayed evaluation of breast cancer symptoms for 6 months)	1,325 (266-2629)	0.30% (0.06-0.53)
4: Reduced chemotherapy (50% of women older than 70 and 25% of women younger than 70 who are diagnosed with ER+/HER2- tumors in Stages I and IIA during the pandemic period would not receive clinically indicated adjuvant chemotherapy)	207 (146-301)	0.04% (0.03-0.06)
5: Disruptions in screening & diagnosis (Scenarios 2 & 3)	2,365 (1576-4580)	0.53% (0.33-0.93)
6: Disruptions in screening & diagnosis & chemotherapy (Scenarios 4 & 5)	2,487 (1713-4875)	0.56% (0.36-0.99)

6563 **Poster Session**

Lower respiratory tract disease (LRTD) in patients with cancer and COVID-19: A COVID-19 and Cancer Consortium (CCC19) study. *First Author: Dimpy P. Shah, University of Texas Health Science Center San Antonio, San Antonio, TX*

Background: Immunodeficiency in patients (pts) with cancer can lead to the progression of common respiratory viral infections to lower respiratory tract disease (LRTD) with potentially high mortality. Understanding risk factors of SARS-CoV-2 related LRTD in pts with cancer is imperative for the development of preventive measures. **Methods:** We examined all patients aged 18 years or older with cancer and laboratory-confirmed SARS-CoV-2 infection reported between March 16, 2020 and February 6, 2021 in the international CCC19 registry. We examined frequency of LRTD (pneumonia, pneumonitis, acute respiratory distress syndrome, or respiratory failure), demographic and clinicopathologic factors associated with LRTD, and 30-day and overall mortality in pts with and without LRTD. **Results:** Of 7,289 pts with a median follow-up time of 42 (21-90) days, 2187 (30%) developed LRTD. Pts of older age (65 yrs or older), male sex, pre-existing comorbidities, baseline immunosuppressants, baseline corticosteroids, and ECOG performance status of 2 or more had substantially higher rates of LRTD compared to those without these risk factors (Table). We did not observe differences in LRTD rates between pts of different racial/ethnic groups, smoking history, hypertension, obesity, cancer status, timing or type of anti-cancer therapy. LRTD was more likely in pts with thoracic malignancy (39%), hematological malignancy (39%) compared to those with other solid tumors (27%). The majority of pts (86%) had symptomatic presentation; however, 8% of pts with asymptomatic presentation developed LRTD. 30-day and overall mortality rates were significantly higher in pts with LRTD than those without LRTD (31% vs. 4% and 38% vs. 6%, P $<$ 0.05). **Conclusions:** COVID-19 related LRTD rate is high and associated with worse mortality rates in pts with cancer. The majority of risk factors associated with LRTD demonstrate underlying immunodeficiency or lung structural damage as a driving force in this population. Identifying pts at high-risk for developing LRTD can help guide clinical management, improve pt outcomes, increase the cost-effectiveness of antiviral therapy, and direct future clinical trial designs for vaccine or antiviral agents. Research Sponsor: American Cancer Society and Hope Foundation for Cancer Research for Cancer, U.S. National Institutes of Health.

Baseline risk factors for COVID-19 related LRTD.

Risk Factor	LRTD rate in presence of a risk factor	LRTD rate in absence of a risk factor
Older age (65 years or older)	1423/3827 (37%)	759/3462 (22%)
Male sex	1223/3449 (35%)	958/3784 (25%)
Cardiovascular comorbidity	858/2117 (41%)	1304/5097 (26%)
Pulmonary comorbidity	567/1455 (39%)	1595/5759 (28%)
Renal comorbidity	473/1062 (45%)	1689/6152 (27%)
Diabetes mellitus	766/1935 (40%)	1396/5279 (26%)
Baseline immunosuppressants	175/402 (44%)	1942/6643 (29%)
Baseline corticosteroids	132/289 (46%)	1909/6546 (29%)
ECOG PS (2+)	416/1016 (41%)	1077/4201 (26%)

6564 **Poster Session**

Predictors of surgery preference and quality of life in DCIS after breast MRI: A trial of the ECOG-ACRIN Cancer Research Group (E4112). *First Author: Soudabeh Fazeli, University of California San Diego Medical Center, San Diego, CA*

Background: Management of ductal carcinoma in situ (DCIS) remains variable, requiring an understanding of patient preferences and concerns to enhance the treatment decision-making process. Pre-operative MRI and surgeon recommendation can further inform surgery choice. Quality of life (QoL) is also an important consideration in treatment decision-making. The aims of this study were to assess patients' treatment preferences before and after MRI and surgeon consultation, concordance between treatment preference and surgery received, and trends in health-related QoL (HRQL) among a prospective cohort of women newly diagnosed with DCIS. **Methods:** A prospective nonrandomized clinical trial by the ECOG-ACRIN Cancer Research Group (E4112) enrolled women diagnosed with unilateral DCIS from 75 institutions between March 2015 and April 2016. Participants underwent either wide local excision (WLE) or mastectomy. Surveys queried patient-reported outcomes (PRO) including treatment preference and concerns, and HRQL before and after surgery. Logistic regression models were used to associate surgery preference and actual surgery received with demographic, clinical and PRO data. Change from baseline in HRQL was assessed using linear regression. **Results:** At study entry, age (OR 0.39, per 5-year increment, 95%CI, 0.21-0.75; p = 0.005) and treatment goals related to the importance of keeping one's breast (OR 0.51, 95%CI 0.34-0.76; p = 0.001) and removal of the breast for peace of mind (OR 1.46, 95%CI 1.09-1.95; p = 0.01) drove surgery preference for mastectomy vs. WLE. After receipt of MRI and surgeon consultation, surgery preference was primarily mediated by MRI upstaging (OR 11.18, 95%CI 3.19-39.16; p < 0.001). Only 4% of women received a type of surgery that did not match their final treatment preference. The strongest predictors of actual surgery received were MRI upstaging (OR 15.80, 95%CI 4.85-51.46) and surgeon recommendation of mastectomy (OR 4.60, 95%CI 1.52-13.94). Receipt of a single surgery was associated with significantly improved mental health from baseline to one year after definitive surgery (p = 0.02 for mastectomy; p = 0.003 for single WLE). Self-reported Black race was an independent predictor of worsened mental (p = 0.001) and physical (p = 0.04) health at one year after definitive surgery, despite no significant racial differences in baseline HRQL. **Conclusions:** Our findings highlight the importance of communication between providers and patients regarding treatment preferences and goals, the clinical significance of MRI findings, and the benefits/risks of available treatment options. Future research to identify modifiable factors associated with declining mental and physical health is needed to inform targeted interventions to mitigate racial disparities and enhance HRQL in patients with DCIS. Research Sponsor: U.S. National Institutes of Health.

6565 **Poster Session**

Initial reporting from the prospective National Cancer Institute (NCI) COVID-19 in Cancer Patients Study (NCCAPS). *First Author: Larissa A. Korde, Clinical Investigations Branch, National Cancer Institute, Bethesda, MD*

Background: Patients (pts) with cancer are at increased risk of SARS-CoV-2 infection and severe COVID-19 disease. Longitudinal follow-up is needed to characterize the severity, sequelae and outcomes in pts with cancer who develop COVID-19. **Methods:** NCCAPS is a prospective, longitudinal study (NCT04387656) aiming to accrue 2,000 pts with cancer undergoing active treatment or prior stem cell transplant for hematologic or solid tumor malignancy. Adult patients are eligible to enroll within 14 days of their first positive SARS-CoV-2 test; pediatric patients may also enroll retrospectively. Clinical data, patient-reported outcomes, blood specimens, and imaging are collected for up to 2 years. This abstract provides initial baseline and 2-month follow-up data. **Results:** As of Jan 22, 2021, 585 pts (552 adults and 33 pediatric pts) had complete baseline data and of these pts, 215 adults had 2 months of complete follow-up data. 23.4% of adults and 42.4% of pediatric pts were of non-White race and/or Hispanic/Latinx ethnicity. The most common cancer diagnoses were breast (19.6%), lung (9.9%) and multiple myeloma (8.9%) in adults and acute leukemia (AML/ALL; 63.6%) in children. The most recent treatment was chemotherapy in 38.2%, immunotherapy in 9.6%, and radiation in 5.4%. Median time from positive SARS-CoV-2 test to study enrollment was 10.5 days in adults and 18 days in pediatric pts. Preliminary analysis of plasma cytokines will be presented. At enrollment, 84.6% of adults had COVID-19 symptoms. 55.9% reported symptoms 2 weeks after their positive SARS-CoV-2 test; this fell to 39.0% at 1 month and 28.8% at 2 months (see Table). Of the 215 adults with complete data at 2 months, sequelae included pulmonary (n=22, 10%), cardiovascular (n=12, 6%) thromboembolic (n=9, 4%), bleeding (n=9, 4%) and gastrointestinal (n=11, 5%). 144 (67%) reported at least one cancer treatment disruption in the first 2 months, most commonly delayed therapy (n=98; 46%).Of the 348 adults with baseline data and SARS-CoV-2 test date prior to Nov 23, 2020, 6.3% had died (median time from SARS-CoV-2 test to death: 27 days), and 22.1% reported at least one hospitalization for COVID-19. No deaths were reported in the pediatric population. **Conclusion**: Cancer pts with COVID-19 report ongoing symptoms after acute infection and a substantial number develop sequelae. Cancer treatment disruptions are common in the initial months following SARS-CoV-2 infection. Longer follow-up will inform whether these treatment disruptions are associated with adverse outcomes. Clinical trial information: NCT04387656. Research Sponsor: U.S. National Institutes of Health.

Symptom, % reporting	Baseline N=542	2 weeks N=249	1 month N=293	2 months N=159
Fatigue/malaise	55.7	34.5	25.9	11.9
Dry Cough	41.5	21.3	11.3	6.3
SOB	30.6	15.3	15.4	8.8
Fever	28.2	5.6	2.0	0.6
Headache	24.9	10.4	6.1	3.1
Loss of taste	21.8	11.2	4.4	5.0
Productive cough	20.5	8.4	4.8	5.7
Loss of smell	19.9	8.8	3.4	4.4
Diarrhea	18.8	8.4	3.8	3.1

6566 **Poster Session**

Initial report on hospitalized cancer patients with COVID-19 from the National Cancer Institute (NCI) COVID-19 in Cancer Patients Study (NCCAPS). *First Author: Nicholas M. Mark, Swedish Medical Center, Seattle, WA*

Background: Hospitalized cancer patients (pts) with COVID-19 have a severe disease course and high mortality. Pts with lung cancer, hematologic malignancies and metastatic disease may be at higher risk. Detailed prospective inpatient data may help to identify those at greatest risk for poor outcomes. **Methods:** NCCAPS is a longitudinal study aiming to accrue 2,000 cancer pts undergoing treatment for hematologic malignancy or solid tumor with COVID-19. For pts' first COVID-19 hospitalization, clinical data, research blood specimens and imaging are collected, and additional clinical data are collected during subsequent hospitalizations. **Results:** As of Jan. 22, 2021, among 757 enrolled adult patients from 204 sites, 124 (16.3%) reported at least one hospitalization for COVID-19, and discharge data was available for 98 hospitalizations in 88 patients. The median age was 67 (range 21-93, 1Q:56, 3Q:72), 35/88 (40%) were female. The most common malignancies in hospitalized adult pts were lymphoma (18.2%), lung cancer (15.9%) and multiple myeloma (10.2%). The most common presenting symptoms were shortness of breath (65%), fatigue/malaise (64%), and fever (49%). 8/88 (9%) pts were neutropenic (ANC < 1000) at presentation; 17/88 (19%) were thrombocytopenic. Median length of stay was 6.5 days (range 1-41, 1Q:4, 3Q:12). Among those hospitalized, 20/88 (22.7%) received care in the ICU or high dependency unit, with a median ICU stay of 7 days (range 1-22, 1Q:2.5, 3Q:9.5); of those admitted to the ICU, 25% (5/20) received invasive mechanical ventilation. Of those in whom inpatient medications were recorded (n = 63), 63% received corticosteroids, 46% received remdesivir, and 14% received convalescent plasma. One pt received bamlanivimab and 2 patients received tocilizumab. Most (46/63; 73%) received anticoagulation, primarily prophylactic low molecular weight heparin; 11/63 (17%) received therapeutic dose anticoagulation. Inpatient D-dimer values were recorded in 43 inpatients, 26 of whom had multiple measurements. 16/98 hospitalizations ended with death (16%). **Conclusions:** Preliminary analysis of NCCAPS data reveals that inpatient hospital admission is common among oncology patients with COVID-19 and mortality rates appear high within this cohort. Hematologic malignancies and lung cancer are the most common underlying diagnoses in patients requiring hospitalization. Corticosteroids and anti-coagulation were the most commonly used therapies. Despite high rates of ICU admission, invasive mechanical ventilation may be instituted less often in an oncology cohort. These observations may inform decisions about vaccine policy and decisions to limit life sustaining treatment. Clinical trial information: NCT04387656. Research Sponsor: U.S. National Institutes of Health.

6567 **Poster Session**

Quality-adjusted time without symptoms of disease progression or toxicity (Q-TWiST) of nivolumab plus cabozantinib (N+C) versus sunitinib (SUN) in treatment-naïve, advanced/metastatic renal cell carcinoma (aRCC): A post-hoc analysis of CheckMate 9ER (CM 9ER) data. *First Author: David Cella, Robert H. Lurie Comprehensive Cancer Center, Northwestern University, Chicago, IL*

Background: In CM 9ER (ClinicalTrial.gov identifier NCT03141177), N+C demonstrated significant progression-free survival gains (median: 17.0 vs. 8.3 months [mos]; hazard ratio [HR]: 0.52; $P < .0001$) and overall survival (OS) benefits (median: not reached vs. 29.5 mos; HR: 0.66; $P < .001$) vs. SUN as a first-line treatment for aRCC (Motzer et al. ASCO-GU 2021). To more fully understand the clinical benefits and risks associated with N+C vs. SUN from a patient perspective, we applied the Q-TWiST method to CM 9ER data to assess the quality-adjusted survival of these two treatment options, after a minimum follow-up of 16 mos (Sept DBL 2020). **Methods:** OS was partitioned into 3 states: time with any grade 3 or 4 adverse events (TOX), time without symptoms of disease or toxicity (TWiST), and time after progression (REL). The Q-TWiST is a metric that combines the quantity and quality (i.e., "utility") of time spent in each of the 3 states TWiST, TOX, and REL. Sensitivity analyses estimated Q-TWiST across varying values of TOX and REL utilities. Subgroup analyses were conducted based on geographic region, programmed cell death-ligand 1 status, and International Metastatic RCC Database Consortium risk score. Based on minimal important difference norms (Revicki et al, Qual Life Res, 2006), a relative gain in Q-TWiST (i.e., Q-TWiST gains divided by OS in SUN) of ≥ 10% and ≥ 15% were qualified as "clinically important" and "clearly clinically important" gains, respectively. Non-parametric bootstrapping was used to generate 95% confidence intervals (CI). **Results:** In the intent-to-treat (ITT) population (N = 651), the Q-TWiST gain in the N+C arm was 4.0 mos (95% CI: 2.4, 5.7) vs. SUN arm, resulting in a relative gain of 16.9%. N+C patients had significantly longer TWiST (4.7 mos [95% CI: 2.9, 6.7]) and TOX (0.5 mos [95% CI: 0.1, 0.9]), but significantly shorter REL (-2.0 mos [95% CI: -4.1, -0.1]) than did SUN patients. Sensitivity analyses were consistent with the main analysis—the Q-TWiST benefit was robust across different ranges of U(TOX) and U(REL), with minimum and maximum Q-TWiST gains of 2.7 mos (11.7% relative gain) and 5.2 mos (22.2% relative gain), respectively. Subgroup analyses were consistent with the ITT population, with all results demonstrating ≥10% ("clinically important") gains favoring N+C. **Conclusions:** In CM 9ER, N+C resulted in a statistically significant and "clearly clinically important" (i.e., ≥ 15%) longer quality-adjusted survival vs SUN. Most gains were driven by added time in relatively good health (i.e., TWiST). These Q-TWiST results may help inform both aRCC patients and their clinicians to assess more comprehensively the clinical benefits and risks of N+C and SUN in making critical treatment decisions. Clinical trial information: NCT03141177. Research Sponsor: Bristol Myers Squibb.

6568 **Poster Session**

Long-term trend of quality-adjusted time without symptoms or toxicities (Q-TWiST) of nivolumab+ipilimumab (N+I) versus sunitinib (SUN) for the first-line treatment of advanced renal cell carcinoma (aRCC). *First Author: Robert J. Motzer, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: After a minimum follow-up of 48 months (mos), the CheckMate 214 trial (phase 3, NCT02231749) continued to demonstrate a significant overall (OS) and progression-free (PFS) survival benefit for N+I vs. SUN in aRCC patients (pts) with intermediate (I) or poor (P) International Metastatic RCC Database Consortium (IMDC) risk factors (median OS: 48.1 vs. 26.6 mos, HR: 0.65, 95% confidence interval [95% CI]: 0.54, 0.78; 48-mos PFS: 32.7% vs. 12.3%, HR: 0.74, 95% CI: 0.62, 0.88) (Albiges et al. ESMO Open 2020). To further understand the clinical benefits and risks of N+I vs. SUN, we evaluated the Q-TWiST over time using up to 57 mos of follow-up in CheckMate 214. **Methods:** OS was partitioned into 3 states: time with any grade 3 or 4 adverse events (TOX), time without symptoms of disease or toxicity (TWiST), and time after progression (REL). The Q-TWiST is a metric that combines the quantity and quality (i.e., "utility") of time spent in each of the 3 states TWiST, TOX, and REL. Prior research (Revicki et al, Qual Life Res, 2006) has established that relative gains in Q-TWiST (i.e., Q-TWiST gain divided by OS in SUN) of $\geq$ 10% and $\geq$ 15% can be considered as "clinically important" and "clearly clinically important", respectively. Non-parametric bootstrapping was used to generate 95% CIs. To observe changes in quality-adjusted survival gains over time, absolute and relative Q-TWiST were calculated up to 57 mos at intervals of 12-mos. **Results:** With 57-mos follow-up, compared to SUN pts, N+I pts (N = 847) had significantly longer time in TWiST state (+7.1 mos [95% CI: 4.2, 10.4]). The between-group differences in TOX state (0.3 mos [95% CI: -0.2, 0.8]) and REL state (-1.2 mos [95% CI: -4.1, 1.5]) were not statistically significant. The Q-TWiST gain in the N+I vs. SUN arms was 6.6 mos (95% CI: 4.1, 9.4), resulting in a 21.2% relative gain. Q-TWiST gains progressively increased over the follow-up period and exceeded the "clinically important" threshold around 27 mos (Table). These gains were driven by steady increases in TWiST gains from 0.4 mos (after 12 mos) to 7.1 mos (after 57 mos). **Conclusions:** In CheckMate 214, N+I resulted in a statistically significant and "clearly clinically important ($\geq$ 15%)" longer quality-adjusted survival vs. SUN, which increased over the longer follow-up time. Q-TWiST gains were primarily driven by time in "good" health (i.e., TWiST), which largely resulted from the long-term PFS benefits seen for N+I vs. SUN. Clinical trial information: NCT02231749. Research Sponsor: Bristol Myers Squibb.

Follow-up (mos)	N+I	SUN	Q-TWiST Gain	Relative Gain
12	9.0 (8.7, 9.3)	8.6 (8.3, 8.9)	0.4 (-0.0, 0.9)	3.8%
24	15.9 (15.1, 16.6)	14.2 (13.4, 14.9)	1.7 (0.6, 2.8)	9.7%
36	21.5 (20.4, 22.6)	18.2 (17.1, 19.4)	3.3 (1.7, 5.0)	14.2%
48	26.7 (25.1, 28.3)	21.5 (19.9, 23.0)	5.2 (3.1, 7.5)	18.5%
57	30.2 (28.3, 32.2)	23.6 (21.6, 25.4)	6.6 (4.1, 9.4)	21.2%

6569 **Poster Session**

Post-intervention lung cancer screening compliance among internal medicine resident physicians at a primary care clinic in Hartford, Connecticut. *First Author: Nerea Lopetegui-Lia, University of Connecticut Health Center, Farmington, CT*

Background: Lung cancer (ca) screening has shown to reduce mortality by up to 20%.Despite this, only 4% of eligible patients in the US undergo screening. Our initial analysis revealed that 18.3% of patients who met screening criteria had an appropriately ordered LDCT scan, with an 8.7% completion rate. The aim of this study was to improve lung ca screening compliance following the USPSTF guidelines among residents from the University of Connecticut Internal Medicine (IM) residency program at a Clinic in Hartford, Connecticut. **Methods:** Care provided to patients by an IM resident at the Gengras Clinic were included. After initial data was gathered, we implemented an intervention to improve screening compliance between October 2019 and March 2020, when SARS-CoV-2 pandemic occurred and routine services were interrupted. USPSTF screening guidelines were emailed monthly to residents and attendings; they were reminded of the importance of lung ca screening; updating the pack-year smoking history; as well as instructions on correctly ordering LDCT and documenting shared decision making, which is needed for insurance approval. In-person reminders also occurred at the clinic. **Results:** Post-intervention, 601 charts were reviewed. 168/601 (27%) patients met screening criteria. 433 patients were excluded due to unclear pack-year, did not meet screening criteria, were deceased or last seen at the clinic prior to the intervention. 63/168 (37.5%) met the criteria and had an appropriately ordered LDCT; 51/168 (30.35%) had a completed LDCT in chart. The remaining 12/168 (7.14%) with an appropriately ordered LDCT, had it scheduled at the time of data collection or it had been cancelled for unclear reasons. 20 patients' LDCT was ordered by their pulmonologist. 94 (62.5%) who met screening criteria did not have a LDCT ordered. 11 patients with a smoking history, who did not meet screening criteria had a LDCT ordered because of clinical suspicion for cancer. Lastly, 4/168 (2.4%) had a diagnosis of personal history of lung ca. **Conclusions:** After our educational intervention, patients who qualified had an increase of LDCT being ordered (37.5% from 18.3%) and completed (30.3% from 8.7%). This is, to our knowledge, the first study of its kind. We identified areas of improvement that were key to achieving higher screening rates: educating all residents and attendings on lung ca screening guidelines; educating patients on the importance of undergoing screening tests; creating a best practice advisory in the electronic medical record system that reminds provider to input pack-year smoking history and if the criteria for screening is met, a pop-up prompting the provider to order LDCT; obtaining insurance approval; and lastly, stressing the importance on screening and overall outcomes. Research Sponsor: None.

6570 **Poster Session**

The landscape of mortality during or within 30 days after non-palliative radiotherapy across 11 major cancer types. *First Author: Michael Xiang, Department of Radiation Oncology, University of California, Los Angeles, Los Angeles, CA*

Background: The rate of peri-RT mortality (death that occurs during or within 30 days after non-palliative radiotherapy) has not been previously characterized. Risk factors and predictors for peri-RT mortality are unknown. **Methods:** Adult and pediatric patients with non-metastatic cancer who received non-palliative external beam radiation between 2004-2016 were identified in the National Cancer Database for 11 cancer types: breast, prostate, genitourinary (non-prostate), bone/soft tissue, gynecological, head/neck, lymphoma, gastrointestinal, small cell lung, non-small cell lung, and central nervous system (CNS). Multivariable logistic regression was used to identify predictors of peri-RT mortality while controlling for 16 covariates, including patient, tumor, and treatment factors. **Results:** Approximately 1.32 million patients were identified. Peri-RT mortality was 2.8% overall but spanned 2 orders of magnitude depending on cancer type, ranging from 0.1% for breast cancer to 8.6% for CNS malignancies. Other cancers with $>$ 5% peri-RT mortality were non-prostate genitourinary, small cell lung, and non-small cell lung. Peri-RT mortality steadily improved from 3.5% in 2004 to 2.0% in 2016 ($P <$ .0001). Major predictors of peri-RT mortality were cancer stage, older age, baseline comorbidity, and lack of private insurance, while male sex, Black race, and geographical region were associated with modestly increased risk (all $P <$ .0001). Conversely, treatment at an academic center, higher patient volume at the treating facility, concurrent chemotherapy, and intensity-modulated radiotherapy were associated with modestly decreased risk (all $P <$ .0001). Among patients receiving stereotactic radiotherapy, peri-RT mortality was 1.0% (adjusted odds ratio 0.27, 95% confidence interval 0.24-0.30, $P <$ .0001), underscoring the excellent safety record of this treatment approach. **Conclusions:** Peri-RT mortality varied considerably as a function of multiple disease-specific and sociodemographic differences, which highlight potential areas of health disparities. Early recognition of patients at increased risk may facilitate closer monitoring or other prophylactic interventions. Research Sponsor: None.

6571 **Poster Session**

Overall survival, quality of life and magnitude of clinical benefit of breast cancer drugs over the last 25 years. *First Author: J. Carlos Tapia, Hospital Sant Pau, Barcelona, Spain*

Background: The American Society of Clinical Oncology Cancer Research Committee (ASCO-CRC), the ASCO Value Framework Net Health Benefit score version 2 (ASCO-VF), and the European Society for Medical Oncology-Magnitude of Clinical Benefit Scale version 1.1 (ESMO-MCBS) are validated tools quantifying the clinical benefit for cancer drugs. Here, we assess the overall survival (OS), quality of life (QoL) and magnitude of clinical benefit of trials supporting breast cancer drug approval by the US Food and Drug Administration (FDA) in the last 25 years. **Methods:** We searched Drugs@FDA website for all breast cancer drug approvals from January 1, 1995 to December 30, 2020. Drug labels and reports of registration trials were reviewed. We collected data on trial characteristics, efficacy, toxicity and QoL. When more than one study supported a single indication, we preferred efficacy-oriented endpoints (typically OS) to QoL. We excluded trials supporting accelerated-approval indications if these were converted to regular approval during the study period. We scored clinical benefit using the ASCO-CRC in palliative setting, and ASCO-VF and ESMO-MCBS in both curative and palliative setting. Substantial clinical benefit was defined as: OS gains $\geq$2.5 months and progression-free survival gains $\geq$ 3 months for ASCO-CRC criteria; ASCO-VF scores $\geq$ 45 and grade of A or B for trials of curative intent and 4 or 5 for those of non-curative intent using ESMO-MCBS. Trends over time were assessed using Chi-squared test for trend. **Results:** We identified 51 trials supporting the approval of 32 individual drugs for 51 indications; 12 (24%) were in the curative setting and 39 (76%) in the palliative setting. At the time of approval, 8 (16%) trials reported significant improvement in OS. QoL was reported in 22 trials (43%). Among these, 8 (36%) showed improvement in QoL. For curative intent, we applied ASCO-VF and ESMO-MCBS score to 11 (92%) trials, finding clinical benefit in 10 (91%) and 2 (18%) trials, respectively. In the palliative setting, we used ASCO-CRC, ASCO-VF and ESMO-MCBS scores to rate 32 (82%), 33 (85%) and 38 (97%) trials. Substantial clinical benefit was observed in 20 (63%), 12 (36%) and 7 (19%) trials, respectively. Over time, there has been a decrease in the number of trials supporting approval based on OS (1996-2003 50% vs 2004-12 38% vs 2013-20 13%, P trend = 0.033). There were no statistically significant changes over time in QoL, ASCO-CRC, ASCO-VF and ESMO-MCBS scores. **Conclusions:** For palliative intent, most trials supporting FDA approval of breast cancer drugs do not meet the ASCO-VF or ESMO-MCBS criteria for substantial clinical benefit. There is substantial inter-framework variability in the assessment of clinical benefit in the curative setting. Over time, there has been a substantial shift towards use of surrogate endpoints as the basis for approval without a clear improvement in substantial clinical benefit. Research Sponsor: None.

6572 **Poster Session**

Should PICCs be avoided in patients with certain solid organ cancers? *First Author: Urvashi Mitbander, Department of Internal Medicine, University of Michigan Health System, Ann Arbor, MI*

Background: Peripherally inserted central catheters (PICCs) are widely utilized in oncology. Previous studies have shown a high risk of catheter-related thrombosis and bloodstream infection in the uniquely susceptible oncologic population; however, most studies are limited by single center, outpatient, retrospective designs. Therefore, we performed a multi-center study to further describe PICC use and complications in the solid tumor population within the inpatient setting. **Methods:** Data was collected on PICC lines inserted across 50 hospitals in Michigan from November 2013 to December 2019. Patients with a solid tumor diagnosis at time of PICC insertion were selected (n = 3,956). Indications for PICC placement, catheter characteristics, and associated complications were compared by metastatic (n = 1,488) and non-metastatic (n = 2,468) disease. Complications were also compared by cancer type. Major complications were defined as central line associated blood stream infection (CLABSI), catheter occlusion, deep vein thrombosis (DVT), and pulmonary embolism (PE). Paired t-test and Pearson Chi-square test were used for analyses. **Results:** PICCs were most commonly placed for antibiotics (n = 1232, 31%) and chemotherapy (n = 907, 23%). The majority of catheters were multi-lumen with 61% (n = 2362) double lumen and 8% (n = 326) triple lumen. Median dwell time was 13 days. Notably, 17% of patients had another central venous catheter (CVC) at time of placement. Metastatic patients were more likely to have a PICC placed for difficult venous access (24.7% vs 17.7%, $p < 0.001$) and total parenteral nutrition (20.2% vs 12.3%, $p < 0.001$) as well as to have a current CVC in place (22% vs 14%, $p < .001$). Non-metastatic patients were more likely to have a PICC placed for chemotherapy (24.1% vs 20.9%, p = 0.02) and have a longer median dwell time (13.0d vs 11.0d, p = 0.04). Of all solid tumor patients, 15.5% (n = 612) experienced a major complication. Catheter occlusion occurred most frequently (n = 402, 10.2%) followed by DVT (n = 138, 3.5%), CLABSI (n = 107, 2.7%), and PE (n = 22, 0.6%). Catheter occlusion was more likely to occur in non-metastatic patients (11% vs 8.8%, p = 0.03). Rates of CLABSI, DVT, and PE did not differ significantly by presence of metastases. Certain cancers had a higher frequency of major complications when compared to the average solid tumor cohort rate of 15.5%; these were malignant brain (17.2%), pancreatic (18.4%), uterine (18.5%), and ovarian tumors (24.2%). **Conclusions:** PICCs are associated with significant complications in 16% of patients with solid organ cancers. Alternate access such as an implanted port should be considered; alternatively, limiting PICC placement in the presence of concurrent CVC or minimizing use of multiple lumen PICCs may limit complications and resultant morbidity. Specifically, these considerations may apply preferentially to patients with certain solid organ cancers with higher rates of PICC associated morbidity. Research Sponsor: Blue Cross/Blue Shield of Michigan and Blue Care Network.

6573 **Poster Session**

A new option in pain prevention with bliss, a therapeutic virtual reality solution in bone marrow biopsy context: Results of a French open-label multicenter randomized phase II/III study (REVEH Trial). *First Author: Katell LE DU, Centre Jean Bernard-Clinique Victor Hugo, Institut Inter-Régional De Cancérologie, Le Mans, France*

Background: The prevention of care-induced pain is a central concern for all healthcare teams in hematology units. Use of MEOPA (Oxygen + Nitrous Oxide) is today a standard of care for relaxation procedure. Distraction through immersion in virtual reality (VR) has already documented its analgesic effects in several phase II trials but comparison with standard treatments in a large randomized study is needed. **Methods:** We conducted an open-label multicenter randomized phase III trial (ClinicalTrials.gov identifier: NCT03483194). We assessed the safety and efficacy of a new therapeutic virtual reality solution for pain distraction, Bliss, in prevention of pain and anxiety before performing a bone marrow biopsy. Bliss is a VR software with four imaginary interactive environments in three dimensions with binaural sound (head-mounted display). Efficacy was evaluated by pain intensity with visual analog scale (score from 0 to 10) just after the biopsy and anxiety by 2 questionnaires (fear of pain before the biopsy and revised STAI questionnaire before and after the biopsy). The primary end point was patient-assessed pain intensity after the bone marrow procedure. **Results:** A total of 126 patients were enrolled with previously untreated malignant hemopathy between September 6, 2018 and May 18, 2020. They were randomly assigned in a 1:1 ratio to receive pain prevention with MEOPA (n=63) or Bliss (n=63) before and during their bone marrow biopsy. All patients received a local anesthesia with lidocaïne before the biopsy. Median age of the study population was 65.5 years old (range 18 to 87) and 54,2% were men. The average pain intensity was 3.5 (standard deviation 2.6) for the MEOPA group and 3.0 (SD 2.4) for the VR group (p=0,26) without any significant difference according to age, gender or hemopathy. Concerning anxiety, 67.5% of patients were afraid before the biopsy and anxiety scores were moderate to very high in 26.3% of patients before the biopsy (STAI questionnaire) and 9.0% after the biopsy for all patients (17.3% of reduction in anxiety for the MEOPA group and 17.2% for the VR group, p=0.83). Immersion in VR was well tolerated in 100% of patients included in the VR group. Physicans were very satisfied by the relaxation procedure in 64.9% of cases (52.5% in the MEOPA group and 77.6% in the VR group, p=0.01) and recommended re-use of the technique in 54.2% in the MEOPA group and 79,1% in the VR group (p=0.02). **Conclusion:** The intensity of pain did not significantly differ in both arms. Bliss-based relaxation method was well tolerated and the satisfaction of patients and physicians was very high in VR group. This study validates the use of immersion in VR with Bliss as a new digital therapeutics and support the integration of the software in the panel of supportive care. Key words: virtual reality, bone marrow biopsy, pain. Clinical trial information: 03483194. Research Sponsor: Roche, Other Foundation, Elsan group.

6574 **Poster Session**

Ovarian function suppression in premenopausal patients with concurrent endocrine therapy use. *First Author: Nicole Margo Grogan, University of Michigan Rogel Cancer Center, Ann Arbor, MI*

Background: The addition of ovarian function suppression (OFS) to endocrine therapy (ET) for premenopausal women with high risk, hormone receptor-positive breast cancer improves disease outcomes. However, in the SOFT-EST study, up to 17% of patients receiving gonadotropin-releasing hormone agonists (GnRHa) did not have appropriate ovarian suppression within the first year of treatment. Few studies have explored the long-term effectiveness of OFS to maintain estrogen suppression. Guidelines for estradiol monitoring during OFS therapy are not clearly defined. **Methods:** We performed a retrospective, single institution review of all patients who received concurrent GnRHa injections and ET since 2010. Only estradiol concentrations that were assessed during OFS treatment were abstracted from the medical record and included in the analysis. The primary endpoint was the percentage of patients with a non-suppressed estradiol concentration (defined as standard estradiol or high-sensitivity estradiol $\geq$ 10 pg/ml) identified during OFS cycle 2 ($>$ 35 days after OFS initiation) and/or later cycles. The secondary endpoint, which included only those patients with estradiol assessment within 35 days of OFS initiation, was the percentage of patients with a non-suppressed estradiol level when measured within the first 35 days after OFS initiation. For both cohorts, differences in age, body mass index (BMI), and previous chemotherapy use were summarized via multivariable logistic regression. **Results:** 148 patients received concurrent OFS and ET. Patients were excluded because of lack of estradiol assessment during OFS therapy (n = 13) and non-compliance with GnRHa injections (n = 4). The average age and BMI were 43.1 years and 29.1 kg/m^2, respectively. 35 of 131 patients (26.7%) had at least one non-suppressed estradiol level during OFS cycle 2 and/or later cycles. The median time to detection of non-suppression was 250 days (range: 53 – 2573 days). Patients whose estradiol concentration remained suppressed throughout treatment with OFS and ET were more likely to be older (OR 1.12 [95% CI 1.05-1.22], p = .02), have a lower BMI (OR 0.88 [95% CI 0.82-0.94], $p < .001$), and have received chemotherapy (OR 6.30 [95% CI 2.06-20.8], p = .002). For the secondary endpoint, 20 of 83 patients (24.1%) had a non-suppressed estradiol level within 35 days of OFS initiation. Lower BMI was associated with achieving ovarian suppression by 35 days (OR 0.85 [95% CI 0.77-0.93], $p < .001$); no association was noted for age or chemotherapy. **Conclusions:** More than one-fourth of patients in this "real world" population had at least one non-suppressed estradiol level during treatment, both the month after the initial OFS dose and at later time points. Patients on OFS, especially those on aromatase inhibitor therapy and those at increased risk of non-suppression, may require frequent and long-term estradiol monitoring during treatment. Research Sponsor: None.

6575 **Poster Session**

Prevalence of discordant QTc values among cancer patients by the Bazett, Fridericia, and Framingham formulae: Evidence for a standardized approach. *First Author: P. Christopher Parish, UNC Eshelman School of Pharmacy, Chapel Hill, NC*

Background: Many chemotherapies have the potential to prolong the QT interval, requiring monitoring of the corrected QT (QTc) to prevent life-threatening arrhythmias. Most clinical guidelines recommend adjusting/holding chemotherapy with Grade 3 or higher toxicity by CTCAE (QTc$\geq$500). Several formulae are used for QTc monitoring including Bazett, Fridericia, and Framingham. The most commonly used formula, Bazett, is well-documented to result in inappropriately high QTc values although the potential impact of this overcorrection on cancer treatment is unknown. We aimed to describe the prevalence of QTc prolongation among cancer patients and the effects on CTCAE adverse event grading by various QTc formulae to determine the potential impact on clinical management. **Methods:** We performed a single-center retrospective analysis of QT values from electrocardiograms (ECGs) collected January 2010-April 2020 and evaluated associations between QTc values, medications, and patient characteristics. QTc prolonging agents were determined by FDA package insert and cross-referenced with CredibleMeds.org. **Results:** 20,017 ECGs were evaluated. 18.6% (3,730) met ACC/ACCF/HRS criteria for prolonged QTc by $\geq$1 QT correction formula (either Bazett, Fridericia, or Framingham). 7.5% (1,494) were prolonged with all three formulae, and 8.6% (1,635) were prolonged only with Bazett. The CTCAE classification using the Bazett formula differed from both Fridericia and Framingham in 37.9% (7,583) of the ECGs. In contrast, Fridericia and Framingham formulae resulted in the same CTCAE classification in 94.5% (18,912). Of 1,789 ECGs classified as Grade 3 toxicity by Bazett, 72.0% (1,288, 6.4% of all ECGs) were classified as Grade 2 or less by both Fridericia and Framingham. 12.0% (2,340) of all ECGs were taken from patients (n = 421) on 24 different QT-prolonging chemotherapies. In 38.8% (909) of the ECGs, the CTCAE classification using the Bazett formula differed from both Fridericia and Framingham while use of Fridericia and Framingham formulae resulted in the same classification in 93.0% (2,176) of the ECGs. Of 293 ECGs classified as Grade 3 toxicity by Bazett, 65.2% (191) were classified as Grade 2 or less by both Fridericia and Framingham. **Conclusions:** To our knowledge, this is the largest analysis of discrepancies between different QTc formulae in patients receiving chemotherapy. These findings demonstrate an unacceptably high rate of discordance between formulae. Discordant data can lead to inconsistent clinical management and adverse event grading underscoring the urgent need to standardize QTc monitoring and reporting. These findings support the discontinuation of the routine use of the Bazett correction formula among cancer patients as CTCAE Grade 3 reporting from the Bazett formula is unreliable in over 65% of cases. Research Sponsor: None.

6576 **Poster Session**

A review of evidence supporting NCCN category 2B off-label recommendations for determination of Medicare reimbursement eligibility. *First Author: Molly Erin DiScala, Tempus Labs, Inc, Chicago, IL*

Background: Antineoplastic indications supported by a category 1 or 2A NCCN recommendation are reimbursed by insurance and Medicare, as are FDA-approved indications. While initial reimbursement requests for "off-label" NCCN category 2B indications may be denied, Medicare will reimburse off-label antineoplastic use supported by evidence from a peer-reviewed publication from one of 26 designated journals. Here, we evaluated the published clinical evidence supporting NCCN category 2B indications. **Methods:** Category 2B drug indications for the 10 most common solid tumor types were identified in the NCCN compendium (n=104). The results were then filtered to include drugs with only category 2B indications in a particular tumor type (n=14). Similarly, FDA-approved indications were excluded, resulting in a list of drugs with only a 2B indication that are not FDA approved in the specified cancer type (n=8). Published clinical studies supporting these category 2B indications were assessed for study type and journal name in PubMed, and journal names were cross-referenced with the CMS-supported list. **Results:** Among the 8 non-FDA-approved drug indications with only category 2B recommendations, 7 (87%) had at least one publication of a clinical trial in one of the 26 designated journals. The only 2B indication without supporting literature was single-agent gemcitabine hydrochloride in bladder cancer. For further details, see Table. **Conclusions:** These results suggest that clinicians should consider pursuing the appeals process and provide supporting evidence in cases of claim denial. While coverage is not guaranteed, the evidence supporting 2B indications frequently meets the criteria identified in the Medicare statute. Further studies will evaluate if these findings extrapolate to less common tumor types. Research Sponsor: None.

Drug	Cancer Type	PubMed ID	Journal Name	Type of Study	Evidence Supported by CMS?
Vandetanib	Non-Small Cell Lung Cancer	27803005	*Annals of Oncology*	Phase 2 RCT	Y
		27825616	*Lancet Oncology*	Non-randomized, Phase 2 Clinical Trial	Y
		25881079	*BMC Cancer (Biomed Central)*	Phase 3 RCT	N
		25366691	*JCO*	Case report	N
Eribulin	Uterine Neoplasms - Uterine Sarcoma	21937277	*Lancet Oncology*	Non-randomized, Phase 2 Clinical Trial	Y
Cisplatin, Vinblastine, and Dacarbazine	CM	19001327	*JCO*	Phase 3 RCT	Y
		25332243	*JCO*	Phase 3 RCT	Y
Talimogene laherparepvec and ipilimumab	CM	26014293	*JCO*	Phase 3 RCT	Y
		28981385	*JCO*	Phase 2 RCT	Y
Binimetinib	CM	28284557	*Lancet Oncology*	Phase 3 RCT	Y
Docetaxel	Uterine Neoplasms	16234823	*British Journal of Cancer*	Non-randomized Phase 2 Clinical Trial	Y
Gemcitabine hydrochloride	Bladder	N/A	N/A	N/A	N
Gemcitabine, Docetaxel, and Capecitabine	Pancreatic	25492104	*Cancer*	Non-Randomized, Phase 2 Clinical Trial	Y

CM: Cutaneous Melanoma, JCO: *Journal of Clinical Oncology*, RCT; Randomized Controlled Trial: Y/N: Yes/No

6577 **Poster Session**

Comprehensive or specialty-specific cancer care in the United States: A story of continuing underperformance. *First Author: Christopher Thomas Aquina, Division of Surgical Oncology, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: "Textbook oncologic outcome" (TOO) is a composite measure representing the "ideal" outcome for patients undergoing cancer surgery and is associated with improved survival. Using TOO as the primary outcome, we asked whether hospitals are high-performing across multiple cancer types. **Methods:** Patients undergoing potentially curative breast, colon, rectal, lung, or pancreatic cancer resection were identified within the National Cancer Database (2010-2016). Organ-specific TOO was defined as: adequate lymph node yield, R0 resection, non-length of stay outlier, no hospital readmission, no 90-day postoperative mortality, and receipt of guideline-concordant chemotherapy and/or radiation. Mixed-effects analyses estimated the risk-adjusted TOO rate for each hospital stratified by cancer type. **Results:** Among 1,094,550 cancer resections (breast = 690,442; colon = 213,918; lung = 121,771; rectum = 40,315; pancreas = 28,104), 434 hospitals performed $\geq$10 resections for each cancer type. Only 11 hospitals (2.5%) ranked in the top quartile for adjusted TOO rate for all five cancer types. Of the 323 hospitals (74.4%) that ranked in the top quartile for one cancer type, 149 hospitals (46.1%) also ranked in the bottom quartile for another cancer type. There was a weak correlation between hospital rankings across cancer types with the strongest correlations between colon and rectal cancer (R^2= 0.148) and lung and pancreatic cancer (R^2= 0.098). **Conclusions:** Most U.S. hospitals do not provide high-quality care across cancer types with respect to TOO. Perhaps this knowledge should be used to guide referral for oncology care. Research Sponsor: None.

6578 **Poster Session**

Associations between patient knowledge of others' experiences and treatment choice in men with localized prostate cancer. *First Author: Aaron J. Katz, University of Kansas Medical Center, Kansas City, KS*

Background: Men with localized prostate cancer must select from multiple treatment options, without one clear best choice. Consequently, personal factors, such as knowing other prostate cancer patients who have undergone treatment, may influence patient decision-making. However, associations between knowledge about others' experiences and treatment decision-making among localized prostate cancer patients has not been well characterized. We used data from a population-based cohort of localized prostate cancer patients to examine whether patient-reported knowledge of others' experiences is associated with treatment choice. **Methods:** The North Carolina Prostate Cancer Comparative Effectiveness & Survivorship Study (NC ProCESS) is a population-based cohort of localized prostate cancer patients enrolled from 2011-2013 throughout the state of North Carolina in collaboration with the North Carolina Central Cancer Registry. All patients were enrolled prior to treatment and followed prospectively. Patient decision-making factors including knowledge of others' experiences with prostate cancer treatment options were collected through patient report. Patient treatment choice was determined through medical record abstraction and cancer registry data. **Results:** Among 1,202 patients, 17% reported knowing someone who pursued active surveillance (AS) while 28%, 46%, and 59% reported knowing someone who received brachytherapy, external beam radiation (EBRT), or radical prostatectomy (RP), respectively; 26% underwent AS, 9% brachytherapy, 21% EBRT, and 39% RP as their initial treatment. In unadjusted analyses, patients with knowledge of others' experiences with brachytherapy, EBRT or RP had more than twice the odds of receiving that treatment compared to patients who did not. Knowledge of others' experience with AS was not associated with choice to undergo AS. Multivariable analysis adjusting for age, race, risk group, and patient-reported goals of care showed knowledge of others' experiences with brachytherapy (OR 4.60, 95% confidence interval [CI] 2.76 to 7.68), EBRT (OR 2.38, 95% CI 1.69 to 3.34), or RP (OR 4.02, 95% CI 2.84 to 5.70) was significantly associated with odds of receiving that treatment. The odds of receiving a particular treatment option were further increased among patients who reported knowing someone who had a "good" experience with the treatment in question. **Conclusions:** This is the first population-based study to directly demonstrate the impact of a patient's knowledge of others' experiences on treatment choice in prostate cancer. These data provide a new consideration to clinicians in their counseling of patients with newly diagnosed prostate cancer, and also impacts research into the informed decision-making process for this disease. Research Sponsor: Patient-Centered Outcomes Research Institute.

6579 **Poster Session**

Knowledge about risks, benefits, and curative potential of immunotherapy among patients with advanced lung cancer or melanoma. *First Author: Laura A Petrillo, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: Immunotherapy is a novel treatment paradigm that has improved survival for patients with advanced melanoma and lung cancer and poses new risks of immune-related adverse events, which are important for patients to recognize promptly. We aimed to describe patients' knowledge about the risks and benefits of immunotherapy, and their understanding of the goal of treatment with immunotherapy. **Methods:** We conducted a cross-sectional study of patients at a single institution who had initiated therapy with an immune checkpoint inhibitor for advanced melanoma, small cell lung cancer, or non-small cell lung cancer in the past 12 weeks. We assessed patients' knowledge about immunotherapy with a 9-item knowledge questionnaire (score range 0-100; higher score represents greater knowledge). We used the Perception of Treatment and Prognosis Questionnaire to assess patients' understanding of the goal of their treatment. We used the two-sample t-test to compare knowledge scores and chi-square test to compare goals of therapy between patients with melanoma and lung cancer. **Results:** A total of 105 patients (57 with melanoma, 48 with lung cancer) completed the study questionnaire. Participants had a median age of 69 years (range 36-89), and 33% (35/105) were female. Participants' mean knowledge score was 69.0 (SD = 23.3). Overall, 91% (96/105) of patients endorsed that immunotherapy works by turning on the body's immune system to recognize and attack cancer cells and 33% (35/105) correctly identified that immunotherapy does not kill all rapidly dividing cells. With respect to immunotherapy side effects, 68% (71/105) of patients reported that immunotherapy side effects can affect any organ in the body and 65% (68/105) endorsed that side effects from immunotherapy can occur at any time, even after the treatment ends. Overall, 34% (36/105) of participants reported that the primary goal of their treatment is to cure their cancer. Participants with melanoma had higher mean knowledge scores compared to those with lung cancer (74.7 vs. 62.3, P = 0.003). Participants with melanoma were also more likely to report that the goal of their immunotherapy was to cure compared to those with lung cancer (58% [33/57] vs. 6% [3/48], P $<$ 0.001) and that their oncologist had said that immunotherapy would cure their cancer (19% [11/57] vs. 0% [0/48], p = 0.005). **Conclusions:** We observed substantial knowledge deficits about immunotherapy and perceptions that immunotherapy is a cure for advanced cancer, particularly among patients with melanoma. These findings underscore the need for interventions to enhance patients' knowledge about immunotherapy and to help them understand the goal of immunotherapy for patients with advanced cancer. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

6580 **Poster Session**

Provision of subspecialized expert oncology (SEO) opinions using Navya Cancer Data Model (NCDM), a technology-based platform: Prospective study to facilitate access to care. *First Author: Tiffany A. Traina, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Outcomes for patients (pts) with cancer may vary widely based on accessibility and quality of care. Subspecialized expert care is associated with improved outcomes yet access to this scarce resource is limited. Providing SEO opinions in legacy ways is time-consuming and difficult to scale. We hypothesized that summarizing comprehensive pt records could enhance efficiency of a remote opinion process. In this prospective pilot, oncologists (MDs) at Memorial Sloan Kettering (MSK) tested the NCDM, a clinically-validated, semi-automated system which abstracts pertinent data elements from medical records into a structured summary to support SEO decision making for remote opinions. **Methods:** From July to December 2020, 12 MSK MDs provided remote opinions to consecutive pts from an international second opinion service who were specifically seeking MSK expertise. NCDM summaries, with relevant DICOM imaging, were provided to MDs via web and mobile app. MDs answered a brief survey about their experience after each opinion. Time spent to read and respond to an NCDM summary was tracked electronically. Pt feedback was collected by prospective phone follow up. **Results:** N = 101 remote opinions. Cancer type (N): breast (24), gastrointestinal (15), heme malignancy (14), prostate (12), renal (8), gynecologic (7), head & neck (11), lung (9) and skin (1). 92% MD response rate. Pt characteristics: median age (60 years, range 17-83); stage of disease (early stage 41%, advanced 59%); 86% of pts had received prior treatment. MDs survey responses: median time to complete record review and render opinion = 4.8 min (IQR 2.7 – 7.9 min); NCDM provided adequate information needed to make a decision in this case = 95.7% (89/93); Decision making was easy in this case with data presented in the NCDM format = 96.8% (90/93). Pt survey responses (71/88): 92% shared recommendation with local MD; 87% received the recommended treatment; 99% stated they would recommend a NCDM enabled remote opinion service to others. **Conclusions:** NCDM summaries enabled subspecialized MSK cancer experts to provide oncology remote opinions with ease. Patients reported high satisfaction with the experience. Technology assisted abstraction and case summary can facilitate access to subspecialized expert opinions at a global scale. Research Sponsor: None.

6581 **Poster Session**

Impact of cancer on the risk of unplanned 30-day readmissions. *First Author: Alexander S. Qian, Department of Radiation Medicine and Applied Sciences, University of California San Diego, La Jolla, CA*

Background: Hospital readmission are associated with unfavorable patient outcomes and increased costs to the healthcare system. Devising interventions to reduce risks of readmission requires understanding patients at highest risk. Cancer patients represent a unique population with distinct risk factors. The purpose of this study was to define the impact of a cancer diagnosis on the risks of unplanned 30-day readmissions. **Methods:** We identified non-procedural hospital admissions between January through November 2017 from the National Readmission Database (NRD). We included patients with and without a cancer diagnosis who were admitted for non-procedural causes. We evaluated the impact of cancer on the risk of 30-day unplanned readmissions using multivariable mixed-effects logistic regression models. **Results:** Out of 18,996,625 weighted admissions, 1,685,099 (8.9%) had record of a cancer diagnosis. A cancer diagnosis was associated with an increased risk of readmission compared to non-cancer patients (23.5% vs. 13.6%, $p < 0.001$). However, among readmissions, cancer patients were less likely to have a preventable readmission (6.5% vs. 12.1%, $p < 0.001$). When considering the 10 most common causes of initial hospitalization, cancer was associated with an increased risk of readmission for each of these 10 causes (OR range 1.1-2.7, all $p < 0.05$) compared to non-cancer patients admitted for the same causes. Compared to patients aged 45-64, a younger age was associated with increased risk for cancer patients (OR 1.29, 95%CI [1.24-1.34]) but decreased risk for non-cancer patients (OR 0.65, 95%CI [0.64-0.66]). Among cancer patients, cancer site was the most robust individual predictor for readmission with liver (OR 1.47, 95%CI [1.39-1.55]), pancreas (OR 1.36, 95%CI [1.29-1.44]), and non-Hodgkin's lymphoma (OR 1.35, 95%CI [1.29-1.42]) having the highest risk compared to the reference group of prostate cancer patients. **Conclusions:** Cancer patients have a higher risk of 30-day readmission, with increased risks among younger cancer patients, and with individual risks varying by cancer type. Future risk stratification approaches should consider cancer patients as an independent group with unique risks of readmission. Research Sponsor: U.S. National Institutes of Health.

6582 **Poster Session**

Bone modifying agents in veterans with castration-resistant prostate cancer. *First Author: Jordan Bauman, University of Michigan, Ann Arbor, MI*

Background: Skeletal related events (SREs) are a known complication for the 80% of men with metastatic prostate cancer who have bone metastases. Previous studies have demonstrated that bone modifying agents (BMAs) such as zoledronic acid and denosumab reduce SREs in men with metastatic castration-resistant prostate cancer who have bone metastases and are now recommended by national guidelines. We sought to investigate factors associated with use of BMAs in Veterans with CRPC across the Veterans Health Administration (VA). **Methods:** Using the VA Corporate Data Warehouse, consisting of aggregated medical record data from 130 facilities, we used an algorithm previously published to identify men with a diagnosis of castration-resistant prostate cancer (CRPC) based on rising prostate specific antigen (PSA) levels while on androgen deprivation therapy and who received systemic treatment for CRPC with one of the commonly used therapies: abiraterone, enzalutamide, docetaxel, ketoconazole between 2010 and 2017. To account for clustering among facilities, we used a multilevel multivariable logistic regression to determine the association of patient and disease-specific variables on the odds of a patient receiving a BMA after they started treatment for CRPC. **Results:** Of 4,998 patients with CRPC in our cohort, 2223 (44%) received either zoledronic acid or denosumab at some point after they were initiated on treatment for CRPC. After adjusting for other variables and accounting for a facility, the odds of receiving a BMA decreased by 3% for every additional year of age (odds ratio [OR] 0.97, 95% confidence interval [CI] 0.96-0.98), and decreased significantly with increasing comorbid conditions (OR 0.94, 95% CI 0.72-0.98 for Charlson Comorbidity Index [CCI] of 1; OR 0.69, 95% CI 0.59-0.81 for CCI 2+). Patients who were Black had 25% lower odds of receiving a BMA than patients who were White (OR 0.75, 95% CI 0.65-0.87). PSA at time of CRPC treatment start had a small but not significant effect on receipt of a BMA (OR 1.04, 95% CI 1.00-1.08) for every unit increase of PSA on the log scale. PSA doubling time was not associated with receipt of a BMA. The presence of a diagnosis code for bone metastases was far lower than expected in this cohort of patients with CRPC (40.7%), and thus was not included in the model. We did not expect the presence of bone metastases to vary significantly among the other independent variables. **Conclusions:** Despite most patients with CRPC historically having bone metastases, less than half of patients with CRPC received a BMA. Patients who are older, had more comorbidities, or were Black were less likely to receive a BMA after starting treatment for CRPC. Understanding factors that lead to different patterns of treatment can guide initiatives toward more guideline-concordant care. Research Sponsor: Megan Caram was funded by a Prostate Cancer Foundation Young Investigator Award.

6583 **Poster Session**

Identifying gaps in the coverage of survivorship care services. *First Author: Anne Hudson Blaes, University of Minnesota, Minneapolis, MN*

Background: Despite advancements in reimbursement, anecdotal evidence suggests patients are not able to access guideline concordant survivorship care services due to a lack of coverage by payers. We present the results of a mixed methods study aimed to determine the practice-reported rates and sources of delay/denial on evidence-based, guideline concordant survivorship care services. **Methods:** A quantitative survey was developed by ASCO's Cancer Survivorship Committee (CSC) to assess which services are being denied by payers for coverage/reimbursement. Questions were limited to disease sites for which practice guidelines exist. 533 ASCO members who provide survivorship care were surveyed, with a focus on obtaining representation from rural/urban, academic/private practice, pediatric/adult, and geographic location across the U.S. Semi-structured telephone interviews were conducted in October and November 2020 with geographic sub sample representation to further explore the nature of and extent to which coverage barriers are experienced for guideline-concordant care, specific to the provider or clinic's primary disease site or specialty. **Results:** 120 responses from 50 states were included. Respondents were primarily clinicians (88%) with the majority treating patients with Medicare/Medicaid/CHIP (60%), followed by private/employer insurance (38%). There was little issue with coverage of hormone therapies. One-third reported issues some of the time with maintenance chemotherapy (38%) and immunotherapy (35%). Coverage denials for screening for recurrence for breast cancer (MRI, 63.5%), Hodgkin Lymphoma (PET/CT 47%; Breast MRI, 44.4%), and lung cancer (Low-dose CT 37.4%) were common. Half of the survey respondents reported denials for supportive care/symptom management services (Table). Private or employer-based insurance denials were most often the source of barriers (57.7%). Through interviews, denials were found to be the same across sites and not unique to a single payer or region. Most had a process to appeal denials for evidence-based services. **Conclusions:** Denial for survivorship care, particularly supportive care services, is common. There is a need for better advocacy with payers, improved policy, and support for providers/practices to implement protocols to obtain coverage for services, particularly in the face of burnout. Research Sponsor: ASCO.

Frequencies of survivorship coverage denials (*for appropriate population).

	Always	Most of the time	Neutral	Some of the time	Never
Dexa scan* (n=117)	0.9	6.0%	6.0%	44.4%	33.3%
Echocardiogram* (n=117)	0.00%	4.3%	7.7%	25.6%	52.1%
Fatigue assessment (n=118)	3.4%	**17.8%**	12.7%	39.8%	21.2%
Mental health services (n=117)	1.7%	**11.1%**	18.0%	32.5%	27.4%
Fertility services (n=117)	5.1%	**18.0%**	13.7%	40.2%	14.5%
Physical therapy (n=117)	1.7%	**10.3%**	11.1%	42.7%	29.1%
Occupational therapy (n=118)	0.9%	**10.2%**	16.1%	39.8%	25.4%
Dental evaluation* (n=116)	3.5%	**19.0%**	14.7%	31.0%	20.7%

6584 **Poster Session**

Clinical trial representativeness and treatment intensity in a real-world sample of women with early-stage breast cancer. *First Author: Nicole E. Caston, University of Alabama at Birmingham, Birmingham, AL*

Background: Early stage breast cancer (EBC) treatment is used in women of all ages, races, and health states. However, as clinical trials often do not represent real-world populations, the extent to which evidence-based treatments are prescribed to populations not well represented in these trials is not known. This study evaluated treatment intensity for patients traditionally well represented, underrepresented, and unrepresented in clinical trials. **Methods:** This retrospective cohort study used the nationwide de-identified electronic health record derived Flatiron Health database for patients diagnosed with EBC between 2011-2020. We categorized treatments as either high- (AC-TH [doxorubicin, cyclophosphamide followed by paclitaxel or docetaxel, trastuzumab]; ACT [paclitaxel or docetaxel, doxorubicin, cyclophosphamide]; TCH [paclitaxel or docetaxel, carboplatin, trastuzumab]; TCHP [paclitaxel or docetaxel, carboplatin, trastuzumab, pertuzumab]) or low-intensity (AC [doxorubicin, cyclophosphamide]; TC [paclitaxel or docetaxel, cyclophosphamide]; TH [paclitaxel or docetaxel, trastuzumab]). Unrepresented patients often have one or more comorbidities and/or prior cancer; underrepresented patients are typically Black, Indigenous, people of color, or of age extremes ($<$ 45, 70+); well represented patients are White and between the ages of 45-69. Odds ratios (OR), predicted proportions, and 95% confidence intervals (CI) from a two-level (patients nested in practice) hierarchical logistic regression model evaluated associations between receipt of high-intensity chemotherapy and patient characteristics of clinical trial representation (age, race/ethnicity, presence of comorbidity). **Results:** Our study included 970 patients with EBC with 13%, 45%, and 41% characterized as unrepresented, underrepresented, and well represented in clinical trials, respectively. In the adjusted model, those aged $\geq$ 70 vs 45-69 had lower odds of receiving a high-intensity treatment (OR 0.40, 95% CI 0.26-0.60), while those aged $<$ 45 vs 45-69 had higher odds of receiving high-intensity treatment (OR 1.82, 95% CI 1.10-3.01). The predicted proportion of patients receiving a high-intensity treatment was 87% (95% CI: 80%-92%) for patients aged $<$ 45, 79% (95% CI: 74%-84%) for patients aged 45-69, and 60% (95% CI: 50%-70%) for patients aged $\geq$ 70. Neither race/ethnicity nor comorbidity status were associated with odds of receiving high-intensity chemotherapy. **Conclusions:** Over half of the EBC population is not well represented in clinical trials. Age was associated with differential treatment intensity, despite a lack of evidence that these differences are appropriate. Widening clinical trial eligibility criteria is one way to better understand survival outcomes, identify potential toxicities, and ultimately make evidence-based treatment decisions using a more diverse sample. Research Sponsor: Robert Wood Johnson Foundation.

6585 **Poster Session**

Patterns and predictors of rehabilitation therapy among older patients with advanced cancer admitted to nursing homes: A SEER-Medicare analysis. *First Author: Huiwen Xu, University of Rochester Medical Center, Rochester, NY*

Background: Functional impairments affect $>$ 40% of hospitalized patients (pts) with advanced cancer. After hospital discharge, about 20% of pts received rehabilitation (rehab) in nursing homes (NHs) to maintain functional independence. There is evidence from broad pt cohorts that Medicare Prospective Payment (PP) financially incentivizes NHs to provide extra rehab. This study examines rehab utilization among pts with advanced cancer admitted to NHs. **Methods:** The 2011-2016 SEER-Medicare data were linked with NH Minimum Data Set 3.0 data, which includes sociodemographic and clinical characteristics at admission. Study cohort included traditional Medicare pts with stage IV breast, lung, and colorectal cancer who were admitted to NHs after hospital discharge. Outcomes: total weekly rehab minutes of physical therapy, occupational therapy, and speech-language pathology; ultra-high rehab ($\geq$720 min/wk); and rehab within 10 minutes of threshold (720-730 min/wk). Function and cognition were assessed by Activities of Daily Living (ADL) [7 domains; total score ranges 0 to 28 (higher = dependent)] and Cognitive Function Scale (intact, mild, moderate, severe impairment). Charlson Comorbidity Index (CCI) and survival from NH admission were computed. Generalized linear mixed models examined predictors of rehab outcomes adjusting for NH random effects. **Results:** A total of 7,453 pts were included (mean age 78.0, 85.8% White, 74.1% lung/ 16.1% colorectal/ 9.7% breast cancer; 76.1% had surgery, 8.9% had chemotherapy; mean CCI 1.9). The mean ADL score was 18.0, with on average 4.7 impairments; 40.2% reported $\geq$ mild cognitive impairment. Pts received on average 498 (SD = 245) min/wk rehab, but the distribution was trimodal. The number of pts who received 720-730 min/wk rehab was 2.7 times of the secondary peak at 500-510. From 2011-2016, the proportion of pts receiving ultra-high therapy (19.5%-48.4%) and within-threshold rehab (11.0%-32.0%) more than doubled. Only 5.9% of pts were documented on admission as having a life expectancy $<$ 6 months, yet 32.1% and 74.3% died in 30 days and 6 months, respectively. Multivariable regressions indicate that compared to pts with $\geq$6 months' expectancy, those with $<$ 6 months' expectancy received less rehab (β = -117.6), especially ultra-high rehab (odds ratio = 0.31). Pts with cognitive impairments received less rehab. **Conclusions:** Rehab utilization in older NH pts with advanced cancer mirrors patterns found in broader cohorts. Under PP, rehab minutes provided strongly followed payment thresholds. Over 5 years, more pts were provided 720-730 min/wk rehab, and 1/3 of these pts were at the end of life. Poor prognostication might contribute to the use of ultra-high rehab. Future work should evaluate whether the new Patient Driven Payment Model avoids excessive rehab use in patients with limited life expectancies. Research Sponsor: NCI UG1CA189961, NIA K24AG056589, NIA R33AG059206.

6586 **Poster Session**

Patient and treatment characteristics of emergency presentations due to immune-mediated toxicities. *First Author: Sharon Hyo-Eun Nahm, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: The prevalence of immune-mediated toxicities from immune checkpoint inhibitors (ICIs) is well described. However, the characteristics and treatment patterns for patients with emergency presentations due to immune-mediated toxicity are less well known. **Methods:** This study of all emergency presentations in patients treated with ICIs was performed at The Christie NHS Foundation Trust, Manchester, United Kingdom from May 2018-February 2020. The aims were to describe the patient and treatment characteristics of those diagnosed with an immune-mediated toxicity. **Results:** In total, 597 patients receiving ICIs had an emergency presentation and 191/597 (32%) were diagnosed with an immune-mediated toxicity. Of these patients, the median age was 64 years and 127/191 (67%) were male. The most common tumour types were melanoma (53%) and lung (22%) and the most common ICI received was ipilimumab + nivolumab combination immunotherapy (42%), followed by pembrolizumab monotherapy (21%) and nivolumab monotherapy (20%). The median number of cycles received was 3 (range 1-54), and 73/191 (38%) previously had $\geq$ grade 2 immune-mediated toxicity. The most common diagnoses were colitis (38%), hepatitis (15%), and pneumonitis (14%). The majority, 180/191 (94%) received steroids and 52/180 (29%) patients required second-line immunosuppression. The most common second-line immunosuppressants used were mycophenolate mofetil (58%) and infliximab (50%). Eleven patients (22%) required more than one second-line immunosuppressant. **Conclusions:** The majority of patients with emergency presentations due to immune-mediated toxicity were being treated with combination immunotherapy for melanoma. More than a third of patients had previous $\geq$ grade 2 immune-mediated toxicity. Over one quarter of patients treated with steroids required second-line immunosuppression. Identifying these characteristics can help inform which patients receiving ICIs seeking medical review need admission to a center with experience in managing immune-mediated toxicity. Research Sponsor: None.

6587 **Poster Session**

Disparity in utilization of multiagent therapy for acute promyelocytic leukemia (APL): A large National Cancer Database (NCDB) analysis. *First Author: Prajwal Dhakal, University of Nebraska Medical Center, Dept of Internal Medicine, Omaha, NE*

Background: Clinical trials have demonstrated a high rate of cure in APL with the use of multiagent therapy; however, overall survival in real world practice is significantly lower than that in the trials (Blood 2020; 136 (s 1): 13-14). We performed a large NCDB analysis to determine the appropriateness of treatment as a possible explanation for worse survival outside of the clinical trials. **Methods:** We included a total of 7190 APL cases reported to NCDB between 2004-2015. Multiple logistic regression analysis was used to evaluate the effect of covariates on probability of multiagent therapy use. **Results:** Only 64% of total patients received multiagent therapy; 29% received singe agent therapy and 4% received unknown therapy. 3% (n = 207) did not receive any treatment for reasons including early death (n = 8), patient refusal (n = 15), perceived contraindication (n = 12) and unknown reasons (n = 182). Compared to patients $>$ 60 years, younger patients aged 0-18 years (hazard ratio [HR] 3.2, 95% confidence interval [CI] 1.8-5.5, $p < 0.001$), 19-40 years (HR 1.6, 95% CI 1.03-2.54, $p = 0.03$) and 41-60 years (HR 1.6, 95% CI 1.3-1.9, $p < 0.001$) were more likely to receive multiagent chemotherapy. Patients with Medicaid were more likely to receive multiagent therapy compared to those with private insurance (HR 1.2, 95% CI 1.01-1.42, $p = 0.04$), possibly because patients with Medicaid are younger. The likelihood of receiving multiagent therapy decreased in uninsured patients (HR 0.6, 95% CI 0.5-0.8, $p < 0.001$). Compared to academic cancer centers, patients treated at community cancer center (HR 0.5, 95% CI 0.3-0.7, $p = 0.001$), comprehensive community cancer center (HR 0.7, 95% CI 0.6-0.8, $p < 0.001$)) and integrated network cancer center (HR 0.8, 95% CI 0.6-0-0.9, $p = 0.01$) were less likely to be treated with multiagent therapy. Lower comorbidity index increased the likelihood of receiving multiagent therapy. The likelihood of receiving multiagent therapy was not influenced by sex, race, annual income, distance traveled to treatment facility and high school education. **Conclusions:** To our knowledge, this is the first large scale analysis of utilization of multiagent therapy in APL in real world practice. In our study, 3% of patients did not receive treatment, a much smaller proportion of patients compared to acute myeloid leukemia, where a quarter to a third of patients do not receive any chemotherapy (Blood Adv; 2018 (2): 1277–1282). However, 29% of APL patients received suboptimal treatment with single agent therapy. The use of single agent therapy was higher in older adults and those with greater comorbidity. About half of the patients were treated outside of academic centers, which was associated with a higher probability of receiving single agent therapy. Uninsured patients were more likely to receive single agent therapy. Our findings highlight disparity based on insurance and health system factors. Research Sponsor: None.

6588 **Poster Session**

Activity of daily living of elderly patients with gastric cancer after surgery. *First Author: Ayako Okuyama, National Cancer Center, Center for Cancer Control and Information Services, Center for Cancer Registries, Chuo-Ku, Japan*

Background: Elderly patients are concerned with the physical burden of cancer treatments. This study aimed at investigating the reduction of the activity of daily living (ADL), length of hospital stay and readmission rate after surgery for gastric cancer. **Methods:** Insurance claim data linked with hospital-based cancer registries in Japan for gastric cancer patients diagnosed in 2015 from 431 hospitals was used. This data is expected to cover 49.0% of new cancer cases in Japan. To compare the effect of the treatment by age group, we analyzed the reduction of ADL between admission and discharge, length of hospital stay and readmission rate after endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) for patients with cT1N0M0, and open surgery for patients with cM0. Patients who aged 40 years or older with independent ADL at admission for their first-course treatment was included. ADL was assessed using Barthel index (0-100 points). ADL decrease by 10 points or more was identified as ADL reduction. **Results:** Overall, 25,521 patients receiving ESD/EMR and 10,527 patients receiving open surgery were identified. ADL reduction after ESD or EMR under 80 years old was less than 1%, while over 80 years old ADL reduction was more than 2.5%. Length of hospital stay (11 days) and unexpected readmission rate (2 to 3 %) was almost similar. ADL reduction after open surgery under 75 years old was less than 3%. This reduction rates have increased with age, 11.5% for over 85 years old. Length of hospital stay also tended to increase by age (21 days for under 65 years old, 29 days for over 85 years old). Unexpected readmission rate for over or 80 years old (1.4%) was slightly higher under 80 years old (less than 1%). **Conclusions:** The effect of ADL reduction after ESD/EMR was not so significant for patients over 80 years old. While ADL reduction after open surgery tended to increase for aged 80 years and older. Providing these information to elderly patients and their families can be important in deciding treatment options. Research Sponsor: the Grants-in-Aid for Scientific Research (KAKENHI20EA1011) in Japan.

The length of hospital stay, ADL reductions and readmission after open surgery.

	40-64 years		65-69 years		70-74 years		75-79 years		80-84 years		Over 85 years	
	n	%	n	%	n	%	n	%	n	%	n	%
All patients	2,676	100.0	1,985	100.0	2,130	100.0	1,885	100.0	1,295	100.0	556	100.0
Sex, male	1,832	68.5	1,478	74.5	1,572	73.8	1,396	74.1	891	68.8	359	64.6
female	844	31.5	507	25.5	558	26.2	489	25.9	404	31.2	197	35.4
Average length of hospital stay, days (SD)	20.8	14.2	23.4	19.3	24.4	19.0	25.7	20.9	27.4	21.4	29.2	22.3
Partial resection	1,500	56.1	1,099	55.4	1,206	56.6	1,092	57.9	792	61.2	403	72.5
Total gastrectomy	1,176	43.9	886	44.6	924	43.4	792	42.0	503	38.8	153	27.5
ADL at discharge												
0−59 points	<10		<10		11	0.5	20	1.1	29	2.2	14	2.5
60-99 points	22	0.8	28	1.4	38	1.8	47	2.5	97	7.5	64	11.5
100 points (independent)	2,624	98.1	1,903	95.9	2,050	96.2	1,761	93.4	1,116	86.2	449	80.8
Over 10 points decrease of ADL	18	0.7	22	1.1	35	1.6	55	2.9	90	6.9	64	11.5
Unexpected readmission	101	3.8	90	4.5	97	4.6	99	5.3	79	6.1	28	5.0

6589 **Poster Session**

Assessment of vitamin D deficiency and COVID-19 diagnosis in patients with breast or prostate cancer using electronic medical records. *First Author: Aaron Galaznik, Acorn AI By Medidata, a Dassault Systèmes Company, New York, NY*

Background: While patients with cancer are known to be at increased risk of infection in part due to the immunocompromising nature of cancer treatments, recent data indicate a particularly high risk for COVID-19 infection and poor outcomes (Wang et al., 2020). A recent study (Meltzer et al., 2020) demonstrated Vitamin D deficiency may increase risk of COVID-19 infection, and a small randomized controlled trial in Spain reported significant improvement in mortality among hospitalized patients treated with calcifediol. Vitamin D deficiency has been reported in two leading causes of cancer deaths: breast and prostate. In this study, we performed a retrospective cohort analysis on nationally representative electronic medical records (EMR) to assess whether Vitamin D deficiency affects risk of COVID-19 among these patients. **Methods:** Patients with breast (female) or prostate (male) cancer were identified between 3/1/2018 and 3/1/2020 from EMR data provided pro-bono by the COVID-19 Research Database (covid19researchdatabase.org). Patients with an ICD-10 code for Vitamin D deficiency or $<$ 20ng/mL 20(OH)D laboratory result within 12 months prior to 3/1/2020 were classified as Vitamin D deficient. COVID-19 diagnosis was defined using ICD-10 codes and laboratory results for COVID-19 at any time after 3/1/2020. Logistic regressions, adjusting for baseline demographic and clinical characteristics, were conducted to estimate the effect of Vitamin D deficiency on COVID-19 incidence in each cancer cohort. **Results:** A total of 16,287 breast cancer and 14,919 prostate cancer patients were included in the study. The average age was 68.9 years in the breast cancer cohort and 73.6 years in the prostate cancer cohort. The breast cancer cohort consisted of 85% Whites, 13% Black or African Americans, and less than 5% of other races. A similar race distribution was observed in the prostate cancer cohort. Unadjusted analysis showed the risk of COVID-19 was higher among Vitamin D deficient patients compared to non-deficient patients in both cohorts (breast: OR = 1.60 [95% C.I.: 1.15, 2.20]; prostate: OR = 1.59 [95% C.I.: 1.08, 2.33]). Similar findings were observed when assessed in subgroups of patients with newly diagnosed cancer in the dataset, as well as after adjusting for baseline characteristics. **Conclusions:** Our study suggests breast and prostate cancer patients may have an elevated risk of COVID-19 infection if Vitamin D deficient. These results support findings by Meltzer et al., 2020 demonstrating a relationship between Vitamin D deficiency and COVID-19 infection. While a randomized clinical trial is warranted to confirm the role for Vitamin D supplementation in preventing COVID-19, our study underscores the importance of monitoring Vitamin D levels across and within cancer populations, particularly in the midst of the global COVID-19 pandemic. Research Sponsor: None.

6590 **Poster Session**

Timing of steroid use and outcomes of immune checkpoint inhibitor: A population based study. *First Author: Nikita Nikita, Thomas Jefferson University, Philadelphia, PA*

Background: Immune checkpoint inhibitors (ICIs) have rapidly become the treatment of choice for multiple cancer types. However, the relationship between the timing of immunosuppressive agents, such as steroids use, preceding ICI initiation and subsequent treatment outcomes remains unknown due to lack of data. This study was undertaken to address this knowledge gap. **Methods:** We used the Surveillance, Epidemiology and End Results (SEER)-Medicare linked data to identify patients with melanoma receiving Ipilimumab, Nivolumab, Pembrolizumab, or Ipilimumab/Nivolumab combination in 2010-2015. Last steroid exposure within 12 months prior to ICI use was categorized (none, 0-1, 1-3, and 3-12 months prior). Cox models were used to generate covariate-adjusted hazard ratios of overall mortality following ICI initiation. Because the hazards were not proportional over time, we allowed the hazard ratios to differ in three periods (<3, 3-6, and more than 6 months post ICIs). **Results:** We identified 3,149 melanoma patients (median age 68 years) using ICIs; among these 1,352 received steroid within 12 months prior. Steroid use within 1 month prior to using ICIs was associated with a 93% and 102% increased risk in overall mortality within 3 months and 3-6 months post ICI initiation. The risk diminished over time (Table). A similar pattern was observed for steroid use 1-3 months prior. Steroid use beyond 4 months prior to ICI was not associated with increased mortality. **Conclusions**: This was the first major study to document that timing of steroid use prior to ICI is associated with the risk of mortality and how the increased risk diminishes over time. Further studies are warranted to confirm the findings and understand potential mechanisms. Research Sponsor: None.

Timing of last steroid use prior to immune check inhibitors (ICIs) and relative risk of all-cause mortality after ICIs.

Timing of last steroid use prior to ICI	<3 months post ICI Hazard Ratios	3-6 months post ICI Hazard Ratios	>6 months post ICI Hazard Ratios
No steroid 12 month prior N= 1,797	Ref	Ref	Ref
Steroid use 0-1 month prior N= 593	1.93 (1.54-2.41)*	2.02 (1.16-2.60)*	1.16 (0.96-1.39)
Steroid use 1-3 month prior N= 305	1.72 (1.28-2.30)*	1.23 (0.84-1.81)	0.89 (0.69-1.15)
Steroid use 3-12 month prior N= 454	0.78 (0.56-1.08)	1.20 (0.88-1.62)	0.92 (0.76-1.11)

6592 **Poster Session**

Phenotyping of clinical trial eligibility text from cancer studies into computable criteria in electronic health records. *First Author: Yun Mai, Sema4, Stamford, CT*

Background: Clinical trial phenotyping is the process of extracting clinical features and patient characteristics from eligibility criteria. Phenotyping is a crucial step that precedes automated cohort identification from patient electronic health records (EHRs) against trial criteria. We establish a clinical trial phenotyping pipeline to transform clinical trial eligibility criteria into computable criteria and enable high throughput cohort selection in EHRs. **Methods:** Formalized clinical trial criteria attributes were acquired from a natural-language processing (NLP)-assisted approach. We implemented a clinical trial phenotyping pipeline that included three components: First, a rule-based knowledge engineering component was introduced to annotate the trial attributes into a computable and customizable granularity from EHRs. The second component involved normalizing annotated attributes using standard terminologies and pre-defined reference tables. Third, a knowledge base of computable criteria attributes was built to match patients to clinical trials. We evaluated the pipeline performance by independent manual review. The inter-rater agreement of the annotation was measured on a random sample of the knowledge base. The accuracy of the pipeline was evaluated on a subset of randomly selected matched patients for a subset of randomly selected attributes. **Results:** Our pipeline phenotyped 2954 clinical trials from five cancer types including Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Prostate Cancer, Breast Cancer, and Multiple Myeloma. We built a knowledge base of 256 computable attributes that included comorbidities, comorbidity-related treatment, previous lines of therapy, laboratory tests, and performance such as ECOG and Karnofsky score. Among 256 attributes, 132 attributes were encoded using standard terminologies and 124 attributes were normalized to customized concepts. The inter-rater agreement of the annotation measured by Cohen's Kappa coefficient was 0.83. We applied the knowledge base to our EHRs and efficiently identified 33258 potential subjects for cancer clinical trials. Our evaluation on the patient matching indicated the F1 score was 0.94. **Conclusions:** We established a clinical trial phenotyping pipeline and built a knowledge base of computable criteria attributes that enabled efficient screening of EHRs for patients meeting clinical trial eligibility criteria, providing an automated way to efficiently and accurately identify clinical trial cohorts. The application of this knowledge base to patient matching from EHR data across different institutes demonstrates its generalization capability. Taken together, this knowledge base will be particularly valuable in computer-assisted clinical trial subject selection and clinical trial protocol design in cancer studies based on real-world evidence. Research Sponsor: None.

6593 **Poster Session**

Efficacy and cost-effectiveness of breast cancer (BC) screening in female survivors of childhood Hodgkin lymphoma (HL). *First Author: Florence Lennie Wong, City of Hope, Duarte, CA*

Background: Female childhood HL survivors treated with ≥10 Gy of chest radiation are at high risk of developing BC. The Children's Oncology Group (COG) guidelines recommend lifetime annual mammography (MAM) and breast Magnetic Resonance Imaging (MRI) starting 8y after chest radiation or age 25, whichever is later, and clinical breast examination (CBE) annually from puberty and semiannually from age 25. Initial model results suggest that CBE adds no survival benefit in this cohort. Digital breast tomosynthesis (DBT) is increasingly replacing digital MAM in clinical practice. Here, we present the efficacy and cost-effectiveness of COG's imaging-based screening recommendations. **Methods:** Life-years (LYs), quality-adjusted LYs (QALYs), BC mortality, and costs (2017 U.S.$) were estimated from simulating the lifetimes of 5-million chest-irradiated 25y old HL survivors who underwent BC screening with each of the following strategies: annual digital MAM, MRI, MAM+MRI, annual DBT or DBT+MRI from age 25 onward. Treatment-related BC risk (in-situ and invasive) and non-BC mortality were estimated from female 5y HL survivors in the Childhood Cancer Survivor Study and from U.S. population rates. Test sensitivity was 70-74% for MAM (based on prior HL studies) and 89% for DBT and MRI (based on women at high risk of *de novo* BC). Costs and quality of life weights were obtained from medical literature. **Results:** For HL survivors with no screening, lifetime BC risk was 42.7% and BC mortality was 18.1%. BC risk and non-BC mortality were, respectively, 7.4- and 5.2-fold higher at age 50 in HL survivors relative to the general population. Screening at ages 25-74 had similar LY gain and BC mortality reduction compared to lifetime screening; hence, we focused on screening for ages 25-74. For all strategies screening provided LY gain of 0.34-0.47 and reduced BC mortality by 6.7-9.8% compared with no screening; incremental cost-effectiveness ratio (ICER), or cost per QALY gained, for MAM alone was $58,726 and for DBT alone was $62,989. ICER of adding MRI to MAM ($385,285) or to DBT ($513,358) indicated lower cost-effectiveness of supplemental MRI (Table). **Conclusions:** Annual screening at ages 25-74y in chest-irradiated HL survivors appears beneficial. Using $100K per QALY gained as cost-effectiveness threshold, annual MAM or DBT are more cost-effective, whereas adding MRI to MAM is less cost-effective. Research Sponsor: American Cancer Society, U.S. National Institutes of Health.

Strategy	LY gained	BC deaths reduced (%)	Cost	QALYs	ICER (vs. No screening)	ICER (vs. Comparator)
No screening	REF	REF	95,073	16.576	NA	NA
Annual imaging (ages 25-74)						
MAM	0.35	7.0	99,477	16.651	58,726	58,726!
MRI	0.34	6.7	107,035	16.652	157,625	Dominated¥
DBT	0.39	8.1	100,328	16.659	62,989	62,989!
MAM+MRI	0.46	9.7	109,726	16.678	144,222	385,285*
DBT+MRI	0.47	9.8	110,662	16.680	150,532	513,358#

!Compared with No screening *Compared with MAM #Compared with DBT ¥ More expensive and less effective than DBT.

6594 **Poster Session**

Leveraging the electronic medical record (EMR) to predict patient reported financial hardship in cancer patients. *First Author: Sandeep Sai Voleti, Mayo Clinic Alix School of Medicine, Scottsdale, AZ*

Background: Patient reported financial hardship (FH) in cancer care is a growing challenge for patients, their caregivers and healthcare providers. As treatment costs escalate, it is imperative to develop effective strategies to proactively recognize and mitigate FH within oncology practice. Using automated processes to screen and refer patients to appropriate resources is a potential option. At Mayo Clinic, screening for FH involves using a single financial strain question ' How hard is it for you to pay for the very basics like food, housing, medical care, and heating?' completed by all cancer patients annually as part of the Social Determinants of Health (SDOH) assessment. In this study, we describe the prevalence and predictors for FH (denoted by the answer 'hard and very hard') in our patient population. **Methods:** Patients receiving cancer care at the three Mayo Clinic sites (Minnesota, Arizona, and Florida) who completed the FH screen at least once were included in this study. Demographics (age, gender, race/ ethnicity, insurance, employment status, marital status, and zip code) and disease state data for included patients was extracted from the EMR and Mayo Clinic Cancer Registry. Disease state was categorized by type of cancer (hematological or solid malignancy) and cancer stage. Zip code was used to derive median income, rural/urban residence and distance from the cancer center. Multivariable logistic regression models were utilized to examine factors associated with FH. **Results:** The final study cohort included 31,969 patients with median age 66 years (IQR 57,73), 51% females, and 76% married. Race/ethnicity composition was 93% White, 3% Black, and 4% Hispanic. 52% of patients had Medicare and 43% had commercial insurance. Other notable factors included 48% retired, 41% working/ students, 76% married, and 72% urban residents. Median time from cancer diagnosis was 1.1 year (IQR 0.1, 3.8) and median income was $64,406 (IQR 53,067, 82,038). 31% of patients had hematological malignancies, 20% of the cancers for which staging information was available were metastatic. FH was reported by 4% (n = 1194) of the patients. A significantly higher likelihood of endorsing FH ($p < 0.001$ for all) was noted in Hispanic (OR 1.64), Black (OR 1.84), American Indian/ Alaskan native (OR 2.02), below median income (OR 1.48), rural (OR 1.17), self-pay (OR 2.77), Medicaid (OR 2.29), Medicare (OR 1.43), unemployed/disabled (OR 2.39), single (OR 2.07), or divorced (OR 2.43) patients. Older age, being retired, and living farther from the cancer center were associated with significantly less likelihood of endorsing FH. **Conclusions:** Our study successfully leveraged the EMR to identify key sociodemographic groups more likely to report FH. An electronic trigger to flag such patients at high-risk of FH and proactively address FH is currently being developed. Research Sponsor: Mayo Clinic Internal Research Funding.

6595 **Poster Session**

Comparative study of prevalence and costs of depression and anxiety among elderly cancer patients. *First Author: Stacey DaCosta Byfield, OptumLabs, Minnetonka, MN*

Background: Depression and anxiety are common among cancer patients and can worsen outcomes. We studied the occurrence of depression and anxiety in three common cancers to investigate whether healthcare costs were greater for cancer patients with two mental health disorders (MHD), depression and anxiety, compared to patients without MHD. **Methods:** This retrospective analysis used deidentified medical and pharmacy claims from a large national U.S. health insurer. Patients were Medicare Advantage enrollees ≥65 years diagnosed with breast, colorectal, or prostate cancer and continuously enrolled from 1/2018–12/2019. We determined statistically whether the annual prevalence of the two MHDs varied by cancer types. Total costs and costs exclusive of MHD-related expenses in five sub-categories were compared: inpatient, emergency room, non-inpatient medical, professional, and pharmacy. Costs from 2019 claims were presented as per-patient per-month (PPPM). Direct depression- and anxiety-related costs were from claims with depression/anxiety diagnoses or drugs. The impact of MHDs on 2019 healthcare spending was examined using multiple linear regression, controlling for demographic and clinical characteristics. LASSO was used for variable selection. Mann-Whitney U tests compared differences in costs by service types between patients with and without MHDs. **Results:** Of 19,304 study patients, 8,916 (46%) had coexisting depression or anxiety: (i) 4% depression only; (ii) 27% anxiety only; (iii) 7% depression and anxiety; and (iv) 8% were on antidepressant without MHDs diagnoses. There were significant differences in the rates of MHDs between the three cancer groups, with the highest frequency in breast cancer (*breast vs colorectal*. 56% vs 49%, $p < 0.0005$; *breast vs prostate*. 56% vs 38%, $p < 0.0005$; *colorectal vs prostate*. 49% vs 38%, $p < 0.0005$). After excluding the MHDs-related costs (PPPM mean = $44), the monthly spending was 54% higher for patients with MHDs ($2,184 MHDs vs. $1,406 non-MHDs). After adjusting for covariates, the PPPM costs were 23%–58% higher for the MHD-cohort vs. the non-MHD cohort for each cancer type (*non-MHD vs. with depression only*, CI 13%–34%, $p < 0.0001$; *non-MHD vs. with anxiety only*, CI 40%-52%, $p < 0.0001$; *non-MHD vs. with depression and anxiety*, CI 48%-70%, $p < 0.0001$; *non-MHD vs. with antidepressant only*, CI 28%-45%, $p < 0.0001$). **Conclusions:** We found high prevalence of MHDs in patients diagnosed with cancer. Analyses showed that total spending was significantly higher in individuals with cancer and MHD for all cost categories. Explanations for higher costs are unclear, as costs remain high even after adjusting for MHD-related care costs. Research on specific healthcare services driving higher costs and the risk factors for depression and anxiety is needed to address broader MHDs to improve cancer care. Research Sponsor: None.

TPS6596 **Poster Session**

Improving patient and caregiver understanding of risks and benefits of immunotherapy for melanoma or lung cancer. *First Author: Laura A Petrillo, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: Immune checkpoint inhibitors (ICI) extend survival for patients with advanced cancer, particularly melanoma and lung cancer, though responses are heterogeneous and treatment may be complicated by immune-related adverse events that are important for patients and their caregivers to recognize. The aim of this trial is to evaluate the feasibility and preliminary efficacy of an educational video and question prompt list (QPL) in improving patients' and caregivers' understanding of what to expect from immunotherapy. **Methods:** In this randomized controlled trial of a novel educational intervention to improve immunotherapy knowledge, we will enroll 140 adult patients with advanced melanoma or lung cancer (small cell or non-small cell) who have a plan to initiate therapy with an ICI and their caregivers. Patients assigned to the intervention will receive a link to a video about the risks and benefits of ICI treatment developed by the study team as well as an ICI-focused QPL that includes questions about the goal and likelihood of benefit of ICIs. We will enroll the first ten patients in an open pilot and we will refine the intervention and study procedures based on pilot findings. We will randomize the remaining 130 patients to receive either the intervention or a usual care control. Randomization will be carried out using the permuted block approach with stratification by cancer type, and patient-caregiver dyads will be assigned to the same study arm. Participants on both arms will complete surveys at enrollment (baseline), 72 hours post-enrollment, and 6 weeks post-enrollment. The primary outcome of the study is feasibility of intervention delivery, defined as 70% of approached patients enrolling in the trial and 80% of enrolled patients watching the video, reviewing the QPL and completing the first assessment. We will also evaluate the preliminary efficacy of the intervention in 1) improving patient and caregiver knowledge, measured by a survey of knowledge questions that we developed and previously pilot tested with a sample of 105 patients; 2) enhancing patient-clinician communication, assessed by evaluating the number of questions patients asked in audio-recorded visits with their oncology clinicians after reviewing the QPL; and 3) reducing anxiety, measured by the State and Trait Anxiety Index. We will assess change in knowledge scores and anxiety from baseline to 72 hours post-enrollment and 6-weeks post-enrollment using the analysis of covariance model, adjusting for baseline scores and relevant covariates. The number of questions asked by patients and caregivers will be assessed by coding transcripts of oncology visits and comparing between arms using the negative binomial model. Study accrual to the open pilot phase began in February 2021. Current enrollment: n = 5. Clinical trial information: 04670445. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

TPS6598 **Poster Session**

The PLATON pilot-study "Platform for analyzing targetable tumor mutations": A PLATON network study. *First Author: Arndt Vogel, Hannover Medical School, Hannover, Germany*

Background: PLATON Network is designed as a platform to improve personalized therapy based on genomic profiles in gastrointestinal cancer patients. PLATON's study-design focuses on patient's molecular profiling and will provide a network web application for interlinking PLATON investigators which integrates information of the participating centers, their patients, the molecular profiles and available clinical trials at PLATON`s study-sites. **Methods:** The PLATON Network is designed as a permanent open, multicenter, prospective, cohort study with biobanking, with a shared platform infrastructure for associated sub-studies. In a first approach the PLATON Network enrolls within its pilot-study 200 patients in Germany of both sexes and ages over 18 at 40 study sites (NCT04484636) with signed informed consent. All patients of the pilot-study are diagnosed with hepatocellular cancer (HCC), intra- and extrahepatic cholangiocellular carcinoma (CCA), gallbladder carcinoma (GBCA), pancreatic cancer (PDCA) or esophagogastric cancer (EC/GC). At the time of enrolment, patients are within their first-line therapy and no local curative therapy is available. Molecular profiling will be performed with the Foundation Medicine Assays FoundationOne CDx and FoundationOne Liquid CDx. Investigators may use the platform for searching clinical trials matching the individual molecular profile of their patients or may identify a patient, who may be eligible for a study or other treatment options available at the corresponding centers of the PLATON network. The interactive network web application will comprise a dashboard and a moderated chat room to interact for example in a virtual Molecular Tumor Board. The first patient was included on the 25th of November 2020. Up to 12th of February 2021, a total of 36 patients HCC (N = 1), CCA (N = 6), PDCA (N = 12), GBCA (N = 0) and EC/GC (N = 16) were enrolled at 11 study-sites and the results of 29 genetic analyses were completed. All cohorts of the pilot-study are open for recruitments up to a maximum of 40 individuals per diagnostic group. Clinical trial information: NCT04484636. Research Sponsor: Roche Pharma AG.

7000 **Oral Abstract Session**

OPTIC primary analysis: A dose-optimization study of 3 starting doses of ponatinib (PON). *First Author: Jorge E. Cortes, Georgia Cancer Center, Augusta, GA*

Background: PON, a third-generation tyrosine kinase inhibitor (TKI), demonstrated deep and long-lasting responses and survival in patients (pts) with chronic-phase chronic myeloid leukemia (CP-CML) resistant/intolerant to second-generation TKI therapy (PACE; NCT01207440); post hoc analysis suggested a relationship between dose and both adverse events and response. Here we present the primary analysis of OPTIC (NCT02467270), an ongoing, randomized, phase 2 trial with a novel response-based dosing regimen of PON in pts with resistant/intolerant CP-CML. **Methods:** Pts with CP-CML resistant/intolerant to ≥2 TKIs or with the *BCR-ABL1* T315I mutation were randomized to PON starting doses of 45 mg (cohort A; 45 mg → 15 mg), 30 mg (B; 30 mg →15 mg), and 15 mg (C) once daily. Doses were reduced to 15 mg with achievement of ≤1% *BCR-ABL1*^{IS} in cohorts A and B. The primary endpoint is ≤1% *BCR-ABL1*^{IS} at 12 mo; secondary endpoints include cytogenetic and molecular responses and safety outcomes. AOEs were adjudicated prospectively by an independent review committee. **Results:** 283 pts were randomized (A/B/C: n=94/95/94) and had the following baseline characteristics: median age 48 y (18–81 y); 98% received ≥2 (55% ≥3) TKIs; 99% had resistant disease; 40% had ≥1 baseline mutations (23% T315I). At the primary analysis with 32 mo median follow-up, 134 pts (47%; n=50/41/43) remained on treatment and 204 pts (72%) had PON exposure ≥12 mo. At 12 mo, 44% (41/93) in A, 29% (27/93) in B, and 23% (21/91) in C achieved ≤1% *BCR-ABL1*^{IS} (Table); primary endpoint was met by cohort A. Dose reductions to 15 mg after achieving response (A/B) were 48/29%. Most common grades ≥3 TEAEs were thrombocytopenia, 27%; neutropenia, 17%; and anemia, 7%. AOEs/serious AOEs were reported in cohorts A (10%/4%), B (5%/4%), and C (3%/3%). Dose reductions or discontinuations for TEAEs (A/B/C) were 46/35/32% and 19/16/14%, respectively. **Conclusions:** The OPTIC primary analysis demonstrates the optimal benefit:risk profile for PON was achieved with a response-based dosing regimen starting with 45 mg/d, followed by dose reduction to 15 mg/d upon achieving ≤*1% BCR-ABL1*^{IS}; 30 mg→15 mg and 15 mg cohorts may provide benefit, especially in pts without T315I mutation (Table). The observed ≤1% *BCR-ABL1*^{IS} responses are supported by robust survival outcomes in pts with CP-CML resistant to second-generation BCR-ABL1 TKI therapy, both with and without *BCR-ABL1* mutations. Clinical trial information: NCT02467270. Research Sponsor: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, with additional funding from Incyte Corporation, Wilmington, DE.

Response[a]	Cohort A 45 mg	Cohort B 30 mg	Cohort C 15 mg
BCR-ABL1^{IS} ≤1% at 12 mo, % (n/N)	44 (41/93)	29 (27/93)	23 (21/91)
BCR-ABL1^{IS} ≤1% by 12 mo by mutation status at baseline, % (n/N)	52 (48/93)	35 (33/93)	25 (23/91)
Response in pts with T315I mutation	60 (15/25)	25 (5/20)	11 (2/19)
Response in pts without T315I mutation	48 (32/66)	38 (28/73)	30 (21/71)
Survival probability at 36 mo, % (95% CI)			
PFS	73 (58, 84)	66 (48, 80)	70 (55, 80)
OS	89 (79, 95)	89 (77, 95)	92 (82, 96)

[a]Includes all pts who are randomized and with measurable *BCR-ABL1*^{IS} at BL.

7001 **Oral Abstract Session**

Combination of ponatinib and blinatumomab in Philadelphia chromosome-positive acute lymphoblastic leukemia: Early results from a phase II study. *First Author: Nicholas James Short, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Achievement of a complete molecular remission (CMR) is associated with superior outcomes in patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL). Ponatinib and blinatumomab both produce high rates of molecular remission in Ph+ ALL. The combination of these two agents may lead to durable responses and reduce the need for allogeneic hematopoietic stem cell transplant (AHSCT). **Methods:** This is a single-arm phase 2 study in adults with newly diagnosed (ND) or relapsed/refractory (R/R) Ph+ ALL. Patients received up to 5 cycles of blinatumomab as a continuous infusion at standard doses. Ponatinib 30mg daily was given during cycle 1. Ponatinib was decreased to 15mg daily once CMR was achieved. After completion of blinatumomab, ponatinib was continued for at least 5 years in responding patients. Twelve doses of prophylactic intrathecal chemotherapy were administered. For patients with ND Ph+ ALL, the primary endpoint was the CMR rate. For patients with R/R Ph+ ALL, the primary endpoint was the overall response rate (defined as the composite of CR/CRi). **Results:** Twenty-eight patients were treated (19 FL and 9 R/R). Median age was 59 years (range, 25-83 years); 62 years (range, 34-83 years) in the ND cohort and 36 years (range, 25-61 years) in the R/R cohort. Transcripts were p190 in 69% of patients the ND cohort and 100% in the R/R cohort. Among R/R patients, 44% were in Salvage 2+. No early death within 4 weeks were observed. Overall, 95% of patients responded; the response rate was 100% in the ND cohort and 88% in the R/R cohort. Among responding patients, 86% achieved CMR: 87% in the ND cohort and 86% in the R/R cohort. Median time to CMR was 1 month (range, 1-13 months). None of the patients in the ND cohort underwent AHSCT; 4 patients (44%) with R/R disease underwent subsequent AHSCT. With a median follow-up of 14 months, the estimated 1-year overall survival (OS) rate was 94% and event-free survival (EFS) rate was 81% for the entire study population. In the ND cohort, no patients have relapsed or died, and the 1-year OS and EFS rates were both 100%. In the R/R cohort, 1-year OS and EFS rates were 88% and 55%, respectively. The treatment was well-tolerated. Most side effects were grade 1-2. No patient discontinued ponatinib due to toxicity. One patient discontinued blinatumomab due to recurrent grade 2 tremor. **Conclusions:** The chemotherapy-free combination of ponatinib and blinatumomab shows encouraging results in Ph+ ALL. The regimen results in high rates of CMR and durable responses, potentially obviating the need for chemotherapy and AHSCT in many patients, particularly when used as frontline therapy. Clinical trial information: NCT03263572. Research Sponsor: Takeda; Amgen.

7002 **Oral Abstract Session**

Phase 2 results of the ZUMA-3 study evaluating KTE-X19, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy, in adult patients (pts) with relapsed/refractory B-cell acute lymphoblastic leukemia (R/R B-ALL). *First Author: Bijal D. Shah, Moffitt Cancer Center, Tampa, FL*

Background: ZUMA-3 is a Phase 1/2 multicenter study evaluating KTE-X19, an autologous anti-CD19 CAR T-cell therapy, in adult pts with R/R B-ALL. Phase 1 efficacy results at the recommended Phase 2 dose (1×10^6 CAR T cells/kg) were encouraging (Shah et al. ASCO 2019 #7006). Here, we present the pivotal Phase 2 results. **Methods:** Eligible adults had R/R B-ALL, > 5% bone marrow (BM) blasts by local evaluation, and ECOG 0–1. Pts received a single infusion of KTE-X19 after conditioning chemotherapy. The primary endpoint was the overall complete remission (CR) rate (CR + CR with incomplete hematologic recovery [CRi]) by central review. Key secondary endpoints were duration of remission (DOR), relapse-free survival (RFS), overall survival (OS), measurable residual disease negativity (MRD–) rate by flow cytometry, and safety. Data are reported in all treated pts. **Results:** As of 9/2020, 55 of 71 enrolled pts received KTE-X19, with a median follow-up of 16.4 mo (range, 10.3–22.1). Adverse events (AEs; n = 8) and ineligibility (n = 4) were the most common reasons enrolled pts did not receive KTE-X19 infusion. Median age was 40 y (range, 19–84), median BM blasts at screening were 65% (range, 5–100), and 47% of pts had ≥3 prior therapies, with 45%, 22%, and 42% having previously received blinatumomab, inotuzumab ozogamicin, or allogeneic stem cell transplant (alloSCT), respectively. The CR/CRi rate was 71% (95% CI, 57–82; 56% CR, 15% CRi); 31% of responders had ongoing responses. Median (95% CI) DOR, RFS, and OS were 12.8 mo (8.7–not estimable [NE]), 11.6 mo (2.7–15.5), and 18.2 mo (15.9–NE), respectively. In responders, median (95% CI) RFS and OS were 14.2 mo (11.6–NE) and not reached (16.2–NE). The MRD– rate was 97% among pts with CR/CRi. Among 25 pts with prior blinatumomab treatment, the CR/CRi rate was 60%. Ten pts (18%) received subsequent alloSCT at a median 98 days post–KTE-X19 infusion. Median DOR remained unchanged when not censoring for alloSCT. Grade ≥3 AEs occurred in 95% of pts, most commonly anemia (49%) and neutropenia (49% [febrile 13%]). Grade ≥3 cytokine release syndrome (CRS; per Lee at al. *Blood* 2014) and neurologic events occurred in 24% and 25% of pts, respectively, and were generally reversible. Two Grade 5 KTE-X19–related events occurred (brain herniation, n = 1; septic shock, n = 1). Median times to onset of CRS and neurologic events were 5 d and 9 d, with median durations of 7.5 d and 7 d, respectively. Median peak CAR T-cell levels (cells/μL) were 40.5 (range, 1.3–1533.4) in pts with CR and 0 in nonresponders. CAR T cells were undetectable by 9 mo in ongoing responders. **Conclusions:** After a median follow-up of 16.4 mo, KTE-X19 demonstrated compelling clinical benefit in heavily pretreated adults with R/R B-ALL, with the median OS not yet reached for responding pts and a manageable safety profile. Clinical trial information: NCT02614066. Research Sponsor: Kite, a Gilead Company.

7003 **Oral Abstract Session**

The results of multicenter phase II, double-blind placebo-controlled trial of maintenance ixazomib after allogeneic hematopoietic cell transplantation (alloHCT) for high-risk multiple myeloma (MM) from the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 1302). *First Author: Taiga Nishihori, Department of Blood & Marrow Transplant and Cellular Immunotherapy, Moffitt Cancer Center, Tampa, FL*

Background: The role of alloHCT and subsequent maintenance for the treatment of high-risk MM has not been fully defined. We evaluated the efficacy of ixazomib maintenance therapy after alloHCT using reduced intensity fludarabine/melphalan/bortezomib (Flu/Mel/Bort)-based conditioning regimen to treat patients with high risk MM. **Methods:** This phase 2 prospective multicenter trial (NCT#02440464) enrolled adults 70 years or younger, with either high-risk MM defined by cytogenetics or plasma cell leukemia (PCL) or relapse within 24 months after autologous HCT. Conditioning regimen consisted of Flu/Mel/Bort. Patients received HLA-matched donor unmanipulated peripheral blood grafts. Graft-versus-host disease (GVHD) prophylaxis was tacrolimus plus methotrexate. Between days +60 and +120 after allogeneic HCT, patients were randomly assigned (1:1, stratified by number of prior progressions) to receive ixazomib at 3 mg orally on days 1, 8, 15 on a 28-day cycle or matching placebo for 12 cycles. The study aimed to enroll 138 patients with 110 patients achieving randomization for a progression-free survival (PFS) comparison ixazomib maintenance vs. placebo. **Results:** Fifty-seven patients from 15 centers were enrolled (2015-18), of whom 52 (91.2%) received allogeneic HCT, and 43 (82.7%) proceeded to randomization (21 assigned to ixazomib and 22 to placebo). Enrollment was delayed by a clinical hold after enrollment of 17 patients due to toxicity concerns related to the conditioning regimen. Remaining patients were enrolled after an amendment reduced bort to a single pre-HCT dose. These and other delays in enrollment led to premature study closure. Median age was 56 (range, 35-65) years, and 33 patients (57.9%) had high-risk MM with 9 patients (15.8%) with primary PCL. At 24 mo post alloHCT, PFS and OS among all alloHCT recipients was 52% and 85% respectively with a corresponding transplant-related mortality (TRM) of 11%. At 21 mo post-randomization, ixazomib vs. placebo groups had similar PFS (55.3% vs. 59.1%) and OS (95% vs. 87%, p = 0.17). Cumulative incidences of grade III-IV acute GVHD at 100 days (9.5% vs. 0%) or chronic GVHD at 12 months (69% vs 64%) were similar. Best response, incidence of progression for ixazomib vs. placebo groups were similar while cumulative incidence of transplant-related mortality (TRM) at 21 months was 0.0% and 4.5% (90%CI: 0.5-16.5%), respectively. **Conclusions:** AlloHCT with reduced intensity fludarabine/melphalan and a single pre-HCT dose of bortezomib is safe and can produce durable disease control in extremely high-risk patients. ixazomib maintenance after alloHCT could not be assessed as intended due to early termination of study, but there was no signal of an impact in outcomes. Clinical trial information: NCT02440464. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

7004 **Oral Abstract Session**

Letermovir prophylaxis and cytomegalovirus reactivation in adult allogeneic hematopoietic cell transplant recipients with graft versus host disease. *First Author: Delaney Wolfe, The Ohio State University, Columbus, OH*

Background: Cytomegalovirus (CMV) is the most common clinically significant infection after allogeneic hematopoietic-cell transplantation (allo-HCT) and is associated with increased mortality. The risk for CMV reactivation increases with HLA mismatch, high dose corticosteroids, and graft versus host disease (GVHD). GVHD contributes to significant morbidity and mortality and is treated with immunosuppressive therapies that further increase CMV infection risk. In a phase III trial, letermovir prophylaxis had a lower incidence of CMV infection post-allo-HCT in patients at high risk of CMV reactivation when compared to placebo when given up to day +100. There is a lack of data concerning the effectiveness of letermovir in patients who develop GVHD and may continue letermovir past day +100. **Methods:** This was a single-center, retrospective study conducted at The Ohio State University. Demographics and transplant details were collected from medical records. The primary outcome was incidence of clinically significant CMV infection (CS-CMVi) within 200 days of allo-HCT. Secondary outcomes included incidence of CMV viremia, duration of letermovir therapy, mortality, and risk factors for CS-CMVi. Early death without CMV was treated as a competing risk for CS-CMVi, while relapse was a competing risk for non-relapse mortality (NRM). Proportional subdistribution or Cox hazards models were used to evaluate the association between use of letermovir and risk of CS-CMVi, NRM, or overall survival (OS) adjusting for potential confounding factors, where use of letermovir and GVHD were treated as time-dependent variables. **Results:** A total of 262 CMV-seropositive patients who received an allo-HCT between June 1, 2016 and June 30, 2020 were included. Of these, 119 patients received letermovir prophylaxis. A total of 111 patients received treatment for CS-CMVi, which included 82 of 143 (57%) who did not receive letermovir compared to 29 of 119 (24%) who received letermovir. Incidence of CMV viremia was significantly reduced with the use of letermovir in all patients (HR 0.21, 95% CI 0.12–0.34, $p < 0.001$) and among patients with acute GVHD grade >2 within 200 days post-allo-HCT (HR 0.12, 95% CI 0.05–0.32, $p < 0.001$), adjusting for age, gender, GVHD prophylaxis and use of ATG or T-cell depleted graft. The median duration of letermovir therapy was 97 days. Nine patients were continued on letermovir indefinitely for recurrent CMV viremia. Patients who received letermovir had decreased NRM (HR 0.41, 95% CI 0.18-0.96, $p = 0.04$) and improved OS (HR 0.46, 95% CI 0.23-0.95, $p = 0.04$). **Conclusions:** Letermovir prophylaxis significantly decreased CS-CMVi and improved NRM and OS in this real-world analysis. In addition, patients with acute GVHD had significantly less CMV viremia, suggesting potential benefit in continuing letermovir prophylaxis in this patient population. Research Sponsor: None.

7005 **Oral Abstract Session**

Prospective longitudinal evaluation of microbiome diversity in patients with hematological malignancy undergoing allogeneic hematopoietic stem cell transplantation (HSCT). *First Author: Emily Walsh, Seres Therapeutics, Cambridge, MA*

Background: Studies suggest that decreased microbial diversity due to chemotherapeutic and antibiotic exposure may be associated with acute graft vs host disease (aGvHD) and mortality in patients undergoing allogeneic HSCT. In addition, disruption of the microbiome by antibiotics may lead to intestinal domination by pro-inflammatory bacteria, resulting in increased risk of aGvHD. This relationship has been described in settings with prophylactic antibiotic use, a standard of care in most transplant centers. Here we assessed how the microbiome and GvHD outcomes differ when prophylactic use of antibiotics is avoided. **Methods:** We collaborated on an observational study (COLLECT) to evaluate changes in microbial diversity over time in subjects undergoing allogeneic HSCT. According to protocol at the University Hospital of Cologne, antibiotics were administered only as empiric treatment for febrile neutropenia or as targeted treatment. Stool was collected weekly from 65 subjects at baseline (pre-HSCT) to day 28 with additional time points taken at day 56, day 90, day 365, and upon diagnosis of intestinal GvHD (GvHD-day 0 and GvHD-day 7). Patients were monitored for incidence of GvHD, including acute GvHD of the liver, intestine, and skin. Microbiome 16SV4 profiles were generated from 381 stool samples. Linear effects models were developed to evaluate the association between Shannon diversity, intestinal domination, and the incidence of intestinal GvHD and mortality. **Results:** Of the 65 subjects, 28 subjects (42%) went on to develop intestinal GvHD, and 16 subjects (25%) did not survive to day 365. A decline in Shannon diversity was observed during the neutropenic period following HSCT. Subjects who went on to develop intestinal GvHD had significantly lower Shannon diversity at the time of stem cell engraftment ($p < 0.0468$). Furthermore, lower diversity was observed throughout the study period in subjects experiencing intestinal GvHD. We developed a linear model evaluating the association between mortality and Shannon diversity and found a significant relationship at days 28 and 90 post HSCT ($p < 0.0001$ and 0.0121, resp). Intestinal domination by Enterobacteriaceae or Enterococcus was significantly associated with the incidence of intestinal GvHD ($p < 0.0082$) or mortality ($p < 0.001$), respectively. **Conclusions:** Data from this observational study (COLLECT) suggests decreases in microbial diversity over time occur in subjects undergoing allogeneic HSCT despite the lack of prophylactic antibiotics. Investigation of whether administration of microbiome therapeutic drugs prior to transplant and/or at the time of engraftment can reduce morbidity and mortality in this high-risk patient population is warranted. Clinical trial information: NCT03148197. Research Sponsor: Seres Therapeutics.

7006 **Oral Abstract Session**

Effect of olutasidenib (FT-2102) on complete remissions in patients with relapsed/refractory (R/R) m*IDH1* acute myeloid leukemia (AML): Results from a planned interim analysis of a phase 2 clinical trial. *First Author: Stéphane De Botton, Institut Gustave Roussy, Villejuif, France*

Background: Olutasidenib, a potent, selective, oral, small molecule inhibitor of mutant IDH1 (m*IDH1*), has exhibited favorable tolerability and clinical activity in high-risk AML patients (pts) in a phase 1 trial (Watts, *Blood* 2019). Here, we present interim analysis results of a phase 2 trial (NCT02719574) in R/R m*IDH1* AML pts receiving olutasidenib monotherapy 150 mg twice daily. **Methods:** The efficacy evaluable (EE) set comprised m$IDH1^{R132X}$ pts whose first dose was ≥180 days before the data cut-off (18-JUN-20). The primary endpoint was CR+CRh (complete remission [CR] or CR with partial hematologic recovery [CRh] according to modified IWG 2003 criteria) rate. CRh was defined as bone marrow blasts <5%, absolute neutrophil count $>0.5\times10^9$/L, *and* platelet count $>50\times10^9$/L. Overall response rate (ORR) comprised CR+CRh+CR with incomplete recovery (CRi) + morphologic leukemia-free state (MLFS) + partial response (PR). Duration of treatment (DOT), duration of response (DOR), and overall survival (OS) were estimated using Kaplan-Meier methodology. **Results:** This clinical trial met its pre-specified early enrollment-stopping criteria for efficacy. A total of 153 pts with R/R AML received olutasidenib; median DOT, 5.5 mo (95% CI: 4.4, 8.7). 43 pts (28%) remain on treatment and 110 (72%) discontinued, most commonly due to: disease progression, 31%; AEs, 14%; death, 10%; and transplant, 8%. For the EE set (123 pts), the median age was 71 y (range: 32–87) with a median number of prior therapies of 2 (1–7). The CR+CRh rate was 33% including 30% of pts in CR (Table). Median duration of CR+CRh was not reached (NR) and 13.8 mo in a sensitivity analysis when HSCT or relapse was deemed end of response. ORR was 46% and median duration of ORR was 11.7 mo. Of responders who were transfusion-dependent at baseline, 56-day platelet transfusion independence (TI) and RBC TI were gained by 100% and 83%, respectively, of pts who achieved CR+CRh, and by 56% and 50% who did not. Median OS was 10.5 mo (EE set). In CR+CRh responders, median OS was NR and the estimated 18-mo OS was 87%. TEAEs in ≥25% of pts were nausea, 38%; constipation, 25%; leukocytosis, 25%. Grade 3/4 all-causality TEAEs in >10% of pts were febrile neutropenia, 20%; anemia, 19%; thrombocytopenia, 16%; neutropenia, 13%. Investigator-assessed IDH1 differentiation syndrome (any grade) was observed in 21 pts (14%); most cases resolved with treatment management; one case was fatal; 19 pts had concomitant leukocytosis. **Conclusions:** Olutasidenib was well tolerated and induced durable CR in a subset of high-risk R/R m*IDH1* AML pts. TI was achieved in all response groups. Clinical benefit, per DOR and OS, extended beyond CR+CRh responders. Clinical trial information: NCT02719574. Research Sponsor: Forma Therapeutics, Inc.

Olutasidenib response rates in R/R m*IDH1* AML: EE population.

Response n (%)	Overall (N = 123)
ORR	57 (46)
CR	37 (30)
CRh	4 (3)
CRi	14 (11)
MLFS	1 (<1)
PR	1 (<1)

7007 **Oral Abstract Session**

Efficacy and safety of aspacytarabine (BST-236) as a single-agent, first-line therapy for patients with acute myeloid leukemia unfit for standard chemotherapy. *First Author: Jessica K. Altman, Lurie Comp Cancer Ctr of Northwestern Univ, Chicago, IL*

Background: Aspacytarabine (BST-236) is a prodrug of cytarabine, the backbone of acute myeloid leukemia (AML) standard of care chemotherapy, associated with toxicity which precludes its administration in older patients and patients with comorbidities. Aspacytarabine is inactive in its intact prodrug form until cytarabine is gradually released at pharmacokinetics which decrease the systemic exposure to peak toxic cytarabine levels, resulting in reduced systemic toxicity and relative sparing of normal tissues, enabling therapy with high cytarabine doses to patients otherwise unfit to receive it. **Methods:** A phase 2b open-label, single-arm study to evaluate the efficacy and safety of aspacytarabine as a first-line single-agent therapy in newly-diagnosed AML patients unfit for standard chemotherapy (NCT03435848). Aspacytarabine is administrated at 4.5 g/m^2/d (containing 3 g/m^2/d cytarabine) in 1-2 induction and 1-3 consolidation courses, each consisting of 6 daily 1-hour infusions. Patients with secondary AML, prior hypomethylating agent (HMA) therapy, and therapy-related AML, are eligible. **Results:** To date, in the ongoing study, 46 newly-diagnosed AML patients unfit for standard chemotherapy (median age 75 years) were treated with aspacytarabine and completed 1-4 courses of 4.5 g/m^2/d aspacytarabine, including 26 patients (63%) with *de novo* AML and 17 (37%) with secondary AML. Six patients (13%) were previously treated with HMA (median 12 courses). The baseline median bone marrow blasts was 52%, and 54% and 29% of patients had adverse or intermediate European LeukemiaNet (ELN) score, respectively. Twenty (43%) patients had ECOG 2. Aspacytarabine is safe and well-tolerated in repeated-course administration. Grade > 2 drug-related adverse events include mainly hematological events and infections. The 30-day mortality rate is 11%. Of 43 patients evaluable for efficacy analysis to date, 15 patients (35%) reached a complete remission (CR) following 1 (13 patients) or 2 (2 patients) induction courses, all with complete hematological recovery (median 27.5 days, range 22-39 days). The CR rates in *de novo* AML patients and patients with adverse ELN score are 46% and 33%, respectively. Of the 11 patients evaluable to date for minimal residual disease (MRD) flow cytometry test, 8 are MRD negative (73%). While aspacytarabine treatment consists of a limited number of courses, median duration of response and median overall survival for responders are not reached at 12 and 24 months, respectively (end of follow up). Updated results will be presented at the meeting. **Conclusions:** The cumulative clinical data suggest that aspacytarabine, a time-limited single-agent treatment, is safe and efficacious as a first-line therapy for patients who are unfit for intensive chemotherapy, which may establish it as a new tolerable AML chemotherapy backbone. Clinical trial information: NCT03435848. Research Sponsor: BioSight Ltd.

7008 **Oral Abstract Session**

Phase 1 first-in-human study of irreversible FLT3 inhibitor FF-10101-01 in relapsed or refractory acute myeloid leukemia. *First Author: Mark J. Levis, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University, Baltimore, MD*

Background: FF-10101-01 is a selective and irreversible FMS-like tyrosine kinase 3 (FLT3) inhibitor with potent *in vitro* activity against *FLT3*-mutated AML. FF-10101-01 is highly active against *FLT3* internal tandem duplication (ITD) mutations associated with high relapse and low survival/remission rates, as well as resistance-conferring D835 and F691 tyrosine kinase domain (TKD) and non-canonical FLT3 activating mutations. Here we report on a Phase 1 dose escalation trial examining the safety, efficacy, pharmacokinetics, and pharmacodynamics of FF-10101-01 in patients (pts) with relapsed/refractory primary or secondary AML. **Methods:** To determine the recommended Phase 2 dose, pts with or without a FLT3 mutation received FF-10101-01 orally once (QD) or twice (BID) daily until unacceptable toxicity was observed or pts had no further clinical benefit (1 cycle = 28 days). Composite complete remission (CRc) and partial remission (PR) rates were assessed. Inhibition of FLT3 phosphorylation was evaluated using a plasma inhibitory activity assay and was correlated with associated FF-10101-01 exposure. **Results:** Fifty-two pts [median age 61 (range, 21-84); 52% female; FLT3: ITD [22 (42%)], TKD [5 (10%)], ITD+TKD [1 (2%)], Wt [24 (46%)] received continuous dosing of FF-10101-01 at 10 - 225 mg QD or 50 - 100 mg BID. Median number of prior therapies was 3 (range, 0-6) and the majority [23/28 (82%)] of pts with known FLT3 mutations had received prior FLT3 inhibitors. The median duration on study was 5.7 (range, 0.1-36) weeks. FF-10101-01 was generally well-tolerated up to total daily doses of 150 mg. The most common treatment related adverse events included nausea [n = 18 (35%)] diarrhea [14 (27%), 2 Grade (Gr) 3/4], elevations in creatine kinase [CK; 14 (27%), 4 Gr 3/4], vomiting [10 (19%)] and increased AST [10 (19%), 2 Gr 3]. Grade 3/4 differentiation syndrome (n = 4, 8%) was observed at 75 - 150 mg/day. Dose-limiting cardiac toxicity (heart failure with reduced ejection fraction; Gr 3 increased troponin/CK) was observed at total daily doses ≥200 mg. The CRc rate was 13% (4/30 pts evaluable for response): 1 CR at 75 mg BID (FLT3-ITD); 1 CRp at 100 mg BID (Wt-FLT3); and 2 CRi's at 50 mg BID, one that previously progressed on gilteritinib. The median time to overall response was ~13.3 weeks. Four pts achieved a PR (≥50% decrease in BM blasts to 5 - 25% abnormal cells) at total daily doses of 50 - 150 mg; 2 had ITD mutations, and all had received prior FLT3 kinase inhibitors. At ≥75 mg BID, trough plasma concentrations were > 90 ng/ml and associated with > 90% p-FLT3 inhibition maintained over the dosing interval. **Conclusions:** The FF-10101-01 FLT3 inhibitor has shown activity in pts with refractory/relapsed AML, including those with activating FLT3-ITD mutations resistant to gilteritinib and other FLT3 kinase inhibitors. Doses of 50-75 mg BID were well tolerated and resulted in sustained FLT3 inhibition. Clinical trial information: NCT03194685. Research Sponsor: FUJIFILM Pharmaceuticals U.S.A, Inc.

7009 **Poster Discussion Session**

Second-line bosutinib (BOS) for patients (pts) with chronic phase (CP) chronic myeloid leukemia (CML): Final 10-year results of a phase 1/2 study. *First Author: Carlo Gambacorti-Passerini, University of Milano-Bicocca, Monza, Italy*

Background: BOS is approved for Philadelphia chromosome (Ph)+ CML resistant/intolerant to prior therapy and newly diagnosed Ph+ CP CML. In a phase 1/2 study, second-line BOS showed durable efficacy and manageable toxicity in pts with imatinib-resistant (IM-R) or -intolerant (IM-I) Ph+ CP CML. **Methods:** This final efficacy and safety analysis of the phase 1/2 study and extension study was based on ≥10 y of follow-up (FU). Ph+ CP CML pts who received BOS starting at 500 mg/d after prior treatment (Tx) with imatinib only were included. **Results:** 19% of pts were on BOS at y 10, and 13% were still on BOS at study completion after ≥10 y; 19% completed ≥10 y of FU. Median duration of Tx and FU were 26 and 54 mo, respectively. Median (range) dose intensity was 436 (87–599) mg/d. The most common primary reasons for permanent Tx discontinuation were lack of efficacy (unsatisfactory response or disease progression; 27%) and adverse events (AEs; 26%). In pts with a valid baseline assessment, cumulative complete cytogenetic response (CCyR), major molecular response (MMR) and MR^4 rates (95% CI), respectively, were 50% (43–56), 42% (35–49) and 37% (30–44) (IM-R: 48% [41–56], 46% [37–55] and 39% [31–48]; IM-I: 53% [41–64], 36% [25–48] and 33% [22–45]). Responses were durable, with estimated probabilities of maintaining CCyR, MMR and MR^4 > 50% after ≥10 y (Table). At 10 y, cumulative incidence of on-Tx progression/death was 24% and Kaplan-Meier (K-M) overall survival 72% (Table); 55 deaths (IM-R: n = 41; IM-I: n = 14) occurred on study, none BOS-related. Any grade Tx-emergent AEs (TEAEs) in ≥40% of pts were diarrhea (86%), nausea (46%) and thrombocytopenia (42%). Pleural effusion, cardiac and vascular TEAEs occurred in 13%, 12% and 11% of pts, respectively. 28% of pts had AEs leading to permanent Tx discontinuation; most common (≥2% of pts) were thrombocytopenia (6%), neutropenia (2%) and alanine aminotransferase increased (2%). **Conclusions:** These 10-y data are consistent with prior results of durable efficacy and manageable toxicity with second-line BOS and support long-term BOS use in CP CML pts after imatinib failure. Clinical trial information: NCT00261846 and NCT01903733. Research Sponsor: Pfizer.

Outcome after ≥10 y	IM-R N = 195	IM-I N = 89	Total N = 284
Pts with CCyR, n/N	88/182	42/80	130/262
Probability of maintaining CCyR, % (95% CI)*,†	61 (49–73)	52 (32–73)	58 (48–69)
Pts with MMR, n/N	58/127	25/70	83/197
Probability of maintaining MMR, % (95% CI) *,†	55 (39–70)	54 (15–93)	56 (41–71)
Pts with MR^4, n/N	50/127	23/70	73/197
Probability of maintaining MR^4, % (95% CI) *,†	55 (38–73)	52 (8–96)	56 (39–72)
Cumulative incidence of on-Tx progression/death, % (95% CI)	29 (23–36)	14 (8–23)	24 (20–30)
Overall survival, % (95% CI)*	71 (63–79)	73 (60–87)	72 (64–79)

Molecular data not on International Scale and not available for pts in China, Russia, South Africa and India. CCyR imputed from MMR in extension study if valid cytogenetic assessment not available on a specific date.
*K-M estimates. †Among responders.

7010 **Poster Discussion Session**

Phase II study of the IDH2-inhibitor enasidenib in patients with high-risk IDH2-mutated myelodysplastic syndromes (MDS). *First Author: Sangeetha Venugopal, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Isocitrate dehydrogenase 2 (*IDH2*) mutations occur in 5% of patients (pts) with MDS. Enasidenib (ENA) is a selective oral inhibitor of the mutant IDH2 enzyme with single-agent activity in relapsed/refractory acute myeloid leukemia (AML). We report the results of the open label phase II study designed to evaluate the efficacy and tolerability of ENA, as monotherapy or in combination with azacitidine (AZA) in pts with higher-risk *IDH2*-mutated MDS (NCT03383575). **Methods:** Pts with higher-risk [Revised International Prognostic Scoring System risk > 3 or high molecular risk (HMR)] MDS/CMML or LB AML naïve to hypomethylating agents (HMA) received ENA100 mg orally daily for 28 d of each 28-d cycle + AZA 75 mg/m2 IV or SC on d 1-7 of each cycle (ENA+AZA), and pts with refractory or progressive MDS to prior HMA therapy received ENA alone (ENA), in 28-d cycles until unacceptable toxicity, relapse, transformation to AML, or progression. The primary endpoint was overall response rate (ORR) [complete remission (CR), marrow CR (mCR), partial remission (PR) and hematologic improvement (HI)]. Other endpoints include safety, and survival outcomes. **Results:** 48 pts received ENA+AZA (n = 26) or ENA (n = 22). The median age was 73 yrs (range, 46-83). Most pts (72%) had HMR: *ASXL1* (39%), and *RUNX1* (17%). Median number Tx cycles was 4 (2–32) in the ENA+AZA, and 7 (1–23) in the ENA arm. Common Tx-related grade 3–4 AEs in the ENA+AZA arm were neutropenia (64%), thrombocytopenia (28%), and anemia (8%); these occurred in 10%, 0%, and 5%, in the ENA arm. Grade 3–4 infections occurred in 32% (ENA+AZA) and 14% (ENA). IDH differentiation syndrome occurred in 3 pts (12%) in the ENA+AZA and 5 pts (24%) in the ENA arm. Two deaths occurred during the initial 60 d, both unrelated to study and due to COVID. In response-evaluable pts (n=46), ORR was 84% (n = 21/25; 24% CR + 8% PR+44% mCR+ 8% HI] in the treatment naïve ENA+AZA and 43% (n = 9/21; 24% CR+5%PR+5% mCR+10% HI) in the HMA failure ENA arm (Table). Most common reason for Tx discontinuation was disease progression (ENA+AZA 20%, ENA 33%).5 pts (20%) received HCT in the ENA+AZA and 1 (5%) in the ENA arm. 7 pts in the ENA+AZA and 5 in the ENA arm were ongoing at data cutoff (Dec 31, 2020). After a median follow up of 12.6 mo, median OS was 32.2 mo in the ENA+AZA and 21.3 mo in the ENA arm. **Conclusions:** ENA is well tolerated and shows promising efficacy in *IDH2*-mutated higher risk MDS. Follow up and accrual is ongoing to better define duration and biomarkers of response. Clinical trial information: NCT03383575. Research Sponsor: brystol meyer squibb.

	Response Evaluable (N = 46)	Arm A (Untreated) ENA+AZA (N = 25)	Arm B (HMA-failure) ENA (N = 21)
Overall response rate (ORR), n (%)	**30 (68)**	**21 (84)**	**9 (43)**
Complete remission (CR)	11 (24)	6 (24)	5 (24)
Partial remission (PR)	3 (7)	2 (8)	1 (5)
Marrow CR (mCR)	12 (26)	11 (44)	1 (5)
Hematological improvement (HI) only	4 (9)	2 (8)	2 (10)
No response (NR), n (%)	**16 (35)**	**4 (16)**	**12 (57)**
Stable disease (SD)	14 (30)	4 (16)	10 (48)
Progressive disease (PD)	2 (4)	0 (0)	2 (10)

7011 **Poster Discussion Session**

Venetoclax and azacitidine combination in chemotherapy ineligible untreated patients with therapy-related myeloid neoplasms, antecedent myelodysplastic syndromes, or myelodysplastic/myeloproliferative neoplasms. *First Author: Vinod Pullarkat, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Patients (pts) with therapy-related myeloid neoplasms (tMN), antecedent myelodysplastic syndrome, or antecedent myelodysplastic/myeloproliferative neoplasms (A-MDS/MPN) may have poor outcomes due to age and adverse genetic/karyotypic features. In the VIALE-A study, pts with tMN and A-MDS/MPN unfit for intensive chemotherapy treated with venetoclax (Ven) and azacitidine (Aza) demonstrated superior response rates and overall survival (OS) than Aza alone. Herein, the efficacy and safety of Ven+Aza among pts with tMN and A-MDS/MPN are described. **Methods:** Data were pooled from pts enrolled in VIALE-A (NCT02993523) comparing pts who received Ven+Aza or placebo (Pbo)+Aza and a prior phase 1b study (NCT02203773) where pts received Ven+Aza. Enrolled pts were ≥18 years, treatment-naïve with no prior exposure to hypomethylating agents, and ineligible for intensive chemotherapy. Pts on Ven+Aza received Ven 400 mg orally (days 1–28) and Aza (75 mg/m^2; days 1-7/28-day cycle). Composite complete remission rate (CRc; complete remission [CR] + CR with incomplete hematologic recovery [CRi]), duration of response (DoR), and OS were assessed. Disease assessments were per modified International Working Group response criteria for AML. **Results:** In this pooled analysis, tMN was observed in (Ven+Aza/Pbo+Aza) 31/9 and A-MDS/MPN in 59/26 pts. Poor-risk cytogenetics were observed in 18 (58%)/6 (67%) with tMN (5 or 5q deletion [del]: 4/1 ; 7 or 7q del: 6/1 ; complex [≥ 3 clonal abnormalities]: 10/4), and 19 (32%)/13 (50%) with A-MDS/MPN (5 or 5q del: 10/5; 7 or 7q del: 6/1; complex: 14/9). *TP53* mutation was observed in 5/3 pts with tMN and 8/0 pts with A-MDS/MPN. Pts with tMN received a median (Ven+Aza/Pbo+Aza) of 5/4 cycles of treatment. CRc was achieved by 19 (61%)/1 (11%). The mDoR was not reached (NR) (95% CI: 17.8, NR)/8.5 (NR, NR) months. The mOS was 16.4 (95% CI: 4.1, NR)/11.3 (0.6, 17.5) months. Pts with A-MDS/MPN received a median (Ven+Aza/Pbo+Aza) of 9/5 cycles of treatment. CRc was achieved by 39 (66%)/7 (27%) pts with mDoR of 17.3 (95% CI: 9.6, NR)/5.8 (1.1, NR) mos. The mOS was 15.9 (95% CI: 11.5, NR)/10.1 (4.7, 14.5) mos. Common grade≥3 adverse events (Ven+Aza/Pbo+Aza) were febrile neutropenia (tMN: 39%/11% and A-MDS/MPN: 36%/12%) neutropenia (tMN: 29%/33%; A-MDS/MPN: 39%31%), and thrombocytopenia (tMN: 32%/33%; A-MDS/MPN: 39%/62%). **Conclusions:** Ven+Aza compared to Aza monotherapy resulted in higher CRc rates with longer DoR and median OS among treatment-naïve pts with tMN and A-MDS/MPN ineligible for intensive chemotherapy. The safety profile was similar to overall pts with the Ven+Aza combination. Outcomes by cytogenetic and molecular risk-groups will be presented. Clinical trial information: NCT02993523, NCT02203773. Research Sponsor: AbbVie, Genentech.

7012 **Poster Discussion Session**

A phase Ib/II study of ivosidenib with venetoclax +/- azacitidine in IDH1-mutated myeloid malignancies.

First Author: Curtis Andrew Lachowiez, M.D. Anderson Cancer Center, Houston, TX

Background: Isocitrate dehydrogenase-1 (*IDH1*$^{+}$) mutations are present in 5-15% of myeloid malignancies, promoting leukemogenesis through production of the oncometabolite 2-hydroxyglutarate resulting in arrested myeloid differentiation. *IDH1*$^{+}$ malignancies demonstrate increased reliance on the anti-apoptotic protein BCL-2, enhancing susceptibility to the BCL-2 inhibitor venetoclax (VEN). We report an interim safety and efficacy analysis of the IDH1 inhibitor ivosidenib (IVO; 500 mg PO daily D15-continuous) combined with VEN (D1-14) +/- azacitidine (AZA; 75mg/m^2 D1-7 every 28 days). **Methods:** Eligible patients age ≥18 with *IDH1*$^{+}$ MDS, newly diagnosed AML (ND: treatment naïve [TN] or secondary/treated secondary AML [sAML]), or relapsed/refractory (R/R) AML enrolled into three dose levels (DL): DL1 (IVO+VEN 400 mg), DL2 (IVO+VEN 800 mg), DL3 (IVO+VEN 400 mg+AZA). Primary objectives included safety and tolerability, and IWG defined overall response (ORR: CR+CRi+CRh+PR+MLFS). Prior receipt of IVO or VEN was exclusionary. **Results:** 25 evaluable patients (DL1: 6, DL2: 6, DL3: 13) enrolled with a median follow-up of 16.1 months. Median age was 67 (range: 44-84). 84% (N=21) of patients had AML (ND: N=13 [TN: 8, sAML: 5], R/R: N=8), while 16% (N=4) had MDS. ELN risk was intermediate and adverse in 16% (N=4) and 56% (N=14). Median *IDH1* VAF at enrollment was 22.7% (range: 5.1%-47.8%). Two patients had received a prior IDH1 inhibitor. The ORR was 92% (DL1: 67%, DL2: 100%, DL3: 100%). Composite CR (CRc: CR+CRi+CRh) was 84% (DL1: 67%, DL2: 100%, DL3: 85%) including 92% (TN: 100%, sAML: 80%), 63%, and 100% of patients with ND-AML, R/R-AML, or MDS. Median number of cycles received was 4 (DL1: 8.5, DL2: 6, DL3: 4) with ongoing responses in 62% (DL1: 33%, DL2: 50%, DL3: 82%) at 1-year. 8 patients transitioned to SCT (DL1: 0, DL2: 2, DL3: 6), and 8 patients remain on study (DL1: 2, DL2: 1, DL3: 5). 1-year OS was 68% for the entire study population (DL1: 50%, DL2: 67%, DL3: 78%), 71% in ND-AML (TN: 86%, sAML: 60%), 50% in R/R-AML, and 100% in MDS. Measurable residual disease negative CRc by multiparameter flow cytometry was attained in 60% (ND-AML: 67%, R/R-AML: 60%, MDS: 33%) correlating with improved OS (median OS: NR vs. 8.5 months, p-value: 0.038). Common grade 3/4 adverse events included febrile neutropenia (28%) and pneumonia (24%). Tumor lysis and differentiation syndrome occurred in two and four patients; all cases resolved with medical management. **Conclusions:** IVO+VEN +/- AZA is an effective treatment regimen in patients with *IDH1*$^{+}$myeloid malignancies. The combination therapy is associated with an acceptable and expected toxicity profile with notable efficacy and high rates of MRD-negative CRc in AML. Enrollment into the study continues. Clinical trial information: NCT03471260. Research Sponsor: V foundation Award.

Outcomes.

	All (N=25)	DL #1 (N=6)	DL #2 (N=6)	DL #3 (N=13)
ORR	23	4	6	13
CRc	21	4	6	11
CR	13	3	3	7
CRh	2	-	2	-
CRi	6	1	1	4
MLFS	1	-	-	1
PR	1	-	-	1
NR	2	2	-	-
EFS	NR (9.4-NR)	9.6 (2.8-NE)	9.4 (7-NE)	NR
OS	NR	9.7 (4.5-NE)	NR (8.5-NE)	NR

7013 **Poster Discussion Session**

Follow-up of patients with *FLT3*-mutated R/R AML in the phase 3 ADMIRAL trial.

First Author: Alexander E. Perl, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: The phase 3 ADMIRAL trial demonstrated the superiority of gilteritinib to salvage chemotherapy (SC) in patients (pts) with *FLT3*-mutated (*FLT3*$^{mut+}$) R/R AML. **Aim/Objective:** A follow-up of ADMIRAL assessed long-term survivors, transplant (HSCT) outcomes. and gilteritinib safety beyond 1 year. **Methods:** A data cut was performed on September 20, 2020—2 years after the primary analysis. Patients who were alive without relapse, pts who underwent HSCT, and adverse events of interest (AEIs) in Years 1 (≤12 months) and 2 (> 12 months) of gilteritinib therapy were evaluated. **Results:** As of September 20, 2020, 17% (n = 63/371) of pts in the intention-to-treat (ITT) population were alive (gilteritinib, n = 49; SC, n = 14); 16 pts assigned to gilteritinib remained on treatment. After a median follow-up of 37.1 months, 26 of the 49 pts in the gilteritinib arm who were alive were also without relapse; 18 of these 26 pts underwent HSCT, with 16 receiving post-HSCT gilteritinib maintenance therapy. Nineteen of the 26 pts in the gilteritinib arm without relapse continued gilteritinib beyond 1 year and remained in CR. Of the 371 ITT pts, 83 (22%) underwent HSCT during the study (gilteritinib, n = 64; SC, n = 19). Pre-HSCT CRc rates were similar across arms (gilteritinib: n = 40/64; 63%; SC: n = 11/19; 58%); 10 of 11 pts preselected for low-intensity SC achieved pre-HSCT CRc (gilteritinib, n = 9; SC, n = 1). Forty of 64 (63%) transplanted pts in the gilteritinib arm received post-HSCT gilteritinib maintenance after achieving pre-HSCT CRc; the 24-month relapse rate in pts who resumed gilteritinib after pre-HSCT CRc was 19%. Post-HSCT treatment with chemotherapy or other tyrosine kinase inhibitors was administered in 26 pts who received gilteritinib before transplantation. Cumulative 24-month relapse rates in gilteritinib-treated pts who achieved pre-HSCT CR and CRc were 20% and 45%, respectively. Median post-HSCT overall survival (landmarked to HSCT date), was similar across arms (gilteritinib, 16.1 months; SC, 15.3 months; HR = 1.076; 95% CI: 0.536, 2.160). Overall, 10.2% (n = 25/246) had ≥24 months of gilteritinib exposure. Most common AEIs during Years 1 and 2 of gilteritinib therapy were elevated ALT/AST levels. Incidences of all AEIs declined in Year 2. Cardiac AEIs in Year 2 were nonfatal cardiorespiratory arrest (n = 1) and ventricular tachycardia (n = 1). One case of differentiation syndrome and cutaneous squamous cell carcinoma occurred in Years 1 and 2, respectively. **Conclusions:** A high proportion of gilteritinib-treated R/R *FLT3*$^{mut+}$ AML pts who were alive without relapse had received HSCT followed by gilteritinib maintenance. Among all transplanted pts in ADMIRAL, pre-HSCT remission rates and post-HSCT survival were similar across arms. Post-HSCT gilteritinib maintenance may relate to the low post-HSCT relapse rate in the gilteritinib arm. The safety profile of gilteritinib is stable at 2 years with no new or significant safety signals. Clinical trial information: NCT02421939. Research Sponsor: Astellas Pharma, Inc. .

7014 **Poster Discussion Session**

Prognostic factors of overall (OS) and relapse-free survival (RFS) for patients with acute myeloid leukemia (AML) in remission after intensive chemotherapy (IC): Multivariate analyses from the QUAZAR AML-001 trial of oral azacitidine (Oral-AZA).

First Author: Gail J. Roboz, Weill Cornell Medicine and The New York Presbyterian Hospital, New York, NY

Background: Demographic and disease factors influence outcomes for patients (pts) with AML. In the phase 3 QUAZAR AML-001 trial, Oral-AZA significantly prolonged OS and RFS vs. placebo (PBO) for pts with AML in first remission after IC (Wei, *NEJM*, 2020). Univariate analyses showed OS and RFS benefits with Oral-AZA vs. PBO across pt subgroups defined by baseline (BL) characteristics. MV analyses were performed to identify BL characteristics independently predictive of OS/RFS in QUAZAR AML-001, and to assess Tx effects of Oral-AZA vs. PBO on survival when adjusted for BL factors. **Methods:** Pts were aged ≥55 yrs with AML in complete remission (CR) or CR with incomplete count recovery (CRi) after induction ± consolidation. Within 4 months of CR/CRi, pts were randomized 1:1 to receive Oral-AZA 300 mg or PBO for 14d/28d cycle. Cox proportional hazards models were used to estimate Tx effects of Oral-AZA vs. PBO on OS and RFS, adjusting for BL age, sex, ECOG PS score, cytogenetic risk at diagnosis (Dx), prior MDS, geographic region, CR/CRi after induction (per investigator) and at BL (per sponsor), MRD status, receipt of consolidation, number of consolidation cycles, platelet count, and ANC. In a stepwise procedure, randomized Tx and BL variables were selected incrementally into a Cox model if $P \leq 0.25$. After each addition, the contribution of the covariate adjusted for other covariates in the model was evaluated and retained in the model if $P \leq 0.15$. **Results***:* Oral-AZA Tx remained a significant independent predictor of improved OS (HR 0.70) and RFS (HR 0.57) *vs.* PBO after controlling for BL characteristics (Table). MRD status, cytogenetic risk, and pt age were each also independently predictive of OS and RFS. Response after induction (CR *vs.* CRi) and BL ANC were predictive of OS but not RFS, whereas prior MDS, CR/CRi at BL, and number of consolidation cycles were only predictive of RFS. **Conclusions:** Tx with Oral-AZA reduced the risk of death by 30% and risk of relapse by 43% vs. PBO independent of BL characteristics. Cytogenetic risk at Dx, MRD status, and pt age also independently predicted survival outcomes. Clinical trial information: NCT01757535. Research Sponsor: Bristol Myers Squibb.

Variable	OS HR [95%CI] *P* value	RFS HR [95%CI] *P* value
CC-486 vs PBO	**0.70 [0.56, 0.88] 0.0017**	**0.57 [0.45, 0.70 <0.0001**
MRD– vs MRD+ at BL	0.54 [0.43, 0.67] <0.0001	0.49 [0.39, 0.61] <0.0001
Int. vs Poor cytogenetic risk at Dx	0.57 [0.42, 0.76] 0.0002	0.49 [0.36, 0.66] <0.0001
Age (continuous)	1.03 [1.01, 1.05] 0.0046	1.02 [1.00, 1.04] 0.0468
ANC (continuous)	1.25 [1.03, 1.50] 0.0202	NIFM
Prior MDS (Y vs N)	NIFM	1.60 [1.11, 2.30] 0.0116
CR vs CRi after induction	0.80 [0.60, 1.06] 0.1138	NIFM
non-CR/CRi vs CRi at BL	NIFM	0.39 [0.18, 0.87] 0.0216
0 vs 2 consolidation cycles	NIFM	1.28 [0.92, 1.78] 0.1355
1 vs 2 consolidation cycles	NIFM	1.35 [1.04, 1.89] 0.0224

NIFM, not in final MV model.

7016 **Poster Discussion Session**

A mixed methods study exploring the role of perceived side effects on treatment decision-making in older adults with acute myeloid leukemia (AML).

First Author: Dawn Maze, Princess Margaret Cancer Centre, Toronto, ON, Canada

Background: AML patients may be treated with intensive chemotherapy (IC), or non-intensive chemotherapy (NIC) or they may receive best supportive care (BSC) or hospice care. Balancing treatment efficacy and toxicities is key in treatment decision-making. IC is efficacious with extensive toxicities, while NIC has lower risk of toxicities but reduced efficacy. This study provides an international, multi-stakeholder perspective on the role of side effects in AML treatment decision-making. **Methods:** We conducted one-on-one, 60-minute interviews with 28 AML patients (>65 years, not receiving IC), 25 of their family members and 10 independent physicians from the US, UK and Canada. Interviews included open-ended questions to explore the treatment decision-making process. Participants also rated the importance of various factors in AML treatment decision-making from 0 (not important) to 3 (very important). **Results:** The sample included patients with varying treatment histories (13 no treatment, 11 on NIC, 3 discontinued NIC, 1 BSC). Side effects were rated as a 'very important' factor in treatment decision-making by a greater proportion of patients not on treatment (n = 9/13; 69.2%) and their relatives (n = 12/13; 92.3%) compared to those with experience of NIC (n = 5/11 who answered, 45.5%), their relatives (n = 3/11; 27.3%), and physicians (n = 4/10; 40.0%). When discussing side effects in detail, there was a disconnect between perceptions of patients not on treatment, and side effects that patients on NIC actually experienced. Many patients with no treatment experience were worried that side effects would be worse than their current symptoms (n = 6/13), referring to constant vomiting, hair loss, organ failure, or death. Fear of side effects was the primary reason for opting not to take treatment (n = 9/13), though it was not clear if these patients were distinguishing between IC and NIC. In contrast, although two patients' experiences of side effects resulted in them discontinuing NIC (n = 2/14), a higher proportion (n = 9/14) reported that the side effects had little impact on their life. Side effects most frequently reported by patients with experience of NIC (n = 11/14) were considered mild and included fatigue, reduced appetite, generally feeling unwell, nausea and injection site irritation (all n = 3). It was most commonly reported that the worst aspect of NIC was the time commitment (n = 4/8 asked). When accounting for different treatments paths no international variation in findings was observed. **Conclusions:** The nature and severity of side effects of AML treatment were perceived to be worse than reality. This incorrect perception may lead to undertreatment of patients and result in worse outcomes. There is a need for more patient education and resources about the lived treatment experience, to enhance understanding and mitigate pre-conceived notions of side effects. Research Sponsor: Pfizer.

7017 **Poster Discussion Session**

A registry-based, observational safety study of inotuzumab ozogamicin (InO) treatment in patients (pts) with B-cell precursor acute lymphoblastic leukemia (ALL) who proceeded to hematopoietic stem cell transplant (HSCT).

First Author: Marcos J.G. De Lima, University Hospitals Cleveland Medical Center, Cleveland, OH

Background: InO is a CD22-directed antibody-drug conjugate indicated for treatment of relapsed/refractory (R/R) ALL. InO has been associated with hepatotoxicity and hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS), particularly post-HSCT. Registry data (Center for International Blood and Marrow Transplant Research [CIBMTR]) was analyzed to assess toxicity in pts with ALL who received InO prior to HSCT. **Methods:** CIBMTR patient data are being collected for a 5-year period after US approval of InO (Aug 2017 – Aug 2022). Data from US pts age ≥18 y treated with InO who proceeded to allogeneic HSCT were included. Using interim data at 3 y, we evaluated post-HSCT outcomes, including clinical status, overall survival, transplant-related (non-relapse) mortality (NRM), relapse, death after relapse (time from HSCT to death after the first 28 d from any cause with prior relapse/progression post-HSCT), and investigator-defined adverse events, including hepatic VOD/SOS. All statistical analyses are descriptive. **Results:** Data accrued from 18 Aug 2017 to 17 Aug 2020 for 131 adult pts (median age 40 y) who proceeded to first allogeneic HSCT: 31% in first complete remission (CR1), 46% in CR2, 13% in ≥CR3, 5% in 1st relapse, 2% in ≥3rd relapse, and 3% in primary induction failure. A majority (70%) had transplants from peripheral blood stem cells, and 47% involved an HLA-identical sibling or other related donor. Nearly half received myeloablative conditioning regimens. Before HSCT, 36% of pts received 1 cycle of InO, 46% had 2 cycles, and 17% had ≥3 cycles. Half (48%) received InO as a single agent. Median time from last dose of InO to HSCT was 2.0 mo (range: 0.4–26.2). At time of data-lock (11 Nov 2020), post-transplant data were available for 131 pts. Outcomes for these pts are shown in the Table. Among a subgroup of adults with active R/R ALL (n = 91) at time of HSCT (median of 4 lines prior therapy), VOD/SOS incidence within 100 d of HSCT was 18%. **Conclusions:** Incidence of VOD/SOS after first HSCT in InO-treated pts with R/R ALL in this study was similar to the 18–19% reported in pooled analyses of 2 clinical trials among InO-treated pts with R/R ALL (Marks et al, *Biol Blood Marrow Transplant* 2019) and in the INOVATE study (Kantarjian et al, *Lancet Haematol* 2017). The NRM at 1 y of 21% (23% R/R ALL) is lower than the NRM at 1 y of 38% reported in the pooled analyses of R/R ALL InO recipients. Research Sponsor: Pfizer.

	Adults (n = 131)
VOD/SOS within 100 d post-HSCT, n (%)	17 (13)
Post-HSCT continued complete remission (CR)*, n (%)	117 (89)
Post-HSCT overall survival, 12 mo, % (95% CI)	55 (45–65)
HSCT-related mortality (NRM), 12 mo, % (95% CI)	21 (14–29)
Post relapse mortality, 12 mo, % (95% CI)	25 (17–33)
Post-HSCT relapse, 12 mo, % (95% CI)	36 (27–45)

*Continued CR is defined as a patient who underwent HSCT during CR, and the CR is sustained post-HSCT.

7018 **Poster Discussion Session**

Measurable residual disease response in acute myeloid leukemia treated with venetoclax and azacitidine.

First Author: Keith Pratz, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA

Background: In the phase 3 VIALE-A trial, rates of composite complete remission (CRc; complete remission [CR] + CR with incomplete hematologic recovery [CRi]) and measurable residual disease response (MRD$<10^{-3}$) were higher in patients (pts) treated with venetoclax (Ven) + azacitidine (Aza) compared to Aza alone (23.4%/7.6%, p<0.001). There is limited evidence of the clinical significance of MRD monitoring in pts receiving low-intensity chemotherapy. Herein, we explored the outcomes of pts treated with Ven+Aza who achieved both CRc and MRD$<10^{-3}$ in the VIALE-A trial (NCT02993523). **Methods:** Enrolled pts were ≥18 years and unfit for intensive chemotherapy. Pts received Ven 400 mg orally; days 1–28 and Aza 75 mg/m^2; days 1-7/28-day cycle. Bone marrow aspirate samples for multiparametric flow cytometry assessments by integrated leukemia-associated immunophenotypes and different than normal procedures were collected for central analysis (Covance Central Laboratory Services) at baseline, end of cycle 1, and every 3 cycles thereafter. Assessments were performed independent of disease responses. MRD response was defined as <1 residual blast /1000 leukocytes (<10^{-3}). CRc, DoR, OS, and EFS were assessed. Disease assessments were per modified International Working Group response criteria for AML. **Results:** 211/286 (74%) pts treated with Ven+Aza with at least one valid post-baseline MRD assessment were considered MRD evaluable; 78/211 (37%) achieved MRD$<10^{-3}$ and 133/211 (63%) had MRD≥10^{-3}. Median age (MRD$<10^{-3}$/ MRD≥10^{-3}) was 76 (range: 49-89)/77 (58-91) yrs. Pts (MRD$<10^{-3}$/ MRD≥10^{-3}) received median of 14.5 (range: 1-28) /7.0 (1-30) cycles of Ven+Aza. At median follow-up of 22.0 (range: 20.1-23.0)/20.8 (19.8-22.3) months (mos), CRc + MRD$<10^{-3}$/ MRD≥10^{-3} was achieved by 67 (86%)/ 97 (73%); 20/67 (30%) achieved CRc + MRD$<10^{-3}$ by end of cycle 1. Median DoR, OS, and EFS were not reached in pts with CRc + MRD$<10^{-3}$ response (Table). The 12-mo estimates for DoR, OS, and EFS for pts with CRc + MRD$<10^{-3}$response were 81.2%, 94.0%, and 83.2%, respectively. Adverse events ≥grade 3 (MRD$<10^{-3}$/ MRD≥10^{-3}) were febrile neutropenia (50%/43%), neutropenia (50%/35%), and thrombocytopenia (44%/44%), similar to the overall population. **Conclusions:** Pts with best response of CRc who achieved MRD$<10^{-3}$ response with Ven+Aza treatment had longer DoR, OS, and EFS than pts who were CRc and MRD positive. Clinical trial information: NCT02993523. Research Sponsor: AbbVie, Genentech.

DoR, OS, and EFS in patients with composite complete response treated with venetoclax and azacitidine.

	12-mos estimate % (95% CI)		Median months (95% CI)	
	MRD<10^{-3} n=67	MRD≥10^{-3} n=97	MRD<10^{-3} n=67	MRD≥10^{-3} n=97
Duration of response	81.2 (69.3, 88.9)	46.6 (35.6, 56.8)	NR (19.3, NR)	9.7 (8.0. 15.8)
Overall survival	94.0 (84.7, 97.7)	67.9 (57.6, 76.2)	NR (24.4, NR)	18.7 (12.9, NR)
Event-free survival	83.2 (71.6, 90.3)	45.4 (35.2, 55.0)	NR (19.7, NR)	10.6 (9.0, 13.9)

CI: Confidence interval; MRD: measurable residual disease; NR: not reached.

7019 **Poster Discussion Session**

Predictive phosphoproteomic signatures for midostaurin plus chemotherapy response in FLT3 mutant positive acute myeloid leukaemia.

First Author: Arran David Dokal, Kinomica Limited, Macclesfield, United Kingdom

Background: Midostaurin is approved for FLT3 mutant-positive (FLT3+) acute myeloid leukemia (AML), however efficacy has also been observed in a subpopulation of FLT3 mutant-negative AML, suggesting that FLT3 mutation is not the only determinant in conferring midostaurin sensitivity. We previously described a phosphoproteomic signature significantly elevated in primary AML blasts that responded to midostaurin *ex vivo* (Casado et al Leukaemia 2018). This signature includes phosphorylation sites on protein kinase C delta (a midostaurin off-target) and its substrate GSK3A. In this study, we tested whether these phospho-signatures could group FLT3+ patients based on clinical responses to midostaurin plus chemotherapy. **Methods:** We obtained FLT3+ bone marrow (BM) and peripheral blood (PB) diagnosis specimens (n=56 cases) from the Leukemia Tissue Bank at Princess Margaret Cancer Centre. These patients were treated with standard chemotherapy plus midostaurin. Phospho-signatures quantified using mass spectrometry were analysed with a classification machine learning algorithm to group patients based on response to treatment as a function of phospho-signature status. Other features (e.g. genetic mutations, HSC-transplant) were also analysed. Differential survival analysis was carried out with Kaplan-Meier and Log Rank test methods. Phospho-signatures for BM and PB samples were analysed independently. **Results:** A first ML model was developed based on the signature described in the Casado et al study. Patients positive for this signature exhibited a survival probability of 243 weeks, compared to 126 weeks in signature negative patients (averages by geometric mean, Log Rank p = 9.88e-05). As the patients in the current study received chemotherapy, in addition to midostaurin, we also identified a new signature consisting of 26 phospho-sites (model 2), which partially overlapped with the first model. Patients positive for model 2 signature showed a markedly longer survival time than negative patients (269 vs 76 weeks, Log Rank p = 1.30e-05 for PB and 241 vs 56, Log Rank p = 2.13e-09 for BM specimens, Table). No other features separated survival as clearly as model 2. **Conclusions:** We have identified phospho-signatures with the potential to further stratify FLT3+ AML for midostaurin treatment. The presence of PRKCD signalling components in signatures provides a rationale for midostaurin activity in sensitive cases. Analysis will also be performed on FLT3 mutant-negative cases to validate the signature in this group. Research Sponsor: Innovate UK, UK Research and Innovation, Pharmaceutical/Biotech Company.

	Signature	Cases	Events	Geometric Mean	SE	Median
PB samples	Negative	9	6	76	42	26
	Positive	25	2	269	15	ND*
BM samples	Negative	16	12	56	27	26
	Positive	37	6	241	20	ND*

Disease free survival in weeks as a function of model 2 phospho-signature. * Kaplan-Meier curves did not reach 50% reduction in disease free survival.

7020 **Poster Discussion Session**

High dimensional mapping of temporal evolution within the marrow microenvironment in response to FLT3 inhibitor therapy.

First Author: Matthew Newman, Oregon Health & Science University, Portland, OR

Background: The advent of genomic sequencing technologies has revealed underlying genetic alterations, such as FLT3 mutations, that can be targeted in acute myeloid leukemia (AML). However, development of resistance limits the durability of response. Recent data has implicated that factors from the bone marrow microenvironment mediate initial resistance to FLT3 inhibitors (FLT3i) in AML. We combined high dimensional characterization techniques, time-of-flight mass cytometry (CyTOF) and RNA sequencing, to examine sequential marrow stromal samples from a subset of patients with FLT3 mutated AML treated with the FLT3i gilteritinib. Here, we report on the heterogeneity and evolution of cell surface and secreted factors over time. **Methods:** RNA sequencing of primary FLT3-ITD stromal samples (N = 29) from pre-study and on-treatment patients enabled prioritization of candidate targets for CyTOF. Target-specific purified antibodies were purchased pre-conjugated to metal lanthanides or conjugated in house according to manufacturer protocols (after validation via traditional flow cytometry). Primary stromal cells were cultured ex vivo until confluent and were harvested and stained according to a standardized protocol, and subsequently run on a Helios (Fluidigm) mass cytometer. A computational approach was employed to compensate and visualize data via the CATALYST R package. A total of four pre-treatment and four post-gilteritinib timepoint isolates (N = 8) were analyzed. **Results:** A 36-target mass cytometry panel revealed protein level differences in patients before and after gilteritinib therapy. Dimensional reduction techniques such as MDS and UMAP showed that samples taken from later timepoints clustered together compared to their earlier counterparts with respect to global protein expression. Inflammatory mediators such as IL1-beta and MCP-1 were upregulated in patient stroma soon after gilteritinib treatment and therefore potentially contribute to early resistance. Novel markers previously implicated in early resistance to targeted therapies in AML such as FGF2 and FGFR1 similarly peaked earlier in treatment, mimicking the clinical course of expression observed in marrow stroma of patients treated with another FLT3 inhibitor quizartinib (Traer et al. Cancer Res. 2016). **Conclusions:** Our findings show that primary marrow stroma evolves during gilteritinib treatment, and that stromal proteins previously reported to promote early resistance to FLT3i are also upregulated during gilteritinib resistance. The heterogeneity of stromal cell isolates detected by mass cytometry highlights the utility of high dimensional tracking of disease course in patients, and may enable a better understanding of how the temporal evolution of the marrow microenvironment contributes to development of resistance to targeted therapies such as gilteritinib and other FLT3i over time. Research Sponsor: U.S. National Institutes of Health.

7021 **Poster Session**

Effect of geriatric assessment (GA) and genetic profiling on overall survival (OS) of older adults with acute myeloid leukemia (AML). *First Author: Vijaya Raj Bhatt, Fred and Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE*

Background: GA can predict the risk of toxicities of chemotherapy in older adults. Genetic risk categories correlate with OS in AML. We previously reported a reduction in early mortality in a pre-planned interim analysis of a phase II trial with the use of GA and genetic profiling to personalize therapy selection (NCT03226418) (Blood 2019; 134(s1):120). Here, we present the results of a propensity score matched analysis demonstrating an improvement in OS over a historical control. **Methods:** Patients ≥60 years with a new diagnosis of AML underwent GA. Patients were considered fit for intensive chemotherapy if they had robust physical function [normal activities of daily living (ADL) and instrumental ADL, and short physical performance battery score of ≥10 out of 12], normal cognitive function (Montreal Cognitive Assessment score of ≥26 out of 30), and hematopoietic cell transplantation comorbidity index (HCT CI) of 0-2 (except for treatment related AML, where a score of 0-2 in addition to the prior history of malignancy was acceptable). Genetic profiling for therapy selection relied on karyotyping and followed the 2017 ELN criteria. Fit patients with good or intermediate-risk AML received intensive chemotherapy. Patients with high-risk AML received low-intensity chemotherapy, or CPX 351 if they were fit and met the FDA-approved indications. Pragmatic aspects of the trial included broad eligibility criteria (e.g. patients on treatment for other malignancy were enrolled) and co-management of patients with community oncologists. Mortality was compared with a historical control treated during the years 2004-2016 (after approval of HMA) and matched on gender, age, Karnofsky Performance Status (KPS), HCT CI and ELN risk category. **Results:** Treatment group (n = 27) vs. historical controls (n = 32) were matched in terms of age (median age, 70 vs. 68.5 years), ELN risk category (adverse risk 59% vs. 53%), HCT CI (median score of 2), KPS (median 80 vs. 85), and gender (male 44% vs. 50%). In the treatment group, 3 patients received intensive chemotherapy: CPX 351 (n = 2) or 7+3+ gemtuzumab (n = 1). Other patients received HMA alone (n = 16), decitabine and midostaurin (n = 3), or azacitidine and venetoclax after the approval of venetoclax (n = 5). Treatment in the historical control included intensive chemotherapy (n = 20) such as 7+3, or mostly HMA based low intensity chemotherapy (n = 12). OS was significantly higher in the treatment group over historical control with 1-year OS of 66% (95% CI 60-87%) vs. 16% (95% CI 7-35%). **Conclusions:** Our model to personalize AML therapy selection represents an innovative approach to precision medicine that incorporates both GA for patient profiling and genetic profiling of leukemia cells. Our results appear promising with superior OS (an absolute difference of 50% in 1-year OS) compared to a matched historical control. Clinical trial information: NCT03226418. Research Sponsor: U.S. National Institutes of Health.

7022 **Poster Session**

Adult Philadelphia-like B-cell acute lymphoblastic leukemia: Characteristics, outcomes, and role of allogeneic hematopoietic cell transplantation in comparison to Philadelphia-positive and Philadelphia-negative acute lymphoblastic leukemia. *First Author: Zaid Abdel Rahman, Mayo Clinic, Jacksonville, FL*

Background: Philadelphia-like Acute Lymphoblastic Leukemia (Ph-like ALL) is a high-risk subset of adult ALL. Until recently, there has not been a systematic platform to recognize this entity in clinical practice. Furthermore, data regarding the role of allogeneic hematopoietic cell transplantation (allo-HCT) is lacking. We conducted this study to identify patients with Ph-like ALL and describe their outcomes in comparison to Ph^+ and Ph^- ALL with emphasis on the role of allo-HCT. **Methods:** To identify cases of Ph-like ALL, available diagnostic cytogenetic pellets for patients in the Mayo Clinic ALL cohort (N=365) were tested using a targeted fluorescence *in situ* hybridization (FISH) panel developed by the Mayo Clinic Genomics Laboratory and includes probes to detect Ph-like-specific rearrangements (i.e., *ABL1, ABL2, PDGFRB, JAK2* and *CRLF2*). **Results:** Thirty-three (9%) patients with Ph-like ALL were identified, the remaining patients were classified as Ph^+ (N=132, 36%) or Ph^- ALL (N=200, 55%). Patients with Ph-like ALL were younger (Median: 39 vs. 50 vs. 49 years, *P*=.01), had higher WBC (Median: 27.9 vs. 21.5 vs. 4.5 x10^9/L, *P*<.001), were less likely to achieve CR (91% vs. 99% vs. 96%, *P*=.02), more likely to be MRD+ (64% vs. 34% vs. 36%, *P*=.03), had a higher relapse rate (5-year: 39% vs. 24% vs. 38%, *P*=.01) and lower OS (5-year: 41% vs. 64% vs. 49%, *P*=.02), see Table. Patients who achieved MRD negativity had better OS (MRD+ vs MRD-, *P*=.01). Importantly, no statistically significant difference in OS, relapse or non-relapse mortality were noted between the 3 groups in patients who underwent allo-HCT in CR1. **Conclusions:** Ph-like ALL is a high risk subgroup with increased prevalence in younger adults. Allo-HCT appears to offset the poor prognosis associated with this entity. A targeted FISH panel offers timely recognition of this entity in a clinical setting. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

Outcome	N	Ph-like ALL (N=33)	Ph+ ALL (N=132)	Ph- ALL (N=200)	P-value
CR - No. (%)	363	30 (90.9%)	131 (99.2%)	188 (95.4%)	**0.02**
MRD positive - No. (%)	142	16 (64.0%)	17 (34.0%)	24 (35.8%)	**0.03**
Overall survival	365				
Cumulative incidence (%) (95% CI)					
1-year after diagnosis		90.3 (80.3, 100)	91.7 (87, 96.5)	82.8 (77.6, 88.2)	**0.02**
3-years after diagnosis		52.9 (34.9, 77.2)	68.7 (60.8, 77.5)	58.6 (51.8, 66.3)	
5-years after diagnosis		41.1 (22.7, 68.8)	64.1 (55.5, 73.7)	49.1 (41.8, 57.6)	
Relapse	365				
Cumulative incidence (%) (95% CI)					
1-year after diagnosis		9.9 (2.4, 23.7)	15.2 (9.7, 21.8)	17.7 (12.7, 23.3)	**0.02**
3-years after diagnosis		38.5 (19.4, 57.4)	23.1 (16.1, 30.8)	35.2 (28.3, 42.1)	
5-years after diagnosis		38.5 (19.4, 57.4)	24.1 (16.9, 32.0)	37.4 (30.3, 44.4)	

P-values result from Fisher's exact test (CR and MRD) or a log-rank test (death and relapse).

7023 **Poster Session**

Updated results from DIAMOND-01 (CLI24-001) trial: A phase I/II study of SEL24/MEN1703, a first-in-class dual PIM/FLT3 kinase inhibitor, in acute myeloid leukemia. *First Author: Scott R. Solomon, Northside Hospital Cancer Institute, Atlanta, GA*

Background: SEL24/MEN1703, a dual PIM/FLT3 kinase inhibitor, in the dose escalation (DE) DIAMOND-01 trial (CLI24-001, NCT03008187), showed an acceptable safety profile up to the recommended dose (RD) of 125 mg along with initial evidence of single agent activity and meaningful target engagement in heavily pre-treated patients (pts) with AML (Solomon et al, EHA 2020; Tomirotti et al, ASH 2020). Here we present updated data including pts enrolled in the Phase II, cohort expansion (CE) of the study. **Methods:** DIAMOND-01 trial enrolled pts unsuitable for chemotherapy having relapsed or refractory (R/R) (DE and CE) or previously untreated (DE) AML. Previous targeted therapies – except PIM inhibitors – were allowed. SEL24/MEN1703 was given orally, QD, 14 days ON / 7 days OFF until progression/unacceptable toxicity. The DE tested MEN1703 escalating doses from 25 to 150 mg, whereas in the CE the RP2D (125 mg) was administered. The key objectives of the CE were the confirmation of the safety profile determined in the DE along with further investigation of single agent activity. Adverse events (AEs) were graded according to NCI-CTCAE v.4.03; responses assessed as per ELN 2017 criteria. **Results:** As of January 21, 2021 (cut-off date), n = 48 pts were treated across DE (n = 25) and CE (n = 23). Median age was 69 (25-84) years. Overall, 20 (43%) and 15 (32%) pts had non de novo AML and primary refractory AML, respectively. Adverse karyotype was reported in 7 (15%) pts. Most frequently reported mutations were FLT3/ITD (23%, n = 11), DNMT3A (15% n = 7), NPM1 (15%, n = 7), IDH1 (13%, n = 6) and IDH2 (4%, n = 2), CEBPA (4%, n = 2), FLT3/TKD (2%, n = 1). Median number of cycles was 2 (1-8). At the RD (n = 30), most frequent serious treatment-emergent AEs (serious TEAEs) were pneumonia (23%), sepsis and febrile neutropenia (13%) and pulmonary mycosis (10%) whereas most frequent G≥3 TEAEs were febrile neutropenia and pneumonia (23%), leukocytosis (20%) and neutrophil count decrease, platelet count decrease, lymphocyte count decrease and sepsis (13%). Responses occurred in 2 pts in the CE, both with IDH1 mutant disease (naïve to IDH inhibitors) who achieved complete remission with incomplete hematologic recovery (CRi). Both responses occurred by Cycle 3, with a duration of 79 (ongoing at cut-off date) and 43 days, respectively. Across DE and CE, 4 CR/CRi occurred, three of which in pts with IDH mutations. A total of 3 out of 6 pts with IDH mutations treated at doses ≥75 mg achieved CR/CRi, including a CR in a patient with IDH2 mutant AML relapsed on Enasidenib. **Conclusions:** SEL24/MEN1703 confirmed a manageable safety profile at RD and showed preliminary single agent efficacy in R/R AML, particularly clustering in pts with IDH mutant disease either naïve or previously exposed to IDH inhibitors. These results warrant further investigation of SEL24/MEN1703 in AML, with potential focus in the IDH mutated subset. Clinical trial information: NCT03008187. Research Sponsor: Menarini Ricerche.

7024 **Poster Session**

Molecular annotation of extramedullary acute myeloid leukemia to identify prevalence of targetable mutations. *First Author: Somedeb Ball, Division of Hematology and Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Extramedullary (EM) involvement, including myeloid sarcoma (MS) and leukemia cutis (LC), is uncommon in patients with acute myeloid leukemia (AML). Mutational landscape of EM-AML is not well characterized, including concordance of sequencing data from EM vs. non-EM site (blood or bone marrow) and the potential for personalized targeted therapy in this patient cohort. **Methods:** In a multicenter retrospective study, clinical and genomic data were collected on EM-AML patients treated at Moffitt Cancer Center, Memorial Healthcare System, and University of Miami, as well as sequenced cases at a central laboratory. Next generation sequencing (NGS) data come from panels that interrogated 24- 406 genes, with 15 genes covered by all panels, including notably, *IDH1*, *IDH2*, *KIT*, *KRAS*, *NPM1*, *NRAS*, and *TP53*. Survival estimates using Kaplan-Meier statistics and multivariate analysis with Cox-regression were performed in SPSS (v.26). **Results:** Our study included 58 patients with EM-AML. Median age at diagnosis was 62 years; 55% of patients were males. In our cohort, 34 (59%) patients had MS, and 19 (33%) had LC. EM-AML was noted during relapse in 60% of evaluable patients (n=45), and 31% had isolated EM disease. Patients with LC had a significantly worse median overall survival (OS) than those with MS (5.7 months vs. 21.9 months, p= 0.008); Pattern of EM involvement (MS vs. LC) remained an independent prognostic factor for OS (p= 0.04) in a multivariate analysis including disease setting (new diagnosis vs. relapse) and ELN risk category. Results of NGS performed during EM presentation were available in 48 patients, 19 of which had NGS data from EM site. Most commonly mutated genes were *NRAS* on EM site NGS (37%) and *NPM1* on non-EM site NGS (28%). Based on EM NGS, 52% patients had a targetable genomic alteration, with 37% mutations in *IDH*, 21% *NPM1*, 5% *FLT3*, and 11% *MLL-PTD*. Five (two with concurrent M+EM disease) out of nine evaluable patients had significant discordance in targetable mutations between EM and non-EM NGS at EM-AML. Three of four patients who received treatment with *IDH1/2* inhibitors based on EM NGS achieved complete response. **Conclusions:** EM-AML has a distinct molecular architecture with an inferior OS in LC vs. MS patients. We conclude that EM site NGS is critical in patients with EM-AML, as 52% have potentially targetable mutations and could benefit from specific targeted therapies. Research Sponsor: None.

Common EM site Mutations	*NRAS*	37%
	IDH1	26%
Common Non-EM site Mutations	*NPM1, DNMT3A*	21%
	NPM1	**28%**
	DNMT3A	21%
	TET2	17%

Targetable Molecular Alterations	Incidence on EM Site NGS (n=19)	Incidence on non-EM Site NGS (n=29)	Overall Incidence (n=48)
IDH1	5 (**26%**)	1 (3%)	6 (12%)
IDH2	2 (11%)	3 (10%)	5 (10%)
FLT3	1 (5%)	4 (14%)	5 (10%)
NPM1	4 (21%)	8 (**28%**)	12 (**25%**)
MLL-PTD	2 (11%)	1 (3%)	3 (6%)

7025 **Poster Session**

Contemporary outcomes for adults with AML requiring ICU admission. *First Author: Danielle Hammond, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients (pts) with AML frequently encounter life-threatening complications requiring transfer to an intensive care unit (ICU). **Methods:** Retrospective analysis of 145 adults with AML requiring ICU admission at our tertiary cancer center 2018-19. Use of life-sustaining therapies (LSTs) and overall survival (OS) were reported using descriptive statistics. Logistic regression was used to identify risk factors for in-hospital death. **Results:** Median age was 64 yrs (range 18-86). 47% of pts had an ECOG status of ≥ 2 with a median of at least 1 comorbidity (Table). 117 pts (81%) had active leukemia at admission. 68 pts (47%) had poor-risk cytogenetics (CG) and 32 (22%) had TP53-mutated disease. 61 (42%), 27 (19%) and 57 pts (39%) were receiving 1st, 2nd and ≥ 3rd line therapy. 33 (23%) and 70 pts (48%) were receiving intensive and lower-intensity chemotherapy, respectively, and 77 pts (53%) were concurrently on venetoclax. Most common indications for admission were sepsis (32%), respiratory failure (24%) and leukocytosis (12%); Table outlines additional ICU admission details. Median OS from the date of ICU admission was 2.0 months (mo) for the entire cohort and 6.9, 1.6 and 1.2 mo in pts with favorable-, intermediate- and poor-risk CG. Median OS of pts receiving frontline vs. ≥ 2nd line therapy was 4.2 vs. 1.4 mo (P<0.001). Median OS in pts requiring 0-1 vs. 2-3 LSTs was 4.1 vs. 0.4 mo (P<0.001). OS was not different by age, co-morbidity burden nor therapy intensity. In a multivariate analysis that included SOFA scores, only adverse CG (OR 0.35, P = 0.028), and need for intubation with mechanical ventilation (IMV; OR 0.19, P = 0.009) were associated with increased odds of in-hospital mortality. **Conclusions:** A substantial portion of pts with AML survive their ICU admission with sufficient functionality to return home and receive subsequent therapy. In contrast to general medical populations, age, co-morbidities, and SOFA scores were not independently predictive of in-hospital mortality. Disease CG risk and the need for IMV were the strongest predictors of ICU survival. This suggests that many pts with AML can benefit from ICU care. Research Sponsor: U.S. National Institutes of Health.

	N=145 N (%)/median [range]
Comorbidities	
HTN	75 (52)
DM	34 (23)
Other cancer	31 (22)
Arrhythmia	28 (19)
CAD	19 (13)
COPD/asthma	19 (13)
CHF	14 (9)
Stroke/TIA/PAD	13 (9)
Admission SOFA score	7 [0-18]
Vasopressor(s) required	64 (44)
Max 1	36 (56)
Max 2	13 (20)
Max 3+	15 (23)
Max respiratory support	
IMV	45 (31)
NIPPV	17 (12)
High flow O_2 (>6 L/min)	13 (9)
None	70 (48)
Dialysis required	21 (15)
Max no. of LSTs required	
0	48 (33)
1	55 (38)
2+	42 (29)
Length of ICU admission (days)	3 [1-60]
Disposition	
Death	57 (39)
Hospice	3 (2)
LTAC or SNF	13 (9)
Home	69 (48)
Other	3 (2)
Received additional AML therapy post ICU admission	64 (75)
Alive	
30d post ICU admission	92 (63.5)
90d post ICU admission	53 (36.6)
1-year post ICU admission	24 (16.6)

7026 **Poster Session**

Preliminary results of V-FAST, a phase 1b master trial to investigate CPX-351 combined with targeted agents in newly diagnosed AML. *First Author: Vinod Pullarkat, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: CPX-351 (US: Vyxeos; EU: Vyxeos Liposomal), a dual-drug liposomal encapsulation of daunorubicin and cytarabine in a synergistic 1:5 molar drug ratio, is approved by the US FDA and EMA for adults with newly diagnosed t-AML or AML with myelodysplasia-related changes. Preclinical data suggest CPX-351 may exert synergistic activity when combined with agents such as the BCL-2 inhibitor venetoclax (VEN) or FLT3 inhibitor midostaurin (MIDO). **Methods:** V-FAST (Vyxeos – First Phase Assessment With Targeted Agents) is an open-label, multicenter, phase 1b master trial (NCT04075747) to evaluate safety and establish the recommended phase 2 dose (RP2D) of CPX-351 combined with targeted agents in patients (pts) aged 18-75 y with untreated AML who are fit for intensive chemotherapy. The study includes a dose-exploration phase (3+3 design) and subsequent expansion phase. Pts received CPX-351 (dose level 1 for first induction [DL1]: 100 units/m^2 on Days 1, 3, and 5) plus VEN (Arm A; DL1: 400 mg on Days 1-14), MIDO (Arm B; DL1: 50 mg BID on Days 8-21), or the IDH2 inhibitor enasidenib ([ENA] Arm C; DL1: 100 mg on Days 8-28) based on mutation testing. **Results:** Among 21 pts with available data enrolled by 11/06/20 (24 pts enrolled total; data cut-off: 01/19/21), the median age was 54 y (range: 35, 69). In Arm A (n = 17), 11 (65%) pts had *de novo* AML, 5 (29%) had an antecedent hematologic disorder (2 [12%] had myelofibrosis), and 2 (12%) had t-AML; 12 (71%) had adverse-risk AML; and 6 (35%) had mutated *TP53*. In Arms B (n = 3) and C (n = 1), all pts had intermediate-risk *de novo* AML. DL1 was the RP2D in Arms A and B; the RP2D in Arm C is still under investigation. In Arm A, 1/6 pts in the dose-exploration phase had 2 dose-limiting toxicities (DLTs) of grade 4 neutropenia and thrombocytopenia that extended beyond 49 days; no DLTs have occurred for Arms B and C. The combinations exhibited manageable safety profiles (Table). Of pts with available response data, complete remission (CR) or CR with incomplete platelet or neutrophil recovery was achieved by 6/14 (43%) pts in Arm A, including 4 (29%) with CR. All pts in Arms B and C achieved CR. **Conclusions:** These preliminary results suggest CPX-351 can be combined with VEN and MIDO with manageable toxicities in newly diagnosed AML pts, with DL1 determined to be the RP2D. The study is ongoing and actively enrolling pts; updated results will be presented at the meeting. Clinical trial information: NCT04075747. Research Sponsor: Jazz Pharmaceuticals.

	Arm A	Arm B	Arm C
n (%)	CPX-351 + VEN (n = 17)	CPX-351 + MIDO(n = 3)	CPX-351 + ENA (n = 1)
Any TEAE	17 (100)	3 (100)	1 (100) 0
Thrombocytopenia	11 (65)	2 (67)	1 (100)
Febrile neutropenia	10 (59)	2 (67)	1 (100)
Nausea	9 (53)	2 (67)	0
Neutropenia	9 (53)	2 (67)	0
Constipation	9 (53)	1 (33)	0
Headache	7 (41)	3 (100)	
Any grade ≥3 TEAE			
Thrombocytopenia	15 (88)	3 (100)	1 (100)
Febrile neutropenia	11 (65)	2 (67)	0
Neutropenia	10 (59)	2 (67)	1 (100)
Early mortality	9 (53)	2 (67)	0
Day 30	0	0	0
Day 60	2 (12)	0	0

TEAE, treatment-emergent adverse event.
TEAEs in ≥40% of pts overall.

7027 **Poster Session**

Cellworks Omics Biology Model (CBM) to predict therapy response and identify biomarkers for all-*trans* retinoic acid (ATRA) benefit as addition to induction chemotherapy in adults with acute myeloid leukemia (AML). *First Author: Scott C. Howard, University of Tennessee Health Sciences Center, Memphis, TN*

Background: ATRA combined with arsenic trioxide revolutionized the treatment of APL. Based on promising *in vitro* data, several clinical trials evaluated ATRA combinations in non-APL AML, in which some patients seemed to benefit from the addition. Thus, predicting response *a priori* is imperative to determine the optimal treatment for each patient. The CBM was used to evaluate the impact of initial therapy with ATRA combined with cytarabine, etoposide, idarubicin (ATRA-CEI) to assess the biomarkers responsible for response in adults with AML. **Methods:** AML patients participating in clinical trial NCT00151242 had their leukemia sequenced as part of the trial, and genomic profiles were used for computational modeling by the CBM, which uses curated data about genomic aberrations from PubMed as input to generate disease-specific protein network maps and predict drug responses. Disease biomarkers unique to each patient were identified using biosimulation. Digital drug simulations were conducted by measuring the effect of ATRA-CEI on a composite cell growth score of cell proliferation, apoptosis and other hallmarks of cancer. ATRA-CEI was mapped to the patient genome along with a mechanism of action and validated based on the genomic profile and its biological consequences. **Results:** Of 171 patients treated with ATRA-CEI, 107 (63%) responded (R) and 64 did not (NR). A subset of 18 patients with favorable genomic features were found to be NR and their non-response was correctly predicted by CBM in all 18 cases. Mutations of *DNMT3A, EZH2, ASXL, FLT-3*, and GART amplification emerged as novel biomarkers of ATRA-CEI failure (only 37 of 107 responders (35%) with these findings, compared to 70 of 107 responders (65%) without these findings (p = 0.0027)). *DNMT3A, EZH2, ASXL1* loss of function mutations activate *FABP5*, a key mechanism of ATRA resistance, and also activate *ABCC1* (PgP), which reduces the efficacy of etoposide and idarubicin by upregulating *MDR1*. In general, monosomy 7 is expected to confer ATRA resistance due to the presence of *EZH2* and *KMT2E* gene deletions. Indeed, 18 of 32 patients with monosomy 7 did not respond. However, the 14 who responded had co-occurrence of deletions involving *IGFBP3, PMS2, HUS1, CDK5, XRCC2/4, AKR1B10,* and others that overcame ATRA resistance associated with monosomy 7 and were identified by CBM. Use of CBM helps avoid unnecessary use of ATRA in patients unlikely to respond (19% of cases) thus reducing toxicity and cost without changing efficacy, and also identifies those likely to respond, even when they have monosomy 7, where non-response is the norm. **Conclusions:** ATRA benefits a subset of patients with non-APL AML. CBM predicted response using computational modeling of all genetic alternations, which explains its success versus traditional one-gene-one-drug approaches. Research Sponsor: None.

7028 **Poster Session**

Clinical utility of whole genome sequencing in hematological neoplasms. *First Author: Jesus Gutierrez-Abril, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Hematological neoplasms are often characterized by acute onset and rapid disease progression. Cytogenetics, FISH, SNP arrays, targeted DNA and RNA sequencing are performed to inform diagnosis, risk stratification and guide treatment decisions. Whole genome sequencing (WGS) offers the opportunity to comprehensively characterize all putative biomarkers in a single assay. However, a limitation in current WGS implementation is the requirement for a germline sample, as sources of control tissue are frequently contaminated with leukemic cells resulting in false negative calls. **Methods:** To evaluate the clinical utility and feasibility of WGS in the diagnostic work up of leukemias, we analyzed 57 B-cell acute lymphoblastic leukemia (B-ALL) from the UKALL14 trial (NCT01085617) with no informative biomarkers at diagnosis. WGS analysis was performed on the leukemic sample and a matching control sample (with minimal residual disease level of <1%). Using this dataset, we trained the development of an unmatched (uWGS) analytical workflow (Isabl) for a tumor only WGS study. This workflow was validated across 20 hematologic neoplasms (12 B-ALL, 6 AML and 2 T-ALL). **Results:** Among the 57 cases, 5 failed QC owing to low tumor content (<25%). Of the remaining 52, putative biomarkers of clinical relevance were identified by WGS in 69% (36/52). These included delineation of aberrant karyotypes where conventional chromosome banding failed (4/52), the detection of newly described fusion genes (such as *IGH-DUX4* and *EP300-ZNF384* in 21/52) and recurrent gene mutations (i.e. *PAX5* P80R, *ZEB2* H1038R in 11/52). uWGS workflow in our training dataset captured 86% of biomarkers identified in the matched analysis (3/3 ploidy, 21/22 fusion and 7/11 coding). Concordance between the matched and uWGS workflow for arm-level and focal copy number alterations (CNAs), structural variants (SVs) and annotated hotspot mutations were 94%, 84%, 83% and 100% respectively. Independent validation of the uWGS workflow across 20 myeloid and lymphoid neoplasms, recapitulated all clinically reported biomarkers (14/15 CNAs, 16/16 SVs) as well as captured two novel findings not previously detected in two B-ALL patients, to include a focal deletion in *BTG1* and the fusion gene *P2RY8-CRLF2*, as well as a *NOTCH1* translocation in T-ALL. **Conclusions:** Our findings demonstrate that comprehensive WGS allows for the detection of the same biomarkers as a range of clinical assays using a single test, as well as the opportunity to discover novel clinical and research findings to support future correlative research and biomarker development. Additionally, we developed and validated an uWGS workflow that allows WGS analysis of hematopoietic neoplasms at diagnosis, enabling detection and reporting of clinically relevant biomarkers. Research Sponsor: CRUK, Other Foundation.

7029 **Poster Session**

Retrospective analysis of a novel molecular genetic risk score, "MRplus", in BCR-ABL1 negative pediatric B-ALL: A single-center experience. *First Author: Sanjeev Kumar Gupta, Dr BRAIRCH, All India Institute of Medical Sciences, New Delhi, New Delhi, India*

Background: Currently, the molecular risk scoring is variably used in the management algorithms of B-ALL across various clinical cohorts. Unlike AML, the usage of molecular genetic abnormalities in the risk-stratification of B-ALL is limited and a consensus is yet to be reached. We have retrospectively analyzed the utility of molecular genetic risk criteria, previously described by Moorman et al. (2014), and Stanulla et al. (2018), in our cohort and hereby propose a novel molecular risk score, "MRplus", obtained by combining both criteria, as a useful way to improve the risk-stratification of BCR-ABL1 negative pediatric B-ALL. **Methods:** In this retrospective observational study, the genomic DNA of untreated BCR-ABL1 negative pediatric B-ALL cases was analyzed at baseline for copy number alterations of IKZF1, PAX5, CDKN2A/B, BTG1, RB1, ETV6, EBF1, ERG, pseudoautosomal region (PAR) genes– (CRLF2, CSF2RA, IL3RA), using multiplex ligation-dependent probe amplification (MLPA)- P335, P202 and P327 kits (MRC Holland). The cases were assigned a score- 0 for low and 1 for high genetic-risk as per the criteria by Moorman et al., and another score as per the criteria by Stanulla et al., 1 for IKZF1-plus cases and 0 for other cases. The final "MRplus" risk-score of 0 (low), 1 (intermediate) or 2 (high) was given by adding both these scores. All patients were treated using Indian Childhood Collaborative Leukemia Group protocol (ICICLE). The post-induction remission status, overall survival (OS) and event free survival (EFS) was noted for all patients. **Results:** Out of 320 cases with median age of 6 years (1-18 years), 141 (44.1%) cases had high genetic-risk (score 1) as per the Moorman's criteria. Thirty-two (10%) cases fulfilled the criteria of IKZF1plus (score 1) as per the criteria of Stanulla et al. The final "MRplus" score of 0, 1 and 2 was obtained in 179 (55.9%), 109 (34.1%) and 32 (10%) cases respectively. Out of these, 284 received treatment including 160, 101, and 23 cases with "MRplus" score 0, 1, and 2 respectively. The follow up period was upto 80 months with a median of 34.6 months. The post-induction remission rate was 90.6%, 78.2%, 73.9% ($p = 0.008$); 4-year OS 68%, 48%, 27% ($p < 0.001$); and 4-year EFS 57%, 36%, 19% ($p < 0.001$) in cases with "MRplus" score 0,1, and 2 respectively. **Conclusions:** The proposed novel "MRplus" scoring at baseline could identify three distinct risk- groups-low, intermediate and high, in BCR-ABL1 negative pediatric B-ALL. This may help in better identification of patients for alternative treatment approaches and also triage patients for further detailed genomic analysis for disease biology; with particular emphasis on those with intermediate and high "MRplus" score. Acknowledgement**:** Institute Research Grants [A-193 (2013-15), A-413 (2016-18) and A-600 (2018-20)] from All India Institute of Medical Sciences (AIIMS), New Delhi, INDIA. Research Sponsor: All India Institute of Medical Sciences (AIIMS), New Delhi, INDIA.

7030 **Poster Session**

TP53/NPM1-mutated acute myeloid leukemia as a molecularly distinct disease entity. *First Author: Frank J Scarpa, NeoGenomics Laboratories, Aliso Viejo, CA*

Background: TP53-mutated acute myeloid leukemia (AML) is a distinct disease entity associated with a dismal prognosis. This disease group is distinguishable by its low frequency of SNVs, unremarkable transcriptional signatures, and lower leukocyte and myeloblast counts compared to TP53 wildtype disease. Response to gold-standard hypomethylating agents is typically transient. NPM1 mutations in this disease subset are rare despite the fact that NPM1c has been shown to negatively regulate the tumor suppressive functions of p53.**Methods:** Bone marrow, peripheral blood, or FFPE tissue samples from 10,118 patients with suspected myeloid disease were sequenced using a dual DNA/RNA 297 gene myeloid panel. Results were validated in a separate independent dataset using a 54 gene TruSight myeloid panel (N = 2463). FISH/cytogenetic data was analyzed across myeloid disease. Patients with confirmed AML (n = 460) were included in the NGS portion of this study. Statistics were performed using Fisher's exact test for categorical variables and two-tailed T-test for continuous variables. **Results:** All TP53-mutated myeloid disease (n = 1282 / 10,118) was associated with fewer co-mutations except DNMT3A (13.4%; n = 172), and complex cytogenetics (36.4%; n = 134/381). TP53+/NPM1+ status across all myeloid disease was not associated with a complex karyotype (7.6% vs 38.5%; 1/13 vs. 133/368, p = 0.02). Among AML patients, NPM1+/TP53+ patients (n = 18) were more co-mutated with DNMT3A (33.3% vs. 10.3%, P = 0.01), FLT3 (33.33% vs. 2.5%, $P < 0.0001$), IDH1 (27.8% vs. 4.4%, P = 0.002), IDH2 (22.2% vs. 6.4%, P = 0.03); and PTPN11 (22.2% vs. 2.5%, P = 0.003) when compared to TP53+/NPM1- patients. NPM1+/TP53+ AML had more mutations in recurrently mutated genes (4.5 vs 2.1; $P < 0.0001$) than TP53+/NPM1- AML. **Conclusions:** TP53+/NPM1+ AML harbors molecular signatures which clearly distinguish it from ordinary TP53-mutated AML, and is more reflective of *de novo* and NPM1+ AML. Further clinical outcome studies are needed to determine the therapeutic and prognostic implications of this subset, and whether other TP53-mutated patients can be better risk stratified. Research Sponsor: None.

	TP53+/NPM1-				TP53+/NPM1+				TP53-/ NPM1+			
Cohort:	297 panel	(n = 203)	TruSight	(n = 215)	297 panel	(n = 18)	TruSight	(n = 14)	297 panel	(n = 239)	TruSight	(n = 272)
Prevalence:												
DNMT3A	10.3% (21)	-	12.6% (27)	-	33.33% (6)	P < 0.01	57.1% (8)	P = 0.0002	47.3% (113)	P = 0.0001	46.3% (126)	P = 0.0001
FLT3	2.5% (5)	-	1.4% (3)	-	33.33% (6)	P = 0.0001	21.4% (3)	P = 0.003	54.4% (130)	P = 0.0001	29.0% (79)	P = 0.0001
IDH1	4.4% (9)	-	2.3% (5)	-	27.8% (5)	P = 0.002	14.3% (2)	P = 0.06	14.6% (35)	P = 0.0004	14.0% (38)	P = 0.0001
IDH2	6.4% (13)	-	4.2% (9)	-	22.2% (4)	P = 0.03	7.1% (1)	P = 0.05	25.1% (60)	P = 0.0001	21.0% (57)	P = 0.0001
PTPN11	2.5% (5)	-	1.4% (3)	-	22.2% (4)	P = 0.003	14.3% (2)	P = 0.06	14.6% (35)	P = 0.0001	13.6% (37)	P = 0.0001
MUTATION COUNT	2 - 2.6	-	2-2.1	-	4.6 - 5	P = 0.0001	4.5 – 5	P = 0.0001	4 – 4.3	P = 0.0001	3 – 3.1	P = 0.0001

7031 **Poster Session**

Predictors of clinical trial enrollment and impact on outcome in children and adolescents with acute lymphoblastic leukemia: A population based study. *First Author: Paul James Gibson, McMaster Children's Hospital, Hamilton, ON, Canada*

Background: Outcomes in pediatric acute lymphoblastic leukemia (ALL) have shown remarkable improvements in large part due to sequential clinical trials. Concerns however persist around whether access to clinical trials is equitable. It is also unclear whether patient outcomes are improved simply by enrolling on a clinical trial. Our objective was to therefore determine which patient and disease-related factors are associated with enrollment, and whether enrollment was associated with clinical outcomes among children and adolescents with ALL in a single-payer health system in Ontario, Canada. **Methods:** We included all Ontario patients diagnosed with ALL between 0-18 years of age from 2002-2012 treated at a pediatric center, identified through a provincial pediatric cancer registry. Clinical trial availability was determined by whether each patient's primary institution had an open frontline trial for which the patient was eligible at the time of their diagnosis, considering individual disease characteristics such as lineage, central nervous system (CNS) status and risk group. Demographic, disease, trial enrolment, and outcome data were obtained through chart abstraction. Logistic regression models determined factors associated with trial enrolment, while Cox proportional hazard models determined factors associated with event-free and overall survival (EFS, OS). **Results:** Of 858 patients, 693 (81%) were eligible for an open clinical trial at their time of diagnosis. 476 (69%) enrolled on a trial. In adjusted analyses, age > 15 years (odds ratio 0.4 vs. age 5-9, 95th confidence interval (95CI) 0.2-0.8; p = 0.01) and CNS3 disease (OR 0.38 vs. CNS1, 95CI 0.17-0.83; p = 0.01) were significantly associated with decreased likelihood of enrolment, while sex and neighborhood income quintile were not associated with enrolment. Adjusted for disease and demographic factors, clinical trial enrolment was not significantly associated with either EFS (hazard ratio (HR) 1.1, 95CI 0.7-1.7; p = 0.83) or OS (HR 1.3, 95CI 0.7-2.5; p = 0.44). **Conclusions:** The majority of patients with ALL eligible for available clinical trials at their time of diagnosis were enrolled. While no disparities in enrolment by income status were noted, adolescents were substantially less likely to participate in trials even within pediatric centers. Studies of mechanisms underlying this disparity are warranted in order to design and implement effective interventions targeting increased enrolment rates in this patient population. Our results however also suggest that clinical trial enrolment on its own is not associated with improved outcomes in the context of a single payer health system. Research Sponsor: C17 Research Network.

7032 **Poster Session**

Distress in a pandemic: The association of the coronavirus disease-2019 (COVID-19) pandemic with distress and quality of life in hematopoietic stem cell transplantation (HSCT). *First Author: Hermioni L. Amonoo, Dana–Farber Cancer Institute, Boston, MA*

Background: The global COVID-19 pandemic has drastically disrupted cancer care, potentially exacerbating patients' distress levels. Patients with hematologic malignancies undergoing HSCT may be especially vulnerable to this pandemic stress given their well-documented heightened psychological distress and impaired quality of life (QOL). However, the association of the COVID-19 pandemic with distress and QOL is not well understood. **Methods:** We conducted a cross-sectional analysis of data from 205 patients with hematologic malignancies undergoing HSCT who were enrolled in a multi-site, randomized supportive care trial. We compared baseline pre-HSCT distress (depression, anxiety, and posttraumatic stress disorder [PTSD] symptoms) and QOL between participants enrolled pre-COVID-19 (i.e., 03/2019-01/2020) and during the COVID-19 pandemic (i.e., 03/2020-01/2021). We used the Hospital Anxiety & Depression Scale, PTSD Checklist, and Functional Assessment of Cancer Therapy-Bone Marrow Transplant to assess symptoms of depression, anxiety, and PTSD, as well as QOL respectively. We used regression models adjusting for age, gender, race, relationship status, and cancer diagnosis to examine the relationship between the period of enrollment and patient-reported distress and QOL. **Results:** Prior to COVID-19, 124 participants enrolled, and 81 participants enrolled during the COVID-19 pandemic. The two cohorts had similar baseline demographic and disease risk factors. Most participants were non-Hispanic (n = 185; 90.2%), White (n = 138; 86.3%), and female (n = 131; 64.5%) with a mean (SD) age of 54.9 (11.7) years. In multivariate regression models, enrollment during COVID-19 was not associated with pre-HSCT depression (B = 0.004; 95% CI, -0.02 to 0.03; p = 0.73), anxiety (B = 0.008; 95% CI, -0.01 to 0.03; p = 0.44), PTSD (B = 0.004; 95% CI, -0.004 to 0.01; p = 0.35) symptoms or QOL (B = -0.003; 95% CI, -0.02 to 0.01; p = 0.68). **Conclusions:** Contrary to the widespread notion that the COVID-19 pandemic has worsened distress in patients with cancer, we found no differences in pre-HSCT distress or QOL in patients with hematologic malignancies undergoing HSCT prior to or during the COVID-19 pandemic. Our findings highlight the need to comprehensively explore the multifactorial causes (e.g., illness experience, treatment burden) of distress and QOL deficits in HSCT recipients irrespective of the COVID-19 pandemic. Research Sponsor: U.S. National Institutes of Health, U.S. National Institutes of Health.

7033 **Poster Session**

Outcomes with COVID-19 in hematopoietic stem cell transplant and cellular therapy patients. *First Author: Muhammad Umair Mushtaq, Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS*

Background: The Coronavirus Disease 2019 (COVID-19) has caused over 25 million infections in the US with over 0.4 million deaths. Hematogenic stem cell transplant (HCT) or cellular therapy (CT) recipients have a high risk of mortality with COVID-19 due to profound immune dysregulation. We aimed to assess the outcomes with COVID-19 in HCT/CT recipients. **Methods:** A single-center prospective study was conducted, including all (n=40) adult HCT/CT patients who were diagnosed with COVID-19 at the University of Kansas from Apr 2020 to Jan 2021. Baseline and disease-related characteristics were ascertained from medical records. Data were analyzed using SPSS version 21 (SPSS Inc, Chicago, IL). Bivariate analyses, using chi-square and t-test, and logistic regression analyses were conducted. **Results:** The study included 40 COVID-19 patients (72.5% Oct 2020-Jan 2021), including allogeneic HCT (n=25), autologous HCT (n=13) and CAR-T CT (n=2) with median time since HCT/CT of 12.4 (1-201.9), 37.2 (0.4-118.7), and 3.8 (2.8-4.8) months. Seventy percent were Caucasians and 17.5 were Hispanics. Primary hematologic malignancy was myeloid (37.5%), lymphoid (35%) or plasma cell disorder (27.5%). Myeloablative conditioning was performed in 65% of patients. Donors were autologous (37.5%), matched sibling (17.5%), matched unrelated (22.5%) and haploidentical (22.5%). COVID-19 was mild (42.5%), moderate (42.5%) or severe (15%). Clinical findings included pneumonia (62.5%), hypoxia (25%) and ICU admission (17.5%) while therapies included remdesivir (47.5%), convalescent plasma (40%), dexamethasone (25%) and monoclonal antibodies (17.5%). Concurrent cancer treatment, other infections and active GVHD were reported in 25% (all myeloma), 20% and 32.5% of patients. After a median follow-up of 74 days (7-269), the mortality rate was 12.5% in all patients and 20% in allo-HCT patients. Significant predictors of COVID-19 severity included allogeneic HCT, concurrent immune suppression and elevated inflammatory markers. (Table). **Conclusions:** Hematopoietic stem cell transplant recipients have an increased risk of mortality with COVID-19. Our findings confirm the need for vaccination prioritization, close monitoring, and aggressive treatment in HCT/CT patients. Research Sponsor: None.

	Total (n=40)	Mild COVID (n=17)	Moderate-severe COVID (n=23)	P value	Deaths (n=5)
Age yrs, median (range)	58 (24-77)	55.5 (24-72)	60 (25-77)	0.273	62 (25-72)
Males, n (%)	27 (67.5)	11 (65)	16 (70)	0.746	4 (80)
Months since HCT/CT, mean (SD)	35 (41)	44 (32)	28 (32)	0.279	42 (47)
Allogeneic HCT, n (%)	25 (62.5)	7 (41)	18 (78)	0.017	5 (100)
Autologous HCT/CAR-T, n (%)	15 (37.5)	10 (59)	5 (22)	0.017	0
Concurrent immune suppression, n (%)	19 (47.5)	4 (23.5)	15 (65)	0.009	5 (100)
CRP, mean (SD)	0.1	0. 1 (0.2)	5.7 (5.2)	<0.001	7 (5.3)
Ferritin, mean (SD)	1535 (2109)	129 (377)	2275 (2274)	0.001	2451 (1739)
Neutrophil-lymphocyte ratio, mean (SD)	15 (24)	5.5 (6.3)	19.7 (28)	0.041	42.5 (45.6)

7034 **Poster Session**

Characterizing advance care planning, palliative care utilization, and location of end-of-life for adult allogeneic hematopoietic stem cell transplant recipients. *First Author: Stephanie Hoffman, University of Michigan Rogel Cancer Center, Ann Arbor, MI*

Background: The impacts of advance care planning (ACP) on end-of-life (EOL) outcomes in allogeneic hematopoietic stem cell transplant (allo HCT) recipients are not well known. ACP includes advance directive (AD) completion, and palliative care (PC) consultation. Using these two components, we aimed to explore the current state of ACP and its impact on EOL outcomes in allo HCT recipients to provide the groundwork for future prospective studies. **Methods:** We performed a retrospective study of deceased adult patients who underwent allo HCT between December 2015-December 2019. We summarized patient characteristics, the rate of AD completion, PC consultation, and location of end-of-life (EOL). Univariate and multivariate analyses were performed to evaluate patient characteristics that may be associated with AD completion, PC consultation and assess the impact of these two factors on location of EOL. **Results:** See Table for summary of patient characteristics. Of the 125 patients included, we found that 66% (n = 82) completed ADs. All patients with ADs completed them prior to undergoing transplant and never modified them. The majority of patients (84%) with an AD expressed the desire to avoid life-sustaining treatment in the event of terminal illness or irreversible coma. PC was consulted for 46% (n = 58) of patients within 6 months prior to time of death (TOD). Regarding location of EOL, 30% of all patients died in the hospital (non-ICU), 20% in the ICU, 38% at home with hospice, and 10% in a hospice facility. Patients with ADs appeared more likely to die outside of the hospital compared to those without (53% vs. 44%, p = 0.4506). By multivariate analysis, there were no significant patient characteristics associated with the presence of an AD or PC consultation. After adjusting for age and comorbidity index, we found that patients with an AD were significantly more likely to die outside of the ICU (OR 3.0, 95% CI 1.2-7.5, p = 0.02), an effect that was further amplified in patients who both had an AD and received PC consultation at any point (n = 30, p = 0.0077). **Conclusions:** Our findings highlight the importance of ACP for EOL outcomes in the allo HCT population. While the rate of AD completion in our study population is higher than that of prior studies, future prospective studies aimed to improve the rate of ACP are needed. Research Sponsor: None.

Patient characteristics	Total patients (n = 125)
Age (median ± standard deviation, years)	60.7 ± 9.8
Female	51 (41%)
Non-Hispanic, White	113 (90%)
English as preferred language	122 (98%)
Comorbidity index (high; intermediate)	62%; 27%
Primary disease (acute leukemia; myelodysplastic syndrome; other	63%; 22%; 14%
Disease relapse after transplant	74 (59%)
Acute GVHD, any grade	70 (56%)
Chronic GVHD, any severity	26 (21%)

7035 **Poster Session**

Early results of phase 1 study of JSP191, an anti-CD117 monoclonal antibody, with non-myeloablative conditioning in older adults with MRD-positive MDS/AML undergoing allogeneic hematopoietic cell transplantation. *First Author: Lori S. Muffly, Stanford University, Stanford, CA*

Background: Myeloablative allogeneic hematopoietic cell transplantation (AHCT) is potentially curative for myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), but toxicities of conditioning limit its use in older or frail patients. Non-myeloablative (NMA) conditioning achieves better tolerability, at the expense of higher rates of relapse. We have developed a first-in-class monoclonal antibody (mAb), JSP191, which inhibits stem cell factor binding to CD117 (c-Kit), thereby depleting normal and MDS/AML disease-initiating hematopoietic stem cells (HSC). In pre-clinical models, anti-CD117 mAbs potently synergize with low dose total body radiation (TBI) to deplete HSC and facilitate donor cell engraftment. We reasoned that adding JSP191 to a standard NMA conditioning of 2 Gy TBI and fludarabine (Flu) would be safe and result in depletion of measurable residual disease (MRD) in older adults with high-risk MDS/AML entering AHCT. **Methods:** We report on the first 6 enrolled subjects in our Phase 1 trial (NCT#04429191) of JSP191/TBI/Flu as AHCT conditioning in MDS/AML patients, ≥ 60 years, with MRD detected by cytogenetics (cyto), difference from normal flow cytometry (flow), and/or next-generation sequencing (NGS). Primary endpoints are safety and tolerability of JSP191/TBI/Flu and JSP191 pharmacokinetics. Secondary endpoints include engraftment, donor chimerism, MRD clearance, GVHD, NRM, EFS, and OS at 1 year. JSP191 at 0.6 mg/kg was administered intravenously; serum concentration of JSP191 was used to confirm timing to begin Flu at 30 mg/m^2/day x 3 days [Transplant Day (TD)-4, -3, -2] and TBI 2 Gy on TD0. Peripheral blood grafts from HLA-matched related or unrelated donors were administered on TD0 (10-13 days after JSP191). GVHD prophylaxis was tacrolimus, sirolimus, and mycophenolate mofetil. **Results:** All subjects are still on trial, and there have been no infusion toxicities and no JSP191-related serious adverse events. All subjects engrafted with neutrophil recovery TD+19 to TD+26, and showed ≥94% donor myeloid chimerism in the blood at TD+28. All 3 evaluable subjects with TD+90 follow up showed complete donor (≥95%) total and myeloid chimerism and MRD elimination (Table). **Conclusions:** These early results are the first to demonstrate that JSP191/TBI/Flu is safe, well-tolerated, and capable of clearing MDS/AML MRD in older adults undergoing NMA AHCT. Clinical trial information: NCT04429191. Research Sponsor: Jasper Therapeutics.

Age/Sex	Dx	Prior Tx	MRD at Screening (NGS VAF or Flow %)	Latest Follow up (TD)	MRD at Latest Follow up
74F	AML	Ven/Aza	DNMT3A (4.7)RUNX1 (1.7)PTPN11 (0.7)	+90	NEG
70M	MDS	Epo	ASXL1 (0.3)PTPN11 (0.4)Del(20q)	+90	NEG
68M	MDS	Aza	DNMT3A (25.2)SRSF2 (0.3)Flow (3.1)	+90	NEG
74M	MDS	None	Complex CytoFlow 0.7	+56	NEG
65M	AML	7+3+midoVen/Aza	ASXL1 (1.5)KMT2A dup	+56	KMT2A dupRUNX1 (0.28)
69M	AML	7+3+GO5+2	SRSF2 (14.6)	+28	SRSF2 (0.69)

7036 **Poster Session**

Phase 1 trial of anti-CD22 recombinant immunotoxin moxetumomab pasudotox combined with rituximab for relapsed/refractory hairy cell leukemia. *First Author: Robert J. Kreitman, Laboratory of Molecular Biology, NCI, NIH, Bethesda, MD*

Background: Anti-CD22 recombinant immunotoxin moxetumomab pasudotox (Moxe) is FDA-approved for hairy cell leukemia (HCL) patients who have received at least two prior systemic therapies including a purine nucleoside analog. In phase 3 testing the complete remission (CR) rate was 41%, and response was higher in patients with lower tumor burden and lower titers of antidrug antibodies (ADA). Phase 1 testing indicated that most CRs were without minimal residual disease (MRD) and eradication of MRD was associated with prolonged CR duration. Monoclonal antibody (Mab) rituximab binds to CD20 on HCL cells and induces apoptosis or immune-mediated killing, but as a single-agent achieved only 13% CRs in relapsed HCL requiring therapy. In a phase 1 trial to determine safety, rituximab was combined with Moxe, with the goal to help reduce tumor burden and to prevent or delay ADA by killing normal B-cells. **Methods:** To allow rituximab sufficient time to accomplish both goals, it was infused 3 days before day 1 of cycle 1 at 375 mg/m^2, and Moxe was given by 30-minute infusion on days 1, 3 and 5. On repeat cycles of Moxe days 1, 3 and 5, rituximab was given on day 1. Cycles were generally spaced 4 weeks apart. Moxe was begun at a lower dose, 30 rather than the 40 mcg/kg dose used in phase 3 in case the rituximab would increase its toxicity. Bone marrow aspirate flow cytometry, which can detect 0.002% HCL cells, was the most sensitive test used for MRD detection, much more sensitive than BRAF V600E digital droplet PCR (ddPCR) or bone marrow biopsy immunohistochemistry (IHC). Patients could receive 4 cycles past MRD-free CR, but not more than 8 cycles. **Results:** Three patients received Moxe at 30 mcg/Kg/dose and 6 received 40 mcg/Kg/dose, all without dose limiting toxicity (DLT). There was no evidence of hemolytic uremic syndrome or capillary leak syndrome. To prevent intravascular hypovolemia due to expected third spacing, patients were encouraged to drink one cup per hour of water or other fluid from days 1 to 8 and take dexamethasone 4 mg orally if headache or nausea prevented good oral hydration. Of the 9 patients, 7 (78%) achieved CR after 2 (n = 6) or 3 (n = 1) cycles, and achieved MRD-free CR after 2 (n = 3), 4 (n = 3) or 6 (n = 1) cycles. No patients became infected with COVID-19. **Conclusions:** This phase 1 trial met its primary endpoint of determining whether rituximab could be safely combined with Moxe and will enroll 4 additional patients to further access clinical activity. Further testing will determine whether addition of a CD20 Mab to Moxe significantly improves clinical outcome compared to Moxe alone, particularly long-term MRD-free CR rate. Clinical trial information: NCT03805932. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

7037 **Poster Session**

The effect of body mass index on efficacy and safety of bosutinib or imatinib in patients with newly diagnosed chronic myeloid leukemia.

First Author: Tim H. Brümmendorf, Universitätsklinikum RWTH Aachen, Aachen, Germany

Background: Bosutinib (BOS) is approved for the treatment (Tx) of Philadelphia chromosome–positive (Ph+) chronic myeloid leukemia (CML) resistant/intolerant to prior therapy and newly diagnosed Ph+ chronic phase (CP) CML. Body mass index (BMI) was shown to influence Tx response with front-line dasatinib vs imatinib (IMA). We report the efficacy and safety of BOS and IMA by BMI in patients (pts) with newly diagnosed CP CML. **Methods:** In the open-label BFORE trial, pts were randomized to receive 400 mg once daily BOS or IMA. Outcomes were assessed according to baseline BMI ≥25 or = 25 kg/m^2. This post hoc analysis was based on the final 5-y analysis (database lock: June 12, 2020). **Results:** In the BOS and IMA arms, respectively, 149 (56.4%) vs 115 (43.6%) pts and 145 (54.3%) vs 122 (45.7%) pts had BMI ≥25 vs = 25. In both the BOS and IMA arms, median Tx duration and time on study was 55 mo for pts with BMI ≥25 or = 25; respective median dose intensity was 394 vs 393 mg/d and 400 vs 400 mg/d. Molecular response (MR) rates are shown in the table. Cumulative incidence of major MR was similar in pts with ≥25 vs = 25 receiving BOS (HR 0.99; 95% CI 0.74−1.31) or IMA (HR 1.09; 95% CI 0.81−1.47). Event-free survival (EFS) and overall survival (OS) rates at 60 mo are shown in the table. Most common reasons for Tx discontinuation were adverse events (AEs) (BOS 28.2 vs 20.0%; IMA 13.3 vs 10.7%) and lack of efficacy (BOS 5.4 vs 5.2%; IMA 16.1 vs 19.8%). In pts with BMI ≥25 vs = 25, dose reductions and interruptions due to Tx-emergent AEs (TEAEs) occurred in 43.6 % vs 46.2% and 66.4% vs 69.7% of pts with BOS and 24.5% vs 24.6% and 40.6% vs 50.8% with IMA. Any grade TEAEs in ≥30% of pts with BMI ≥25 vs = 25 were diarrhea (73.8 vs 73.1%), nausea (40.9 vs 31.9%), thrombocytopenia (30.9 vs 41.2%), increased alanine (37.6 vs 28.6%) and aspartate aminotransferase (30.2 vs 20.2%) with BOS and diarrhea (49.0 vs 29.5%), nausea (46.2 vs 37.7%), muscle spasms (33.6 vs 26.2%), neutropenia (14.7 vs 32.0%) and thrombocytopenia (10.5% vs 30.3%) with IMA. **Conclusions:** Efficacy of BOS was consistent in pts with BMI ≥25 or = 25; however, with IMA a low (vs high) BMI appeared to be associated with worse survival outcomes. Differences in certain TEAEs were observed between BMI subgroups in both treatment arms. Clinical trial information: NCT02130557. Research Sponsor: Pfizer Inc.

	BOS			IMA		
	BMI ≥25 n = 149	BMI < 25 n = 115		BMI ≥25 n = 145	BMI < 25 n = 122	
Cumulative rate by 60 mo, %			OR (95% CI)*			OR (95% CI)*
MMR	73.2	74.8	0.84 (0.48–1.50)	66.2	63.1	1.18 (0.69–2.01)
MR^4	57.0	59.1	0.89 (0.54–1.47)	49.7	46.7	1.06 (0.64–1.75)
MR$^{4.5}$	45.6	50.4	0.76 (0.46–1.25)	39.3	33.6	1.30 (0.76–2.21)
			HR (95% CI)			HR (95% CI)
Cumulative incidence of on-Tx progression/death at 60 mo, %	5.4	8.7	0.69 (0.28–1.70)	1.4	18.9	0.07 (0.02–0.30)
Kaplan-Meier OS at 60 mo, %	97.1	91.9	0.36 (0.11–1.18)	98.5	90.0	0.17 (0.04–0.76)

Note: OR > 1 and HR = 1 favor BMI ≥25 kg/m^2. * Adjusted for Sokal risk group and region as determined at randomization. MMR = major molecular response.

7038 **Poster Session**

Novel application of Kaplan-Meier methods to model tolerance for nonadherence to imatinib in patients with chronic myeloid leukemia (CML) in the ADAGIO study.

First Author: Mavis Obeng-Kusi, Center for Health Outcomes and Pharmacoeconomic Research, and Department of Pharmacy Practice and Science, Tucson, AZ

Background: Although adherence to imatinib treatment has been shown to be critical for attaining treatment response among patients with CML, some studies have suggested a 7.3-9.9% nonadherence tolerance margin before loss of treatment effects. We aimed to model probabilistically the margin of tolerance required to ensure treatment response among patients prescribed imatinib and the margin, if any, before treatment response is at risk. **Methods:** We performed a post hoc analysis of the ADAGIO study conducted in Belgium on 169 evaluable patients (*Blood* 2009). Using the pill count ratio as, what in conventional survival analysis would be, the time variable, we modeled the cumulative likelihood of treatment response as a function of increasing pill count adherence. We applied Kaplan-Meier methods to model the likelihood of complete cytogenetic (CCyR), complete hematological (CHR), major molecular (MMR) and optimal (OR) (as defined by the European Leukemia Net) response as a function of 90-day pill count adherence. Kaplan-Meier methods thus estimated the tolerance for nonadherence to imatinib by calculating the 1 minus Kaplan-Meier estimate for treatment response. **Results:** Analyses (see Table) showed that ~100% adherence of prescribed dose is associated with probabilities (rounded) of 0.84 for CHR, 0.83 for CCyR, 0.82 for OR, and 0.77 for MMR; compared to, 0.37 (CHR and CCyR), 0.35 (OR), and 0.39 (MMR) at 90% adherence. (of 0.7698 (MMR). Increasing the intake of imatinib from 90% to 100% of the prescribed dose increased the likelihood of the various treatment responses by 1.95 to 2.35-fold. **Conclusions:** Our findings challenge any previously estimated tolerance for nonadherence. There is virtually no margin for nonadherence if the objective is to optimize the likelihood of treatment response, and only a minimal margin to avoid impaired treatment response. Under such adherence, response rates similar to those in the pivotal IRIS trial can be obtained. Clinicians must assess and promote patient adherence, and patients must be perfectly adherent. Research Sponsor: None.

Probability of treatment response as a function of 90-day pill count adherence.

Pill count ratio	Complete hematological response	Complete cytogenetic response	Major molecular response	Optimal response
90%	0.3746	0.3714	0.3938	0.3512
100%	0.8416	0.8335	0.7698	0.8236
Fold change	2.25	2.24	1.95	2.35

7039 **Poster Session**

Outcomes before and after dose reduction in patients with newly diagnosed chronic myeloid leukemia receiving bosutinib or imatinib.

First Author: Michael W Deininger, University of Utah Health Care, Salt Lake City, UT

Background: Bosutinib (BOS) is approved for patients (pts) with Philadelphia chromosome-positive chronic myeloid leukemia (CML), at a starting dose of 400 mg QD in newly diagnosed pts in chronic phase (CP). This analysis evaluated the impact dose reduction has on the outcomes of BOS and imatinib (IMA) in pts with CP CML. **Methods:** In the open-label BFORE trial, 536 pts with newly diagnosed CP CML were randomized to receive 400 mg QD BOS (N = 268) or IMA (N = 268; 3 untreated). Dose could be reduced to 300 mg QD for toxicity. Following sponsor approval, dose reduction to BOS 200 mg QD was permitted for 4 wks maximum; after this time, dose escalation or treatment discontinuation was required. Maintenance of response after dose reduction was defined as having a response > 6 mo after the first reduction. Database lock: June 12, 2020, 5 y after the last pt enrolled. **Results:** In the BOS arm, dose reduction to 300 (without further reduction) or 200 mg QD was seen in 82 (31%) and 33 (12%) pts, and median time to dose reduction was 85 and 205 d. In the IMA arm, 50 (19%) pts had a dose reduction to 300 mg QD, and median time to dose reduction was 92 d. Most common (≥2% of pts) treatment-emergent adverse events (TEAEs) leading to dose reduction were increased alanine aminotransferase (8%), thrombocytopenia (7%), diarrhea (7%), increased lipase (6%), increased aspartate aminotransferase (4%), nausea (4%), neutropenia (3%), rash (3%) and abdominal pain (2%) with BOS, and neutropenia (4%) with IMA. Of the pts who remained on 400 mg QD BOS (n = 153) or IMA (n = 214), respectively, 120 (78%) and 139 (65%) achieved major molecular response (MMR). Among pts who had a BOS dose reduction to 300 mg QD, 51/82 (62%) had MMR > 6 mo after dose reduction: 14 (17%) maintained MMR before and after dose reduction and 37 (45%) achieved MMR for the first time after dose reduction. Seven (9%) pts had MMR before dose reduction but discontinued treatment before the next > 6 mo assessment. In the IMA arm, 32/50 (64%) pts had MMR > 6 mo after dose reduction: 9 (18%) maintained MMR before and after dose reduction and 23 (46%) achieved MMR for the first time after dose reduction. One (2%) pt had MMR before dose reduction but discontinued treatment before the next > 6 mo assessment and 1 (2%) pt lost a previously attained MMR after dose reduction. Among pts who had a BOS dose reduction to 200 mg QD, 12/33 (36%) had MMR > 6 mo after dose reduction: 7 (21%) maintained MMR before and after dose reduction and 5 (15%) achieved MMR for the first time after dose reduction. Six (18%) pts had MMR before dose reduction but discontinued treatment before the next > 6 mo assessment. Similar trends were seen for complete cytogenetic response. **Conclusions:** Management of TEAEs through BOS or IMA dose reduction enabled pts to continue treatment, with a substantial number of pts achieving MMR for the first time after dose reduction. Clinical trial information: NCT02130557. Research Sponsor: Pfizer Inc.

7040 **Poster Session**

Health-related quality of life (HRQoL) in patients (pts) with myelodysplastic syndromes (MDS) in the Connect Myeloid Disease Registry.

First Author: Dennis A. Revicki, Outcomes Research Consulting, Sarasota, FL

Background: At diagnosis, disease risk and transfusion burden (TB) can impact HRQoL in pts with MDS. The impact of disease status and higher transfusion requirements on HRQoL has not been well studied. We used data from the Connect Myeloid Disease Registry, an ongoing, prospective, observational cohort study that includes adult pts with lower-risk (LR) and higher-risk (HR) MDS, to investigate factors influencing baseline (BL) and subsequent HRQoL. **Methods:** BL and Month 6 (M6) data from pts enrolled from Dec 12, 2013 to Mar 6, 2020 (data cutoff) were analyzed. Pts were stratified by International Prognostic Scoring System (IPSS) risk (LR, HR), treatment (Tx) within 45 days post-enrollment (no Tx, best supportive care [BSC], active Tx), and TB 16 weeks post-BL (non-transfusion dependent [NTD], low TB [LTB]; 1−3 transfusions, high TB [HTB]: ≥4 transfusions). Pts completed EQ-5D, FACT-An trial outcome index (TOI), and FACT-Fatigue (FACT-F) questionnaires at BL and quarterly thereafter. Clinically meaningful change, based on minimally important differences, was defined as a change of ±0.07 for EQ-5D, ±6 for FACT-An TOI, and ±3 for FACT-F. **Results:** At data cutoff, 830 (489 LR, 341 HR) pts were enrolled. Median age was 74 years. 278 pts received no initial Tx, 161 BSC, and 378 active Tx. At BL, 470 were NTD, 197 LTB, and 163 HTB. Of 670 pts still on-study at M6, 462 completed the questionnaires at both BL and M6. At BL, clinically meaningful differences were observed in FACT-An TOI and FACT-F scores, but not EQ-5D, between LR- and HR-MDS and the Tx subgroups. From BL to M6, no clinically meaningful changes were observed in mean scores for each questionnaire. For the TB subgroups, meaningful differences were observed at BL in FACT-An TOI and FACT-F scores, but not EQ-5D (Table). From BL to M6, meaningful decreases in scores were reported by 26%, 30%, and 35% of NTD, LTB, and HTB pts in EQ-5D, 41%, 43%, and 48% for FACT-An TOI, and 40%, 42%, and 48% for FACT-F; increases were reported by 19%, 19%, and 20% pts for EQ-5D, 31%, 32%, and 39% for FACT-An TOI, and 30%, 39%, and 40% for FACT-F. **Conclusions:** This preliminary analysis suggests that pts with HR-MDS, and transfusion-dependent pts, generally had worse HRQoL at BL, providing further support to initiating active Tx in pts with TB. Possible limitations of the analysis are lower completion rates in pts with more severe disease, and EQ-5D may not capture changes in these subgroups at M6. A longer follow-up may help delineate the impact of Tx on HRQoL assessments in pts with MDS. Clinical trial information: NCT01688011. Research Sponsor: Bristol Myers Squibb.

Mean HRQoL scores in pts with MDS.

		EQ-5D	FACT-An TOI		FACT-F	
		BL (n = 807)	M6 (n = 459)	BL (n = 803)	M6 (n = 463)	BL (n = 810)	M6 (n = 464)
IPSS risk	LR	0.80	0.79	92.3	92.4	23.4	24.1
	HR	0.75	0.79	83.9	87.5	20.5	22.2
Tx	None	0.81	0.80	96.0	95.9	25.6	25.9
	BSC	0.78	0.77	87.2	88.2	20.3	21.7
	Active	0.76	0.78	84.3	87.3	20.6	22.2
TB	NTD	0.80	0.81	92.9	95.9	24.2	25.7
	LTB	0.75	0.75	83.6	82.0	19.4	19.6
	HTB	0.76	0.75	83.6	84.3	19.8	20.8

7041 **Poster Session**

Comparison of dose modification strategies to address expected hematologic toxicities in treatment-naïve higher-risk (HR) MDS patients treated with venetoclax + azacitidine. *First Author: Jacqueline Suen Garcia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Venetoclax (Ven) is a selective, potent BCL-2 inhibitor. Ven + azacitidine (Aza) were associated with a combined complete remission (CR)/marrow CR (mCR) rate of 79% in a phase 1b study of patients (pts) with HR-MDS. Here we compared two different dose modification strategies to manage expected hematologic toxicities in two safety expansion cohorts with similar follow-up periods. **Methods:** Pts ≥18y diagnosed with treatment-naïve IPSS intermediate-2 or high-risk MDS with ECOG ≤2 were enrolled. Aza 75 mg/m^2 (iv or subQ daily) was administered for 7 days (d) and Ven was administered at 400 mg for 14d in each 28d cycle. In both cohorts, dose modification during Cycle 1 was not recommended; dose modifications in subsequent cycles were prescribed for AEs. In Safety Expansion Cohort 1 (SE1), either Aza or Ven were initially reduced according to investigator's choice for significant neutrophil or platelet toxicity. Dose reductions per protocol were 33% for Aza and 50% for Ven (for 14d each cycle). In subsequent cycles, Ven duration could be shortened to 9d of each cycle. In Safety Expansion Cohort 2 (SE2), dose modification guidelines recommended stepwise reductions, first in Aza dose (first to 50 mg/m^2, then 36 mg/m^2) and subsequently in Ven duration to 7d of each cycle (Ven 400 mg). The impact of each dose modification strategy on safety and efficacy in SE1 *vs* SE2 was compared. Worsening of treatment-emergent adverse events (TEAE) grades from baseline (BL) was analyzed by cycle. Responses were evaluated using IWG 2006 criteria. Analyses included all pts who received ≥1 dose of study drug. **Results:** We compared 22 pts in SE1 and 21 pts in SE2 with median (range) follow-up of 7.5 (1.0–8.9) and 7.9 (1.8–10.1) mos, respectively. A similar frequency of ≥ G3 hematologic TEAEs (approx %) were reported in SE1 and SE2, respectively, including anemia (14% and 33%), febrile neutropenia (46% and 48%), leukopenia (36% and 19%), neutropenia (55% and 48%) and thrombocytopenia (32% and 38%). Infections (59% and 38%) were more frequent in SE1 than SE2. In a longitudinal analysis, there were more TEAE grade increases from BL to Cycle 1 in SE2 vs SE1. This could be accounted by pts in SE1 and SE2 having unbalanced susceptibility to AEs at BL, as SE1 and SE2 pts received identical Aza + Ven doses in Cycle 1. Response rates were identical: 86% of pts in both SE1 and SE2 had CR or mCR. For pts with mCR, hematologic improvement occurred in 50% of SE1 and 46% of SE2 pts. **Conclusions:** No obvious hematologic differences were observed when reducing Aza before Ven (SE2) in MDS compared to investigator's choice (SE1). Both approaches had a similar acceptable safety profile without compromising efficacy for pts with HR-MDS. Clinical trial information: NCT02942290. Research Sponsor: AbbVie.

	Any Grade Hematologic TEAEs & Infections > 20%	
%	SE1n = 22	SE2n = 21
Infections	59	38
Neutropenia	55	48
Febrile neutropenia	46	48
Thrombocytopenia	36	48
Leukopenia	36	19
Anemia	14	48

7042 **Poster Session**

Model-based analysis to support dose selection of pevonedistat (PEV) combined with azacitidine (AZA) in patients (pts) with higher-risk myelodysplastic syndromes (MDS)/chronic myelomonocytic leukemia (CMML) and acute myeloid leukemia (AML). *First Author: Xiaofei Zhou, Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA*

Background: PEV+AZA has been studied in higher-risk MDS/CMML and AML, with encouraging efficacy and an acceptable safety profile without added myelosuppression. This pooled analysis was performed to evaluate the impact of PEV exposure on safety and efficacy. **Methods:** Data from three studies (NCT01814826, NCT02782468 and NCT02610777) were used in the PEV exposure–safety analyses, including ≥ grade 3 neutropenia (NEU3), febrile neutropenia (FN), ≥ grade 3 thrombocytopenia, ≥ grade 3 alanine aminotransferase elevation, ≥ grade 3 aspartate aminotransferase elevation and ≥ grade 3 treatment-emergent adverse event (TEAE3), in pts with higher-risk MDS/CMML and AML who received PEV+AZA. Data from NCT02610777 were used for exposure–efficacy analyses, including overall survival (OS), event-free survival (EFS), complete response (CR) and CR+partial response (PR), in pts with higher-risk MDS/CMML who received PEV+AZA. The exposure metrics for individual pts were derived from a previously developed population pharmacokinetic model with pooled data from eight phase 1/2 studies. PEV exposure–safety relationships for the toxicity endpoints, exposure–CR and exposure–CR+PR, were estimated by logistic regression. Age, sex, race, baseline Eastern Cooperate Oncology Group (ECOG) Performance Status score and disease type were evaluated as covariates. Cox proportional-hazards models were used to evaluate the PEV exposure–survival for higher-risk MDS/CMML, with age, sex, baseline ECOG PS score, Revised International Prognostic Scoring System score (IPSS-R) and disease type as potential covariates. **Results:** In total, 135 pts (median age, 74 years; male, 64%; Caucasian, 82%) and 41 pts (median age, 74 years; male, 76%; Caucasian, 90%; median IPSS-R, 5.5) were included in PEV exposure–safety and exposure–efficacy analyses, respectively. PEV exposure was significantly related to the incidence of NEU3 (p = 0.003), FN (p = 0.02) and TEAE3 (p = 0.02), supporting PEV dose reductions for pts with treatment-related toxicities. Relationships between PEV exposures and CR, CR+PR, EFS or OS indicated consistent clinical benefit across ranges of PEV exposure following a starting dose of 20 mg/m^2. **Conclusions:** The association between exposure and safety supports PEV dose reductions for pts with treatment-related toxicities. The exposure–efficacy analyses indicated consistent clinical benefit across ranges of PEV exposure following a starting dose of 20 mg/m^2. These results support a favorable benefit–risk profile of the 20 mg/m^2 PEV dose on days 1, 3 and 5 in combination with AZA 75 mg/m^2 for 7 days in 28-day cycles. Clinical trial information: NCT01814826, NCT02782468, NCT02610777. Research Sponsor: Millennium Pharmaceuticals, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, Cambridge, MA, USA.

7043 **Poster Session**

Predictors of hypomethylating agent discontinuation among patients with higher-risk myelodysplastic syndromes. *First Author: Amer Methqal Zeidan, Yale University School of Medicine and Yale Cancer Center, New Haven, CT*

Background: Real-world studies have shown that persistence with intravenous (IV) and subcutaneous (SC) hypomethylating agents (HMAs) among patients (pts) with higher-risk myelodysplastic syndromes (MDS) is poor, with over one-third of treated pts receiving <4 cycles or having a ≥90-day gap in therapy, despite recommendations for at least 4-6 cycles to elicit response in absence of progression/unacceptable toxicity. Survival outcomes have also been shown to be worse, and direct medical costs higher, among HMA non-persistent vs persistent pts. We explored factors associated with early discontinuation of HMA therapy in this population. **Methods:** This was a retrospective cohort study among pts from the 2010-2016 SEER-Medicare linked database with a diagnosis of refractory anemia with excess blasts (RAEB; a surrogate for higher-risk MDS) from 2011-2015. Included pts had to have received HMA therapy and have ≥12 months' continuous follow-up after diagnosis. Discontinuation was defined as stopping HMA therapy before 4 cycles. Multivariable logistic regression was used to assess predictors of HMA discontinuation. **Results:** In total, 664 pts with RAEB and treated with HMAs were included. Overall, 193 (29%) discontinued before 4 cycles; of these, 91 (47%) discontinued after 1 cycle, 57 (30%) 2 cycles, and 45 (23%) 3 cycles. Compared with pts continuing for ≥4 cycles, pts discontinuing before 4 cycles were generally older and more likely to be single/separated/divorced/widowed, have more comorbidities, and have poor performance status (PS) (Table). These trends were most pronounced among pts discontinuing HMA therapy after only 1 cycle vs ≥4 cycles (Table). In multivariable analysis, age 71-75 vs ≥80 y (odds ratio [OR] 0.556, p=0.017) and poor PS (OR 1.585, p=0.019) remained significant predictors of HMA discontinuation. Among treatment-related factors, the most statistically significant association with HMA discontinuation was observed for GCSF use (OR 0.453, p<0.001). Number of pills/day was not a predictor of HMA discontinuation (OR 1.009, p=NS). **Conclusions:** In this real-world study, almost one-third of RAEB pts treated with IV/SC HMAs discontinued before 4 cycles, with almost half of these pts discontinuing after only 1 cycle. Predictors of HMA discontinuation included older age and poor PS. Novel approaches are needed to improve persistence with HMA therapy, particularly among these higher-risk groups. Research Sponsor: Taiho Oncology, Inc.

Patient characteristics by number of cycles prior to discontinuation.

		1 cycle n=91	2 cycles n=57	3 cycles n=45	Total <4 cycles n=193	Total ≥4 cycles n=471	p value (<4 vs ≥4)
Age, y	Mean (SD)	79.2 (6.0)	79.8 (7.2)	78.0 (6.5)	79.1 (6.5)	77.3 (6.2)	<0.001
Marital status, %	Single/separated/divorced/widowed	39	33	31	35	30	0.024
	Married	47	54	58	52	62	
	Unknown	14	12	11	13	8	
Charlson Comorbidity Index, %	0-1	42	51	64	50	64	0.004
	2	18	11	11	14	11	
	3+	41	39	24	36	26	
Poor PS, %	Yes	63	44	53	55	40	<0.001
	No	37	56	47	45	60	

7044 **Poster Session**

Using tissue microarray to detect inflammasome signaling components that contribute to the pathogenesis of myelodysplastic syndrome. *First Author: Tony Kurian, Moffitt Cancer Center & University of South Florida, Tampa, FL*

Background: Myelodysplastic syndromes (MDS) are characterized by aberrant maturation, ineffective hematopoiesis, cytopenia, and progression to acute myeloid leukemia. MDS pathogenesis is multifactorial and potentially linked to constitutive innate immune stimulation converging upon the NLRP3 inflammasome to induce pyroptosis, a caspase-1 dependent cell death. Inflammasome assembly is initiated by both *cell-extrinsic* stimuli including S100A9, the TLR4 and CD33 ligand, and *cell-intrinsic* danger signals licensing caspase-1 which activates IL1b and beta-catenin resulting in cell death and cellular proliferation leading to maturation and differentiation blocks. Further, EYA2 has been suggested to be an inflammasome activator, whereas cPLA2 has been suggested to be an inhibitor. The purpose of this study is to determine whether immunohistochemistry (IHC) may be utilized to assess expression of inflammasome components. **Methods:** An IRB protocol was approved prior to initiating this study. We retrospectively identified 43 low risk MDS patients. A tissue microarray (TMA) was constructed utilizing MDS bone marrow biopsy samples (2-3 representative cores per sample). IL-1, S100A9, EYA2, cPLA2, beta-catenin, and TLR4 expression were assessed by IHC after validation of each antibody. IHC expression was scored independently by two hematopathologists by calculating scores (product of staining intensity x percent expression). IHC expression was compared using Spearman correlation estimate. Demographic and clinical data were collected and correlated with IHC expression using Kruskal-Wallis test, Spearman correlation, and Logrank test. **Results:** Patients were median 72 years of age, 67% men and included 47% MDS-MLD, 35% MDS-RS, 14% MDS-SLD, 2% MDS del5q and 2% MDS-U. IL-1 expression correlated with beta-catenin expression, r = 0.42, 95% CI 0.115 to 0.658 (p = 0.007). There was a trend towards significance between IL-1 and cPLA2, r = 0.30 (p = 0.067); S100A9 and cPLA2, r = 0.31 (p = 0.052); and S100A9 and EYA2, r = 0.31 (p = 0.057). Percentage EYA2 expression correlated with blast count, r = 0.425 (p = 0.008). The IHC expression of these antigens did not correlate with WHO MDS subclassification, IPSS, R-IPSS, disease progression, or survival (p > 0.05). **Conclusions:** IHC staining of inflammasome activators using TMA may allow better characterization of molecular pathways contributing the MDS pathogenesis. A correlation was seen between expression of antigens known to be increased downstream of NLRP3 inflammasome activation. Furthermore, increased expression of EYA2 correlated with blast count. A future study will compare expression patterns between normal, low risk MDS and high risk MDS samples and correlate these findings with clinical outcome data to further elucidate the pathogenesis of MDS and identify potential targetable markers for novel therapeutic strategies. Research Sponsor: USF Fellow Research Award.

7045 **Poster Session**

Outcomes of allogeneic hematopoietic cell transplantation in patients with myelofibrosis: A systematic review and meta-analysis. *First Author: Jan Philipp Bewersdorf, Yale University School of Medicine, New Haven, CT*

Background: Allogeneic hematopoietic cell transplant (allo-HCT) remains the only potentially curative therapeutic modality for patients with primary or secondary myelofibrosis (MF). However, many patients (pts) are ineligible for allo-HCT and transplant-related mortality can be substantial. Data on the efficacy and safety of allo-HCT are mixed and largely derived from retrospective studies. **Methods:** To synthesize the available evidence, we conducted a systematic review and meta-analysis searching Cochrane Library, Google Scholar, Ovid Medline, Ovid Embase, PubMed, Scopus, and Web of Science Core Collection from inception to October 11, 2020 for studies on allo-HCT in MF. Databases were searched using a combination of controlled vocabulary and free text terms for relevant studies on the efficacy and safety of allo-HCT in pts with primary and secondary MF. This study protocol has been registered on PROSPERO (CRD42020188706). Random-effects models were used to pool response rates for the co-primary outcomes of 1-year, 2-year and 5-year overall survival (OS). **Results:** We identified 4247 studies after duplicate removal. 393 studies were assessed as full-texts for eligibility and 43 studies (38 retrospective, 1 prospective study, 4 phase II clinical trials) with 8739 pts were included in this meta-analysis. Study quality was limited by the absence of randomized clinical trials and retrospective design of most studies. Rates of 1-year, 2-year, and 5-year OS were 66.7% (95% confidence interval: 63.5-69.8%), 64.4% (57.6-70.6%), and 55.0% (51.8-58.3%), respectively. Rates of 1-year, 2-year, and 5-year non-relapse mortality were 25.9% (23.3-28.7%), 29.7% (24.5-35.4%), and 30.5% (25.9-35.5%), respectively. Among evaluable studies, rates of 1-year, 2-year, and 5-year relapse-free survival were 65.3% (56.5-73.1%), 56.2% (41.6-69.8%), and 53.6% (39.9-66.9%), respectively. Adverse events related to all-HCT were manageable with rates of acute and chronic graft-versus-host disease in 44.0% (39.6-48.4%; grade III/IV: 15.2%) and 46.5% of patients (42.2-50.8%; extensive or moderate/severe: 26.1%), respectively. Subgroup analyses did not show any significant difference between conditioning regimen intensity (myeloablative vs reduced-intensity), median patient age, and proportion of DIPSS-intermediate-2/high pts. **Conclusions:** Given the poor prognosis of patients not receiving transplant and in the absence of curative non-transplant therapies, our results support consideration of allo-HCT for eligible pts with MF. However, additional studies in pre- and post-allo-HCT setting are necessary to enhance patient selection (e.g. by incorporation of molecular markers), to optimize transplant strategies (e.g. peri-transplant ruxolitinib, conditioning regimens, and donor selection), symptom management and decrease non-relapse mortality. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, U.S. National Institutes of Health.

7046 **Poster Session**

Association of transfusion independence with improved overall survival in myelofibrosis patients receiving momelotinib. *First Author: Ruben A. Mesa, UT Health San Antonio, San Antonio, TX*

Background: Momelotinib (MMB) is a potent JAK1, JAK2 and ACVR1 inhibitor with clinical activity against the hallmark features of myelofibrosis (MF), namely anemia, constitutional symptoms and splenomegaly, across the continuum of JAKi naïve or previously JAKi treated intermediate/high risk MF patients as demonstrated in the previously conducted Phase 3 SIMPLIFY-1 & -2 clinical trials (S1, S2). S1 enrolled JAKi-naïve patients with MF (n = 432) double-blind randomized 1:1 to MMB or ruxolitinib (RUX). S2 enrolled patients with MF with hematological toxicity during prior RUX therapy (n = 156) randomized 2:1 to open-label MMB or best available therapy (BAT; consisting of RUX in 88% of patients). In both trials, following the 24-week randomized treatment (RT) period, patients could continue MMB (MMB→MMB) and those randomized to RUX/BAT could cross-over to MMB (RUX/BAT→MMB) for extended treatment (ET). Previously published data from the SIMPLIFY studies demonstrate robust overall survival (OS) for MMB-treated patients in S1 and S2 (median not reached and 34.3 months, respectively) with a maximum follow up of approximately 5 years and median of 2.9 years in S1 and 2.3 years in S2. **Methods:** OS data for patients receiving MMB in S1 and S2 are reported here for subgroups defined by Week 24 (W24) transfusion independence (TI) responders vs non-responders, and also other efficacy endpoints. Survival was estimated using KM analysis with descriptive log-rank tests for comparison applied (all p-values are descriptive). **Results:** As previously reported, W24 TI rates were higher in the MMB arms of S1 (67% vs 49%) and S2 (43% vs 21%). In S1, W24 TI responders in the MMB group show an OS advantage, with median OS not reached and 3-year survival of 80% (HR = 0.30; p = 0.0001) compared to MMB TI non-responders. Similarly in S2, W24 TI responders in the MMB group show a trend toward better OS compared to TI non-responders (HR = 0.57; p = 0.0652). The HRs in S1 for MMB responders vs non-responders for W24 SRR and TSS were 0.59 (p = 0.0904) and 0.65 (p = 0.1657), respectively. Alternative analyses using OS defined from W24 demonstrated consistent results. **Conclusions:** These new analyses suggest JAKi naïve patients receiving MMB who maintain or achieve TI at W24 have favorable OS compared to MMB TI non-responders, with a similar trend observed in S2. These findings are consistent with anemia and transfusion dependency being key predictors of shortened OS in MF and suggest that TI response at W24 may become a surrogate for clinical benefit, supporting the clinical relevance of MMB's differentiated pro-erythropoietic ACVR1 inhibition. Clinical trial information: NCT01969838. Research Sponsor: Sierra Oncology / Gilead Sciences.

7048 **Poster Session**

Clinical characteristics, treatment patterns, and overall survival of real-world patients with idiopathic multicentric Castleman disease. *First Author: Aaron B. Cohen, Flatiron Health, New York, NY*

Background: Castleman disease (CD) has three subtypes: Unicentric (UCD), Human herpesvirus-8 associated multicentric (HHV-8 MCD) and idiopathic multicentric (iMCD). Outcomes for patients with iMCD are poor and treatment options are limited, with only one FDA-approved therapy (siltuximab in April 2014). Further, the lack of CD-specific ICD codes until 2017 has limited real-world evaluation. We identified iMCD patients in an electronic health record (EHR)-derived dataset and described their clinical characteristics, treatment patterns, and real-world overall survival (rwOS). **Methods:** Patients with a possible diagnosis of CD as of 8/31/20 were identified from the nationwide deidentified Flatiron Health EHR-derived database using patient-level structured data (e.g., ICD-9/10 codes) and unstructured data (e.g., clinician notes), curated via technology-enabled manual abstraction to confirm CD diagnosis and treatments received. Descriptive statistics summarized patient characteristics and treatment patterns. Patients without structured data within 90 days after diagnosis were excluded from treatment patterns analyses. 5-year rwOS rate was estimated from diagnosis date using the Kaplan-Meier estimator. **Results:** 747 patients with possible CD were identified, of whom 453 were confirmed to have CD by abstraction (172 UCD, 100 iMCD, 36 HHV-8 MCD, and 145 unclassified). IMCD patients were predominantly female (53%), white (58%), and treated at community sites (70%). Of the 52 iMCD patients with evidence of structured data within 90 days after diagnosis and who had at least one documented line of therapy, the most common first-line therapies were siltuximab-based therapy (42.3%), rituximab monotherapy (36.5%), and chemotherapy-based treatment (13.5%). Among 28 iMCD patients with evidence of second-line therapy, the most common treatment was rituximab monotherapy (35.7%). Among 60 iMCD patients diagnosed on or after siltuximab approval in April 2014 (including those without evidence of any treatment), 26 (43%) received siltuximab at some point. 5-year rwOS rate for the 100 iMCD patients was 75% [95% CI: 63-89%]. **Conclusions:** This is the first study to utilize a large EHR-derived database to describe characteristics, treatment patterns, and overall survival of iMCD patients in real-world practice. Less than half of iMCD patients diagnosed on or after the date of FDA approval for siltuximab received it at some point. Future work should focus on characterizing the drivers of poor patient outcomes. Research Sponsor: Flatiron Health, an independent subsidiary of the Roche Group.

7049 **Poster Session**

Phenotypes and prognostic factors in adults with Langerhans cell histiocytosis. *First Author: Gaurav Goyal, University of Alabama at Birmingham, Birmingham, AL*

Background: Langerhans cell histiocytosis (LCH) can manifest as single system (SS) disease, multisystem (MS) disease, or pulmonary LCH (smoking-related). There is a paucity of data on prognostic factors including risk organ (RO) involvement (liver, spleen, and bone marrow) in adult LCH, which we sought to address in this study. **Methods:** Single-center retrospective study of patients ≥18y diagnosed with LCH from 1998 to 2020. Univariate and multivariate analyses for progression free survival (PFS) and overall survival (OS) were conducted using age, sex, organ involvement, LCH subtype, year of diagnosis, BRAF V600E status, and treatments. **Results:** We included 219 patients with LCH; median age 43y (range 19-88), females 51%, SS unifocal (23%), SS multifocal (6%), pulmonary (31%) and MS (40%). Commonly involved organs included lung (53%), bone (42%), skin (24%), pituitary (16%), and CNS (12%). BRAF V600E was positive in 40/88 (46%). Median follow-up duration was 6.1y (95% CI, 5.1- 7.1). On univariate analysis, factors associated with worse PFS were bone LCH, RO involvement, multifocal/MS LCH, and radiation therapy alone; those with worse OS included RO involvement, MS disease, BRAF V600E+, and age ≥45y at diagnosis. In multivariate analysis, BRAF V600E and age ≥45y at diagnosis were associated with worse mortality (Table). Median PFS was not reached (NR-NR) for SS unifocal LCH, 5mo (0-12.7) for SS multifocal LCH, 110mo (84.7-135.3) for pulmonary LCH, and 27mo (17.2-36.8) for MS LCH. 5-year OS was 97.4% for SS unifocal LCH, 100% for SS multifocal LCH, 96.1% for pulmonary LCH, and 79.9% for MS LCH. 41 (18.7%) developed a second primary malignancy (SPM), of which 11 were hematologic neoplasms. There was a trend towards a higher prevalence of SPMs in patients with BRAF V600E (28% vs. 17%; p = 0.22). **Conclusions:** In our large single-center study, PFS for multifocal and MS LCH was worse than SS unifocal or pulmonary LCH. RO involvement was not associated with outcomes in multivariate analysis. Overall prognosis was excellent for all subtypes except MS LCH. BRAF V600E and older age were associated with worse OS. The prevalence of SPMs was very high and needs to be explored further. Research Sponsor: None.

PFS	*Univariate*	*p*	*Multivariate*	*p*
Organ	1.62 (1.05 – 2.51)	*0.03*		*0.78*
Bone	1.56 (0.94 – 2.57)	*0.08*		*0.69*
Pituitary	3.06 (1.75 – 5.36)	*< 0.001*		*0.23*
Risk organ				
LCH	Reference	-	37.4 (3.9 – 355.2)	*0.02*
SS unifocal	34.8 (9.38 – 129.04)	*< 0.001*	11.8 (0.85 – 163.1)	*0.002*
SS multifocal	5.2 (1.56 – 17.35)	*< 0.001*	17.1 (1.99 – 146.7)	*0.07*
PulmonaryMS	12.37 (3.84 – 39.9)	*< 0.001*		*0.01*
First Line Treatment	1.59 (0.98 – 2.56)	*0.06*	3.5 (0.98 – 12.7)	*0.72*
Chemotherapy	0.396 (0.23 – 0.69)	*0.001*		*0.93*
Smoking reduction	2.09 (1.15 – 3.78)	*0.02*		*0.05*
Radiation				
BRAF V600E		*0.17*		*0.24*
OS		**p**		**p**
Risk organ involvement	6.99 (3.2 – 15.3)	*< 0.001*		*0.99*
Pulmonary LCH	3.8 (0.86 – 16.97)	*0.08*		*0.98*
MS LCH	5.17 (1.2 – 22.2)	*0.03*		*0.12*
BRAF V600E	4.67 (1.19 – 18.3)	*0.03*	6.06 (1.01 – 36.4)	*0.05*
Age ≥45y	6.46 (2.81 – 14.9)	*< 0.001*	48.5 (2.38 – 1034)	*0.01*

7050 **Poster Session**

$BRAF^{V600E}$ frequency and impact on outcomes in adults with langerhans cell histiocytosis. *First Author: Aldo A. Acosta-Medina, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Langerhans cell histiocytosis (LCH) is an inflammatory myeloid neoplasm manifesting as unifocal, multifocal, multisystem (MS) or pulmonary LCH (smoking-related). In pediatric LCH, somatic $BRAF^{V600E}$ prevalence is reported at 55-70%, and associated with increased risk of multisystem disease and early treatment failure. Our aim was to describe the prevalence of $BRAF^{V600E}$ mutation and evaluate its association with clinical manifestations and outcomes in adults with LCH. **Methods:** A retrospective review of adult patients diagnosed with LCH consecutively seen at Mayo Clinic from 2011 to 2020 was performed.Evaluation of association of $BRAF^{V600E}$ mutational status and clinical factors was conducted by the Chi-square test for independence. Progression-free survival (PFS) and overall survival (OS) were analyzed via the Kaplan Meier method and compared with the log-rank test to assess the effect of $BRAF^{V600E}$. **Results:** Of the total LCH cohort (n= 128), 88 patients with available $BRAF^{V600E}$ results were included in the study. Median age at diagnosis was 41y (range 19 - 88); 52.3% were male. 40 (45.5%) patients had a $BRAF^{V600E}$ mutation. Increasing age was associated with $BRAF^{V600E}$ (10-year increase OR 1.42, 95%CI 1.07-1.89; p= 0.017). No correlation was observed between $BRAF^{V600E}$ status and site of disease, risk organ (RO: liver, spleen, marrow) involvement, or MS disease. Patients with $BRAF^{V600E}$ were 4 times more likely to receive targeted therapy (*BRAF* inhibitor) than non-$BRAF^{V600E}$ patients (p= 0.018). After a median follow up of 46 mo (95% CI 30.8-61.2), PFS was similar between $BRAF^{V600E}$ and non-$BRAF^{V600E}$ patients (p= 0.167). However, patients with $BRAF^{V600E}$ had a worse 3-year OS compared with non-$BRAF^{V600E}$ patients (84% vs. 97.1%, p= 0.027). Patients who died had a significantly higher age at LCH diagnosis (median 62 vs. 38 years; p= 0.0002). **Conclusions:** In our cohort of adults with LCH, $BRAF^{V600E}$ was less frequent than reported in pediatric literature and was associated with worse OS. The frequency of $BRAF^{V600E}$ was positively correlated with increasing age. Contrary to reports in pediatric LCH, there were no significant associations between $BRAF^{V600E}$ and high-risk or multisystem disease. Research Sponsor: None.

	$BRAF^{V600E}$ n = 40	$BRAF^{WT}$ n = 48	*P-value*
Age, median (range)	43.5 (19-88)	39.5 (21-64)	0.017
Organ/gland involvement, n (%)	25 (62.5)	25 (52.1)	0.222
Bone	15 (37.5)	18 (37.5)	1.00
Lung	8 (20)	13 (27.1)	0.438
Pituitary	7 (17.5)	4 (8.3)	0.218
Central nervous system			
RO involvement, n (%)	7 (14.6)	7 (17.5)	0.710
LCH Classification, n (%)	10 (25)	14 (29.2)	0.662
Unifocal	3 (7.5)	6 (12.5)	0.441
Multifocal	5 (12.5)	5 (10.4)	0.759
Pulmonary	22 (55)	23 (47.9)	0.508
Multisystem			
Targeted therapy (BRAF- or MEK-inhibitor), n (%)	10 (25)	3 (6.3)	0.018
3-year PFS, %	43.2	60.1	0.167
3-year OS, %	84.0	97.1	0.027

TPS7051 **Poster Session**

A phase 4 study to evaluate outpatient blinatumomab in patients with minimal/measurable residual disease (MRD) positivity (+) of B-cell precursor acute lymphoblastic leukemia (BCP-ALL). *First Author: Sharif Khan, Saint Francis Hospital, Inc, Greenville, SC*

Background: The prognosis for adults with relapsed or refractory BCP-ALL is poor. MRD+ is the strongest predictor of relapse. Blinatumomab, a CD3/CD19-directed BiTE® (bispecific T-cell engager) molecule, is an effective treatment for patients with MRD+.[1] Blinatumomab is administered as a continuous intravenous infusion (cIV) 28 days per cycle. Severe adverse events (AEs) such as cytokine release syndrome (CRS) and neurologic toxicity (NT) may occur; thus, hospitalization is recommended for the first 3 days of cycle 1 and the first 2 days of cycle 2 for MRD+ patients. However, the incidence of severe AEs is low in MRD+ BCP-ALL patients (CRS: 2%, NT: 13%).[1] We believe that with the use of effective digital monitoring devices, blinatumomab can be safely administered for the entire 28-day cIV cycle as an outpatient. **Methods:** Adult patients (n = 45) with BCP-ALL in complete remission and MRD+ (≥0.1% blasts) are being enrolled at 25 planned treatment sites, endpoint: grade ≥3 AE during monitoring (Amgen NCT04506086). Patient suitability for blinatumomab and outpatient monitoring is established. Patients will receive 2-4 cycles of blinatumomab. Cycles are initiated in the outpatient setting, digital monitoring devices activated and attached, and patients sent home. Once home, patients set up the home hub and real-time remote data transfer to the healthcare professional (HCP) begins. The devices are worn continuously, 24 hours a day for the first 3 days of cycle 1 and the first 2 days of cycle 2 only. Devices: Current Health's Wearable Monitoring System (CHWMS) is an FDA-cleared platform for wireless and wearable health monitoring of patients at home. The CHWMS provides continuous oxygen saturation, respiratory rate, and heart rate; an axillary temperature sensor is worn and provides continuous temperature. Patients manually measure blood pressure every 3-6 hours around the clock. Patients have an integrated mobile device (tablet) to initiate contact with the HCP if needed. HCP/designee has a mobile device (smart phone) and receives vital signs as a constant live feed transmitted from the CHWMS device. The CHWMS platform generates a loud audible alert based on pre-specified vital sign alarming thresholds or if there is an interruption in data transfer. HCP may initiate direct audio and video contact with the patient, assess the patient's condition, and make an appropriate intervention. HCP may also initiate patient contact in the absence of an alert. Patients are required to have a caregiver present during the entire period of outpatient monitoring. Patients have a full set of replacement devices as well as a 24/7 hotline for device support. Trial enrollment is underway. This study may generate feasibility data on the effectiveness of home monitoring during blinatumomab infusion in patients with MRD+ BCP-ALL. [1]Gökbuget, *Blood*, 2018. Clinical trial information: NCT04506086. Research Sponsor: Amgen Inc.

TPS7052 **Poster Session**

V2 Trial: A phase I study of venetoclax and CPX-351 for young patients with relapsed/refractory acute leukemia. *First Author: Laura Agresta, Michigan State University College of Human Medicine, East Lansing, MI*

Background: Despite significant advances in therapy for acute myeloid leukemia (AML), 30-40% of young patients will relapse, after which prognosis is poor. In young patients, curative-intent salvage therapy involves intensive re-induction followed by hematopoietic stem cell transplant. Recently, the COG Phase II study of CPX-351 (liposomal cytarabine:daunorubicin, Vyxeos™) in pediatric patients with AML in first relapse (NCT02642965) demonstrated a CR/CRi rate of 81.3%. Separately, our first-in-pediatrics CPX-351 Phase I (NCT01943682) showed 48% in a heavily pre-treated pediatric cohort with multiply relapsed and refractory (R/R) AML. Our integrated pilot study of single cell RNA sequencing (scRNA-seq) done before, during, and after CPX-351 showed p53 targets over time with enrichment for genes regulating apoptosis (ex.: FAS, BAX), suggesting blasts may be primed for apoptosis following CPX-351. Venetoclax is a small molecule inhibitor of the anti-apoptotic protein BCL-2, a regulator of apoptotic balance in some leukemias. Based on our preclinical data, we developed a Phase I study to investigate venetoclax with CPX-351 for the treatment of young patients with R/R acute leukemias. **Methods:** The V2 Trial (NCT03826992) is a single-institution Phase I study to evaluate the safety and tolerability of venetoclax with CPX-351 in patients ages 1-39 years with R/R acute leukemias. Inclusion diagnoses include AML, mixed phenotype acute leukemia (MPAL), *KMT2A*-rearranged acute lymphoblastic leukemia (ALL), and T-ALL. Exclusion criteria include CNS status 3, bone marrow failure syndromes, and prior cardiotoxic exposures above acceptable risk thresholds. Subjects receive a single course of CPX-351 at the FDA approved adult dose on Days 1, 3, 5 with concurrent daily venetoclax. In the dose exploration phase, venetoclax dosing is 400 mg daily (or allometrically-scaled equivalent) for 21 (Dose Level 0) or 14 days (Dose Level -1) using a rolling 6 design. Primary endpoints are determination of the recommended phase 2 dose of venetoclax in combination with CPX-351 and description of toxicities. Secondary endpoints include estimations of $CR/CR_p/CR_i$ +/- MRD negativity in the context of a phase I study and evaluation of therapy-related cardiac dysfunction. Correlative studies include analysis of venetoclax pharmacokinetics with concomitant CPX-351. At the initial dose level, DLT were encountered and the study is now continuing enrollment at Dose Level -1. Clinical trial information: NCT03826992. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Cincinnati Children's Hospital Medical Center internal funding.

TPS7053 **Poster Session**

A prospective phase I/IIa trial to evaluate the safety and efficacy of GTA002, an off-the-shelf, *ex vivo*-cultured allogeneic NK cell preparation in patients with acute myeloid leukemia in complete morphological remission who have measurable residual disease. *First Author: Michael Heuser, Department of Hematology, Hemostasis, Oncology and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany*

Background: Acute myeloid leukemia (AML) is a malignant disease with poor long-term prognosis in patients who cannot achieve morphological and molecular remission. Although insights into AML biology and treatment modalities have improved over recent years and even though many patients achieve morphological complete remission (CR), most are still relapsing. These relapses are due to residual leukemia stem cells that can be identified as minimal/measurable residual disease (MRD), with MRD serving as a predictive factor for relapse and mortality. Elimination of MRD in patients having reached CR is seen as essential for optimal and persistent clinical responses. A promising approach is the development of adoptive immunotherapies aimed at directly eradicating tumor cells using T-cells or natural killer (NK) cells. NK cells are part of the body's innate immune system and play a key role in controlling viral infections and conducting tumor immunosurveillance. Furthermore, NK cells can be applied clinically in an allogeneic setting, enabling the supply of high numbers of immune effector cells, which were not exposed to cytotoxic chemotherapeutics. A proprietary *ex vivo* expansion and differentiation method in a fully closed, automated manufacturing platform was developed to generate GTA002, an "off-the-shelf" (allogeneic), cryopreserved NK cell preparation, generated from CD34+ hematopoietic stem and progenitor cells derived from umbilical cord blood. The safety and tolerability of the product was already demonstrated in a Phase I trial in elderly patients with AML (PMLA25) (Dolstra et al. 2017). **Methods:** We are currently conducting a prospective 2-stage, open-label, single arm, multicenter Phase I/IIa trial to evaluate the safety and efficacy of GTA002 in 33 adults with AML who are in CR with MRD and who are not proceeding to allogeneic HSCT (ClinicalTrials.gov Identifier: NCT04632316). Patients enrolled in the clinical trial receive a lymphodepleting conditioning regimen consisting of cyclophosphamide and fludarabine (Cy/Flu) followed by up to 3 NK cell infusions 4 days apart and will be followed up for 12 months. The dose escalation stage of the trial will assess the safety and tolerability of repeat NK cell infusions in a 3+3 design with 3 cohorts and a cumulative dose range of 325 to 3,000 $x10^6$ viable NK cells. The expansion stage will evaluate the safety, tolerability and efficacy of NK cell infusions in 24 additional subjects. The primary efficacy endpoint is the cumulative incidence of the MRD response and secondary efficacy endpoints include the duration of the MRD response, event-free survival, overall survival and cumulative incidence of relapse. Enrollment in the first cohort (one single NK cell infusion) started in December 2020. Clinical trial information: EudraCT number 2019-003686-17. Research Sponsor: Glycostem Therapeutics BV.

TPS7054 **Poster Session**

Phase 3 VERONA study of venetoclax with azacitidine to assess change in complete remission and overall survival in treatment-naïve higher-risk myelodysplastic syndromes. *First Author: Amer Methqal Zeidan, Yale University School of Medicine and Yale Cancer Center, New Haven, CT*

Background: Patients with higher-risk myelodysplastic syndromes (HR-MDS) experience peripheral cytopenias, disease progression to acute myeloid leukemia, and high mortality with expected median overall survival of less than 2 years. Allogeneic hematopoietic cell transplantation (allo-HCT) is the only potentially curative treatment. Patients ineligible for transplantation are treated with hypomethylating agents such as azacitidine (Aza), which is not curative and provides limited improvement in clinical benefit. Venetoclax (Ven) is a selective, potent, oral B-cell lymphoma-2 (BCL-2) inhibitor that is approved in the U.S. in combination with hypomethylating agents for treating older or comorbid patients with newly diagnosed acute myeloid leukemia ineligible for intensive chemotherapy. Ven is approved in the U.S. as first-line treatment for chronic lymphocytic leukemia or small lymphocytic lymphoma. For patients with treatment-naïve HR-MDS, Ven + Aza demonstrated manageable safety and a combined complete remission (CR)/marrow CR (mCR) rate of 79% in a single arm phase 1b study (NCT02942290). To confirm these benefits, the VERONA study, a randomized, double-blind, phase 3 study (NCT04401748) of patients with treatment-naïve HR-MDS, will assess the safety and efficacy of Ven combined with Aza including CR rate and overall survival. **Methods:** Patients (≥18 years) with newly diagnosed HR-MDS per WHO 2016 classification with = 20% bone marrow blasts per marrow biopsy/aspirate at screening will be enrolled at ~200 sites globally (~500 patients). Patients must have intermediate risk or higher IPSS-R (score > 3), ECOG ≤2, and be hematopoietic stem cell transplant (HSCT) eligible without any pre-arranged donor, or HSCT ineligible without a plan for HSCT at Study Day 1. *De novo* patients without prior hypomethylating agents, chemotherapy for MDS, or allogenic stem cell transplantation are eligible. Patients will be randomized 1:1 to receive placebo or Ven 400 mg oral tablet once daily on Days 1-14, both in combination with Aza 75 mg/m^2 (intravenous or subcutaneous) on Days 7-0-0 or Days 5-2-2 per 28-days. Patients will receive study treatment until disease progression, unacceptable toxicity, HCT, withdrawal of consent, or discontinuation. The primary endpoints are CR rate (as adjudicated by investigator) per IWG 2006 criteria and overall survival. Secondary outcomes are red blood cell transfusion independence, platelet transfusion independence, change in fatigue as measured by Patient-Reported Outcomes Measurement Information System (PROMIS)-fatigue SF 7a scale score, time to deterioration in physical functioning domain of EORTC QLC-C30 scale, overall response (CR + partial response), and modified overall response (CR + mCR + partial response). Exploratory objectives are predictive biomarkers and pharmacokinetics. Clinical trial information: NCT04401748. Research Sponsor: AbbVie.

TPS7055 **Poster Session**

Magrolimab + azacitidine versus azacitidine + placebo in untreated higher risk (HR) myelodysplastic syndrome (MDS): The phase 3, randomized, ENHANCE study. *First Author: Guillermo Garcia-Manero, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MDS is a clonal myeloid disorder characterized by cytopenia and ineffective hematopoiesis. The median age of diagnosis is approximately 70 yrs of age and prognosis and treatment are guided by the Revised International Prognostic Scoring System (IPSS-R) criteria. Patients with intermediate, high and very high risk MDS (HR-MDS) have a median overall survival (OS) of 0.8 to 3.7 years. Despite the high unmet need in this patient population, azacitidine (AZA) is the only approved therapy for HR-MDS which has improved overall survival in clinical trials to date. However, these agents lead to low complete response (CR) rates (10-17%) with limited OS (= 2 years), indicating a need for alternative therapy. Magrolimab is a first-in-class monoclonal antibody that blocks the macrophage inhibitory immune checkpoint CD47, a "do not eat me" signal overexpressed on tumor cells. Binding of magrolimab to CD47 leads to phagocytosis of tumor cells. AZA increases expression of prophagocytic "eat me" signals, facilitating synergy with magrolimab. In an ongoing phase 1b study, the combination of magrolimab + AZA led to high response rates (ORR 91%, with a CR of 42%) and an acceptable safety profile without significant immune-related adverse events. ENHANCE (NCT04313881) is a phase 3 trial comparing the efficacy and safety of magrolimab + AZA with that of AZA + placebo (PBO) in previously untreated patients with HR-MDS. **Methods:** Patients ≥18 years old with previously untreated intermediate to very high risk MDS by IPSS-R are eligible for ENHANCE. Randomization is 1:1 to magrolimab + AZA or AZA + PBO with no crossover allowed. Magrolimab or placebo is administered intravenously (IV) with an initial 1 mg/kg priming dose to mitigate on target anemia. An intra-patient dose escalation regimen up to 30 mg/kg is then administered through Cycle 1, 30 mg/kg weekly dosing in Cycle 2, with 30 mg/kg Q2W dosing occurring in Cycle 3 and beyond. AZA is administered per regional prescribing information. Patients may remain on treatment until disease progression, relapse, loss of clinical benefit, or until unacceptable toxicities occur. Two primary efficacy endpoints are CR rate and OS. For patients undergoing allogeneic stem cell transplantation (ASCT), data for the CR rate will be censored at the time of ASCT and OS will be censored at the last known alive date. Secondary efficacy endpoints include RBC transfusion independence rate, event-free survival, minimal residual disease-negative rate, time to AML transformation, and patient-reported Functional Assessment of Cancer Therapy (FACT)-Anemia response rate. Biomarkers of immune cell recruitment, immune cell signaling, and bone marrow penetration of magrolimab will also be explored. Planned enrollment is approximately 520 patients globally, which began in September 2020. Accrual is ongoing. Clinical trial information: NCT04313881. Research Sponsor: Gilead Sciences, Inc.

TPS7056 **Poster Session**

IMerge: A phase 3 study to evaluate imetelstat in transfusion-dependent subjects with IPSS low or intermediate-1 risk myelodysplastic syndromes that are relapsed/refractory to erythropoiesis-stimulating agent treatment. *First Author: Uwe Platzbecker, Department of Hematology and Cell Therapy, University Clinic Leipzig, Leipzig, Germany*

Background: Current treatment options for red blood cell (RBC) transfusion-dependent (TD) patients (pts) with lower risk (LR) myelodysplastic syndromes (MDS) relapsed after or refractory to erythropoiesis-stimulating agents (ESAs) have limited efficacy and durability; new approaches are needed. Imetelstat is a first-in-class telomerase inhibitor that targets cells with short telomeres and active telomerase, characteristics observed in MDS pts across all disease stages. IMerge (MDS3001) is a Phase 2/3 global study of imetelstat for TD pts with non-del(5q) LR MDS post ESA therapy. The results from Phase 2 part indicated that imetelstat achieved durable RBC transfusion independence (RBC-TI) and the most frequently reported adverse events were manageable and reversible grade ≥3 cytopenias. Among 38 pts with median follow-up of 24 months, 8-week, 24-week and 1-year TI rates were 42%, 32% and 29%, respectively; these responses were seen across different LR MDS subtypes. Median TI duration was 20 months and the longest TI was 2.7 years. A high and durable hematologic improvement-erythroid (HI-E) rate of 68% for a median duration of 21 months were also achieved. Reduction of variant allele frequency of mutations by imetelstat treatment was observed in some pts and correlated with clinical benefits (Platzbecker et al EHA 2020; Steensma et al JCO 2020). These results support the Phase 3 part of the trial. **Methods:** IMerge is two-part, Phase 2/3 study (ClinicalTrials.gov: NCT02598661). The Phase 3 part of the study is open for enrollment to adult pts with International Prognostic Scoring System (IPSS) low or intermediate-1 risk, non-del(5q) MDS who are TD, are relapsed after or refractory to ESAs, and have not received treatment with lenalidomide or hypomethylating agents. The study is a randomized (2:1) double-blind, placebo-controlled trial to compare efficacy of imetelstat vs placebo that will enroll approximately 170 pts and will be conducted at approximately 120 centers in North America, Europe, Asia and Middle East. Imetelstat is administered as 2-hour IV infusion every 4 weeks at 7.5 mg/kg. The primary endpoint of the study is to assess the rate of RBC-TI lasting ≥8 weeks. Secondary endpoints include safety, rate of RBC-TI ≥24 weeks, time to RBC-TI start, RBC-TI duration, rate of HI-E, the amount and relative change in RBC transfusions, rate of CR or PR, overall survival, progression of MDS, pharmacokinetics, and quality of life. Biomarkers relevant to the mechanism of action of imetelstat will be assessed to demonstrate target inhibition and their association with clinical responses. Cytogenetics and mutation analyses will be performed to evaluate the impact of imetelstat on reduction/depletion of malignant clones leading to disease modification. The study is currently recruiting pts. Clinical trial information: NCT02598661. Research Sponsor: Geron Corporation.

TPS7057 **Poster Session**

BOREAS: A global phase 3 study of KRT-232, a first-in-class murine double minute 2 (MDM2) inhibitor in *TP53*^{WT} relapsed/refractory (R/R) myelofibrosis (MF). *First Author: Srdan Verstovsek, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The prognosis for patients (pts) with MF who have primary resistance to or who have progressed after treatment with ruxolitinib (RUX) is poor (median OS is ~13 months), highlighting the unmet need for novel treatments in this setting. MDM2 is a key negative regulator of the tumor suppressor protein p53 that is overexpressed in CD34+ cells in MF pts. Elevated MDM2 expression attenuates p53 activity, resulting in proliferation of malignant CD34+ cells. KRT-232 is a potent, selective, orally available MDM2 inhibitor that restores p53 function resulting in apoptosis of malignant stem and progenitor cells. KRT-232 has the potential to demonstrate disease-modifying effects in MF pts who are R/R to prior JAK inhibitor (JAKi) therapy. The FDA has granted KRT-232 Fast Track designation for the treatment of JAKi R/R MF. Clinical proof-of-concept for KRT-232 in R/R MF was established in phase 2 of this study. Once-daily dosing of KRT-232 at 240 mg (Day 1-7 of 28-day cycle) yielded a best spleen volume reduction (SVR) ≥35% by central review in 16% of pts, best total symptom score (TSS) response > 50% in 30% of pts, and 87% reduction of CD34+ cells in peripheral blood at Week 24. Spleen responses were superior in pts who were off RUX vs those on RUX at baseline imaging (best SVR ≥35%: 29% vs 0%). KRT-232 demonstrated a tolerable safety profile that included prophylaxis for nausea/vomiting (Al-Ali. EHA 2020). **Methods:** BOREAS is a randomized, controlled, open-label, global phase 3 study in MF pts (primary MF/post–polycythemia vera MF/post–essential thrombocythemia MF) who are R/R to JAKi. Pts aged ≥18 y with confirmed MF per WHO criteria, intermediate-1, 2, or high-risk disease (per DIPSS), ECOG performance status ≤2, adequate hematologic function (platelets ≥50 x 10^9/L), and wild-type p53 will be enrolled; pts with JAKi treatment = 28 d before baseline MRI/CT will be excluded. Pts will be randomized (2:1) to KRT-232 (240 mg on Day 1-7/28-day cycle; n = 188) or best available treatment (BAT; n = 94) and stratified by MF type (primary vs secondary) and baseline TSS (≤10 vs > 10). BAT options include hydroxyurea, chemotherapy, or supportive care (including; but not limited to: corticosteroids and androgens); treatment selection is at the discretion of the investigator. Pts in BAT arm with documented disease progression at any time (spleen volume increase ≥25% from baseline or confirmed leukemic transformation) or those who complete Week 24 assessments may crossover to the KRT-232 arm. Primary endpoint is rate of SVR ≥35% by MRI/CT at Week 24 (central review). Key secondary endpoints are ≥50% reduction in TSS rate at Week 24 (per MFSAF v4.0), PFS, OS, best overall SVR ≥35%, and duration of spleen response. Enrollment is planned at 137 sites in 21 countries in North and South America, Europe, and Asia-Pacific (ClinicalTrials.gov: NCT03662126). Clinical trial information: NCT03662126. Research Sponsor: Kartos Therapeutics, Inc.

TPS7058 **Poster Session**

A phase 3, randomized, double-blind, placebo-controlled study of ruxolitinib plus parsaclisib in patients with JAK- and PI3K-inhibitor treatment-naïve myelofibrosis. *First Author: Abdulraheem Yacoub, University of Kansas Medical Center, Westwood Campus, Westwood, KS*

Background: Ruxolitinib (JAK1/JAK2 inhibitor) significantly improves outcomes in patients with myelofibrosis (MF); however, a subset of patients may experience a suboptimal response. Recent phase 2 data showed that addition of PI3Kδ inhibitor parsaclisib to ruxolitinib monotherapy resulted in additional alleviation of MF symptoms and splenomegaly in patients with MF (Yacoub. EHA2020. S216). This phase 3, randomized, double-blind study (INCB 50465-313; NCT04551066), evaluates the combination of ruxolitinib and parsaclisib in patients with MF who are naïve to Janus kinase (JAK) and PI3K inhibitor therapies. **Methods:** Eligible patients are aged $\geq$18 years with a diagnosis of primary MF, post-polycythemia vera MF, or post-essential thrombocythemia MF, have a Dynamic International Prognostic Scoring System (DIPSS; Passamonti. Blood. 2010;115:1703-1708) risk category of at least Intermediate (INT)-1, palpable spleen $\geq$5 cm below left subcostal margin; total symptom score $\geq$10 at screening, ECOG PS 0–2, and life expectancy $\geq$24 weeks. Patients will be excluded if they previously received therapy with any JAK inhibitor, any PI3K inhibitor, any experimental or standard drug therapy for MF $\leq$3 months of first study dose and/or lack of recovery from all toxicities related to previous therapies to grade $\leq$1, have recent history of inadequate bone marrow reserve (eg, platelet count = 50×10^9/L) or have inadequate liver or renal function at screening. Approximately 440 patients will be randomized (1:1) to ruxolitinib plus parsaclisib 5 mg QD or ruxolitinib plus matching placebo, with stratification at randomization by DIPSS risk category (high vs INT-2 vs INT-1) and platelet count ($\geq100\times10^9$/L vs 50 to = 100×10^9/L inclusive). Treatment will begin on Day 1, with starting ruxolitinib dose level determined by baseline platelet count, and will continue as long as treatment is tolerated and discontinuation criteria are not met. When the last enrolled patient has completed 24 weeks of treatment, the study will be unblinded and patients randomized to ruxolitinib plus placebo who have adequate hematology parameters will be able to crossover to receive parsaclisib together with continued ruxolitinib. The primary objective is the evaluation and comparison of spleen volume at Week 24 for patients who received ruxolitinib plus parsaclisib versus ruxolitinib plus placebo. Secondary objectives include evaluation and comparison of patient-reported MF symptoms, overall survival, time to onset and duration of response in spleen volume, and safety and tolerability for ruxolitinib plus parsaclisib versus ruxolitinib plus placebo. Sites are opening across the United States, Europe, Asia, and New Zealand. Clinical trial information: NCT04551066. Research Sponsor: Incyte Corporation.

7500 **Oral Abstract Session**

First results of a head-to-head trial of acalabrutinib versus ibrutinib in previously treated chronic lymphocytic leukemia. *First Author: John C. Byrd, The Ohio State University Wexner Medical Center, Columbus, OH*

Background: Increased selectivity of the Bruton tyrosine kinase inhibitor (BTKi) acalabrutinib (Aca) vs ibrutinib (Ib) may improve tolerability. We conducted an open-label, randomized, non-inferiority, phase 3 trial to compare Aca vs Ib in patients (pts) with chronic lymphocytic leukemia (CLL). **Methods:** Previously treated CLL pts with del(17p) or del(11q) by central lab were randomized to receive oral Aca 100 mg BID or Ib 420 mg QD (stratified by del(17p) status, ECOG PS [2 vs ≤1], and number of prior therapies [1–3 vs ≥4]) until progression or unacceptable toxicity. Primary endpoint was progression-free survival (PFS) as assessed by IRC; secondary endpoints of all grade atrial fibrillation (AF), grade ≥3 infection, Richter transformation, and overall survival (OS) were assessed in hierarchical order. **Results:** 533 pts (Aca, n=268; Ib, n=265) were randomized (median age 66 y; median 2 prior therapies; del(17p) 45.2%; del(11q) 64.2%). At a median follow-up of 40.9 mo (range 0.0–59.1), Aca was noninferior to Ib with a median PFS of 38.4 mo in both arms (HR 1.00; 95% CI 0.79–1.27). Aca was statistically superior to Ib in all-grade AF incidence (9.4% vs 16.0%; *P*=0.023). Among the other secondary endpoints, incidences of grade ≥3 infection (Aca: 30.8%, Ib: 30.0%) and Richter transformation (Aca: 3.8%, Ib: 4.9%) were comparable between arms. Median OS was not reached in either arm (HR 0.82 [95% CI 0.59–1.15]), with 63 (23.5%) deaths in the Aca arm and 73 (27.5%) in the Ib arm. Among any-grade AEs in ≥20% of pts in either arm, Aca was associated with a lower incidence of hypertension (9.4%, 23.2%), arthralgia (15.8%, 22.8%), and diarrhea (34.6%, 46.0%) but a higher incidence of headache (34.6%, 20.2%) and cough (28.9%, 21.3%). AEs led to treatment discontinuation in 14.7% of Aca- vs 21.3% of Ib-treated pts. Among any-grade events of clinical interest, cardiac, hypertension, and bleeding events were less frequent with Aca (Table). **Conclusions:** In this first head-to-head trial of BTKis in CLL, Aca demonstrated non-inferior PFS with less cardiotoxicity and fewer discontinuations due to AEs vs Ib. Clinical trial information: NCT02477696. Research Sponsor: Acerta Pharma, a member of the AstraZeneca Group.

Selected events of clinical interest.

	Acalabrutinib (n = 266)		Ibrutinib (n = 263)	
Events, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Cardiac events	64 (24.1)	23 (8.6)	79 (30.0)	25 (9.5)
Atrial fibrillation[a]	25 (9.4)	13 (4.9)	42 (16.0)	10 (3.8)
Ventricular tachyarrhythmias	0	0	1 (0.4)	1 (0.4)
Hypertension[b]	25 (9.4)	11 (4.1)	61 (23.2)	24 (9.1)
Bleeding events	101 (38.0)	10 (3.8)	135 (51.3)	12 (4.6)
Major bleeding events[c]	12 (4.5)	10 (3.8)	14 (5.3)	12 (4.6)
Infections	208 (78.2)	82 (30.8)	214 (81.4)	79 (30.0)
Second primary malignancies excluding non-melanoma skin cancers	24 (9.0)	16 (6.0)	20 (7.6)	14 (5.3)

[a]Includes atrial fibrillation and atrial flutter [b]Includes hypertension, blood pressure increased, and blood pressure systolic increased [c]Any hemorrhagic event that was serious, grade ≥3, or a CNS hemorrhage (any grade).

7501 **Oral Abstract Session**

Fixed-duration (FD) first-line treatment (tx) with ibrutinib (I) plus venetoclax (V) for chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL): Primary analysis of the FD cohort of the phase 2 captivate study. *First Author: Paolo Ghia, Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milan, Italy*

Background: CAPTIVATE (PCYC-1142) is a multicenter phase 2 study of first-line I+V in CLL. We previously reported results from the Minimal Residual Disease (MRD) cohort wherein undetectable MRD (uMRD) was achieved in over two-thirds of patients (pts) with 12 cycles of I+V, and 30-mo PFS rates were ≥95% irrespective of subsequent randomized treatment (Wierda, ASH 2020). We now present results from the FD cohort, evaluating fixed-duration tx with I+V. **Methods:** Pts aged ≤70 y with previously untreated CLL/SLL received 3 cycles of I then 12 cycles of I+V (I 420 mg/d orally; V ramp-up to 400 mg/d orally). Primary endpoint was CR rate, including CR with incomplete recovery (CRi); secondary endpoints were ORR, duration of response, uMRD rate ($<10^{-4}$ by 8-color flow cytometry), PFS, OS, tumor lysis syndrome (TLS) risk reduction, and adverse events (AEs). **Results:** 159 pts were enrolled (median age 60 y). High-risk features included del(17p)/*TP53* mutation, 17%; del(11q), 18%; complex karyotype, 19%; and unmutated IGHV, 56%. 147 (92%) and 149 (94%) pts completed planned tx with I and V, respectively. Median time on study was 27.9 mo (range, 0.8–33.2). With fixed-duration I+V, CR rate was 55% (95% CI 48–63) in the overall population and was consistent across high-risk subgroups. Of the 88 pts who achieved CR, 78 (89%) had durable CR (duration ≥1 y); 1 died 7 mo after CR, and 9 with <1 y follow-up were not evaluable. ORR was 96%. Best uMRD response was achieved in 77% of pts in peripheral blood (PB) and 60% of pts in bone marrow (BM). 24-mo PFS was 95%; 24-mo OS was 98%. Results were similar in pts without del(17p) (n=136) (Table). In pts with del(17p)/*TP53* mutation (n=27), CR rate was 56%, uMRD rate was 81% (PB) and 41% (BM), and 24-mo PFS was 84% (95% CI 63–94). Of 34 pts with high baseline TLS risk based on tumor burden, 32 (94%) shifted to medium or low risk after I lead-in; no TLS occurred. AEs were primarily grade 1/2. Most common grade 3/4 AEs were neutropenia (33%), hypertension (6%), and neutrophil count decreased (5%). AEs led to discontinuation of I in 4% and V in 2%. **Conclusions:** First-line I+V is an all-oral, once-daily, chemotherapy-free, fixed-duration regimen that provides deep, durable responses in pts with CLL/SLL, including those with genomic high-risk features. CR, uMRD rates, PFS, and OS appear favorable. The safety profile of I+V was consistent with known AEs for each agent; no new safety signals were identified. Clinical trial information: NCT02910583. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

Efficacy	Pts without del(17p) n=136	All pts N=159
CR/CRi, n (%)	76 (56)	88 (55)
Durable CR/CRi , n/N (%)*	66/76 (87)	78/88 (89)
ORR, n (%)	130 (96)	153 (96)
uMRD in PB, n (%)	104 (76)	122 (77)
uMRD in BM, n (%)	84 (62)	95 (60)
24-mo PFS rate, % (95% CI)	96 (91-98)	95 (90-97)
24-mo OS rate, % (95% CI)	98 (93-99)	98 (94-99)

*Progression-free ≥12 cycles from first CR.

7502 **Oral Abstract Session**

First-in-human study of lisaftoclax (APG-2575), a novel BCL-2 inhibitor (BCL-2i), in patients (pts) with relapsed/refractory (R/R) CLL and other hematologic malignancies (HMs). *First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL*

Background: The BCL-2i venetoclax is active in certain HMs but can increase the risk of tumor lysis syndrome (TLS), requiring a 5-week dose ramp-up for CLL patients. Cases of severe neutropenia with venetoclax treatment have also been reported. Lisaftoclax is a novel, potent, selective BCL-2i that is active against HMs and is under clinical development. **Methods:** This first-in-human global phase I dose study assessed the safety, PK, PD, efficacy, and MTD/RP2D of lisaftoclax in patients with R/R CLL and other HMs. Lisaftoclax was orally administered daily in a 28-day cycle. Patients with CLL or intermediate-high TLS risk were initiated on a daily ramp-up schedule until the assigned dose before the study cycles. **Results:** On January 7, 2021, 35 pts had been enrolled and treated with lisaftoclax at doses ranging from 20 to 1,200 mg, with a median (range) of 2 (1-13) prior lines of treatment, and had diagnoses of R/R CLL or SLL (n = 15), MM (n = 6), FL (n = 5), WM (n = 4), and either AML, MCL, DLBCL, MDS, or HCL (n = 1 each). No DLT has been observed, even though 1,200 mg was considered as the highest dose treated. The MTD has not been reached, and no laboratory or clinical TLS has been reported. Any grade TRAEs in > 10% of pts included neutropenia (22.9%) and anemia (17.1%; hematologic), and fatigue (28.6%), diarrhea (17.1%), and nausea (11.4%; nonhematologic). Grade >3 TRAEs were neutropenia (14.3%) and thrombocytopenia, leukopenia, lymphopenia, fatigue, and nausea (2.9% of pts each). In CLL/SLL pts, grade 3-4 TRAEs included neutropenia (13.3%) and thrombocytopenia (6.7%), which did not cause treatment-related discontinuation. In all, 12 of 35 pts (34.3%) had non-treatment-related SAEs, and only two pts experienced > 1 SAE. With a median (range) treatment of 7 (3-20) cycles, 12 of 14 evaluable R/R CLL/SLL pts achieved PR, for an ORR of 85.7% and a median (range) time to response of 3 (2-7) cycles. Absolute lymphocyte counts (ALCs) were reduced at lisaftoclax doses as low as 20 mg/day. The preliminary PK profile showed that exposures increased with lisaftoclax doses from 20 to 1,200 mg (average half-life: 4-5 hours). On BH3 profiling, lisaftoclax rapidly triggered changes in BCL-2 complex in CLL/SLL pt samples, which were consistent with rapid clinical reductions in ALCs. **Conclusions:** Lisaftoclax was well tolerated up to 1,200 mg/day. No TLS was observed, even with the daily ramp-up schedule. There were no significant new or unmanageable safety findings, and the ORR in R/R CLL/SLL pts was 85.7%. Grade 3-4 TRAEs were infrequent, even at dose levels of 800 mg and above. BCL-2i lisaftoclax offers a treatment alternative for patients with R/R CLL/SLL and other HMs, with a daily ramp-up schedule that may be more pt "user friendly" and a favorable preliminary safety profile. Internal study identifier APG2575-001. Clinical trial information: NCT03537482. Research Sponsor: Ascentage Pharma Group Corp Limited (Hong Kong).

7503 **Oral Abstract Session**

ECOG-ACRIN E1411 randomized phase 2 trial of bendamustine-rituximab (BR)-based induction followed by rituximab (R) ± lenalidomide (L) consolidation for Mantle cell lymphoma: Effect of adding bortezomib to front-line BR induction on PFS. *First Author: Mitchell Reed Smith, GW University, Washington, DC*

Background: Optimal initial therapy for mantle cell lymphoma (MCL) remains uncertain. The randomized phase 2 NCTN trial E1411 tested if progression-free survival (PFS) is prolonged by addition of bortezomib (V) (1.6 mg/m2 SC/IV days 1, 8) to bendamustine-rituximab (BVR vs BR) induction and/or by addition of lenalidomide (L) to rituximab (LR vs R) consolidation. Here we report efficacy and toxicity of induction BVR vs BR. **Methods:** 373 pts, accrued 2012–16, stratified by MIPI and age (≥60) received 1 of 4 arms: A) BR induction x 6 followed by R x 2 yrs, B) BVR followed by R, C) BR followed by LR or D) BVR followed by LR. Eligible pts had untreated MCL, ≥ age 18 (amended from ≥60 when S1106 for < 65 closed), ECOG PS 0-2 and adequate hematologic and organ function. Pts without progressive disease during induction proceeded to consolidation. Primary induction objective was whether adding bortezomib (BVR) (Arms B + D) to BR (Arms A + C) improves PFS, irrespective of consolidation R vs LR. Design of 360 eligible treated pts would provide 93.8% power to detect 10% improvement in 2-yr PFS from 70% hypothesized for BR, corresponding to 37.4% reduction in hazard using stratified log-rank test at 1-sided 10% alpha. Efficacy population was 179 (BVR) and 180 (BR), induction treatment completed in 144 vs 153, progressive disease during induction 6 vs 7 and registration to consolidation 140 vs 145. **Results:** Baseline demographics did not differ between the groups, with median age 67 (range 42-90) and 13% < 60 yr, 73% men, ECOG PS 0-1 97%, MIPI Low/Med/Hi 37/29/34%. Estimated PFS at 2 yrs 79.6% BVR (95% CI 73.8-85.9) vs 74.5% BR (95% CI 68.2-81.4) (1-sided stratified log-rank p = 0.268). With median PFS follow-up 51 mos, median PFS estimated at 64.1 and 64.0 mos. Overall response rate (ORR) for BVR was 88.9% (CR 65.5%) vs 89.5% (CR 60.5%) BR (z-test 1 sided p = 0.577 for ORR). Treatment related deaths during induction were 2 in BVR (cardiac arrest, hepatitis) and 1 in BR (tumor lysis). Grade ≥ 3 toxicities were 88.1% (163/185) BVR vs 77.5% (145/187) BR. For BVR vs BR grade ≥ 3 neutropenia occurred in 52 vs 39 pts, though febrile neutropenia (7 vs 6), anemia (7 vs 8) and thrombocytopenia (18 vs 16) did not differ. Peripheral neuropathy (PN) grade 2 was 8 sensory for BVR vs 2 sensory/1 motor for BR, while grade 3 PN was 6 sensory/1 motor for BVR vs 0 with BR. The only non-hematologic grade ≥ 3 toxicity in > 5% of pts was rash (9 vs 12 pts). **Conclusions:** Bortezomib did not significantly improve the primary endpoint of PFS when added to BR as initial MCL therapy. ORR and CR rates at end of induction were also similar. Follow-up continues to assess the entire treatment regimen, including consolidation R vs LR, but the PFS > 5 yrs, high ORR and MRD negativity rate (Smith et al ASH 2019) in this BR-based trial support BR as a platform for MCL induction therapy. Clinical trial information: NCT01415752. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

7504 **Oral Abstract Session**

Real-world (RW) treatment (tx) patterns and outcomes of 3,455 previously untreated mantle cell lymphoma (MCL) patients (pts) in U.S. routine clinical practice.

First Author: Peter Martin, Weill Cornell Medicine, New York-Presbyterian Hospital, New York, NY

Background: MCL is a non-Hodgkin lymphoma with heterogeneous biology and outcomes. We characterized RW tx patterns and outcomes of MCL pts to identify factors associated with outcomes in the US. **Methods:** This retrospective study included adult MCL pts diagnosed Jan 2011-Nov 2020 in the nationwide Flatiron Health EHR-derived deidentified database. Pt characteristics, tx patterns, time to next tx (rwTTNT, defined as start of first-line [1L] tx to subsequent tx or death) and rwOS were evaluated. **Results:** 3455 pts were included, 85.3% from a community oncology setting. In 2946 (85.2%) pts with documented 1L MCL tx, median age was 69.5 y (range 27.7-85.3); 9.5% had blastoid/pleomorphic MCL. 262 (39.6%) and 235 (35.6%) of 661 pts with available MCL international prognostic index (MIPI) had intermediate and high risk, respectively. 150/1253 pts (12.0%) with available ECOG PS had PS $\geq$ 2. Chemoimmunotherapy was the most common 1L tx, including BR in 1223 (41.5%), R-CHOP in 512 (17.4%) and cytarabine (ara-C)-containing tx in 414 (14.1%). 667 pts received R maintenance (MR). In 1036 pts $<$ 65 y, 243 pts received 1L stem cell transplant (SCT), mainly autologous. In 1L-treated pts, with median follow-up of survivors of 45.3 mos (range 0.03-117.2), median rwTTNT was 24 mos; 36-mo rwOS was 67%. The Table shows tx received and outcomes by age and SCT status. MVA analyses showed age $\geq$ 65 y, ECOG PS $\geq$ 2, LDH/ULN $\geq$ 1, WBC $\geq$ 10 $\times$ 10^9/L, bulky disease ($\geq$ 5 cm) and blastoid/pleomorphic morphology were associated with shorter rwTTNT and rwOS; MR was independently associated with longer rwTTNT and rwOS. In pts $<$ 65 y who were alive and did not initiate subsequent tx within 6 mos of 1L tx ("SCT-eligible"), 36-mo rwTTNT and rwOS were similar between pts treated with vs without SCT: 65% vs 59% and 86% vs 85%, respectively. **Conclusions:** In this large RW cohort of primarily community-based US practices, median 1L rwTTNT for MCL pts was ~ 2 y. BR was the most commonly used 1L tx. SCT was uncommon even in pts $<$ 65 y, suggesting RW considerations may influence SCT eligibility and availability. Also, SCT was not clearly associated with rwOS. As with other reports, older age and high-risk disease features were predictive of worse outcome in RW, while MR appeared to be associated with better outcomes. Outcomes across the board appear worse than prospective trials, suggesting a need to focus on developing tx that can be delivered effectively in the community setting. Research Sponsor: Janssen Research and Development.

Tx and outcomes in 1L MCL.

	Age < 65 y at 1L tx (n = 1036)		Age ≥ 65 y at 1L tx (n = 1910)	
	No SCT (n = 793)	Received SCT (n = 243)	No SCT (n = 1835)	Received SCT (n = 75)
1L tx received, n (%)				
Ara-C–containing	189 (23.8)	130 (53.5)	67 (3.7)	28 (37.3)
BR	244 (30.8)	42 (17.3)	914 (49.8)	23 (30.7)
R-CHOP	172 (21.7)	48 (19.8)	273 (14.9)	19 (25.3)
Pt outcome, % (95% CI)				
36-mo rwTTNT	40 (36-44)	63 (57-71)	37 (35-40)	63 (51-77)
36-mo rwOS	75 (72-79)	86 (81-91)	61 (58-63)	82 (72-94)

7505 **Oral Abstract Session**

The combination of venetoclax, lenalidomide, and rituximab in patients with newly diagnosed mantle cell lymphoma induces high response rates and MRD undetectability.

First Author: Tycel Phillips, University of Michigan Medical School, Ann Arbor, MI

Background: MCL is a rare lymphoma without a standard of care but several regimens have demonstrated clinical activity, the majority based on traditional chemotherapy. We hypothesized that adding venetoclax (V) to R2 would be safe and effective in MCL pts irrespective of age, morphology or stage. Here we present safety and efficacy data from the on-going phase 1b study of R2 + V in pts with newly diagnosed MCL. **Methods:** This multi-center phase 1 study (NCT03523975) enrolled pts aged $\geq$18 yrs with untreated MCL. The primary objective was to characterize the safety and tolerability of R2 + V and determine the MTD. During induction (12 months (m)) pts received lenalidomide (L) 20 mg daily on day 1-21, Rituximab (R) was given weekly during c1 then on day 1 of every even cycle, V was escalated over 4 weeks to 400 mg beginning day 8. Each cycle is 28 days (d). The DLT period was 42 d beginning C1D8. In maintenance, R every 8 weeks for 36m, L at 10 mg or half of last dose during induction for 24 m and V for minimum 12 m. No pts have been transplanted. Pts with progression (PD) came off study. MRD was analyzed in parallel with scans during induction by clonoSEQ assay (Adaptive Biotechnologies). **Results:** As of Feb. 1st, 2021, we have enrolled all 28 planned pts on study. Pt characteristics/responses are summarized in Table. Among the 28 pts who have received at least one dose, the median treatment duration so far is 278d (IQR 170-560), with 24 pts still on treatment (Tx). 1 pt is off from a unrelated condition. All pts escalated to V 400 mg w/o any DLTs noted. Treatment-emergent adverse events (TEAEs) were reported in 100% of pts, and grade 3+ TEAEs were reported in 26 (93%) patients. The most common all-grade TEAEs ($\geq$50% of pts), regardless of relationship to study Tx, were fatigue, neutropenia and diarrhea. Grade $\geq$3 TEAEs reported in $\geq$50% pts were neutropenia (68%) and thrombocytopenia (50%). No pts have withdrawn or d/c Tx due to AEs. There was one grade 5 event, in a non-evaluable pt, related to a PE that occurred prior to DLT period. In the 28 evaluable pts the ORR (CR/PR) was 96% (27/28 pts) with CR/CRu of 89%. Of the responding pts, two had PD, one w/ CR and one w/ PR. All pts with PD had baseline *TP53* mutation. MRD testing was successful in all pts. At time of submission 20 of 28 (71%) were MRD - at 10^{-6}. **Conclusions:** Interim results show that at the MTD the combination of V 400 mg daily, L 20 mg, with R is safe with a manageable toxicity profile and a high ORR and MRD - in pts with newly diagnosed MCL. Safety data is consistent with the AE profile noted for each drug without any unexpected or unique AEs. Updated results including BH3 profiling will be presented at the meeting. Clinical trial information: NCT03523975. Research Sponsor: Abbvie, Rogel Cancer Center.

Sex, male, % (n)	**64% (18)**
Age, years, median (IQR)	65 (57, 69)
Race, white, % (n)	100% (28)
Tx duration, d, median (IQR)	278 (170, 560)
Stage IV, % (n)	96% (27)
MIPI High, % (n)	64% (18)
Blast/Pleo, % (n)	21% (6)
Ki-67 $\geq$30%, % (n)	68% (19)
ORR	**96%**
CR/CRu	**89%**
MRD -	**71%**

7506 **Oral Abstract Session**

Myeloablative versus non-myeloablative consolidative chemotherapy for newly diagnosed primary central nervous system lymphoma: Results of CALGB 51101 (Alliance).

First Author: Tracy Batchelor, Brigham and Women's Hospital, Boston, MA

Background: Optimal consolidative therapy for primary central nervous system lymphoma (PCNSL) is not defined. Avoidance of whole brain radiation may reduce risk of neurotoxicity. Non-radiation consolidative options include myeloablative chemotherapy with autologous stem cell transplantation (HDT/ASCT) or non-myeloablative chemotherapy. **Methods:** This is a randomized phase 2, National Clinical Trials Network study of induction methotrexate (MTX) (8 g/m^2 days 1, 15), temozolomide (TMZ) (150-200 mg/m^2 D7-11), and rituximab (RTX) (C1 D3, 10, 17, 24 and C2 D3, 10) in four 28-day cycles followed by one cycle of cytarabine (ARA-C) (2 g/m^2 BID, D1, 2) (MTRA). After induction, patients (pts) received consolidation with thiotepa (5 mg/kg BID, D -5, -4) plus carmustine (400 mg/m^2, day -6) and ASCT (Arm A) or one cycle of ARA-C (2 g/m^2 BID, D1-4) plus infusional etoposide (40 mg/kg over 96h) (Arm B). Pts were stratified on age and performance status and randomized 1:1 before induction. The primary endpoint was progression-free survival (PFS) from randomization. With 110 pts, there was 84% power to detect an improvement in PFS using a log-rank test (1-sided α= 10%), assuming a median PFS of 3 months for pts who progress during induction, and a median PFS of 2 years (yrs) for Arm B and 4.5 yrs for Arm A consolidation. This report includes the results for the primary endpoint analysis. **Results:** 113 pts (median age 61 yrs, range 33-75) were randomized (Arm A: 57, Arm B: 56) across 27 centers. 108 eligible pts who received induction therapy were included in the primary endpoint analysis (Arm A: 54, Arm B: 54). 72/108 pts started consolidation and 70/72 completed consolidation per protocol (Arm A: 36, Arm B: 34). With a median follow-up of 3.8 years, median PFS from randomization was 6 yrs (95% CI 3.9-not reached) in Arm A vs 2.4 yrs (95% CI 0.6-not reached) in Arm B (p = 0.02). However, more pts randomized to Arm B went off treatment before consolidation due to progression or death (28% vs 11%, p = 0.05). PFS landmarked at start of consolidation demonstrated a trend for improved PFS favoring Arm A (HR 0.58, 95% CI 0.25-1.36; p = 0.21). Median OS was not reached in either arm, and 3-yr estimates were 83% (95% CI 69-91; Arm A) vs 72% (95% CI 57-82; Arm B). Toxicities were similar between arms with no treatment-related mortality during consolidation. **Conclusions:** MTRA induction followed by myeloablative consolidation (Arm A) had improved PFS vs MTRA induction followed by non-myeloablative consolidation (Arm B), though more progressions or deaths leading to treatment discontinuation prior to consolidation in Arm B were noted. Both consolidation regimens were well-tolerated with encouraging PFS and OS in newly-diagnosed PCNSL. Support: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org. Clinical trial information: NCT01511562. Research Sponsor: U.S. National Institutes of Health.

7507 **Oral Abstract Session**

CALGB 50801 (Alliance): PET adapted therapy in bulky stage I/II classic Hodgkin lymphoma (cHL).

First Author: Ann S. LaCasce, Dana-Farber Cancer Institute, Boston, MA

Background: Bulky disease is associated with inferior outcomes in patients with early stage cHL. Historically, most patients (pts) receive chemotherapy followed by radiotherapy (RT), which is associated with long-term toxicity. We tested a PET-adapted approach to reduce the need for RT in pts with early PET-negative (PET-) disease and escalate therapy in pts with PET-positive (PET+) disease. **Methods:** Eligible pts aged 18-60 years (yrs) had stage IA-IIB cHL with disease bulk $>$10 cm or $>$.33 max intrathoracic diameter on chest x-ray. Pts received 2 cycles of doxorubicin-bleomycin-vinblastine-dacarbazine (ABVD) followed by centrally reviewed PET. PET- was defined as Deauville of 1-3. Pts who achieved a negative PET scan (PET2-) received 4 additional cycles of ABVD. PET2+ pts received 4 cycles of escBEACOPP plus 30 Gy involved-site radiation therapy. The primary endpoint was progression-free survival (PFS) estimated from PET2. With 93 pts and assuming 30% PET2+, there was 80% power to rule out that PFS of PET2+ pts was substantially inferior to PFS of PET2- pts (HR 4.1, 3-yr PFS 40% vs 80%) if the true PFS of PET2+ pts was closer to that of PET2- pts (HR 2.29, 3-yr PFS 60% vs 80%) with one-sided alpha=0.15. With few events and mature follow-up, we report results 3 yrs after the last pt was enrolled. **Results:** Between May 2010 and October 2017, 101 pts enrolled. Excluding 6 ineligible pts (3 without baseline DLCO, 2 did not meet definition of bulk, 1 stage IIIB) and 1 pt without PET2, 94 were evaluable. 78% of pts were PET2- (73 PET2-, 21 PET2+). Median age was 30 yrs (range: 18 to 58) and 53.2% were female. Distribution of stage was: 1A - 7.4%, IB - 2.1%, IIA – 39.4%, IIB - 51.1%; 61.9% PET2+ pts had stage IIB disease. Therapy was generally well tolerated. Grade $>$ 3 neutropenia occurred in 86% of pts with 8% of PET2- and 10% of PET2+ with grade $>$ 3 febrile neutropenia. 3-yr PFS estimates were 93.1% (95% CI: 87.4-99.1%) in PET2- pts, 89.7% (95% CI: 77.2-100.0%) in PET2+ pts (HR=1.01, 85% upper bound 2.32), and 92.3% (95% CI: 87.0-98.0%) for all pts. The protocol-defined primary endpoint was met as the PFS hazard ratio for PET2+ vs PET2- was less than 4.1 (one sided p=0.04). With a median follow-up of 5.5 yrs, 3 PET2- pts died (HL, anaplastic astrocytoma and COPD) and 1 PET2+ died of progressive disease. 3-yr overall survival (not a primary or secondary outcome of the study) estimates were 98.6% (95% CI: 95.9-100.0%) in PET2- pts, 94.4% (95% CI: 85.4-100.0%) in PET2+ pts (HR: 1.2, 95% CI: 0.12, 11.60), and 97.7% (95% CI: 94.7-100.0%) for all pts. **Conclusions:** Excellent PFS outcomes were observed in all pts using a PET-adapted approach that allowed omission of RT in 78% of pts. In addition, PET2+ pts treated with escalation to BEACOPP and consolidative RT did not have inferior outcomes. Support: U10CA180821, U10CA180882; https://acknowledgments.alliancefound.org; ClinicalTrials.gov Identifier: NCT01118026. Clinical trial information: NCT01118026. Research Sponsor: U.S. National Institutes of Health.

7508 **Oral Abstract Session**

Efficacy and safety of tisagenlecleucel (Tisa-cel) in adult patients (Pts) with relapsed/refractory follicular lymphoma (r/r FL): Primary analysis of the phase 2 Elara trial. *First Author: Stephen J. Schuster, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: Most pts with r/r FL experience multiple relapses and progressively worse clinical outcomes with each line of therapy, underlining a need for novel therapies. Tisa-cel has demonstrated durable responses and manageable safety in adult pts with r/r diffuse large B-cell lymphoma. Here we report the primary analysis of ELARA, an international, single-arm phase 2 trial of tisa-cel in adult pts with r/r FL. **Methods:** Eligible pts (≥18 y) had r/r FL (grades [Gr] 1-3A) after ≥2 lines of therapy or had failed autologous stem cell transplant. Bridging therapy was permitted followed by disease assessment prior to tisa-cel infusion. Pts received tisa-cel ($0.6\text{-}6\times10^8$ CAR+ viable T cells) after lymphodepleting chemotherapy. The primary endpoint was complete response rate (CRR) by central review per Lugano 2014 criteria. Secondary endpoints included overall response rate (ORR), duration of response (DOR), progression-free survival (PFS), overall survival (OS), safety, and cellular kinetics. Predefined primary analysis occurred when ≥90 treated pts had ≥6 mo of follow-up. **Results:** As of September 28, 2020, 98 pts were enrolled and 97 received tisa-cel (median follow-up, 10.6 mo). At study entry, median age among treated pts was 57 y (range, 29-73), 85% had stage III-IV disease, 60% had a FLIPI score ≥3, 65% had bulky disease, and 42% had LDH > upper limit of normal. The median number of prior therapies was 4 (range, 2-13); 78% of pts were refractory to their last treatment (76% to any ≥2 prior regimens) and 60% progressed within 2 y of initial anti-CD20–containing treatment. Of 94 pts evaluable for efficacy, the CRR was 66% (95% CI, 56-75) and the ORR was 86% (95% CI, 78-92). CRRs/ORRs were comparable among key high-risk subgroups. Estimated DOR (CR) and PFS rates at 6 mo were 94% (95% CI, 82-98) and 76% (95% CI, 65-84), respectively. Of 97 pts evaluable for safety, 65% experienced Gr ≥3 adverse events within 8 weeks post-infusion, most commonly neutropenia (28%) and anemia (13%). Any-grade cytokine release syndrome (per Lee scale) occurred in 49% of pts (Gr ≥3, 0%). Any-grade neurological events (per CTCAE v4.03) occurred in 9% of pts (Gr 3, 0%; Gr 4, 1 pt and recovered). Three pts died from progressive disease. Cellular kinetic parameters for tisa-cel were estimated using transgene levels (by qPCR) in peripheral blood. C_{max} and $AUC_{0\text{-}28d}$ were similar between responders (CR or partial response) and non-responders (stable or progressive disease). Maximum transgene levels were reached by a median of 10 days in responders and 12.9 days in non-responders; transgene persistence was detected up to 370 days and 187 days, respectively. **Conclusions:** These data demonstrate the efficacy and acceptable safety of tisa-cel in pts with r/r FL, including high-risk pts after multiple lines of prior therapy, and suggest that tisa-cel may be a promising therapy for pts with r/r FL. Clinical trial information: NCT03568461. Research Sponsor: Novartis.

7509 **Poster Discussion Session**

Acalabrutinib ± obinutuzumab versus obinutuzumab + chlorambucil in treatment-naïve chronic lymphocytic leukemia: Elevate-TN four-year follow up. *First Author: Jeff Porter Sharman, Willamette Valley Cancer Institute and US Oncology Research Center, Eugene, OR*

Background: Early results from ELEVATE-TN (NCT02475681) at a median follow-up of 28.3 mo demonstrated superior efficacy of acalabrutinib (A) ± obinutuzumab (O) compared with O + chlorambucil (Clb) in patients (pts) with treatment-naïve (TN) chronic lymphocytic leukemia (CLL) (Sharman et al. Lancet 2020;395:1278-91). Results from a 4-year update are reported here. **Methods:** Pts received A±O or O+Clb. Crossover to A monotherapy was permitted in pts who progressed on O+Clb. Investigator-assessed (INV) progression-free survival (PFS), INV overall response rate (ORR), overall survival (OS), and safety were evaluated. **Results:** 535 pts (A+O, n=179; A, n=179; O+Clb, n=177) were randomized with a median age of 70 y; 63% had unmutated IGHV and 9% del(17p). At a median follow-up of 46.9 mo (range, 0.0–59.4; data cutoff: Sept 11, 2020), the median PFS was not reached (NR) for A+O and A pts vs 27.8 mo for O+Clb pts (both $P<0.0001$). In pts with unmutated IGHV, the median PFS was NR (A+O and A) vs 22.2 mo among O+Clb pts (both $P<0.0001$). In pts with del(17p), the median PFS was NR (A+O and A) vs 17.7 mo for O+Clb ($P<0.005$). Estimated 48-mo PFS rates were 87% for A+O, 78% for A, and 25% for O+Clb. Median OS was NR in any treatment arm with a trend towards significance in the A+O group (A+O vs O+Clb, $P=0.0604$); estimated 48-mo OS rates were 93% (A+O), 88% (A), and 88% (O+Clb). ORR was significantly higher with A+O (96.1%; 95% CI 92.1–98.1) vs O+Clb (82.5%; 95% CI 76.2–87.4; $P<0.0001$); ORR with A was 89.9% (95% CI 84.7–93.5; $P=0.035$ vs O+Clb). Complete response/complete response with incomplete hematologic recovery (CR/CRi) rates were higher with A+O (26.8%/3.9%) vs O+Clb (12.4%/0.6%); 10.6%/0.6% had CR/CRi with A. Common adverse events (AEs) and AEs of interest are shown in the Table. Overall treatment discontinuation rates were 25.1% (A+O), 30.7% (A), and 22.6% (O+Clb); the most common reasons were AEs (12.8%, 12.3%, 14.7%, respectively) and progressive disease (4.5%, 7.8%, 1.7%). Most pts (77.4%) completed O+Clb treatment. **Conclusions:** With a median follow-up of 46.9 mo (~4y), the efficacy and safety of A+O and A monotherapy was maintained, with an increase in CR since the interim analysis (from 21% to 27% [A+O] and from 7% to 11% [A]) and low rates of discontinuation. Research Sponsor: None.

	A+O (n = 178)		A (n = 179)		O+Clb (n = 169)	
	Any grade	G ≥ 3	Any grade	G≥3	Any grade	G≥3
Common AEs (in ≥30% of pts [any grade] in any group), n (%)						
Diarrhea	73 (41.0)	9 (5.1)	72 (40.2)	1 (0.6)	36 (21.3)	3 (1.8)
Headache	71 (39.9)	2 (1.1)	68 (38.0)	2 (1.1)	20 (11.8)	0
Neutropenia	60 (33.7)	55 (30.9)	22 (12.3)	20 (11.2)	76 (45.0)	70 (41.4)
Nausea	41 (23.0)	0	41 (22.9)	0	53 (31.4)	0
Infusion-related reaction	25 (14.0)	5 (2.8)	0	0	68 (40.2)	10 (5.9)
Selected AEs of interest, n (%)						
Bleeding	84 (47.2)	5 (2.8)	75 (41.9)	5 (2.8)	20 (11.8)	0
Hypertension	14 (7.9)	6 (3.4)	13 (7.3)	5 (2.8)	7 (4.1)	6 (3.6)
Atrial fibrillation	7 (3.9)	1 (0.6)	11 (6.1)	2 (1.1)	1 (0.6)	0

7510 **Poster Discussion Session**

Copanlisib + rituximab versus rituximab + placebo in patients with relapsed follicular (FL) or marginal zone lymphoma (MZL): Subset analysis from the phase III CHRONOS-3 trial. *First Author: Matthew J. Matasar, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Rituximab (R) monotherapy is an approved treatment for patients (pts) with relapsed indolent NHL (iNHL) who have a prolonged progression-free and treatment-free interval after last R-based therapy or who are unwilling/unfit to receive chemotherapy. Copanlisib (C) is a PI3K inhibitor approved as monotherapy in pts with relapsed FL who have progressed after ≥2 systemic therapies. The recent Phase III CHRONOS-3 study in pts with relapsed iNHL treated with C+R vs placebo (P)+R (NCT02367040) met its primary endpoint with a significant 48% reduction in the risk of disease progression or death (Matasar et al. AACR 2021). We report here a pre-planned subset analysis in pts with relapsed FL or MZL. **Methods:** Pts with relapsed iNHL who were progression- and treatment-free for ≥12 months (mo) after last R-based therapy or ≥6 mo if unwilling/unfit to receive chemotherapy were randomized 2:1 to receive C+R or P+R. C 60 mg/P was given i.v. on days 1, 8, and 15 (28-day cycle); R 375 mg/m^2 was given i.v. on days 1, 8, 15, and 22 of cycle 1 and on day 1 of cycles 3, 5, 7, and 9. Primary endpoint was centrally assessed progression-free survival (PFS) by Cheson 2014 criteria. Secondary endpoints included objective response rate (ORR), duration of response (DoR), complete response rate (CRR), time to progression (TTP), and treatment-emergent adverse events (TEAEs). All randomized pts were assessed for efficacy; pts were assessed for safety if they received ≥1 dose of C/P or R. The data cut-off date was August 31, 2020. **Results:** From a total dataset of 458 iNHL pts, 250 pts with FL/MZL (184 FL/66 MZL) were randomized to C+R and 120 (91 FL/29 MZL) to P+R. Median age was 62 years (range 28-91) and the arms were well balanced. With a median follow-up of 18.5 mo, C+R significantly reduced the risk of disease progression/death vs P+R (HR = 0.55 [95% CI 0.40, 0.76]; 1-sided p = 0.0001); median PFS was 22.2 mo (95% CI 19.1, 33.1) vs 15.4 mo (95% CI 11.0, 19.2), respectively. Median TTP was 27.5 mo for C+R vs 15.4 mo for P+R (HR = 0.500; 1-sided p = 0.00001). ORRs were 82.4% (CRR 37.6%) for C+R and 50.8% (CRR 18.3%) for P+R; median DoR was 23.9 mo vs 17.9 mo, respectively. Most common TEAEs (all grades [G]/G3+) in pts with FL/MZL receiving C+R (n = 249) were hyperglycemia (72.7%/59.0%), hypertension (53.8%/43.0% [all G3]), and diarrhea (35.3%/5.6% [all G3]). For pts receiving P+R (n = 116), the most common TEAEs were hyperglycemia (23.3%/7.8% [all G3]), hypertension (19.8%/8.6% [all G3]), neutropenia (18.1%/13.8%), and upper respiratory tract infection (18.1%/0%). **Conclusions:** C+R demonstrated superior efficacy vs P+R in pts with relapsed FL/MZL and had a manageable safety profile, consistent with C and R as monotherapy. Copanlisib is the first PI3K inhibitor to be safely combined with R in relapsed FL/MZL, representing a potential new therapeutic option. Clinical trial information: NCT02367040. Research Sponsor: Funding: Bayer AG. Writing support: Complete HealthVizion.

7511 **Poster Discussion Session**

Obinutuzumab (G)-atezolizumab (atezo)-lenalidomide (len) for the treatment of relapsed/refractory (R/R) follicular lymphoma (FL): Final analysis of a phase Ib/II trial. *First Author: Nilanjan Ghosh, Hematologic Oncology and Blood Disorders, Levine Cancer Institute/Atrium Health, Charlotte, NC*

Background: G-len has promising activity and manageable toxicity in R/R FL (Morschhauser et al. 2019). We report the final analysis of an open-label, multicenter, Phase Ib/II trial (NCT02631577) that evaluated the immunomodulatory triplet G-atezo-len in pts with R/R FL. **Methods:** An initial 3+3 dose-escalation to identify the Phase II len dose was followed by an expansion phase with G-atezo-len. Enrolled pts (aged ≥18 years) received induction with 6, 28-day cycles of G 1000 mg IV on Day [D] 1, 8, and 15 of Cycle [C] 1 and D1 of C2–6, atezo 840 mg IV on D1 and 15 of C2–6, and len 15/20 mg (dose escalation) or 20 mg (expansion) orally on D1–21 of C1–6. Responders received 24 months (mos) of maintenance with G 1000 mg D1 every 2 mos, atezo 840 mg D1–2 every mo, and len 10 mg D1–21 mos 1–12. The primary endpoint was complete response at end of induction by PET-CT assessed by Independent Review Committee (modified Lugano 2014 criteria; Morschhauser et al. ICML 2019). Exploratory endpoints described herein included progression-free survival (PFS), overall survival (OS), and duration of response (DOR). Adverse events (AEs) were also assessed. **Results:** At the final analysis (October 7, 2020), 38 pts had completed the trial. Median age was 62 years, 26% had a high-risk FLIPI score, 45% were refractory to their last line of therapy, and 37% had progression of disease within 24 mos of their first-line of therapy (POD24). Median treatment duration was 26 mos (range: 0.4–30). The 36-mo PFS rate for the overall population (median observation time, 35.9 mos; range: 3–47) was 64% (95% CI, 45–79), OS was 85% (95% CI, 70–93), and median DOR was 38 mos (95% CI, 35–NE). 36-mo PFS rates for the following subgroups are provided in the table: double refractory (rituximab and an alkylator); with/without POD24; minimal residual disease (MRD) +/-. In total, 32 pts (84%) had a Grade 3/4 AE (majority hematologic), and 18 (47%) had a serious AE. Five pts (13%) during induction and six pts (16%) during maintenance had an AE that led to discontinuation of any drug. Two fatal AEs were reported (1 merkel carcinoma, 1 sarcomatoid carcinoma; both unrelated to any study drug). The most common atezo AEs of special interest were hyperthyroidism (13%), hypothyroidism (11%), increased ALT and AST (both 8%), increased lipase (8%), and hepatocellular injury (5%). **Conclusions:** G-atezo-len is efficacious in pts with R/R FL, with data from the final analysis suggesting a potential for improved outcomes versus the G-len doublet. AEs were consistent with the safety profile of the individual drugs. Clinical trial information: NCT02631577. Research Sponsor: This study was sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by A. Lynch, PhD, of Ashfield MedComms, an Ashfield Health Company, and funded by F. Hoffmann-La Roche Ltd.

36-mo PFS rates.

	Subgroup						
	MRD- (N=16)	MRD+* (N=5)	Double refractory (N=12)	Not double-refractory (N=20)	With POD24 (N=12)	Without POD24 (N=20)	Overall (N=32)
36-mo PFS rate, % (95% CI)	79 (48–93)	0	70 (33–89)	67 (40–84)	64 (30–85)	73 (46–88)	64 (45–79)

*All pts progressed before 36 mos; median PFS was 10.7 mos (range: 1.8–18).

7512 **Poster Discussion Session**

Polatuzumab vedotin (Pola) + rituximab (R) + lenalidomide (Len) in patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): Primary analysis of a phase 1b/2 trial.

First Author: Catherine S. Magid Diefenbach, Perlmutter Cancer Center at NYU Langone Health, New York, NY

Background: The combination of Pola-R-Len may enhance anti-tumor response in R/R DLBCL. We report the primary analysis of the R/R DLBCL cohort in a Phase 1b/2 study (GO29834; NCT02600897). **Methods:** Pts received induction with 6 x 28-Day (D) cycles (C) of: Pola 1.8mg/kg intravenous (IV; C1−6: D1); R 375mg/m^2 IV (C1−6: D1) and oral Len 10–20mg (dose escalation) or recommended Phase 2 dose (RP2D) daily on D1–21. Pts with a response at end of induction (EOI) received 6 months (mo) consolidation with R 375mg/m^2 (D1 every 2 mo) and Len 10mg (D1–21 monthly). Primary endpoints were safety/tolerability and positron emission tomography (PET)-complete response (CR) rate at EOI by independent review committee (IRC) by modified Lugano criteria. **Results:** At primary analysis (Sep 08, 2020), 57 pts were enrolled. Median age was 71 years (range 28–92); male (67%); Ann Arbor Stage III–IV (86%); International Prognostic Index 3–5 (60%); median 2 prior therapies; prior bone marrow transplant (11%); prior CAR-T therapy (5%); primary refractory (49%) and refractory to last therapy (65%). Grade 3–4 adverse events (AEs) were experienced by 75% of pts, most commonly, neutropenia (58%), thrombocytopenia (14%), infections (14%) and anemia (11%). AEs led to Len dose reduction in 25% and interruption in 63% of pts. One Grade 5 treatment-related AE (neutropenic sepsis) was reported. In total, 49 pts were treated at RP2D (Pola 1.8mg/kg + Len 20mg). IRC PET-CR rate at EOI was 29% (Table). A best overall response (BOR) assessed by investigator (INV) was seen in 36/49 (74%) pts with 17/49 (35%) pts achieving a CR; of these, 14/17 (82%) remain in remission at the cutoff date. Median duration of response (DOR) was 8.1 mo (95% confidence interval [CI]: 4.7–not evaluable [NE]). After a median follow-up of 9.7 mo, median progression-free survival (PFS) and overall survival (OS) were 6.3 mo (95% CI: 4.5–9.7) and 10.9 mo (95% CI: 7.4–NE), respectively. **Conclusions:** Our study of the novel triplet combination, Pola-R-Len, demonstrates a tolerable safety profile. This first efficacy report of Pola-R-Len shows promising activity in a difficult-to-treat R/R DLBCL population, particularly in pts achieving CR, a large proportion of whom remain in remission at the cutoff date. Further evaluation of Pola-R-Len and the impact of consolidation therapy is warranted to address the significant unmet need in this patient population. Clinical trial information: NCT02600897. Research Sponsor: Study sponsored by F. Hoffmann-La Roche Ltd/Genentech, Inc. Third-party editorial assistance, under direction of authors, was provided by Angela Rogers, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by F. Hoffmann-La Roche Ltd.

Efficacy results (RP2D).

Outcome	Pola-R-Len (N=49)
PET-ORR (IRC) at EOI, n (%)	17 (35)
PET-CR (IRC) at EOI*, n (%)	14 (29)
PET-CR (INV) at EOI, n (%)	13 (27)
BOR (INV)†, n (%)	36 (74)
Best CR (INV), n (%)	17 (35)
Median DOR (INV), mo (95% CI)	8.1 (4.7–NE)
Median PFS (INV), mo (95% CI)	6.3 (4.5–9.7)
Median OS (INV), mo (95% CI)	10.9 (7.4–NE)

*Primary efficacy endpoint; †Defined as best response of CR or partial response during the study. ORR, overall response rate.

7513 **Poster Discussion Session**

Long-term analyses from L-MIND, a phase II study of tafasitamab (MOR208) combined with lenalidomide (LEN) in patients with relapsed or refractory diffuse large B-cell lymphoma (R/R DLBCL).

First Author: Johannes Düll, Medizinische Klinik und Poliklinik II, Universitätsklinik Würzburg, Würzburg, Germany

Background: L-MIND (NCT02399085) is an ongoing, open-label, Phase II study of tafasitamab (MOR208), an Fc-modified, humanized, anti-CD19 monoclonal antibody, plus LEN in ASCT-ineligible patients (pts) with R/R DLBCL. Primary analyses and 2-year efficacy results were previously presented; we report an updated efficacy analysis with ≥35 months follow up (cut-off: October 30, 2020). **Methods:** Pts were aged ≥18 years with ASCT-ineligible R/R DLBCL, had 1–3 prior systemic therapies (Tx), including ≥1 CD20-targeting regimen, with an ECOG status of 0–2. Pts received 28-day cycles (C) of tafasitamab (12 mg/kg IV), once weekly during C1–3, with a loading dose on Day 4 of C1, then every 2 weeks (Q2W) during C4–12. LEN (25 mg PO) was administered on Days 1–21 of C1–12. After C12, progression-free pts received tafasitamab Q2W until disease progression. The primary endpoint was objective response rate (ORR), assessed by IRC. Secondary endpoints included duration of response (DoR), progression-free survival (PFS) and overall survival (OS). **Results:** Eighty of 81 enrolled pts received tafasitamab + LEN and were included in the full analysis set (1 prior Tx, n=40; 2+ prior Tx, n=40). At data cut-off, the overall ORR was 57.5% (n=46/80), including complete response (CR) in 40% of pts (n=32/80) and partial response (PR) in 17.5% of pts (n=14/80) (Table). Kaplan-Meier estimates: median DoR=43.9 months (95% CI: 26.1–not reached [NR]), and NR in pts who achieved a CR (95% CI: 43.9–NR); median PFS=11.6 months (95% CI: 6.3–45.7), with median follow-up 33.9 months; median OS=33.5 months (95% CI: 18.3–NR), with median follow-up 42.7 months. There were no unexpected toxicities or new safety signals. **Conclusions:** Combination Tx with tafasitamab + LEN followed by tafasitamab monotherapy provided durable responses in pts with R/R DLBCL not eligible for ASCT, with a manageable safety profile. These long-term data indicate the potential of tafasitamab + LEN followed by extended tafasitamab monotherapy in achieving prolonged remission and survival benefit in this patient population, especially at first relapse. Clinical trial information: NCT02399085. Research Sponsor: MorphoSys AG, Planegg, Germany.

Tafasitamab + LEN	1 prior Tx (N=40)	2+ prior Tx (N=40)	Overall (N=80)
Best Objective Response, n (%)			
CR	19 (47.5)	13 (32.5)	32 (40.0)
PR	8 (20.0)	6 (15.0)	14 (17.5)
SD	7 (17.5)	6 (15.0)	13 (16.3)
PD	5 (12.5)	8 (20.0)	13 (16.3)
NE*	1 (2.5)	7 (17.5)	8 (10.0)
ORR (CR + PR), n (%) [95% CI]†	27 (67.5) [50.9–81.4]	19 (47.5) [31.5–63.9]	46 (57.5) [45.9–68.5]
Median DoR, months (95% CI)‡	43.9 (9.1–NR)	NR (15.0–NR)	43.9 (26.1–NR)
Median PFS, months (95% CI)‡	23.5 (7.4–NR)	7.6 (2.7–NR)	11.6 (6.3–45.7)
Median OS, months (95% CI)‡	45.7 (24.6–NR)	15.5 (8.6–NR)	33.5 (18.3–NR)

*No valid post-baseline response assessments. †Two-sided 95% Clopper-Pearson exact method based on a binomial distribution. ‡Kaplan-Meier estimate. Data cut-off: October 30, 2020.

7514 **Poster Discussion Session**

Multicenter phase II study of romidepsin plus lenalidomide for patients with previously untreated peripheral T-cell lymphoma (PTCL).

First Author: Jia Ruan, Weill Cornell Medicine and New York Presbyterian Hospital, New York, NY

Background: PTCL are aggressive malignancies associated with poor prognosis when treated with cytotoxic chemotherapy. Novel agents, such as HDAC inhibitor romidepsin and immunomodulatory agent lenalidomide, have shown clinical activities as single agents and in combination in R/R PTCL. We hypothesize that upfront treatment with these agents is an effective and well-tolerated option to defer chemotherapy, particularly in patients who are not candidates for intensive approach. We report the findings of the first chemo-free combination of romidepsin plus lenalidomide as initial treatment for PTCL (ClinicalTrials.gov-NCT02232516). **Methods:** Patients with untreated PTCL who were over 60 or noncandidates for chemotherapy based on comorbidity CIRS score were eligible. Treatment was initiated with romidepsin 10 mg/m2 IV on d 1, 8, 15, and lenalidomide 25 mg PO on d 1-21 of 28-day cycle for up to 1 year, unless discontinued prior due to POD, toxicities, or withdrawal of consent. The primary objective was to evaluate ORR per Cheson criteria. Secondary objectives included safety, PFS, OS, DOR, and delay to chemotherapy. The sample size was 20 evaluable patients, which allows to estimate the underlying true response rate with the margin of error of an approximate 95% confidence interval equal to 0.22, assuming the true ORR = 0.5. **Results:** The study enrolled 29 subjects at 3 US centers, including 16 (55%) AITL, 11 (38%) PTCL-NOS, 1 ATLL and 1 EATCL. The median age was 75 (range 49-84), and M:F ratio was 1:1. Nineteen (66%) had stage III/IV disease, 23 (79%) had elevated LDH, and 9 (31%) had IPI 3-5. Treatment was well tolerated with expected side effects. Grade 3-4 hematologic toxicities included neutropenia (45%), thrombocytopenia (34%) and anemia (28%). Grade 3-4 non-hematologic toxicities included hyponatremia (45%), hypertension (38%), hypoalbuminemia (24%), fatigue (17%), hyperglycemia (14%), hypokalemia (14%), dehydration (10%), lung infection (10%) and sepsis (10%). At a median follow-up of 8 months, 20 subjects were evaluable with at least one response assessment, and received a median treatment of 6 cycles. The ORR was 75% (95%CI: 50.9%, 91.3%) with CR at 30% (11.9%, 54.3%). For AITL, the ORR was 85% (54.6%, 98.1%) with CR at 38% (13.9%, 68.4%). Median DOR was 4.2 months for all responders, and 14.3 months for CR patients. The estimated 1-yr PFS was 54.3% with 3-yr PFS at 36.2%, and the estimated 1-yr OS was 76.0% with 3-yr OS at 51.3%. Two subjects moved onto consolidative ASCT in remission, and 4 received additional cytotoxic chemotherapy after progression. **Conclusions:** This study provides the first demonstration that chemo-free biologic combination of romidepsin and lenalidomide is feasible and effective as initial therapy for PTCL patients who are not candidates for cytotoxic chemotherapy. These data justify further evaluation of such novel agents as a frontline strategy. Clinical trial information: NCT02232516. Research Sponsor: BMS/Celgene.

7515 **Poster Discussion Session**

Outcomes in ZUMA-5 with axicabtagene ciloleucel (axi-cel) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) who had the high-risk feature of progression within 24 months from initiation of first anti-CD20–containing chemoimmunotherapy (POD24).

First Author: Caron A. Jacobson, Dana-Farber Cancer Institute, Boston, MA

Background: POD24 is an indicator of poor survival in iNHL (Casulo & Barr. *Blood*. 2019). In the ZUMA-5 Phase 2 study of axi-cel anti-CD19 CAR T-cell therapy in pts with R/R iNHL, overall response rates (ORR) after 17.5 months median follow-up were similarly high in those with and without POD24 (93% and 92%; Jacobson et al. ASH 2020. #700). Here, we report updated outcomes with longer follow-up in pts with POD24 in ZUMA-5. **Methods:** Adults with R/R follicular lymphoma (FL) or marginal zone lymphoma (MZL) after ≥2 lines of therapy underwent leukapheresis followed by conditioning therapy and axi-cel infusion (2×10^6 CAR T cells/kg). Axi-cel–treated pts with available data on progression after an anti-CD20 mAb + alkylating agent were included. The updated efficacy analysis occurred when ≥80 treated pts with FL had ≥18 months follow-up. **Results:** Of 129 pts at baseline, 81 pts (63%; 68 FL, 13 MZL) had POD24 and 48 pts (37%; 40 FL, 8 MZL) did not have POD24. Median prior lines of therapy in pts with and without POD24 were 3 and 3.5, respectively. High-risk characteristics of pts with and without POD24 included stage III/IV disease, 83% and 94%; ≥3 FLIPI, 44% and 43%; high tumor bulk (GELF), 51% and 44%; and refractory disease, 77% and 63%, respectively. With 23.3 months median follow-up, ORR among efficacy-evaluable pts with POD24 (n = 61) and without POD24 (n = 37) was 92% each (complete response rates, 75% and 86%). At data cutoff, 52% of pts with POD24 and 70% without POD24 had ongoing responses. Median duration of response, progression-free survival, and overall survival were not reached in pts with and without POD24; 18-month estimated rates were 60% and 78%, 55% and 84%, and 85% and 94%, respectively. Incidences of Grade ≥3 adverse events were similar in pts with and without POD24 (84% and 88%), including cytopenias (69% and 65%) and infections (15% and 21%). Grade ≥3 cytokine release syndrome (CRS) occurred in 9% and 2% of pts with and without POD24, respectively; Grade ≥3 neurologic events (NEs) occurred in 17% of pts each. Median times to onset were similar in pts with and without POD24 for CRS (4 days each) and NEs (8 days and 7 days); median durations of CRS (7 days and 5 days) and NEs (11 days and 13 days) were also similar between groups. In efficacy-evaluable pts with FL, median peak CAR T-cell levels were similar in pts with and without POD24 (35.8 cells/μL and 34.5 cells/μL). Peak levels of key inflammatory biomarkers and axi-cel product attributes were generally similar in pts with and without POD24. **Conclusions:** Axi-cel showed a high rate of durable responses in pts with POD24 iNHL, a population with high-risk disease. Efficacy results, as well as safety and pharmacological profiles, appeared largely comparable between groups, with the exception of PFS rates. Clinical trial information: NCT03105336. Research Sponsor: Kite, a Gilead Company.

7516 **Poster Discussion Session**

Preliminary safety and efficacy of PBCAR0191, an allogeneic, off-the-shelf CD19-targeting CAR-T product, in relapsed/refractory (r/r) CD19+ NHL. *First Author: Bijal D. Shah, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL*

Background: Although autologous CD19-directed CAR T products have demonstrated unprecedented efficacy in chemorefractory patients, manufacturing failure or delays remain important barriers to care, limiting utility for those with more rapidly growing disease and/or impaired T cell fitness. Here, we present an update to preliminary safety, efficacy, and correlative data for the subjects dosed with at least 3 x 10^6 CAR-T+ cells/kg, or equivalent, of PBCAR0191, an off-the-shelf allogeneic CAR T product. **Methods:** Subjects were required to have evaluable CD19+ r/r NHL, adequate organ function, 2+ prior treatment regimens, and no active GvHD, CNS disease, infections or active medical issues. Prior stem cell transplant and/or CAR-T therapy were allowed. All subjects were lymphodepleted prior to administration of PBCAR0191with either standard (sLD; 30/500mg/m2/day x 3 days fludarbine/cyclophosphamide) or enhanced (eLD; 30 x 4 days and 1000mg/m2/day x 3 days flu/cy) lymphodepletion. Correlative laboratory samples were taken at baseline and while patients remained on study for CAR T cell expansion, persistence, response to treatment and safety assessments. **Results:** As of February 2021, 13 subjects were evaluable meeting these criteria. Demographics, baseline disease characteristics, and prior therapy data are presented in the table. Median time from eligibility confirmation to PBCAR0191 infusion was 6.5 days (1 day to start LD). To date, most adverse events (AE) reported were mild, with no cases of GvHD or Grade ≥3 CRS/ ICANS. PBCAR0191 related serious AEs were reported for 31% (4/13) of the subjects and 1 subject (9%) died of Febrile neutropenia on day 42 after treatment. Infections and cytokine release related AEs occurred at higher frequency in the eLD group. Efficacy of PBCAR0191 in 13 NHL subjects with available 28 day follow up is presented in the table. Peak PBCAR0191 expansion was increased 56-fold and was associated with CR rate of 71% in eLD group versus 33% in sLD group. Duration of response assessment is ongoing. **Conclusions:** PBCAR0191 has demonstrated dose and LD-dependent cell expansion kinetics with encouraging anti-tumor activity. Host-versus-graft rejection may have a role in depth and durability of response. CR rates with PBCAR0191 are preliminarily comparable to those observed with autologous CAR T in this population. Updated response durability assessment will be presented at the time of the meeting. Clinical trial information: NCT03666000. Research Sponsor: Precision BioSciences.

		sLD (N = 6)	eLD (N = 7)	Total (N = 13)
Age (y)	*Median (min-max)*	56 (44-81)	60 (34-64)	59 (34-81)
Aggressive	*DLBCL/MCL/High grade*	6 (100%)	4 (57%)	10 (77%)
# Subjects with 4+ Prior lines of Rx (%)		3 (50%)	5 (71%)	8 (62%)
Overall response rate (Day ≥28)		3 (50%)	7 (100%)	10 (77%)
Complete response rate (Day ≥28)		2 (33%)	5 (71%)	7 (54%)
ICANS or CRS (Gr ≥3)		0	0	0
CRS (Gr 1 or 2)		3 (50%)	3 (43%)	6 (46%)
ICANS (Gr 1 or 2)		2 (33%)	2 (29%)	4 (31%)
Infection (Gr ≥3)		0	2 (29%)	2 (15%)

7517 **Poster Discussion Session**

Engineered immunostimulatory cells can convert PBMCs from chronic lymphocytic leukemia (CLL) patients into potent tumor killing immune cells. *First Author: Joshua W. Keegan, Brigham and Women's Hospital and Harvard Medical School, Boston, MA*

Background: Alloplex Biotherapeutics has developed a cellular therapeutic that uses ENgineered Leukocyte ImmunoSTimulatory cell lines called ENLIST cells to activate and expand populations of tumor killing effector cells from human peripheral blood mononuclear cells (PBMCs). This process leads to a 300-fold expansion of NK cells, CD8+ T cells, NKT cells, and TCR$\gamma\delta$ T cells that are called SUPLEXA cells, which will be cryopreserved and transferred back into patients as an autologous immune cell therapy for cancer. In this study, PBMCs from CLL patients were used to generate SUPLEXA cells as a first approach to comparatively profile SUPLEXA cells from cancer patients and normal healthy volunteers (NHVs). **Methods:** ENLIST cell lines were engineered by expressing curated immunomodulatory proteins in the SK-MEL-2 melanoma cell line. Two million (M) PBMCs from 10 CLL patients or 2 NHVs were incubated with 0.4 M freeze/thaw killed ENLIST cells for 5 days in XVIVO-15 medium with 2% heat-inactivated human AB serum (XAB2) and then split 1:15 in XAB2 containing IL-7 and IL-15 to expand. After 9 days, SUPLEXA cells were harvested and cryopreserved. **Results:** Original PBMCs and matched SUPLEXA cells from each donor were thawed and characterized by mass cytometry (CyTOF) using a 47-marker antibody panel. CyTOF staining results of PBMCs from CLL patients demonstrated approximately 95% leukemia cells and few T cells, NK cells, B cells, and monocytes. CyTOF staining of SUPLEXA cells from all 10 CLL patients showed expansion of NK cells (17%), CD8 T cells (11%), and CD4 T cells (7.5%) that were similar in phenotype to SUPLEXA cells from NHVs showing high expression of granzymes and perforin that are indicative of potent tumor cell killing activity. Cancer cells in the original CLL PBMC samples were reduced to 0.78%. However, a population of non-T/non-B cells (60% ± 9.5%) was detected in SUPLEXA cells from all CLL patients that require further characterization. Next, SUPLEXA cells from CLL and NHV patients were comparatively tested for tumor cell killing activity at 2:1, 1:1, and 1:2 effector to target cell (MEL-14 melanoma cells expressing RFP) ratios. Percent killing of tumor cells by SUPLEXA cells prepared from CLL patients (77.8% ± 2.6% at 2:1) and NHVs (81.5% ± 0.3% at 2:1) were nearly identical at all effector to target ratios. **Conclusions:** We demonstrate for the first time that PBMCs from CLL patients can be converted into SUPLEXA cells despite low numbers of normal immune cells at baseline and the known immunologic impairment present in CLL patients. Importantly, SUPLEXA cells derived from CLL patients acquire potent tumor killing activity that is indistinguishable from SUPLEXA cells prepared from NHVs. Taken together, these findings support the feasibility of converting PBMCs from CLL patients with low percentages of NK and T cells into an autologous cellular therapy for cancer. Research Sponsor: Alloplex Biotherapeutics.

7518 **Poster Discussion Session**

Subcutaneous epcoritamab in patients with relapsed/refractory B-cell non-Hodgkin lymphoma: Safety profile and antitumor activity. *First Author: Michael Roost Clausen, Vejle Hospital, Vejle, Denmark*

Background: Epcoritamab is a CD20xCD3 bispecific antibody that induces T-cellmediated killing of CD20positive malignant B-cells. We present updated data, including progression-free survival (PFS) from the dose escalation part of the first-in-human phase 1/2 study of epcoritamab in pts with relapsed or refractory (R/R) B-cell non-Hodgkin lymphoma (B-NHL; NCT03625037). **Methods:** Adults with R/R CD20+ B-NHL received flat-dose 1 mL SC epcoritamab (step-up dosing approach) in 28-day cycles (q1w: cycles 12; q2w: cycles 36; q4w thereafter) until disease progression or unacceptable toxicity. Step-up dosing and standard prophylaxis were used to mitigate severity of cytokine release syndrome (CRS). **Results:** At data cut off (1/31/2021), 68 pts with B-NHL were enrolled across histologies including diffuse large B-cell lymphoma (DLBCL; n = 46 [67.6%]; de novo and transformed), follicular lymphoma (FL; 12 [17.6%]), mantle cell lymphoma (MCL; 4 [5.9%]), and others (6 [8.8%]). Majority were heavily pretreated (median [range] prior lines: DLBCL, 3 [16]; FL, 4.5 [118]); including prior CAR-T (n = 6) and prior ASCT (n = 10). At median follow-up of 14.1 mo (DLBCL, 10.2 mo; FL, 15.2 mo), treatment was ongoing in 15 (22%) pts. Most common treatment-emergent adverse events (AEs) were pyrexia (69%), CRS (59%), and injection site reaction (47%). CRS events were all grade 1 or 2 and most occurred in cycle 1; neurotoxicity was limited (6%; grade 1: 3%; grade 3: 3%; all transient). One case of tumor lysis syndrome was observed (1.5%; grade 3); there were no cases of febrile neutropenia or treatment-related death. Overall response is shown for DLBCL ≥12 mg and ≥48 mg and FL ≥12 mg, corresponding to the minimal efficacy threshold (Table). Responses deepened over time (PR converted to CR: DLBCL, 6 pts; FL, 3 pts). Median time to response was 1.4 mo (DLBCL) and 1.9 mo (FL). Among DLBCL pts achieving CR with ≥6 mg (n = 11), none relapsed while on treatment. The median PFS for pts with DLBCL ≥12 mg (n = 22) was 9.1 mo (95% CI: 1.6, NE; median follow-up 9.3 mo) and for pts with DLBCL ≥48 mg (n = 11) median PFS was not reached (median follow-up 8.8 mo). Updated analyses will be presented. **Conclusions:** With longer follow-up, SC epcoritamab demonstrated substantial single-agent activity, inducing deep and durable clinically meaningful responses, with a consistent safety profile. Notably no severe (grade ≥3) CRS events, no febrile neutropenia, and limited neurotoxicity was observed. Clinical trial information: NCT03625037. Research Sponsor: This study was funded by Genmab A/S and AbbVie Inc.

	DLBCL		FL	MCL
	≥12 mg	4860 mg	1248 mg	0.7648 mg
Evaluable pts	22	11	5	4
ORR, n (%)	15 (68.2)	10 (91)	4 (80)	2 (50)
CR, n (%)	10 (45.5)	6 (55)	3 (60)	1 (25)
PR, n (%)	5 (22.7)	4 (36)	1 (20)	1 (25)
SD, n (%)	1 (4.5)	0	0	1 (25)
PD, n (%)	5 (22.7)	0	1 (20)	0

7519 **Poster Discussion Session**

Glofitamab step-up dosing (SUD): Complete response rates in updated efficacy data in heavily pretreated relapsed/refractory (R/R) non-Hodgkin lymphoma (NHL) patients (pts). *First Author: Carmelo Carlo-Stella, Humanitas University and Humanitas Research Hospital, Milan, Italy*

Background: Glofitamab (RG6026), a T-cell-engaging, bispecific, full-length antibody, allows bivalent binding to CD20 (B-cells), and monovalent binding to CD3 (T-cells). In NP30179 (NCT03075696), an ongoing multicenter, Phase I dose-escalation and expansion study, 0.6–25mg glofitamab fixed-dosing with obinutuzumab pretreatment (Gpt), showed high, durable complete responses and manageable safety in heavily pretreated R/R NHL (Dickinson, et al. EHA 2020). Glofitamab SUD, in addition to Gpt, allowed dose escalation up to 30mg to maximize efficacy, while mitigating cytokine release syndrome (CRS) (Hutchings, et al. JCO 2021). We present updated efficacy data from glofitamab monotherapy SUD cohorts. **Methods:** Gpt (1000mg) was given to pts 7 days pre-glofitamab initial dose. Intravenous SUD of glofitamab was given on Day (D) 1 and 8 of Cycle (C) 1 and then at the target dose from C2D1 (2.5/10/16mg or 2.5/10/30mg); treatment continued for up to 12 cycles, every 21 days. Response rates were based on the Lugano criteria (Cheson, et al. JCO 2014). **Results:** Fifty-two pts received glofitamab SUD; 17 and 35 pts received 2.5/10/16mg and 2.5/10/30mg, respectively. Twenty-eight pts (53.8%) had aggressive NHL (aNHL) and 24 pts had indolent NHL (iNHL). Pts had a median age of 68 (44–85) years and received a median of 3 (1–12) prior lines of therapy. Forty (76.9%) and 38 (73.1%) pts were refractory to their most recent and any prior CD20 therapy, respectively. After a median follow-up of 6.3 months, an updated efficacy analysis was conducted on December 1, 2020. For pts with aNHL (N = 28), the best overall response (OR) and complete metabolic response (CMR) rates were 64.3% and 57.1%, respectively; a trend of improved response was observed with increased target dose, with a CMR rate of 71.4% at 2.5/10/30mg (N = 14). Notably, 4/5 pts (80%) with mantle cell lymphoma (2.5/10/16mg, n = 2; 2.5/10/30mg, n = 2) had CMR. For aNHL, 13/16 CMRs are ongoing, with 8 CMRs lasting > 3 months. For pts with iNHL (N = 24), OR and CMR rates were 79.2% and 70.8%, respectively; 14/17 CMRs are ongoing, with 10 CMRs lasting > 3 months. As of August 3, 2020, common adverse events (52 pts) were CRS (63.5%), neutropenia (38.5%), and pyrexia (32.7%). CRS was mostly confined to C1: 24/50 pts had CRS after 2.5mg; 20/49 pts after 10mg; 2/16 and 8/32 pts had CRS after 16 and 30mg (C2D1), respectively. Grade [Gr] 1 and 2 CRS was reported in 18 (34.6%) and 12 (23%) pts, respectively; 3 pts had Gr 3 CRS; none had Gr 4/5 events (ASTCT 2019). Updated data, including biomarker data on baseline CD20 expression and CD8 levels in the tumor, will be presented. **Conclusions:** Updated data for glofitamab monotherapy SUD show higher preliminary response rates than previously reported in pts with R/R NHL who have failed multiple lines of therapy. CRS was mostly manageable, of low grade, and confined to the first cycle of treatment. Clinical trial information: NCT03075696. Research Sponsor: NP30179 is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under direction of authors, was provided by Khalida Rizi, MPharm, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by F. Hoffmann-La Roche Ltd.

7520 **Poster Discussion Session**

Promising tolerability and efficacy results from dose-escalation in an ongoing phase Ib/II study of mosunetuzumab (M) with polatuzumab vedotin (Pola) in patients (pts) with relapsed/refractory (R/R) B-cell non-Hodgkin's lymphoma (B-NHL).

First Author: L Elizabeth Budde, City of Hope National Medical Center, Duarte, CA

Background: Mosunetuzumab (M), a full-length, humanized, IgG1 bispecific antibody targeting CD20 and CD3, has shown promising efficacy and safety as monotherapy for R/R B-NHL (NCT02500407; Assouline, et al. ASH 2020). The combination of M with the anti-CD79b antibody-drug conjugate, Pola, showed synergistic anti-lymphoma activity in a mouse xenograft model. These data supported a Phase Ib/II, open-label, multicenter trial of M-Pola for R/R B-NHL (GO40516, NCT03671018). Here we present early clinical data from the Phase Ib cohort. **Methods:** Pts with R/R follicular lymphoma (FL, grade [Gr] 1–3a) or aggressive NHL (aNHL), including *de novo* diffuse large B-cell lymphoma (DLBCL), transformed FL (trFL) and FL Gr 3b (FL3b), received Cycle (C) 1 step-up doses of M on Day (D) 1 (1mg) and D8 (2mg), the target dose on C1D15, then continued at the target dose on C2D1 onwards. M was given every 21 days for eight cycles (or 17 cycles if stable disease or a partial response after C8). Pola (1.8mg/kg) was given with M on D1 of each cycle for six cycles. **Results:** As of November 17, 2020, 22 pts had received M-Pola (M target doses: 9mg, n=7; 20mg, n=3; 40mg, n=6; 60mg [with D1 dose of 30mg from C3 onwards], n=6). Pts had DLBCL (n=12), FL (n=3), FL3b (n=3) and trFL (n=4). Pt characteristics include: median age of 70 (38–81) years; median of 3 (1–10) prior lines of therapy; 7 (32%) pts had prior CAR-T therapy; 17 (77%) and 19 (86%) pts had disease refractory to last prior therapy and prior anti-CD20 therapy, respectively. Median follow-up duration was 9.6 (0.7–23.7) months. The most frequent treatment-related adverse events (AEs) were neutropenia (45.4%), fatigue, nausea and diarrhea (all 36.4%). Cytokine release syndrome (CRS) was observed in 2 pts (9.1%; both Gr 1 by ASTCT 2019 criteria). One dose-limiting toxicity (Gr 3 new onset atrial fibrillation) was observed in the 40mg cohort. The maximum tolerated dose was not exceeded. The most common Gr ≥3 and serious AEs were both neutropenia, observed in 8 (36.4%) and 3 (13.6%) pts, respectively. Two (9.3%) Gr 5 AEs occurred: sudden cardiac death (n=1) and respiratory failure (n=1); neither was deemed treatment related. No immune effector cell-associated neurotoxicity was observed. The Table shows preliminary efficacy data. Preliminary efficacy in the dose-escalation cohort. **Conclusions:** These data indicate that M-Pola has an acceptable safety profile, with no Gr ≥2 CRS observed, and promising efficacy in pts with R/R NHL with predominantly aggressive disease. The Phase II expansion cohort in R/R DLBCL is ongoing, with no mandatory hospitalization required. Clinical trial information: NCT03671018. Research Sponsor: Study GO40516 is sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under direction of authors, was provided by Katie Buxton and Khalida Rizi of Ashfield MedComms, and funded by F. Hoffmann-La Roche Ltd/Genentech, Inc.

Response, n (%)	All pts (n=22)	aNHL pts (n=19)	Post-CAR-T pts (n=7)	FL pts (n=3)
Overall response rate	15 (68.2)	12 (63.2)	4 (57.1)	3 (100)
Complete response rate	12 (54.5)	9 (47.4)	2 (28.6)	3 (100)

7521 **Poster Session**

Effect of time to relapse on overall survival (OS) in mantle cell lymphoma (MCL) patients (pts) following frontline high-dose therapy and autologous hematopoietic cell transplantation (autoHCT).

First Author: Peter A. Riedell, The University of Chicago, Chicago, IL

Background: In MCL, outcomes are heterogeneous and the clinical significance of the timing of relapse following autoHCT and its impact on OS is not well defined. Using the CIBMTR database, we evaluate the effect of post-autoHCT time to relapse on OS over time. **Methods:** Adult MCL pts treated with up to two lines of rituximab-based induction therapy followed by first autoHCT within 1-year of diagnosis were identified between 2000-2018. Primary outcomes included OS and post-relapse OS. A dynamic landmark analysis was performed at 6-month intervals following autoHCT to evaluate the impact of relapse on OS while adjusting for significant patient- and disease-related variables. Post-relapse OS was evaluated in pts who experienced relapse. **Results:** Of the 461 pts included in the analysis, the median age was 60 years (range 29-78), 57% had a KPS of ≥ 90, 83% had stage III-IV disease at diagnosis, and 76% had extranodal involvement. BEAM was the most common conditioning regimen (58%) and 23% of pts received post-autoHCT maintenance rituximab. With a median follow-up of 67 months, the 5-year progression-free survival was 45.8% with a 5-year OS of 69.6%. On multivariate analysis, age ≥60 years was associated with worse OS (HR= 1.55, 95% CI 1.08-2.24, p=0.0191) at all landmark timepoints. Additionally, the impact of relapse on OS varied with time (p=0.006) and was greatest at the 6-month (HR=7.68), 12-month (HR=6.68), and 18-month (HR=5.81) landmark timepoints. The risk of death for relapsing pts decreased with time and was mirrored by an improvement in adjusted OS for both relapsing and non-relapsing pts. In total, 9.3% of patients relapsed prior to the 18-month landmark timepoint. Relapse at the 6-month, 12-month, and 18-month landmark timepoints correlated with a poor median post-relapse OS of 9 months, 24 months, and 34 months, respectively (Table). Conversely, patients relapsing after the 18-month landmark timepoint experienced a median post-relapse OS ranging from 44-67 months. **Conclusions:** In MCL, early relapse (< 18-months) following autoHCT defines a high-risk group with inferior post-relapse OS. This population should be considered for clinical trials or novel therapeutic approaches including early utilization of chimeric antigen receptor T-cell therapy. Research Sponsor: U.S. National Institutes of Health.

Median OS of relapsing and non-relapsing patients following frontline autoHCT for MCL.

Landmark timepoint	Median OS of relapsing patients, months	Median OS of non-relapsing patients, months
6 months	9	131
12 months	24	128
18 months	34	126
24 months	44	132
30 months	48	126
36 months	50	144
42 months	47	138
48 months	51	132
54 months	67	126
60 months	-	120

7522 **Poster Session**

Progression-free survival at 24 months as a landmark after autologous stem cell transplant in relapsed or refractory diffuse large B-cell lymphoma.

First Author: Aung M. Tun, The University of Kansas Cancer Center, Westwood, KS

Background: Patients with newly diagnoseddiffuse large B-cell lymphoma (DLBCL) who achieve event-free survival at 24 months (EFS24) following immunochemotherapy (IC) have excellent overall survival (OS) similar to that of age- and sex-matched general population. The standard of care for patients with relapsed or refractory (RR) DLBCL following frontline IC is salvage therapy followed by autologous stem cell transplant (ASCT). The goal of this study is to evaluate the role of progression-free survival (PFS) at 24 months (PFS24) as a landmark after ASCT in patients with RR DLBCL. **Methods:** Patients with RR DLBCL after frontline R-CHOP or R-CHOP-like IC who underwent salvage therapy and ASCT at Mayo Clinic or University of Iowa between 07/2000 and 4/2020 were identified from institutional lymphoma transplant databases. Clinical characteristics, treatment information, and outcome data were abstracted. Post-ASCT PFS, OS, and post-relapse survival (PRS) were plotted by Kaplan-Meier method, and cumulative incidences of relapse vs non-relapse mortality (NRM) and different causes of death were compared accounting for competing events. Statistical analyses were performed in EZR v1.54. **Results:** A total of 437 patients were identified. Median age at ASCT was 61 years (range 19-78), and 280 (64%) were male. After a median post-ASCT follow up of 8.0 years (95% CI 7.2-8.7), 215 patients had a relapse (or disease progression), 180 within 2 years and 35 after 2 years. For the entire cohort, post-ASCT relapse rate was much higher than NRM rate (48.1 vs 9.1% at 5-year). Median PFS and OS after ASCT was 2.7 and 5.4 years, respectively. Lymphoma was the primary cause of death after ASCT. In contrast, for patients who had achieved PFS24 (n = 220), rates of post-PFS24 relapse and NRM were similar (14.8% and 12.3% at 5-year). Median PFS and OS after achieving PFS24 was 10.0 and 11.5 years, respectively. Lymphoma related and unrelated death rates were similar after achieving PFS24 (Table). For all patients who had a post-ASCT relapse, median PRS was 0.7 years (95% CI 0.5-0.9), and late relapse (> 2 vs ≤2 years after ASCT) was associated with better PRS (median 2.3 [1.7-4.8] vs 0.5 [0.3-0.7] years, p < 0.001). **Conclusions:** Post-ASCT PFS24 is an important prognostic predictor of post-ASCT outcomes in patients with RR DLBCL following frontline IC. Research Sponsor: None.

	Starting landmark	
	ASCT (n = 437)	Achieved PFS24 (n = 220)
5-year rate of (%)		
Relapse	48.1 (43.2-52.8)	14.8 (10.1-20.3)
NRM	9.1 (6.5-12.2)	12.3 (7.8-17.8)
Median PFS, years	2.7 (1.5-4.3)	10.0 (8.4-13.1)
5-year PFS (%)	42.8 (38.0-47.6)	72.9 (65.6-78.9)
Median OS, years	5.4 (4.2-7.4)	11.5 (9.9-NA)
5-year OS (%)	51.9 (46.9-56.7)	79.3 (72.3-84.8)
5-year rate of deaths from (%)		
Lymphoma	36.0 (31.3-0.40.6)	6.5 (3.4-11.0)
Treatment-related complications	6.3 (4.2-8.9)	4.2 (1.8-8.1)
Other causes	4.8 (3.0-7.3)	8.1 (4.6-12.9)
Unknown causes	1.0 (0.3-2.5)	1.8 (0.5-4.9)

7523 **Poster Session**

Up to seven years of follow-up in the RESONATE-2 study of first-line ibrutinib treatment for patients with chronic lymphocytic leukemia.

First Author: Paul M. Barr, Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY

Background: Ibrutinib, a once-daily Bruton's tyrosine kinase inhibitor, is the only targeted therapy with significant progression-free survival (PFS) and overall survival (OS) benefit in multiple randomized phase 3 studies versus established therapies in patients (pts) with previously untreated chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). Extended long-term follow-up data for the RESONATE-2 study of first-line ibrutinib vs chlorambucil in older pts with CLL/SLL are reported. **Methods:** In the phase 3 RESONATE-2 study, older pts (≥65 years [y]) with previously untreated CLL/SLL and without del(17p) (N=269) were randomly assigned 1:1 to once-daily single-agent ibrutinib 420 mg until disease progression (PD) or unacceptable toxicity (n=136) or chlorambucil 0.5–0.8 mg/kg up to 12 cycles (n=133). Outcomes included PFS, OS, overall response rate (ORR), and safety. Long-term responses were investigator-assessed per 2008 iwCLL criteria. **Results:** With up to 7y of follow-up (median, 74.9 months; range, 0.1–86.8), significant PFS benefit was sustained for pts treated with ibrutinib vs chlorambucil (hazard ratio [HR] 0.160 [95% confidence interval (CI): 0.111–0.230]). At 6.5y, PFS was 61% in pts treated with ibrutinib vs 9% in pts treated with chlorambucil. This PFS benefit was observed across all subgroups, including in ibrutinib-treated pts with high-risk genomic features of unmutated IGHV (HR 0.109 [95% CI: 0.063–0.189]) or del(11q) (HR 0.033 [95% CI: 0.010–0.107]). OS at 6.5y was 78% with ibrutinib treatment. ORR was 92% for ibrutinib-treated pts with complete response (CR/CRi) rate increasing to 34% with this follow-up. Ongoing rates of grade ≥3 adverse events (AEs) of interest remained low for hypertension (5–6y interval: 5%, n=4; 6–7y: 4%, n=3) and atrial fibrillation (5–6y: 1%, n=1; 6–7y: 1%, n=1); no grade ≥3 major hemorrhage occurred in 5–7y. Dose reductions due to grade ≥3 AEs occurred in 1% (n=1) of pts during the 5–6y and 6–7y intervals. Across full follow-up, 31 pts had dose reductions due to any-grade AEs of whom 22/31 (71%) had resolution or improvement the AE. Primary reason for discontinuations in 5–7y was PD (5–6y: 5%, n=4; 6–7y: 6%, n=4). Any-grade AEs leading to discontinuations were seen in 3% (n=2) of pts from 5–6y and none in 6–7y. With over 7y of follow-up, 47% of pts remain on single-agent ibrutinib. **Conclusions:** Extended long-term data from RESONATE-2 demonstrate the sustained PFS and OS benefit of first-line ibrutinib treatment for pts with CLL, including for pts with high-risk genomic features. Responses continue to deepen over time. Rates of grade ≥3 AEs of interest continued to be low at up to 7y follow-up and further discontinuations and dose reductions due to AEs were rare; most AEs leading to dose reduction resolved or improved. Ibrutinib remains well tolerated with no new safety signals observed. Clinical trial information: NCT01722487, NCT01724346. Research Sponsor: Pharmacyclics LLC, an AbbVie Company, Pharmaceutical/Biotech Company.

7524 **Poster Session**

Survival trends in chronic lymphocytic leukemia in the era of oral targeted therapies in the United States: SEER database analyses (1985 to 2017). *First Author: Neda AlRawashdh, University of Arizona, Tucson, AZ*

Background: The survival of chronic lymphocytic leukemia (CLL) patients has progressively improved after the approval of new targeted therapy for first-line treatment and relapsed disease. We performed a corresponding analysis from the U.S. population-based SEER database (1973–2017) to explore the trend of survival and the effect of advanced CLL treatment on overall survival in CLL patients. **Methods:** Data were extracted from SEER*Stat for all patients 15 years or older with a primary diagnosis of CLL with or without subsequent cancers. A period analysis was performed to estimate the 5- and 10-year relative survival rates for patients diagnosed (dx) during different calendar periods from 1985 to 2017, based on gender and age at time of diagnosis (15–44, 45–54, 55–64, 65–74, 75–84, 85 years or older). A mixture cure model was used to examine the proportion of long-term survivors per gender and age category among CLL patients diagnosed between 1985 and 2015. Cox proportional hazard modeling was used to calculate the hazard ratios (HRs) of death adjusted for gender and age at diagnosis for two cohorts: (a) diagnosed in 2000–2003 and followed to 2012; (b) 2004–2007 and followed to 2015. **Results:** For males, the 5-year age-adjusted relative survival rate improved progressively from 72.0% (dx 1985-1989) to 88.2% (dx 2010-2014); for females, from 76.8% (dx 1985-1989) to 90.8% (dx 2010-2014). The corresponding 10-year age-adjusted relative survival rates were 47.3% (dx 1985-1989) and 72.5% (dx 2005-2009) for males; and 58.2% (dx 1985-1989) and 78.7% (dx 2005-2009) for females. The table below shows the proportions of long-term survivors for the 1985–2017 cohort as estimated in the mixed cure model. The HRs (95%CI) of death for cohort (b) in comparison to cohort (a) were 0.58 (0.43–0.78), 0.58 (0.48–0.70), 0.57 (0.49–0.67), 0.68 (0.54–0.85); and 0.83 (0.68–1.02) for age categories of 45–54, 55–64, 65–74, 75–84, and 85 years or old. **Conclusions:** Survival is significantly improved by calendar period among patients diagnosed after 2004 and treated in the era of advanced therapies. Females and younger patients had a higher probability of long term survival. Future studies should consider such covariates as treatment type, disease stage and genetics. Research Sponsor: None.

Estimated cure proportions for CLL patients diagnosed between 1985-2015.

Age	Overall cured proportion (95%CI)	Cured proportion in males (95%CI)	Cured proportion in females (95%CI)
45-54	0.43 (0.38-0.49)	0.35 (0.29-0.42)	0.59 (0.52-0.64)
55-64	0.41 (0.37-0.44)	0.35 (0.32-0.39)	0.50 (0.46-0.54)
65-74	0.12 (0.10-0.70)*	0.08 (0.007-0.98)	0.16 (0.12-0.22)
75-84	0.003 (0.001-0.98)*	no cure	0.14 (0.11-0.20)
85+	0.02 (0.001-0.99)*	no cure	0.06 (0.02-0.26)

*Indicates a high variation in CLL survival per gender.

7525 **Poster Session**

Updated results of the selective Bruton tyrosine kinase (BTK) inhibitor TG-1701, as monotherapy and in combination with ublituximab and umbralisib (U2) in patients (pts) with B-cell malignancies. *First Author: Chan Cheah, Sir Charles Gairdner Hospital, Comprehensive Cancer Centre, Nedlands, Australia*

Background: TG-1701 is a selective, covalent BTK inhibitor administered once daily (QD). Both the "U2" combination (anti-CD20 mAb ublituximab + the PI3Kδ-CK1ε inhibitor umbralisib) and BTK inhibition are highly active in treatment-naïve (TN) and relapsed/refractory (R/R) CLL, each having previously demonstrated superiority over standard chemoimmunotherapy. Here we report the results of the dose escalation of TG-1701 monotherapy and TG-1701+U2. **Methods:** Pts with R/R CLL and lymphoma were enrolled in a Ph 1 study initially evaluating dose escalation (DE) of oral TG-1701 QD continuously administered in 28-day cycles (100, 200, 300, and 400 mg). After characterizing the safety profile of TG-1701 monotherapy, we implemented a parallel DE arm of TG-1701+U2. Select dose levels of TG-1701 monotherapy were expanded in CLL, MCL and Waldenström's (WM) . All pts were treated until disease progression. The primary objectives are to characterize the safety profile and define the recommended Ph 2 doses for the drugs alone and in combination. **Results:** As of 03 February 2021, 123 pts were treated with TG-1701: 25 in the monotherapy DE arm, 61 in the 200 mg disease-specific cohorts (20 CLL [5 TN], 21 MCL [4 TN], 20 WM [8 TN]), 20 in the 300 mg CLL cohort (4 TN), and 17 in the 1701+U2 DE arm. The median # of prior therapies was 1 (range, 1 - 10). All pts were BTKi-naïve. All 123 pts were evaluable for safety. TG-1701 was well tolerated and the maximum tolerated dose (MTD) for monotherapy was not reached at 400 mg (demonstrating near 100% saturation of the BTK at all dose levels studied). Treatment emergent adverse events (TEAE) of clinical interest included atrial fibrillation (AF 4.0% of pts, G $\geq$3 in 1 case), G $\geq$3 hypertension (2.4%), and bleeding events (18.7%, all G1-2). No cases of ventricular tachyarrhythmia were reported. TEAEs leading to TG-1701 dose reduction occurred in 6.5% of pts. TEAEs leading to treatment discontinuation occurred in 1.6% of pts (AF, COVID-19). At the data cut-off, 119 pts were evaluable for response, including 40 in DE (Table). The median duration of response has not been reached among responders overall. The median follow-up (mFU range) was 15.9 mos (1.3 - 28.6+) in DE and 8.5 mos (1.4 -15.6+) in disease-specific cohorts. **Conclusions:** TG-1701 exhibits an encouraging safety and efficacy profile. The combination of 1701+U2 has been well tolerated and dose escalation continues. The combination shows enhanced depth of response over TG-1701 monotherapy. Recruitment to this study continues. Response per investigator review by treatment group. Clinical trial information: NCT03671590. Research Sponsor: TG Therapeutics.

	DE arm (N = 23)	200 mg CLL (N = 20)	200 mg MCL (N = 20)	200 mg WM (N = 20)	300 mg CLL (N = 19)	1701+U2 DE arm (N = 17)
ORR %	56.5	95.0	60.0	95.0	100	82.3
CR %	0	0	0	0	0	23.5
Very good PR %	4.3	NA	NA	0	NA	5.9
PR %	47.8	95.0	60.0	70.0	100	52.9
Minor response %	4.3	NA	NA	25.0	NA	0
mFU mos	17.5	11.6	8.2	9.7	5.8	14.3

7526 **Poster Session**

Identification of genetic markers associated with ibrutinib-related cardiovascular toxicity. *First Author: Issam Hamadeh, Department of Hematologic Malignancies and Blood Disorders, Levine Cancer Institute, Atrium Health, Charlotte, NC*

Background: Cardiovascular side effects (CVSEs: atrial fibrillation, hypertension, etc.) are common in patients with chronic lymphocytic leukemia (CLL) treated with ibrutinib and often lead to dose reductions or discontinuation. However, the etiology of ibrutinib related CVSEs has not been elucidated. This study sought to interrogate the association between ibrutinib related CVSEs and polymorphisms in genes of the Bruton Tyrosine Kinase (BTK) signaling pathway (identified through Ingenuity Pathway Analysis) **Methods:** Newly diagnosed and relapsed patients with CLL who underwent treatment with ibrutinib between December 2019 and November 2020 at Levine Cancer Institute were identified. Buccal swabs were collected through an IRB approved specimen collection protocol. Data extraction included: demographics, CLL stage, cytogenetics, previous treatments, ibrutinib start dates and dose, drug related SEs, and other medications. DNA isolated from buccal swabs was genotyped for 40 single nucleotide polymorphisms (SNPs) in *GATA4, SGK1, KCNQ1, KCNA4, NPPA* and *SCN5A* genes using a custom NGS panel. Logistic regression analysis evaluated the association between SNPs and CVSEs. **Results:** In 50 evaluable patients, the median age was 71 years (range:48-90) and 50% received frontline ibrutinib monotherapy. CVSEs occurred in 20% of patients (n=10). In univariate analysis, 4 SNPs in 3 genes were significantly associated with CVSEs (Table). Because the genes were in the same pathway, a genetic risk score was developed which indicated that patients with at least 2 SNPs had a 12-fold increase in risk of CVSEs (Table). **Conclusions:** Our findings provide insights into the genetic determinants of ibrutinib related CVSEs. If replicated in a larger study, this will facilitate utility of pharmacogenetic testing (for *GATA4, KCNQ1* and *KCNA5* polymorphisms) as a clinical tool to individualize ibrutinib treatment. Research Sponsor: Atrium foundation.

Results of logistic regression analysis.

		95% Confidence Interval		
Gene/SNP	Odds Ratio	Lower limit	Upper limit	P-value
Univariate logistic regression analysis				
GATA4				
rs804280 (AA vs. AC+CC)	4.5	1.1	19.0	0.05
KCNQ1				
rs163182 (GG vs. GC+CC)	5.3	1.1	25.0	0.04
rs2237895 (AA vs. AC+CC)	12.0	1.4	111.0	0.01
KCNA5				
rs2284136 (CC vs. CT+TT)	8.0	1.1	70.0	0.03
Genetic risk score				
Genetic risk score (1 vs. 0)*	12.2	1.4	105.4	0.01

*:score of 1 if presence of $\geq$ 2 SNPs and 0 if $\leq$ 1 SNP.

7527 **Poster Session**

Herpes zoster in chronic lymphocytic leukemia: Effect of vaccination and treatment. *First Author: Nirav Antao, Saint Louis VA Medical Center, St. Louis, MO*

Background: Patients with Chronic Lymphocytic Leukemia (CLL) are susceptible to infections due to impaired humoral immunity as a complication of the disease, treatments received and age at diagnosis. Herpes zoster (HZ) is a painful, vesicular rash from reactivation of varicella-zoster virus that is common in immunocompromised patients. While HZ vaccines can reduce both varicella-zoster reactivation and post-herpetic neuralgia, vaccination rates are low. The aim of this study is to determine the effect of vaccination on rates of HZ infection in patients with CLL. **Methods:** We identified patients diagnosed with CLL between September 1999 and October 2015 using Veterans Administration Central Cancer Registry (VACCR). Pharmacy records were used to identify patients who received treatment for CLL and HZ. HZ events were defined as patients with International Classification of Diseases 9th Revision (ICD-9) codes for HZ infection (053) or prescriptions of acyclovir or valacyclovir at a dose of 1500 mg/day or higher or famciclovir at a dose of 1000 mg/day or higher without a diagnosis of Herpes simplex or Bell's palsy, or an ICD-9 code and prescription above. Cox proportional hazards regression model was used to assess the association between vaccination as a time-varying exposure and developing HZ while controlling age at CLL diagnosis, co-morbidity score, and receipt of first and second line chemotherapy. The study was approved by the St. Louis VA Medical Center institutional review board. **Results:** A cohort of 7155 patients with CLL was identified using VACCR. 2640 patients (36.9%) and 1161 patients (16.2%) received first and second line chemotherapy respectively. Mean age at first chemotherapy was 69.5 years. We detected 1115 cases of HZ (15.6%) using ICD-9 codes, prescriptions or both. 615 patients (8.6%) received HZ vaccinations. Patients with HZ were younger (mean 68.0 vs. 69.8 years, $p < 0.001$), had similar co-morbidities, and were more likely to get treatment for CLL (58.1% vs. 33.0%, $p < 0.001$). Using a time-varying analysis, there was a trend for HZ vaccine to decrease the risk of developing HZ (HR 0.71, 95% CI 0.49-1.04, $p = 0.082$). When adjusting for age and co-morbidity, patients with CLL treated with first line chemotherapy had a higher risk of HZ (HR 2.34, 95% CI 2.02-2.71, $p < 0.001$) compared to those never receiving therapy. Second line chemotherapy increased risk of HZ (HR 1.32, 95% CI 1.13-1.55, $p < 0.001$) beyond first line treatment. **Conclusions:** HZ is prevalent in patients with CLL and affects younger patients who require chemotherapy. The risk of developing HZ increases in recipients of first and second line chemotherapy. In the time-varying analysis, there was a trend towards decreased infection in patients who received HZ vaccination. Further studies in a more modern cohort that assess infection risk using a larger vaccinated group with the newer and more effective HZ vaccine are warranted. Research Sponsor: None.

7528 **Poster Session**

Brentuximab vedotin with chemotherapy in adolescents and young adults (AYAs) with stage III or IV Hodgkin lymphoma: A subgroup analysis from the phase 3 Echelon-1 study. *First Author: Howland E. Crosswell, Bon Secours Hematology Oncology, Bon Secours, St. Francis Health System, Greenville, SC*

Background: Hodgkin lymphoma (HL) is a rare disease that commonly occurs in adolescents and young adults (AYAs) which is typically defined as 15 to 39 years. Given their young age at presentation, key factors in treatment selection include a high cure rate and limiting long-term toxicities. Brentuximab vedotin (Adcetris®; A) is a CD30-directed ADC approved in combination with doxorubicin, vinblastine, and dacarbazine chemotherapy (A+AVD) for adults with previously untreated stage III/IV cHL based on results from the phase 3 ECHELON-1 trial. Recent 5-year data demonstrated a significantly improved PFS per investigator (INV) vs doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) (HR, 0.69; 95% CI, 0.54–0.9; P = 0.003) (Straus 2020). Here we describe key efficacy and safety results for AYA pts enrolled in ECHELON-1. **Methods:** ECHELON-1 (N = 1334) is a global, open-label, multicenter, randomized trial of pts with previously untreated stage III/IV cHL. A total of 771 AYAs (57.8%) received either A+AVD (n = 396) or ABVD (n = 375) with a PET scan after cycle 2 (PET2). An analysis of PFS (time from randomization to progression or death from any cause) per INV was conducted. **Results:** After a median follow-up of 60.7 months (95% CI, 60.4-61.0), there was a 36% reduction in the risk of progression or death in AYAs receiving A+AVD vs ABVD (HR 0.64; 95% CI, 0.45-0.92; P = 0.013) with a 5-year PFS of 86.3% vs 79.4%, respectively, similar to the ITT population. The PFS benefit of A+AVD vs ABVD was independent of PET2 status; PET2 positivity (Deauville 4-5) was 6% and 8%, respectively. On the A+AVD arm, 81 AYAs (20%) had at least 1 subsequent anticancer therapy vs 96 AYAs (26%) on the ABVD arm; 26 AYAs (7%) received subsequent high dose chemotherapy and autologous stem cell transplant vs 32 AYAs (9%) on the A+AVD and ABVD arms, respectively. Resolution or improvement of peripheral neuropathy (PN) were similar in both arms; 224 AYAs (88%) on the A+AVD had resolution or improvement of PN vs 133 AYAs (89%) on the ABVD arm. Ongoing PN was predominantly Gr 1 (62%) and Gr 2 (26%), with 8 AYAs (13%) on the A+AVD arm and 1 AYA (5%) on the ABVD arm reporting ongoing Gr 3 PN. Finally, 7 AYAs (1.8%) and 5 AYAs (1.4%) on the A+AVD and ABVD arms, respectively, reported a secondary malignancy. Subsequent pregnancies were reported in female pts (44 A+AVD; 26 ABVD) and partners of male pts (31 A+AVD; 30 ABVD). No stillbirths were reported. All but 1 pt in each arm was < 40. **Conclusions:** Consistent with the ITT population, AYAs treated with A+AVD compared to ABVD had a durable PFS benefit at this significant 5-year milestone. No impact on the rate of secondary malignancies and a numerically greater number of pregnancies were observed, outcomes of interest to AYAs. Additionally, the majority of PN events improved or resolved over time. A+AVD should be considered a treatment option for AYAs with stage III/IV cHL. Clinical trial information: NCT01712490. Research Sponsor: Seagen Inc., Takeda.

7529 **Poster Session**

A phase II study of penpulimab, an anti-PD-1 antibody, in patients with relapsed or refractoryclassic Hodgkin lymphoma (cHL). *First Author: Yuqin Song, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Lymphoma, Peking University Cancer Hospital & Institute, Bejing, China*

Background: Penpulimab is a humanized IgG1 monoclonal antibody (mAb) that blocks PD-1 binding to PD-L1. Penpulimab, with its unique binding epitope, was engineered to eliminate Fc-mediated effector function that compromises anti-tumor immune cell function, and to optimize receptor occupancy by improving duration of drug binding. Fc-mediated effector functions, such as ADCC/ADCP, have been observed in most IgG4 anti-PD-1 mAbs but is absent in penpulimab, thereby potentially reducing the occurrence of immune-related adverse reactions. Penpulimab also demonstrated a slower PD-1 antigen binding off-rate than marketed anti-PD-1 mAbs, thereby resulting in better cellular activity and higher receptor occupancy. Penpulimab's numerous contacts with N58 glycosylation on the BC loop of PD-1 may also contribute to a slower binding off-rate. These structural differentiations of penpulimab enhance its anti-tumor activity and produce a superior safety profile. **Methods:** AK105-201 is a multicenter, single-arm, open-label study of penpulimab in relapsed/refractory (R/R) cHL. All pts received penpulimab 200 mg Q2W until progression or unacceptable toxicity. Eligible pts had prior autologous stem cell transplant (ASCT) or at least 2 lines of prior chemotherapy. The primary endpoint was ORR based on the Lugano 2014 criteria as assessed by an independent review committee (IRC). Key secondary endpoints included CR rate, DCR, PFS, duration of response (DoR), safety, and tolerability. **Results:** As of 8 November 2020, of 94 pts (59.6% male, median age 32.0 yrs [31-71], 26.6% was ECOG 1) enrolled, 56 pts remained on treatment, 4 pts completed 24-months treatment and 25 had discontinued (17 due to disease progression, 3 due to AE). After a median follow-up of 15.8 months, the IRC-assessed ORR in the 85 pts evaluable for efficacy was 89.4% (95% CI: 80.8%, 95.0%). A total of 40 patients (47.1%) achieved CR. Median duration of response was not reached with range from 1.7 to 24.5+ months. Median PFS was not reached with 12-months PFS rate was 72.1% (95% CI: 60.5%, 80.8%). Treatment-related adverse events (TRAEs, with unlikely-related events included) occurred in 97.9% of pts (≥ G3 in 26.6% [25/94], treatment discontinuation in 5.3% [5/94]). Treatment-related SAEs occurred in 10.6%. Most frequent TRAEs (≥20%) were hypothyroidism (31.9%), upper respiratory tract infection (25.5%), fever (24.5%), and ALT elevations (23.4%). Grade ≥3 TRAEs reported in ≥2 pts were platelet count decreased (3.2%), hyperlipemia (3.2%), rash (3.2%), neutrophil count decreased (2.1%). Grade 3 immune-related AEs (irAEs) were reported in 4.3%: IgA nephropathy, pneumonitis, rash, psoriasis (each n = 1) and no G4 or G5 irAEs reported. **Conclusions:** Penpulimab was shown to be highly active in achieving in a CR rate of 47.1% in pts with R/R cHL while demonstrating lower rates of SAEs, TRAEs leading to discontinuation, and Grade ≥3 irAEs. Clinical trial information: NCT03722147. Research Sponsor: Akeso Biopharma Inc.

7530 **Poster Session**

Salvage therapies in transplant-eligible relapsed classic Hodgkin lymphoma, are novel regimens better? *First Author: Sanjal Desai, Mayo Clinic, Rochester, MN*

Background: Clinical trials of novel salvage therapies (ST) have encouraging outcomes for relapsed/refractory classic Hodgkin lymphoma (R/R cHL) eligible for autologous stem cell transplant (ASCT). In this observational study, we report efficacies and outcomes of different ST in ASCT-eligible R/R cHL. **Methods:** Consecutive ASCT-eligible R/R cHL pts at 3 Mayo Clinic sites were included. Demographics and clinical variables at relapse were recorded by medical records review. Time to event endpoints were defined from relapse. Univariate associations were confirmed in multivariate models of age, sex, B symptoms, stage, bulky disease (BD, single mass > 6 cm) extra nodal disease (END), primary refractory disease (PRD) and early relapse (ER, within 1 year). **Results:** From Jan 2008 to May 2020, 207 ASCT-eligible pts with R/R cHL were included. Median age was 33 (24-43) years, 53% were male, 52% had advanced stage, 24% had BD, 36% had B symptoms, 41% had END, 11% had PRD and 43% had ER. All patients received ST and underwent ASCT; 43 (21%) received 2 ST, 14 (7%) 3 ST and 4 (0.5%) received 4 ST. 6 groups of ST were identified: ifosfamide, carboplatin and etoposide (ICE), bendamustine/brentuximab (BBV), brentuximab vedotin (BV), gemcitabine-based therapy (Gem), checkpoint inhibitor (CPI), and others. Table lists response to first line ST. BBV had significantly higher overall response rate (ORR) and complete response (CR) as first ST in univariate and multivariate models. 114 (79%) after ICE, 30 (97%) after BBV, 15 (56%) after BV, 25 (76%) after Gem, 8 (73%) after CPI and 15 (79%) after other ST underwent ASCT. Higher number of pts were bridged to ASCT after BBV than ICE ($p<0.01$). 110 (53%) went to ASCT in CR, 74 (36%) in partial response (PR) and 11% in progressive disease (PD). 43 received BV maintenance (BVm) after ASCT. Pts going to ASCT in PR or PD had significantly lower progression free survival (PFS) compared to pts in CR (2 yr PFS: 62%, 18% vs 77%, respectively, $p<0.0001$) in univariate and multivariate models. There was no difference in PFS and overall survival (OS) by type of ST. BVm was associated with higher PFS (HR 0.3 (CI_{95} 0.2-0.8)) and higher number of ST was associated with lower OS (HR 2 (CI_{95} 1.4-3)) in multivariate model ($p<0.001$). For pts transplanted in CR, there was no significant difference in PFS and OS by type of ST but higher number of ST predicted lower OS (HR 2.4 (CI_{95} 1.2-3.5), $p<0.01$). **Conclusions:** Type of ST did not predict survival, response to and number of ST did. For pts with CR, number of ST not type of ST predicted survival. BBV had higher response rates, higher rates of bridge to ASCT, and may be a preferable ST than ICE. Large, randomized trials are needed to evaluate efficacy of BBV compared to ICE. Research Sponsor: None.

Type of ST	Total N(%)	ORR N(%)	CR N(%)	*P* value
ICE	136 (68)	105 (71)	68 (52)	<0.001
BBV	24 (12)	24 (100)	21 (84)	<0.001
BV	8 (3)	4 (50)	1 (12)	NS
Gem	23 (11)	20 (86)	11(50)	NS
CPI	4 (2)	3 (75)	2 (50)	NS
Others	9(4)	1 (11)	1 (11)	NS

7531 **Poster Session**

A phase Ib study of a PI3Kδ inhibitor Linperlisib in patients with relapsed or refractory peripheral T-cell lymphoma. *First Author: Jie Jin, First Hospital Affiliated Zhe Jiang Medical University, Hangzou, China*

Background: PI3Kδ inhibitors have been shown to have important roles in blocking mitogenic and survival signaling within the tumor cell and the tumor microenvironment and activate antilymphoma immune responses. Linperlisib is an oral highly selective small molecule inhibitor of PI3Kδ and has been demonstrated to be well-tolerated with a favorable PK profile in patients with lymphomas at the RP2D. This phase Ib study is evaluating the efficacy and safety of Linperlisib in relapsed or refractory peripheral T-cell lymphoma (PTCL), a highly aggressive malignancy with few treatment options for patients. **Methods:** Eligible PTCL patients who must have received at least 1 prior systemic conventional therapy were administrated Linperlisib 80mg orally once daily (RP2D) in 28 days cycle until disease progression, unacceptable toxicity, or withdrawal from the study. Tumor response was assessed by IWG 2007 criteria with CT performed every 2 cycles. The primary endpoint was the overall response rate (ORR), and the secondary endpoint was toxicity assessed by NCI-CTCAE5.0. **Results:** As of February 2, 2021, 36 PTCL patients were enrolled in this exploratory trial. Most patients were stage III (38.2%) or IV (50%). Of the 27 evaluable patients to date, the PTCL histologies were PTCL-NOS (n=12), AITL (n=10), ALCL (n=3), NKTCL (n=1) and MEITL (n=1). 19 of the 27 evaluable patients had Investigator confirmed responses for a 70.4% ORR including 25.9% CR (7pt) and 44.4% PR (12pt). In the major subtypes, ORR was 50% (6/12) PTCL-NOS and 80% (8/10) AITL, respectively. A disease control rate of 100% was observed, and most responses occurred by first assessment at C2D28. One subject who had a CR at C2D28 is currently in cycle 9 and continuing on Linperlisib. 36 patients experienced at least 1 AE in the trial, with 95% of AEs ≤ grade 2. Consistent with previously treated lymphoma patients, no unexpected toxicities were observed. The most common TRAEs (≥10%) were neutrophil count decreased (55.6%), leukocyte count decreased (33.3%), hypertriglyceridemia (22.2%), aspartate aminotransferase increased (16.7%), hypercholesterolemia (16.7%), alanine aminotransferase increased (11.1%), creatinine increased (11.1%), rash (11.1%), thrombocyte count decreased (11.1%) and electrocardiogram T wave abnormal (11.1%). No AE grade 4 was observed. 6 patients (16.7%) experienced at least one SAE, in which 4 (11.1%) SAEs were considered to be drug-related, including neutrophil count and leukocyte count decreased (2.8%), gastritis (2.8%), and pneumonia (5.6%). **Conclusions:** The oral PI3Kd inhibitor Linperlisib had significant activity in patients with relapsed or refractory PTCL. Toxicities with Linperlisib therapy were generally tolerable and manageable. Further efficacy and safety is being evaluated. Clinical trial information: NCT04108325. Research Sponsor: Shanghai Yingli Pharmaceutical Co., Ltd.

7532 **Poster Session**

CD19 CAR T-cell product type independently impacts CRS and ICANS severity in patients with aggressive NHL. *First Author: Jordan Gauthier, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: CD19-targeted chimeric antigen receptor-engineered (CD19 CAR) T cells achieve high response rates in patients (pts) with relapsed or refractory (R/R) aggressive B-cell non-Hodgkin lymphoma (NHL), but are limited by cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). Pivotal trial data suggested distinct toxicity risks across CD19 CAR T-cell products, but differences in pt and disease characteristics may have confounded these observations. Thus, we assessed the independent impact of 3 CD19 CAR T-cell products (axicabtagene ciloleucel[axicel], tisagenlecleucel [tisacel], and JCAR014) on CRS and ICANS severity in 136 pts with R/R aggressive NHL. **Methods:** We retrospectively analyzed aggressive NHL pts treated at our institutions with cyclophosphamide and fludarabine lymphodepletion (LD) followed by CD19 CAR T-cell therapy. Axicel and tisacel pts were treated off trial using commercial products. JCAR014 (defined-composition 4-1BB-costimulated CD19 CAR T cells) was administered in all pts at the dose of $2x10^6$/kg on a phase I/II clinical trial (NCT01865617). CRS and ICANS were graded according to the ASTCT criteria and CTCAE 4.03, respectively. We used multivariable proportional odds logistic regression to model CRS and ICANS grade. **Results:** The CAR T-cell product was axicel, tisacel, or JCAR014 in 50%, 28%, and 22% of pts, respectively. Compared to axicel pts, we observed higher preLD LDH levels in tisacel and JCAR014 pts, and lower preLD albumin with tisacel ($p < 0.001$) with comparable age and hematopoietic cell transplantation comorbidity (HCT-CI) indexes across CAR T-cell products. Higher day-28 overall response rate by Lugano criteria was observed after axicel (71%) compared to tisacel (56%) and JCAR014 (53%). Adjusting for age, HCT-CI, preLD LDH, preLD albumin, CAR T-cell product type was associated with CRS severity (tisacel versus [vs] axicel, OR = 0.45, p = 0.05; JCAR014 vs axicel, OR = 0.29, p = 0.005;). Age had limited or no impact on CRS severity (OR 95%CI, 0.97-1.02), while the effect of HCT-CI was undetermined (OR 95%CI, 0.85-1.27). In a multivariable model including the same covariates as above, CAR T-cell product type (tisacel vs axicel, OR = .14, $p < .001$; JCAR014 vs axicel, OR = 0.31, p = 0.009), preLD LDH (OR, 3.96 per log10 increase; p = 0.04) and age (OR per 10-year increase, 1.32; p = .06) were associated with ICANS severity. Interaction effect testing suggested effect modification of age by the CAR T-cell product type (tisacel/JCAR014 versus axicel, p = 0.06); using a multivariable model including this interaction term, the predicted probabilities of grade ≥3 ICANS in a 70 year-old after axicel, tisacel, and JCAR014 were 40%, 6%, and 8%, respectively. **Conclusions:** CAR T-cell product type independently impacts CRS and ICANS severity in NHL pts. Our findings provide key insights to guide patient and CAR T-cell product selection. Research Sponsor: U.S. National Institutes of Health.

7533 **Poster Session**

Update of a phase II, multicenter study of high-dose chemotherapy with autologous stem cell transplant followed by maintenance romidepsin for T-cell lymphoma. *First Author: Niloufer Khan, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Peripheral T-cell lymphomas (PTCL) have suboptimal outcomes with conventional chemotherapy. Autologous hematopoietic stem cell transplant (AHCT) is a therapeutic strategy for patients in first complete or partial remission (CR1 or PR1), with median progression-free survival (PFS) after AHCT of 36-48% by intent to treat (d'Amore et al JCO 2012, Reimer et al JCO 2009). Romidepsin (romi) is a histone deacetylase inhibitor approved for treatment of relapsed/refractory T-cell lymphoma. We present updated data of the first multicenter study to evaluate PFS of patients (pts) receiving maintenance therapy with romi after AHCT. **Methods:** This was a phase 2, open-label, investigator-initiated study (expected PFS 45%, desired PFS 70%; success achieved if 15 or more pts out of 25 were progression-free at 2 years post-AHCT). 26 pts transplanted in CR1 or PR1 were evaluable for the primary endpoint of 2-year PFS (Cohort 1, Table). An exploratory cohort (Cohort 2, n=7) enrolled pts either transplanted ≥ CR/PR2 (n=5) or with high risk histologies (n=2). Pts underwent AHCT with carmustine, etoposide, cytarabine and melphalan (BEAM) conditioning. Maintenance romi 14 mg/m2 started days 42-80 post AHCT; every other week through 6 mon, every 3 weeks through 1 year and every 4 weeks through 2 years post AHCT. PFS was estimated by Kaplan-Meier. **Results:** 47 pts consented; 13 did not receive romi (no AHCT, n=2; relapse before romi, n=3; cardiac comorbidity, n=3, patient declined, n=5). 1 consented pt did not have PTCL. 15 out of the first 25 pts in Cohort 1 were progression free after 2 years; median follow up of 31 mon (21 - 36 mon). Estimated 2-year PFS was 62% (45-83%, 95% CI); median PFS 30 mon (12.0- NA, 95% CI). In Cohort 2, estimated 2-year PFS was 43% (18 – 100, 95% CI); median follow up of 30 mon (range, 24 – 37 mon); median PFS 14 mon (5 – NA, 95% CI). Across cohorts, 5 pts required dose reduction. The most common toxicities (≥10% of pts, all grades) were fatigue (n=24, 73%), decreased platelets (n=16, 48%) and anemia (n=16, 48%). **Conclusions:** While the study did not meet its desired primary efficacy endpoint, maintenance romi was well-tolerated with an estimated 2-year PFS of 62%, greater than historical data. A larger, randomized study would be needed to determine the superiority of this approach. Clinical trial information: NCT01908777. Research Sponsor: Celgene.

Characteristics	Cohort 1 (n=26)	Cohort 2 (n=7)
Histology		
Angioimmunoblastic T-cell Lymphoma	11 (42%)	1 (14%)
Peripheral T-cell Lymphoma, Not otherwise specified	7 (27%)	0
Anaplastic Large Cell Lymphoma, ALK-	5 (19%)	1 (14%)
Anaplastic Large Cell Lymphoma, ALK+	1 (4%)	3 (43%)
NK/T-cell Lymphoma	0	2 (29%)
Enteropathy-associated T-cell Lymphoma	1 (4%)	0
Monomorphic Epitheliotropic Intestinal T-cell Lymphoma	1 (4%)	0
Median age (range)	59 (37-73)	59 (23-68)
CR/PR, n (%)	23 (88%)/3 (12%)	6 (86%)/1 (14%)
Median time from AHCT to first romidepsin, days (range)	75 (42-102)	49 (44-80)

7534 **Poster Session**

Polatuzumab vedotin + obinutuzumab + venetoclax in patients with relapsed/refractory (R/R) follicular lymphoma (FL): Primary analysis of a phase 1b/2 trial. *First Author: Rajat Bannerji, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Polatuzumab vedotin (Pola) + obinutuzumab (G) demonstrated activity and tolerability in a Phase 1b/2 trial of patients (pts) with R/R FL (Phillips, et al. Blood 2016). Preclinical studies with venetoclax (Ven) showed that concurrent treatment with Pola promotes MCL-1 degradation, a known mechanism of resistance to Ven, and enhances *in vivo* anti-tumor efficacy (Amin, et al. AACR 2020). Here, we report the primary safety/efficacy analysis with Pola-G-Ven in a Phase 1b/2 study of pts with R/R FL (GO29833; NCT02611323). **Methods:** Pts received induction treatment every 21 days (D) x six cycles (C) of: Pola 1.4–1.8mg/kg intravenously (IV) in dose escalation (DE) or recommended Phase 2 dose (RP2D) on D1; G 1000mg IV (C1: D1, D8, D15; C2–6: D1); and oral Ven 200–800mg (DE or RP2D; D1–21). Pts with complete response/partial response/stable disease (CR/PR/SD) at end of induction (EOI) received maintenance with G (1000mg on D1 every 2 months [mo] for 24 mo) and Ven (200–800mg daily) for 8 mo. Primary endpoints were safety/tolerability and positron emission tomography (PET)-CR rate at EOI by independent review committee (IRC) using modified Lugano criteria. **Results:** At the primary analysis (Oct 05, 2020), 74 pts were enrolled. Median pt age was 64 years (range 36–78); male (57%); Ann Arbor Stage III–IV (86%); FL International Prognostic Index high risk ≥3 (55%); bulky disease ≥7cm (16%); prior lines of therapy ≥2 (74%); refractory to: last prior therapy (51%), any prior anti-CD20 therapy (55%), both anti-CD20 therapy and an alkylating agent (double refractory; 55%). Grade 3–4 adverse events (AEs) were experienced by 73% of pts; most commonly, neutropenia (39%), thrombocytopenia (19%), and infections (16%; mainly pneumonia). AEs led to dose reduction in 38% and interruption in 68% of pts (mainly modifications to Ven). One fatal AE was reported (pneumonia). In total, 49 pts were treated at RP2D (Pola 1.8mg/kg + Ven 800mg) and were evaluable for efficacy. PET-CR rate at EOI by IRC was 57% (Table). With a median follow-up of 14.4 mo (range 8.2–28.4), the 12-mo progression-free survival (PFS) was 73% (95% confidence interval: 59.4–86.9). Median PFS was not reached. **Conclusions:** The safety profile of Pola-G-Ven is consistent with the known profiles of the individual drugs. Response rates at EOI with Pola-G-Ven are encouraging in this R/R FL patient population. Additional follow-up is needed to assess PFS benefit during maintenance treatment and beyond. Clinical trial information: NCT02611323. Research Sponsor: The GO29833 study was sponsored by F. Hoffmann-La Roche Ltd and Genentech, Inc. Third party medical writing assistance, under the direction of authors, was provided by Carla Smith, MSc, of Ashfield MedComms, and was funded by F. Hoffmann-La Roche Ltd.

Responses at EOI by modified Lugano criteria (RP2D; N=49).

N (%)	INV	IRC
ORR	38 (78)	35 (71)
CR	28 (57)	28 (57)
PR	10 (20)	7 (14)
SD	6 (12)	8 (16)
PD	3 (6)	4 (8)
Missing/unevaluable	2 (4)	2 (4)

INV, investigator-assessed; ORR, objective response rate; PD, progressive disease.

7535 **Poster Session**

Comparative efficacy of tisagenlecleucel (tisa-cel) and lisocabtagene maraleucel (liso-cel) in patients with relapsed/refractory diffuse large B-cell lymphoma (r/r DLBCL). *First Author: Stephen J. Schuster, Abramson Cancer Center of the University of Pennsylvania, Philadelphia, PA*

Background: Chimeric antigen receptor T-cell therapies tisa-cel and liso-cel are effective treatments for r/r DLBCL (Schuster 2019, Abramson 2020). This study compared efficacy outcomes of tisa-cel and liso-cel in r/r DLBCL using matching-adjusted indirect comparison (MAIC). **Methods:** Individual patient-level data (IPD) from JULIET (tisa-cel; NCT02445248; 02/2020 datacut) were weighted to match the patient population in TRANSCEND (liso-cel; NCT02631044; 08/2019 datacut). Baseline prognostic factors available in both trials were adjusted for age, sex, histology, ECOG performance status [ECOG PS], left ventricular ejection fraction, radiologic sum of product diameters, lactate dehydrogenase, prior stem cell transplantation [SCT], use of bridging therapy, and number of and refractoriness to prior therapies, in the MAIC. Overall survival (OS), progression-free survival (PFS), complete response (CR) rate, and overall response (OR) rate were compared. Primary analyses compared infused patients in JULIET (N=106, excluding 8 without lymphodepleting chemotherapy [LDC] and 1 large cell neuroendocrine carcinoma) with efficacy-evaluable set in TRANSCEND (N=256, infused patients). A scenario analysis compared JULIET infused to TRANSCEND primary analysis set (PAS) (N=133, dose level 2, excluding those with ECOG PS 2, prior allogeneic SCT, primary mediastinal B-cell lymphoma, follicular lymphoma [FL] 3B, or transformation from indolent lymphoma besides FL). Sensitivity analyses included JULIET patients with only fludarabine-based LDC or only adjusted significantly different baseline prognostic factors. Safety outcomes were not compared because adverse event management has evolved and differed between the two trials; MAIC is unable to adjust for such differences. **Results:** After adjusting for differences in baseline characteristics, OS, PFS, and CR were comparable between tisa-cel infused patients and the liso-cel efficacy-evaluable set (Table). The results were consistent across all scenario and sensitivity analyses. OR rate trended higher in the TRANSCEND efficacy-evaluable set (72.7% vs. 62.9%, p=0.07) and was higher in TRANSCEND PAS than in the respectively matched JULIET infused set (74.4% vs. 60.9%, $p < 0.05$). **Conclusions:** The MAIC results indicate there is no evidence suggesting differences in OS, PFS and CR between tisa-cel and liso-cel in r/r DLBCL. Analyses using IPD from both trials and/or real-world evidence are warranted to confirm these findings. Research Sponsor: Novartis Pharmaceutical Corporation.

MAIC of Tisa-cel Infused vs. Liso-cel Efficacy-evaluable set.

	Tisa-cel vs. liso-cel (95% CI); p-value
OS, hazard ratio (HR)	1.12 (0.62, 2.05); p=0.71; 1-year OS rate: 55.1% vs 57.9%
PFS, HR	1.16 (0.64, 2.09); p=0.63; 1-year PFS rate: 47.4% vs 44.1%
CR, rate difference	-5.4% (-15.5%, 4.7%); p=0.29
OR, rate difference	-9.7% (-20.0%, 0.6%); p=0.07

7536 **Poster Session**

Favorable tumor immune microenvironment (TME) and robust chimeric antigen receptor (CAR) T-cell expansion may overcome tumor burden (TB) and promote durable efficacy with axicabtagene ciloleucel (axi-cel) in large B-cell lymphoma (LBCL). *First Author: Justin Chou, Kite, A Gilead Company, Santa Monica, CA*

Background: Axi-cel is an autologous anti-CD19 CAR T-cell therapy approved for patients (pts) with relapsed/refractory LBCL after ≥2 prior systemic therapies. In the pivotal ZUMA-1 study, pts with high pretreatment (preTx) TB (estimated by sum of product diameters [SPD]) had lower peak CAR T-cell expansion normalized to TB and less frequent durable response rates vs pts with low TB (< 30% vs > 60%, respectively; *Blood Adv.* 2020;4:3268). The number of $CD8^+$ and $CCR7^+CD45RA^+$ product T cells infused and favorable immune contexture in preTx TME were also associated with axi-cel response (*Blood Adv.* 2020;4:3268; Galon et al. ASCO 2020. #3022). As potential barriers to axi-cel efficacy are not fully elucidated, we systematically analyzed preTx TME characteristics, including myeloid-related biomarkers and product attributes, to identify such challenges in ZUMA-1 pts with high TB. **Methods:** Samples from evaluable pts in ZUMA-1 Phase (Ph) 1 and Ph2 Cohorts (C) 1–3 were analyzed (NCT02348216; Ph1 and Ph2 C1+2, ≥2-y follow-up; C3, ≥6-mo follow-up). PreTx immune TME was analyzed by multiplex immunohistochemistry (n = 18) and gene expression analysis (n = 30) as previously described (Rossi et al. AACR 2018. #LB-016; Galon et al. ASCO 2020. #3022). CAR T-cell product characteristics and other covariates were evaluated as previously described (*Blood Adv.* 2020;4:3268). Correlative analyses of these covariates with clinical outcomes were performed by Wilcoxon or Kruskal-Wallis test. Median TB (by SPD) from ZUMA-1 Ph1 and Ph2 C1+2 was used as a cutoff for high (> 3721 mm^2) vs low (≤3721 mm^2) TB. Durable response refers to pts in ongoing response at time of data cutoff. **Results:** PreTx immune TME features related to suppressive myeloid-related activity, most notably *ARG2*, *TREM2*, and *IL-8* gene expression, were elevated in pts who failed to respond or relapsed without documented loss of CD19 expression. *ARG2* and *TREM2* levels in preTx biopsies were negatively associated with $CD8^+$ T-cell density. Pts with high TB who achieved durable response had low preTx *ARG2* and *TREM2* levels in TME and enhanced CAR T-cell expansion after axi-cel compared to pts with high TB who relapsed. High ratio of T-cell to suppressive myeloid cell markers (T/M ratio) in preTx biopsies associated positively with CAR T-cell expansion (peak and peak normalized to TB) and durable response in pts with high TB. **Conclusions:** Axi-cel may overcome high TB in pts with a favorable immune TME alongside robust CAR T-cell expansion. Favorable immune TME is characterized by reduced suppressive myeloid cell activity (low *ARG2* and *TREM2* expression) and increased T/M ratio. These data suggest possible actionable strategies to overcome high TB in the context of CAR T-cell therapy. [JC and VP contributed equally] Clinical trial information: NCT02348216. Research Sponsor: Kite, a Gilead Company.

7537 **Poster Session**

Combination of sintilimab, anlotinib and pegaspargase "sandwich" with radiotherapy in localized natural killer/T cell lymphoma: A multicenter, phase 2 study. *First Author: Zhiming Li, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: NK/T-cell lymphoma (NKTL) is a rare and distinct subtype NHL. Most newly diagnosed NKTL cases were localized-stage. For localized NKTL, RT alone is inadequate due to high systemic failure rate. Chemoradiation has been increasingly applied. However, current chemotherapy (CT) regimens have severe toxicity and infection, which reduce the completion of RT and patients' medical compliance. Therefore, novel regimens with mild toxicity are needed. Sintilimab, a fully human anti-PD-1 monoclonal antibody, has showed encouraging antitumor efficacy in pts with r/r NKTL. Anlotinib, a multiple-targeted TKI that mainly blocks VEGF/VEGFR pathway, has been approved for several solid tumor types in china. Anti-angiogenesis therapy could improve efficacy of ICI in multiple tumor types. This multicenter, single-arm, phase 2 study aims to evaluate the efficacy and safety of sandwich chemoradiotion of sintilimab combined with anlotinib and pegaspargase (PEG-ASP) in newly diagnosed localized NKTL pts. **Methods:** Patients with pathologically confirmed previously untreated stage NKTL were enrolled. All enrolled patients received 3 cycles of sintilimab (200mg D1 ivdrip) combined with anlotinib (12mg po D1-14) and PEG-ASP (2500U/m^2 D1) every 3 weeks followed by RT, then received additional 3 cycles of combination therapy as described above. The primary endpoint was overall response rate (ORR) by LUGANO 2014 criteria. **Results:** A total of 39 pts were enrolled, and 24 pts eligible for response evaluation (70.8% men; median age, 46 y [range 20-64]; 58.3% stage). According to PINK-E system, 8 pts (33.3%) were identified as intermediate risk group and 16 patients were low risk group. 23 of 24 patients completed protocol-specified therapeutic schemes, one patient discontinued the study after the second cycle due to disease progression. ORR was 95.8% (23/24, 95%CI: 76.9%-84.1%). Surprisingly, all the responded patients achieved CR, while 66.7% (16/24, 95%CI: 44.7%-83.6%) patients achieved CR after the second cycle. Median PFS and OS have not been reached. 1-year OS and PFS was 100% and 95.8%, respectively. All grade TRAEs occurred in 84.6% of all enrolled patients and 92.1% were grade 1-2. The most common TRAE was lymphocytopenia (9.9%). Of note, grade 3-4 hematological toxicity was reported in only one patient (4.2%). All AEs were resolved after symptomatic treatment, without systematic corticosteroid intervention. **Conclusions:** Sintilimab combined with anlotinib and PEG-ASP upfront and after radiotherapy was effective and could be well tolerated in localized NKTL, achieving promising CRR and rapid and long-term remission with mild toxicity. Further investigation of survival outcome is warranted. Clinical trial information: NCT03936452. Research Sponsor: None.

7538 **Poster Session**

Safety and efficacy of VIP152, a CDK9 inhibitor, in patients with double-hit lymphoma (DHL). *First Author: Victor Moreno, START Madrid-FJD, Fundación Jiménez Díaz Hospital, Madrid, Spain*

Background: PTEFb/CDK9-mediated transcription of short-lived anti-apoptotic survival proteins and oncogenes like MCL-1 and MYC plays a critical role in a variety of cancers. VIP152 (formerly BAY 1251152), a potent and highly selective CDK9 inhibitor, has been evaluated in a Phase 1 dose-escalation study in patients with advanced cancer. The maximum tolerated dose was 30 mg once weekly administered in consecutive 21-day cycles, based on neutropenia as the dose-limiting toxicity (JCO 2018;36:2507; NCT02635672). DHL is defined as dual rearrangement of the MYC gene and either the BCL2 or BCL6 genes; the resulting overexpression of MYC and BCL2/BCL6 make it particularly difficult to treat. Patients with DHL have a poor prognosis and no standard of care. Considering the impact of CDK9 inhibition on MYC, an exploratory cohort of patients with DHL was added to the study. **Methods:** Patients with refractory or relapsed DHL were eligible. VIP152 was administered once weekly as a 30-minute IV infusion on Days 1, 8 and 15 of a 21-day cycle. Tumor response was assessed according to the revised Cheson criteria (2007). **Results:** To date a total of 7 patients have been enrolled and were evaluable at the time of data cutoff (24NOV2020). The patients were mostly men (6/7 pts, 86%) with a median (range) age of 70 (58-84) years. All patients received ≥2 prior therapies, including 2 patients with bone marrow transplant. Three of 7 patients (29%) had ≥3 prior therapies. The median time on treatment was 22 days (range 8-1361 days). The most common adverse events of any grade were: constipation, fatigue, nausea (each 3/7 pts, 43%) and abdominal pain, diarrhea, lymphocyte count decrease, neutrophil count decrease, skin infection, tumor pain, and vomiting (each 2/7 pts, 29%). Most were Grade 1 and Grade 2. The Grade 3 adverse events were fatigue, lymphocyte count decrease, neutrophil count decrease (each 1/7 pts, 14%) and tumor pain (2/7 pts, 29%). One Grade 4 lymphocyte count decrease was reported. Two patients had a serious adverse event (Grade 3 syncope and Grade 3 tumor pain). Two patients had dosing held for an adverse event; however, no patient withdrew from treatment due to any adverse events. One death occurred due to disease progression. Pharmacodynamic biomarker analysis showed significant reduction of MYC, PCNA, and MCL-1 mRNA in all patients across multiple timepoints. Antitumor activity consisted of 2 complete metabolic responses in 7 patients (29%) based on investigator-assessed FDG-PET scans. Due to the COVID pandemic, the patients withdrew consent after 3.7 and 2.3 years, respectively, of treatment. Both patients were in complete metabolic response. **Conclusions:** VIP152 had a manageable safety profile, on-target pharmacodynamic activity and signs of durable monotherapy antitumor activity in patients with DHL. These encouraging results warrant further evaluation of VIP152 in patients with MYC-driven lymphoma and solid tumors. Clinical trial information: NCT02635672. Research Sponsor: Bayer AG.

7539 **Poster Session**

Lenalidomide plus rituximab in patients with rituximab-resistant indolent B-cell and mantle cell lymphomas: 10-year follow-up. *First Author: Aditi Gupta, University of Pennsylvania Health System, Philadelphia, PA*

Background: Lenalidomide (len) plus rituximab is now a standard-of-care option for indolent B-cell non-Hodgkin lymphomas (iNHL) and mantle cell lymphomas (MCL). We previously demonstrated the efficacy of len plus rituximab in patients (pts) with rituximab-refractory iNHL and MCL (Chong *et al.* Clin Can Res 2015). We now report the longest experience to date with this regimen. **Methods:** We conducted an open-label phase II trial in pts with iNHL or MCL and rituximab resistance, defined as failure to respond or progression of disease within 6 months (mo) of rituximab or a rituximab-containing regimen. Pts received len 10 mg daily for 8 weeks, followed by 4 weekly doses of rituximab 375 mg/m^2 and continued len maintenance until disease progression, toxicity or pt choice. **Results:** 50 pts (30 FL, 14 MCL, 2 MZL, 4 SLL) were treated between 2008-2012. Median follow-up was 10.5 years (yr). Pts received a median of 3 prior therapies (range: 1–7). Progression free survival (PFS) for all pts at 5 and 10 yrs was 20.0% [95%CI 8-35] & 13% [95%CI 3-30%]; 5- and 10-yr response duration (RD) was 27% [95% CI 12-46] and 18% [95% CI 4-40], respectively; 5- and 10-yr overall survival (OS) was 58% [95%CI 43-70] and 45% [95%CI 30-58], respectively. 5-yr OS from the time pts were deemed rituximab-resistant is 64.0% and 10-yr OS 51.9%. For pts with FL, 5- and 10-yr PFS were both 13%, and 5- and 10-yr OS were 60% and 40%. For MCL, 5- and 10-yr PFS were both 25% and 5- and 10-yr OS were 50% and 36%. At 10.5 yr, 4 pts (2 FL, 1 MCL, 1 MZL) remain in complete remission (CR), 3 of whom discontinued len at 7.0-yr, 8.8-yr and 10.1-yr in CR. 1 pt with FL discontinued study in CR after 11.6-yr but continues on commercial len at 5 mg daily. The most common grade 1–2 adverse events (AEs) requiring dose reductions were neuropathy (n = 3) and diarrhea (n = 5), which all resolved with dose reduction. The most common grade 3–4 AEs requiring dose reductions were neutropenia (n = 6, 12%) and tumor flare (n = 3, 6%). Pts discontinued therapy due to toxicity at a median of 4.9 mo (range 0.3–25.7) from len start due to grade 3–4 rash (n = 2), grade 2 abdominal pain (n = 1), and grade 3–4 thrombocytopenia (n = 2). Only 1 patient discontinued len after > 1 yr (25.7 mo) due to persistent diarrhea. The pt who developed grade 2 abdominal pain was retreated with len without recurrence of pain and sustained a second CR for 5 yrs. 5 (10%) pts developed secondary cancers at a median of 15.5 mo (range: 0.8–50.5) from starting len, including 2 hematological (acute myeloid leukemia, B-acute lymphoblastic leukemia) and 3 solid cancers (NSCLC, renal cell carcinoma, prostate cancer). Prior to enrollment, 4/5 of the patients with secondary cancers had received alkylating agents and 3/5 had received anthracyclines. **Conclusions:** These data represent the longest reported outcomes for len plus rituximab in NHLs. We demonstrate durable responses and a manageable safety profile with rituximab plus low-dose len. Clinical trial information: NCT00783367. Research Sponsor: Celgene.

7540 **Poster Session**

First-MIND: A phase Ib, open-label, randomized study to assess safety of tafasitamab (tafa) or tafa + lenalidomide (LEN) in addition to R-CHOP in patients with newly diagnosed DLBCL. *First Author: David Belada, 4th Department of Internal Medicine–Hematology, University Hospital and Faculty of Medicine, Hradec Králové, Czech Republic*

Background: Tafasitamab is a humanized, Fc-modified anti-CD19 monoclonal antibody that enhances antibody-dependent cellular cytotoxicity and phagocytosis. It is FDA-approved with LEN for adult patients (pts) with relapsed/refractory (R/R) DLBCL ineligible for autologous stem cell transplantation. First-MIND (NCT04134936) is a Phase Ib, open-label, randomized study of tafa + R-CHOP or tafa + LEN + R-CHOP in newly diagnosed DLBCL. **Methods:** Eligible pts were ≥18 years, treatment-naïve, with histologically confirmed DLBCL not otherwise specified, international prognostic index (IPI) 2–5 and ECOG performance status (PS) 0–2. Pts with known double- or triple-hit and transformed lymphoma were excluded. Treatment (Tx) comprised six 21-day cycles of tafa (12 mg/kg IV, Day [D] 1, 8, 15) + R-CHOP (arm A) or tafa (12 mg/kg IV, D1, 8, 15) + LEN (25 mg orally, D1–10) + R-CHOP (arm B). G-CSF and VTE prophylaxis was mandatory. Primary objective is safety; secondary objectives are ORR, PET-CR rate at end of Tx, PFS, long-term safety, pharmacokinetics, immunogenicity. **Results:** From Dec 2019 to Aug 2020, 83 pts were screened in Europe and the US; 66 were randomized (33 per arm). Data cut-off for this analysis: 9 Dec 2020; study is ongoing. Median age was 64.5 years (range 20–86). Overall, 30% (20/66) of pts were ≥70 years and many had high-risk disease: IPI 2 29%, IPI 3 46%, IPI 4 26%. ECOG PS: 47% of pts were ECOG PS 0, 44% PS 1, 9% PS 2. Most pts had stage III/IV disease (92%); 46% had bulky disease. All pts experienced a treatment-emergent adverse event (TEAE). Grade ≥3 neutropenia and thrombocytopenia occurred in 54.5% and 12.1% (arm A) and 66.7% and 30.3% (arm B) of pts, respectively (Table). Serious TEAEs occurred in 42.4% (arm A) and 51.5% (arm B) of pts. There were three deaths, unrelated to tafa and/or LEN (sepsis, urosepsis, and COVID-19 pneumonia). R-CHOP dose intensity was maintained in both arms. Among 60 pts who completed tumor assessments after cycle 3, ORR was 89.7% (arm A) and 93.5% (arm B). **Conclusions:** These data suggest R-CHOP + tafa or tafa + LEN is tolerable in pts with Tx-naïve DLBCL and that R-CHOP dosing is not affected. Toxicities are similar to those expected with R-CHOP or R-CHOP + LEN. Updated safety and early efficacy data will be presented at the conference. Clinical trial information: NCT04134936. Research Sponsor: MorphoSys AG, Planegg, Germany.

	R-CHOP + tafa (n = 33)	R-CHOP + tafa + LEN (n = 33)		
TEAEs, n (%)	Any grade	Grade ≥3	Any grade	Grade ≥3
Neutropenia	19 (57.6)	18 (54.5)	23 (69.7)	22 (66.7)
Thrombocytopenia	6 (18.2)	4 (12.1)	12 (36.4)	10 (30.3)
Febrile neutropenia	6 (18.2)	6 (18.2)	6 (18.2)	6 (18.2)
Diarrhea	8 (24.2)	1 (3.0)	10 (30.3)	2 (6.1)
Infusion related reactions*	4 (12.1)	0	6 (18.2)	1 (3.0)†
Infections + infestations	16 (48.5)	7 (21.2)	16 (48.5)	9 (27.3)
Nervous system disorders‡	17 (51.5)	2 (6.1)	20 (60.6)	4 (12.1)

*Related to both rituximab and tafa; †Related to rituximab; ‡The majority of events were polyneuropathies related to vincristine.

7541 **Poster Session**

Preliminary results of a phase I trial of FT516, an off-the-shelf natural killer (NK) cell therapy derived from a clonal master induced pluripotent stem cell (iPSC) line expressing high-affinity, non-cleavable CD16 (hnCD16), in patients (pts) with relapsed/refractory (R/R) B-cell lymphoma (BCL). *First Author: Paolo Strati, The University of Texas MD Anderson Cancer Center, Department of Lymphoma/Myeloma, Houston, TX*

Background: FT516 is an investigational, NK cell cancer immunotherapy derived from a clonal master iPSC line. FT516 is engineered with a novel hnCD16 Fc receptor, demonstrated preclinically to maximize antibody-dependent cellular cytotoxicity (Zhu et al. Blood 2020). FT516 can be mass produced and made available off-the-shelf for broad pt access and multi-dose administration. **Methods:** This is a Phase I trial of FT516 combined with rituximab (R) in pts with R/R BCL. Treatment consists of 2 cycles, each with 3 days lympho-conditioning (fludarabine 30 mg/m^2 and cyclophosphamide 500 mg/m^2) and 1 dose of R followed by 3 weekly infusions of FT516 (planned doses 30-900 million/dose) with IL-2 (6 MIU after each FT516 dose). The primary objective is to identify the incidence of dose-limiting toxicity (DLT)/dose cohort and the recommended Phase II dose using a standard 3+3 design. Additional objectives include safety, tolerability, preliminary activity, pharmacokinetics, and immunogenicity. **Results:** Six pts (5 DLBCL, 1 FL, median age 65.5 y) have completed (5) or discontinued (1) study treatment after the DLT period (data cutoff 9 Dec 2020): 2 received 30 million cells/dose, 3 received 90 million cells/dose, and 1 received 300 million cells/dose. All pts received > 1 prior R-containing regimen, and median number of prior therapies was 3 (range 2-6), including CAR-T in 3 pts. FT516 was primarily administered in the outpatient setting. No FT516-related Grade ≥3 adverse events (AEs) or serious AEs, and no events of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), or graft-versus-host disease (GvHD) of any grade were reported. DLT (Grade 4 neutrophil count decreased, not recovered to baseline by D29) was reported in the first pt at 30 million cells/dose and R dosing of 375 mg/m^2 weekly x 4/cycle, resulting in modification of R dosing to once/cycle; no DLTs were observed with modified R dosing. Most common all grade AEs in ≥3 pts: fatigue (4 pts) and decreased appetite, nausea, neutrophil count decreased, and headache (3 pts each). Grade ≥3 AEs in ≥2 pts: neutrophil count decreased (3 pts) and febrile neutropenia and platelet count decreased (2 pts each); none considered related to FT516. Host anti-product B- or T-cell immunogenicity was not observed. Three of 4 pts treated at ≥90 million cells/dose achieved objective response (2 complete responses [CRs] and 1 partial response). **Conclusions:** Administration of up to 6 doses of FT516 cells, including up to 300 million cells/dose, appears to be safe and tolerable, without CRS, ICANS, or GvHD. Activity was observed, including CRs, in heavily pretreated pts. Dose escalation is ongoing. Updated clinical and translational data will be presented. Clinical trial information: NCT04023071. Research Sponsor: Fate Therapeutics, Inc.

7542 **Poster Session**

Survival trends of older adult patients with diffuse large B-cell lymphoma: A National Cancer Database analysis. *First Author: Xavier Andrade-Gonzalez, Mayo Clinic, Rochester, MN*

Background: 60-70% of patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) can be cured with R-CHOP or R-CHOP-like immunochemotherapy. However, patients ≥80 years of age were either excluded or underrepresented in modern DLBCL trials, and their outcomes are understudied. The aim of this study is to define the survival trends and risk factors for inferior survival in older adult patients with DLBCL. **Methods:** Patients with newly diagnosed DLBCL were identified from the National Cancer Database (2004-2017, representing the rituximab era). Clinical characteristics, treatment, and outcomes were compared between patients ages ≥ 80, 65-79, and < 65 years. The Kaplan-Meier method and Cox proportional hazards model were used for survival analysis. **Results:** A total of 231,756 patients with newly diagnosed DLBCL were identified; 46,250 (20%) were ≥80 years, 87,702 (38%) were 65-79 years, and 97,904 (42%) were < 65 years. Patients ≥80 years were more likely to have a higher Charlson-Deyo Comorbidity Index score (CDS) (CDS ≥2, 12% vs 11% vs 8%, p = 0.001), less likely to receive systemic chemotherapy (63% vs 83% vs 89%, p < 0.001), and more likely to receive treatment at a non-academic center (71% vs 65% vs 48%, p < 0.001), compared to patients 65-79 and < 65 years, respectively. Median overall survival (OS) was significantly worse for patients ≥80 years compared to patients 65-79 years (11.6 vs 61.0 months, p = 0.001) and patients < 65 years (11.6 vs 178.1 months, p = 0.001). During the study period, the median OS had only minimally improved for patients ≥80 years (10.6 months in 2004-2007 vs 11.5 months in 2008-2011 vs 12.3 months in 2012-2016, p = 0.006). In contrast, the OS improvement appears more meaningful in patients 65-79 years (median in months: 51 vs 61.2 vs 65.9, p = < 0.001) and patients < 65 years (median in years: 14.6 vs 11.3 vs not reached, p < 0.001) in the prespecified intervals (2004-07, 2008-11, and 2012-16). In multivariate analysis, the most substantial risk factor for worse survival in patients ≥80 years was not receiving systemic therapy (hazard ratio [HR] = 3.26, 95%CI = 3.01-3.54, p = 0.001). Other risk factors associated with worse survival included high-risk IPI score (HR = 2.16, 95%CI = 1.96-2.39, p = 0.001), CDS score ≥2 (HR = 1.56, 95%CI = 1.40-1.73, p = 0.001), male sex (HR = 1.16, 95%CI = 1.09-1.24, p = 0.001), B symptoms at diagnosis (HR = 1.16, 95%CI = 1.08-1.25, p = 0.001), and treatment at a non-academic center (HR = 1.1, 95%CI = 1.01-1.20, p = 0.001). **Conclusions:** Patients ≥ 80 years of age with DLBCL have a significantly inferior survival which has not meaningfully improved in recent years. More than 1/3 of patients ≥ 80 years did not receive systemic therapy. Older adult patients with DLBCL should be assessed for fitness for chemotherapy using validated geriatric assessment tools. Novel therapeutic strategies with favorable safety profiles are urgently needed for this expanding patient population. Research Sponsor: None.

7543 **Poster Session**

CNS relapse in DLBCL patients below 60 years treated with R-ACVBP, R-CHOEP, or R-CHOP: A joint analysis of LYSA and GLA/DSHNHL. *First Author: Catherine Thieblemont, AP-HP at Saint-Louis Hospital, Hematooncology, Paris University, Paris, France*

Background: Central nervous system (CNS) relapse occurs in 2-6% of DLBCL patients (pts) increasing to 10% or more in high-risk groups. Intrathecal (IT) or intravenous high-dose methotrexate (HD MTX) have limited if any prophylactic impact on CNS relapse. To address the role of systemic first-line therapy in pts tolerating intensified strategies (R-ACVBP, R-(Mega)CHOEP, R-CHO(E)P), we compared CNS relapses occurring in a large cohort of pts ≤60 years. **Methods:** We conducted a retrospective analysis including previously untreated pts with DLBCL by central review, age 18-60 years, from multicenter clinical trials conducted by LYSA and GLA/DSHNHL (Table). We assessed the risk of CNS relapse in matched cohorts based on the aaIPI. **Results:** A total of 2203 pts were included. Median age was 47 years (18-60). 455 pts were treated with R-ACVBP, 444 with R-(Mega)CHOEP, 1304 with R-CHOP. Distribution of CNS IPI was not significantly different comparing R-ACVBP to R-CHO(E)P groups within aaIPI categories (Table). PFS and OS were comparable according to treatment within aaIPI groups, also adjusted for prognostic factors. No CNS events occured during observation time of 3 years in pts with aaIPI 0. In pts with aaIPI 1, no CNS event occured in the R-ACVPB arm, the 3y-cumulative incidence of CNS relapse for pts treated with R-CHO(E)P group was 1.0% (95%CI 0.3-1.7). In pts with aaIPI 2,3 and intermediate/high CNS IPI, four (1.6%) treated with R-ACVBP experienced relapse in the CNS compared to 15 (3.9%) pts treated with R-(Mega)CHO(E)P (3y-cumulative incidence 1.6% (95%CI 0-3.2) vs. 4.0% (95%CI 2.0-6.0). **Conclusions:** CNS relapse was extremely rare in younger DLBCL pts with aaIPI 0 or 1; prophylactic measures are not warranted. In pts with aaIPI 2,3 (and intermediate/high CNS-IPI), only 4 (1.6%) CNS relapses were seen with the R-ACVBP while 15 (3.9%) relapses did occur after R-(Mega)CHO(E)P. This analysis underlines the important role of the systemic therapy in controling CNS relapse. Research Sponsor: None.

Distribution of the clinical trials.

	aaIPI = 0 n = 652		aaIPI = 1 n = 924		aaIPI = 2,3 n = 627	
	LNH03-1B, FLYER, MInT, UNFOLDER		LNH03-2B, MInT, UNFOLDER		LNH03-3B*, LNH07-3B*, MegaCHOEP#	
	R-ACVBP n = 76	R-CHO(E)P n = 576	R-ACVBP n = 134	R-CHO(E)P n = 790	R-ACVBP n = 245	R-(Mega)CHO(E)P n = 382
CNS IPI groups						
0-1 – low risk	76 (100%)	575 (100%)	107 (80%)	641 (81%)	–	–
2-3 – int risk	0 (0%)	1 (0.2%)	27 (20%)	149 (19%)	185 (76%)	303 (79%)
4-6 – high risk	–	–	–	–	60 (24%)	79 (21%)
MTX prophylaxis (at least one course)	0 (0%)	8/554* (18%)	133 (99%)	179/742* (24%)	245 (100%)	125/309* (40%)
MTX IT	76 (100%)	0 (0%)	123 (92%)	0 (0%)	145 (59%)	0 (0%)
HD MTX IV						

7544 **Poster Session**

Atezolizumab + obinutuzumab + venetoclax in patients with relapsed or refractory indolent non-Hodgkin's lymphoma (R/R iNHL): Primary analysis of a phase 2 trial from LYSA. *First Author: Charles Herbaux, Centre Hospitalier Régional Universitaire de Lille, Institute of Hematolog-Tranfusion, Lille, France*

Background: R/R iNHL treatment remains challenging. Atezolizumab (ATE) and obinutuzumab (OBI) are monoclonal antibodies acting respectively to inhibit T-lymphocyte exhaustion or by inducing lymphoma cells cytotoxicity, whereas venetoclax (VEN) is a small molecule inhibiting BCL-2. Combining tumor-targeted therapies with agents that enhance anti-tumor immunity represents an attractive treatment paradigm. This LYSA sponsored multicenter phase 2 trial (NCT03276468) evaluated ATE, OBI and VEN combination in R/R B-cell lymphomas. Herein, we present primary efficacy and safety data from the iNHL cohort including Follicular Lymphoma (FL) and Marginal Zone Lymphomas (MZL). **Methods:** Patients ≥18 years with biopsy-confirmed R/R FL and MZL who failed at least one line of therapy were eligible. OBI was given IV at 1 g on day (D) 1, 8 and 15 of cycle (C) 1 and on D1 from C2 to C8 every 3 weeks. ATE was given IV, 1.2 g every 3 weeks, started at D2 of C1, then administered at D2 of each cycle for 24 cycles. VEN was given orally at 800 mg/D at full dose, starting on D8C1 for 24 cycles. The primary endpoint was the Overall Response Rate (ORR) evaluated by Lugano criteria at the end of induction (EOI) after 8 cycles of ATE, OBI and VEN (M6) or at premature treatment discontinuation. **Results:** At the time of the primary analysis (08 Jan 2021), 78 patients were enrolled. *FL cohort* (n = 58): the median follow-up was 14.5 months. Main baseline characteristics were: Ann Arbor Stage III/IV, 85.7%; FLIPI HR, 47.3%; > 2 prior lines of therapy, 32.1%; and exposed to ASCT, 30.4%. The ORR on PET scan at EOI was measured at 53.6% [41.8%-65.1%], including 30.4% of CMR. 37 patients (63%) received the full induction treatment. *MZL cohort* (n = 20; 13 nMZL, 5 eMZL, 2 sMZL): the median follow-up was 11.9 months. Main baseline characteristics were: Ann Arbor Stage IV, 100%; bone marrow infiltration, 38.9%; ≥ 2 extra-nodal sites, 50%; and > 2 prior lines of therapy, 22.2%. The ORR on CT scan at EOI was measured at 66.76% [44.6%-84.4%], including 16.7% of CR and 50.0% PR. 11 patients (55%) received the full induction treatment. At time of the present analysis, responses in the 2 cohorts seem durable with only 21,4% of responders who have reported relapse/progression. Out of the 78 pts, a total of 55 (70.5%) pts experienced grade 3–4 adverse event (AE) and 1 patient experienced an AE that led to discontinuation of any drug. Main AE of grade 3 or more were hematologic cytopenias, with only one febrile neutropenia (1.3%). Three pts experienced immune-related AE (1 grade 2 myositis and 2 grade 3 colitis), no tumor lysis syndrome was observed. **Conclusions:** ATE, OBI and VEN triplet appears to be well tolerated, with no unexpected toxicity brought by the combination. The ORR at EOI seems to be comparable to other innovative regiments in this setting, with durable responses to date. Clinical trial information: NCT03276468. Research Sponsor: None.

7545 **Poster Session**

Obinutuzumab short-duration infusion (SDI) in previously untreated advanced follicular lymphoma: Results from the end of induction analysis of the phase IV GAZELLE study. *First Author: Miguel Angel A. Canales Albendea, Hospital Universitario La Paz, Madrid, Spain*

Background: Obinutuzumab (G)-chemotherapy (chemo) has demonstrated improved progression-free survival compared with rituximab (R)-chemo in previously untreated advanced follicular lymphoma (FL). G is currently administered by IV infusion over ~3–4 hours. A shorter duration of infusion in Cycle (C) 2 and subsequent cycles, as is standard practice with R, could improve convenience for patients (pts) and efficiency for infusion facilities. We report the primary analysis of the prospective, open-label, multicenter, single-arm, Phase IV, GAZELLE study (NCT03817853), which evaluated the safety of G administered as a 90-minute (min) SDI from C2 onwards in pts with FL. **Methods:** Pts with previously untreated FL received G (1000mg) intravenously on Day (D) 1, 8, and 15 of C1, and on D1 thereafter, plus chemo (bendamustine, CHOP, or CVP) for 6–8 cycles. In C1, pts received G at the standard infusion rate. Pts without a Grade (Gr) ≥3 infusion-related reaction (IRR) in C1 were eligible to receive G as a 90-min SDI from C2. Pts with a Gr 3 IRR in C1 received the standard G infusion in C2, and were eligible for G SDI in subsequent cycles if no Gr ≥3 IRRs occurred. Pts with a second Gr 3/4 IRR discontinued G. At the end of induction (EOI), responding pts received maintenance G (1000mg) as SDI for 2 years or until disease progression (PD). The primary endpoint was incidence of Gr ≥3 IRRs during C2. IRRs were defined as any event occurring ≤24 hours from infusion judged to be related to treatment. Secondary endpoints included adverse events (AEs) and investigator-assessed overall response rate at EOI. **Results:** As of December 3, 2020, 113 pts had received study treatment. Median age was 62.0 years, 50.4% were male, 61.9% had stage IV FL, and 45.1% were classified as high-risk FLIPI. Of the 110 pts who were eligible for G SDI from C2, no pt experienced a Gr ≥3 IRR with SDI in C2 (Table). One pt experienced a Gr 3 IRR with SDI in C5, presenting hypertension. All other IRRs with SDI were Gr 1/2. No Gr 4/5 IRRs were reported. Other AEs were similar to those observed in previous studies. At the clinical cut-off date, 104 pts had a CT imaging-based response assessment at EOI and 9 pts had no response assessment; 76/113 (67.3%) had a complete response, 22 (19.5%) had a partial response, and six (5.8%) had PD. **Conclusions:** In GAZELLE, G SDI in C2 and beyond appeared to be safe. No Gr 3 IRRs were observed in C2 and only one Gr 3 IRR was reported in subsequent cycles. The safety profile of G SDI was comparable with the established profile of G in advanced FL. Clinical trial information: NCT03817853. Research Sponsor: GAZELLE was sponsored by F. Hoffmann-La Roche Ltd. Third-party medical writing assistance, under the direction of all authors, was provided by Aisling Lynch and Louise Profit of Ashfield MedComms, and was funded by F. Hoffmann-La Roche Ltd.

IRRs by cycle.

		C1									
IRR, n (%)	**C1 overall**	**D1**	**D2***	**D8**	**D15**	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**All cycles**
All Gr	65/113 (57.5)	57/113 (50.4)	4/51 (7.8)	6/112 (5.4)	5/111 (4.5)	13/110 (11.8)	9/108 (8.3)	7/108 (6.5)	6/107 (5.6)	5/105 (4.8)	2/55 (3.6)	71/113 (62.8)
Gr ≥3	6/113 (5.3)	5/113 (4.4)	1/51 (2)	0	0	0	0	0	1/107 (0.9)	0	0	7/113 (6.2)

*timepoint applicable only to pts treated with bendamustine.

7546 **Poster Session**

Duration of response to loncastuximab tesirine in relapsed/refractory diffuse large B-cell lymphoma by demographic and clinical characteristics: Subgroup analyses from LOTIS 2. *First Author: Paolo Caimi, University Hospitals Cleveland Medical Center/Case Western Reserve University, Cleveland, OH*

Background: Outcomes for patients with refractory/relapsed diffuse large B-cell lymphoma (R/R DLBCL) are poor, particularly for those with high-risk clinical characteristics. There remains an unmet need for new treatment options for these patients. Loncastuximab tesirine (Lonca) is an antibody-drug conjugate comprising a humanized anti-CD19 antibody conjugated to a potent pyrrolobenzodiazepine dimer toxin. LOTIS 2 was a pivotal Phase 2 study that demonstrated substantial single-agent anti-cancer activity of Lonca in patients with R/R DLBCL. Efficacy and safety data were presented at ASH 2020 (Caimi *et al*, ASH 2020; abstract 1183). Here we present subgroup analyses of duration of response (DoR) to Lonca by demographic and clinical characteristics. **Methods:** Adult patients with R/R DLBCL who had received ≥2 prior therapies were enrolled in this Phase 2, multicenter, single-arm, open-label study of single-agent Lonca (150 μg/kg every 3 weeks for 2 doses, followed by 75 μg/kg thereafter for up to 1 year). The primary analysis has previously been reported, with a primary endpoint of overall response rate (ORR). Patients are being followed-up every 12 weeks for up to 3 years. DoR was a key secondary efficacy endpoint, defined as time from the first documentation of response (central review) to disease progression or death. We analyzed pre-specified demographic and clinical characteristic subgroups for DoR. **Results:** As of data cut-off (August 6, 2020), ORR in the total population (N = 145) was 48.3% (24.8% had complete response [CR] and 23.4% had partial response [PR]). Median DoR (mDoR) for the 70 responders was 12.58 months. mDoR for patients with CR and PR was 13.37 months and 5.68 months, respectively. Overall, subgroups with high-risk characteristics for poor prognosis had a DoR comparable to the whole study population. mDoR for patients with double-/triple-hit DLBCL was 13.37 months, with advanced stage disease was 12.58 months, and with transformed disease was 12.58 months. The mDoR for older patients was longer than for younger patients (≥75 years, 13.37 months; 65 to < 75 years, 12.58 months; < 65 years, 9.26 months). Patients with DLBCL refractory (defined as no response to therapy) to first-line, most recent line, and all prior lines of therapy had mDoRs of 9.63 months, 9.26 months, and 9.63 months, respectively. **Conclusions:** Durable responses were observed with the recommended Phase 2 dose regimen of Lonca in heavily pre-treated patients and those at high risk of poor prognosis, including older patients and those with double-/triple-hit, advanced stage, transformed, and primary refractory DLBCL. Updated DoR data will be presented at the meeting. Clinical trial information: NCT03589469. Research Sponsor: ADC Therapeutics SA.

7547 **Poster Session**

Outcomes with KTE-X19 in patients (pts) with relapsed/refractory (R/R) mantle cell lymphoma (MCL) in ZUMA-2 who had progression of disease within 24 months of diagnosis (POD24). *First Author: Michael Wang, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: KTE-X19 is an autologous anti-CD19 CAR T-cell therapy approved in the US and EU for the treatment of R/R MCL. In the ZUMA-2 study of KTE-X19 in R/R MCL, the objective response rate (ORR) at a median 17.5-mo follow-up was 92% (67% complete responses [CR]; Wang et al. ASH 2020 #1120). Here, we report results in pts with or w/o POD24, an indicator of poor outcomes (Visco et al. *Br J Haematol* 2019). **Methods:** Eligible pts with R/R MCL underwent leukapheresis and conditioning chemotherapy followed by a single infusion of KTE-X19. Efficacy results are reported for the 60 treated pts with ≥1 y of follow-up (median 17.5 mo); safety results are presented for all 68 treated pts. **Results:** High-risk disease characteristics were common in pts with (n=33) and w/o POD24 (n=35), although pts with POD24 had higher tumor burden and lactate dehydrogenase (LDH) levels, and more had blastoid type MCL (Table). ORR in pts with (n=28) and w/o POD24 (n=32) was 93% and 91%, with CR rates of 61% and 72%. In pts with and w/o POD24, median progression-free survival (PFS) was 11.3 mo (range, 0.9–30.3) and 29.3 mo (range, 0–35.9). Medians for duration of response (DOR) and overall survival (OS) were not reached in either group. Most common Grade ≥3 adverse events (AEs) in pts with vs w/o POD24 were neutropenia (91% vs 80%), thrombocytopenia (61% vs 46%), and anemia (55% vs 51%); Grade ≥3 cytokine release syndrome (CRS) and neurologic events occurred in 9% vs 20% and 27% vs 34%, respectively. There were no cases of Grade 5 CRS, KTE-X19–related secondary cancers, or replication-competent retrovirus in either group. In pts with vs w/o POD24, median peak CAR T-cell levels and median area under the curve were 53.4 cells/μL (range, 0.2–2566) and 583.4 cells/μL (range, 1.8–27,743.6) vs 112.4 cells/μL (range, 0.2–2589) and 1588.3 cells/μL (range, 3.8–27,238.7); by 12 mo, B cells were detectable in 8/11 (73%) vs 7/15 pts (47%) in ongoing response. **Conclusions:** KTE-X19 provided a high CR rate across all pts, with median DOR and OS not reached. Pts with POD24 had more aggressive high-risk disease characteristics (tumor burden, LDH levels, and blastoid MCL) and generally lower CAR T-cell expansion and PFS vs pts w/o POD24. Earlier intervention with CD19-directed CAR T-cell therapy may benefit pts with MCL with known high-risk factors. Clinical trial information: NCT02601313. Research Sponsor: Kite, a Gilead Company.

Characteristics	**With POD24 n = 33**	**W/o POD24 n = 35**
Median age, y	65	66
Median prior therapies, n	3	3
Received ≥3 prior therapies, %	88	74
Ibrutinib	85	86
Acalabrutinib	21	26
Ibrutinib and acalabrutinib	6	11
Auto-SCT	36	49
Disease stage III/IV, %	97	97
Extranodal disease, %	52	60
LDH ≥1.5×ULN, %	24	9
Intermediate-/high-risk MIPI, %	48	63
MCL Morphology, %		
Classical	48	69
Pleomorphic	6	6
Blastoid	33	17
Median tumor burden (SPD), mm^2 (range)	2254.6(260–14,390)	1380.2(293–16,878)
Ki-67 Proliferation Index, %	n = 23	n = 20
≥50%	74	65
≥30%	83	81
***TP53* status**	n = 20	n = 16
Mutated, %	15	19

7548 **Poster Session**

Updated outcomes with axicabtagene ciloleucel (axi-cel) retreatment (reTx) in patients (pts) with relapsed/refractory (R/R) indolent non-Hodgkin lymphoma (iNHL) in ZUMA-5. *First Author: Julio C. Chavez, University of South Florida H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: ZUMA-5 is a Phase 2 study of axi-cel anti-CD19 CAR T-cell therapy in pts with R/R iNHL (follicular lymphoma [FL]; marginal zone lymphoma [MZL]). In the primary analysis, 11 pts (9 FL; 2 MZL) were retreated with axi-cel, achieving an overall response rate (ORR) of 100% (91% complete response [CR] rate) at a median follow-up of 2.3 mo post-reTx, with no Grade ≥3 cytokine release syndrome (CRS) or neurologic events (NEs; Chavez et al. ASH 2020. #2036). Here, we report updated clinical and translational outcomes with longer follow-up in pts retreated with axi-cel in ZUMA-5. **Methods:** Eligible pts with FL or MZL had R/R disease after ≥2 lines of therapy. Pts were considered for reTx if they progressed after a response at mo 3, had no evidence of CD19-negative relapse in biopsy, had no axi-cel neutralizing antibodies, and had no Grade 4 CRS or NEs with 1st Tx. Retreatment was per investigator discretion. At both Txs, pts received axi-cel (2×10^6 CAR T cells/kg) after conditioning chemotherapy. **Results:** As of 9/14/2020, 13 pts with iNHL (11 FL; 2 MZL) received axi-cel reTx, with 2 pts retreated after the primary analysis. Before their 1st Tx, pts had median 4 prior lines of therapy; 85% had stage 3–4 disease; 82% had FLIPI of ≥3; 46% were POD24; 77% had refractory disease. Among the 13 retreated pts, 85% had a CR to 1st Tx. Median 1st duration of response (DOR) was 8.2 mo. Detectable CD19 was confirmed in all evaluable biopsies from retreated pts at relapse, and median time from 1st Tx to reTx was 10.6 mo. Following reTx, the ORR was 100% (77% CR rate). After a median follow-up of 11.4 mo, the median DOR had not yet been reached; 46% of retreated pts had ongoing responses at data cutoff. At 1st Tx, CRS occurred in 9 pts (5 Grade 1, 4 Grade 2); NEs occurred in 5 (3 Grade 1, 1 Grade 2, 1 Grade 3). At reTx, CRS occurred in 8 pts (6 Grade 1, 2 Grade 2); NEs occurred in 4 (3 Grade 1, 1 Grade 2). Median peak levels of biomarkers typically associated with severe CRS and NEs were similar at reTx and 1st Tx (IL-6, 7.7 vs 5.7 pg/mL; IL-2, 1.8 vs 0.9 pg/mL; IFN-γ, 62.9 vs 64.2 pg/mL). In the 11 retreated pts with FL, tumor burden (median sum of product diameters [SPD]) was lower before reTx vs 1st Tx (1416 vs 4770 mm^2). Engraftment index (CAR T-cell expansion relative to SPD) is an indirect proxy for effector:target ratio and a key covariate of response to axi-cel (Locke et al. *Blood Adv.* 2020). Though median peak CAR T-cell levels appeared lower at reTx vs 1st Tx (5.2 vs 14.3 CAR+ cells/μL blood), engraftment index was similar (0.003 vs 0.005 cells/μL×mm2). **Conclusions:** Axi-cel reTx achieved deep and durable responses, with an acceptable safety profile. Tumor CD19 positivity was maintained at relapse, and engraftment index was similar at both Txs, comparing favorably to previous reports in aggressive lymphomas (Locke et al. ASCO 2020. #8012). These data suggest axi-cel reTx is a promising option for pts with R/R iNHL. Clinical trial information: NCT03105336. Research Sponsor: Kite, a Gilead Company.

7549 **Poster Session**

NVG-111, a novel ROR1xCD3 bispecific antibody for non-Hodgkin lymphoma. *First Author: David Granger, NovalGen Ltd , London, United Kingdom*

Background: Receptor tyrosine kinase-like Orphan Receptor 1 (ROR1) is a type I transmembrane protein is highly expressed on an array of haematological and solid tumours. NVG-111 is a humanised, tandem scFv ROR1xCD3 bispecific antibody previously shown to elicit potent killing of tumour cells *in vitro* and *in vivo* by engaging a membrane-proximal epitope in the Wnt5a-binding Frizzled domain of ROR1 and redirecting T cell activity. The *in vitro* potency and pharmacodynamic responses to NVG-111 were assessed to support progression to a first-in-human study. **Methods:** The potency of NVG-111 *in vitro* was determined by evaluating the concentration response for cytotoxicity, T cell activation, and cytokine release in co-cultured Jeko-1 and unstimulated human T cells. Comparative data were generated for the marketed CD19xCD3 bispecific antibody, blinatumomab. Potency data for NVG-111 were used together with allometric scaling from murine PK studies to inform planned clinical doses. **Results:** NVG-111 demonstrated T cell-dependent cytotoxicity, T cell activation and levels of cytokine release similar in potency to blinatumomab. Cytotoxic responses of both NVG-111 and blinatumomab were more potent than T cell activation and cytokine release. Dose response curves for NVG-111 showed a decrease in activity beyond the concentration of maximal response (ie "hook effect"). We hypothesise this is due to receptor saturation, inhibiting synapse formation. NVG-111 has progressed to a Phase 1/2 first-in-human study in patients with debulked, relapsed/refractory chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL), the drug given as add-on to ≥2nd line therapy with a Bruton's tyrosine kinase inhibitor, or venetoclax. Phase 1 includes escalating doses of 0.3 to 360 μg/day via continuous infusion over 3 cycles (each 21 days on, 7 days off) to establish safety, PK, pharmacodynamics (PD) and recommended phase 2 dose (RP2D). Predicted exposure at 0.3 μg/day is ~EC_{20} for cytotoxicity *in vitro* and below the lowest EC_{10} for cytokine release. PD biomarkers in the study include systemic cytokines. Phase 2 will study efficacy and safety of the RP2D in CLL and MCL, with primary endpoint complete response rate; other efficacy endpoints include minimal residual disease and progression free survival. **Conclusions:** NVG-111 shows potent T-cell mediated lymphoma cell cytotoxicity *in vitro* at concentrations well below those associated with extensive cytokine release. NVG-111 is in an ongoing Phase 1/2 study and may present a novel option for adoptive immunotherapy in patients with non-Hodgkin lymphoma and potentially other cancers. Clinical trial information: 2020-000820-20. Research Sponsor: NovalGen Ltd.

	NVG-111 EC_{50} (pg/mL)	NVG-111 Max. Response	Blinatumomab EC_{50} (pg/mL)	Blinatumomab Max. Response
Cytotoxicity	60	97%	56	97%
T cell activation	997	63%	887	69%
Cytokine release				
- IFNg	920	5167pg/mL	1250	6537pg/mL
- TNFa	1450	212pg/mL	1080	330pg/mL
- IL6	N/A	16.3pg/mL	N/A	9.8pg/mL

7550 **Poster Session**

Efficacy and safety of the PI3Kδ inhibitor zandelisib (ME-401) on an intermittent schedule (IS) in patients with relapsed/refractory follicular lymphoma (FL) with progression of disease within 24 months of first-line chemoimmunotherapy (POD24). *First Author: John M. Pagel, Swedish Cancer Institute, Seattle, WA*

Background: FL patients (pts) with POD24 have poorer survival and may benefit from novel therapies at relapse. Zandelisib, a potent, selective, and structurally differentiated oral PI3kδ inhibitor was evaluated in a dose escalation/expansion Phase 1b study for FL demonstrating a high objective response rate (ORR) and well tolerated when given on IS (J Clin Oncol 2020;38:#8016). We report here results based on POD24 status (NCT02914938). **Methods:** Eligible pts had ≥1 prior therapy, adequate bone marrow and organ function, ECOG performance status ≤2, and no prior PI3K therapy. Zandelisib was administered at 60 mg once daily for 8 weeks followed by IS on days 1-7 of each subsequent 28-day cycle, either as monotherapy or with rituximab at 375 mg/m^2 for 8 doses in Cycles 1-6. Treatment was continued until disease progression, intolerance, or withdrawal of consent. Imaging scans were obtained after 2 and 6 cycles, and then every 6 cycles. Response was reported based on Lugano criteria. **Results:** 37 FL pts were enrolled and received zandelisib on IS as monotherapy (N = 18) or in combination with rituximab (N = 19). Median number of prior therapies = 2 (range, 1-5). The ORR was 86.5% (32/37) with 27% CR (complete response). In the monotherapy group the ORR and CR were 77.8 % (14/18) and 27.8% and with rituximab 94.7% (18/19) and 26.3% respectively. Median duration of response (DOR) among all pts was not reached with a median follow-up of 16.9 months (mos) (1.2-33.1+). 22 pts (59%) were POD24, of which 15 (68%) had ≥2 prior lines of therapy. Despite more refractory disease, ORR among the POD24 pts was 81.8% (Table). Zandelisib on IS was well tolerated. 3 pts (8%) discontinued therapy due to an adverse event (AE) for any cause. Grade (Gr) 3 AE of special interest (AESI) were 2 (5.4%) diarrhea, 2 (5.4%) colitis, 3 (8.1%) rash, 3 (8.1%) ALT elevation, 1 (2.7%) AST elevation and no pulmonary infection. **Conclusions:** Zandelisib administered on IS as monotherapy or with rituximab resulted in a high-rate of durable responses in FL, both in POD24 and non-POD24 groups and therapy was well-tolerated with low rate of Gr 3 class-related AESI and discontinuation rate due to AE's. Zandelisib as monotherapy is being evaluated in a global Phase 2 study in FL and MZL after failure of 2 prior therapies (NCT03768505). A Phase 3 study of zandelisib plus rituximab in FL and MZL after failure of prior immunochemotherapy will begin enrollment in 2021. Clinical trial information: NCT02914938. Research Sponsor: MEI Pharma, Inc.

	POD24 N = 22	Non-POD24 N = 15
Age, median (range)	61.5 (38 - 82)	63 (47 - 87)
Prior therapies, median (range)	2 (1 – 4)	1 (1 –5)
Disease refractory to rituximab, N (%)	14 (63.6%)	1 (6.7%)
Disease refractory to last therapy, N (%)	14 (63.6%)	1 (6.7%)
Follow-up, median (range) in mos	19.4 (1.8- 36.5)	18.2 (3.0 – 30.4)
ORR, N (%)	18 (81.8%)	14 (93.3%)
CR rate, N (%)	4 (18.2%)	6 (40%)
KM-DOR ≥ 12 mos	56.7 %	80 %

7551 **Poster Session**

Long-term follow-up results of a phase II study of dose-adjusted (DA)-EPOCH-R with high-dose methotrexate (HD-MTX) for newly diagnosed stage II-IV CD5-positive diffuse large B-cell lymphoma (CD5+ DLBCL). *First Author: Kana Miyazaki, Mie University Graduate School of Medicine, Tsu, Japan*

Background: CD5+ DLBCL is characterized by a poor prognosis and frequent central nervous system (CNS) relapse after standard immunochemotherapy. In the primary analysis of our multicenter phase II study of DA-EPOCH-R/HD-MTX for newly diagnosed stage II-IV CD5+ DLBCL, the 2-year (yr) progression-free survival (PFS) was 79% and the 2-yr CNS relapse rate was 9% at a median follow-up of 3.1 yrs (Miyazaki, et al. 2020). The aim of this preplanned 5-yr follow-up was to assess PFS, overall survival (OS), the CNS relapse rate, and late toxicity. **Methods:** A total of 47 patients (pts) with newly diagnosed stage II-IV CD5+ DLBCL between 20-75 yrs old and ECOG PS of 0-3 were enrolled. The treatment included 4 cycles of DA-EPOCH-R followed by 2 cycles of HD-MTX ($3.5\ g/m^2$) and 4 additional cycles of DA-EPOCH-R. Intrathecal administration of MTX and/or cytarabine was not allowed. 45 (96%) pts completed the protocol treatment. The data were updated as of December 1, 2020. **Results:** The median follow-up of alive pts was 6.0 yrs (range, 5.0-7.7). The pts' characteristics were as follows: age, 37-74 yrs (median, 62); male, 38%; ECOG PS > 1, 4%; stage III/IV, 57%; IPI HI/H, 47%; CNS-IPI high, 21%; and ABC/GCB/unclassified (n = 46), 85%/9%/7%. The 5-yr PFS and OS were 72% (95% CI, 57-83%) and 79% (95% CI, 64-88%), respectively. The 5-yr PFS and OS of pts with CD5+ ABC DLBCL (n = 39) were 72% and 74%, respectively. The 5-yr CNS relapse rate in all 47 pts was 9% (95% CI, 3-22%). There were no CNS relapse events after the primary analysis. Neither grade 3/4 late adverse events nor cardiac events of any grade were observed. Possible second malignancies were recorded in 6 (13%) pts. Among them, one pt who received R-ICE as salvage therapy experienced acute myeloid leukemia. The other 2 pts had colon cancers treated with endoscopic polypectomy/mucosal resection. **Conclusions:** Both the survival benefit and safety of DA-EPOCH-R/HD-MTX were maintained during a 5-yr follow-up, indicating the excellent efficacy, and safety of this approach as a first-line therapy for CD5+ DLBCL. Clinical trial information: UMIN000008507. Research Sponsor: Japan Agency for Medical Research and Development, AMED.

7552 **Poster Session**

Real-world evidence of axicabtagene ciloleucel (Axi-cel) for the treatment of large B-cell lymphoma (LBCL) in the United States (US). *First Author: Caron A. Jacobson, Dana-Farber Cancer Institute, Boston, MA*

Background: Axi-cel is approved in the US for the treatment of adult patients with relapsed or refractory LBCL after 2 or more lines of systemic therapy. Post-market long term follow up study of commercial Axi-cel recipients using the Center for International Blood and Marrow Transplant Research was recently completed. **Methods:** From October 2017 to August 2020, 1,500 Axi-cel recipients from 79 centers were enrolled. Of these, 1001 patients with at least 6 months of follow-up were included in this analysis. Outcomes include complete and overall responses rates (CR and ORR), duration of response (DOR), progression-free and overall survival (PFS and OS), cytokine release syndrome (CRS) (Lee D 2014 and American Society for Transplantation and Cellular Therapy [ASTCT]), immune effector cell associated neurotoxicity syndrome (ICANS), hematologic recovery and subsequent neoplasm (SN). Subgroup analysis by sensitivity to therapy, defined as responsive to the last line of therapy prior to Axi-cel. Median follow-up was 12 months (range, 6-28 months). **Results:** The median age overall was 62 years, 37% were ≥ 65 years, 83% with Eastern Cooperative Oncology Group (ECOG) performance score 0-1, 28% with transformed lymphoma, 14% with high grade lymphoma, 29% with prior autologous transplant, and 66% with chemotherapy-resistant disease prior to Axi-cel. The median time from diagnosis to Axi-cel infusion was 15 months. Best ORR was 70% (CR 53%). Landmark analysis of patients in CR at 6 months post Axi-cel demonstrates a low number of subsequent progression/death events. With respect to outcomes for chemotherapy-sensitive disease versus resistant disease, the ORR, CR, 12-month PFS and OS were 78% vs. 66%, 60% vs. 48%, 55% (95% CI, 48-62%) vs. 40% (95% CI, 37-44%), and 70% (95% CI, 63-76%) vs. 54% (95% CI, 50-58%), respectively. CRS of any grade was reported in 83% of patients. Incidence of Grades ≥ 3 CRS was 10% according to Lee et al 2014, and 13% according to ASTCT Consensus Grading. Median time to any grade CRS was 4 days (range, 1-28 days), and 93% of CRS cases resolved with a median duration of 7 days (range, 1-121 days). ICANS were reported in 576 (57%) patients, grade >3 was 26%. The median time to onset of ICANS was 7 days (range, 1-82 days), and 86% resolved with a median duration of 9 days (range, 1 to 115 days). Twenty-nine patients (2.9%) reported SN: hematologic (N = 17), solid tumors (N = 12). **Conclusions:** This is the largest report on Axi-cel in the real-world setting and demonstrates consistent efficacy outcomes and further characterizes safety outcomes. Patients in CR at 6 months have sustained disease control with low number of relapse events. Although patients with therapy-sensitive disease experience better outcomes than patients with therapy-resistant, the overall outcomes on both groups of patients are favorable. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

7553 **Poster Session**

Initial results of the combination of PI3Kδ inhibitor zandelisib (ME-401) and the BTK inhibitor zanubrutinib in patients (pts) with relapsed or refractory (R/R) B-cell malignancies. *First Author: Jacob Drobnyk Soumerai, Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA*

Background: Dual inhibition of PI3Kδ and BTK pathways may overcome existing or acquired monotherapy resistance. Dual inhibition of these pathways displays synergistic activity in cell lines that is evident even at suboptimal concentrations [Blood 2015;125(14):2306-09]. Zandelisib is a potent, selective, and structurally differentiated oral PI3Kδ inhibitor (i), and zanubrutinib is an oral BTKi. Based on their efficacy as monotherapy, we hypothesized that the combination of zandelisib and zanubrutinib can be well tolerated and may improve the depth and durability of responses. We evaluatedthis combination therapy in pts with R/R B-cell malignancies to determine the optimal dose and schedule for further evaluation in disease-specific expansion cohorts (NCT02914938). **Methods:** This is a multi-cohort Phase 1b study enrolling pts with FL, CLL, MZL, MCL, DLBCL, or high grade B-cell lymphoma (HGBCL), ≥1 prior therapy, adequate bone marrow and organ function, ECOG performance status ≤2, and no prior PI3Ki or BTKi therapy. For this combination therapy, two dose levels were evaluated in 28-day cycles: Cohort 10A: zandelisib 60 mg once daily for 2 cycles followed by an intermittent schedule (IS) on days 1-7 of subsequent 28-day cycles and zanubrutinib 160 mg twice daily (bid). Cohort 10C: zandelisib 60 mg on days 1-7 starting in Cycle 1 and zanubrutinib at 80 mg bid. Dose limiting toxicity (DLT) observation period was 28 days for cohort 10A and extended to 56 days for cohort 10C. Response was assessed at month 3, 7, 13 and then every 6 months until progression. **Results:** 20 pts treated, 7 in cohort 10A and 13 in cohort 10C: 8 FL, 5 CLL, 2 DLBCL, 2 HGBCL, 2 MZL, and 1 MCL. Median age 70 years (range, 44-85) and median prior therapies 2 (1-8). Median follow-up of 2.9 months (0.5-17.4+). There were no DLT in cohort 10A, grade (Gr) ≥3 adverse events (AE) occurred after day 28 in 4 pts, including Gr 4 neutropenia (1 pt), Gr 3 neutropenia, fatigue and CMV colitis (1 pt), Gr 3 AST/ALT and rash (1 pt) and Gr 3 AST/ALT (1 pt). In cohort 10C, 2 pts had DLT with Gr 3 AST/ALT in Cycle 2, with 1 pt successfully resuming both drugs and 1 discontinued treatment due to recurrence of Gr 3 AST/ALT upon rechallenge. Other Gr 3 AE were all laboratory findings: 1 pt (CLL) had laboratory TLS, neutropenia and thrombocytopenia and 2 pts (FL, DLBCL) had neutropenia. Response rate was 100% (2 CR 14 PR) in the following 16 pts with indolent NHL and MCL evaluable for response: FL (2 CR, 6 PR), CLL (5 PR), MCL (1 PR) and MZL (2 PR). No pt with aggressive B-cell lymphomas has responded. **Conclusions:** The combination of zandelisib 60 mg on IS from Cycle 1 and zanubrutinib 80 mg bid is well tolerated and achieves a high ORR in R/R indolent B-cell malignancies. This schedule is being evaluated in expansion cohorts in R/R FL and MCL. Clinical trial information: NCT02914938. Research Sponsor: None.

7554 **Poster Session**

Outpatient practice pattern and remote patient monitoring for axicabtagene ciloleucel CAR-T therapy in patients with aggressive lymphoma. *First Author: Radhika Bansal, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: Chimeric antigen receptor T-cell therapy (CAR-T) are commonly administered inpatient due to concern for early onset cytokine release syndrome (CRS), especially with axicabtagene ciloleucel (axi-cel). We report Mayo Clinic Rochester experience for hospital-based outpatient (HBO) management of patients (pts) receiving axi-cel and identify opportunities for improvement. HBO is closely integrated with inpatient practice and includes the same specialty trained clinical team. It is the first point of contact 24/7 for pts and triage evaluations. Lymphodepletion chemotherapy and CAR-T infusion is given on HBO followed by daily monitoring till day 8 and thereafter, as clinically needed until admission criteria is met. **Methods:** We retrospectively analyzed database of pts who received axi-cel between 1/2018 and 1/2021. After 06/2020, remote patient monitoring (RPM) tools were implemented to collect patient-reported neurologic symptoms and vital signs via bluetooth-enabled devices 4 times daily through month 1. Adverse data trends are addressed by the HBO team. **Results:** Among 72 recipients, 89% received their cells outpatient; 8% remained outpatient for the entire month. CRS and neurotoxicity incidence were comparable to those reported from CIBMTR. Median time to first admission was 2 days (Table). Use of bridging therapy, increased CRP and LDH were associated with early admission (≤3 days). Median time to tocilizumab, steroid, oxygen support, vasopressor was 4 days after admission. Half of HBO visits required intervention such as blood transfusions, IV medications through the first month. Nine pts had enrolled in RPM to date; with 8 having evaluable data. With 4 scheduled entries/day, a median of 1 entry/day was skipped and 2 entries/day were answered incompletely. An average of 57 additional unscheduled entries were generated per pt. Among a median of 373 (range 91-522) readings per pt over the first month, 4% (2%-20%) of the readings generated alerts. An average of 4 alerts were seen within 48 hours prior to admission. Data including additional subjects will be presented at ASCO meeting. **Conclusions:** We report a feasible outpatient care model for management of axi-cel recipients with safe outcomes. Clinical characteristics associated with more aggressive disease are associated with likelihood of early admission. Early RPM experience suggest use of digital tools could improve monitoring compliance and may predict evolution to symptoms requiring escalation of care. Research Sponsor: None.

Reason for hospitalization.

Indication (N=59)	N (%)	DOA
Fever	51 (86)	3(0-25)
Doubling CRP without fever	4 (7)	2.5 (1-7)
Neurologic symptoms	2 (3)	1.5 (1-2)
Other symptoms	2 (3)	10.5 (0-21)
Indication using RPM (N=6) *	**N (%)**	**Time from last RPM alert, median (range), hours**
Fever	6 (100)	4.6 (1.2-17.1)

DOA- Day of admission, median (range), days *Patients admitted on day 0 prior to RPM=2.

7555 **Poster Session**

Vaccine titers in lymphoma patients receiving chimeric antigen receptor T-cell therapy. *First Author: Radhika Bansal, Division of Hematology, Mayo Clinic, Rochester, MN*

Background: While CAR-T therapy is not myelo-ablative, patients with aggressive lymphoma treated with CD19 chimeric antigen receptor T cell therapy (CAR-T) are lymphodepleted and have prolonged B cell aplasia. The impact of CAR-T on immunologic protection from vaccine-preventable diseases (and thus the need to revaccinate) is not known. We report the vaccine titers of patients treated with axicabtagene ciloleucel (axi-cel) at Mayo Clinic. **Methods:** Retrospective chart review of adult lymphoma patients who received axi-cel from 9/2018 to 9/2020 for anti-viral and anti-bacterial titers prior to CAR-T infusion and at month 3 (MO3) post CAR-T. **Results:** Prior to CAR-T therapy, positive titer rate was highest for tetanus and lowest for Strep pneumoniae (Strep PNA) (Table). Similar trends were seen whether patients had stem cell transplant (ASCT) within 2 years of CAR-T (i.e. within immunization timeframe post ASCT) or not (Table). Compared to patients who had ASCT, those who did not had higher rate of positive titer for Strep PNA and lower rate for hepatitis B, Mumps, and VZV. The same trend for seropositive rate were observed at MO3 post CAR-T. Patients with IgG<400 mg/dl received IVIG supplement for prophylaxis. Among the 23 patients who received IVIG, variable rate of conversion from negative to positive titers were seen for measles (1/2, 50%), mumps (2/3, 67%), rubella (2/3, 67%), varicella-zoster (VZV, 3/3, 100%), hepatitis A (6/6, 100%), hepatitis B (6/7, 86%) and Strep PNA (0/10, 0%). For patients who did not receive IVIG prophylaxis, there was one loss of seropositivity for Strep PNA (1/4, 25%). **Conclusions:** The presence of protective vaccine titers is variable for patients receiving CAR-T, regardless of recent ASCT. The loss of protective titers post CART was low. IVIG variably impacted vaccine titer status. Immunization remains important for patients with ASCT prior to CART, without completion of post ASCT immunization protocol. Further study is needed to inform the need for immunization and optimal timing post CART. Research Sponsor: None.

	PRE-CAR-T			MONTH 3				
Positive titer/Total (%)	Prior ASCT	No ASCT	Total	Prior ASCT	No ASCT	IVIG	No IVIG	Total
Strep PNA	1/12 (8)	3/18 (17)	4/30 (13)	1/10 (10)	4/25 (16)	1/14 (7)	4/21 (19)	5/35 (14)
Hepatitis B	4/13 (31)	4/22 (18)	8/35 (23)	12/14 (86)	10/17 (59)	14/15 (93)	8/16 (50)	22/31 (71)
Hepatitis A	7/14 (50)	9/20 (45)	16/34 (47)	9/13 (69)	13/18 (72)	14/15 (93)	8/16 (50)	22/31 (71)
MEASLES	11/13 (85)	21/25 (84)	32/38 (84)	10/12 (83)	12/15 (80)	12/14 (86)	10/13 (77)	22/27 (81)
MUMPS	9/13 (69)	19/25 (76)	28/38 (74)	10/12 (83)	13/15 (87)	12/14 (86)	11/13 (85)	23/27 (85)
RUBELLA	12/13 (92)	21/25 (84)	33/38 (87)	11/12 (92)	15/15 (100)	13/14 (93)	13/13 (100)	26/27 (96)
VZV	12/13 (92)	19/25 (76)	31/38 (82)	12/12 (100)	14/15 (93)	13/14 (93)	13/13 (100)	26/27 (96)
Tetanus Toxoid	13/13 (100)	23/24 (96)	36/37 (97)	12/12 (100)	15/15 (100)	14/14 (100)	13/13 (100)	27/27 (100)

Sero-positivity for routine immunization pre and post CAR-T.

7556 **Poster Session**

Phase 1/2 study of cirmtuzumab and ibrutinib in mantle cell lymphoma (MCL) or chronic lymphocytic leukemia (CLL). *First Author: Hun Ju Lee, Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Cirmtuzumab (Cirm) is a humanized monoclonal antibody that inhibits the tumor promoting activity of ROR1 and had demonstrated additive/synergistic activity with many anti-cancer agents including ibrutinib (Ibr). **Methods:** Patients (Pts) with relapsed or refractory (RR) MCL or treatment naïve (TN) or RR CLL were enrolled. In Part 1 (Dose Escalation), doses of Cirm IV q2wks x5 then q4wks of 2-16 mg/kg and 300 or 600 mg were examined. Safety of Cirm alone was assessed during the first 28 days, then Ibr was started at approved doses for each indication. Cirm 600 mg IV q2wks x3 then q4wks in combination with Ibr starting day 0 was chosen as the recommended dosing regimen for use in Part 2 (Expansion) and Part 3 (CLL only, Cirm/Ibr vs. Ibr alone). **Results:** Twelve evaluable MCL pts were enrolled into Part 1, and 5 into Part 2. Median number of prior regimens was 2 (1-5), including pts relapsing after Ibr (4), auto-SCT (3), auto-SCT/ allo-SCT (1), auto-SCT/CAR-T (1). In CLL, 34 evaluable pts (12 TN and 22 RR) enrolled into Part 1 (18) or Part 2 (16). At least 74% of CLL pts in Parts 1 and 2 were high risk as determined by unmutated IGHV, del17p, and/or del11q. In Part 3, 22 evaluable pts received Cirm/Ibr (15) or Ibr (7). As of the 30OCT2020 safety cut-off for MCL and CLL, common TEAEs (all grades) included diarrhea (41%), contusion (39%), fatigue (39%), URI (31%), hypertension (25%) arthralgia (23%). Grade ≥3 neutropenia was 13% and thrombocytopenia 1%. There were no Cirm dose reductions or discontinuations for toxicity. Overall, Cirm did not appear to negatively impact the safety of Ibr. Efficacy (MCL): As of the 02FEB2021 efficacy cutoff, the best response of 17 evaluable pts in Parts 1 and 2 included an objective response rate (ORR) of 82%, 41% CR/CMR, 41% PR, 12% SD, and 6% PD. CR/CMR remain durable from 8-28+ mos**.** Most responses occurred rapidly after ~3 mos of Cirm/Ibr. Notably, responses were achieved in all pts who received prior SCT+/- CAR-T (4CR, 1PR) or prior Ibr (2CR, 2PR). At a median follow-up of 14.6 mos, the median PFS (mPFS) had not been reached (NR) (95% CI: 17.5, NA). Efficacy (CLL): The best response of 34 evaluable pts in Parts 1 and 2 included 91% ORR, 3% CR, 88% PR/PR-L, 9% SD, 0% PD. In Part 3, both arms achieved 100% ORR (all PRs). At a median follow-up of 20.2 mos, the mPFS was NR (95% CI: NA, NA), and the PFS estimate at 24 months was 95% for R/R, and 87% for TN, respectively, for evaluable CLL pts receiving Cirm/Ibr. **Conclusions:** Cirm/Ibr is a well-tolerated, active regimen in both MCL and CLL. For MCL, the mPFS of NR (95% CI: 17.5 , NA) and CRR (41%), with all CRs remaining without PD, compare favorably to mPFS of 12.8 mos (95% CI 8.5-16.6) and CRR (20%) reported for single agent Ibr (Rule 2017). For CLL, the high ORR and PFS are encouraging, particularly for RR CLL. The study is ongoing, with MCL enrollment expanded to study Cirm + Ibr in pts who have had a suboptimal response to an Ibr regimen, or who have failed other approved BTKi agents. Clinical trial information: NCT03088878. Research Sponsor: Oncternal Therapeutics, Inc., Other Foundation.

7557 **Poster Session**

Survival outcomes, treatment toxicity, and healthcare utilization in older adults with aggressive non-Hodgkin lymphoma (NHL). *First Author: Mitchell W. Lavoie, Massachusetts General Hospital, Boston, MA*

Background: Aggressive NHLs frequently affect older adults, and are often treated with intensive systemic therapy that is potentially curative but can cause substantial toxicities. Although balancing treatment efficacy with the risk of complications is critically important for older adults with NHL, few studies have described these patients' survival outcomes, rates of toxicities, and healthcare utilization. **Methods:** We conducted a retrospective analysis of adults > 65 years diagnosed with aggressive NHL and treated with systemic therapy at Massachusetts General Hospital from 4/2000-7/2020. We abstracted patient demographic and clinical information, survival outcomes, treatment toxicity (rates and grade), and healthcare utilization outcomes (intensive care unit [ICU] admissions and unplanned hospitalizations within six months of treatment initiation) from the electronic health record. Using multivariable logistic regression, we examined patient and disease factors associated with rates of grade 3+ non-hematologic toxicity and unplanned hospitalization. **Results:** Of 295 patients (median age = 73 years [age 65-69: 32.5%; age 70-74: 26.1%; age 75-79: 20.0%; age 80+: 21.4%], 39.0% female), most had advanced stage disease (59.5%) and an ECOG performance status of 0 or 1 (83.1%). The most common diagnosis was de novo diffuse large B-cell lymphoma (DLBCL) or grade 3B follicular lymphoma (69.2%). Most common therapies were CHOP (65.8%) and EPOCH (17.0%) with or without Rituximab. With a median follow up of 5.9 years, 5-year overall survival (OS) was 74.2%. Among patients age 65-69, 70-74, 75-79, and 80+ years, 5-year OS by age group were 82.1%, 72.2%, 73.5%, and 66.3%, respectively. Overall, 42.4% had grade 3+ toxicity, while 8.1% had grade 4 or 5 toxicity. The rates of unplanned hospitalization and ICU admission during the first 6 months of therapy were 41.0% and 6.1%, respectively. In multivariable analysis, hypoalbuminemia (OR 4.22, 95%, $p < 0.001$) and number of comorbidities (OR 1.75, $p < 0.001$) were associated with a greater likelihood of grade 3+ toxicity. Hypoalbuminemia (OR 2.76, $p = 0.003$), number of comorbidities (OR 1.61, $p = 0.001$), and receipt of EPOCH (OR 5.41, $p = 0.012$) were associated with a greater likelihood of unplanned hospitalization. **Conclusions:** The majority of older adults receiving upfront therapy for aggressive NHL survive beyond 5 years, yet nearly half experience substantial treatment toxicities and unplanned hospitalizations. Our findings underscore the need to develop supportive care interventions to enhance the care experience for older adults with NHL. Research Sponsor: Leukemia and Lymphoma Society.

7558 **Poster Session**

Prognostic role of lymphocyte to monocyte ratio in patients treated with CAR-T for aggressive lymphoma. *First Author: Henan Zhang, Mayo Clinic, Rochester, MN*

Background: A low absolute lymphocyte to monocyte ratio (ALC/AMC) has been found to predict decreased survival in lymphoma patients receiving chemotherapy and stem cell transplant. We report its clinical significance and additional cellular phenotype changes in patients receiving chimeric antigen receptor T-cell (CART) therapy. **Methods:** Records were reviewed for patients (pts) who received axicabtagene ciloleucel between 6/2016 and 12/2020. Receiver operator curve was generated using nominal logistic regression to predict CR as best response. Survivals were calculated using Kaplan- Meier method. Blood immune phenotype were assayed by multiparametric flow. Principle component analysis (PCA) was performed using ClusterVis. **Results:** Low ALC/AMC (≤0.8) prior to lymphodepletion (LD) chemotherapy on day -5 was associated with lower CR rate (AUC=0.68, Table). Our cohort of 81 pts had similar baseline characteristics except that noted in Table. Low ALC/AMC ratio is associated with shorter EFS and OS (EFS: 2.6 vs. 6.4 months, P<0.0001; OS: 5.3 months vs. not reached, P=0.0006), respectively. Prognostic association remained significant in multivariate analysis including ASCT, bridging therapy and CRP. Interestingly, compared to the high ALC/AMC group, the low ALC/AMC group had decreased CD8 Tem, increased CD16+CCR2+ monocytes and increased monocytes' producing IL12, IL-10, and IL-1β (n=26). Unsupervised PCA identified 3 clusters: 1. Low ALC/AMC, all non-CR; 2. High ALC/AMC, some non-CR; 3. High ALC/AMC, all CR. Compared to cluster 1 and 2, cluster 3 had increased CD4 Tnaive, CD8 Tcm and IL-17 producing CD4 T and NK cells. **Conclusions:** ALC/AMC is a clinically accessible test that is strongly associated with CAR-T response and survival. Immune characterization revealed that the biologic effect is not just associated with cell ratio. Increased inflammation has been found to negatively impact CAR-T response, with some cytokines known to be from the myeloid lineage. We show that CRP is elevated in the low ALC/AMC group with increased cytokine production by monocytes. In addition, presence of T cell subset and IL-17 producing cells, before LD, are associated with clinical response. Further investigation on optimizing host immunity may help improve clinical outcome with CAR-T. Research Sponsor: Center for Individualized medicine Mayo Clinic.

Patient demographics.

Variable	All patients (N=81)	ALC/AMC >0.8 (N=52)	ALC/AMC ≤0.8 (N=29)	P- Value
Age (yr), median (range)	58 (26-76)	57 (26-75)	59 (29-76)	0.4
Male, n (%)	53 (65)	37 (71)	16 (55)	0.09
Lymphoma stage ≥ III, n (%)	78 (94)	49 (95)	27 (93)	0.77
International prognostic index ≥3, n (%)	42 (52)	25 (48)	17 (58)	0.3
Previous ASCT, n (%)	38 (47)	30 (58)	8 (28)	**0.027**
Bridging therapy, n (%)	50 (61)	28 (54)	22 (76)	0.08
CRP, day 0 (mg/l), median (range)	17.2 (2.9- 251.7)	11.65 (3-251.7)	32.3 (2.9- 191.7)	**0.005**
Ferritin, day 0 (mcg/l), median (range)	528 (72- 12980)	487 (72-12980)	648 (72- 6058)	0.17
CR rate, n (%)	42 (52)	34 (65)	8 (28)	**0.0009**

7559 **Poster Session**

Efficacy and safety of zanubrutinib versus rituximab-based chemoimmunotherapy in Waldenström macroglobulinemia (WM): Matching-adjusted indirect comparisons. *First Author: Jorge J. Castillo, Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Given a lack of WM randomized trials directly comparing zanubrutinib with chemoimmunotherapy, this study aimed to indirectly compare zanubrutinib with bendamustine-rituximab (BR) and with dexamethasone-rituximab-cyclophosphamide (DRC) separately through matching-adjusted indirect comparisons (MAIC). **Methods:** MAIC were conducted to re-weight the individual data of 102 WM patients (83 relapsed/refractory [R/R] and 19 treatment-naïve [TN]) treated with zanubrutinib in the ASPEN trial (NCT03053440) so that the weighted average baseline characteristics of patients treated with zanubrutinib matched those of 71 R/R patients treated with BR, and 72 TN patients treated with DRC separately. Matching variables for MAIC with BR included age, prior lines of therapy, IgM concentration, International Prognostic Scoring System for WM score, and extramedullary disease (EMD); and for MAIC with DRC included age, platelet count, hemoglobin concentration, and EMD. Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS) of comparators were digitized to re-create patient-level data. Comparisons of survival and adverse event incidence between treatments were conducted using Cox proportional hazards models and modified Poisson models. **Results:** Compared to DRC, zanubrutinib was associated with longer PFS (hazard ratio [HR]: 0.39 [95% confidence interval 0.18-0.82] and 0.35 [0.14-0.86] pre- and post-matching, respectively) and longer OS (HR: 0.56 [0.20-1.53] and 0.47 [0.14-1.62] pre- and post-matching, respectively), and insignificantly higher incidences of neutropenia (risk ratio [RR]: 1.63 [0.71-3.77] and 1.47 [0.58-3.74] pre- and post-matching, respectively). Compared to BR, zanubrutinib was associated with longer PFS (HR: 0.32 [0.15-0.69] and 0.37 [0.15-0.91] pre- and post-matching, respectively), longer OS (HR: 0.31 [0.12, 0.80] and 0.29 [0.10-0.85] pre- and post-matching, respectively), lower incidences of neutropenia (RR: 0.45 [0.26-0.78] and 0.50 [0.27-0.91] pre- and post-matching, respectively) and lower incidences of pneumonia (RR: 0.18 [0.02-1.55] and 0.26 [0.03-2.28] pre- and post-matching, respectively). **Conclusions:** Zanubrutinib demonstrated longer PFS than DRC, and longer PFS and OS than BR in WM, before and after matching adjustment based on patient characteristics. Research Sponsor: BeiGene, Ltd.

		MAIC of zanubrutinib vs DRC		MAIC of zanubrutinib vs BR	
Outcomes	Zanubrutinib pre-matching (N = 102)	Zanubrutinib post-matching DRC (N = 53)	DRC (N = 72)	Zanubrutinib post-matching BR (N = 50)	BR (N = 71)
PFS, 12-month rate, %	94	92	85	94	79
PFS, 24-month rate, %	85	90	68	81	59
OS, 12-month rate, %	97	95	92	98	87
OS, 24-month rate, %	90	94	85	88	77
Anaemia, %	5.0	4.2	NR	3.6	NR
Hypertension, %	5.9	3.1	4.2	9.5	NR
Neutropenia, %	15.8	14.3	9.7	17.5	35.2
Pneumonia, %	1.0	0.6	NR	1.5	5.6
Thrombocytopenia, %	5.9	4.4	0.0	5.2	NR

NR, not reported.

7560 **Poster Session**

Immune priming with nivolumab followed by nivolumab and rituximab in first-line treatment of follicular lymphoma: The phase 2 1st FLOR study. *First Author: Eliza Anne Hawkes, Austin Health and Olivia Newton-John Cancer Research Institute, Heidelberg, Australia*

Background: Standard of care immunochemotherapy in front-line (1L) follicular lymphoma (FL) is highly efficacious but not without significant toxicity. High rates of grade 3-5 adverse events (AEs), primarily infection and bone marrow suppression, are experienced in up to 75% of patients. A more tolerable but equally effective approach is required. PD-1 inhibition, in combination with rituximab (R), increases T cell anti-tumour effect & enhances NK cell antibody dependent cell cytotoxicity, with proven efficacy in relapsed FL. The concept of 'priming' the immune system with nivolumab (N) prior to tumour-directed therapy has rationale and evidence, but the safety of this approach in 1L FL is not described. **Methods:** '1st FLOR' (NCT03245021) is an open-label, multi-centre, phase 2, Simon's 2-stage study of N + R (N = 39). Key eligibility were stage III-IV grade 1-3A FL requiring 1L systemic therapy; ECOG ≤2; adequate organ function. All patients (pts) receive induction N 240mg IV 2-weekly for 4 cycles. Pts with complete response (CR) receive 4 further cycles of 240mg IV N monotherapy then 12 cycles of maintenance N 480mg IV 4-weekly. Pts with < CR had 240mg N plus 375mg/m^2 IV R 2-weekly for 4 cycles followed by maintenance N+R (N 480mg 4 weekly for 12 cycles; R 12 weekly for 8 cycles). Primary endpoint (EP) was ≥ G3 toxicity rate during induction. Secondary EPs; response rate by Lugano response criteria, overall toxicity, PFS, OS. **Results:** Between September 2017 to March 2020, 39 pts were enrolled. Baseline characteristics included median age of 54 (range: 28-79). stage IV disease in 67%, B Symptoms & bulk (≥7cm) in 23% each, intermediate-high risk FLIPI in 74%. The primary EP was met, with only 16 pts (41%) having ≥G3 toxicity at end of induction. Non-immune AEs were predominantly G1-2; most commonly infection (67%) & fatigue (64%). G3-4 Immune-related AEs were infrequent and included pancreatitis plus hepatitis (N = 1), pancreatitis alone (N = 1), rash (N = 1), transaminitis (N = 2), hypocortisolism (N = 1), hyperglycaemia (N = 3) and asymptomatic lipase/amylase increase (N = 3). Median follow-up was 17.5 months (range: 7-39). Overall response rate was 92% (36/39) with CR in 54% (21/39). Median time to CR was 5 months (m) (range: 2-25). Nine pts (23%) discontinued treatment; 7 due to progressive disease (1 pt died of transformed FL), 2 developed constitutional symptoms (1 stable disease, 1 partial response). In 25 evaluable pts, 12m PFS & OS is 72% (CI 51-88) & 96% (CI 80-100). Biomarker analysis is in progress. **Conclusions:** Immune-priming with single-agent N, then combination N+R in 1L FL is associated with favourable toxicity and high ORR & CR rates potentially providing an alternative to chemotherapy. Acknowledgements: Bristol-myers Squibb provided funding and nivolumab for this study. Clinical trial information: NCT03245021. Research Sponsor: Bristol-Myers Squibb.

7561 **Poster Session**

Treatment free remission (TFR) and overall response rate (ORR) results in patients with relapsed/refractory Waldenstrom's macroglobulinemia (WM) treated with CLR 131. *First Author: Sikander Ailawadhi, Mayo Clinic, Jacksonville, FL*

Background: Phospholipid ethers (PLE) provide a novel mechanism to specifically target tumor cells leveraging high lipid raft content in their cell membranes. PLE/phospholipid drug conjugates are specifically designed to have high affinity to lipid rafts which upon binding results in trans-membrane flipping with the ability to deliver an attached warhead directly to the cytosol. CLR 131 (I-131-CLR1404) is a novel PLE molecule armed with I-131 resulting in targeted tumor cell radiotherapy which is being examined in relapsed or refractory WM through an open-label, Phase 2 trial, CLOVER-1 (NCT02952508). **Methods:** The primary objective of this study is to determine the efficacy and safety of CLR 131 in select B-cell malignancies. Eligibility criteria for WM pts include receipt of at least 2 prior treatment regimens unless ineligible to receive standard agents and have measurable disease: either IgM or extramedullary disease. CLR 131 is administered in up to 4 IV infusions (15-20 min) over 3 months. Adverse events (AEs) are graded by NCI-CTCAE v4.03; responses are assessed by the VIth WM Criteria for Response Assessment [Owen 2013]. **Results:** 6 pts with WM were enrolled in the study with data current as of 8 Jan 2021. The median age was 69 (range 54-81) with 4 females and 2 males who had a median of 2 prior regimens (range 1-5) and received a mean total body dose of 92.76 mCi CLR 131. 3 of 6 patients were MYD88 wild type (WT) of which 2 were dual WT (MYD88 WT & CXCR4 WT). The overall response rate (ORR) was 100% and the major response rate (MRR) was 83%, including 1 pt with a CR, 4 PR, and 1 MR. For those pts who were dual WT, the MRR was 100% and 1 pt who was MYD88 WT (CXCR4 is unknown) had a complete response. The median time to initial response was 48 days. Median duration of response (DOR) and treatment free remission (TFR) have not been reached; ongoing mean DOR is 335 days and mean TFR is 384 days. 100% of MYD88 WT patients have exceeded 6.5 months of follow up with average TFR of 18.1 months. The primary treatment emergent AEs in pts with WM included fatigue and cytopenias, in line with prior experience with CLR 131 in other B-cell malignancies. The most commonly observed cytopenias included Grade 3 or 4 thrombocytopenia (100%), neutropenia (83%), anaemia (66%) and decreased white blood cell count (33%). Of note, no cases of bleeding or febrile neutropenia were observed. **Conclusions:** Initial results for CLR 131 show efficacy across multiple WM patient genotypes including dual WT patients with durable DOR and TFR after 2 to 4 infusions. CLR 131 represents a novel and promising approach to the treatment of MYD88 WT patients who have a historical median time to progression of 1.3 years. These encouraging data led to the pivotal global CLOVER-WaM trial (N=50) in WM patients who have failed or had a suboptimal response to a Bruton Tyrosine Kinase inhibitor. CLOVER-WaM is currently enrolling. Clinical trial information: NCT02952508. Research Sponsor: Cellectar Biosciences.

7563 **Poster Session**

A novel index using inflammatory markers improves the diagnosis of hemophagocytic lymphohistiocytosis in patients with hematologic malignancies. *First Author: Adi Zoref Lorenz, Hematology Institute, Meir Medical Center, Sackler faculty of medicine, Tel Aviv University, Kfar Saba, Israel*

Background: Hemophagocytic lymphohistiocytosis (HLH) is a life-threatening inflammatory syndrome that may accompany hematologic malignancies (HM). The diagnosis of HLH in patients with HM (HM-HLH) is confounded by a number of factors: the most commonly used HLH-2004 diagnostic criteria are derived from studies in infants while the Hscore used in adults is not specific for HMs; moreover, most parameters in these scoring systems may reflect features of the underlying HM rather than HLH associated inflammation; and finally specific diagnostic cutoff values for laboratory abnormalities in HM-HLH have not been defined. We therefore conducted a study to optimize the HLH-2004 laboratory thresholds for the diagnosis of HM-HLH. **Methods:** A multi-center retrospective study in adult patients with HM in whom testing for HLH was performed. HM-HLH was defined as fulfillment of 5/8 HLH-2004 diagnostic criteria. We established the optimal diagnostic cutoff levels for HLH-2004 laboratory parameters using receiver operating curves (ROC) and combined the best performing parameters into a combined index, using binary logistic regression. We then created a clinical decision tree using a Classification and Regression Tree (CART) analysis with all available parameters, using cross validation. We also determined the prognostic value of our combined diagnostic tool. **Results:** 225 adults were analyzed (112 with HM-HLH per HLH-2004 and 113 with HM only). 35% of patients were evaluated for HLH routinely upon HM diagnosis. Soluble CD25 (sCD25) and ferritin best discriminated HM-HLH from HM, with an area under the curve (AUC) of 0.83 for each. ROC analysis demonstrated an optimal cutoff of > 4190 U/mL for sCD25 (sensitivity/specificity 91%/69%) and an optimal cutoff of > 2636 ng/ml for ferritin (sensitivity/specificity 64%/86%) for HM-HLH. We term the combination of elevated sCD25 and ferritin using optimized cutoff levels the 'optimized HLH inflammatory' (OHI) index. This OHI index was highly specific for the diagnosis of HM-HLH (specificity of 92%, sensitivity 79%). CART analysis demonstrated that OHI index positivity was sufficient to diagnose HM-HLH. In patients without a positive OHI index an Hscore > 168 and either splenomegaly or triglycerides > 279 ng/dL can still diagnose HM-HLH. By following this decision pathway, approximately 92% of patients were accurately classified based on HLH-2004. Furthermore, the OHI was better (odds ratio (OR) 7.9; 95% confidence interval (CI) 4.2-14.6) than Hscore >169 (OR 5.5; CI 3.9-9.6) and > 5/8 HLH-2004 (OR 5.3; CI 3-9.3) at predicting mortality at 1 year. **Conclusions:** The OHI index derived here is a simple tool that can accurately diagnose HLH and predict mortality in patients with hematologic malignancies. Some patients may not need full HLH workup before intervening with therapy that is HLH directed and not only malignancy directed. Research Sponsor: None.

7564 **Poster Session**

Post-transplant lymphoproliferative disorder in kidney transplant patients: A multicenter report. *First Author: Elise A. Chong, Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA*

Background: Post-Transplant Lymphoproliferative Disorder (PTLD) is a complication of transplantation that often arises due to reactivation of the Epstein-Bar Virus (EBV). Given the rarity of this disease, a full understanding of its presentation and optimal therapies has yet to be determined. **Methods:** A multicenter retrospective analysis was performed utilizing data from kidney transplant patients (pts) who developed PTLD at the Hospital of the University of Pennsylvania and the Cleveland Clinic. The association between categorical variables and clinical response were assessed via Fisher's exact testing. **Results:** 117 pts had diagnoses of PTLD after kidney transplantation. The median age at PTLD diagnosis was 52 yrs (range 17-89 yrs), and the median time from transplantation to diagnosis was 3.6 yrs (range: 7 days-36 yrs). Pt characteristics included: 84% Caucasian, 57% male, and 11% combined kidney and pancreas transplant patients. 68% pts had received unrelated donor transplants; 41% had prior rejection episodes. PTLD histology was 72% monomorphic and 28% polymorphic. Polymorphic PTLD was more likely to be EBV+ than monomorphic PTLD (81% vs. 54%, p = 0.05). At diagnosis, immunosuppression included: steroids (95%), mycophenolate (44%), azathioprine (40%), sirolimus (30%), cyclosporine (46%), and/or tacrolimus (45%). Common PTLD symptoms included fever (34%), pain (38%), weight loss (30%), fatigue (30%), and/or mass (26%). The most common sites of involvement were lymph nodes (64%), kidney allograft (22%), and/or GI tract (17%). At diagnosis, 61% of patients' tumors were EBV+ and 59% of patients had elevated serum LDH. Overall, the majority of pts responded to first-line PTLD therapy, with 61% CR and 14% PR. Reduction of immunosuppression (RI) alone (36% of pts) led to 48% CR and 12% PR; RI with rituximab (16%) led to 47% CR and 7% PR; and RI with chemotherapy (14%) resulted in 58% CR and 42% PR. Patients treated with RI as well as resection (n = 18) of their limited stage disease had better outcomes (p = 0.05). Overall survival for all patients was 10.7 years (95%CI: 5.2-13 years). PTLD patients < 40 yrs were more likely to achieve CR after first line therapy (p < 0.001), have allograft involvement (p = 0.003), and have a polymorphic histology (p = 0.002). Allograft involvement tended to occur sooner after transplant (p = 0.001) and was more likely to present with allograft failure (p = 0.007). PTLD with allograft involvement had better response to first therapy than regular PTLD (p = 0.007) and often responded well to complete resection and RI. **Conclusions:** Pts with PTLD may achieve a CR through different initial therapies. Younger patients and those able to undergo complete resection of disease and RI had better prognoses. Allograft involvement by PTLD carries a good prognosis and should be identified and treated differently from other presentations. Research Sponsor: None.

7565 **Poster Session**

Phased variants improve DLBCL minimal residual disease detection at the end of therapy. *First Author: David Matthew Kurtz, Stanford Cancer Institute, Stanford, CA*

Background: Detection of circulating tumor DNA (ctDNA) has prognostic value in diverse tumors, including DLBCL. Despite uses for assessing molecular response to therapy, current methods using immunoglobulin or hybrid-capture sequencing have suboptimal sensitivity, particularly when disease-burden is low. This contributes to a high false negative rate at key milestones such as at the end of therapy (EOT; Kumar A, *ASH* 2020). We explored the utility of detecting multiple mutations (phased variants, PVs) on individual cell-free DNA (cfDNA) strands to improve MRD in DLBCL. **Methods:** We applied Phased Variant Enrichment and Detection Sequencing to track PVs from 485 specimens from 117 DLBCL patients undergoing first-line therapy. We sequenced cfDNA prior to, during, and after therapy to assess the prognostic value of MRD. We compared the performance of PhasED-Seq to current techniques, including SNV-based CAPP-Seq and duplex sequencing. **Results:** To establish its detection limit for ctDNA, we compared the background error-profile of of PVs and SNVs in cfDNA sequencing from healthy subjects. PV-detection by PhasED-Seq demonstrated a lower background profile than SNVs, even when considering duplex molecules (n = 12; 8.0e-7 vs 3.3e-5 and 1.2e-5; $P < 0.0001$). We also assessed analytical sensitivity within a ctDNA limiting dilution series from 3 patients, simulating tumor fractions from 0.1% to 0.00005% (1:2,000,000). PhasED-Seq outperformed SNV-based methods and duplex sequencing for recovery of expected tumor content below 0.01% ($P < 0.0001$ and $P = 0.005$ respectively by paired t-test). We then explored disease detection in clinical samples. We identified SNVs and PVs from pretreatment tumor or plasma and followed these variants in serial cfDNA. Using SNV-based methods, 40% and 59% of patients had undetectable ctDNA after 1 or 2 cycles (n = 82 and 88). However, 24% and 25% of these cases had detectable ctDNA by PhasED-Seq. Importantly, MRD detection by PhasED-Seq was prognostic for event-free survival even in patients with undetectable ctDNA by SNVs. We next explored the utility of PhasED-Seq at the EOT in 19 subjects, 5 of whom experienced eventual disease progression. While only 2/5 cases with progression had detectable disease at EOT using SNVs, PhasED-Seq detected all 5/5 cases. PhasED-Seq also correctly identified all patients (14/14) without clinical relapse as having no residual disease, including one patient who discontinued therapy after 1 cycle due to toxicity, but remains in remission > 5 years after this single treatment. This resulted in superior classification of patients for EFS using PVs compared with SNVs (C-statistic: 0.98 vs 0.60, $P = 0.02$). **Conclusions:** Tracking PVs results in significantly lower background rates than SNV-based approaches, enabling detection to parts per million range. PhasED-Seq improves on disease detection in DLBCL at the EOT, allowing possible MRD-driven consolidative approaches. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

7566 **Poster Session**

IL-1 receptor antagonist for prevention of severe immune effector cell-associated neurotoxicity syndrome. *First Author: Caspian Oliai, UCLA Medical Center, Los Angeles, CA*

Background: Progress in chimeric antigen receptor (CAR) T-cell therapy has included reduction in life-threatening toxicity. Rates of severe cytokine release syndrome (CRS) have declined from 50% in early trials to 7% in the most recent real-world experience. However, rates of severe immune effector cell-associated neurotoxicity (ICANS) associated with axicabtagene ciloleucel (Axicel) remain unchanged. IL-1 is a major driver of ICANS pathophysiology that is produced upstream of IL-6. The IL-1 receptor antagonist, Anakinra, can prevent neurotoxicity in animal models when given at fever onset. We present our early experience of the first 13 participants enrolled into a phase II trial evaluating Anakinra to prevent severe ICANS (NCT4205838). **Methods:** This investigator-sponsored trial included adults eligible for standard-of-care Axicel for large B-cell lymphoma after ≥2 lines of intensive chemoimmunotherapy. Participants received Anakinra 100 mg SQ q6h x 12-36 doses until ICANS returned to grade ≤1. The trigger to initiate Anakinra was any grade ICANS or grade ≥3 CRS in the absence of ICANS. A protocol modification, made after the first 3 participants were treated, changed the trigger for Anakinra to grade ≥2 CRS. In addition to Anakinra, all participants received standard-of-care interventions for CRS and ICANS. The primary objective is to estimate the efficacy of Anakinra in preventing severe ICANS (grade ≥3) according to ASTCT 2018 consensus grading. **Results:** To date, 13 participants have been enrolled, and 7 met criteria to initiate Anakinra and received the first dose prior to severe ICANS. Median age was 56 years (range, 23-84 years). Of the 7 participants whom received Anakinra prior to severe ICANS, only 1 of 7 (14%) developed grade 3 ICANS. The most common adverse event was injection site reaction, which peaked at grade 2. There were no unexpected toxicities. Once the protocol was amended to initiate Anakinra for grade ≥2 CRS (N = 4), no participant developed severe ICANS, and only one participant met the institutional standard to receive corticosteroids (Table). **Conclusions:** Anakinra is feasible to initiate in the non-prophylactic setting in patients at increased risk for severe ICANS. These early results demonstrate potential to reduce severe ICANS associated with Axicel to a rate similar to other CAR T-cell products, and to reduce corticosteroid use. Further enrollment to the pre-planned sample size of N=36 is required to demonstrate statistical efficacy. Serum IL-1 analysis is also ongoing. Clinical trial information: NCT4205838. Research Sponsor: John Timmerman, MD study investigator-sponsor.

Maximum ICANS and CRS grades in participants who received Anakinra prior severe ICANS.

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Age	23	84	81	56	58	32	47
Max CRS grade	3	2	2	2	2	2	2
Max ICANS grade	3	1	2	0	0	0	2
Anakinra trigger	CRS gr 3	ICANS gr 1	ICANS gr 2	CRS gr 2	CRS gr 2	CRS gr 2	CRS gr 2
Duration of ICANS ≥ gr 3	10 hrs	-	-	-	-	-	-
Dexamethasone 10 mg-equivalent doses	10	15	6	0	0	0	3

TPS7567 **Poster Session**

Randomized, phase III study of early intervention with venetoclax and obinutuzumab versus delayed therapy with venetoclax and obinutuzumab in newly diagnosed asymptomatic high-risk patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): EVOLVE CLL/SLL study (SWOG S1925, NCT#04269902). *First Author: Deborah Marie Stephens, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: Currently, asymptomatic patients with CLL/SLL are observed without treatment until development of symptoms or cytopenias. Historically, early intervention studies with chemoimmunotherapy have not resulted in an overall survival (OS) benefit and have resulted in toxicity. The introduction of targeted therapies, such as venetoclax and obinutuzumab (VO), have provided tolerable/efficacious options for CLL patients. In the CLL14 study, *symptomatic* CLL patients receiving frontline therapy with VO had longer progression-free survival (PFS) and deeper remissions [more minimal residual disease-undetectable (MRDu)] compared with those receiving chlorambucil and obinutuzumab (Fischer 2019). The CLL-International Prognostic Index (CLL-IPI; Table) is a validated prognostic model to predict which patients are highest risk for a shorter time to first therapy and shorter OS. We aim to use VO as early intervention in *asymptomatic*, high-risk patients with CLL to potentially lengthen OS and thus alter the natural history of the disease. **Methods:** On 12/14/20, we activated the S1925 study for adult patients with CLL or SLL, who were diagnosed within 12 months of enrollment. Eligible patients have a CLL-IPI score ≥ 4 (Table) or complex cytogenetics (≥3 cytogenetic abnormalities) and do not meet any criteria for initiation of treatment by the International Working Group for CLL (IWCLL; Hallek 2018) guidelines. Enrolled patients are randomized in a 2:1 manner to early versus delayed (at the time IWCLL indication for treatment is met) therapy with VO. VO is administered for a fixed duration of 12 months as previously described (Fischer 2019). The primary endpoint is OS. We hypothesize that early intervention with VO will improve the rate of 6-year OS from 60% to 80%. This design requires 222 eligible patients for 88% power (2-sided α=0.05) for the primary comparison. To allow for 10% ineligibility, we will enroll 247 patients. Estimated accrual time is 4 years. Secondary endpoints include: rates of response, PFS, and relapse-free survival; safety; time to 2nd CLL-directed therapy; and quality of life (FACT-Leukemia total score). The primary translational objective is to evaluate the prognostic association between OS and peripheral blood MRD status at 15 months after treatment initiation by flow cytometry. Additional exploratory objectives include the association of other clinical outcomes, baseline prognostic factors, and IWCLL-defined response with MRD status at multiple timepoints. Currently, enrollment is open. Clinical trial information: NCT04269902. Research Sponsor: U.S. National Institutes of Health.

Calculation of CLL-IPI Score.

Characteristic	Points
Del(17p) or *TP53* mutation	4
β-2-microglobulin ≥ 3.5mg/L	2
Unmutated IGHV status	2
Rai Stage 1-4	1
Age > 65 years	1

TPS7568 **Poster Session**

A phase 3 study to evaluate the efficacy and safety of tafasitamab plus lenalidomide and rituximab versus placebo plus lenalidomide and rituximab in patients with relapsed/refractory (R/R) follicular lymphoma (FL) or marginal zone lymphoma (MZL). *First Author: Laurie Helen Sehn, BC Cancer Centre for Lymphoid Cancer and University of British Columbia, Vancouver, BC, Canada*

Background: Most patients with the indolent non-Hodgkin lymphoma (NHL) subtypes FL or MZL respond to first-line treatment but relapse is common, and there is no single standard treatment for patients with R/R FL or MZL. Tafasitamab is an Fc-engineered humanized monoclonal antibody (mAb) against CD19 which is broadly expressed in FL and MZL, and regulates B-cell proliferation via B-cell receptor signaling. In preclinical studies, tafasitamab has shown activity against NHL cell lines in combination with rituximab (anti-CD20 mAb) and lenalidomide (LEN). Tafasitamab monotherapy has shown promising clinical activity in a phase 2a study in patients with R/R NHL (NCT01685008), with an ORR of 29% (n/N = 10/34) in patients with FL and 33% (n/N = 3/9) in patients with MZL. In an ongoing phase 2, single-arm study (L-MIND, NCT02399085), tafasitamab plus LEN followed by tafasitamab alone demonstrated an ORR of 57.5% (n/N = 46/80) in patients with R/R diffuse large B-cell lymphoma (FDA approved indication). These preclinical and clinical observations from phase 2 trials suggest a potential clinical benefit of tafasitamab plus LEN and rituximab for patients with R/R FL or MZL. **Methods:** This phase 3 double-blind, placebo-controlled, randomized study is designed to investigate whether tafasitamab plus LEN and rituximab provides improved clinical benefit compared with LEN and rituximab in patients with R/R FL or R/R MZL. Patients will be randomized 1:1 to receive tafasitamab (12 mg/kg IV on days 1, 8, 15, and 22 of a 28-day cycle [cycles 1–3], then days 1 and 15 [cycles 4–12]) plus LEN (20 mg PO QD, days 1–21/ cycle for 12 cycles) and rituximab (375 mg/m^2 IV on days 1, 8, 15, and 22 of cycle 1, then day 1 of cycles 2–5), or placebo (0.9% saline solution IV) plus LEN and rituximab. The primary study endpoint is PFS (investigator assessed [INV] by Lugano 2014 criteria) for patients with FL. Key secondary endpoints are PFS (INV) in overall population (FL and MZL), PET-CR rate (INV) at end of treatment (4–8 weeks after last treatment) and OS in patients with FL. Inclusion criteria include age ≥18 y, histologically confirmed FL (grade 1, 2, or 3a) or MZL (nodal, splenic, or extranodal), documented R/R disease, ≥1 prior systemic anti-CD20 therapy (including anti-CD20 refractory disease), ECOG PS ≤2, adequate systemic organ function, and high tumor burden (per GELF criteria). Exclusion criteria include prior rituximab plus LEN treatment, history of radiotherapy for other diseases (≥25% of bone marrow), nonhematologic malignancy, congestive heart failure (LVEF < 50%), active systemic infection, known CNS lymphoma, or severe immunocompromised state. inMIND (NCT04680052, EudraCT2020-004407-13) is currently enrolling patients; planned enrollment is 528 patients with R/R FL and 60–90 patients with R/R MZL. Clinical trial information: NCT04680052. Research Sponsor: Incyte Corporation.

TPS7569 **Poster Session**

Phase 3 trial (GCT3013-05) of epcoritamab versus standard of care in patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL). *First Author: Catherine Thieblemont, Assistance Publique & Hôpitaux de Paris (APHP), Hopital Saint-Louis, Hemato-Oncologie, Université de Paris, Paris, France*

Background: Patients (pts) with DLBCL who are refractory to/or have relapsed (R/R) after treatment with chemotherapy and anti-CD20 monoclonal antibody (mAb) have a poor prognosis. There is a need for new treatment options to improve outcomes. Epcoritamab, a novel subcutaneous (SC) bispecific antibody, binds to CD3 on T-lymphocytes and CD20 on B-cell non-Hodgkin lymphoma (NHL) cells to induce potent and selective killing of malignant CD20+ B-cells. In an ongoing phase 1/2 dose-escalation trial in heavily pretreated pts with B-cell NHL (N = 68), epcoritamab demonstrated a tolerable safety profile and substantial single-agent anti-tumor activity, with a complete response (CR) rate of 55% and an overall response rate (ORR) of 91% in pts with R/R DLBCL (at ≥48 mg doses; n = 12) (NCT04663347; Hutchings, ASH, 2020). Furthermore, all 4 evaluable R/R DLBCL pts previously treated with chimeric antigen receptor T-cell (CAR-T) therapy achieved an objective response with 2 achieving CR. These encouraging data support the potential for epcoritamab to improve clinical outcomes in pts with R/R DLBCL. Here we describe the phase 3 trial of epcoritamab versus standard of care (SOC) treatments in pts with R/R DLBCL (NCT04628494). **Methods:** GCT3013-05 is a randomized, open-label, worldwide, multicenter, phase 3 study designed to evaluate the efficacy of epcoritamab versus investigator's choice of SOC with R-GemOx (rituximab, gemcitabine, oxaliplatin) or BR (bendamustine, rituximab) in adults with R/R disease of one the following CD20+ B-cell NHL histologies: I) DLBCL, not otherwise specified including de novo DLBCL or DLBCL histologically transformed from follicular lymphoma; II) "double-hit" or "triple-hit" DLBCL (high-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 translocations); or III) follicular lymphoma grade 3B. Other key eligibility criteria include: ≥1 line of prior chemotherapy that included treatment with an anti-CD20 mAb, Eastern Cooperative Oncology Group performance status 0–2, and prior failure of/ineligibility for autologous stem cell transplantation. Prior CAR-T therapy is allowed. A total of 480 pts will be randomized 1:1 to receive either SC epcoritamab at the recommended phase 2 dose (28-day cycles; weekly, biweekly, or monthly schedule depending on cycle number) until disease progression or unacceptable toxicity; or up to 4 cycles of biweekly treatment with intravenous (IV) R-GemOx (8 doses); or up to 6 cycles of IV BR (6 doses; dosing every 3 weeks). The primary endpoint is overall survival. Key secondary endpoints include progression-free survival, ORR, duration of response, time to response, and safety. The study is currently enrolling in Australia, Belgium, Denmark, France, Spain, and will open for enrollment in additional countries. Clinical trial information: NCT04628494. Research Sponsor: This study was funded by Genmab A/S and AbbVie Inc.

TPS7570 **Poster Session**

A phase 1 dose escalation and cohort expansion study of the safety and efficacy of allogeneic CRISPR-Cas9–engineered T cells (CTX110) in patients (Pts) with relapsed or refractory (R/R) B-cell malignancies (CARBON). *First Author: Joseph McGuirk, Department of Blood and Bone Marrow Transplant, The University of Kansas Medical Center, Kansas City, KS*

Background: Diffuse large B-cell lymphoma (DLBCL) is the most common form of non-Hodgkin lymphoma (NHL), and although > 50% of pts achieve long-term remission with first-line therapy, pts with R/R disease as well as those with R/R grade 3b follicular lymphoma (FL), double-, or triple-hit high-grade lymphomas have poor long-term outcomes (Crump 2017; Kahl 2016; Jain 2012). Autologous (auto) chimeric antigen receptor (CAR) T cell therapy has provided additional options for pts with R/R disease, but only when leukapheresis and manufacturing prove feasible (Jacobson 2020). Allogeneic (allo) CAR-T cells were designed specifically to address these unmet needs by using healthy donor T cells to produce a readily available product and remove the need for bridging chemotherapy. We are currently investigating the safety and efficacy of CTX110, an allo anti-CD19 CAR-T cell product modified by using CRISPR/Cas9-editing to disrupt the endogenous T-cell receptor (TCR) alpha constant (TRAC) locus in order to remove TCR expression and disrupt β_2-microglobulin, which eliminates major histocompatibility complex (MHC) class I expression. Disruption of the TCR should significantly reduce or eliminate risks of graft-versus-host disease and elimination of MHC class I expression may increase CAR-T cell persistence by mitigating CTX110 rejection. In addition, the anti-CD19 CAR transgene construct is precisely inserted into the TRAC locus. **Methods:** The Phase 1 CARBON trial (NCT04035434) is an open-label, multicenter, global study evaluating the safety and efficacy of CTX110 in pts ≥18 y with R/R DLBCL NOS, double- or triple-hit DLBCL, or transformed or grade 3b FL with ≥2 prior lines of therapy or who are ineligible for/refused prior auto hematopoietic stem cell transplant (HSCT). Pts who received prior auto CAR-T or allo HSCT are excluded. Pts will receive lymphodepleting chemotherapy with fludarabine 30mg/m^2 and cyclophosphamide 500mg/m^2 for 3 days, followed by CTX110 infusion. In part A, dose escalation will be performed using a 3+3 design. Upon completion of dose finding, the cohort will be expanded to further assess safety signals and efficacy including the primary efficacy endpoint of overall response rate. Key secondary efficacy endpoints include duration of response, progression-free survival, and overall survival. The trial is currently open and enrolling. Clinical trial information: NCT04035434. Research Sponsor: CRISPR Therapeutics.

TPS7571 **Poster Session**

Brentuximab vedotin in combination with lenalidomide and rituximab in subjects with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) (Trials in Progress). *First Author: Nancy L. Bartlett, Division of Oncology, Washington University School of Medicine, St. Louis, MO*

Background: The majority of patients (pts) with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) who relapse after HSCT, or who are not candidates for HSCT have poor outcomes and are in need of novel therapies. Brentuximab vedotin (BV) is a CD30-directed ADC and preclinical data provide a strong rationale for combining BV, lenalidomide, and rituximab in the treatment of R/R DLBCL. In addition, in a phase 1 trial in which 37 pts with R/R DLBCL were treated with BV + lenalidomide, the ORR was 56.7% (73.3% in CD30+ pts; manuscript in preparation). The median duration of remission was 13.2 months in pts with a CR or PR and 11.7 months in pts with CR, PR, or stable disease > 6 months. The PFS and median OS were 11.2 months and 14.3 months, respectively and results were similar in the CD30+ and CD30 < 1% groups. The clinical activity and manageable safety profiles of BV, lenalidomide, and rituximab as single agents, make the combination a viable option in multiply relapsed and heavily pretreated pts. **Methods:** This is a randomized, double-blind, placebo-controlled, active-comparator, multicenter phase 3 study designed to evaluate the efficacy of BV vs placebo, in combination with lenalidomide + rituximab, in subjects with R/R DLBCL (NCT04404283). Prior to randomization, there will be a safety and PK run-in period where 6 pts will receive BV, lenalidomide + rituximab, and safety and PK will be evaluated after the first cycle of treatment; 6/6 subjects have been enrolled. Key eligibility criteria include: pts aged ≥18 with R/R DLBCL with an eligible subtype; ≥2 prior lines of therapy and must be ineligible for, or have declined, stem cell transplant, and chimeric antigen receptor T-cell (CAR-T) therapy; ECOG 0 to 2; fluorodeoxyglucose-avid disease by PET and bidimensional measurable disease of at least 1.5 cm by CT. Patients (n = 400) will be randomized 1:1 to receive either BV or placebo in combination with lenalidomide + rituximab and will be stratified by CD30 expression (positive [≥1%] versus < 1%), prior allogeneic or autologous stem cell transplant therapy (received or not), prior CAR-T therapy (received or not), and cell of origin (GCB or non-GCB). The primary endpoints are PFS per BICR in the ITT and CD30+ populations. Key secondary endpoints are OS in the ITT and CD30+ populations, and ORR per BICR. Other secondary endpoints include CR rate, duration of response, and safety and tolerability of the combination. Disease response will be assessed by BICR and the investigator according to the Lugano Classification Revised Staging System. Radiographic disease evaluations, including contrast-enhanced CT scans and PET, will be assessed at baseline, then every 6 weeks from randomization until Week 48, then every 12 weeks. PET is not required after CR is achieved. The trial is currently enrolling and will be open in 16 countries. Clinical trial information: NCT04404283. Research Sponsor: Seagen Inc.

TPS7572 **Poster Session**

ESCALADE: A phase 3 study of acalabrutinib in combination with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) for patients ≤65y with untreated non-germinal center B-cell–like (non-GCB) diffuse large B-cell lymphoma (DLBCL). *First Author: Laurie Helen Sehn, British Columbia Cancer Centre for Lymphoid Cancer, Vancouver, BC, Canada*

Background: R-CHOP remains the standard of care for DLBCL. Although most patients (pts) can be cured, 3540% will experience relapsed/refractory disease, leading to poor outcomes in the majority of pts. Covalent irreversible Bruton tyrosine kinase inhibitors (BTKi) have shown higher responses in pts with non-GCB DLBCL than with GCB DLBCL. In untreated non-GCB DLBCL pts, the phase 3 PHOENIX study (Younes et al. *J Clin Oncol.* 2019;37:1285-95) showed that addition of the BTKi ibrutinib to R-CHOP (R-CHOP-I) did not improve outcomes in the intent-to-treat population. However, pts age < 60y treated with R-CHOP-I had significantly improved progression-free survival (PFS) and overall survival (OS) compared with those receiving R-CHOP alone. Acalabrutinib (A) is a second-generation BTKi with enhanced kinase selectivity and potential for better efficacy and tolerability than first-generation BTKis. There is a strong rationale for combining A with R-CHOP in pts with untreated DLBCL, and safety of A + R-CHOP has been shown in a phase 1b/2 study (Davies et al. ASH 2020). The aim of this study is to determine if the addition of A to R-CHOP leads to improved PFS in pts age ≤65y with untreated non-GCB DLBCL. **Methods:** ESCALADE (ACE-LY-312; NCT04529772) is a phase 3, randomized, global, double-blind study of A vs placebo in combination with R-CHOP for treatment of newly diagnosed non-GCB DLBCL. The study is recruiting adults ≥18y and ≤65y with previously untreated DLBCL stage IIIV disease with a Revised International Prognostic Index (R-IPI) score of 25. Prior to randomization, all pts will receive an initial R-CHOP cycle (cycle 1) as standard-of-care treatment to prevent delays in therapy initiation. Based on central Gene Expression Profile (GEP) testing performed after enrollment, pts with non-GCB DLBCL (activated B-cell like or unclassified) will be randomized into 2 arms to receive A 100 mg twice daily plus R-CHOP or placebo plus R-CHOP from cycle 2 to cycle 6 followed by 2 additional cycles of rituximab + A or placebo (cycles 7 and 8). All pts will receive primary prophylaxis with granulocyte colony-stimulating factors accompanying all R-CHOP cycles. The study aims to randomize 600 pts (~300 per arm). The primary objective is to evaluate whether the addition of A to R-CHOP will prolong PFS. Secondary endpoints include event-free survival, complete response rate, OS, pharmacokinetics, and safety. Key exclusion criteria are central nervous system involvement, primary mediastinal lymphoma, high-grade B-cell lymphoma, diagnosis or treatment of malignancy other than DLBCL, and history of indolent lymphoma. Approximately 250 sites globally will enroll pts. Enrollment began in Q3 of 2020. Clinical trial information: NCT04529772. Research Sponsor: Acerta Pharma, a member of the AstraZeneca Group.

TPS7573 **Poster Session**

Coastal: A phase 3 study of the PI3Kδ inhibitor zandelisib with rituximab (R) versus immunochemotherapy in patients with relapsed indolent non-Hodgkin's lymphoma (iNHL). *First Author: Wojciech Jurczak, National Research Institute of Oncology, Kraków, Poland*

Background: Patients (pts) with iNHL treated with front-line immunochemotherapy may benefit from an alternative, chemotherapy-free regimen at relapse. Zandelisib, a potent, selective, and structurally differentiated oral PI3Kδ inhibitor, achieved an 87% response rate, with median duration of response not reached in iNHL when given as a monotherapy or in combination with R. A low rate ($<$ 10%) of Grade $\geq$ 3 immune-mediated adverse events of special interest associated with PI3kδ inhibitors is observed in patients administered zandelisib on an intermittent schedule (IS) (JCO 2020 38:15_suppl, 8016). An open-label, phase 2 study (TIDAL, NCT03768505) of zandelisib as monotherapy is ongoing in pts with relapsed/refractory follicular lymphoma (FL) and marginal zone lymphoma (MZL). **Methods:** The COASTAL study is a randomized, open-label, controlled multicenter phase 3 trial to investigate the safety and efficacy of zandelisib in combination with R versus standard immunochemotherapy in pts with iNHL. Key eligibility criteria: adults with relapsed or refractory FL or MZL who received $\geq$1 prior lines of therapy which must have included an anti-CD20 antibody in combination with chemotherapy or lenalidomide (L); at least one bi-dimensionally measured lesion $>$ 1.5 cm; adequate bone marrow, renal and hepatic function; ECOG performance status score of 0 to 1. Key exclusion criteria: histologically confirmed diagnosis of FL grade 3b or transformed disease; administration of 2 prior immunochemotherapy regimens; prior PI3K inhibitor therapy; known lymphomatous involvement of the central nervous system. Subjects will be randomized 1:1 to receive R-zandelisib or immunochemotherapy (R-CHOP or R-B) and stratified by type and number of prior treatment regimens, histology, and duration of treatment-free interval after last therapy. Zandelisib will be given in a 28-day cycle comprising of daily dosing for 2 cycles followed by IS dosing on days 1-7 of each 28-day subsequent cycle for a duration of 2 years. Rituximab or immunochemotherapy will be given for a total of 6 cycles. Disease response will be assessed by an Independent Response Review Committee according to the modified Lugano Classification. Radiographic tumor assessment will be performed approximately every 12 weeks for the first 9 months, every 16 weeks for the next 12 months, and every 24 weeks thereafter. The primary efficacy endpoint is progression-free survival. The major secondary endpoints include ORR, complete response rate, overall survival, and safety. The trial will enroll approximately 534 pts in ~200 sites globally and will begin enrollment in mid-2021. Clinical trial information: NCT04745832. Research Sponsor: MEI Pharma, Inc.

TPS7574 **Poster Session**

Phase 3 randomized study of loncastuximab tesirine plus rituximab versus immunochemotherapy in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL): LOTIS-5. *First Author: Mehdi Hamadani, Division of Hematology and Oncology, Medical College of Wisconsin, Milwaukee, WI*

Background: Patients (pts) with DLBCL for whom frontline therapy is unsuccessful and who are ineligible for autologous stem cell transplantation have poor outcomes with salvage therapy. Single-agent loncastuximab tesirine (Lonca), an antibody-drug conjugate comprising a humanized anti-CD19 monoclonal antibody conjugated to a pyrrolobenzodiazepine dimer (PBD) toxin, showed antitumor activity and manageable toxicity in pts with R/R B-cell non-Hodgkin lymphoma in a Phase 1 trial (Hamadani et al. *Blood* 2020; blood.2020007512) and in pts with R/R DLBCL in a Phase 2 trial (Caimi et al. *Blood* 2020; 136(Suppl 1):35–37). Rituximab (R) is part of standard immunochemotherapy for DLBCL, both as frontline therapy and in subsequent treatments. LOTIS-5 aims to evaluate Lonca + R (Lonca-R) versus (vs) standard immunochemotherapy of R + gemcitabine + oxaliplatin (R-GemOx) in pts with R/R DLBCL. **Methods:** This is a Phase 3 randomized, open-label, 2-part, 2-arm, multicenter study (NCT04384484). A non-randomized safety run-in (Part 1) will compare the safety of Lonca-R with previous safety data for Lonca after the first 20 pts have completed Cycle 1. Part 2 will be started if no significant increase in toxicity occurs; ~330 pts will be randomized 1:1 to receive Lonca-R or R-GemOx. The primary objective of the study is to evaluate the efficacy of Lonca-R vs R-GemOx. The primary endpoint is progression-free survival by independent review. Secondary endpoints include overall survival; objective response rate; complete response rate; duration of response; frequency and severity of adverse events; changes from baseline in safety laboratory and clinical variables; concentration and pharmacokinetic parameters of Lonca (conjugated and total antibody, and unconjugated warhead); immunogenicity; and changes in patient-reported outcomes. Time-to-event endpoints will be assessed for the intent-to-treat population using a stratified log-rank test. The dosing regimen of Lonca-R in both parts of the study will be 150 μg/kg Lonca + 375 mg/m^2 R every 3 weeks (Q3W) for 2 cycles and then 75 μg/kg Lonca + 375 mg/m^2 R for 6 cycles. The dose regimen of R-GemOx in Part 2 will be 375 mg/m^2 R, 1000 mg/m^2 Gem, and 100 mg/m^2 Ox Q2W for 8 cycles. Key inclusion criteria include age $\geq$18 years; pathologic diagnosis of DLBCL (including pts with DLBCL transformed from indolent lymphoma) or high-grade B-cell lymphoma with *MYC* and *BCL2* and/or *BCL6* rearrangements; $\geq$1 line of prior systemic therapy; not a candidate for stem cell transplantation; and measurable disease per 2014 Lugano Classification. The study opened in September 2020 and enrollment is ongoing. The trial design was presented at 62nd American Society of Hematology Annual Meeting and Exposition, December 5–8, 2020. Research Funding: ADC Therapeutics SA. Clinical trial information: NCT04384484. Research Sponsor: ADC Therapeutics SA.

TPS7575 **Poster Session**

A phase III trial evaluating glofitamab in combination with gemcitabine plus oxaliplatin versus rituximab in combination with gemcitabine and oxaliplatin in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL). *First Author: Mark Hertzberg, Prince of Wales Hospital, Sydney, Australia*

Background: Prognosis is poor for patients with R/R DLBCL, particularly those who are ineligible for autologous stem cell transplant (ASCT) or who relapse after second-line therapy (Gisselbrecht C, et al. Br J Haematol 2018). While chimeric antigen receptor therapies have shown favorable response rates in R/R DLBCL, convenient off-the-shelf options are needed, especially for patients with rapidly progressing disease (Sermer D, et al. Blood Adv 2020). Glofitamab is a full-length, humanized, immunoglobulin G1 bispecific antibody with two regions that bind to CD20 (B cells) and one region that binds to CD3 (T cells). In an ongoing Phase I study in patients with R/R non-Hodgkin lymphoma, glofitamab monotherapy has induced high response rates with a manageable safety profile (NCT03075696; Hutchings M, et al. ASH 2020). Rituximab in combination with gemcitabine and oxaliplatin (R-GemOx) is widely used for patients with R/R DLBCL who are not eligible for ASCT (Mounier N, et al. Haematologica 2013). **Methods:** GO41944 (NCT04408638) is a Phase III, open-label, randomized trial designed to evaluate the safety and efficacy of glofitamab plus gemcitabine and oxaliplatin (glofit-GemOx) vs R-GemOx in patients with R/R DLBCL. Eligible patients must be aged $\geq$ 18 years, have histologically confirmed DLBCL (excluding transformed indolent disease, and high-grade B-cell lymphoma (BCL) with MYC and BCL2 and/or BCL6 rearrangements), and have received $\geq$ 1 prior systemic therapies; patients who have failed only one prior line of therapy must not be eligible for high-dose chemotherapy followed by ASCT. Prior treatment with GemOx, R-GemOx or a CD20xCD3 bispecific antibody is not permitted. Patients are randomized 2:1 to receive up to eight 21-day cycles of either glofit-GemOx (intravenous [IV], followed by up to four cycles of glofitamab monotherapy) or R-GemOx (IV). A single dose of obinutuzumab is administered seven days prior to the first glofitamab administration. Randomization is stratified by number of prior lines of therapy and outcome of last systemic therapy (relapsed vs refractory). The primary objective is overall survival from time of randomization. Secondary efficacy objectives include progression-free survival, complete and overall response rates, duration of response, and time to deterioration in physical functioning and fatigue, and in lymphoma symptoms. Safety objectives comprise rate of adverse events, change from baseline in targeted vital signs and clinical laboratory test results, and tolerability. Pharmacokinetic, immunogenicity and biomarker endpoints will also be explored. The study started on February 17, 2021; an estimated enrollment of 270 patients by the study completion date of March 2022 is anticipated. Clinical trial information: NCT04408638. Research Sponsor: Study GO41944 is sponsored by F. Hoffmann-La Roche Ltd/Genentech, Inc. Third-party medical writing assistance, under the direction of authors, was provided by Katie Buxton, BSc, of Ashfield MedComms, and funded by F. Hoffmann-La Roche Ltd/Genentech, Inc.

TPS7576 **Poster Session**

Randomized, double-blind, placebo-controlled phase 3 study of ibrutinib plus rituximab in patients with previously untreated marginal zone lymphoma (MZL). *First Author: Ariela Noy, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: First-line treatment options for patients with MZL include single-agent immunotherapy, chemotherapy, or chemoimmunotherapy. While chemoimmunotherapy has a higher toxicity profile than immunotherapy alone, it may lead to longer progression-free survival (PFS). Rituximab, an anti-CD20 antibody, is FDA approved for the first-line treatment of follicular lymphoma but not specifically for advanced MZL. Ibrutinib is a Bruton's tyrosine kinase inhibitor approved in the United States for patients with MZL who require systemic therapy and have received $\geq$1 prior anti-CD20-based therapy. The combination of ibrutinib and rituximab has proven effective and is well tolerated in other B-cell lymphomas; it may serve as an effective chemotherapy-free option for the treatment of previously untreated MZL. **Methods:** NCT04212013 is a multicenter, double-blind, placebo-controlled, randomized, phase 3 study designed to compare the efficacy of ibrutinib + rituximab vs placebo + rituximab in patients with previously untreated MZL. Adults ($\geq$18 y) with histologically documented MZL (splenic, nodal, and extranodal subtypes), no prior systemic treatment for MZL (prior splenectomy or other local surgical or radiation treatment allowed), measurable disease on CT scan, documented evidence of need for treatment, and Eastern Cooperative Oncology Group performance status $\leq$2 are eligible. Patients will be randomly assigned 1:1 to receive ibrutinib 560 mg once daily or placebo; all patients will also receive rituximab 375 mg/m^2 on days 1, 8, 15, and 22 of cycle 1. Subcutaneous dosing after dose 1 is allowed. Treatment with ibrutinib or placebo will continue for 30 mo or until disease progression, unacceptable toxicity, patient or investigator decision to withdraw, noncompliance, death, or study termination. Clinical assessments will occur every 4 weeks until week 13, at week 25, and then every 6 mo thereafter. Imaging assessments will be conducted at week 13, at week 25, and then every 6 mo thereafter. Response will be investigator assessed per the revised International Working Group for Non-Hodgkin Lymphoma (RECIL) criteria. At month 30, patients who have a complete response (CR) will discontinue treatment; patients who have a partial response (PR) or stable disease may continue treatment at investigator discretion. Safety will be assessed throughout the study and for 30 days after the last dose of study treatment. The primary endpoint is CR rate at month 30. Secondary endpoints include overall response rate (CR + PR), duration of response, PFS, overall survival, and safety. Enrollment has started and will continue until approximately 138 patients are enrolled. Clinical trial information: NCT04212013. Research Sponsor: Pharmacyclics LLC, an AbbVie Company.

8000 **Oral Abstract Session**

Upfront autologous stem cell transplantation (ASCT) versus carfilzomib-cyclophosphamide-dexamethasone (KCd) consolidation with K maintenance in transplant-eligible, newly diagnosed (NDTE) multiple myeloma (MM). *First Author: Kwee Yong, University College Hospital, London, United Kingdom*

Background: Upfront ASCT for NDTE MM remains under evaluation with high MRD rates following novel induction and consolidation (cons) strategies. Current phase 3 trials support ASCT, however these employ lenalidomide maintenance which predominantly benefits standard risk (SR) patients (pts). The CARDAMON trial investigated the role of ASCT using K based induction and maintenance. **Methods:** NDTE pts received 4 x KCd induction (K 20/56 mg/m^2 biweekly, C 500 mg D 1,8,15, d 40mg weekly) before 1:1 randomisation to ASCT or 4 x KCd cons. All received 18 months K maintenance (56mg/m^2 D1,8,15). Flow cytometric MRD (10^{-5}) was assessed post induction, pre-maintenance and at 6 months maintenance. Primary endpoints were ≥VGPR post induction and 2-year PFS from randomisation. 210 randomised pts were needed to exclude a 10% non-inferiority margin with 15% 1-sided alpha, 80% power. **Results:** 281 pts were registered, median age 59y (33–74), 24% high risk [t(4;14), t(14;16), t(14;20) or del(17p)]. Post induction, ≥VGPR rate was 58.5%, ORR was 87% with similar responses for high risk vs SR. 52 pts did not proceed to PBSCH (6 MR, 16 PD, 19 toxicity, 4 deaths: 3 infection, 1 cardiac event, 7 other). 109 were randomised to ASCT, 109 to KCd cons. ≥VGPR rate was 78.5% after cons and 80.0% after ASCT (p = 0.8). Median KCd cons dose was 55.5 mg/m^2, 99 (90.8%) pts completed 4 cycles, 104 (95.4%) pts received ASCT. After 2.6 years follow-up, median PFS was not reached for ASCT vs 3.8 years for cons (HR: 0.82 (70% CI 0.65, 1.05, p = 0.4). Observed 2-year PFS for ASCT was 75.5% vs 70.7% for cons; calculated difference in 2-year PFS rate (cons vs ASCT) was -4.5% (70% CI -9.2%, +1.1%, non-inferior). High risk pts had inferior outcomes to SR overall regardless of randomisation (2-year PFS ASCT: 52% vs 82% (HR 4.09); cons 48% vs 77% (HR 2.83)). 2 year PFS did not differ according to randomisation: SR 82% (ASCT) vs 77% (cons) HR: 1.29 (0.71-2.35); high risk: 52% (ASCT) vs 48% (cons) HR: 1.06 (0.50-2.23). MRD negativity post induction was 24.3% and similar by genetic risk. MRD negative rates were higher post ASCT (53.1%) than cons (35.8%) (p = 0.02) independent of genetics: SR 49% (ASCT) vs 36% (cons); high risk: 57% (ASCT) vs 32% (cons). G3+ adverse events to induction were infections (18.7%), hypertension (11.2%), anaemia (10.4%), cardiac disorders (3.6%), vomiting (2.2%), fatigue (2.2%), diarrhoea (1.8%). **Conclusions:** In NDMM receiving KCd induction and K maintenance, KCd cons was non-inferior to ASCT. High risk pts had inferior outcomes, that were not influenced by ASCT or cons randomisation. Clinical trial information: NCT02315716. Research Sponsor: Amgen.

	ASCT			Consolidation		
Disease response (%)	All (107)	High risk (25)	Std Risk (76)	All (107)	High Risk (25)	Std Risk (75)
CR/sCR	14.3	16	13.1	24.3	24	24
VGPR	65.7	60	67.1	54.2	44	57.3
PR	16.2	20	15.8	11.2	8	12
No response	1.0	0	1.3	1.8	0	2.6
Withdrawn for toxicity or PD	2.9	4	2.6	8.4	24	4

8001 **Oral Abstract Session**

Depth of response and minimal residual disease status in ultra high-risk multiple myeloma and plasma cell leukemia treated with daratumumab, bortezomib, lenalidomide, cyclophosphamide and dexamethasone (Dara-CVRd): Results of the UK optimum/MUKnine trial. *First Author: Martin F. Kaiser, The Institute for Cancer Research, London, United Kingdom*

Background: Patients with ultra high-risk (UHiR) newly diagnosed multiple myeloma (NDMM) and patients with plasma cell leukemia (PCL) continue to have dismal outcomes and are underrepresented in clinical trials. Recently, improved responses with anti-CD38 monoclonal antibody combination therapy have been reported for NDMM patients. We report here outcomes for NDMM UHiR and PCL patients treated in the OPTIMUM/MUKnine (NCT03188172) trial with daratumumab, cyclophosphamide, bortezomib, lenalidomide, dexamethasone (Dara-CVRd) induction, augmented high-dose melphalan (HDMEL) and ASCT. With final analysis follow-up surpassed in Feb 2021, we report here early protocol defined endpoints from induction to day 100 post ASCT. **Methods:** Between Sep 2017 and Jul 2019, 107 patients with UHiR NDMM by central trial genetic (≥2 high risk lesions: t(4;14), t(14;16), t(14;20), gain(1q), del(1p), del(17p)) or gene expression SKY92 (SkylineDx) profiling, or with PCL (circulating plasmablasts > 20%) were included in OPTIMUM across 39 UK hospitals. Patients received up to 6 cycles of Dara-CVRd induction, HDMEL and ASCT augmented with bortezomib, followed by Dara-VR(d) consolidation for 18 cycles and Dara-R maintenance. Primary trial endpoints are minimal residual disease (MRD) status post ASCT and progression-free survival. Secondary endpoints include response, safety and quality of life. Data is complete but subject to further data cleaning prior to conference. **Results:** Median follow-up for the 107 patients in the safety population was 22.2 months (95% CI: 20.6 – 23.9). Two patients died during induction due to infection. Bone marrow aspirates suitable for MRD assessment by flow cytometry (10^{-5} sensitivity) were available for 81% of patients at end of induction and 78% at D100 post ASCT. Responses in the intention to treat population at end of induction were 94% ORR with 22% CR, 58% VGPR, 15% PR, 1% PD, 5% timepoint not reached (TNR; withdrew, became ineligible or died) and at D100 post ASCT 83% ORR with 47% CR, 32% VGPR, 5% PR, 7% PD, 10% TNR. MRD status was 41% MRDneg, 40% MRDpos and 19% not evaluable post induction and 64% MRDneg, 14% MRDpos and 22% not evaluable at D100 post ASCT. Responses at D100 post ASCT were lower in PCL with 22% CR, 22% VGPR, 22% PR, 22% PD, 12% TNR. Most frequent grade 3/4 AEs during induction were neutropenia (21%), thrombocytopenia (12%) and infection (12%). Grade 3 neuropathy rate was 3.7%. **Conclusions:** This is to our knowledge the first report on a trial for UHiR NDMM and PCL investigating Dara-CVRd induction and augmented ASCT. Response rates were high in this difficult-to-treat patient population, with toxicity comparable to other induction regimens. However, some early progressions highlight the need for innovative approaches to UHiR NDMM. Clinical trial information: NCT03188172. Research Sponsor: Myeloma UK and research support by Celgene and Janssen.

8002 **Oral Abstract Session**

Carfilzomib-based induction/consolidation with or without autologous transplant (ASCT) followed by lenalidomide (R) or carfilzomib-lenalidomide (KR) maintenance: Efficacy in high-risk patients. *First Author: Francesca Gay, European Myeloma Network, Gimema, Italy*

Background: Cytogenetic abnormalities (CA) are one of the most powerful prognostic factors in multiple myeloma (MM). In the FORTE study, carfilzomib-lenalidomide-dexamethasone induction/consolidation with ASCT (KRd_ASCT) significantly improved progression-free survival (PFS) vs KRd without ASCT (KRd12, HR 0.64) or carfilzomib-cyclophosphamide-dexamethasone (KCd) plus ASCT (KCd_ASCT, HR 0.53). KR maintenance significantly improved PFS vs R (HR 0.63). **Methods:** MM patients (pts) were randomized to KRd_ASCT vs KCd_ASCT vs KRd12 and, thereafter, to KR vs R maintenance. Subgroup analyses according to FISH evaluated the impact of each single high-risk (HiR) CA [del17p, t(4;14), t(14;16), del1p and 1q gain (3 copies) or amp1q (≥4 copies)] and that of combined CA, defining HiR by the presence of ≥1 HiR CA and double-hit (DH) by the presence of ≥2 HiR CA. Pts negative for all the HiR CA were considered at standard risk (SR). The primary objective was the impact of treatment on PFS according to pt risk. **Results:** 396 out of 474 enrolled pts were included in the analysis with complete FISH data: 243 HiR, 105 DH and 153 SR. Among HiR pts, 60 had del17p, 65 t(4;14), 20 t(14;16), 44 del1p, 126 1q gain and 49 amp1q. SR pts benefited from intensification with KRd_ASCT vs KRd12 (HR 0.47, p = 0.05) and KCd_ASCT (HR 0.38, p = 0.01), with a 4-year PFS of 80%, 67% and 57%, respectively. In HiR pts, KRd_ASCT improved PFS vs KRd12 (HR 0.6, p = 0.04) and KCd_ASCT (HR 0.57, p = 0.01), with a 4-year PFS of 62%, 45% and 45%, respectively. The advantage with KRd_ASCT vs KRd12 (HR 0.53, p = 0.07) and KCd_ASCT (HR 0.49; p = 0.03) was also observed in DH pts (4-year PFS 55%, 31% and 33%, respectively). Analyses by single CA were limited by the small number of pts in each subgroup, but a trend towards a PFS benefit from KRd_ASCT vs KRd12 was seen in pts with del17p (HR 0.61, p = 0.3), t(4;14) (HR 0.59, p = 0.2) and 1q gain (HR 0.45, p = 0.02). In pts with del1p, KRd_ASCT (HR 0.24, p = 0.06) and KRd12 (HR 0.33, p = 0.09) showed superiority over KCd_ASCT, while amp1q pts had the worst outcome regardless of treatment (KRd_ASCT vs KCd_ASCT, HR 1.16, p = 0.73; KRd12 vs KCd_ASCT, HR 1.34, p = 0.45). KR improved PFS vs R in SR (3-year PFS 90% vs 73%, HR 0.42, p = 0.06), HiR (3-year PFS 69% vs 56%, HR 0.6, p = 0.04) and DH pts (3-year PFS 67% vs 42%, HR 0.53, p = 0.1). Despite the small subgroups, a beneficial trend with KR vs R was observed in pts with del17p (HR 0.59, p = 0.37), t(4;14) (HR 0.59, p = 0.3), 1q gain (HR 0.54, p = 0.07) and del1p (HR 0.23, p = 0.08), while amp1q pts showed the worst outcome and no benefit from KR vs R (HR 0.83, p = 0.7). **Conclusions:** KRd_ASCT and KR maintenance are highly effective in SR and also in HiR and DH pts, with impressive 4-year PFS from diagnosis (KRd_ASCT: HiR 62%, DH 55%) and 3-year PFS from maintenance (KR: HiR 69%, DH 67%), thus supporting their use in HiR pts, who represent an unmet medical need. Clinical trial information: NCT02203643. Research Sponsor: Amgen; Bristol-Myers Squibb (Celgene).

8003 **Oral Abstract Session**

Subcutaneous daratumumab + bortezomib, cyclophosphamide, and dexamethasone (VCd) in patients with newly diagnosed light chain (AL) amyloidosis: Updated results from the phase 3 ANDROMEDA study. *First Author: Efstathios Kastritis, Department of Clinical Therapeutics, National and Kapodistrian University of Athens, Athens, Greece*

Background: Systemic AL amyloidosis is a plasma cell disease characterized by the deposition of insoluble amyloid fibrils causing organ dysfunction and death. Primary results from the ANDROMEDA study showed that addition of subcutaneous (SC) daratumumab (DARA) to the standard of care combination of bortezomib, cyclophosphamide, and dexamethasone (VCd) was superior to VCd alone, with higher rates of hematologic complete response (CR) and an acceptable safety profile. DARA-VCd was approved for newly diagnosed AL amyloidosis in January 2021. Here we present an update of the primary ANDROMEDA study results with longer follow-up. **Methods:** ANDROMEDA is a randomized, open-label, active-controlled phase 3 study. Adult patients (pts) with newly diagnosed AL amyloidosis were randomized 1:1 to DARA-VCd or VCd and were treated for 6 28-day Cycles (Cyc). Bortezomib (1.3 mg/m^2), cyclophosphamide (300 mg/m^2 maximum weekly dose 500 mg), and dexamethasone (40 mg) were given weekly. DARA SC was given weekly (Cyc 1–2) and every 2 weeks (wk) (Cyc 3–6). After Cyc 6, pts in the DARA-VCd group received DARA SC alone every 4 wk for up to 24 Cyc from first dose. Disease status was evaluated every 4 wk in Cyc 1–6 and every 8 wk after Cyc 7. The primary endpoint was overall hematologic CR rate in the intent-to-treat population. Secondary endpoints were major organ deterioration progression-free survival (PFS), organ response rate, time to hematologic response, survival, and safety. **Results:** Of 388 randomized pts, 195 were randomized to DARA-VCd and 193 to VCd. As of November 2020, the median treatment duration was 18.5 months (mo) for DARA-VCd and 5.3 mo for VCd; 78 pts (40%) in the DARA-VCd group were still on treatment. The overall hematologic CR rate continued to be higher with DARA-VCd than VCd (59% vs 19%; odds ratio [OR] 5.9; 95% CI 3.7–9.4; P< 0.0001). More pts achieved a very good partial response or better (≥VGPR) with DARA-VCd than VCd (79% vs 50%; OR 3.7; 95% CI 2.4–5.9; P< 0.0001). Among responders, median time from randomization to ≥VGPR was shorter for DARA-VCd than VCd (0.56 vs 0.82 mo). Cardiac response rates were higher with DARA-VCd than VCd at 6 mo (42% vs 22%) and at 12 mo (57% vs 28%); renal response rates were 54% vs 27% at 6 mo and 57% vs 27% at 12 mo. A total of 71 deaths occurred (DARA-VCd, n = 31; VCd, n = 40). From Cyc 7 onward in the DARA-VCd group, no grade 3/4 treatment-emergent adverse events occurred in ≥5% of pts. There were no systemic administration-related reactions with DARA-VCd after Cyc 6. Analysis of major organ deterioration PFS will be updated after ~200 events have occurred. **Conclusions:** Updated results from the ANDROMEDA study reinforce the clinical superiority of DARA-VCd over VCd in pts with newly diagnosed AL amyloidosis. Based on its recent approval, DARA-VCd represents a new standard of care in AL amyloidosis. Clinical trial information: NCT03201965. Research Sponsor: Janssen Research & Development, LLC.

8004 **Oral Abstract Session**

Daratumumab (DARA) maintenance or observation (OBS) after treatment with bortezomib, thalidomide and dexamethasone (VTd) with or without DARA and autologous stem cell transplant (ASCT) in patients (pts) with newly diagnosed multiple myeloma (NDMM): CASSIOPEIA Part 2. *First Author: Philippe Moreau, Hematology, University Hospital Hotel-Dieu, Nantes, France*

Background: D-VTd plus ASCT was approved for transplant-eligible (TE) NDMM based on part 1 of CASSIOPEIA. We report a prespecified interim analysis of CASSIOPEIA part 2: DARA maintenance vs OBS in pts with ≥partial response (PR) in part 1, regardless of induction/consolidation (ind/cons) treatment. **Methods:** CASSIOPEIA is a 2-part, randomized, open-label, phase 3 study in TE NDMM. Pts received 4 cycles ind and 2 cycles cons with D-VTd or VTd. 886 pts who achieved ≥PR were rerandomized to DARA 16 mg/kg IV Q8W for up to 2 yr (n = 442) or OBS (n = 444) until progressive disease per IMWG. Pts were stratified by ind (D-VTd vs VTd) and depth of response (minimum residual disease [MRD] status and post cons response ≥PR). Primary endpoint was progression-free survival (PFS) after second randomization. This interim analysis assessed efficacy and safety after 281 PFS events. A preplanned hierarchical procedure tested key secondary endpoints: time to progression (TTP), ≥complete response (CR), MRD negativity rates by NGS and overall survival (OS). **Results:** At median follow-up of 35.4 mo, median PFS was not reached (NR) with DARA and 46.7 mo with OBS (HR 0.53; 95% CI 0.42–0.68; P <0.0001). PFS advantage for DARA was consistent across most subgroups. However, a prespecified analysis showed significant interaction with ind/cons treatment arm (P< 0.0001). PFS HR for DARA vs OBS was 0.32 (95% CI 0.23–0.46) in the VTd arm and 1.02 (0.71–1.47) in the D-VTd arm. Median TTP was NR for DARA vs 46.7 mo for OBS (HR 0.49; 95% CI 0.38–0.62; P <0.0001). More pts in the DARA vs OBS arm achieved ≥CR (72.9% vs 60.8%; OR 2.17; 95% CI 1.54–3.07; P <0.0001). MRD negativity (in ≥CR pts at 10^{-5}) was 58.6% with DARA vs 47.1% with OBS (OR 1.80; 95% CI 1.33–2.43; P= 0.0001). Median OS was NR in either arm. Most common (≥2.5%) grade 3/4 adverse events (AEs) with DARA vs OBS were pneumonia (2.5% vs 1.4%), lymphopenia (3.6% vs 1.8%), and hypertension (3.0% vs 1.6%). Serious AEs occurred in 22.7% (DARA) vs 18.9% (OBS) of pts; the most common (≥2.5%) was pneumonia (2.5% vs 1.6%). 13 (3.0%) pts discontinued DARA due to an AE. The rate of infusion-related reactions was 54.5% (DARA-naïve pts) and 2.2% (prior DARA pts); 90% were grade 1/2.Second primary malignancies occurred in 5.5% (DARA) vs 2.7% (OBS) of pts. **Conclusions:** CASSIOPEIA part 2 demonstrated a clinical benefit of DARA maintenance in TE NDMM pts, with significantly longer PFS for DARA vs OBS. With current follow-up, maintenance PFS benefit appeared only in pts treated with VTd as ind/cons. Pts who received D-VTd ind/cons with or without DARA maintenance achieved similar PFS; longer follow-up is needed for PFS2 and OS. DARA significantly increased deeper response and MRD negativity rates vs OBS, and was well tolerated with no new safety signals. Clinical trial information: NCT02541383. Research Sponsor: Janssen Research & Development, LLC.

8005 **Oral Abstract Session**

Ciltacabtagene autoleucel, a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor T-cell (CAR-T) therapy, in relapsed/refractory multiple myeloma (R/R MM): Updated results from CARTITUDE-1. *First Author: Saad Zafar Usmani, Levine Cancer Institute/Atrium Health, Charlotte, NC*

Background: CARTITUDE-1 (NCT03548207) is a phase 1b/2 study evaluating ciltacabtagene autoleucel (cilta-cel; JNJ-68284528), a CAR T-cell therapy with two BCMA–targeting single-domain antibodies, in patients (pts) with R/R MM. Here, we report updated results in pts with a longer duration (median 12.4 months) of follow-up. **Methods:** Eligible pts had MM and received ≥3 prior regimens or were double refractory to a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), and had received a PI, IMiD, and anti-CD38 antibody. After apheresis, bridging therapy was permitted. Pts received a single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg; range $0.5\text{-}1.0\times10^6$) 5–7 days (d) after lymphodepletion (300 mg/m^2 cyclophosphamide, 30 mg/m^2 fludarabine daily for 3 d). The primary objectives were to characterize cilta-cel safety, confirm the recommended phase 2 dose (RP2D; phase 1b), and evaluate efficacy (phase 2). Cytokine release syndrome (CRS) was graded by Lee *et al* (Blood 2014) and neurotoxicity by CTCAE, v5.0 (in phase 1b). CRS and ICANS were graded by ASTCT criteria (in phase 2). Here, Lee *et al* and CTCAE v5.0 were mapped to ASTCT for CRS and ICANS, respectively. **Results:** As of Sept 1, 2020, 97 pts with a median of 6 prior lines received cilta-cel. Overall response rate per independent review committee (primary endpoint) was 97% (95% CI, 91–99), with 67% achieving stringent complete response (sCR). Median time to first response was 1 month (range, 1–9), and median time to CR or better was 2 months (range, 1–15). Responses deepened over time, and median duration of response was not reached. Of 57 pts evaluable for minimal residual disease (MRD) assessment, 93% were MRD-negative at 10^{-5}. The 12-month progression-free survival (PFS) and overall survival rates (95% CI) were 77% (66–84) and 89% (80–94), respectively; median PFS was not reached. Grade 3/4 hematologic AEs ≥20% included neutropenia (95%), anemia (68%), leukopenia (61%), thrombocytopenia (60%), and lymphopenia (50%). CRS occurred in 95% of pts (4% grade 3/4), with median time to onset of 7 d (range, 1–12), and median duration of 4 d (range, 1–14, excluding 1 pt with 97-d duration). CRS resolved in all but one with grade 5 CRS/haemophagocytic lymphohistiocytosis. CAR T-cell neurotoxicity occurred in 21% of pts (grade ≥3, 10%). Fourteen deaths occurred during the study after cilta-cel infusion: none within the first 30 days, 2 within 100 days; and 12 more than 100 days post infusion, of which 5 were due to disease progression, and 4 due to treatment-related AEs. **Conclusions:** A single infusion of cilta-cel yielded early, deep, and durable responses in heavily pretreated pts with MM, with a manageable safety profile at the RP2D. Cilta-cel is under further investigation in other MM populations in earlier lines of therapy and in outpatient settings. Clinical trial information: NCT03548207. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8006 **Oral Abstract Session**

Efficacy and safety of elranatamab (PF-06863135), a B-cell maturation antigen (BCMA)-CD3 bispecific antibody, in patients with relapsed or refractory multiple myeloma (MM). *First Author: Nizar J. Bahlis, Arnie Charbonneau Cancer Institute, University of Calgary, Calgary, AB, Canada*

Background: Elranatamab (PF-06863135) is a humanized bispecific monoclonal antibody (IgG2a) that targets BCMA, a member of the tumor necrosis factor receptor superfamily expressed in MM, and CD3 on T cells. We reported results for intravenous (IV) dosing (Raje et al. Blood. 2019;134(S1):1869) and now update for subcutaneous (SC) dosing from the ongoing Phase 1 study (MagnetisMM-1). **Methods:** Patients (pts) received elranatamab at 80, 130, 215, 360, 600, and 1000μg/kg SC weekly. A modified toxicity probability interval method was used for escalation, with monitoring for dose-limiting toxicity (DLT) to end of the first cycle. Treatment-emergent adverse events (TEAEs) were graded by Common Terminology Criteria for Adverse Events (v4.03), and cytokine release syndrome (CRS) by American Society for Transplantation and Cellular Therapy criteria (Lee et al. Biol Blood Marrow Transplant. 2019;25:625). Response was assessed by International Myeloma Working Group criteria. Pharmacokinetics, cytokine profiling, and T cell immunophenotyping were performed. **Results:** 30 pts had received elranatamab as of 4-Aug-2020 at 80 (n = 6), 130 (n = 4), 215 (n = 4), 360 (n = 4), 600 (n = 6), or 1000 (n = 6) μg/kg SC weekly. Pts had a median of 8 prior treatments; 87% had triple refractory disease, 97% had prior anti-CD38 therapy, and 23% had prior BCMA-directed antibody drug conjugate or chimeric antigen receptor T cell therapy. The most common all causality TEAEs included lymphopenia (n = 24, 80%; 20% G3, 60% G4), CRS (n = 22, 73%; none > G2), anemia (n = 17, 57%; 43% G3, 3% G4), injection site reaction (n = 16, 53%; none > G2), thrombocytopenia (n = 16, 53%; 23% G3, 17% G4), and neutropenia (n = 12, 40%; 17% G3, 17% G4). Both CRS and immune effector cell-associated neurotoxicity syndrome (n = 6, 20%) were limited to ≤G2 with median durations of 2 and 1.5 days, respectively. No DLT was observed. Exposure increased with dose, and T_{max} ranged from 3–7 days. Cytokine increases occurred with the first dose, and increased T-cell proliferation was observed in peripheral blood. The overall response rate (ORR) for doses ≥215μg/kg was 75% (n = 15/20) including partial response (PR; n = 6), very good PR (VGPR; n = 3), complete response (CR; n = 1), and stringent CR (sCR; n = 5). Median time to response was 22 days, and 3 of 4 pts (75%) with prior BCMA-directed therapy achieved response (VGPR, n = 2 and sCR, n = 1). Updated data, including duration of response, will be presented. **Conclusions:** Elranatamab demonstrated a manageable safety profile, and SC doses ≥215μg/kg achieved ORR of 75% with CR/sCR rate of 30%. These results demonstrate the safety and efficacy of SC elranatamab in this relapsed/refractory population and support ongoing development of elranatamab for pts with MM, both as monotherapy and in combination with standard or novel therapies. Clinical trial information: NCT03269136. Research Sponsor: Pfizer.

8007 **Oral Abstract Session**

Updated phase 1 results of teclistamab, a B-cell maturation antigen (BCMA) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM). *First Author: Amrita Y. Krishnan, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: BCMA-targeted immunotherapies offer considerable promise for relapsed/refractory MM. Teclistamab (JNJ-64007957) is a BCMA × CD3 bispecific IgG4 antibody that redirects CD3+ T cells to BCMA-expressing MM cells. We present updated results of patients (pts) treated at the recommended phase 2 dose (RP2D) in the first-in-human phase 1 study of teclistamab. **Methods:** Eligible pts had MM and were relapsed, refractory or intolerant to established therapies. Primary objectives were to identify the RP2D (part 1) and characterize safety and tolerability of teclistamab at the RP2D (part 2)**.** Teclistamab was given intravenously (IV; range 0.3–19.2 μg/kg [biweekly]; range 19.2–720 μg/kg [weekly]) or subcutaneously (SC; range 80.0–3000 μg/kg weekly) in different cohorts, with step-up dosing used for ≥38.4 μg/kg doses. Adverse events (AEs) were graded by CTCAE v4.03 (cytokine release syndrome [CRS] by Lee et al 2014). Response was assessed per IMWG criteria. **Results:** As of Feb 4, 2021, 156 pts received teclistamab (IV n = 84; SC n = 72). The RP2D, identified as weekly SC 1500 μg/kg teclistamab with 60.0 and 300 μg/kg step-up doses, was given to 40 pts (median follow-up 4.3 mo [range 1.1–10.4+]). Pts dosed at the RP2D (median age, 62.5 y [range, 39–84]; 65% male) had received a median of 5 prior lines of therapy (range 2–11; 100% triple-class exposed; 65% penta-drug exposed; 83% triple-class refractory; 35% penta-drug refractory; 85% refractory to their last line of therapy). There were no dose-limiting toxicities at the RP2D in part 1. The most common AEs at the RP2D were CRS (70%; grade 3/4 0) and neutropenia (60%; grade 3/4 40%); grade 1 neurotoxicity was reported in 1 (3%) pt. Median time to CRS onset was later with SC vs IV dosing (day after SC injection vs day of IV infusion). The overall response rate in response-evaluable pts treated at the RP2D (n = 40) was 65%; 58% achieved a very good partial response or better and 30% achieved a complete response (CR) or better; median time to first confirmed response was 1.0 mo (range 0.2–3.1). At the RP2D, median duration of response was not reached; 23 of 26 responders (88%), after median follow-up of 5.3 mo (range 1.2–10.4+), were alive and continuing on treatment with responses deepening over time. Of 14 evaluable pts across all cohorts, 9 with CR were minimal residual disease–negative at 10^{-6}. At the RP2D, teclistamab exposure was sustained across the dosing interval and exceeded target levels, and consistent T cell activation was observed. **Conclusions:** Teclistamab at the RP2D (weekly 1500 μg/kg SC) was well-tolerated and showed encouraging efficacy with durable, deepening responses, supporting further investigation as monotherapy and in combination with other agents. With the extended exposure profile at the RP2D and delayed and low-grade CRS observed with SC administration, alternative SC dosing strategies are being explored. Clinical trial information: NCT03145181. Research Sponsor: Janssen Research & Development, LLC.

8008 **Oral Abstract Session**

Updated results of a phase 1, first-in-human study of talquetamab, a G protein-coupled receptor family C group 5 member D (GPRC5D) × CD3 bispecific antibody, in relapsed/refractory multiple myeloma (MM).

First Author: Jesus G. Berdeja, Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN

Background: New immunotherapy targets in MM are needed as patients (pts) continue to relapse. The orphan receptor GPRC5D is expressed on malignant plasma cells in MM. Talquetamab (JNJ-64407564) is a bispecific IgG4 antibody that redirects T cell killing to MM cells by binding to the novel target, GPRC5D, and CD3. We present updated results of talquetamab at the recommended phase 2 dose (RP2D) from a phase 1 trial in relapsed/refractory MM. **Methods:** Eligible pts with MM who had relapsed or refractory disease or were intolerant to standard therapies received talquetamab intravenously (IV; range 0.5–180 μg/kg) or subcutaneously (SC; range 5.0–800 μg/kg) weekly or biweekly. Primary objectives were identification of the RP2D (part 1) and talquetamab safety and tolerability at the RP2D (part 2). Adverse events (AEs) were graded by CTCAE v4.03 (cytokine release syndrome [CRS] per Lee 2014). Response was assessed per IMWG criteria. **Results:** As of Feb 8, 2021, 174 pts received talquetamab, 102 by IV and 72 by SC; in parts 1 and 2, 28 pts were treated at the RP2D, identified as weekly SC 405 μg/kg, with 10.0 and 60.0 μg/kg step-up doses. Pts treated at the RP2D had a median age of 61.5 y (range 46–80) and a median of 5.5 prior lines of therapy (range 2–14; 100%/79% triple-class/penta-drug exposed; 71%/18% triple-class/penta-drug refractory; 86% refractory to last line of therapy; 21% with prior B-cell maturation antigen–directed therapy). No dose-limiting toxicities occurred at the RP2D in part 1. Most common AEs at the RP2D were CRS (79%; grade 3 4%; median time to onset: day after SC injection), neutropenia (64%; grade 3/4 54%), anemia (57%; grade 3/4 29%) and dysgeusia (57%; all grade 1/2); infections were reported in 32% of pts (grade 3/4 4%) and neurotoxicity in 7% (grade 3/4 0). In all, 75% of pts dosed at the RP2D had skin-related AEs (grade 3/4 0), including 18% with nail disorders. The overall response rate at the RP2D in response-evaluable pts (n = 24) was 63%, with 50% reaching very good partial response or better; 9/17 (53%) evaluable triple-class refractory pts and 3/3 (100%) penta-drug refractory pts had a response. Median time to first confirmed response at the RP2D was 1.0 mo (range 0.2–3.8); responses were durable and deepened over time (median follow-up 6.2 mo [range 2.7–9.7+] for responders at the RP2D). At the RP2D, exposure was maintained over the maximum EC_{90} target level from an ex vivo cytotoxicity assay, and consistent T cell activation was seen. **Conclusions:** At the RP2D of weekly 405 μg/kg SC, talquetamab showed a high clinical response rate and was well-tolerated in pts with relapsed/refractory MM; based on pharmacokinetic data, other SC dosing strategies are being explored. The promising efficacy, safety profile and convenience of SC dosing support monotherapy development and combination approaches with this novel agent. Clinical trial information: NCT03399799. Research Sponsor: Janssen Research & Developent, LLC.

8009 **Poster Discussion Session**

MASS-FIX versus standard methods to predict for PFS and OS among multiple myeloma patients participating on the STAMINA trial.

First Author: Angela Dispenzieri, Division of Hematology, Mayo Clinic, Rochester, MN

Background: Measuring response among patients with multiple myeloma is essential for the care of patients. Deeper responses have been associated with better progression free survival (PFS) and overall survival (OS). Serum (SIFE) and urine immunofixation are the currently used markers for biochemical documentation of CR after which marrow is tested for plasma cell clearance. Next generation flow cytometry and sequencing are used to document the presence of minimal residual disease (MRD). Mass spectrometry of blood by MALDI (Mass-Fix) is a new simple, inexpensive, sensitive, and specific means of detecting monoclonal immunoglobulins. To better test the hypothesis that Mass-Fix is superior to existing methodologies to predict for survival outcomes—especially SIFE– samples from the STAMINA trial (NCT01109004), a trial comparing 3 transplant approaches among patients who have already received induction, were employed. **Methods:** Five-hundred and seventy-five patients were included. Samples from enrollment post-induction (post-I) and 1-year post enrollment (1YR) were tested when available. Four response parameters were assessed univariately: Mass-Fix, SIFE, complete response, and MRD by next generation flow cytometry. Mass spectrometry spectra were evaluated in a blinded fashion. Complete response was according to the 2006 International Myeloma Working Group criteria. Multivariate Cox proportional hazard models using stepwise regression were developed to explore the independent effect of the different response parameters on PFS and OS and interactions with other risk factors. **Results:** Of the 4 response measures, only MRD and Mass-Fix predicted for PFS and OS at multiple testing points on multivariate analyses (Table). Of the 4 post-I measurements, only MRD predicted for PFS; however, Mass-Fix was the only post-I measurement to predict for OS. Of all the 1-year measures, both 1YR Mass-Fix and 1YR MRD positivity predicted for inferior PFS and OS. In models including MRD and Mass-Fix, SIFE and CR were not prognostic for PFS or OS. **Conclusions:** Mass-Fix is a powerful means to track monoclonal proteins. The full utility of Mass-Fix was not exploited given the absence of a diagnostic sample and the fact that only serum (and not urine) was tested. Despite these limitations, it performed well at pre-induction and at 1 year. Mass-Fix provides a convenient and non-invasive means of predicting for myeloma outcomes. Clinical trial information: NCT01109004. Research Sponsor: This manuscript was prepared using BMT CTN 0702 Research Materials obtained from the NHLBI. This project was also supported by Grant Number P30 CA015083 and CA186781 from the National Cancer Institute and by the Predolin Foundation. Support for the clinic.

Multivariate PFS and OS.

Post-induction sample	PFS RR (95%CI)	P	OS RR (95%CI)	P
MRD positive	1.50 (1.07, 2.08)	0.017	-	-
Mass-Fix positive	-	NS	1.64 (1.05, 2.57)	0.03
<CR	-	NS	-	-
SIFE positive	-	NS	-	-
1-year sample				
MRD positive	3.01 (1.93, 4.70)	<0.0001	2.77 (1.50, 5.12)	0.0012
Mass-Fix positive	1.62 (1.11, 2.35)	0.012	1.93 (1.04, 3.56)	0.036
<CR	-	NS	NS	NS
SIFE positive	-	NS	NS	NS

RR, risk ratio; NS, not significant.

8010 **Poster Discussion Session**

Analysis of minimal residual disease in bone marrow by NGF and in peripheral blood by mass spectrometry in newly diagnosed multiple myeloma patients enrolled in the GEM2012MENOS65 clinical trial.

First Author: Noemi Puig, Hematology Department, Hospital Universitario de Salamanca, Salamanca, Spain

Background: Analysis of minimal residual disease (MRD) in the bone marrow (BM) of patients with multiple myeloma (MM) is accepted by the IMWG to evaluate treatment efficacy and is a well-established prognostic factor. However, there is an unmet need to explore the clinical value of MRD in peripheral blood (PB). **Methods:** Newly diagnosed MM patients enrolled in the GEM2012MENOS65 trial received six induction (Ind) cycles of bortezomib, lenalidomide, and dexamethasone (VRD) followed by autologous stem cell transplantation (ASCT) and 2 further cycles of consolidation (Cons) with VRD. MRD was analyzed in BM using Next Generation Flow (NGF) and in serum by Mass Spectrometry (MS) using IgG/A/M, κ, λ, free κ and free λ specific beads, both after Ind, at day 100 after ASCT, and after Cons. Sequential samples from the first 184 patients were analyzed. **Results:** Results of both methods were in agreement (NGF+/MS+ and NGF-/MS-) in 83% of cases post-Ind (152/184), 80% post-ASCT (139/174) and 76% post-Cons (128/169). Stratifying by the log range of MRD by NGF, discordances (NGF+/MS- and NGF-/MS+) seemed to increase at the lower MRD ranges, being 22%, 21% and 19% from $\geq 10^{-5}$ to $<10^{-4}$ and 21%, 21%, 23% at $\geq x10^{-6}$(post-Ind, ASCT and Cons, respectively). Analysis of discordances showed that they could be partly explained by the higher percentages of cases found to be positive by MS as compared by NGF at part of the time-points analyzed and at each log range of MRD. From $\geq 10^{-5}$ to $<10^{-4}$, MRD was detected by NGF in 36%, 28%, 20% of cases post-Ind, ASCT and Cons, respectively *vs* MS in 37%, 29%, 21% of them; at $\geq x10^{-6}$, NGF was positive in 11%, 14%, 19% of cases *vs* MS in 23%, 19% and 16% of them. Considering NGF as a reference, the negative predictive value (NPV) of MS per MRD range ($\geq 10^{-5}$ to $<10^{-4}$ and $\geq x10^{-6}$, respectively) was: post-Ind: 83% (p<0,0001), 94% (p=0,034); post-ASCT 86% (p<0,0001), 90% (p=0,022); post-Cons 89% (p<0,0001), 85% (p=0,0469). Despite these discordances, the prognostic value of each technique in terms of undetectable MRD and progression-free survival (PFS) was consistent at all time-points (Table) and further, discordant cases (NGF+/MS- and NGF-/MS+) did not display a significantly different PFS as compared to NGF-/MS- cases. **Conclusions:** The results of MRD assessed by NGF in BM and by MS in PB show a significant concordance and are associated with a similar prognostic value analyzed in terms of PFS. Given its high NPV, MRD in peripheral blood by MS provides a gateway for BM aspiration/biopsy and MRD assessment by NGF. Research Sponsor: PETHEMA-GEM.

	Post-Ind		Post-ASCT		Post-Consol		
Groups	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**% PFS after 2 years**
MS + vs MS -	0.02	3.2 (1.3-8,3)	0.06	2.5 (1.0- 6.5)	0.005	5.5 (1.7-17.2)	70 vs. 95
NGF + vs NGF -	0.02	3.3 (1.3-9.1)	0.02	3.3 (1.2-8.9)	0.002	6.2 (1.9-19.6)	72 vs. 97
MS+ NGF+ vs MS- NGF-	0.02	3.4 (1.2-9.3)	0.03	3.3 (1.1-9.5)	0.001	9.4 (2.5-35.8)	63 vs. 96

8011 **Poster Discussion Session**

Interim analysis of a phase 2 minimal residual disease (MRD)-adaptive trial of elotuzumab, carfilzomib, lenalidomide, and dexamethasone (Elo-KRd) for newly diagnosed multiple myeloma (MM).

First Author: Benjamin Avi Derman, University of Chicago, Chicago, IL

Background: The addition of a monoclonal antibody to triplet induction regimens in patients (pts) with MM with intent for autologous stem cell transplant (ASCT) has resulted in higher overall and deep response rates. In this study we are investigating the impact of the addition of Elo to KRd on complete response (CR) and/or MRD-negative rates in newly diagnosed MM regardless of transplant eligibility. **Methods:** Pts were enrolled from four MM Research Consortium sites into this phase 2 study. All patients receive 12 cycles of Elo-KRd in 28-day cycles: Elo per standard dosing, K 20/56/70 mg/m^2 days 1, 8 and 15, R 25 mg days 1-21, and dexamethasone 40 mg days 1, 8, 15, 22. ASCT eligible candidates can undergo stem cell collection after cycle 4 and then resume treatment; pts who elect to proceed to ASCT are censored for response at that time. Pts MRD(-) ($<10^{-5}$) by NGS after cycles 8 (C8) and 12 (C12) proceed to Elo-Rd until progression. Patients who convert from MRD(+) to MRD(-) between C8 and C12 receive an additional 6 cycles of Elo-KRd (total 18 cycles) followed by Elo-Rd, and pts MRD(+) after C12 receive an additional 12 cycles of Elo-KRd (total 24) followed by Elo-Rd. The primary endpoint of the study is sCR and/or MRD(-) rate after C8 E-KRd. MRD status was determined by ClonoSEQ next generation sequencing (NGS, $<10^{-5}$) [Adaptive Biotechnologies]. An improvement in the sCR and/or MRD(-) rate by NGS from a historical 30% to 50% at the end of C8 will be considered promising. **Results:** 44 pts are enrolled, 39 of whom are evaluable for response (cutoff Jan 10 2021). Median age is 62 years (range 43-81, 23% age >70) and 23 (52%) have high-risk cytogenetic abnormalities (HRCA) including 13 (30%) with >2 high-risk abnormalities (6 pts unknown cytogenetics). 34/39 (87%) have MRD trackable by clonoSEQ. The rate of sCR and/or MRD(-) by NGS at the end of C8 is 19/33 (58%), meeting the statistical threshold for establishing efficacy (2 pts censored for elective ASCT before C8 and 4 pts receiving therapy but have not reached C8). With a median follow-up of 24 months, estimated 2-year progression free survival is 87% (100% for standard risk, 79% for HRCA) and estimated 2-year overall survival is 89% (82% for HRCA). No pt who was MRD(-) by NGS after C8 has progressed, including 6 pts with HRCA. Serious adverse events occurred in 30 pts (68%). 89% experienced treatment emergent AEs, the most common (>10%) of which was pneumonia (14%). One pt had grade 5 myocardial infarction. **Conclusions:** Elo-KRd demonstrates tolerability consistent with known toxicities of these agents and met the primary endpoint of sCR and/or MRD(-) of >50% after 8 cycles. With longer follow-up, the study results may validate that an MRD-adaptive design for de-escalation of therapy in MM can generate deep responses while reducing treatment exposure. Clinical trial information: NCT02969837. Research Sponsor: Bristol Myers Squibb.

8012 **Poster Discussion Session**

Prospective comparison of whole body MRI and FDG PET/CT for detection of multiple myeloma and correlation with markers of disease burden: Results of the iTIMM trial. *First Author: Martin F. Kaiser, Institute of Cancer Research, London, United Kingdom*

Background: Early and sensitive detection of bone marrow disease and stratified patient management according to clinical risk can confer survival advantages in multiple myeloma (MM). Whole body MRI (WB MRI) and Fluorodeoxyglucose (FDG) PET/CT are included in international guidelines for imaging in patients with a suspected diagnosis of MM. However prospective studies comparing detection of MM by contemporary WB MRI as per recent MY-RADS consensus against FDG PET/CT are lacking. We report here protocol-defined endpoints from the prospective iTIMM (NCT02403102) study, comparing WB MRI and PET/CT, their relationship with serum and bone marrow estimates of disease burden, as well as molecular tumor characteristics. **Methods:** Patients with newly diagnosed MM or at first relapse planned to receive chemotherapy and autologous stem cell transplantation were enrolled in iTIMM. Matched baseline WB MRI and FDG PET/CT were performed and baseline clinical data including tumor genetics collected. Scans were double reported for presence of focal and diffuse disease by expert MRI and PET/CT radiologists, blinded to each other's assessment. Paired methods were used to compare burden and patterns of disease on WB MRI compared to FDG PET/CT at baseline. Primary and secondary trial endpoints include relationship between post-treatment WB MRI response and progression-free survival, for which follow-up is ongoing. Exploratory endpoints include comparison of baseline WB MRI and PET/CT and their correlation with laboratory parameters, for which data is complete and reported here. **Results:** From May 2015 to March 2018, sixty patients (35 male; mean age 60 years) underwent baseline WB MRI as per MY-RADS consensus and FDG PET/CT. At least one focal lesion was detected in 50/60 patients (83.3%) by WB MRI and in 36/60 patients (60%) by PET/CT. WB MRI was more sensitive ($P< 0.05$) across anatomical regions except for ribs and cervical spine. Four patients in our study showed two or more focal lesions ≥5 mm only on WB MRI but not PET/CT. All lesions detected by WB MRI but not PET/CT resolved in follow-up scans after treatment, excluding false positives. In 49/60 (81.7%) patients, diffuse disease was detected by WB MRI, compared to 10/60 (16.7%) by PET-CT; WB MRI was more sensitive across all anatomical areas ($P< 0.05$). Plasma cell infiltration and paraprotein levels were significantly higher for patients with diffuse disease on WB MRI, but not on PET/CT. All genetically high-risk tumours, defined by t(4;14), t(14;16), del(1p), gain(1q) or del(17p), showed diffuse infiltration on WB MRI. **Conclusions:** WB MRI increases detection of focal and diffuse disease compared with FDG PET/CT, including improved detection of focal lesions meeting criteria for active disease as per International Myeloma Working Group diagnostic criteria, proposing it as a gold standard for tumor imaging in MM. Clinical trial information: NCT02403102. Research Sponsor: Cancer Research UK and NIHR Biomedical Research Centre at the Royal Marsden Hospital and Institute of Cancer Research.

8013 **Poster Discussion Session**

CARTITUDE-2: Efficacy and safety of ciltacabtagene autoleucel (cilta-cel), a BCMA-directed CAR T-cell therapy, in patients with progressive multiple myeloma (MM) after one to three prior lines of therapy. *First Author: Mounzer Agha, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Cilta-cel is a CAR T-cell therapy expressing two BCMA-targeting, single-domain antibodies designed to confer avidity. The multicohort, phase 2 CARTITUDE-2 study (NCT04133636) is evaluating cilta-cel safety and efficacy in various clinical settings for patients (pts) with MM and exploring suitability of outpatient administration. Here, we present initial results from Cohort A. **Methods:** Cohort A pts had progressive MM after 1–3 prior lines of therapy (LOT), including a proteasome inhibitor (PI) and immunomodulatory drug (IMiD), were lenalidomide refractory, and had no prior exposure to BCMA-targeting agents. A single cilta-cel infusion (target dose: 0.75×10^6 CAR+ viable T cells/kg) was given 5–7 days (d) after start of lymphodepletion (daily cyclophosphamide [300 mg/m^2] and fludarabine [30 mg/m^2] for 3 d). The primary objective was minimal residual disease (MRD) 10^{-5} negativity. Secondary outcomes were response rates (IMWG) and safety (per CTCAE; CRS and ICANS by ASTCT). **Results:** As of Feb 2021 data cutoff (median follow-up: 5.8 months [mo]; range: 2.5–9.8 mos), 20 pts (65% male; median age 60 years [38–75]) received cilta-cel; 1 pt was treated in an outpatient setting. Pts received a median of 2 prior LOT (1–3); 12 pts received < 3 prior lines and 8 received 3 prior LOT. All pts were exposed to PI, IMiD, and dexamethasone, 95% to alkylating agents, and 65% to daratumumab. The majority (95%) were refractory to the last LOT; 40% were triple refractory. Overall response rate was 95% (95% CI: 75–100), 75% (95% CI: 51–91) achieved stringent CR/CR, and 85% (95% CI: 62–97) achieved ≥VGPR. Median time to first response was 1.0 mo (0.7–3.3); median time to best response was 1.9 mo (0.9–5.1). Median duration of response was not reached. All pts (n = 4) with MRD-evaluable samples at 10^{-5} at data cutoff were MRD-negative. Hematologic AEs ≥20% were neutropenia (95%; gr 3/4: 90%), thrombocytopenia (80%; gr 3/4: 35%), anemia (65%; gr 3/4: 40%), lymphopenia (60%; gr 3/4: 55%), and leukopenia (55%; all gr 3/4). CRS occurred in 85% of pts; 10% were gr 3/4. Median time to CRS onset was 7 d (5–9), with a median duration of 3.5 d (2–11). CAR T-cell neurotoxicity occurred in 20% of pts (all gr 1/2). Three pts had ICANS (1 gr 1; 2 gr 2); median time to onset was 8 d (7–11) and median duration was 2 d (1–2). One pt had gr 2 facial paralysis; time to onset was 29 d with a duration of 51 d. One death occurred due to COVID-19 (assessed as treatment (tx)-related by investigator). Safety profile was manageable in the pt treated in an outpatient setting. **Conclusions:** A single cilta-cel infusion at the recommended phase 2 dose led to early and deep responses with a manageable safety profile in pts with MM who had 1–3 prior LOT. Updated efficacy and safety findings will inform suitability of outpatient tx in this and other cohorts of CARTITUDE-2 as well as the CARTITUDE-4 study. Clinical trial information: NCT04133636. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8014 **Poster Discussion Session**

Long-term follow-up results of a multicenter first-in-human study of the dual BCMA/CD19 Targeted FasT CAR-T GC012F for patients with relapsed/refractory multiple myeloma. *First Author: Hua Jiang, Shanghai Chang Zheng Hospital, Shanghai, China*

Background: The dual CAR-T GC012F developed on the novel FasT CAR-T platform targeting B cell maturation antigen (BCMA), and CD19 was designed to improve depth of response and overall efficacy for CAR-T as therapy for Multiple Myeloma. Here, we present updated data for study (NCT04236011; NCT04182581) including additional pts treated. **Methods:** From October 2019 to July 2020, 19 heavily pretreated Relapsed/Refractory Multiple Myeloma (RRMM) pts (age 27-71) with a median of 5 prior lines (range 2-9) received a single infusion of GC012F. 94.7% (18/19) were high risk (HR- defined by mSMART), 5 pts had extramedullary disease, 1 pts presented with plasma cell leukemia, and 15/19 were refractory to last therapy. 4/19 pts had received prior anti- CD38, 18/19 pts prior IMiD. 18/19 pts were refractory to PI, 17 pts to IMiD, 3 pts being primary refractory. After lymphodepletion over 2-3 days (30 mg/m^2/d, 300mg/ m^2/d Flu/Cy) CAR-T cells were administered as single infusion at 3 dose levels: 1x10^5/kg (DL1) n=1, 2x10^5/kg (DL2) n=9 and 3x10^5/kg (DL3) n=9. **Results:** As of Jan 12, 2021 cut-off, 19 pts were evaluated for response. Overall response rate (ORR) was 94.7% - all responses VGPR or better (94.7% - 16/18 sCR, 2/18 VGPR) with all pts MRD- by flow cytometry (10^{-4}-10^{-6}) - earliest response d 28 post infusion. 100% of pts achieved a reduction of paraprotein, 18/19 a 100% reduction. Best response was MRD- sCR in 16/19 patients (84.2%). In DL3 (n=9) 4 additional pts were response evaluable for 6 mth follow-up: 100% (9/9) of pts achieved MRD-sCR as best response, 87.5% (7/8) of response evaluable pts maintained MRD-sCR at landmark analysis of 6 mths. At data cut off, the median time to follow up was 13.8 mths (6.1-16.4) – median duration of response not yet reached. Cytokine Release Syndrome (CRS) and ICANs were graded by ASBMT criteria: grade 1-2 n=16 (84.2%), grade 3 n=2 (10.5%). Median duration of CRS was 4 d (1-8 d). No grade 4/5 CRS or ICANS were observed. 2 deaths occurred on study and were assessed as not related to therapy – one reported previously; one patient was diagnosed with pseudomonas pneumonia on Day 52, refused life-saving treatment and passed. CAR-T median Tmax was 10 d (range 8-14d), median peak copy number (Cmax) was 127548 (16,011-374,346) copies /ug DNA with long duration of persistence of up to 60 weeks at time of data cut off. Patients continue to be monitored for safety and efficacy. **Conclusions:** BCMA-CD19 dual FasT CAR-T GC012F showed early, deep and durable responses with a high ORR (94.7% - VGPR and better) including a high MRD- sCR rate (DL3=100%, n=9) in high risk RRMM pts including those refractory to anti-CD38, PI and IMIDs with a favorable safety profile consistent with previous findings. BCMA-CD19 dual FasT CAR-T GC012F may present a new treatment approach for patients with RRMM including those with high-risk features refractory to standard of care. Clinical trial information: NCT04236011; NCT04182581. Research Sponsor: Gracellbio.

8015 **Poster Discussion Session**

Phase 1 Study of CART-ddBCMA, a CAR-T therapy utilizing a novel synthetic binding domain, for the treatment of subjects with relapsed and refractory multiple myeloma. *First Author: Matthew J. Frigault, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: CART-ddBCMA is an autologous CAR-T cell therapy encoding a novel non-scFv synthetic binding domain targeting BCMA with a 4-1BB costimulatory motif and CD3-zeta T-cell activation domain. The novel binding domain is based on a computationally-derived triple-helix protein scaffold that is small (73 amino acids), stable, engineered to reduce immunogenicity, and can be modified to bind alternative targets. **Methods:** ARC-101 (NCT04155749), ARM 1 (CART-ddBCMA) is a Phase 1, multi-center, open-label, dose escalation trial enrolling subjects who have received ≥3 prior regimens, including proteasome inhibitor(s), immunomodulatory agent(s), and anti-CD38 antibody, or are triple-refractory. Subjects undergo lymphodepletion with fludarabine and cyclophosphamide, then receive CART-ddBCMA as a single infusion. Planned dose levels are 100, 300, and up to 900 x 10^6 CAR+ T cells. The primary endpoint is incidence of adverse events (AEs), including dose-limiting toxicities (DLTs). Secondary endpoints include clinical response per IMWG criteria, MRD, DOR, PFS, OS, and CAR-T cell kinetics. **Results:** As of 29 Jan 2021, 10 subjects received CART-ddBCMA, 9 subjects were evaluable, and 1 subject was pending assessment. Median age was 66 years [min:max 54 to 75]. 6 subjects received 100 x 10^6 CAR+ T cells, and 4 subjects received 300 x 10^6 CAR+ T cells. Median CAR+ expression was 74.5% (min:max 61-87%) of total T cells. Of the evaluable subjects, median follow-up after cell infusion was 208 days (min:max 45 to 355+ days), 9/9 subjects were penta-refractory, 1 subject was also refractory to BCMA-directed ADC. 8/9 had high-risk cytogenetics (1 subject's sample not evaluable), and 6/9 subjects had extramedullary disease. No DLTs were reported. Per ASTCT Consensus Grading (Lee et al, 2019), 8 subjects developed G1/2 CRS, 1 subject in the higher dose cohort developed G3 CRS that rapidly resolved with tocilizumab. 1 subject developed G2 ICANS which rapidly resolved with intervention. 7 subjects received tocilizumab; 3 received dexamethasone. ORR was 100% (9/9) per IMWG criteria including 4 sCR, 1 VGPR, and 4 PR. 1 subject with PR relapsed and was retreated. All other subjects have ongoing responses; observations included sFLC normalization and elimination of detectable bone marrow disease by Month 1. Ongoing responses for subjects not yet achieving CR continue to deepen. 7 subjects were evaluable by MRD of which 5 are MRD-negative, and 2 are pending results. CAR-T cell expansion, as measured by vector transgene copies per microgram genomic DNA was observed in all patients. **Conclusions:** Early efficacy results are encouraging, with 9/9 (100%) ORR and manageable toxicities. 8/9 responses are ongoing and responses continue to deepen. These data are encouraging in high-risk subjects with penta-refractory myeloma. Subjects continue to be enrolled and treated. Clinical trial information: NCT04155749. Research Sponsor: Arcellx.

8016 **Poster Discussion Session**

Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy, in relapsed and refractory multiple myeloma: Updated KarMMa results. *First Author: Larry D. Anderson, Jr, The University of Texas Southwestern Medical Center, Dallas, TX*

Background: Patients (pts) with RRMM previously exposed to immunomodulatory agents, proteasome inhibitors (PIs), and CD38 antibodies (mAbs) have poor outcomes with subsequent treatments. Ide-cel, a BCMA-directed CAR T cell therapy, showed frequent, deep, and durable responses in heavily pretreated pts with RRMM in the pivotal KarMMa trial (Munshi NC, et al. *J Clin Oncol* 2020;38[suppl 15]. Abstract 8503). Here, we present updated data. **Methods:** Pts with ≥ 3 prior regimens (including immunomodulatory agent, PI, and CD38 mAb) and refractory to their last regimen per IMWG criteria were eligible (NCT03361748). Pts received 150450 $\times$ 10^6 CAR+ T cells (target dose range) after 3 days of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2). Endpoints included overall response rate (ORR; primary) and complete response (CR) rate (key secondary). Additional secondary endpoints included progression-free survival (PFS), overall survival (OS), and safety. **Results:** KarMMa enrolled 140 pts, and 128 received ide-cel. Pts had a median age of 61 years and a median of 6 (range, 3-16) prior regimens; 84% were triple-class refractory, and 26% were penta-class refractory (lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab). Most pts (88%) had bridging therapy. Median follow-up was 15.4 mo (data cutoff, 7 Apr 2020). ORR was 73% and median PFS was 8.8 mo in all treated pts; both increased with higher dose (Table). At the highest target dose (450 $\times$ 10^6 CAR+ T cells), the ORR was 81%, the CR rate was 39%, and the median PFS increased to 12.2 months with longer follow-up. Responses were observed in all subgroups including difficult-to-treat subsets (eg, extramedullary disease [ORR, 70%], high tumor burden [71%], and R-ISS stage III disease [48%]). OS continues to mature and the median has not been reached; the 15-month event-free rate for OS was 71%. Cytopenias (97%) and cytokine release syndrome (CRS; 84%) were the most common any-grade toxicities. CRS was mostly grade 1/2; 5 pts (4%) had grade 3, 1 had grade 4 (at 300 $\times$ 10^6), and 1 had grade 5 (at 300 $\times$ 10^6). Investigator-identified neurotoxicity was reported in 23 pts (18%); 4 pts (3%) had grade 3 and 0 had grade ≥ 4. Tocilizumab was used in 67 and 3 pts with CRS and neurotoxicity, respectively. **Conclusions:** Updated results from the KarMMa trial continue to demonstrate deep, durable responses with ide-cel in heavily pretreated pts with RRMM. Efficacy and safety reflect prior reports and support a favorable clinical benefit-risk profile for ide-cel across the target dose range. Clinical trial information: NCT03361748. Research Sponsor: Celgene, a Bristol-Myers Squibb Company and bluebird bio.

Dose, $\times$ 10^6 CAR+ T cells	150 (n = 4)	300 (n = 70)	450 (n = 54)	Total (N = 128)
ORR, n (%)	2 (50)	48 (69)	44 (81)	94 (73)
CR/sCR, n (%)	1 (25)	20 (29)	21 (39)	42 (33)
Median DOR, mo*	†	9.9	11.3	10.7
Median PFS,mo*	†	5.8	12.2	8.8

sCR, stringent CR. *Kaplan-Meier estimate. †Not reported due to small n.

8017 **Poster Discussion Session**

Updates from ICARIA-MM, a phase 3 study of isatuximab (Isa) plus pomalidomide and low-dose dexamethasone (Pd) versus Pd in relapsed and refractory multiple myeloma (RRMM). *First Author: Paul G. Richardson, Dana-Farber Cancer Institute, Boston, MA*

Background: Isa is an approved monoclonal antibody that binds to a specific epitope on the CD38 receptor. The Phase 3 ICARIA-MM study (NCT02990338) demonstrated significantly improved progression-free survival (PFS) with Isa-Pd vs Pd (P= 0.001) and a manageable safety profile (Attal M, et al. *Lancet* 2019;394:2096-2107). Here we report updated ICARIA results. **Methods:** Pts with RRMM (N = 307) who have received ≥2 prior therapies, including lenalidomide (Len) and a proteasome inhibitor (PI), were randomized to Isa-Pd (n = 154) or Pd (n = 153). Isa was administered intravenously at 10 mg/kg weekly for 4 weeks, and every other week thereafter. This preplanned second interim analysis assessed longer term outcomes, including time to next treatment (TTNT), overall survival (OS), time from randomization to disease progression on first subsequent therapy or death (PFS2), and safety. **Results:** Pts had a median of 3 prior lines of therapy (IQR 2–4; table). As of Oct 1, 2020 (median follow-up, 35.3 months [mo]), 27 Isa-Pd pts (18%) vs 12 Pd pts (8%) were still on treatment; 60% vs 72% had proceeded to subsequent therapy. Median TTNT was 15.5 mo with Isa-Pd vs 8.9 mo with Pd (hazard ratio [HR] 0.56; 95% confidence interval [CI] 0.42–0.74; P< 0.0001); 24% vs 58% of pts with subsequent therapy received daratumumab (dara). Overall response rate (ORR) in subsequent treatment with dara monotherapy was higher after Pd (38%) than Isa-Pd (14%), but was similar (32% vs 31%) with dara combination therapy (table). Median PFS2 in the intent-to-treat population was 17.5 mo with Isa-Pd vs 12.9 mo with Pd (HR 0.76; 95% CI 0.58–0.99; P= 0.0202). Median OS was 24.6 mo with Isa-Pd vs 17.7 mo with Pd (HR 0.76; 95% CI 0.58–1.01; one-sided P= 0.0280). Median treatment duration was 47.6 weeks (range 1.3–171.6) with Isa-Pd vs 24.0 weeks (range 1.0–168.6) with Pd. Serious treatment-emergent adverse event (TEAEs) were seen in 73% of Isa-Pd pts vs 60% of Pd pts. Most frequent non-hematologic TEAEs (any grade) with Isa-Pd were infusion reaction (38%), upper respiratory tract infection (34%), and diarrhea (30%). Grade 3–4 neutropenia (85% vs 71%) and thrombocytopenia (34% vs 25%) were more frequent with Isa-Pd than with Pd. **Conclusions:** Isa-Pd demonstrates a significant improvement in TTNT and PFS2 compared with Pd. A strong trend in OS benefit was also seen in the Isa-Pd arm, with approximately 7 mo improvement in median OS. The overall safety profile remains unchanged from prior analyses. Funding: Sanofi. Clinical trial information: NCT02990338. Research Sponsor: Sanofi.

Prior treatments, n (%)	Isa-Pd (n = 154)	Pd (n = 153)
Len	154 (100)	153 (100)
PI	154 (100)	153 (100)
Len-refractory	144 (94)	140 (92)
PI-refractory	118 (77)	115 (75)
ORR on subsequent dara combination treatments, n/N* (%)		
ALL	4/13 (31)	7/22 (32)
+Immunomodulator	2/5 (40)	2/7 (29)
+Alkylator	0/4 (0)	1/5 (20)
+PI	2/5 (40)	4/12 (33)

*N = number of patients with best overall response assessment.

8018 **Poster Discussion Session**

Oral selinexor, pomalidomide, and dexamethasone (XPd) at recommended phase 2 dose in relapsed refractory multiple myeloma (MM). *First Author: Darrell White, Queen Elizabeth II Health Sciences Centre and Dalhousie University, Halifax, NS, Canada*

Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins (TSPs), is associated with poor prognosis in MM, and contributes to proteasome inhibitor (PI) and immunomodulatory drug (IMiD) resistance. Selinexor (SEL) is a novel, oral, first-in-class selective inhibitor of nuclear export (SINE) compound that blocks XPO1, forcing the nuclear retention and activation of TSPs. SEL is approved with low-dose dexamethasone (dex) ± bortezomib (BOR) for patients (pts) with previously treated MM. In the Phase 3 BOSTON study, once weekly (QW) SEL, QW BOR, and dex (XVd) significantly increased progression-free survival (PFS) and overall response rate (ORR) with marked reduction of peripheral neuropathy as compared to standard twice weekly BOR/dex (Vd), despite XVd utilizing 40% less BOR and 25% less dex than Vd. Pomalidomide (POM) plus dex (Pd) has an ORR of 31% and median PFS (mPFS) of 4 months in MM pts refractory to BOR and lenalidomide (LEN). We hypothesized that the addition of once weekly SEL to Pd (XPd) would be an active, all-oral combination with an acceptable safety profile in pts with LEN refractory and BOR treated MM. **Methods:** In the SPd arm of the multi-arm Phase 1b/2 STOMP study, SEL was evaluated at 60, 80, or 100 mg QW or 60 or 80 mg twice weekly in combination with Pd. Study objectives were to determine the maximum tolerated dose and recommended Phase 2 dose (RP2D), and assess the safety and activity of the SPd regimen including in pts receiving the RP2D. **Results:** As of 4 Jan 2021, 65 pts (33 male) were enrolled with median age of 64 years (range 37-85 years) and median of 3 (range 1-10) prior lines of therapy. Previously treated/refractory rates were LEN 100%/85%, BOR 92%/49%, carfilzomib 43%/37%, POM 31%/29%, and daratumumab (dara) 26%/26%. RP2D was SEL 60 mg QW, POM 4 mg (days 1-21), dex 40 mg QW. Common hematologic, treatment-related adverse events (TRAEs) included (all grades, grades ≥3) neutropenia (63%, 55%), anemia (58%, 32%), and thrombocytopenia (54%, 31%). Non-hematologic TRAEs included nausea (62%, 2%), fatigue (55%, 11%), and decreased appetite (45%, 2%). Among POM naïve or nonrefractory MM pts (N = 44), ORR was 57% (1 sCR, 1 CR, 8 VGPR, 15 PR); mPFS was 12.2 months. In pts treated with RP2D (N = 20), ORR was 65% (1 sCR, 5 VGPR, 7 PR); mPFS was not reached with a median follow-up time of 3.9 months. In POM-refractory pts and those with prior dara, ORR was 44% (7/16) and 60% (9/15), respectively. **Conclusions:** SEL, once weekly, can be safely combined with Pd in pts with heavily pretreated MM. No new safety signals were identified. The all-oral combination of XPd is highly active with an ORR of 65% at RP2D (compared to expected ORR ≤30% for Pd) and produces durable responses with a mPFS of 12.2 months overall. These data support a planned Phase 3 study with an all-oral combination of XPd vs Pd in pts who have been previously treated with LEN, a PI, and an anti-CD38 mAb. Clinical trial information: NCT02343042. Research Sponsor: Karyopharm Therapeutics.

8019 **Poster Discussion Session**

Survival among older patients with previously treated multiple myeloma treated with selinexor, bortezomib, and dexamethasone (XVd) in the BOSTON study. *First Author: Thierry Facon, University of Lille, CHU Lille, Service des Maladies du Sang, Lille, France*

Background: Multiple myeloma (MM) typically affects older populations, which are more vulnerable to toxicity with anti-MM treatments. These patients (pts) have significant morbidity and mortality, resulting in a need for dose modifications or alternative suboptimal treatment options. Significant improvements were observed in the BOSTON study with XVd vs Vd in median progression-free survival (PFS), overall response rate (ORR), and rates of peripheral neuropathy (PN); median overall survival (OS) trended in favor of XVd. **Methods:** The phase 3 randomized BOSTON trial (NCT03110562) is a controlled, open-label study of once weekly XVd vs. twice weekly standard Vd in pts with MM and 1-3 prior treatment regimens. We performed post-hoc analyses to compare survival benefits in pts ≥65 vs < 65 years of age. **Results:** The BOSTON study enrolled a total of 402 pts between June 2017 and February 2019 that were randomized into XVd or Vd arms. The numbers of pts treated with XVd or Vd who were ≥65 were 109/132 and 86/75 who were < 65, respectively. Baseline characteristics were similar by age although pts ≥65 years were less likely to have received ASCT than those < 65 years (48.4% vs. 25.3%). Median PFS was prolonged with XVd compared with Vd, across both age groups: ≥65 (HR, 0.55 [95% CI, 0.37-0.83] P = 0.002) and < 65, (HR, 0. 74 [95% CI, 0.49-1.11], P = 0.07). Vd was associated with a lower ORR (64.4%) than treatment with XVd (76.1%) (OR, 1.77 [95% CI, 1.00-3.11], P = 0.024) in pts ≥65, while the ORR in those < 65 was 76.7% with XVd and 58.7% (OR, 2.33 [95% CI, 1.18-4.59], P = 0.007) with Vd. As of Jan 2021, the median OS for the overall population was not reached for both arms (HR = 0.86; p = 0.193), with 61 and 75 deaths in the XVd and Vd arms, respectively. Median OS was not reached in pts ≥65 with XVd and was 28.6 months with Vd (HR = 0.60; 95% CI, 0.38-0.94; p = 0.012), while there was no difference in the OS for pts < 65 (HR = 1.52; 95% CI, 0.86-2.68; p = 0.926). Pts ≥65 had a lower incidence of death with XVd as compared to Vd (29 vs 56) and there were 32 deaths with XVd and 19 with Vd in pts < 65. Grade ≥3 treatment-emergent adverse events were not observed more often in older compared to younger pts. Amongst pts ≥65, PN of any grade was lower with XVd (32.1%) compared to Vd (46.5%); (OR 0.57 [95% CI 0.34-0.97], p = 0.017), including a lower incidence of grade ≥3 PN (XVd 4.6% vs. Vd 11.6%). Pts < 65 followed a similar trend of PN AEs of any grade: XVd, 32.6%; Vd, 48.0% (OR 0.42 [95% CI 0.21-0.82], p = 0.006). **Conclusions:** In an older patient population with a poor prognosis, XVd was associated with a significant survival benefit, improved PFS and OR with reduced PN, and requires relatively short and infrequent clinic visits. XVd may be a simple, effective regimen for pts ≥65 years of age. Clinical trial information: NCT03110562. Research Sponsor: None.

8020 **Poster Discussion Session**

Oral ixazomib-dexamethasone versus oral pomalidomide-dexamethasone for lenalidomide-refractory, proteasome inhibitor-exposed multiple myeloma (MM) patients: A global, multicenter, randomized, open-label, phase 2 trial. *First Author: Meletios A. Dimopoulos, Therapeutic Clinic, General Hospital of Athens Alexandra, Athens, Greece*

Background: MM patients (pts) often receive several lines of therapy with multiple drug combinations and, as lenalidomide (R)-containing regimens are commonly used as first-line therapy, R-free options for subsequent lines are necessary. Additionally, as pts age and become less tolerant to treatment, more convenient regimens, such as all-oral options, with less toxicity are needed. Dexamethasone (dex)-based doublets are effective and tolerable in this setting. **Methods:** Proteasome inhibitor (PI)-exposed and/or intolerant and R-refractory pts who had ≥2 prior therapies (N = 122) were randomized 3:2 to receive: ixazomib (ixa) 4 mg (5.5 mg from cycle 2 if tolerated) on day (d) 1, 8, 15, and dex 20 mg (≥75 years [yrs], 10 mg) on d 1, 2, 8, 9, 15, 16, 22, 23; or pomalidomide (pom) 4 mg on d 1–21, and dex 40 mg (≥75 yrs, 20 mg) on d 1, 8, 15, 22, in 28-d cycles until progressive disease (PD) or unacceptable toxicity. Pts were stratified by age (< 65 vs ≥65 yrs), International Staging System (ISS) disease stage at study entry (I/II vs III), and prior lines of therapy (2 vs ≥3). The study was powered to test the primary endpoint of progression-free survival (PFS). **Results:** In the ixa-dex (n = 73) vs pom-dex (n = 49) arms, median age was 72 vs 68 yrs (36% vs 18% ≥75 yrs), 25% vs 22% of pts had ISS stage III MM, and 52% vs 53% had received ≥3 prior therapies (per stratification). At data cutoff (5/31/2020), 19% vs 20% of pts were ongoing on treatment with ixa-dex vs pom-dex; primary reasons for discontinuation were PD (47% vs 57%) and adverse events (AEs; 23% vs 12%). With median follow-up of 15.3 vs 17.3 months (mos), median PFS (mPFS) was 7.1 vs 4.8 mos with ixa-dex vs pom-dex (hazard ratio [HR] 0.847; 95% confidence interval [CI] 0.535–1.341; p = 0.477); the Table shows mPFS by prior lines, and secondary endpoints. Pts received a median of 6 cycles with both ixa-dex (range 1–25) and pom-dex (range 1–27); 64% of ixa-dex pts were able to escalate to a 5.5 mg dose of ixa. 69% vs 81% of ixa-dex vs pom-dex pts had grade (G) ≥3 AEs, 51% vs 53% had serious AEs, 39% vs 36% had an AE leading to drug discontinuation, 44% vs 32% had an AE leading to dose reduction, and 13% vs 13% died on study. Health-related quality of life (HRQoL; EORTC QLQ-C30/MY20, and EQ-5D-5L) was maintained, and similar between arms. **Conclusions:** Ixa-dex prolonged PFS vs pom-dex in these heavily pretreated, PI-exposed and/or intolerant, R-refractory pts, but the difference was not statistically significant. Ixa-dex was well tolerated, with lower G≥3 AE rates vs pom-dex, and comparable HRQoL. Clinical trial information: NCT03170882. Research Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

8021 **Poster Session**

High-dose lenalidomide and melphalan as conditioning for autologous stem cell transplantation in relapsed or refractory multiple myeloma. *First Author: Adriana C. Rossi, NYPH Weill Cornell, New York, NY*

Background: Autologous stem cell transplantation (ASCT) remains a standard of care of eligible patients with multiple myeloma, despite the many novel therapies introduced over the past decade. High dose melphalan (HDM) is the only approved regimen to date. Lenalidomide (LEN) is an oral immunomodulatory drug which has become the backbone of myeloma therapy from induction through salvage and maintenance. Early studies noted a dose response relationship, and found myelosuppression to be the dose limiting toxicity. We previously reported on our phase 1 study of high dose lenalidomide (HDLEN) with HDM in conditioning for ASCT, where no DLT was noted up to 350mg PO daily of LEN. Here we report the phase 2 data of patients undergoing ASCT with combination conditioning regimen. **Methods:** 50 patients with relapsed/refractory multiple myeloma (RRMM) underwent ASCT using HDLEN+HDM conditioning. HDLEN was dosed at 350mg PO daily from day -5 to day -1 and HDM was dosed 100mg/m2 on days -2 and -1. TPatients were heavily pre-treated: 32% had prior HDM-ASCT, 96% had received prior lenalidomide, and 42% prior pomalidomide; 40% prior anti-CD38 mAB. Of note, 68% entered the study with progressive disease at time of enrollment. **Results:** Overall response rate was 96%, with 80% being ≥VGPR. Median progression free survival (PFS) was noted at 14.3 months, while overall survival (OS) was 68.2 months. PFS was similar when patients were stratified by prior ASCT, depth of response at enrollment, or presence of high risk FISH. Toxicities were mostly hematologic (100% neutropenia and thrombocytopenia, 90% anemia) , GI (88% diarrhea, 72% nausea, 42% vomiting) and metabolic (30-96% derangement in electrolytes), and similar to historical controls receiving HDM alone. Second malignancies were noted in 2 patients. **Conclusions:** HDLEN/HDM is a well tolerated and effective conditioning regimen for ASCT in patients with RRMM. This regimen merits further investigation as ASCT is likely to remain an integral part of the treatment of RRMM patients, yet few advancements have been made to this modality. HDLEN may be particularly useful in patients with high risk disease and those progressing after multiple lines of therapy. HDLEN added little toxicity to HDM and SPMs were not more frequent than expected per SEER database for patients in this age range. Clinical trial information: NCT01054196. Research Sponsor: Celgene.

Best response, n (%)	N = 50
Stable Disease	2 (4)
Partial Response	8 (16)
Very Good Partial Response	22 (44)
Unconfirmed Complete Response	1 (2)
Complete Response	8 (16)
Stringent Complete Response	9 (18)
Overall Response Rate	48 (96)

8022 **Poster Session**

Improved outcomes with maintenance therapy after salvage autologous hematopoietic cell transplantation (AHCT) in multiple myeloma: A CIBMTR study. *First Author: Oren Pasvolsky, Institute of Hematology, Davidoff Cancer Center, Rabin Medical Center, Petah- Tikva, Israel*

Background: Maintenance therapy in multiple myeloma (MM) after first autologous hematopoietic cell transplantation (AHCT1) is considered standard of care. Data regarding maintenance therapy after a salvage AHCT (AHCT2) in the setting of relapsed MM are scarce. Therefore, we used data from the Center for International Blood and Marrow Transplant Research (CIBMTR) registry to examine the use of maintenance therapy after AHCT2 in MM patients and its effect on post-transplant patient outcomes. **Methods:** We included US adult MM patients who underwent AHCT2 after melphalan conditioning regimen from 2010-2018, and excluded patients who underwent tandem transplants. Outcomes of interest included non-relapse mortality (NRM), relapse/progression (REL), progression-free and overall survival (PFS, OS). Cox proportional hazards models were developed to study the main effect (maintenance use) with other covariates of interest including age, sex, race, performance status, HCT-comorbidity index, MM subtype, stage, creatinine, cytogenetic, conditioning melphalan dose, disease status at transplant, and time from AHCT1 to AHCT2. **Results:** Of 522 patients, 342 received maintenance therapy and 180 did not after AHCT2. Baseline characteristics were similar between the two groups. Median follow up was 58 months in the maintenance group and 61.5 months in the no-maintenance group. Common maintenance regimens included immunomodulatory drugs (IMID)-lenalidomide (N = 145, 42%) or pomalidomide (N = 46, 13%) and proteasome inhibitor, bortezomib (N = 45, 13%). Univariate analysis showed superior outcomes at 5 years in maintenance compared to the no-maintenance group: NRM 2 (0.7-3.9)% vs 9.9 (5.9-14.9)%, p < 0.001, REL 70.2 (64.4-75.8)% vs 80.3 (73.6-86.3)%, p 0.003, PFS 27.8% (22.4-33.5) vs. 9.8% (5.5-15.2) , p < 0.001, and OS 54% (47.5-60.5) vs 30.9% (23.2-39.2) p < 0.001, respectively. IMID-containing maintenance regimens were associated with an improved 5-year PFS and OS compared to other maintenance regimens. Use of maintenance therapy retained its association with improved outcomes in multivariate analysis, including NRM: hazard ratio (HR) 0.19 (0.08-0.44), p 0.0001, REL: HR 0.58 (0.47-0.72), p < 0.0001, PFS HR 0.52 (0.43-0.64), p < 0.0001, and OS HR 0.46 (0.36-0.60), p < 0.0001. We conducted additional analyses to investigate a possible selection bias in the maintenance group including landmark analysis at 100-days and 6-months post-AHCT2 as well as a subgroup analysis of patients who received melphalan 200mg/m^2 as conditioning for AHCT2 (as a surrogate for fitness)- all these analyses also showed improved outcomes in the maintenance group. Second cancers were reported in 17 (5%) patients in the maintenance group and 6 (3%) patients and no-maintenance group (p 0.39). **Conclusions:** Maintenance therapy after AHCT2 is associated with superior outcomes in MM patients. Research Sponsor: U.S. National Institutes of Health.

8023 **Poster Session**

Phase 2 study of MGTA-145 + plerixafor for rapid and reliable hematopoietic stem cell (HSC) mobilization for autologous transplant in multiple myeloma. *First Author: Surbhi Sidana, Stanford University, Stanford, CA*

Background: MGTA-145 (GroβT), a CXCR2 agonist, has shown promising activity for HSC mobilization with plerixafor in pre-clinical models and healthy volunteers. **Methods:** This phase 2 single center study evaluates HSC mobilization with MGTA-145 + plerixafor and same day apheresis in patients with multiple myeloma. Patients received plerixafor 0.24 mg/kg (0.16 mg/kg if renal dysfunction) SQ, followed 2 hours later by MGTA-145 (0.03 mg/kg) IV over 3-10 minutes and apheresis within 30 minutes. Mobilization was repeated for a second day if day 1 yield was < 6 x 10^6 CD34+ cells/kg. This interim analysis reports on mobilization in 10 patients (of 25 planned), including safety cohort of first 6 patients completing transplant. Primary endpoint is collection of 2 x 10^6 CD34+ cells/kg. **Results:** Median age was 63 years (range: 46-68), 50% were female, 22% had ISS stage 3 & 50% had high-risk FISH. Induction therapy was VRD in 7 and daratumumab + VRD in 3 patients; median induction duration: 4 months (3-6) & median lenalidomide exposure: 6 cycles (4-6), with > VGPR in 70%. Median total stem cell yield (CD34+ cells/kg x 10^6) was 7.1 (3-16.2), day 1 yield was 5.4 (1.1-16.2) & yield per apheresis session was 4 (1.1-16.2). 100% of patients met the primary endpoint of collecting sufficient HSCs in < 2 days of mobilization + apheresis to proceed to transplant (2 x 10^6 CD34+ cells/kg). Secondary endpoints of 4 and 6 x 10^6 CD34+ cells/kg in < 2 days were met in 90% & 80% patients. 30% patients underwent 1 apheresis, while 70% underwent 2 sessions. MGTA-145 was well tolerated. At least 1 adverse event (AE) was seen in 90% of patients, 20% had grade 2 AEs (anemia, hypokalemia) and 20% had grade 3 AEs (worsening of baseline grade 3 anemia; hypocalcemia); all resolved. Acute & transient bone pain was seen in 40% of patients (back-2, hip-1, sternum-1), all grade 1, all on day 1, & resolved without intervention after 6 minutes (3-10). All 6 patients in the safety cohort have completed transplant with melphalan 200 mg/m^2. Median of 4.1 (3.4-5.6) x 10^6 CD34+ cells/kg were infused. All patients have engrafted timely (DiPersio Blood 2009); median time to neutrophil engraftment: 12 days (11-13) & platelet engraftment: 17 days (16-19). Apheresis graft analysis is available in these 6 patients. Grafts with MGTA-145+plerixafor showed high enrichment for CD90+CD45RA- among CD34+ cells, a CD34 subset of long term engrafting HSCs (median: 31% of CD34+ cells, 27-52), higher than seen with G-CSF (6%, Goncalves TCT 2021). 67% of grafts were minimal residual disease negative with next generation flow cytometry. **Conclusions:** This is the first study to evaluate the novel regimen of MGTA-145 + plerixafor for same day stem cell mobilization & collection in myeloma/hematologic malignancies, with 100% efficacy in interim analysis and the first to demonstrate successful engraftment in patients with cells collected with this GCSF free regimen. Clinical trial information: NCT04552743. Research Sponsor: Magenta Therapeutics , U.S. National Institutes of Health, PI (Sidana) has a KL2 grant from NIH, although study per se was not sponsored via NIH funds.

8024 **Poster Session**

Effects of refractory status to lenalidomide on safety and efficacy of selinexor, bortezomib, and dexamethasone (XVd) versus bortezomib and dexamethasone (Vd) in patients with previously treated multiple myeloma. *First Author: Xavier Leleu, Department of Hematology, CHU la Miletrie and Inserm CIC 1402, Poitiers, France*

Background: Lenalidomide (LEN) is typically a frontline therapy for newly diagnosed MM. Patients (pts) with MM refractory to LEN are less likely to repond to other IMiDs and represent a signification area of unmet medical need. In the BOSTON study in the ITT population, XVd was associated with significant improvements in median progression-free survival (PFS), overall response rate (ORR), and rates of peripheral neuropathy, with trends in overall survival (OS) favoring XVd. **Methods:** The BOSTON trial (NCT03110562) is a Phase 3 randomized, controlled, open-label study of once weekly XVd vs twice weekly Vd in pts with MM and 1-3 prior therapies. We performed post-hoc analyses on two different subgroups to compare outcomes based on refractory status to LEN and immunomodulatory drug (IMiD) therapy. These post hoc analyses evaluated if PFS, overall response rate (ORR), time to next treatment (TTNT) and safety was influenced by prior treatment with LEN when comparing XVd with Vd. **Results:** Amongst the 402 pts in BOSTON, 160 had MM refractory to any IMiD (XVd = 74, Vd = 86). Of those, 106 were documented to be refractory to LEN (XVd = 53, Vd = 53) and 296 were not refractory to LEN (XVd = 142, Vd = 154). Baseline characteristics were generally well balanced between subgroups. In these subgroups based on refractory status to IMiD or LEN, median PFS was significantly longer in the XVd arm as compared to Vd (IMiD refractory, 13.9 vs. 8.4 months (mo), p = 0.005; LEN refractory, 10.2 vs. 7.1 mo, p = 0.012; not LEN refractory, 15.4 vs 9.6 mo, p = 0.014). Significant increases in TTNT were observed with XVd treatment in pts that were IMiD refractory (14.8 vs. 10.2 mo, p = 0.003), LEN refractory (13.0 vs. 7.6 mo, p = 0.015), and not refractory to LEN (19.1 vs 12.9 mo, p = 0.005). ORR was improved with XVd compared to Vd regardless of refractory status (IMiD refractory, 68.9% vs 55.8%, p = 0.045; LEN refractory, 67.9% vs. 47.2%, p = 0.016; and not refractory to LEN, 79.6% vs 67.5%, p = 0.010). The most common treatment-emergent AEs for the XVd/Vd arms for all subgroups were thrombocytopenia (66.2/30.6%; 71.7/40.4%; 55.6/22.4%), nausea (48.6/11.8%; 50.9/11.5%; 50.0/9.2%), and fatigue (40.5/20.0%; 45.3/21.2%; 40.8/17.1%) for IMiD, LEN, and not LEN refractory, respectively. Incidence of PN AEs of any grade were reduced compared to pts treated with Vd (IMiD refractory, 27% vs. 42.4%; LEN refractory, 30.2% vs 36.5%; not refractory, LEN 33.1% vs 50.7%). **Conclusions:** In pts with previously treated MM, PFS, ORR, and TTNT were significantly improved regardless of documented refractory status to any IMiD or to LEN-specifically. These analyses support the use of the XVd combination for pts with disease refractory to LEN and likely to any IMiD. Clinical trial information: NCT03110562. Research Sponsor: None.

8025 **Poster Session**

The clinical study of anti-BCMA CAR-T with single-domain antibody as antigen binding domain. *First Author: Lu Han, Department of Immunology, Affiliated Cancer Hospital of Zhengzhou University and Henan Cancer Hospital, Zhengzhou, China*

Background: Relapsed/refractory (RR) multiple myeloma (MM), RRMM, remains as an incurable disease and has a 5-year survival rate of nearly 50%. To address the unmet medical need, an autologous CAR-T cell therapy was developed previously with a humanized single-domain antibody (sdAb) targeting BCMA as the antigen binding domain, 4-1BB and CD3ζ as cytoplasmic domain. **Methods:** An investigator-initiated clinical trial (IIT) was conducted in China to assess the safety and efficacy of the sdAb-based CAR-T. The trail was started in June 2018 and the last patient infused in June 2019. As of 1 February 2021, 34 were treated and followed up. The patients had received multiple lines of prior treatment (including bortezomib, lenalidomide, and others). Following a lymphodepleting regimen of cyclophosphamide (300-600 mg/m^2, d-5, -4) and fludarabine (25-30 mg/m^2, d-5 to d-3), patients were infused with 2.5-10.0 $\times$ 10^6 CAR$^+$ cells/kg body weight. CAR-T was infused immediately after preparation and quality control performed in all patients except one, who was infused a 10.0 $\times$ 10^6 CAR$^+$ cells/kg dose of frozen cells. Efficacy was assessed based on the IMWG criteria, toxicity was graded by CTCAE 4.02, and CRS grading was based on the grading system by CARTOX working group. **Results:** All 34 patients had the tumor burden of plasma cells in bone marrow, or M protein or free light chains (FLCs) in serum, 7 patients were accompanied with extramedullary diseases. The efficacy shows the best ORR is 88.2% (30/34), sCR rate is 55.9% (19/34). The mPFS was 12.1 months, several patients shows continuous sCR after 2 years. No obvious correlation between efficacy and dosage were found in three dose groups of 2.5$\times$10^6 CAR$^+$ cells/kg (6 pts), 5.0$\times$10^6 CAR$^+$ cells/kg (23 pts) or 10.0$\times$10^6 CAR$^+$ cells/kg (5 pts). The observed adverse events include thrombocytopenia (≥grade 3, 38.2%), neutropenia (≥grade 3, 44.1%), leukopenia (≥grade 3, 32.4%), lymphopeniPa (≥grade 3, 26.5%), and anemia (≥grade 3, 20.6%). CRS was monitored occurring in 29 patients (any grade, 85.3%, ≥grade 3, 2.9%). **Conclusions:** Our result demonstrates that the CART employing one humanized sdAb targeting BCMA is safe and efficacious for clinical application. The phase I clinical trial has been initiated in China for searching the RP2D using the cryopreserved CAR-T cells. Clinical trial information: NCT03661554. Research Sponsor: Henan Medical Science and Technology Foundation (grant number 2018020484; SBGJ2018085); Henan Provincial Scientific and Technological Project (grant number 162300410095).

8026 **Poster Session**

Isatuximab plus carfilzomib and dexamethasone versus carfilzomib and dexamethasone in elderly patients with relapsed multiple myeloma: IKEMA subgroup analysis. *First Author: Thierry Facon, Department of Haematology, Lille University Hospital, Lille, France*

Background: A prespecified interim efficacy analysis of the Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib (K) and dexamethasone (d) (Isa-Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (HR 0.531; 99% CI, 0.318–0.889; *P*=0.0007), with a clinically meaningful increase in minimal residual disease negativity (MRD-) (29.6% vs 13.0%) and complete response (CR) (39.7% vs 27.6%) rates, and a manageable safety profile. This subgroup analysis of IKEMA examined efficacy and safety in pts aged <70 and ≥70 years. **Methods:** Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n=179) or Kd (n=123). The primary end point was PFS, as assessed by an independent response committee. We compared outcomes in pts <70 vs ≥70 years; division into different or additional age groups resulted in smaller sample sizes. **Results:** Of the 302 randomized pts, 71.5% were aged <70 years (Isa-Kd: 70.9%; Kd: 72.4%) and 28.5% were aged ≥70 years (Isa-Kd: 29.1%; Kd: 27.6%). Consistent with the significant improvement of PFS in the overall population, the addition of Isa to Kd resulted in improved PFS independently of age (Table). The CR, ≥very good partial response (VGPR), and MRD- rates were higher with Isa-Kd vs Kd. Within the Isa-Kd arm, CR rate and ≥VGPR rate were similar in elderly and younger pts. MRD- was observed in 32.3% of younger pts and 23.1% of elderly pts with Isa-Kd. In both arms, Grade ≥3 and serious treatment-emergent adverse events (TEAEs) were more frequently reported in elderly pts vs pts <70 years old (Table). For both age groups, the incidence of Grade ≥3 TEAEs was higher whereas the incidence of serious TEAEs was similar between Isa-Kd and Kd. In the elderly subgroup, 3 (5.9%) pts receiving Isa-Kd and 1 (2.9%) receiving Kd had fatal TEAEs (Isa-Kd, infection; Kd, general health deterioration due to progressive disease). The most common Grade ≥3 TEAEs in pts aged <70 and ≥70 years treated with Isa-Kd vs Kd were hypertension (18.3% vs 17.0% [<70 years] and 25.5% vs 26.5% [≥70 years]) and pneumonia (14.3% vs 9.1% [<70 years] and 21.6% vs 20.6% [≥70 years]). **Conclusions:** The addition of Isa to Kd improved PFS and quality of response in elderly pts, with a manageable safety profile, consistent with the benefit observed in the overall IKEMA study population. Isa-Kd provides a potential new treatment option for elderly pts with RMM. Funding: Sanofi. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

	<70 Years		≥70 Years	
	Isa-Kd (n = 127)	Kd (n = 89)	Isa-Kd (n = 52)	Kd (n = 34)
PFS HR (95% CI)	0.609 (0.384–0.968)		0.364 (0.176–0.751)	
CR, %	40.2	29.2	38.5	23.5
≥VGPR, %	72.4	56.2	73.1	55.9
MRD-, %	32.3	13.5	23.1	11.8
Grade ≥3 TEAEs, %*	71.4	63.6	90.2	76.5
Serious TEAEs, %*	54.0	52.3	72.5	70.6
Fatal TEAEs, %*	2.4	3.4	5.9	2.9
TEAEs leading to definitive discontinuation, %*	7.1	10.2	11.8	23.5

*n = 126; n = 88; n = 51; n = 34.

8027 **Poster Session**

Effects of weekly selinexor, bortezomib, dexamethasone (XVd) versus standard twice weekly bortezomib and dexamethasone (Vd) on *RAS*-mutated previously treated multiple myeloma (MM). *First Author: Christopher James Walker, Karyopharm Therapeutics Inc, Newton, MA*

Background: Activating mutations of the RAS genes *NRAS*, *KRAS*, and *HRAS* (*RAS*^{mut}) occur in up to 50% of MM and portend poor survival and high recurrence rates. MM cells with *RAS*^{mut} are susceptible to inhibition of germinal center kinase (GCK), resulting in IKAROS degradation independent of cereblon (CRBN). Selinexor is a selective inhibitor of nuclear export (SINE) compound that can induce IKAROS degradation through CRBN-independent pathways to overcome immunomodulatory drug resistance. We explored the benefit of selinexor treatment for pts with *RAS*^{mut} MM. **Methods:** In the randomized BOSTON study, pts with MM after 1-3 therapies received weekly XVd or twice weekly Vd. In the single-arm STORM study pts with penta-treated, triple class refractory MM were treated with twice weekly Xd. Both treatment regimens are now FDA approved. Mutations were assessed post-hoc by exome sequencing of 119 and 52 pts from BOSTON and STORM, respectively. Pts were considered *RAS*^{mut} if their MM had *NRAS*, *KRAS* or *HRAS* mutations in codons 12, 13 or 61. **Results:** There were 54 pts (45%) with *RAS*^{mut} in BOSTON (XVd = 26, Vd = 28), and 17 (33%) in STORM. In BOSTON, pts with *RAS*^{mut} MM treated with XVd had significantly longer progression-free survival (PFS) than those treated with Vd (median [med] = 12.9 vs 6.7 months [mo], hazard ratio [HR] = 0.48 [95% CI 0.24-0.97], p = 0.039). For pts treated with Vd, those with *RAS*^{mut} had significantly shorter overall survival (OS) compared to *RAS*$^{wild\text{-}type\ (WT)}$ (med = 16.8 mo vs not reached [NR], HR = 2.87 [95% CI 1.03-7.99], p = 0.035). PFS was not significantly different (med = 6.74 vs 9.82 mo, HR = 1.64 [95% CI 0.88-3.07], p = 0.122). Amongst pts on XVd, there was no difference in survival between *RAS*^{mut} and *RAS*^{WT} pts (PFS: med = 12.8 vs 12.9 mo, HR = 1.08 [95% CI 0.52-2.26], p = 0.83; OS: med = NR vs NR, HR = 0.94 [95% CI 0.36-2.45], p = 0.91). In STORM, pts with *RAS*^{mut} had shorter OS compared to *RAS*^{wt} pts (med = 6.1 vs NR, HR = 2.05 [95% CI 1.22-5.19], p = 0.010). Preliminary studies to explore the mechanisms of action related to *RAS*^{mut} MM sensitivity to XVd demonstrated that selinexor treatment in vitro leads to downregulation of GCK. **Conclusions:** Despite typically having the worst outcomes, pts with *RAS*^{mut} MM had a similar benefit from XVd as *RAS*^{WT} MM, showing that the XVd combination can overcome *RAS*^{mut}. Mechanistically, selinexor induced down regulation of GCK and enhanced killing of *RAS*^{mut} MM cells. With a manageable safety profile, the XVd regimen could provide a viable treatment option to improve survival of pts with MM with RAS mutations. Clinical trial information: NCT03110562. Research Sponsor: None.

	PFS		OS	
	p-value	HR (95% CI)	p-value	HR (95% CI)
BOSTON *RAS*$_{mut}$ XVd vs Vd	0.039	0.48 (0.24-0.97)	0.22	0.57 (0.23, 1.41)
BOSTON XVd arm *RAS*^{mut} vs *RAS*^{WT}	0.83	1.08 (0.52, 2.26)	0.91	0.94 (0.36, 2.45)
BOSTON Vd arm *RAS*^{mut} vs *RAS*^{WT}	0.12	1.64 (0.88, 3.07)	0.035	2.87 (1.03, 7.99)
STORM (Xd) *RAS*^{mut} vs *RAS*^{WT}	0.28	1.58 (0.69, 3.63)	0.010	2.51 (1.22, 5.19)

8028 **Poster Session**

Incidence, mitigation, and management of neurologic adverse events in patients with multiple myeloma (MM) treated with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-2. *First Author: Hermann Einsele, Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany*

Background: Cilta-cel (JNJ-68284528) is a chimeric antigen receptor T (CAR-T)-cell therapy with 2 BCMA-targeting, single-domain antibodies designed to confer high avidity binding. CARTITUDE-2 (NCT04133636) is a phase 2, multicohort, open-label study assessing the efficacy and safety of cilta-cel in patients (pts) with MM in various clinical settings. Here, we describe the mitigation and management strategies implemented to identify and reduce the risk for neurologic adverse events (AEs) in Cohort A pts (progressive MM after 1−3 prior lines of therapy). **Methods:** Eligible pts (≥18 years of age) had MM per IMWG criteria, measurable disease, ECOG ≤1, progressive disease after 1−3 prior lines of therapy (including a PI and IMiD) and were lenalidomide refractory (no prior BCMA-targeting agent). Cilta-cel (0.75×10^6 [range $0.5–1.0\times10^6$] CAR+ viable T cells/kg) was given as a single infusion 5–7 days after start of lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 daily for 3 days). Monitoring and mitigation strategies for neurologic AEs include providing more effective bridging therapy to reduce tumor burden prior to lymphodepletion, frequent assessment of CAR-T-related ICANS using the ICE tool, regular handwriting assessments to detect micrographia, and neuroimaging (brain MRI) and EEG for pts with prior neurologic disease. Management strategies include evaluating infectious and paraneoplastic etiologies upon observation of ICANS ≥Grade (gr) 1, administration of tocilizumab (if concurrent CRS, all gr of ICANS) and/or dexamethasone (gr 2/3) or methylprednisolone (gr 4). ICANS and CRS were graded by ASTCT criteria; neurotoxicities not classified as ICANS were graded per CTCAE Version 5.0. **Results:** As of 15 Jan 2021 (median follow-up: 5.8 months [range: 2.5–9.8 months]), 20 pts in Cohort A received cilta-cel. Median age was 60 years (range: 38–75); 65% were male. Neurotoxicities occurred in 4 pts (20%). Three pts had ICANS (gr 1/2); median time to onset of symptoms was 8 days (range: 7–11) and median duration was 2 days (range: 1–2). Two of the 3 pts received supportive measures to treat ICANS, including levetiracetam and steroids; all 3 had concurrent CRS and all recovered. One pt developed isolated facial paralysis (gr 2) on Day 29 after cilta-cel infusion, and recovered 51 days after the onset of event following treatment with dexamethasone for 28 days. No movement or neurocognitive disorders were reported. **Conclusions:** Neurologic AEs were generally manageable in pts with MM following treatment with cilta-cel. With a median of 5.8 months of follow-up, there were no movement or neurocognitive disorders in pts from Cohort A. These results suggest that early detection and management of neurologic AEs can lead to better treatment outcomes. Clinical trial information: NCT04133636. Research Sponsor: Janssen Research & Development, LLC, Pharmaceutical/Biotech Company.

8029 **Poster Session**

Personalized, ctDNA analysis to detect minimal residual disease and identify patients at high risk of relapse with multiple myeloma. *First Author: Binod Dhakal, Medical College of Wisconsin, Milwaukee, WI*

Background: Despite treatment with high-dose chemotherapy followed by autologous stem cell transplantation (AHCT), MM patients invariably relapse. MRD-negativity post-AHCT has emerged as the most important prognostic marker. Currently, MRD in MM is monitored via bone marrow aspirate sampling. Marrow MRD assays are limited by the spatial heterogeneity of marrow MM localization; extramedullary disease and sampling variability of marrow aspiration. Sensitive, non-invasive blood-based MRD assay is an unmet need. ctDNA as a noninvasive biomarker can be utilized to predict relapse in MM. Here we attempt to evaluate MRD using ctDNA in AHCT recipients with MM. **Methods:** In this retrospective, single-center study, we analyzed ctDNA MRD in blood samples collected from 28 patients with MM after upfront AHCT. A total of 80 plasma timepoints were available pre and post AHCT with a median follow-up of 92.4 months. Multiparameter flow cytometry (MFC) at 10-4 level was used to assess the MRD from the BM biopsy. Individual bone marrow aspirates or FFPE slides from the time of MM diagnosis and matched normal blood were whole-exome sequenced, and somatic mutations were identified. MRD assessment at 3 months post-AHCT was performed by ctDNA analysis using a personalized, tumor-informed (Signatera^{TM}, bespoke mPCR NGS assay). The prognostic value of ctDNA was evaluated by correlating MRD status with clinical outcomes. **Results:** Table provides the baseline disease characteristics. Median age was 67 [41-75] years and 16 [57.1%] were males. ctDNA was detectable in 70.8% (17/24) of pre-AHCT, 53.6% (15/28) of ~3 months post-AHCT, and 39.2% (11/28) of patients during the surveillance phase post-AHCT. Of the 15 ctDNA MRD positive patients, 93.3% (n=14) experienced relapse on follow-up (hazard ratio: 5.64; 95% CI: 1.8-17; p=0.0003). Patients negative for ctDNA at 3 months post-AHCT had significantly superior progression-free survival (PFS) compared to positive (median PFS, 84 months vs. 31 months; p=0.003) The positive predictive value (PPV) for relapse among patients positive for ctDNA at 3 months post-AHCT was 93.3%, and significantly higher than marrow MFC of 68.4%. **Conclusions:** Our study shows the feasibility that a tumor-informed assay on archival blood samples is predictive of relapse post-AHCT. Future prospective studies with real-time marrow NGS and ctDNA samples are needed to define the role of ctDNA in MM and its prognostic significance. Research Sponsor: None.

Baseline characteristics.

Characteristics	N=28 (%)
Isotype	
IgG kappa/lambda	20 (71)
IgA kappa/lambda	3 (11)
Light chain	5 (18)
ISS stage	
I	15 (54)
II	11 (39)
III	1 (3.5)
Unknown	1 (3.5)
High risk cytogenetics	4 (14)
Induction	
VRD	13 (46)
CyBorD	11 (39)
Others	4 915)
Post-Transplant response	
Complete/near complete response	14 (50)
Very good partial response	5 (18)
Partial response	9 (32)

8030 **Poster Session**

Cilta-cel versus conventional treatment in patients with relapse/refractory multiple myeloma. *First Author: Luciano J. Costa, University of Alabama at Birmingham, Birmingham, AL*

Background: CARTITUDE-1 is a single arm study of Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) anti-BCMA CAR-T cell therapy in US patients (pts) with relapsed multiple myeloma (RRMM) refractory to both IMiD and proteasome inhibitor (PI) or with at least 3 prior lines of therapy and previously exposed to anti-CD38 monoclonal antibody (MoAb). While recently reported efficacy results of cilta-cel were encouraging, it is unknown how they compare with similar pts receiving conventional (non CAR-T) treatment. **Methods:** We utilized a contemporary US-based dataset of pts with MM refractory to anti-CD38 MoAb (MAMMOTH) to identify pts who would meet eligibility for CARTITUDE-1 and who received conventional therapy. We analyzed the intent-to-treat population (ITT) in CARTITUDE-1, defined as pts who underwent apheresis (N=113) and a modified ITT population (mITT) defined as subset of pts who received cilta-cel at the RP2D (N=97). From the MAMMOTH dataset, we identified a population corresponding to CARTITUDE-1 ITT (N=190) and a mITT population, pts without death or progression within 47 days (median time between apheresis and cilta-cel infusion) from onset of therapy (N=122). We calculated propensity scores (PS) with demographics, N of prior therapies, cytogenetics and refractoriness to MM agents as covariates. An analyst blinded to outcomes performed nearest neighbor 1:1 PS matching. We analyzed overall response rate (ORR), progression-free (PFS) and overall survival (OS) for ITT and mITT in CARTITUDE-1 vs matching MAMMOTH cohorts. **Results:** Ninety-five ITT (75 received bridging therapy, 82 received cilta-cel) and 69 mITT (54 received bridging) CARTITUDE-1 pts matched MAMMOTH pts (Table). Among the pts in the MAMMOTH ITT cohort 34% received pomalidomide, 24% anti-CD38 MoAb, 19% carfilzomib and 35% cytotoxic chemotherapy in next therapy. ORR in the ITT cohorts was higher in CARTITUDE-1 (84% vs. 28%). Compared to their MAMMOTH counterparts, pts in CARTITUDE-1 ITT cohort had improved PFS (12 mo. 73% vs. 12%) and OS (12 mo. 83% vs 39%). Between the mITT cohorts, CARTITUDE-1 pts had superior ORR (96% vs. 30%), PFS (12 mo 79% vs. 15%) and OS (12 mo. 88% vs. 41%). **Conclusions:** In pts with RRMM beyond therapy with IMID, PI, and anti-CD38 MoAb, treatment with cilta-cel is associated with higher response rate and superior PFS and OS when compared to conventional treatment. Research Sponsor: Janssen.

	ITT (apheresis) CARTITUDE (N=95)	ITT matches, MAMMOTH (N=95)		mITT (treated) CARTITUDE (N=69)	mITT matches, MAMMOTH (N=69)	
Mean Age -years (sd)	62.4 (8.5)	62 (8.5)		62.6 (7.7)	62.7 (9.4)	
High cytogenetic risk	22%	24%		25%	23%	
Mean N lines of therapy (sd)	6.2 (3.0)	6.3 (2.4)		5.9 (2.9)	6 (1.9)	
Triple-class refractory	97%	96%		96%	96%	
Penta exposed	80%	76%		75%	75%	
Penta refractory	43%	42%		35%	42%	
ORR	84%	28%	P<0.001	96%	30%	P<0.001
PFS	HR=0.11, 95% C.I. 0.05-0.22		P<0.001	HR=0.02, 95% C.I. 0.01-0.14		P<0.001
OS	HR=0.20, 95% C.I. 0.10-0.39		P<0.001	HR=0.05, 95% C.I. 0.01-0.22		P<0.001

8031 **Poster Session**

Assessing financial difficulty in patients with multiple myeloma: Preliminary results of ALLIANCE A231602CD. *First Author: Rena M. Conti, Boston University Questrom School of Business, Boston, MA*

Background: New orally administered anticancer treatments have launched in recent years, promising gains in survival and quality of life, but with high prices.Financial difficulties encountered over the course of cancer diagnosis and treatment is a growing concern. These difficulties include inability to pay for basic necessities, presence of medical debt, and high out of pocket burdens relative to income. The primary objective of this study was to estimate the proportion of patients with multiple myeloma (MM) who experience financial difficulties in the past 12 months.**Methods:** Data collection entailed a comprehensive, theoretically grounded telephone survey and companion medical chart abstraction. Subjects included individuals with a current diagnosis of MM whose current or recent treatment included pharmaceutical-based care and who were not enrolled in a treatment-based trial. Practices eligible to recruit respondents included 44 NCORP affiliates of the Alliance. 14 geographically diverse NCORP affiliates participated between 11/2019 and 6/2020. The primary endpoint of the study was the proportion of subjects who reported financial difficulty in the past 12 months, as measured by the EORTC QLQ-C30 item #28. This proportion and 95% Wilson score confidence interval were estimated for all MM patients who responded to the financial difficulty question ((# reported financial difficulty)/(total # in that category who answered the question)). NCI Central IRB approved this study. **Results:** 393 subjects were recruited. 304 subjects completed the survey (77.4% response rate). Mean age was 67.5 years (SD 9.8), 143 (46.4%) were female, 24 (7.8%) self-reported race as 'Black or African American', 82 (26.6%) reported insured by government insurance Medicare only, 116 (38.2%) reported highest education as high school or below, and 94 (30.5%) reported high income. Mean time from diagnosis to survey enrollment was 3.6 years (SD 4.5). 292 (95.1%) were currently receiving treatment and 192 (62.5%) reported currently receiving a pre-defined 'expensive' oral pharmaceutical-based cancer treatment. 20.2% (95% CI:16.1%, 25.0%) reported financial difficulties. **Conclusions:** This is the first national study to systematically assess the prevalence of financial difficulties and its correlates among MM patients. Approximately 1 in 5 surveyed patients reported financial difficulties. Results of this study aim to inform efforts to improve financial navigation and resources for cancer patients. Research Sponsor: U.S. National Institutes of Health, Leukemia and Lymphoma Society.

8032 **Poster Session**

5-Hydroxymethylcytosines in circulating cell-free DNA and overall survival in patients with multiple myeloma. *First Author: Brian C Chiu, Department of Public Health Sciences, The University of Chicago, Chicago, IL*

Background: The epigenetic mark 5-methylcytosines (5mC) have been associated with poor prognosis and survival in multiple myeloma (MM), but the prognostic role of 5-hydroxymethylcytosines (5hmC) as marks of tissue-specific enhancers generated from 5mC through active demethylation is unknown. We showed that 5hmC can be profiled in circulating cell-free DNA (cfDNA) and is associated with relapse/death in another lymphoproliferative disorder diffuse large B-cell lymphoma. To date, no study has investigated genome-wide 5hmC profiles in cfDNA for its prognostic significance in MM. **Methods:** A total of 354 newly diagnosed MM patients at the University of Chicago Medical Center were prospectively enrolled between 2010-2017. Blood samples were collected at the time of diagnosis. Patients were followed through 31 December 2020 (avg. follow-up = 77.8 mths). We collected baseline clinical, laboratory, and cytogenetic data from electronic medical records. Vital status was ascertained in 351 of the 354 patients (deaths = 73) using the National Death Index. We profiled genome-wide 5hmC in cfDNA using the 5hmC-Seal and next-generation sequencing. The 5hmC-Seal data were mapped to the human genome reference (hg19) and annotated to gene bodies. Overall survival (OS) was defined as time from diagnosis until death from any cause. We used Cox proportional hazards model and the elastic net regularization to identify genes with modified 5hmC levels that are associated with OS. Patients were randomly divided into a training set (n = 264) and testing set (n = 87). **Results:** The median age at diagnosis was 61.8 years and 47% (n = 165) were males. We used the differential 5hmC enrichment levels of a preliminary four-gene marker panel (i.e., *YPEL1*, *VIPR2*, *PLAC8L1*, and *CYP2D6*) to compute a weighted prognostic score (wp-score). In the training set (deaths = 55), MM patients with high wp-score had worse OS (Hazard Ratio [HR] = 2.2, 95% Confidence Interval [CI]: 1.3-3.9; p = 0.004). The same trend was observed in the testing set (deaths = 18) (HR = 3.5, 95% CI: 1.1-10.6; p = 0.02). The 5hmC-based wp-score remained significantly associated with OS after controlling for standard prognostic factors, suggesting that 5hmC-based wp-score for this 4-gene panel is an independent prognostic factor for MM. We also explored population-specific 5hmC and wp-score. We found that 5hmC profiles in cfDNA differ between Blacks (n = 117) and Whites (n = 234). In addition, 5hmC marker genes associated with OS differ between Blacks (13 genes) and Whites (20 genes). **Conclusions:** Our results suggest that 5hmC in cfDNA at the time of diagnosis correlate with OS in MM and the 5hmC marker genes associated with OS differ between Blacks and Whites. These findings suggest that a plasma-derived cfDNA 5hmC-modified gene panel holds promise as a noninvasive approach for predicting prognosis in MM and may be integrated in clinical practice to improve precision care. Research Sponsor: U.S. National Institutes of Health.

8033 **Poster Session**

Relationship between corneal exam findings, best-corrected visual acuity (BCVA), and ocular symptoms in patients with relapsed or refractory multiple myeloma (RRMM) receiving belantamab mafodotin (belamaf). *First Author: Evangelos Terpos, National and Kapodistrian University of Athens School of Medicine, Athens, Greece*

Background: Belantamab mafodotin (GSK2857916; belamaf; BLENREP) is a B-cell maturation antigen (BCMA)-targeting antibody–drug conjugate approved in the US and EU as a monotherapy for the treatment of adult patients with RRMM. Ocular events (OEs) during the pivotal DREAMM-2 trial (NCT03525678) included corneal exam findings (punctate keratopathy and microcyst-like epithelial changes), BCVA changes, and ocular symptoms. Dose reductions or delays based on corneal exam findings and BCVA were used to manage OEs. Here we performed a *post hoc* investigation of relationships between corneal exam findings, BCVA changes, and patient-reported ocular symptoms to explore if BCVA changes and symptoms could guide dosing, rather than corneal exams. **Methods:** Eye evaluations (including a corneal exam and BCVA assessment of Snellen visual acuity) were performed on all patients receiving single-agent belamaf (2.5 mg/kg) by ophthalmologists at baseline and prior to each belamaf dose. Changes in the corneal epithelium (Ker) and BCVA were both assessed as per protocol-defined criteria and assessment of grade (Gr) was based on the worse eye. BCVA grading was relative to baseline. Patient-reported ocular symptoms were reported as per the Common Terminology Criteria for Adverse Events. **Results:** In 12.5% of eye evaluations Gr 3–4 Ker was associated with minimal or no (Gr ≤1) BCVA changes. When patient-reported ocular symptoms were also considered, only 7.5% of evaluations found Gr 3–4 Ker with Gr ≤1 BCVA changes or ocular symptoms. Mild or no (Gr ≤2) Ker was associated with Gr ≤1 BCVA changes in 59.5% of evaluations, or in 38.8% of evaluations with no ocular symptoms reported. Overall, Gr 3–4 Ker were found in 24.9% of evaluations; by contrast, patients had Gr 2–4 BCVA changes or ocular symptoms in 53.7% of evaluations. Association of corneal epithelium changes (Ker) with BCVA changes and ocular symptoms. **Conclusions:** These findings highlight that BCVA changes and ocular symptoms should be further investigated to determine if they can be used as alternatives (eg, frequency of eye examinations based on symptoms) for the management of belamaf dosing to potentially reduce the burden on patients and healthcare professionals. Clinical trial information: NCT03525678. Research Sponsor: GlaxoSmithKline, Drug linker technology licensed from Seagen Inc.; mAb produced using POTELLIGENT Technology licensed from BioWa.

Ker + BCVA changes only (evaluations, n=773); n (%)	
Gr 3–4 Ker & Gr ≤1 BCVA	97 (12.5)
Gr 3–4 Ker & Gr 2–4 BCVA	96 (12.4)
Gr ≤2 Ker & Gr ≤1 BCVA	460 (59.5)
Gr ≤2 Ker & Gr 2–4 BCVA	120 (15.5)
Ker + BCVA changes or ocular symptoms (evaluations, n=773); n (%)	
Gr 3–4 Ker & (Gr ≤1 BCVA, no symptoms)	58 (7.5)
Gr 3–4 Ker & (Gr 2–4 BCVA, or symptoms)	135 (17.4)
Gr ≤2 Ker & (Gr ≤1 BCVA, no symptoms)	300 (38.8)
Gr ≤2 Ker & (Gr 2–4 BCVA, or symptoms)	280 (36.2)

8034 **Poster Session**

Isatuximab plus carfilzomib and dexamethasone in patients with relapsed multiple myeloma according to prior lines of treatment and refractory status: IKEMA subgroup analysis. *First Author: Roman Hajek, Department of Hemato-Oncology, University Hospital Ostrava and University of Ostrava, Ostrava, Czech Republic*

Background: Patients (pts) with multiple myeloma (MM) often relapse and become refractory to successive lines of therapy, warranting better treatment options. The Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) plus carfilzomib and dexamethasone (Kd) significantly improved progression-free survival (PFS) compared with Kd in pts with relapsed MM (RMM) (HR 0.53; 99% CI 0.32–0.89; *P*= 0.0007). We evaluated the efficacy and/or safety of Isa-Kd by number of prior lines of therapy (1 vs > 1) and refractoriness to lenalidomide (Len) or bortezomib (Bor). **Methods:** Pts were randomized (3:2) to Isa-Kd (n = 179) or Kd (n = 123). Isa (10 mg/kg IV) was given weekly for 4 weeks, then every 2 weeks. K (20 mg/m^2 days 1-2, then 56 mg/m^2) was given twice-weekly 3 of 4 weeks, and d (20 mg) twice-weekly. The primary endpoint was PFS; key secondary endpoints were very good partial response or better (≥VGPR), minimal residual disease negativity (MRD-), and complete response (CR) rates. **Results:** Of the 302 randomized pts, 44.7% had 1 prior line, 55.3% had > 1 prior line, 32.8% were Len-refractory, and 30.1% were Bor-refractory. PFS was improved with Isa-Kd vs Kd in pts who received 1 prior line and > 1 prior line, as well as in pts refractory to Len, Len at last regimen, Bor, or Bor at last regimen (Table). The addition of Isa to Kd improved depth of response (≥VGPR, MRD-, and CR rates) in all subpopulations analyzed by prior treatment. Grade ≥3 treatment-emergent adverse events (TEAEs) were generally similar between the prior line subgroups (77.2% [Isa-Kd] vs 64.8% [Kd], 1 prior line; 76.5% [Isa-Kd] vs 69.1% [Kd], > 1 prior line) and the overall safety population (76.8% [Isa-Kd] vs 67.2% [Kd]). Serious AEs were 62.0% vs 48.1% in the 1 prior line subgroup, and 57.1% vs 64.7% in the > 1 prior line subgroup; TEAEs leading to discontinuations were 8.9% vs 11.1%, 1 prior line and 8.2% vs 16.2%, > 1 prior line. **Conclusions:** The addition of Isa to Kd improved PFS and depth of response, irrespective of prior lines of therapy or refractory status, consistent with the benefit observed in the overall IKEMA study population. Isa-Kd had a manageable safety profile regardless of number of prior lines. Isa-Kd is a potential new treatment option for pretreated pts with RMM. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

		n		PFS, HR (95% CI)	≥VGPR, %		MRD-, %		CR, %	
		Isa-Kd	Kd	-	Isa-Kd	Kd	Isa-Kd	Kd	Isa-Kd	Kd
Overall		179	123	0.53 (0.32-0.89)*	72.6	56.1	29.6	13.0	39.7	27.6
Number of prior lines as per randomization	1	80	55	0.59 (0.31-1.12)	75.0	61.8	33.8	18.2	41.3	36.4
	> 1	99	68	0.48 (0.29-0.78)	70.7	51.5	26.3	8.8	38.4	20.6
Refractory to Len	Yes	57	42	0.60 (0.34-1.1)	66.7	35.7	24.6	9.5	38.6	11.9
Refractory to Len at last regimen	Yes	36	31	0.69 (0.35-1.39)	72.2	38.7	27.8	9.7	47.2	12.9
Refractory to Bor	Yes	52	39	0.62 (0.33-1.16)	55.8	51.3	17.3	10.3	28.8	17.9
Refractory to Bor at last regimen	Yes	32	23	0.38 (0.16-0.92)	62.5	47.8	25.0	8.7	31.3	17.4

*99% CI.

8035 **Poster Session**

Daratumumab (DARA) maintenance therapy following DARA + cyclophosphamide, bortezomib, and dexamethasone (CyBorD) induction therapy in multiple myeloma (MM): End-of-study analysis of LYRA. *First Author: Robert M. Rifkin, US Oncology Research, Rocky Mountain Cancer Centers, Denver, CO*

Background: LYRA is a community practice-based, phase 2, single-arm study (NCT02951819) evaluating DARA + CyBorD as an immunomodulatory drug-sparing regimen in MM. The primary analysis demonstrated the safety and efficacy of DARA + CyBorD in newly diagnosed MM (NDMM) and relapsed MM (RMM), and an update showed that DARA maintenance therapy deepened responses. We present the final end-of-study analysis of LYRA. **Methods:** US pts aged ≥18 years with MM per IMWG criteria and ≤1 prior line of therapy received 4-8 induction cycles of DARA + CyBorD (cyclophosphamide 300 mg/m^2 PO weekly [QW]; bortezomib 1.5 mg/m^2 SC on Days [D] 1, 8, and 15; dexamethasone 40 mg PO or IV QW every 28 days; DARA IV 8 mg/kg on D1 and D2 of cycle [C]1, 16 mg/kg QW C1D8-C2, 16 mg/kg Q2W C3-6, and 16 mg/kg Q4W C7-8). After induction, eligible pts could receive autologous stem cell transplantation (ASCT). Pts received up to 12 maintenance cycles with DARA 16 mg/kg IV Q4W and were followed for up to 36 months after induction. **Results:** In total, 101 (NDMM, n = 87; RMM, n = 14) pts were enrolled; 36% of pts had high-risk cytogenetics. NDMM and RMM pts received a median of 6 and 8 induction cycles, respectively. Among NDMM pts, 44.8% (39/87) underwent ASCT and 72.4% (63/87) completed 12 months of maintenance. Rates of ≥VGPR and ≥CR were 82.1% and 48.7% in NDMM pts who underwent ASCT, and 70.2% and 29.8% in NDMM pts who did not (Table). With a median follow-up of 35.7 months, median progression-free survival (PFS) and overall survival (OS) were not reached for NDMM pts. Estimated 36-month PFS rates were 69.3% and 72.6% for NDMM pts who did and did not receive ASCT, respectively; estimated 36-month OS rates were 94.9% and 84.3% (Table). Among RMM pts, 7.1% (1/14) underwent ASCT and 50.0% (7/14) completed 12 months of maintenance; efficacy outcomes are shown in the Table. Grade 3/4 treatment-emergent adverse events (TEAEs) occurred in 62.0% of all pts, with the most common (≥10%) being neutropenia (14.0%). Serious TEAEs occurred in 33.0% of pts, the most common being pneumonia (4.0%) and pulmonary embolism (3.0%). TEAEs led to death in 2.0% of pts, all unrelated to study treatment. Infusion-related reactions occurred in 56.0% of pts; the majority were mild (4.0% of pts had grade 3/4 events). **Conclusions:** DARA used for induction with CyBorD and maintenance as monotherapy resulted in durable, deep responses in pts with NDMM or RMM, with a 3-year PFS rate of 70% in NDMM irrespective of ASCT status. With longer follow-up, no new safety concerns were identified. Clinical trial information: NCT02951819. Research Sponsor: Janssen Research & Development, LLC.

	NDMM who received ASCT (n = 39)	NDMM who did not receive ASCT (n = 47)	RMM (n = 14)
ORR, %	97.4	83.0	85.7
sCR	23.1	17.0	28.6
≥CR	48.7	29.8	64.3
≥VGPR	82.1	70.2	71.4
	(n = 39)	(n = 48)	(n = 14)
Estimated 36-mo PFS, % (95% CI)	69.3 (43.0-85.3)	72.6 (54.0-84.7)	31.7 (5.6-63.4)
Estimated 36-mo OS, % (95% CI)	94.9 (81.0-98.7)	84.3 (69.8-92.2)	50.0 (22.9-72.2)

8036 **Poster Session**

Characteristics of neurotoxicity associated with idecabtagene vicleucel (ide-cel, bb2121) in patients with relapsed and refractory multiple myeloma (RRMM) in the pivotal phase II KarMMa study. *First Author: Salomon Manier, Centre Hospitalier Regional Universitaire de Lille, Lille, France*

Background: Ide-cel, a BCMA-directed CAR T cell therapy, showed promising efficacy in patients (pts) with RRMM in the KarMMa study with an ORR of 73% and a CRR of 33% across target doses of 150–450 $\times$ 10^6 CAR+ T cells (Munshi NC, et al. *J Clin Oncol* 2020;38[suppl 15]. Abstract 8503). Associations of neurotoxicity (NT) with pt and disease characteristics, pt management, and impact on outcomes in the KarMMa study are reported here. **Methods:** Enrolled pts were triple-class exposed and refractory to their last regimen, with ide-cel given at target doses of 150, 300, or 450 $\times$ 10^6 CAR+ T cells after lymphodepletion (NCT03361748). Investigator-identified NT events were captured under the single preferred term of neurotoxicity and graded according to NCI CTCAE v4.03. Events were managed with corticosteroids (CS), anakinra (ANR), and tocilizumab (Toci) as needed. **Results:** Of 128 pts treated with ide-cel, NT was reported in 23 (18%); 12 pts (9%) had maximum grade (gr) 1 NT, 7 (5%) had gr 2, and 4 (3%) had gr 3. No gr 4 or 5 NT occurred. Most baseline characteristics were similar in pts with and without NT, including stage III disease (22% and 15%), high-risk cytogenetics (39% and 34%), and extramedullary disease (35% and 40%); exceptions were high tumor burden (65% and 48%) and sex (48% and 62% men). NT (any gr/gr 3) occurred in 0%/0%, 17%/1%, and 20%/6% of pts at doses of 150, 300, and 450 $\times$ 10^6 CAR+ T cells. Median time to onset was similar regardless of gr, and there were no late-onset events (Table). NT was managed with CS in 10 pts (43%), Toci in 3 (13%), and ANR in 1 (4%). Median (range) time to first use of CS was 2 d (1–6). ORR and DOR were similar in pts with and without NT (Table). All NT occurred in the proximity of cytokine release syndrome (CRS) events with the start date of NT events either overlapping with or occurring within 1 wk of the start of a CRS event. **Conclusions:** NT occurred early in the KarMMa study, was generally of short duration, and was mostly gr 1/2 with no gr ≥4 events. All NT was proximal to CRS. Pts with NT had a favorable ORR after ide-cel treatment. These results continue to demonstrate the durable efficacy and tolerability of ide-cel in pts with RRMM. Clinical trial information: NCT03361748. Research Sponsor: Celgene, a Bristol-Myers Squibb Company, and bluebird bio.

NT events	Gr 1 (n = 12)	Gr 2 (n = 7)	Gr 3 (n = 4)	Any gr (n = 23)
Time to onset, median (range), d	2 (1–10)	2 (1–4)	3 (1–4)	2 (1–10)
No. of events	13	7	4	24
Duration/event, %				
1–5 d	69	43	25	54
6–10 d	31	29	0	25
>10 d	0	14	75	17
Ongoing	0	14	0	4
Median (range), d[a]	3 (1–9)	6 (1–26)	14 (2–22)	3 (1–26)
CS / Toci / ANR, %	17 / 8 / 0	57 / 0 / 0	100 / 50 / 25	43 / 13 / 4

Efficacy	No NT (n = 105)	NT, any gr (n = 23)
Response, % (95% CI)		
ORR	73 (64.9–81.8)	74 (56.0–91.9)
CRR	35 (26.1–44.4)	22 (4.9–38.6)
PFS, median (95% CI), mo	8.9 (5.7–11.9)	6.1 (3.0–11.1)
DOR,[b] median (95% CI), mo	11.0 (8.0–11.3)	10.0 (4.0–NE)
OS, median (95% CI), mo	19.4 (18.0–NE)	NE (12.3–NE)

Data cutoff: 14 Jan 2020. NE, not estimable. [a]Ongoing NT excluded. [b]Among responders.

8037 **Poster Session**

ANCHOR (OP-104): Melflufen plus dexamethasone (dex) and bortezomib (BTZ) in relapsed/refractory multiple myeloma (RRMM)—Optimal dose, updated efficacy and safety results. *First Author: Roman Hajek, Department of Hemato-oncology, University Hospital Ostrava, Ostrava, Czech Republic*

Background: Development of resistance to standard treatments for RRMM highlights the need for novel therapies. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and rapidly releases alkylating agents inside tumor cells. Melflufen + dex showed clinical activity and an acceptable safety profile in HORIZON (Richardson et al. *J Clin Oncol.* 2020 Dec 9 [Epub]). This is an update of the BTZ arm of the phase 1/2a ANCHOR study (NCT03481556). **Methods:** Patients (pts) with RRMM were intolerant or refractory to a prior IMiD, with 1-4 prior lines of therapy (LoTs). Prior treatment with a proteasome inhibitor (PI) was allowed, but pts could not be refractory to PIs in the last LoT. Melflufen (30, 40, or 20 mg intravenously; d 1 of each 28-d cycle) was administered with BTZ (1.3 mg/m^2 subcutaneous) + oral dex (20 mg on d 1, 4, 8, and 11 and 40 mg on d 15 and 22; dex dose reduced if aged ≥ 75 y). The primary objective in phase 1 was to determine the optimal phase 2 dose of melflufen for this combination. **Results:** As of the data cutoff date (October 19, 2020), 13 pts received melflufen (30 mg, n = 6; 40 mg, n = 7) + dex and BTZ. In the 30 mg and 40 mg cohorts, respectively, median age was 78.5 y (range, 70-82) and 70.0 y (range, 61-76); median prior LoTs was 3.5 (range, 2-4) and 2.0 (range, 1-4); 33% and 50% of evaluable pts had high-risk cytogenetics; 83% and 71% were refractory to last LoT; 100% and 86% received a prior PI; 33% and 14% were refractory to PIs. In the 30 mg and 40 mg cohorts, respectively, median treatment duration was 6.5 mo (range, 1.4-29.0) and 8.7 mo (range, 2.1-19.6); 4 (67%) and 4 pts (57%) were still on treatment; 2 and 3 pts discontinued (30 mg: progressive disease [PD] and other [1 pt each]; 40 mg: adverse event [AE], lack of efficacy, and PD [1 pt each]). Confirmed overall response rate in the 30 mg and 40 mg cohorts, respectively, was 50% (1 very good partial response [VGPR] and 2 partial response [PR]) and 71% (1 complete response, 3 VGPR, and 1 PR). Most common grade 3/4 treatment-related AEs (TRAEs) were thrombocytopenia (30 mg: 50%; 40 mg: 100%) and neutropenia (30 mg: 33%; 40 mg: 71%); grade 3/4 nonhematologic TRAEs were infrequent; 3 pts discontinued study treatment due to treatment-emergent AEs (30 mg: cardiac failure chronic and osteolysis [1 pt each]; 40 mg: thrombocytopenia [1 pt]). Serious TRAEs occurred in 2 pts (33%) in the 30 mg cohort (neutropenia and pneumonia [1 pt], syncope [1 pt]) and 1 pt (14%) in the 40 mg cohort (thrombocytopenia and neutropenia). No dose-limiting toxicities occurred at either dose level. Fatal AEs occurred in 1 pt in the 30 mg cohort (cardiac failure chronic; unrelated to study treatment). **Conclusions:** ANCHOR determined that the optimal dose of melflufen is 30 mg + dex and BTZ; results showed clinical activity in heavily pretreated pts. Recruitment is ongoing; updated data will be presented. Clinical trial information: NCT03481556. Research Sponsor: Oncopeptides AB.

8038 **Poster Session**

Once weekly selinexor, carfilzomib, and dexamethasone (XKd) in carfilzomib nonrefractory multiple myeloma (MM) patients. *First Author: Cristina Gasparetto, Duke University Medical Center, Durham, NC*

Background: Exportin 1 (XPO1) mediates the nuclear export and functional inactivation of tumor suppressor proteins (TSPs), is associated with poor prognosis in MM, and contributes to proteasome inhibitor (PI) and immunomodulatory drug (IMiD) resistance. Selinexor (SEL) is a novel, oral, first-in-class selective inhibitor of nuclear export (SINE) compound that blocks XPO1, forcing the nuclear retention and activation of TSPs. SEL in combination with low dose dexamethasone (dex) ± bortezomib (BOR) is FDA approved for previously treated MM. The synergy of SEL with the PI BOR has been confirmed in the phase 3 BOSTON study in MM patients (pts) with 1-3 prior therapies; once weekly (QW) SEL, QW BOR, and dex (XVd) significantly increased progression-free survival (PFS), time to next therapy, and overall response rate (ORR) as compared to standard twice weekly BOR/dex (Vd), despite XVd using 40% less BOR and 25% less dex than standard Vd. We hypothesized that the addition of QW SEL to the PI carfilzomib (CAR)-dex (XKd) would be an active and tolerable regimen in pts with heavily pretreated MM. **Methods:** In the XKd arm of the multi-arm Phase 1b/2 STOMP study, SEL at 80 or 100 mg QW was evaluated in combination with CAR at 56 or 70 mg/m^2 QW plus dex at 40 mg QW in pts with heavily pretreated MM not refractory to CAR. Study objectives were to determine the maximum tolerated dose and recommended phase 2 dose (RP2D) and assess the safety and activity of the XKd regimen. **Results:** As of 4Jan2021, 27 pts were enrolled: 18 (67%) were male, median age 71 years (range 50-76), and median of 4 (range 1-8) prior lines of therapy. All 27 pts were previously treated with BOR, 26 (96%) lenalidomide (LEN), 19 (70%) pomalidomide (POM), 18 (67%) daratumumab (dara). The majority (67%) of pts were triple-class pretreated (PI, IMiD, and anti-CD38 mAb), and 44% had triple-class refractory MM. Nine pts (33%) had MM quad-refractory to BOR, LEN, POM, and dara. Common hematologic treatment-related adverse events (TRAEs) (total, grade ≥3) included thrombocytopenia (74%, 56%), anemia (59%, 19%), and neutropenia (30%, 7%). Non-hematologic TRAEs included nausea (67%, 4%), fatigue (52%, 7%), and anorexia (52%, 4%). RP2D was identified as SEL 80 mg QW, CAR 56 mg/m^2 QW, and dex 40 mg QW. As of 3Feb2021, ORR was 78% (21/27) with 5 pts reaching CR (19%), 8 VGPR (30%), and 8 PR (30%). Median PFS was 23.7 months. Among 18 pts pretreated with dara, ORR was 67% and median PFS 23.7 months. In 9 pts whose MM was refractory to BOR, LEN, POM, and dara, ORR was 67% with 4 VGPR (44%). **Conclusions:** In pts with heavily pretreated MM, weekly XKd is highly active with an ORR of 78% and deep responses (≥VGPR 48%) with an overall PFS of 23 months. All AEs including grade 3/4 thrombocytopenia can be managed with appropriate supportive care and dose modifications. These data support further investigation of XKd in pts with previously treated MM including those previously treated with dara. Research Sponsor: Karyopharm Therapeutics.

8039 **Poster Session**

Phase Ib trial of vactosertib in combination with pomalidomide in relapsed multiple myeloma: A corticosteroid-free approach by targeting TGF-β signaling pathway. *First Author: Ehsan Malek, University Hospitals of Cleveland, Cleveland, OH*

Background: Immunosuppression and osteoclast activation are two hallmarks of the bone marrow environment in Multiple Myeloma (MM). Corticosteroids have been used historically as part of anti-myeloma regimens due to their anti-plasma cell activity, however they potentially could suppress immune system and activate osteoclast further; therefore there is an unmet need for corticosteroid-free approaches in the era of emerging anti-cancer immunotherapy modalities. There is an abundance of Transforming Growth Factor-beta (TGF-β), a crucial cytokine in suppression of immune system as well as catabolic bone remodeling, in the MM microenvironment. Vactosertib (Vacto) is a small molecule TGF-β type I receptor inhibitor that has shown single agent activity against myeloma in the syngeneic 5T33MM murine mouse model. Here, we report the phase Ib trial of Vacto in combination with pomalidomide (Pom) without any corticosteroids (NCT03143985). **Methods:** pts with relapsed MM with at least two lines of therapies enrolled on a 3 + 3 dose escalation design and received Vacto, 60 mg/d, 120 mg/d, 100 mg BID and 200 mg BID in combination with standard dose of Pom (4mg) without corticosteroids. The primary objectives of the study was to assess safety and recommended phase 2 dose. Vacto tablets, taken once or twice daily for 5 days followed by 2 days without treatment, is administered in 28-day cycles, until progression of disease or intolerable toxicity. **Results:** 15 pts were enrolled on the study (Table). The most common non-hematologic adverse event (AE) was grade II fatigue and pain in one pt, one episode of grade III renal failure that took less than 7 days to get back to baseline on another patient, sinus bradycardia that reversed to sinus rythem and an Afib that was rate controlled with beta blocerks. No grade IV non-hematologic AE was observed. Three pts had grade III hematologic AE, no grade IV hematologic AE. Three out of 15 pts experienced progression of disease (PFS-6: 80%). **Conclusions:** The phase Ib data shows safety of this agent in combination with Pom. The efficacy assessment (PFS-6: 80%) is higher than the historical control (PFS-6: 20% in randomized Phase II study by Richardson et al. Blood. 2014) with Pom only (PFS-6: 20%) or Pom with corticosteroids (PFS-6: 40%). Further advancement of this agent in clinical trial pipelines for MM is planned. Clinical trial information: NCT03143985. Research Sponsor: Medpacto Inc.

Patients' characteristics.

Parameter	60 mg/d			120 mg/d			100 mg BID			200 mg BID					
Age	70	77	70	64	64	69	75	56	77	70	56	66	72	69	67
Gender	F	F	M	F	M	M	F	F	F	M	F	M	F	M	M
lines of therapy	3	4	3	5	3	2	3	1	4	2	2	2	2	4	3
Bony lesions	Y	Y	N	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	Y
Response assessment	MR	PR	SD	MR	SD	PD	PR	PD	MR	PD	SD	PR	PR	PR	SD

PR: Partial response, MR: Minimal response, SD: Stable disease, PD: Progressive disease.

8040 **Poster Session**

Using mobile wearables to establish sleep bioprofiles in newly diagnosed multiple myeloma (MM) patients. *First Author: Gil Hevroni, SUNY Downstate Medical Center, Brooklyn, NY*

Background: Passive monitoring using wearables can objectively measure sleep over extended time periods. MM patients (PTs) are susceptible to fluctuating sleep patterns due to pain and dexamethasone (dex) treatment. In this prospective study, we remotely monitored sleep patterns on 40 newly diagnosed MM (NDMM) PTs while administering electronic PT reported outcome (ePRO) surveys. The study aim was to establish sleep bioprofiles during therapy and correlate with ePROs. **Methods:** Eligible PTs for the study had untreated NDMM and assigned to either Cohort A – PTs < 65 years or Cohort B – PTs ≥ 65 years. PTs were remotely monitored for sleep 1-7 days at baseline [BL] and continuously up to 6 therapy cycles. PTs completed ePRO surveys (EORTC - QLQC30 and MY20) at BL and after each cycle. Sleep data and completed ePRO surveys were synced to Medidata Rave through Sensorlink technology. Associations between sleep measurement trends and QLQC30 scores were estimated using a linear mixed model with a random intercept. **Results:** Between Feb 2017 - Sep 2019, 40 PTs (21 M and 19 F) were enrolled with 20 in cohort A (mean 54 yrs, 41-64) and 20 in cohort B (mean 71 yrs, 65-82). Regimens included KRd 14(35%), RVd 12(30%), Dara-KRd 8(20%), VCd 5(12.5%), and Rd 1(2.5%). Sleep data was compiled among 23/40 (57.5%) PTs. BL mean sleep was 578.9 min/24 hr for Cohort A vs. 544.9 min/24 hr for Cohort B (p = 0.41, 95% CI -51.5, 119.5). Overall median sleep trends changed for cohort A by -6.3 min/24 hr per cycle (p = 0.09) and for cohort B by +0.8 min/24 hr per cycle (p = 0.88). EPRO data trends include global health +1.5 score/cycle (p = 0.01, 95% CI 0.31, 3.1), physical +2.16 score/cycle (p < 0.001, 95% CI 1.26, 3.07), insomnia -1.6 score/cycle (p = 0.09, 95% CI [-3.47, 0.26]), role functioning +2.8 score/cycle (p = 0.001, 95% CI 1.15, 4.46), emotional +0.3 score/cycle (p = 0.6, 95% CI -0.73, 1.32), cognitive -0.36 score/cycle (p = 0.44, 95% CI -1.29,0.56), and fatigue -0.36 score/cycle (p = 0.4, 95% CI -1.65, 0.93). No association between sleep measurements and ePRO were detected. Difference in sleep on dex days compared to all other days during the sample cycle period for cohort A was 81.4 min/24 hr (p = 0.004, 95% CI 26, 135) and for cohort B was 37.4 min/24 hr (p = 0.35, 95% CI -41, 115). **Conclusions:** Our study provides insight into wearable sleep monitoring in NDMM. Overall sleep trends in both cohorts do not demonstrate significant gains or losses, and these trends fit with HRQOL ePRO insomnia responses. Upon further examination, we demonstrate objective differences (younger PTs) in intra-cyclic sleep measurements on dex days compared to other cycle days (less sleep by > 1 hr). For older patients, less variation in sleep profiles was detected during dex days, possibly due to higher levels of fatigue or longer sleep duration. Sleep is an integral part of well-being in the cancer patient. Future studies should continue to characterize sleep patterns as it relates to HRQOL. Research Sponsor: None.

8041 **Poster Session**

LocoMMotion: A prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma (RRMM) receiving ≥3 prior lines of therapy. *First Author: Maria-Victoria Mateos, Hospital Clinico Universitario de Salamanca, Salamanca, Spain*

Background: Multiple myeloma (MM) remains incurable despite advances in medical treatment that have improved survival. Even with these improvements, most patients with MM eventually progress through standard drug classes of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), anti-CD38 monoclonal antibodies (mAbs), and others. There are currently no prospective data on real-world standard-of-care (SOC) in patients who progress after PIs, IMiDs, and anti-CD38 mAbs. Here, we present interim results from LocoMMotion (NCT04035226), the first prospective efficacy and safety study of real-life SOC in patients with RRMM. **Methods:** Eligible patients (aged ≥18 years [y]) with a diagnosis of MM were enrolled between August 2019 and October 2020 from 75 sites across 9 European countries and the US. Patients were included if they received ≥3 prior lines of therapy or were double-refractory to a PI and IMiD, had measurable disease at screening, received at least a PI, an IMiD, and anti-CD38 mAb with documented progressive disease since their last line of therapy, and had an ECOG PS score of 0 or 1. Responses were assessed per International Myeloma Working Group response criteria. A Response Review Committee assessed the overall response rate (ORR, primary objective) of real-life current SOC. Secondary objectives of the study included additional efficacy and safety evaluation of real-life SOC. **Results:** The data cut-off was November 4, 2020 for the first interim analysis of 225 patients with a median follow-up of 3.7 months (range: 0–12.7), 22 (9.8%) patients were from the US and 203 (90.2%) were from Europe. Median age was 68 y (range: 41–89), 124 (55.1%) were male, 162 (72.0%) had a baseline ECOG PS score of 1, and median time since initial MM diagnosis was 6.0 y (range: 0.3–22.8). Patients had received a median of 4.0 (range: 2–13) prior lines of therapy; all patients were triple-class exposed, 166 (73.8%) were triple-class refractory, and 208 (92.4%) were refractory to last line of therapy. The ORR with real-life SOC salvage therapy was 20.1% (95% CI: 15.0–26.0) in the response-evaluable population (n = 219). Treatment-emergent adverse events (TEAEs) were reported in 148 (65.8%) patients, 95 (42.2%) were grade ≥3. The most common grade ≥3 TEAEs were anemia, thrombocytopenia, and neutropenia. Fifteen deaths (6.7%) occurred due to TEAEs during the study. Treatment is ongoing in 121 (53.8%) patients. **Conclusions:** The interim results of this first, prospective study of real-life SOC treatment in heavily pretreated, triple-class exposed patients with RRMM demonstrate that patients continue to progress after multiple lines of therapy and have poor outcomes. Therefore, there is a need for new treatments with novel mechanisms of action for this patient population. Clinical trial information: NCT04035226. Research Sponsor: Janssen-Cilag International NV, Pharmaceutical/Biotech Company.

8042 **Poster Session**

Isatuximab plus carfilzomib and dexamethasone in relapsed multiple myeloma patients with high-risk cytogenetics: IKEMA subgroup analysis. *First Author: Ivan Spicka, Clinical Department of Hematology, 1st Medical Department, Charles University, Prague, Czech Republic*

Background: A prespecified interim efficacy analysis of the Phase 3 IKEMA study (NCT03275285) demonstrated that isatuximab (Isa) + carfilzomib (K) and dexamethasone (d) (Isa-Kd) significantly improved progression-free survival (PFS) compared with Kd in patients (pts) with relapsed multiple myeloma (RMM) (HR 0.531; 99% CI, 0.318–0.889; *P*= 0.0007), with a clinically meaningful increase in minimal residual disease negativity (MRD-) (29.6% vs 13.0%) and complete response (CR) (39.7% vs 27.6%) rates, and a manageable safety profile. This subgroup analysis of IKEMA examined efficacy and safety in pts with high-risk cytogenetics [t(4;14), del(17p), and t(14;16)] and/or gain(1q21). **Methods:** Pts with 1–3 prior lines of therapy were randomized 3:2 to receive Isa-Kd (n = 179) or Kd (n = 123). High-risk cytogenetics was assessed by central laboratory analysis and defined as ≥1 of the following: del(17p): 50% cutoff; t(4;14) or t(14;16): 30% cutoff. Assessment of gain(1q21) was prespecified as ≥3 copies: 30% cutoff. **Results:** Of the randomized pts, 23.5% (Isa-Kd) and 25.2% (Kd) had ≥1 high-risk cytogenetic abnormality (CA); 26.3% (Isa-Kd) and 25.2% (Kd) had isolated gain(1q21). The addition of Isa to Kd improved PFS for pts with ≥1 high-risk CA and standard-risk pts (Table); pts with t(4;14) (HR 0.549; 95% CI, 0.232–1.301) had a more pronounced treatment effect than pts with del(17p) (HR 0.837; 95% CI, 0.281–2.496). A clear PFS benefit with Isa-Kd was also seen for pts with isolated gain(1q21) and gain(1q21) combined with other high-risk CA (Table). The trend toward improved CR, ≥very good partial response (VGPR), and MRD- rates with the addition of Isa was more pronounced in pts with gain(1q21) than in pts with high-risk CA alone. Grade ≥3 treatment-emergent adverse events (TEAEs) were more common with Isa-Kd vs Kd, but the incidence of serious and fatal TEAEs was similar with both arms for high-risk pts (Table). **Conclusions:** The addition of Isa to Kd improved PFS in pts with high-risk CA and disease response in pts with gain(1q21) isolated or combined with high-risk CA, with a manageable safety profile, consistent with the benefit observed in the overall IKEMA population. Isa-Kd is a potential new treatment option for the difficult-to-treat subgroup of pts with RMM and high-risk cytogenetics. Funding: Sanofi. Clinical trial information: NCT03275285. Research Sponsor: Sanofi.

	High Risk		Standard Risk		Isolated Gain(1q21)		Gain(1q21) + High-Risk CA	
%	Isa-Kd n = 42	Kd n = 31	Isa-Kd n = 114	Kd n = 77	Isa-Kd n = 47	Kd n = 31	Isa-Kd n = 25	Kd n = 19
PFS HR vs Kd (95% CI)	0.724 (0.361–1.451)		0.440 (0.266–0.728)		0.462 (0.219–0.972)		0.678 (0.299–1.537)	
CR	23.8	22.6	46.5	26.0	46.8	22.6	32.0	26.3
≥VGPR	57.1	54.8	78.9	54.5	80.9	51.6	64.0	52.6
MRD-	21.4	22.6	36.0	11.7	36.2	9.7	28.0	21.1
Grade ≥3 TEAEs	85.7	63.3	76.1	76.6	78.3	67.7	88.0	66.7
Serious TEAEs	64.3	66.7	57.5	59.7	63.0	51.6	60.0	66.7
Fatal TEAEs	0	0	4.4	5.2	6.5	3.2	0	0
TEAEs leading to definitive discontinuation	4.8	10.0	9.7	18.2	10.9	19.4	0	0

8043 **Poster Session**

Ixazomib (IXA), carfilzomib (CAR), elotuzumab (ELO) or daratumumab (DAR) with lenalidomide and dexamethasone (LEN+DEX) versus LEN+DEX only in relapsed/refractory multiple myeloma (R/R MM): A comparative cost-effectiveness analysis. *First Author: Mavis Obeng-Kusi, Center for Health Outcomes and Pharmacoeconomic Research, and Department of Pharmacy Practice and Science, Tucson, AZ*

Background: IXA, CAR, ELO and DARin combination with LEN+DEXhave been found superior in efficacy compared to LEN+DEX in the management of R/R MM. Applying indirect treatment comparisons from a network meta-analysis (NMA), this economic evaluation aimed to estimate the comparative cost-effectiveness and cost-utility of these four triplet regimens in terms of progression-free survival (PFS). **Methods:** In the absence of direct treatment comparison from a single clinical trial, NMA was used to indirectly estimate the comparative PFS benefit of each regimen. A 2-state Markov model simulating the health outcomes and costs was used to evaluate PFS life years (LY) and quality-adjusted life years (QALY) with the triplet regimens over LEN+DEX and expressed as the incremental cost-effectiveness (ICER) and cost-utility ratios (ICUR). Probability sensitivity analyses were conducted to assess the influence of parameter uncertainty on the model. **Results:** The NMA revealed that DAR+LEN+DEX was superior to the other triplet therapies, which did not differ statistically amongst them. As detailed in the Table, in our cost-effectiveness analysis, all 4 triplet regimens were associated with increased PFSLY and PFSQALY gained (g) over LEN+DEX at an additional cost. DAR+LEN+DEX emerged the most cost-effective with ICER and ICUR of $667,652/PFSLYg and $813,322/PFSQALYg, respectively. The highest probability of cost-effectiveness occurred at a willingness-to-pay threshold of $1,040,000/QALYg. **Conclusions:** Our economic analysis shows that all the triplet regimens were more expensive than LEN +DEX only but were also more effective with respect to PFSLY and PFSQALY gained. Relative to the other regimens, the daratumumab regimen was the most cost-effective. Research Sponsor: None.

Results of probabilistic sensitivity analysis: ICER (i$ / PFSLYg) / ICUR (i$/PFSQALYg).

CAR+LEN+DEX				
$4,265,380 / -$7,108,967	**IXA+LEN+DEX**			
$3,129,200 / $391,150	$4,549,425/ -$1,654,336	**ELO+LEN+DEX**		
-$37,723 / -$31,436	$492,566/$747,970	$53,986/ $52,566	**DAR+LEN+DEX**	
$1,479,497/ $1,834,576	$943,750/ $876,339	$1,424,507/ $2,513,835	$667,652/ $813,322	**LEN+DEX**

LEN Lenalidomide, DEX Dexamethasone, CAR Carfilzomib, IXA Ixazomib, ELO Elotuzumab, DAR Daratumumab, ICER Incremental cost-effectiveness ratio, ICUR Incremental cost-utility ratio, g gained, i$ incremental dollars, PFS Progression-free survival, LY Life-year, QALY Quality-adjusted life year.

8044 **Poster Session**

ISB 1342: A first-in-class CD38 T cell engager for the treatment of relapsed refractory multiple myeloma. *First Author: Marie-Agnès Doucey, Ichnos Sciences, Epalinges, Switzerland*

Background: ISB 1342 is a bispecific antibody heterodimer based on the Ichnos proprietary Bispecific Engagement by Antibodies based on T cell receptor (BEAT) platform. ISB 1342 is a first-in-class CD38 T cell engager under investigation in subjects with relapsed multiple myeloma refractory to proteasome inhibitors (PIs), immunomodulators (IMiDs) and daratumumab (study ISB 1342-101). **Methods:** ISB 1342 was engineered with a single chain variable fragment (scFv) arm that specifically recognizes a cluster of differentiation (CD)3-epsilon (CD3ε) and a fragment antigen binding (Fab) arm which specifically recognizes CD38 and does not compete with daratumumab. By co-engaging CD3ε on T cells and CD38 on tumor cells, ISB 1342 redirects T cells to kill CD38-expressing tumor cells. This mechanism of action is differentiated from existing monospecific CD38 targeting therapies and was designed to overcome resistance to daratumumab in multiple myeloma. **Results:** *In vitro,* ISB 1342 killed a large range of CD38-expressing tumor cell lines (EC50:12 to 90 pM) with 8 to 239-fold superior efficacy than daratumumab. ISB 1342 was also able to efficiently kill CD38 low-intermediate-expressing tumor cells that were poorly killed by daratumumab. ISB 1342 retained the potency to kill CD38 low-intermediate-expressing tumor cells when used in sequential or concomitant combination with daratumumab. In addition, the presence of soluble CD38 or glucocorticoid did not impact ISB 1342 killing potency. ISB 1342 was constructed with a double LALA mutation that dampens the binding to Fcγ receptors and C1q. Consistently, ISB 1342 showed only residual Fc-mediated effector functions and its mechanism of tumor cell killing critically relies on the engagement and the activation of T lymphocytes. ISB 1342 showed a favorable on target specificity profile *in vitro* and was unable to activate T cells in the absence of CD38 positive target cells. Further, ISB 1342-induced tumor cell killing was not associated with a detectable T cell fratricide *in vitro*. Finally, the potency of ISB 1342 was assessed *in vivo* in a therapeutic model of a subcutaneously established Daudi tumor co-xenografted with human PBMCs. In marked contrast to daratumumab, which induced only a partial tumor control, ISB 1342 induced complete tumor eradication when injected intravenously weekly at 0.5 mg/kg. As anticipated, the ISB 1342 control molecule (ISB 1342_13DU) made of an irrelevant CD38 binder failed to control tumor growth. The release of the Granzyme A and B, TNF-alpha and CXCL-10 in the tumor micro-environment one week post-treatment was strongly and significantly increased by ISB 1342 but not by daratumumab and ISB 1342_13DU; this represents a correlate of anti-tumor immunity associated with ISB 1342 efficacy *in vivo*. **Conclusions:** Hence the higher potency of ISB 1342 relative to daratumumab supports the ongoing clinical development in multiple myeloma patients. Research Sponsor: Glenmark and Ichnos Sciences.

8045 **Poster Session**

Comparison of outcomes with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-1 versus real-world standard of care (RW SOC) for patients (pts) with triple-class exposed relapsed/refractory multiple myeloma (RRMM). *First Author: Thomas G. Martin, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA*

Background: Pts with RRMM who are triple-class exposed (to immunomodulatory drugs [IMiDs], proteasome inhibitors [PIs] and an anti-CD38 antibody) cycle through multiple salvage regimens with progressively worse outcomes. CARTITUDE-1 (NCT03548207) is a single-arm phase 1b/2 study evaluating cilta-cel, a chimeric antigen receptor T-cell therapy with 2 B-cell maturation antigen–targeting single-domain antibodies, in pts with RRMM who received ≥3 prior lines of therapy (LOT) or were double refractory to an IMiD and PI, were triple-class exposed, had ECOG score of 0 or 1, and had disease progression ≤12 mo after the last LOT. Here, we compare efficacy outcomes for pts who received cilta-cel in CARTITUDE-1 (N = 97) with pts treated with SOC in a synthetic cohort from RW clinical practice. **Methods:** The Flatiron database, a primarily US community-based MM registry (Sep 2020 data cutoff), was used to identify a RW pt cohort who met CARTITUDE-1 (Sep 2020 data cutoff) eligibility criteria, including organ function. Progression-free/overall survival (PFS/OS) were compared between the cilta-cel–treated US pts and RW SOC cohort, using inverse probability of treatment (tx) weighting (IPTW) propensity scores adjusting for unbalanced baseline covariates of prognostic significance. Sensitivity analyses were conducted using multivariate Cox regression models and propensity score matching. **Results:** Baseline characteristics were similar between the 2 cohorts after propensity score weighting (Table). SOC tx regimens in the RW cohort primarily included pomalidomide (33%), carfilzomib (32%), daratumumab (13%), elotuzumab (16%), and ixazomib (8%). Pts had improved PFS and OS with cilta-cel (N = 97; median follow-up 12.4 mo) vs RW SOC (N = 196; median follow-up 9.2 mo) with a reduction in risk of progression/death and death by 84% and 78%, respectively (Table). Cilta-cel treatment benefit was robust across sensitivity analyses. **Conclusions:** Cilta-cel shows significantly better efficacy outcomes over RW SOC for PFS and OS, highlighting its potential as an effective tx option in pts with triple-class exposed RRMM. Clinical trial information: NCT03548207. Research Sponsor: Janssen Research & Development, LLC.

	CARTITUDE-1 N = 97	RW Cohort Observed N = 196	RW Cohort IPTW-Adjusted N = 102
Baseline characteristic, %			
Age < 65 y	64	41	67
< 6 y since MM diagnosis	46	81	44
High-risk cytogenetics*	24	18	22
ISS stage III	14	32	11
Prior LOT > 4	66	69	73
Time to progression on last LOT ≤4 mo	50	29	52
Triple-class refractory only†	45	43	43
Outcomes		§	§
PFS, HR (95% CI)‡		0.17 (0.11, 0.26)	0.16, (0.10, 0.27)
OS, HR (95% CI)‡		0.26 (0.15, 0.46)§	0.22 (0.11, 0.45)§

*del17p, t(14;16), t(4;14); †At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody; ‡CARTITUDE-1 vs RW cohort; §$P \leq 0.0001$. CI, confidence interval; HR, hazard ratio.

8046 **Poster Session**

Health-related quality of life (HRQoL) in patients with relapsed/refractory multiple myeloma (RRMM) treated with pomalidamide and dexamethasone ± subcutaneous daratumumab: Patient-reported outcomes (PROs) in APOLLO. *First Author: Evangelos Terpos, National and Kapodistrian University of Athens, Athens, Greece*

Background: APOLLO (NCT03180736) is a phase 3 trial of pomalidomide and dexamethasone (Pd) ± subcutaneous daratumumab (1800 mg, co-formulated with recombinant human hyaluronidase PH20 in 15 mL) in patients with RRMM and ≥1 prior line of therapy including lenalidomide and a proteasome inhibitor. After 16.9 months (mo) median follow-up, D-Pd significantly reduced the rate of progression or death by 37% relative to Pd. Patients with RRMM have reduced HRQoL compared with age- and sex-matched populations. Here, we present PROs from the APOLLO trial. **Methods:** Patients were randomized 1:1 to D-Pd or Pd and treated in 28-day cycles until disease progression/unacceptable toxicity. PROs were assessed on Day 1 of each cycle using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30-item (EORTC QLQ-C30), EORTC QLQ Multiple Myeloma Module 20-item (MY20), and EuroQol 5-dimensional descriptive system. PRO analyses were performed on patients from the intent-to-treat population with a baseline (BL) and ≥1 post-BL assessment. Treatment effect was assessed by a mixed effects model with repeated measures. Time to worsening was estimated using the Kaplan-Meier method. **Results:** A total of 304 patients were included (151 D-Pd, 153 Pd). Median treatment duration was 11.5 mo with D-Pd vs 6.6 mo with Pd. At Cycle 16 (Cyc 16), 63 and 40 patients remained on treatment in the D-Pd and Pd groups, respectively. Compliance rates for PRO instruments were high and comparable between groups. Patients treated with D-Pd had a reduction in pain (maximum improvement: 6.8 points at Cyc 12) measured with the EORTC QLQ-C30 and no mean change in disease symptoms or the treatment side effects subscales of the EORTC QLQ-MY20. Group mean physical and emotional functioning were unchanged from BL with D-Pd but worsened in the Pd group (maximum worsening: 6.4 at Cyc 4 and 9.1 points at Cyc 14). The proportion of patients with a meaningful improvement from BL was 55.0% vs 49.0% for disease symptoms, 43.0% vs 35.3% for physical functioning, and 41.7% vs 31.4% for emotional functioning with D-Pd vs Pd, respectively. Median time to worsening was ~4 mo, except for the disease symptoms subscale (~10 mo); there were no differences between groups. **Conclusions:** When daratumumab was added to Pd, patients did not experience any decrements in HRQoL while on treatment, but some patients experienced reductions in pain as well as clinically meaningful improvements in symptoms and emotional/physical function. These findings complement the clinical benefits of D-Pd in RRMM patients and further support its use in this RRMM population. Clinical trial information: NCT03180736. Research Sponsor: Janssen Research & Development, LLC, Other Foundation.

8047 **Poster Session**

Teclistamab and talquetamab modulate levels of soluble B-cell maturation antigen in patients with relapsed and/or refractory multiple myeloma. *First Author: Suzette Girgis, Janssen R&D, Spring House, PA*

Background: B-cell maturation antigen (BCMA, CD269) is a single transmembrane protein that is selectively expressed in the B-cell lineage and is a validated target for multiple myeloma. BCMA exists as both surface protein and as a free soluble form (sBCMA). γ-secretase activity at the transmembrane domain leads to a shed BCMA protein fragment of approximately 6 kilodalton that can exist as free circulating sBCMA in blood. Teclistamab and talquetamab are CD3 bispecific antibodies that have been developed to recruit CD3$^+$ T-cells to BCMA$^+$ or GPRC5D$^+$ multiple myeloma (MM) cells, respectively. The objective of this work was to evaluate sBCMA in relapsed and/or refractory MM patients in response to treatment with teclistamab or talquetamab. **Methods:** Serum samples from relapsed and/or refractory MM patients in teclistamab and talquetamab phase 1 studies (64007957MMY1001 and 64407564MMY1001) were collected (at various timepoints between baseline and cycle 4 or end of treatment) and analyzed for sBCMA by an electrochemiluminescence ligand binding assay. Soluble BCMA data were quantitatively analyzed in reference to patient's tumor burden and response, as well as pharmacokinetic data. **Results:** Teclistamab and talquetamab modulated levels of sBCMA in patients with high (≥ 50%) and low (< 50%) frequency of tumor plasma cells (TPCs), as well as in high and low risk cytogenetic groups. In cycle 3, majority of the responders had reduction in sBCMA [88% (50 out of 57) for teclistamab and 98% (49 out of 50) for talquetamab] compared to baseline. On the contrary, non-responders (progressive disease, stable disease, or minimal response) seemed to show an increase in sBCMA [80% (33 out of 41) for teclistamab and 49% (24 out of 49) for talquetamab] from baseline. Patients with deep responses tend to have higher magnitude of sBCMA reduction compared to others. Based on few patients who responded to teclistamab or talquetamab and then relapsed, sBCMA seemed to have an initial reduction followed by an increase in the levels. Soluble BCMA corelated with % bone marrow TPCs. Majority of patients with plasmacytoma (limited data) seemed to have high sBCMA; suggesting sBCMA could be a comprehensive marker for tumor burden. Teclistamab preliminary population pharmacokinetic analysis showed that sBCMA did not appear to impact teclistamab exposure, suggesting that sBCMA was not acting as a sink for teclistamab. **Conclusions:** Teclistamab and talquetamab induced changes in levels of sBCMA that correlated with clinical activity, further supporting clinical development of these bispecific antibodies. Lastly, the results support that sBCMA is a potential surrogate marker of myeloma tumor burden, and as a valuable marker for response in MM patients. Clinical trial information: NCT03145181 and NCT03399799. Research Sponsor: Janssen Research & Development, LLC.

8048 **Poster Session**

Melflufen plus dexamethasone (dex) in patients (pts) with relapsed/refractory multiple myeloma (RRMM) exposed/refractory to prior alkylators: A pooled analysis of the O-12-M1 and HORIZON studies.

First Author: Paula Rodríguez-Otero, Clinica Universidad De Navarra, Pamplona, Spain

Background: Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and rapidly releases alkylating agents inside tumor cells. Melflufen has a mechanism of action distinct from other alkylating agents (Slipicevic et al. AACR 2020. Abs. 1843). In the O-12-M1 (NCT01897714) and HORIZON (OP-106; NCT02963493) studies, melflufen plus dex showed meaningful efficacy and a clinically manageable safety profile in pts with RRMM (Richardson et al. *Lancet Haematol.* 2020;7:5; Richardson et al. *J Clin Oncol.* 2020;Dec 9 [Epub]). This pooled analysis examines pts from these studies exposed to prior alkylators. **Methods:** Both the O-12-M1 and HORIZON studies included pts with RRMM who received ≥ 2 prior lines of therapy (LoTs) and had a primary endpoint of overall response rate (ORR). Secondary endpoints included progression-free survival (PFS) and safety. Data from the 2 studies were pooled and analyzed according to previous exposure and refractoriness to alkylators before study entry. Refractoriness to prior alkylator therapy was defined as disease that failed to achieve a minimal response or progressed while on therapy, or within 60 d of last therapy. **Results:** Of 202 pts (HORIZON: n = 157, cutoff January 14, 2020; O-12-M1: n = 45, cutoff October 29, 2019), 178 (88%) had been exposed to alkylators in ≥ 1 prior LoT (see Table for subgroups). Pts exposed and refractory to alkylators in ≥ 2 LoTs had the highest number of pts refractory to an alkylator in the last LoT (61%), and 82% were refractory to an alkylator within 12 mo of study entry. Meaningful response rates were seen in all subgroups, except for pts who were exposed and refractory to alkylators in ≥ 2 prior LoTs (see Table). PFS trended toward being shorter with higher exposure and refractoriness to prior alkylators. Results should be interpreted with caution due to limited pt numbers. Grade 3/4 adverse events (AEs) were similar between pts exposed to prior alkylators (O-12-M1: 85%; HORIZON: 89%) and the overall population (O-12-M1: 84%; HORIZON: 89%). The most common AEs were hematologic, but were mostly reversible and clinically manageable. Nonhematologic AEs were infrequent and primarily grade 1/2. **Conclusions:** Melflufen in combination with dex showed meaningful efficacy and a clinically manageable safety profile in pts with RRMM exposed/refractory to prior alkylators. Clinical trial information: NCT02963493 and NCT01897714. Research Sponsor: Oncopeptides AB.

Efficacy by subgroup.

Patients		n	ORR, % (95% CI)	Median PFS, (95% CI), mo
Total		202	29.7 (23.5, 36.5)	4.4 (3.7-5.1)
Alkylator exposed	**Alkylator refractory**			
0	NA	24	50.0 (29.1, 70.9)	7.1 (3.7-9.0)
≥ 1	0	62	33.9 (22.3, 47.0)	5.3 (4.2-7.9)
1	1	43	23.3 (11.8, 38.6)	4.6 (3.0-6.5)
≥ 2	1	40	35.0 (20.6, 51.7)	3.7 (2.4-4.9)
≥ 2	≥ 2	33	9.1 (1.9, 24.3)	3.1 (1.7-4.0)

NA, not applicable.

8049 **Poster Session**

Prognostic impact of depth of response in Waldenström macroglobulinemia patients treated with fixed duration chemoimmunotherapy.

First Author: Nirosha D. Perera, Department of Internal Medicine, Mayo Clinic, Rochester, MN

Background: The treatment paradigm of Waldenström macroglobulinemia (WM) continues to evolve as new therapies expand our options for this indolent and incurable disease. While more profound responses are generally associated with longer treatment-free intervals, the impact of depth of response from fixed duration therapy in WM patients' survival needs further evaluation. In this international, multicenter cohort study, we report the prognostic impact of depth of response in WM. **Methods:** 319 WM patients treated with frontline fixed duration therapy [Dexamethasone/Rituximab/Cyclophosphamide (DRC), Bendamustine/Rituximab (BR), or Bortezomib/Dexamethasone/Rituximab (BDR)] were included. Response at the completion of therapy (6 months) was used in a landmark analysis for progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) (defined as time from 6 months post treatment response to event or censor). Response was defined by modified IWWM-6 criteria. Associations between clinical variables and outcomes were evaluated using Cox proportional-hazard models. **Results:** The median age at the time of treatment initiation was 64 years (range: 29-94), 59% were men, and risk category by International Prognostic Scoring System (IPSS)-WM was low (n=67, 23%), intermediate (n=83, 29%), and high-risk (n=141, 48%). Evaluable responses at 6 months from frontline therapy [DRC (n=105; 41%), BR (n=83; 32%), BDR (n=68; 27%)] were available in 256 patients and included in the landmark analysis. Median follow-up was 63 months (95% CI: 59-70). The rate of major response (PR or better) at 6 months was 74% for the entire cohort. Five-year PFS rates from completion of therapy for patients who attained major response vs. those who did not were 71% and 43%, respectively ($p<0.001$). Five-year TTNT rates for patients who attained major response vs. not were 84% and 54%, respectively ($p<0.001$). Five-year OS rates for patients who attained major response vs. not were 92% and 77%, respectively ($p<0.001$). In multivariable analyses including other WM prognostic factors evaluated at initiation of frontline therapy, attaining a major response at 6 months was associated with superior PFS (HR 0.33, $p<0.001$), TTNT (HR 0.23, $p<0.001$), and OS (HR 0.31, p=0.001–Table). **Conclusions:** Achieving a major response at 6 months after frontline chemoimmunotherapy emerges as a significant prognostic factor for PFS, TTNT and OS in patients with WM. Research Sponsor: Mayo Clinic Division of Hematology for abstract submission fee and analysis software.

Multivariable Cox models for OS.

	HR (95% CI)	p-value
Major response at 6 months	0.3 (0.1-0.6)	0.002
Age > 65 years	5.2 (1.9-14)	0.001
Hemoglobin level ≤11.5 g/dl	1.2 (0.5-2.7)	0.57
Platelet count ≤100,000/uL	1.6 (0.5-4.7)	0.36
Serum β2-microglobulin ≥3 mg/l	1.3 (0.6-2.7)	0.47
Serum IgM level >7,000 mg/dl	0.2 (0.03-2.0)	0.21
Bone marrow involvement ≥50%	0.5 (0.2- 1.3)	0.19

HR: Hazard ratio; CI: Confidence interval.

8050 **Poster Session**

An animal model of MGUS/SMM to investigate the role of cellular senescence in progression to MM.

First Author: Hengwei Zhang, University of Rochester, Rochester, NY

Background: Multiple Myeloma (MM) is an incurable cancer of plasma cells that arises from precursor stages, monoclonal gammopathy of undetermined significance (MGUS) and/or smoldering MM (SMM). Mechanisms for the transformation of MGUS/SMM to MM are not fully known. There is no approved therapy for MGUS/SMM and research is limited by a lack of animal models. Here, we describe the use of a novel animal model of disease progression derived from patients with MGUS/SMM to study the impact of cellular senescence (CS) on the development of MM. **Methods:** CD 138+ plasma cells and CD138- stromal cells were isolated via magnetic beads from bone marrow aspirates of patients with MGUS/SMM and co-cultured CD138+/CD138- with different ratios. For the animal model CD138+/CD138- cells from MGUS/SMM patients were injected into the tibias of NSG mice (1:10). After 4 weeks, CD138+ cells were harvested and again co-transplanted into the tibia of a 2nd NSG mouse with the CD138- cells (1:10). Mice underwent serial imaging and tibias were histologically examined after 4 weeks in the 2nd mouse. CS gene expression was compared by RNAseq between patients with SMM and healthy older adults. The primary CD138- cells were stained for SA-β-gal. Human mesenchymal stem cells (hMSCs) induced by H_2O_2 for CS vs control were co-cultured with CD138+ cells. Patient derived CD138- cells were treated with anti-senolytic drugs, dasatinib (D) and quercetin (Q) and cell growth in co-culture with CD138+ plasma cells was measured. D+Q treated patient-derived CD138+/CD138- cells were co-transplanted into our NSG mouse model and followed with serial imaging. **Results:** CD138- stromal cells from patients with MGUS/SMM support the growth of CD138+ plasma cells (10:1). CD138- cells were found to gain CD138+ expression, suggesting another source for the plasma cell growth. Imaging of our mouse model showed the development of lytic lesions in the tibias of 5/5 mice versus no lytic lesions in mice transplanted with CD138+ cells alone. Staining of the lytic lesions revealed CD138+ plasma cells. Our RNA seq showed significantly increased expression of CS genes, CDKN2A, p16 and p19 (3 fold) in CD138- cells of SMM patients and confirmed by qPCR (8 fold) compared to healthy older adults. The primary stromal cell culture from MGUS/SMM patients showed the presence of SCs by SA-β-gal staining. H_2O_2 induced senescent hMSCs stimulate cell survival and growth of CD138+ cells. CD138- cells cultured with conditioned media from H_2O_2 induced hMSCs demonstrated more CD138+ cells than vehicle treated CD138- cells. Conversely, D + Q pre-treated CD138- cells lost the ability to promote CD138+ cells in co-culture. Our animal model treated with D+Q showed less bone erosion in tibias compared to untreated mice. **Conclusions:** Our work demonstrates a novel animal model for studying disease progression in patients with MGUS or SMM and demonstrates a role for CS in MM disease progression. Research Sponsor: University of Rochester.

TPS8051 **Poster Session**

LIGHTHOUSE (OP-108): A phase 3 study of melflufen in combination with dexamethasone (dex) and daratumumab (dara) versus dara in relapsed/refractory multiple myeloma (RRMM) patients (pts).

First Author: Maria-Victoria Mateos, Hospital Clínico Universitario de Salamanca/IBSAL/CIC, Salamanca, Spain

Background: Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that leverages aminopeptidases and rapidly releases alkylating agents inside tumor cells. Melflufen + dex showed clinical efficacy and was well tolerated in pts with heavily pretreated RRMM (HORIZON; Richardson et al. *J Clin Oncol.* 2020 Dec 9 [Epub]). The ongoing phase 1/2 ANCHOR study (OP-104) established the optimal dose for melflufen + dex and dara, showing meaningful clinical activity and manageable safety at both melflufen doses tested in pts with RRMM (Ocio et al. ASH 2020. Oral 417). The aim of this study (OP-108; NCT04649060) is to evaluate the efficacy and safety of melflufen + dex and dara vs dara in pts with RRMM previously treated with an IMiD and a proteasome inhibitor (PI), similar to the indication for dara monotherapy. **Methods:** Pt enrollment has begun (N = 240 planned). Pts must be ≥ 18 y, double refractory to (or intolerant of) an IMiD and a PI or had ≥ 3 prior lines of therapy (LoTs) including an IMiD and a PI, have measurable disease, and Eastern Cooperative Oncology Group performance status ≤ 2. Pts with primary refractory disease and refractoriness to an anti-CD38 antibody are excluded. Pts will be randomized 1:1 to open-label melflufen + dex and dara (Arm A) or single-agent dara (Arm B) until progressive disease [PD] or unacceptable toxicity, stratified by prior LoT number. Pts in Arm B with PD can opt to receive Arm A triplet therapy. Arm A: melflufen 30 mg intravenously on d 1 of each 28-d cycle; dex 40 mg/wk orally (20 mg if aged ≥ 75 y); dara 1800 mg subcutaneously on d 1, 8, 15, and 22 of cycle 1 and 2, d 1 and 15 of cycles 3-6, and d 1 of cycles 7+. Arm B: dara at the same dosage as Arm A. Primary objective: superiority (P value from the 2-sided statistical test < 0.05; upper limit of the 2-sided 95% CI for the hazard ratio < 1) of progression-free survival (PFS) in pts treated with triplet therapy vs dara. An estimated sample of 240 pts with 160 expected events (PD or death) and 15% assumed dropout rate would provide 90% power at a 2-sided log rank test at 5% significance level to detect a hazard ratio for death of 0.6. Key secondary endpoints: overall response rate (ORR; ≥ partial response [PR]), duration of response, and safety. Response will be assessed by a blinded independent review committee based on International Myeloma Working Group criteria. Other secondary endpoints: clinical benefit rate (≥ minimal response), time to response, time to progression, time to next treatment, and overall survival. Exploratory endpoints include: minimal residual disease in pts achieving ≥ very good PR, PFS following next line of treatment (PFS-2), pt-reported outcomes, pharmacokinetics, translational biomarkers, response rate in pts with extramedullary disease, and efficacy (including ORR) in Arm B pts who receive Arm A triplet therapy after PD. Clinical trial information: NCT04649060. Research Sponsor: Oncopeptides AB.

TPS8052 **Poster Session**

ECOG-ACRIN EAA181: Effective quadruplet utilization after treatment evaluation (EQUATE)—a randomized phase 3 trial for newly diagnosed multiple myeloma (NDMM) not intended for early autologous transplantation. *First Author: Shaji Kumar, Department of Hematology, Mayo Clinic Rochester, Rochester, MN*

Background: The monoclonal antibody (MoAb) daratumumab (dara) has been approved for treatment of newly diagnosed Multiple Myeloma (NDMM) in combination with lenalidomide (len) and dexamethasone (DRd) in patients who are not eligible to undergo stem cell transplantation (SCT). Ongoing trials are examining the role of adding bortezomib (Btz) to DRd, but it remains unclear if all patients benefit from a quadruplet regimen. Availability of sensitive assays to detect measurable/minimal residual disease (MRD) in MM and emerging data demonstrating significant prognostic value for attaining MRD negativity, offers an unprecedented opportunity to develop individualized treatment approaches. An important question is to identify who benefits from adding a fourth drug to the MoAb-IMiD triplet, thus individualizing therapy based on depth of response. We hypothesize that prolonged intensive therapy with the addition of Btz for consolidation and maintenance after DRd induction therapy for NDMM will improve survival outcomes with a more pronounced effect when used in MRD positive patients. **Methods:** Patients with NDMM, R-ISS Stage I or II, who are not eligible to undergo SCT or those willing to defer SCT to first relapse and have not received more than 1 cycle of any NDMM therapy will be enrolled, provided they have measurable disease, adequate organ and marrow function, have received no more than once cycle of therapy for MM and significant peripheral neuropathy or chronic obstructive pulmonary disease. Importantly, a dominant clone should be identified by lymphotrack assay for future MRD monitoring. Once enrolled, induction therapy will be in 28 day cycles consisting of daraSC (1800 mg) weekly for 2 cycles, every other week for cycles 3-6 and then every 4 weeks for 9 cycles, along with len 25 mg days 1-21 of each cycle and dex 40 mg (20 mg for those $>$ 75 years) weekly. At end of 9 cycles (induction), patients will undergo MRD testing by next generation sequencing and will be classified into MRD positive or negative subgroups. Using MRD as an integral biomarker, the trial employs a randomized biomarker-stratified design as proposed by Freidlin et al. to determine efficacy for each MRD subgroup. Patients will be stratified by MRD status and R-ISS stage and randomized to receive 9 cycles of consolidation with DRd, without (control arm) or with (experimental arm) Btz (1.3 mg/m2 weekly for 3 of 4 weeks), followed by DR maintenance until progression The primary endpoint is consolidation OS. Sample size considerations rest on estimates of MRD subgroup prevalence at the end of induction and operating characteristics establishing the treatment effect within the MRD positive subgroup as primary and MRD negative subgroup as key secondary. The total accrual goal is 1450 patients. Clinical trial information: NCT04566328. Research Sponsor: CTEP.

TPS8053 **Poster Session**

KarMMa-4: Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T-cell therapy in high-risk newly diagnosed multiple myeloma. *First Author: Saad Z. Usmani, Levine Cancer Institute, Charlotte, NC*

Background: High-risk (R-ISS stage III) newly diagnosed multiple myeloma (NDMM) has a poor prognosis (median PFS, 29 mo), highlighting the need for novel disease-targeting approaches (Palumbo A, et al. *J Clin Oncol* 2015;33:2863-2869). Ide-cel, a BCMA-directed CAR T cell therapy, demonstrated deep, durable responses in heavily pretreated patients (pts) with relapsed and refractory MM (RRMM; Raje N, et al. *N Engl J Med* 2019;380:1726-1737; Munshi NC, et al. *J Clin Oncol* 2020;38[suppl 15]. Abstract 8503), including those with high-risk (R-ISS stage III) RRMM. In this population, earlier use of ide cel—when there may be more bone marrow reserve, more healthy peripheral blood mononuclear cells, a less compromised immune status, and less extensive disease to debulk before cell therapy—may result in improved outcomes vs standard therapies and offer an opportunity to replace transplant with CAR T cell therapy. **Methods:** KarMMa-4 (NCT04196491), a multicenter, open-label, phase 1, single-arm study, is currently evaluating ide-cel in pts with high-risk NDMM, defined as R-ISS stage III (ISS stage III [serum β_2 microglobulin $\geq$ 5.5 mg/L] and cytogenetic abnormalities t(4;14), del(17p), and/or t(14;16) by interphase FISH; or ISS stage III and serum LDH $>$ ULN). Pts must have received $\leq$ 3 cycles of the induction regimens listed below, be aged $\geq$ 18 years, and have ECOG PS 0-1. Nonsecretory MM and CNS involvement are exclusion criteria. Pts can enroll between induction cycles 1 and 3. Permitted cycle 1 regimens are carfilzomib + lenalidomide (LEN) + dexamethasone (DEX) ± daratumumab (DARA; KRd ± DARA), LEN + bortezomib (BOR) + DEX ± DARA (RVd ± DARA), or cyclophosphamide + BOR + DEX (CyBorD). Induction cycles 2-4 are limited to KRd or RVd, with DEX omitted during cycle 3. Pts will undergo T cell collection via leukapheresis after cycle 3, and ide-cel will be manufactured during cycle 4. Stem cell collection for future use may be conducted after cycle 3 (following leukapheresis) or 4 (before lymphodepletion). Ide-cel is infused after 2 days of rest following lymphodepletion with 3 days of fludarabine 30 mg/m^2 + cyclophosphamide 300 mg/m^2. LEN-based maintenance may be provided upon bone marrow recovery or 90 days after ide-cel infusion, whichever is later. Dose-limiting toxicity and safety are the primary endpoints. Secondary endpoints include complete response (CR) rate and overall response rate, duration of response, time to CR, time to start of maintenance, feasibility of initiating maintenance, PFS, overall survival, and pharmacokinetics. Exploratory endpoints include LEN maintenance safety, minimal residual disease, immunogenicity and biomarkers. The starting ide-cel target dose is 450 $\times$ 10^6 CAR+ T cells, with dose escalation/de-escalation (150, 300, and 800 $\times$ 10^6 CAR+ T cells). Upon determination of optimal target dose, 12 pts will be enrolled in the dose-expansion phase. Clinical trial information: NCT04196491. Research Sponsor: Celgene, a Bristol-Myers Squibb Company and bluebird bio.

TPS8054 **Poster Session**

Subcutaneous daratumumab (DARA SC) plus lenalidomide versus lenalidomide alone as maintenance therapy in patients (pts) with newly diagnosed multiple myeloma (NDMM) who are minimal residual disease (MRD) positive after frontline autologous stem cell transplant (ASCT): The phase 3 AURIGA study. *First Author: Nina Shah, Department of Medicine, University of California San Francisco, San Francisco, CA*

Background: DARA, a human anti-CD38 IgGκ monoclonal antibody, is approved in many countries as monotherapy in relapsed/refractory MM (RRMM) and in combination with standard of care (SoC) in RRMM and NDMM. However, no clinical studies have yet compared DARA maintenance versus SoC maintenance. The ongoing phase 3 AURIGA study will evaluate the addition of DARA to lenalidomide maintenance among pts with NDMM who are MRD positive after SoC induction and ASCT. The primary endpoint is the conversion rate to MRD negativity after 1 year of maintenance therapy. **Methods:** This open-label, multicenter, randomized phase 3 study will enroll approximately 214 pts in the United States aged 18-79 years with NDMM who receive $\geq$4 cycles of induction followed by ASCT. Pts must enroll within 6 months of ASCT, be naïve for anti-CD38 treatment, have a very good partial response or better per IMWG criteria, and be MRD positive at a threshold of 10^{-5} by next generation sequencing (NGS) within 30 days of screening. Pts will be stratified by cytogenetic risk (high vs standard/unknown) and randomized 1:1 to 28-day cycles of lenalidomide maintenance (10 mg PO; D1-28 [dose increasing to 15 mg if tolerated]) ± DARA SC (DARA 1,800 mg co-formulated with recombinant human hyaluronidase PH20 [rHuPH20; 2,000 U/mL; ENHANZE® drug delivery technology, Halozyme, Inc., San Diego, CA, USA; QW Cycle 1-2, Q2W Cycles 3-6, Q4W C7+). Treatment will continue for up to 36 cycles or until disease progression, unacceptable toxicity, or patient withdrawal. The primary endpoint is MRD conversion rate after 12 months of maintenance treatment, defined as the proportion of pts who achieve MRD negativity (10^{-5}) by NGS. Additional MRD assessments occur after 18, 24, and 36 months of maintenance. While MRD negativity is associated with improved long-term outcomes for pts with MM and is an emerging, validated prognostic factor, this study is among the first to use MRD negativity as a primary study endpoint. Importantly, MRD negativity allows for earlier efficacy assessment than traditional endpoints such as progression-free survival (PFS) and overall survival (OS). Secondary endpoints include overall MRD conversion rate at any time, sustained MRD negativity lasting $\geq$12 months, PFS, OS, response rates, duration of complete response, changes in health-related quality of life, and safety. Due to the COVID-19 pandemic, this study has been amended to improve enrollment access by allowing up to 12 months from start of induction therapy to ASCT to mitigate against ASCT delays and to allow greater flexibility for screening and laboratory assessments. Clinical trial information: NCT03901963. Research Sponsor: Janssen Research & Development, LLC.

TPS8055 **Poster Session**

A randomized, open-label, phase 3 study of low-dose selinexor and lenalidomide (Len) versus len maintenance post autologous stem cell transplant (ASCT) for newly diagnosed multiple myeloma (NDMM): ALLG MM23, Sealand. *First Author: HANG QUACH, St. Vincent's Hospital, University of Melbourne, Melbourne, VIC, Australia*

Background: Len maintenance post ASCT is standard of care for patients (pts) with NDMM. Deep responses (CR or better) post ASCT correlates with better progression free survival (PFS). In a meta-analysis of len maintenance post ASCT (McCarthy PL et al. J Clin Oncol. 2017), only 10.7% of pts achieve CR post ASCT, and 72% of pts who discontinued len maintenance did so because of progressive disease (PD). Selinexor is a selective inhibitor of nuclear export that blocks exportin 1, thus retaining tumour suppressor proteins within the nucleus while blocking proto-oncoprotein translation. It is approved in combination with bortezomib and dexamethasone (dex) for pts with MM who have had at least 1 prior line of treatment, or with dex for pts with penta-refractory MM by the FDA. The oral bioavailability and weekly schedule of selinexor makes it suitable in combination with len for maintenance therapy. Given the encouraging activity (ORR 92%) and tolerability of selinexor, len and dex from the phase 1b/2 STOMP study, we hypothesise that combination low-dose selinexor and len (XR) will be well tolerated and effective, increasing CR and MRD negativity rate post ASCT, thus prolonging PFS compared to len. **Methods:** ALLG MM23 SeaLAND, is an ongoing randomised, multi-centre, phase 3 trial. Eligible pts ($>$ 17 years of age) have measurable disease, have undergone 3-6 cycles (C) of induction containing a proteasome inhibitor (PI) and/or immunomodulatory drug and recovered post melphalan-conditioned ASCT with adequate haematopoiesis, renal and liver function, and with ECOG performance status . Registration occurs prior to ASCT with screening between 75 to 115 days post ASCT. The study includes a lead-in safety phase of 20 patients with XR: Len 10mg daily days 1 to 21 and Selinexor 40mg weekly in a 28-day cycle. If well tolerated, Selinexor escalates to 60mg po weekly from C2 and Len to 15mg po daily from C4. Two safety reviews will occur after the 10th and 20th patients completes C2, respectively. Upon meeting safety criteria, a sample size of 290 pts will be randomised 1:1 to XR or lenalidomide (R). Therapy will continue until PD. The primary endpoint is PFS at 3 years post randomisation. Secondary endpoints include ORR and MRD-negativity rate (International Myeloma Working Group Response Criteria), PFS on next treatment line (PFS2), OS, safety and tolerability, quality of life, and cost effectiveness. Main analysis occurs after 232 patients complete 3-years of follow-up. Exploratory objective is to correlate immunological and molecular profiles to treatment response and resistance. ALLG MM23 SeaLAND is a multisite bi-national investigator-initiated trial lead by Australia and New Zealand's national cooperative group, the Australasian Leukaemia & Lymphoma Group. Clinical trial registration: ACTRN12620000291987p. Clinical trial information: 12620000291987. Research Sponsor: Karyopharm Therapeutics Inc.

8500 **Oral Abstract Session**

IMpower010: Primary results of a phase III global study of atezolizumab versus best supportive care after adjuvant chemotherapy in resected stage IB-IIIA non-small cell lung cancer (NSCLC). *First Author: Heather A. Wakelee, Stanford University Medical Center, Stanford, CA*

Background: Adjuvant platinum-based chemotherapy (chemo) provides only a modest 5-year survival benefit in fully resected, high-risk early-stage NSCLC. We report the primary disease-free survival (DFS) results from the pre-planned interim analysis of IMpower010, a randomized phase 3 open-label trial of adjuvant atezolizumab (atezo; anti–PD-L1) vs best supportive care (BSC) after adjuvant chemo in patients (pts) with early-stage resected NSCLC. **Methods:** Eligible pts had completely resected (4-12 weeks prior to enrollment) Stage IB (≥4 cm)-IIIA NSCLC (AJCC/UICC v7) and ECOG PS 0-1. A total of 1280 pts were enrolled, and 1269 pts received up to four 21-day cycles of cisplatin-based chemo (plus pemetrexed, docetaxel, gemcitabine or vinorelbine). Of these pts (n=1269), 1005 were subsequently randomized 1:1 to 16 cycles of atezo 1200 mg Q3W or BSC. The primary endpoint of investigator-assessed DFS and secondary endpoint of overall survival (OS) were tested hierarchically: first DFS in the PD-L1 TC ≥1% (SP263) subgroup with Stage II-IIIA disease, then DFS in all randomized pts with Stage II-IIIA disease, then DFS in the ITT population (Stage IB-IIIA) and finally OS in the ITT population. Efficacy assessments were based on randomized pts. Safety was assessed in the safety-evaluable population, defined as pts who received ≥1 dose of atezo or who had ≥1 post-baseline safety assessment if randomized to the BSC arm. **Results:** At data cutoff (January 21, 2021), median follow-up was 32.2 months in the ITT population. Baseline characteristics were generally balanced between arms. Atezo showed statistically significant DFS benefit vs BSC in the PD-L1 TC ≥1% Stage II-IIIA and all randomized Stage II-IIIA populations; the significance boundary was not crossed for DFS in the ITT population (Table). OS data were immature and not formally tested. Pts in the atezo arm received a median of 16 (range, 1-16) atezo doses. Any-grade AEs occurred in 92.7% (atezo) and 70.7% (BSC); events were Grade 3/4 in 21.8% and 11.5%, respectively. Grade 5 treatment-related AEs occurred in 0.8% of pts in the atezo arm. AEs leading to atezo discontinuation occurred in 18.2% of atezo-treated pts. **Conclusions:** IMpower010 met its primary endpoint, showing DFS benefit with adjuvant atezo vs BSC after adjuvant chemo in pts with resected Stage II-IIIA NSCLC, with pronounced benefit in the PD-L1 TC ≥1% subgroup. The safety profile of atezo was consistent with prior experience of atezo monotherapy across indications and lines of therapy. Funding: F. Hoffmann-La Roche Ltd. Clinical trial information: NCT02486718. Research Sponsor: F. Hoffmann-La Roche.

	PD-L1 TC ≥1% Stage II-IIIA		All Randomized Stage II-IIIA		ITT	
	Atezo (n=248)	BSC (n=228)	Atezo (n=442)	BSC (n=440)	Atezo (n=507)	BSC (n=498)
Median DFS, mo	NR	35.3	42.3	35.3	NR	37.2
Stratified HR (95% CI)	0.66 (0.50, 0.88)		0.79 (0.64, 0.96)		0.81 (0.67, 0.99)[a]	
2-sided *P* value	0.0039		0.0205		0.0395	

NR, not reached.
[a]Did not cross significance boundary.

8501 **Oral Abstract Session**

Adjuvant gefitinib versus cisplatin/vinorelbine in Japanese patients with completely resected, EGFR-mutated, stage II-III non-small cell lung cancer (IMPACT, WJOG6410L): A randomized phase 3 trial. *First Author: Hirohito Tada, Suita Tokushukai Hospital, Suita, Japan*

Background: Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor is a standard of care for *EGFR* mutation-positive, untreated metastatic non-small cell lung cancer (NSCLC). However, the efficacy and safety of adjuvant gefitinib for patients with completely resected lung cancer harboring *EGFR* mutation over cisplatin-based adjuvant chemotherapy were not known in 2011 when this study was initiated. **Methods:** From September 2011 to December 2015, we randomly assigned 234 patients with completely resected, *EGFR* mutation-positive (exon 19 deletion or L858R), stage II–III NSCLC to receive either gefitinib (250 mg, once daily) for 24 months or cisplatin (80 mg/m^2 on day 1) plus vinorelbine (25 mg/m^2 on days 1 and 8) (cis/vin) every 3 weeks for four cycles. The primary endpoint was disease-free survival (DFS) according to a central review in the intent-to-treat (ITT) population. **Results:** Two patients in the gefitinib arm withdrew consent and were excluded from the ITT population. No treatment-related deaths were seen in the gefitinib arm, but three treatment-related deaths were reported in the cis/vin arm. Median duration of follow-up was 71 months. Median DFS was numerically longer in the gefitinib arm (36 months) than in the cis/vin arm (25.2 months). However, Kaplan-Meier curves began to overlap around 5 years after surgery, and no significant difference in DFS was seen, with a hazard ratio (HR) of 0.92 (95% confidence interval (CI), 0.67–1.28; P = 0.63). Overall survival was also not significantly different (median not reached in either arm). Five-year survival rates for gefitinib and cis/vin arms were 78.0% and 74.6%, respectively, with an HR for death of 1.03; 95%CI, 0.65–1.65; P = 0.89. Exploratory subset analysis revealed that patients ^{3}70 years old in the gefitinib arm (n = 19/27 with G to cis/vin) survived longer than those in the cis/vin arm (HR 0.31; 95%CI, 0.10–0.98; P = 0.046). **Conclusions:** Adjuvant gefitinib appeared to prevent early relapse, but did not significantly prolong DFS or OS in patients with completely resected stage II–III, *EGFR*-mutated NSCLC. The apparent non-inferiority of DFS/OS may justify the use of adjuvant gefitinib in selected subset of patients, especially those deemed unsuitable for cis/vin adjuvant therapy.Clinical trial information: UMIN000006252. Research Sponsor: Astra-Zeneca.

8502 **Oral Abstract Session**

CTONG1103: Final overall survival analysis of the randomized phase 2 trial of erlotinib versus gemcitabine plus cisplatin as neoadjuvant treatment of stage IIIA-N2 EGFR-mutant non–small cell lung cancer. *First Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong Provincial Peoples Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Median Overall survival (mOS) of stage IIIA resected NSCLC was 59.4 months (m) in CTONG 1104 adj gefitinib and 26.2m in SAKK neoadjuvant chemo trial. EMERGING-CTONG1103 showed neo-adjuvant/adjuvant erlotinib treatment significantly improved progression-free survival (PFS) vs standard doublet chemotherapy in patients (pts) with epidermal growth factor receptor (*EGFR*) mutation-positive resectable stage IIIA (N2) non-small-cell lung cancer (NSCLC). Here, we present the final overall survival (OS) results from the study. **Methods:** This was a multicenter (17 centers in China) phase II randomized controlled trial of erlotinib (E) versus gemcitabine plus cisplatin (GC) as neoadjuvant/adjuvant therapy in pts with stage IIIA-N2 NSCLC with EGFR mutations in exon 19 or 21. From Dec 2011 to Dec. 2017, 386 pts sites were screened and 72 pts were randomly assigned to neoadjuvant/adjuvant E arm (N = 37) or GC arm(N = 35). Patients received erlotinib 150 mg/d (neoadjuvant therapy, 42 days; adjuvant therapy, up to 12 months) or gemcitabine 1,250 mg/m^2 plus cisplatin 75 mg/m^2 (neoadjuvant therapy, two cycles; adjuvant therapy, up to two cycles). Assessments were performed at 6 weeks and every 3 months postoperative. The primary end point was objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1; secondary end points were pathologic complete response, downstaging rates of pathological lymph nodes, PFS, OS, safety, and tolerability. Data cut-off date was January, 29 2021. **Results:** With a median follow-up of 62.5 months, the median OS was 42.2months based on 47 (65.3%) events in ITT whole population. The mOS was 42.2m in E and 36.9m in GC (HR 0.83, 95%CI 0.47-1.47, p = 0.513). The 3-,5-year OS rate were 58.6%, 40.8% in E and 55.9%, 27.6% in GC respectively (p3-y = 0.819, p5-y = 0.252). All predefined subgroups including age, gender, EGFR mutation type had no significant difference in statistics between two arms. Subsequent treatments (ST) especially targeted therapy contributed most to OS (HR = 0.35 ,95% CI 0.18- 0.70). Median OS of pts receiving ST was 45.8m (n = 38), 34.6m in other treatment (n = 12), 24.6m in without ST (n = 15). For E mOS were 46.4 (n = 15; target therapy), 42.2m (n = 8; other) and 24.6m (n = 9; without, p = 0.021), for GC 42.6 (n = 23; target therapy), 30.1m (n = 4;other) and 24.6m(n = 6; without, p = 0.130). The RR was 53.3%, DCR 93.3%, mPFS 10.9m and mPPS 21.9m for patients with rechallenged EGFR TKI in E arm (n = 15). No novel unexpected SAE was observed during follow up. **Conclusion:** Erlotinib as neoadjuvant/adjuvant therapy for resected N2 NSCLC was feasibility and had a promising OS. The PFS survival advantage of E did not translate to OS difference in EMERGING trial (NCT01407822). Clinical trial information: NCT01407822. Research Sponsor: Chinese Thoracic Oncology Group (CTONG).

8503 **Oral Abstract Session**

Surgical outcomes from the phase 3 CheckMate 816 trial: Nivolumab (NIVO) + platinum-doublet chemotherapy (chemo) vs chemo alone as neoadjuvant treatment for patients with resectable non-small cell lung cancer (NSCLC). *First Author: Jonathan Spicer, McGill University Health Center, Montréal, QC, Canada*

Background: CheckMate 816 (NCT02998528) is a randomized phase 3 study of neoadjuvant NIVO + chemo vs chemo in resectable NSCLC. The study met its first primary endpoint, demonstrating significantly improved pathological complete response (pCR) with neoadjuvant NIVO + chemo. Here we report key surgical outcomes from the study. **Methods:** Adults with stage IB (≥ 4 cm)–IIIA (per AJCC 7th ed) resectable NSCLC, ECOG PS ≤ 1, and no known *EGFR*/*ALK* alterations were randomized to NIVO 360 mg + platinum-doublet chemo Q3W or chemo Q3W for 3 cycles (n = 179 each). Definitive surgery was to be performed within 6 weeks of treatment. Primary endpoints are pCR (defined as 0% viable tumor cells in lung and lymph nodes) and event-free survival; both are evaluated by blinded independent review. Feasibility of surgery and surgery-related adverse events (AEs) are exploratory endpoints. **Results:** Baseline characteristics were comparable between arms; 64% of patients (pts) were stage IIIA. Definitive surgery rates were 83% with NIVO + chemo (n = 149) vs 75% with chemo (n = 135). Reasons for cancelled surgery were disease progression (12 and 17 pts, respectively), AEs (2 pts/arm), or other scenarios (14 and 19 pts, respectively; including pt refusal, unresectability, poor lung function). Minimally invasive surgery rates were 30% and 22%, and conversion from minimally invasive to open surgery rates were 11% and 16% for NIVO + chemo and chemo, respectively. Lobectomy was performed in 77% vs 61% of pts, and pneumonectomy in 17% and 25% for NIVO + chemo vs chemo, respectively. AEs were responsible for delays of surgery in 6 pts in the NIVO + chemo arm and 9 pts in the chemo arm. An R0 resection was achieved in 83% vs 78% of pts and median residual viable tumor (RVT) cells in the primary tumor bed were 10% vs 74% for NIVO + chemo vs chemo. There was no increase in median (Q1, Q3) duration of surgery and length of hospitalization between NIVO + chemo vs chemo (184 [130, 252] vs 217 [150, 283] min; and 10.0 [7, 14] vs 10.0 [7, 14] days, respectively). Any-grade and grade 3–4 surgery-related AEs were reported in 41% vs 47% and 11% vs 15% of the NIVO + chemo vs chemo arms, respectively. Grade 5 surgery-related AEs were reported in 2 vs 0 pts in the NIVO + chemo vs chemo arms; 0 vs 3 pts died due to treatment-related AEs, respectively. **Conclusions:** In CheckMate 816, neoadjuvant NIVO + chemo did not impede the feasibility and timing of surgery, nor the extent or completeness of resection vs chemo alone; treatment was tolerable and did not increase surgical complications. NIVO + chemo led to increased depth of pathological response. The surgical outcome data from CheckMate 816 along with significant improvement in pCR support NIVO + chemo as a potential neoadjuvant option for patients with stage IB to IIIA resectable NSCLC. Clinical trial information: NCT02998528. Research Sponsor: Bristol Myers Squibb.

8504 **Oral Abstract Session**

Video-assisted thoracoscopic versus open lobectomy in patients with early-stage lung cancer: One-year results from a randomized controlled trial (VIOLET). *First Author: Eric Kian Saik Lim, Royal Brompton and Harefield Hospitals, London, United Kingdom*

Background: Video assisted thoracoscopic surgery (VATS) is a popular access for lung cancer resection. However, there is limited information from RCTs from in-hospital to one-year clinical efficacy, safety and oncologic outcomes of a minimal access approach. **Methods:** VIOLET is a parallel group multi-center RCT conducted in 9 centers in the United Kingdom that recruited participants with known or suspected (cT1-3, N0-1 and M0) lung cancer (ISRCTN13472721). Trial protocol: https://bmjopen.bmj.com/content/9/10/e029507.info. **Results:** From July 2015 to February 2019, 503 participants were randomized to VATS (n=247) or open (n=256) lobectomy. Patients allocated to VATS had less pain with a mean difference (MD) in visual analogue score of -0.54 (95%CI -0.99 to -0.10) despite less analgesic consumption (mean ratio 0.90, 95%CI 0.80 to 1.01). After discharge pain was consistent on multiple sub-scales including overall pain (MD -7.19, -10.59 to -3.80), chest pain (MD -4.66, -7.96 to -1.36) and an 18% relative risk (RR) reduction in incision pain (RR 0.82; 0.72 to 0.94) up to one-year. Better functional recovery continued in VATS arm after discharge with better physical function (primary outcome) with MD of 4.65 (1.69 to 7.61; P=0.002) at 5 weeks and overall improvement in global health status with a MD of 4.21 (1.62 to 6.79; P=0.001). In hospital, VATS arm had fewer complications (RR 0.74, 0.66 to 0.84; P<0.001) with no difference in serious adverse events (RR 0.98, 0.59 to 1.63; P=0.948). Median hospital stay was one day shorter in the VATS arm (4 vs 5 days) corresponding to hazard ratio (HR) for discharge of 1.34, 95%CI 1.09 to 1.65; P=0.006). After discharge VATS arm had 19% less serious adverse events (RR 0.81, 0.66 to 1.00; p=0.053) and lower readmission rates (29.0% vs. 35.9% respectively) to one-year. Of those with lymph node disease, 50.9% in the VATS and 45.9% in open arms received adjuvant treatment. There was no difference in the time to uptake of adjuvant chemotherapy (HR 1.12, 0.62 to 2.02; p=0.716). Recurrence with clinical follow up and CT at one-year was similar with 7.7% versus 8.1% in the VATS and open groups respectively. Progression-free survival (HR 0.74, 0.43 to 1.27; p=0.27) and overall survival HR 0.67, 0.32 to 1.40; p=0.282) was not significantly different. **Conclusions:** VATS lobectomy for lung cancer is associated with less pain, fewer in-hospital complications and shorter hospital stay, achieved without any compromise to early oncologic outcomes nor serious adverse events. Superior functional recovery continues in the post-operative period with improved physical function, lower re-admission rates and no difference in disease-free and overall survival up to one-year. Clinical trial information: ISRCTN13472721. Research Sponsor: UK National Institute of Healthcare Research.

8505 **Oral Abstract Session**

Phase 3 comparison of high-dose once-daily (QD) thoracic radiotherapy (TRT) with standard twice-daily (BID) TRT in limited stage small cell lung cancer (LSCLC): CALGB 30610 (Alliance)/RTOG 0538. *First Author: Jeffrey A Bogart, SUNY Upstate Medical University, Syracuse, NY*

Background: Although level 1 evidence is lacking, the majority of patients (pts) with LSCLC are treated with a high dose QD TRT regimen in clinical practice. CALGB 30610/RTOG 0538 was designed to determine if administering high dose TRT would improve overall survival (OS), compared with standard 45 Gy BID TRT, in LSCLC pts treated with chemoradiotherapy. **Methods:** Eligible pts had LSCLC, ECOG performance status (PS) 0-2 and regional lymph node involvement excluding contralateral hilar or supraclavicular nodes. This phase 3 trial was conducted in 2 stages. In the first stage, pts were randomized 1:1:1 to 45 Gy BID over 3 weeks, 70 Gy QD over 7 weeks, or 61.2 Gy concomitant boost (CB) over 5 weeks. For the second stage, the study planned discontinuation of one high dose arm based on interim toxicity analysis with patients then randomized 1:1 in the two remaining arms. TRT was given starting with either the 1st or 2nd (of 4 total) chemotherapy cycles. The primary endpoint was OS measured from date of randomization. **Results:** The trial opened 03/15/2008 and closed 12/01/2019 upon completing accrual, with the CB arm discontinued 3/11/2013 after interim analysis. This analysis includes 638 pts randomized to 45 Gy BID TRT (n = 313) or 70 Gy QD TRT (n = 325). Median age was 63 years (range 37-81), the majority of pts were Caucasian (86%), female (52%), and with ECOG PS 0-1 (95%). After median follow-up of 2.84 years (IQR:1.35 -5.61) for surviving pts, QD compared to BID did not result in a significant difference in OS (HR 0.94, 95% CI: 0.76-1.2 , p = 0.9). Median, 2- and 4-year OS for QD were 30.5 months (95% CI: 24.4-39.6), 56% (95% CI: 0.51-0.62), and 39% (95% CI: 0.33-0.45), and for BID 28.7 months (95% CI: 26.2-35.5), 59% (95% CI: 0.53-0.65), and 35% (95% CI: 0.29-0.42). QD also did not result in a significant difference in PFS (HR 0.96, 95% CI: 0.78-1.18, p = 0.94). Most grade 3+ hematologic and non-hematologic adverse events (AEs) were similar between cohorts. Rates of grade 3+ febrile neutropenia, dyspnea, esophageal pain and dysphagia for QD were 12.6% ,7%, 11.6% and 11.3% , and for BID 13.6%, 4%, 11.2 % and 9.5% . Grade 5 AEs were reported in 3.7% and 1.7% of the QD and BID cohorts, respectively. Results will be updated at presentation. **Conclusions:** High dose QD TRT to 70 Gy did not significantly improve OS compared with standard 45 Gy BID TRT. Nevertheless, favorable outcomes on the QD arm provide the most robust evidence available supporting high dose once-daily TRT as an acceptable option in LSCLC. Outcomes from this study, the largest conducted in LSCLC to date, will help guide TRT decisions for this patient population. Support: U10CA180821, U10CA180882; Clinical trial information: NCT00632853. Research Sponsor: U.S. National Institutes of Health.

8506 **Oral Abstract Session**

Stereotactic ablative radiotherapy in operable stage I NSCLC patients: Long-term results of the expanded STARS clinical trial. *First Author: Joe Y. Chang, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: We published a pooled analysis of 2 randomized trials (STARS/ROSEL) that compared lobectomy with mediastinal lymph node dissection (L-MLND) vs stereotactic ablative radiotherapy (SABR) in operable stage I NSCLC. There were no significant differences in disease progression but significantly higher 3-year overall survival (OS) in the SABR arm (95% vs 79%). Owing to concerns regarding the small sample size (n = 58), short follow-up (3 years), and non-uniform use of video-assisted thoracoscopic surgery (VATS), we expanded the STARS protocol to a single-arm SABR trial with a protocol-specified comparison to a published, longitudinally-followed institutional cohort of stage IA NSCLC status post VATS L-MLND (n = 229). **Methods:** Inclusion criteria were stage IA NSCLC (≤3 cm, N0M0 and staged by PET/CT with EBUS) with Zubrod performance status (PS) 0-2, baseline FEV1 > 40% and DLCO > 40% and deemed operable by a multidisciplinary team. SABR utilized 4-dimensional CT simulation and volumetric image guidance; 54 Gy in 3 fractions were delivered to planning target volumes (PTVs) located peripherally, or 50 Gy in 4 fractions to more central PTVs. All patients were followed by chest CT every three months for the first two years, every 6 months for another three years, and then annually. Non-inferiority of SABR could be claimed if the 3-year OS was not lower than the historical VATS L-MLND cohort by more than 12%. We conducted a risk-factor matched comparison study of the primary outcome between the SABR and the historical VATS L-MLND. **Results:** The median follow-up among the 80 SABR patients was 61 months (range, 34-79 months). The OS and progression-free survival (PFS) were 91% (95% CI: 85~98%) and 80% (95% CI: 72~89%) at 3 years, and 87% (95% CI: 79~95%) and 77% (95% CI: 68~87%) at 5 years, respectively. The 5-year cumulative incidence rate counting death as competing risk was 6.3% (95% CI: 2.3~13.2%) local, 12.5% (95% CI: 6.4~20.8%) regional, and 8.8% (95% CI: 3.8~16.2%) distant (any recurrence 17.6% (95% CI: 10.1~26.7%)). The 5 year cumulative incidence rate of second lung primary was 6.9% (95% CI: 2.5~14.6%). There were 1.3% grade 3 and no grade 4-5 toxicities. The propensity score matched (age, gender, tumor size, histology, PS) comparison of SABR vs VATS L-MLND revealed no significant differences in PFS (p = 0.063), lung cancer-specific survival (p = 0.075), or cumulative incidence rates of local (p = 0.54), regional (p = 0.97), or distant failures (p = 0.33). The SABR arm was associated with significantly higher OS (91% vs 82% at 3 years and 87% vs 72% at 5 years; p = 0.012 from log-rank test). The hazard ratio was 0.411 (95% CI: 0.193~0.875; p = 0.021). **Conclusions:** The long-term OS and PFS of SABR is not inferior to VATS L-MLND for operable stage IA NSCLC. SABR remains a promising approach for this population, but multidisciplinary management is strongly recommended. Clinical trial information: NCT02357992. Research Sponsor: Varian Medical Systems.

8507 **Oral Abstract Session**

A randomized phase II trial of oral vinorelbine as second-line therapy for patients with malignant pleural mesothelioma. *First Author: Dean Anthony Fennell, University of Leicester and University Hospitals of Leicester, Leicester, United Kingdom*

Background: All patients with malignant pleural mesothelioma (MPM) eventually relapse following standard chemotherapy. However, there is no standard treatment option in this setting. Vinorelbine, exhibits useful clinical activity but has not been formally evaluated in a randomised clinical trial, despite its widespread off-label use worldwide. BRCA1 regulates spindle assembly checkpoint in MPM and predicts vinorelbine sensitivity in preclinical models [1,2], suggesting that BRCA1 negative patients may be chemoresistant. **Methods:** VIM, a Cancer Research UK funded, investigator-initiated randomised controlled phase 2 multicentre UK trial, enrolled patients with MPM who had progressed after first-line chemotherapy. Pts were randomised 2:1 to either vinorelbine (60mg/m^2 weekly Q21d escalating to 80mg/m^2 from cycle 2) + active supportive care (ASC) versus ASC until disease progression, unacceptable toxicity or withdrawal of consent. The primary outcome was progression free survival (PFS) defined as the time from randomisation to any progression (based on Modified RECIST criteria for assessment of response in malignant pleural mesothelioma) or death. The trial had 90% power to detect a hazard ratio of 0.65 at the one-sided 20% significance level. Secondary endpoints were overall survival (OS), tolerability and safety. **Results:** Between May 2016 and Oct 2018, 154 patients were recruited from 10 UK sites and randomised to vinorelbine + ASC (n=98) or ASC alone (n=56). In the Intention-to-treat analysis, after 129 events, median PFS was 4.2 months (m) for vinorelbine + ASC compared to 2.8m for ASC alone (Hazard Ratio (HR) 0.59; 95% CI: 0.41 to 0.85; one-sided p = 0.0017). 108 deaths were reported. Median OS was 9.3m for vinorelbine + ASC compared to 9.1m for ASC alone (HR=0.79; 95% CI: 0.53 to 1.17; two-sided p = 0.24). Toxicity data and subgroup analyses including the impact of BRCA1 deficiency will be presented. **Conclusion:** The trial met its primary endpoint. Vinorelbine demonstrates useful clinical efficacy in relapsed MPM, supporting its off-label use, as a treatment option for patients with relapsed MPM.[1] Busacca et al, J Pathol 2012, 227(2), 200. [2] Busacca et al, Mol Cancer Res, 2021, 20(2) 379. Clinical trial information: NCT02139904. Research Sponsor: Clinical Trials Advisory and Awards Committee , Cancer Research UK Core funding.

8508 **Poster Discussion Session**

Real-world multiomic characterization of small cell lung cancer subtypes to reveal differential expression of clinically relevant biomarkers. *First Author: Sonam Puri, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: The dominant expression of four lineage-defining transcription factors (*ASCL1*, *NEUROD1*, *YAP1*, or *POU2F3*) has enabled the classification of small cell lung cancer (SCLC) into four subtypes (SCLC-A/N/Y/P, respectively). Emerging evidence suggests that *YAP1* expression is associated with a T-cell inflamed phenotype, and SCLC has significant intra-tumor heterogeneity mediated by MYC-driven activation of NOTCH signaling. We performed a large-scale analysis of real-world SCLC patient samples to examine the expression of clinically relevant biomarkers across SCLC subtypes. **Methods:** Comprehensive molecular profiling of 437 small cell lung neuroendocrine tumors (including 7.3% high-grade neuroendocrine lung carcinomas) was performed using next-generation DNA sequencing (592-gene panel), RNA sequencing (whole transcriptome), and immunohistochemistry at Caris Life Sciences (Phoenix, AZ). Tumors were stratified into 5 subgroups (SCLC-A/N/Y/P and -mixed) based on the relative expression of the four transcription factors. RNA expression of key genes and previously validated immune signatures (T-cell inflamed, NK cell, and STING pathway signatures) were evaluated across subgroups. Significance was tested by Chi-square, Fisher's exact test, or Mann-Whitney U test. **Results:** Median age of the study cohort was 66 years (IQR: 59-72) and 50.6% of patients were female. The majority (67.3%) of samples were derived from metastatic sites. Stratification of tumors by expression resulted in 35.7% SCLC-A, 17.6% SCLC-N, 21.1% SCLC-Y, 6.4% SCLC-P, and 19.2% SCLC-mixed samples. Compared to tumors from metastatic sites, *YAP1* expression was significantly increased ($p < 0.001$) in primary tumors. Amongst the 14 tumors obtained from the CNS, SCLC-N (36%, n = 5) was the most common subtype identified. dMMR/MSI-high (negative MMR protein expression/ ≥46 altered loci per tumor) was rare overall (0.5%, n = 2); TMB (median of 9-10 mut/Mb) was similar between the SCLC subtypes. SCLC-Y was associated with the highest expression of T-cell inflamed, NK cell and STING pathway signatures ($p < 0.0001$ each). *MYC* and *NOTCH* gene expression (*NOTCH1/2/3/4*) strongly correlated with *YAP1* expression. Analysis of co-mutations revealed that *EGFR*-sensitizing mutations (L858R and Exon 19 deletions) were recurrent (5.2%, n = 4) in SCLC-N tumors. The expression of *SNF11*, *SSTR2*, and *MYC* varied significantly among SCLC subtypes ($p < 0.001$ each), with the highest median expression of *SNF11* and *SSTR2* observed in SCLC-N, while *MYC* expression was highest in SCLC-P. **Conclusions:** Our analysis represents the largest real-world dataset of human SCLC tumors profiled by whole transcriptomic sequencing. The differential expression of immune genes and predictive biomarkers across SCLC subtypes may inform therapeutic vulnerabilities for rational and personalized treatment approaches in SCLC. Research Sponsor: None.

8509 **Poster Discussion Session**

Signatures of plasticity and immunosuppression in a single-cell atlas of human small cell lung cancer. *First Author: Joseph Minhow Chan, MSKCC, New York, NY*

Background: Small cell lung cancer (SCLC) is an aggressive malignancy that includes subtypes defined by differential expression of *ASCL1*, *NEUROD1*, and *POU2F3* (SCLC-A, -N, and -P, respectively), which are associated with distinct therapeutic vulnerabilities. The emerging consensus on SCLC subtypes has led to new questions, such as whether subtypes are associated with different disease stages, metastatic potential, or immune microenvironments; whether there is plasticity between subtypes; and whether novel SCLC phenotypes exist. Single cell RNA sequencing (scRNA-seq) offers a unique opportunity to address these questions by dissecting intratumoral transcriptional heterogeneity and the surrounding tumor microenvironment (TME). However, efforts to apply this technology to human SCLC tumors have been limited, as these tumors are infrequently resected. **Methods:** We have optimized protocols to process both surgical resections and biopsies to construct the first single-cell atlas of SCLC patient tumors (N = 21), with comparative lung adenocarcinoma (LUAD) and normal lung data. We leverage computational methods including diffusion maps and non-negative matrix factorization to perform a deep annotation of SCLC phenotypes and the surrounding immune TME. We perform validation experiments using flow cytometry, Vectra, and immunohistochemistry in independent SCLC cohorts, as well as genetic manipulation in preclinical SCLC models. **Results:** Our data reveals substantial transcriptional heterogeneity in SCLC both within and across tumors and confirms a pro-metastatic gene program in SCLC-N subtype characterized by epithelial-mesenchymal transformation and axonogenesis. Beyond known subtypes, we discover a *PLCG2*-high tumor cell population with stem-like, pro-metastatic features that recurs across subtypes and predicts significantly worse overall survival. Manipulation of *PLCG2* expression in cells confirms correlation with key metastatic markers. Treatment and subtype are associated with substantial phenotypic changes in the SCLC immune microenvironment, with greater T-cell dysfunction in SCLC-N than SCLC-A. Moreover, the recurrent, *PLCG2*-high subclone is associated with exhausted CD8+ T-cells and a pro-fibrotic, immunosuppressive monocyte/macrophage population, suggesting possible tumor-immune coordination to promote metastasis. **Conclusions:** This atlas of SCLC illustrates how canonical subtypes and a novel *PLCG2*-high recurrent tumor subclone enlist diverse gene programs to create tumor heterogeneity and facilitate metastasis in a profoundly immunosuppressed TME. Our dataset provides further insight into tumor and immune biology in SCLC at single-cell resolution, with potential implications for design of novel targeted therapies and immunotherapeutic approaches. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

8510 **Poster Discussion Session**

Updated results from a phase 1 study of AMG 757, a half-life extended bispecific T-cell engager (BiTE) immuno-oncology therapy against delta-like ligand 3 (DLL3), in small cell lung cancer (SCLC). *First Author: Taofeek K. Owonikoko, Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA*

Background: DLL3, an inhibitory Notch ligand, is a promising target as it is highly expressed in SCLC compared to normal tissue. AMG 757, a half-life extended BiTE immuno-oncology therapy, binds DLL3 on tumor cells and CD3 on T cells, leading to T cell-dependent killing of tumors. Results from the first nine dosing cohorts showing preliminary efficacy of AMG 757 (confirmed partial response [PR], 14% of pts) were previously presented. Here, updated safety, efficacy, and pharmacokinetic data from 10 cohorts from the ongoing phase 1 study of AMG 757 in SCLC are reported (NCT03319940). **Methods:** AMG 757 (0.003100 mg) was administered IV every 2 weeks ± step dosing. Eligible patients (pts) had SCLC that progressed after ≥1 platinum-based regimen. Antitumor activity was assessed by modified RECIST 1.1. **Results:** As of 11 Jan 2021, 64 pts enrolled at 10 dose levels (DLs; 0.003100 mg) had received ≥1 AMG 757 dose and were available for analyses. Median age was 64 (range, 3280) y; 63 pts (98%) had ECOG PS 01 and median number of prior lines of therapy was 2 (range, 16), with 28 pts (44%) receiving prior PD-1/PD-L1 therapy. Median treatment duration was 6 (range, 0.171) wk. Treatment-related AEs occurred in 53 pts (83%): 16 (25%) ≥ grade (G) 3, 4 (6%) ≥G4, 1 (2%) G5 (pneumonitis; DL5 [0.3 mg]). AEs led to discontinuation in 1 pt (G3 encephalopathy, DL10 [100 mg]). Cytokine release syndrome (CRS; graded per Lee 2014 criteria) was reported in 27 pts (42%): G2 in 7 (11%), ≥G3 in 1 (2%). CRS presented mainly as fever (31%), tachycardia (17%), nausea (13%), fatigue (9%), and hypotension (9%). CRS was usually reversible and was managed with supportive care, corticosteroids, and/or anti-IL-6R. CRS did not lead to any treatment discontinuations. Sixty pts treated across 10 DLs, with a median follow-up of 4.2 (range, 0.218.6) mo, were evaluated for efficacy. Confirmed PR across all DLs was reported in 8/60 pts (13%), with 5/8 pts (63%) pts achieving unconfirmed PR at 100 mg (DL10). The median time to response was 1.7 (range, 1.23.7) mo. The estimated duration of response was >6 months in 71% pts (95% CI: 26, 92) with any PR. Disease control rate was 43%, with any tumor shrinkage in 23/60 pts (38%). AMG 757 serum exposures increased approximately dose proportionally within the evaluated dose range. **Conclusions:** AMG 757 has an acceptable safety profile at doses up to 100 mg. Responses were rapid and durable. Encouraging anti-tumor activity was seen across dose ranges, with ongoing unconfirmed PR in 5/8 pts (63%) at the highest DL. The study is ongoing; updated data, including response rates and duration of response, will be presented. Clinical trial information: NCT03319940. Research Sponsor: Amgen Inc.

8511 **Poster Discussion Session**

Five-year survival outcomes with durvalumab after chemoradiotherapy in unresectable stage III NSCLC: An update from the PACIFIC trial. *First Author: David R. Spigel, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: In the placebo-controlled Phase III PACIFIC trial of patients with unresectable Stage III NSCLC whose disease had not progressed after platinum-based concurrent chemoradiotherapy (cCRT), durvalumab improved overall survival (OS) (stratified hazard ratio [HR] 0.68; 95% confidence interval [CI] 0.53–0.87; p=0.0025; data cut-off [DCO] Mar 22, 2018) and progression-free survival (PFS) (stratified HR 0.52, 95% CI 0.42–0.65; p<0.0001; DCO Feb 13, 2017) based on the DCOs used for the primary analyses, and the degree of benefit remained consistent in subsequent updates. Durvalumab was associated with a manageable safety profile, and did not detrimentally affect patient-reported outcomes, compared with placebo. These findings established consolidation durvalumab after CRT (the 'PACIFIC regimen') as the standard of care in this setting. We report updated, exploratory analyses of OS and PFS, assessed approximately 5 years after the last patient was randomized. **Methods:** Patients with WHO PS 0/1 (and any tumor PD-L1 status) whose disease did not progress after cCRT (≥2 overlapping cycles) were randomized (2:1) 1–42 days following cCRT (total prescription radiotherapy dose typically 60–66 Gy in 30–33 fractions) to receive 12 months' durvalumab (10 mg/kg IV every 2 weeks) or placebo, stratified by age (<65 vs ≥65 years), sex, and smoking history (current/former smoker vs never smoked). The primary endpoints were OS and PFS (blinded independent central review; RECIST v1.1) in the intent-to-treat (ITT) population. HRs and 95% CIs were estimated using stratified log-rank tests in the ITT population. Medians and OS/PFS rates at 60 months were estimated with the Kaplan–Meier method. **Results:** Overall, 709/713 randomized patients received treatment in either the durvalumab (n/N=473/476) or placebo (n/N=236/237) arms. The last patient had completed study treatment in May 2017. As of Jan 11, 2021 (median follow-up duration of 34.2 months in all patients; range, 0.2–74.7 months), updated OS (stratified HR 0.72, 95% CI 0.59–0.89; median 47.5 vs 29.1 months) and PFS (stratified HR 0.55, 95% CI 0.45–0.68; median 16.9 vs 5.6 months) remained consistent with the results from the primary analyses. The 60-month OS rates were 42.9% and 33.4% with durvalumab and placebo, respectively, and 60-month PFS rates were 33.1% and 19.0%, respectively. Updated treatment effect estimates for patient subgroups will be presented. **Conclusions:** These updated survival analyses, based on 5-year data from PACIFIC, demonstrate robust and sustained OS plus durable PFS benefit with the PACIFIC regimen. An estimated 42.9% of patients randomized to durvalumab remain alive at 5 years and approximately a third remain both alive and free of disease progression. Clinical trial information: NCT02125461. Research Sponsor: AstraZeneca.

8512 **Poster Discussion Session**

KEYNOTE-799: Phase 2 trial of pembrolizumab plus platinum chemotherapy and radiotherapy for unresectable, locally advanced, stage 3 NSCLC. *First Author: Salma K. Jabbour, Department of Radiation Oncology, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ*

Background: KEYNOTE-799 (NCT03631784) is an ongoing study of the anti–PD-1 antibody pembrolizumab (pembro) plus concurrent chemoradiation therapy (cCRT) in patients (pts) with unresectable, locally advanced stage III NSCLC. Prior results from this study in a subset of pts (primary efficacy population) showed an ORR of 69.6% in cohort A (squamous and nonsquamous, n = 112) and 70.5% in cohort B (nonsquamous, n = 61), and grade ≥3 pneumonitis in 8.0% and 7.9% of pts, respectively. Here, we present results for all pts enrolled in KEYNOTE-799. **Methods:** This nonrandomized, multisite, open-label phase 2 trial enrolled pts aged ≥18 y with previously untreated, unresectable, pathologically confirmed, stage IIIA–C NSCLC with measurable disease per RECIST v1.1. Pts in cohort A (squamous and nonsquamous) received 1 cycle of carboplatin AUC 6 and paclitaxel 200 mg/m^2 and pembro 200 mg. After 3 wks, pts received carboplatin AUC 2 and paclitaxel 45 mg/m^2 QW for 6 wks and 2 cycles of pembro 200 mg Q3W plus standard thoracic radiotherapy (TRT). Pts in cohort B (nonsquamous only) received 3 cycles of cisplatin 75 mg/m^2, pemetrexed 500 mg/m^2,and pembro 200 mg Q3W, and TRT in cycles 2 and 3. All pts received an additional 14 cycles of pembro 200 mg Q3W. Primary endpoints were ORR per RECIST v1.1 by blinded independent central review (BICR) and the incidence of grade ≥3 pneumonitis (per NCI CTCAE v4.0). Efficacy and safety were assessed in all pts as-treated. **Results:** Of 216 pts enrolled in KEYNOTE-799 (cohort A, n = 112; cohort B, n = 104), 112 in cohort A and 102 in cohort B received treatment. As of October 28, 2020, the median (range) time from first dose to database cutoff was 18.5 (13.6–23.8) mo in cohort A and 13.7 (2.9–23.5) mo in cohort B. ORR (95% CI) was 70.5% (61.2%–78.8%) in cohort A and 70.6% (60.7%–79.2%) in cohort B. Median DOR was not reached in either cohort (Table). ORR was similar regardless of PD-L1 status ([TPS <1% and TPS ≥1%]; Cohort A, 66.7% and 75.8%; Cohort B, 71.4% and 72.5%) and tumor histology (Cohort A, squamous, 71.2% and nonsquamous, 69.2%). Grade ≥3 pneumonitis occurred in 9 pts (8.0%) in cohort A and 7 (6.9%) in cohort B. Grade 3–5 treatment-related AEs occurred in 72 pts (64.3%) in cohort A and 51 (50.0%) in cohort B. **Conclusions:** Pembro plus cCRT continues to demonstrate promising antitumor activity, regardless of PD-L1 TPS and tumor histology, and manageable safety in pts with previously untreated, locally advanced, stage III NSCLC with longer follow-up. Clinical trial information: NCT03631784. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

	Cohort A n = 112	Cohort B n = 102
ORR, % (95% CI)	70.5 (61.2–78.8)	70.6 (60.7–79.2)
Median DOR, mo (range)	NR (1.7+ to 19.7+)	NR (1.8+ to 21.4+)
DOR ≥12 mo, %	79.7	75.6
Median PFS, mo (95% CI)	NR (16.6–NR)	NR (NR–NR)
12-mo PFS rate, %	67.1	71.6
Median OS, mo (95% CI)	NR (NR–NR)	NR (21.9–NR)
12-month OS rate, %	81.3	87.0

NR, not reached.
"+" indicates no PD since the time of last disease assessment.

8513 **Poster Discussion Session**

AFT-16: Phase II trial of neoadjuvant and adjuvant atezolizumab and chemoradiation (CRT) for stage III non-small cell lung cancer (NSCLC). *First Author: Helen J. Ross, Thoracic Oncology, Phoenix, AZ*

Background: A minority of the approximately 40,000 US patients diagnosed annually with stage III NSCLC can be cured by concurrent CRT. Standard adjuvant immune checkpoint inhibitors (ICI) improve outcome for those patients who complete CRT with good performance status (PS) and without disease progression, but most patients diagnosed with unresectable stage III NSCLC will not meet the criteria for adjuvant ICI. AFT-16 investigated safety and efficacy of neoadjuvant and adjuvant atezolizumab as a strategy that may allow more patients to benefit from ICI. **Methods:** Eligible patients received 4 cycles (cy) of atezolizumab 1200 mg IV q 21 days followed by CRT with 60 Gy + weekly carboplatin and paclitaxel (CP), CP consolidation and adjuvant atezolizumab to complete 1 year of therapy (17 cy). The primary endpoint of disease control rate at 12 weeks (wks) has been reported. Secondary endpoints reported here include overall response rate, safety, and progression-free and overall survival (PFS, OS) measured from the start of induction therapy. Correlative science data and quality of life endpoints will be reported elsewhere. **Results:** 64 patients with unresectable stage III NSCLC, PS 0-1 and no active autoimmune disease or significant organ dysfunction were enrolled at 13 Alliance for Clinical Trials in Oncology sites from 11/2017 to 7/2019. 62 patients who received at least one dose of atezolizumab are included in this analysis. Median age was 63.9 years (range 38.1-86.5). Patients were 51.6% female, 77.4% white, 88.7% current & former smokers and 56.5% PS 0. All patients are off study treatment. Mean cycles of treatment received was 9 (1-17). 46 patients were alive at median follow up 24.1 mo (range 3 – 34.1 mo). PFS at 12 and 18 mo from start of induction atezolizumab was 66% (95%CI 55-79) and 57% (95%CI 45-71) respectively. Median PFS was 23.7 mo (95%CI 13.2-NE). OS at 18 mo was 84% (95%CI 75-94). Median OS is not yet estimable. Atezolizumab was well tolerated. One grade (gr) 4 Guillain-Barre syndrome and 1 each gr 3 pneumonia, pneumonitis and colitis were attributable to neoadjuvant atezolizumab. The remaining 9 severe adverse events were unrelated to ICI. **Conclusions:** Atezolizumab prior to and following CRT for stage III unresectable NSCLC was well tolerated with encouraging PFS and OS without unexpected safety signals. Analysis of correlative endpoints and quality of life are ongoing. Further study of induction atezolizumab is warranted in patients with unresectable stage III NSCLC. Support: https://acknowledgments.alliancefound.org; Clinical trial information: NCT03102242. Research Sponsor: Alliance for Clinical Trials in Oncology Foundation.

8514 **Poster Discussion Session**

Racial differences in incidence, outcomes, and genomic alterations in small cell lung cancer. *First Author: Leyla Bayat, University Hospital Case Western Medical Center, Cleveland, OH*

Background: While the incidence of small cell lung cancer (SCLC) has been decreasing in recent years, an increasing proportion of our patients are younger African American (AA) women. There have been no studies describing these changes as well its impact on outcome and potential genomic differences amongst white and AA populations. **Methods:** We maintain a clinical/genomic/pathological database of all patients with SCLC treated at our comprehensive cancer center starting from 1998. We compared the baseline characteristics and outcomes (Overall survival [OS] and progression-free survival [PFS]) between AA and white patients, and between females and males. In addition, we looked at genomic alterations in >350 cancer-related genes and compared the frequency and types of mutations in our study population. **Results:** A total of 917 patients with SCLC were included (median age 66 years, 486 female, 179 African American). Amongst the African American patients, 67.6% were female, a striking difference compared to the white population, where only 49.1% were women (P<0.001). In multivariable analysis, there was no association between gender or race with OS or PFS (P> 0.05). There was an increase in mutational frequency in AA women compared to both AA men and white patients. PIK3CA and KIT mutations were more frequent in females while APC mutations were more frequent in males (P=0.041 for all comparisons). There was a trend toward increased mutational frequencies in TP53, PTEN, and NOTCH1 in AA patients. The relative frequency of gene alterations is shown in the table. In univariable analysis, NOTCH1 mutation was associated with improved OS (HR 0.24 [0.06-0.96], P=0.04). **Conclusions:** In this large cohort of patients with SCLC followed over 2 decades, there was a striking 2-fold higher incidence of SCLC in AA females than in AA males, although there were no differences in OS or PFS by sex or race. Several genomic alterations occur in higher frequencies in AA patients and AA women, in particular, have higher mutational frequencies. Research Sponsor: None.

	Male (n = 51)	Female (n = 51)	p-value
STK11 (wild/mutant)	46/5	50/1	0.092
AKT2 (wild/mutant)	50/1	47/4	0.169
FBXW7 (wild/mutant)	50/1	47/4	0.169
PIK3CA (wild/mutant)	51/0	47/4	0.041
APC (wild/mutant)	47/4	51/0	0.041
KIT (wild/mutant)	51/0	47/4	0.041
ATRX (wild/mutant)	51/0	48/3	0.079
AXL (wild/mutant)	51/0	48/3	0.079
EP300 (wild/mutant)	51/0	48/3	0.079
MYST3 (wild/mutant)	48/3	51/0	0.079
NFE2L2 (wild/mutant)	48/3	51/0	0.079
PDGFRA (wild/mutant)	51/0	48/3	0.079

Relative frequency of each alteration in female and male patients.

8515 **Poster Discussion Session**

Impact of socioeconomic disparities on diagnosis and overall survival in small cell lung cancer: A National Cancer Database analysis. *First Author: Logan Roof, Cleveland Clinic, Cleveland, OH*

Background: Small cell lung cancer (SCLC) accounts for approximately 13% of all lung cancer diagnoses in the United States. The demographics of this disease have evolved over time; in the 1970s 28% of patients with SCLC were female, while in the early 2000s, 50% were female. Remarkable differences in incidence, mortality rates, and trends by race and geographic location have also been noted. There has been a paucity of data regarding changes in epidemiology and patient demographics in SCLC since the early 2000s. Given recent treatment advances, the impact these factors have on patient outcomes for SCLC requires further evaluation. **Methods:** We identified all patients with SCLC in the NCDB from 2004 to 2016. Differences in demographic, disease, and treatment characteristics were assessed by year of diagnosis using Chi-square test. The effect of age, race, insurance status, income, distance to treatment center, and education level on overall survival (OS) was assessed by log-rank test. **Results:** There were 137,253 cases of SCLC diagnosed in the NCDB between 2004-2010 and 124,796 cases between 2011-2016. Patients diagnosed after 2010 were significantly older, had more comorbidities, had more stage IV disease, were more frequently treated at academic centers, more commonly had government primary payer insurance, and lived significantly further away from their treatment center. There were significant differences in gender, race/ethnicity groups, education level, and residence area, with more females, more African Americans, more patients without a high school diploma, and more rural patients diagnosed after 2010. OS in general improved between the two time periods, with median OS of 8.41 months (95% CI: 8.34-8.48%) and 5-year OS rate of 6.8% (95% CI: 6.6-6.9%) in patients diagnosed between 2004-2010 and median OS of 8.61 months (95% CI: 8.54-8.67%) and 5-year OS rate of 8.7% (95% CI: 8.5-8.9%) in patients diagnosed after 2010, despite an increase in stage IV disease in the latter group. Some of the differences in demographics were associated with changes in OS. Older patients, male patients, Caucasian patients, patients with stage IV disease, patients with government primary payer insurance, and rural patients all had significantly worse OS. Patients without comorbidities and patients treated at an academic center had significantly better OS. OS was found to significantly increase as both income and education level increase. **Conclusions:** SCLC continues to be a frequent cancer diagnosis. Despite improvement in overall survival during the time frame studied, there were significant disparities noted in key demographics that negatively affect access to healthcare resources, including rural communities, distance to an academic center, income, insurer, and education level. Collective efforts to impact these disparities will likely lead to improved outcomes for patients with SCLC. Research Sponsor: None.

8516 **Poster Discussion Session**

Racial disparities in lung adenocarcinoma: The contribution of African ancestry. *First Author: Michelle Jeung-Eun Lee, Morehouse School of Medicine, Atlanta, GA*

Background: Racial disparities in lung cancer are well-known with African Americans disproportionally affected by lung cancer in terms of incidence and survival. Previous comparative analyses of molecular features of lung cancer revealed racial differences in genomic profiles, which supports somatic differences arising from genetic ancestry. Using The Cancer Genome Atlas (TCGA), we investigated the genetic alterations in lung adenocarcinomas (LUAD) on individuals of African (AFR) ancestry. **Methods:** The genomic and clinical data of TCGA PanCancer Atlas LUAD were downloaded through the GDC Data Portal. Given that substantial proportion of the US population consist of genetically admixed populations, we utilized The Cancer Genome Ancestry Atlas (TCGAA) and LAMP for estimates of genetic ancestry and quantitative ancestral compositions. This dataset contains 518 samples, including 393 self-reported whites and 52 African Americans. For each case the proportion of European, AFR, East Asian, native American ancestry was estimated. The dominant ancestry was defined as ≥50% of admixture from one reference population. Differences in gene mutation frequency were analyzed based on AFR ancestry proportion. The Kaplan-Meier curves were generated, and Cox regression analyses were performed. **Results:** Global ancestry analysis identified 50 AFR ancestry cases with mean ancestry of 78.3%. The dominant AFR ancestry group matched the self-reported race with 96% accuracy. We identified 9 subjects with ≥90% AFR ancestry, 22 subjects with 80-90% AFR ancestry, 12 subjects with 70-80% AFR ancestry, and 7 subjects with 50-70% AFR ancestry. TP53 was the most frequently mutated gene, and ≥90% AFR ancestry had the highest rate of mutations (77.8%) compared with 80-90% AFR ancestry (68.2%), and 70-80% AFR ancestry (66.8%). We evaluated classic driver gene mutations (EGFR, KRAS, NRAS, PIK3CA, ALK) and found only 33% of ≥90% AFR ancestry subjects carry a known driver mutation, compared to 58-77% in lower proportion of AFR ancestry subjects. Higher AFR ancestry was associated with worse overall survival (OS) and progression free survival (PFS). Median OS was 14.5 months for ≥90% AFR ancestry compared to 71.47 months in 70-80% AFR ancestry (P = 0.048). ≥90% AFR ancestry had median PFS of 12.8 months compared to 33.5 months in 80-90% AFR ancestry, and 47.1 months in 70-80% AFR ancestry (P = 0.002). **Conclusions:** This study demonstrates the power of genomic study to investigate the etiology of health disparities by analyzing the effect of ancestry on genetic alterations in LUAD. Our results reveal different mutation loads even among AFR ancestry patients. We observed that AFR ancestry is associated with worse OS, suggesting possible influence of germline ancestry in subsequent somatic alterations. Further work is needed to explore how genetic ancestry impacts tumorigenesis and cancer progression to eliminate lung cancer disparities. Research Sponsor: None.

8517 **Poster Discussion Session**

Residual ctDNA after treatment predicts early relapse in patients with early-stage NSCLC. *First Author: Davina Gale, Cancer Research UK Cambridge Institute, Cambridge, United Kingdom*

Background: Liquid biopsies based on circulating tumor DNA (ctDNA) analysis are being investigated for detection of residual disease and recurrence. Conclusive evidence for utility of ctDNA in early-stage non-small cell lung cancer (NSCLC) is awaited. Due to low ctDNA levels in early-stage disease or post-treatment, effective methods require high analytical sensitivity to detect mutant allele fractions (MAF) below 0.01%. **Methods:** We analysed 363 plasma samples from 88 patients with NSCLC recruited to the LUng cancer CIrculating tumour DNA (LUCID) study, with disease stage I (49%), II (28%) and III (23%). 62% were adenocarcinomas. Plasma was collected before and after treatment, and at 3, 6 and 9 months after surgery (N = 69) or chemoradiotherapy (N = 19). Additional plasma was collected at disease relapse for 17 patients. Median follow-up was 3 years, and 40 patients progressed or died of any cause. We employed the RaDaR™ assay, a highly sensitive personalized assay using deep sequencing of up to 48 tumor-specific variants. Variants identified by tumor exome analysis were tested by deep sequencing of tumor tissue and buffy coat DNA to verify somatic mutations and exclude clonal hematopoiesis. The RaDaR assay demonstrated 90% sensitivity at 0.001% MAF in analytical validation studies. **Results:** ctDNA was detected in 26% of samples, at median MAF of 0.047% (range: 0.0007% to > 2%), and prior to treatment in 87%, 77% and 24% for disease stage III, II and I respectively. For 62 patients, plasma was collected at a landmark timepoint, between 2 weeks and 4 months after initial treatment. ctDNA detection at the landmark timepoint was strongly predictive of clinical disease relapse, with Hazard Ratio of 20.7 (CI: 7.7-55.5, p-value < 0.0001). All 11 cases with ctDNA detected at landmark had disease progression, a median of 121 days after detection, and these included all 8 patients that relapsed within 300 days of treatment. Across 27 patients whose disease progressed during the study, ctDNA was detected at any timepoint post-treatment in 17 cases, with a median lead time of 203 days, and up to 741 days prior to clinical progression. ctDNA was detected post-treatment, in 13 of the 15 patients that progressed and had ctDNA detected prior to treatment. **Conclusions:** Our results support an emerging paradigm shift, by demonstrating that liquid biopsies can reliably detect recurrence of NSCLC at a pre-clinical stage, many months before clinical progression, thereby offering the opportunity for earlier therapeutic intervention. Clinical trial information: NCT04153526. Research Sponsor: Cancer Research UK.

8518 **Poster Discussion Session**

Leveraging phased variants for personalized minimal residual disease detection in localized non-small cell lung cancer. *First Author: David Matthew Kurtz, Division of Oncology, Stanford University School of Medicine, Stanford, CA*

Background: Detection of circulating tumor DNA (ctDNA) has prognostic value in lung cancer and could facilitate minimal residual disease (MRD) driven approaches. However, the sensitivity of ctDNA detection is suboptimal due to the background error rates of existing assays. We developed a novel method leveraging multiple mutations on a single cell-free DNA molecule ("phased variants" or PVs) resulting in an ultra-low error profile. Here we develop and apply this approach to improve MRD in localized NSCLC. **Methods:** To identify the prevalence of PVs, we reanalyzed whole genome sequencing (WGS) from 2,538 tumors and 24 cancer types from the pan-cancer analysis of whole genomes (PCAWG). We applied Phased Variant Enrichment and Detection Sequencing (PhasED-Seq) to track personalized PVs in localized NSCLC. We compared PhasED-Seq to a single nucleotide variant (SNV)-based ctDNA method. **Results:** In the PCAWG dataset, we found that PVs were common in both lung squamous cell carcinomas (LUSC, median 1,268/tumor; rank 2nd) and adenocarcinomas (LUAD, median 655.5/tumor; rank 3rd). However, PVs did not occur in stereotyped genomic regions. Thus, to leverage PhasED-Seq, we performed tumor/normal WGS to identify PVs, followed by design of personalized panels targeting PVs to allow deep cfDNA sequencing. We performed personalized PhasED-Seq for 5 patients with localized NSCLC. PVs were identified from WGS of tumor FFPE and validated by targeted resequencing in all cases (median 248/case). The background rate of PVs was lower than that of SNVs, even when considering duplex molecules (background: SNVs, 3.8e-5; duplex SNVs, 1.0e-5; PVs, 1.2e-6; P < 0.0001). We next assessed PhasED-Seq for MRD detection in 14 patient plasma samples. Both SNVs and PhasED-Seq had high specificity in healthy control cfDNA (95% and 97% respectively). Using SNVs, ctDNA was detected in 5/14 samples; PhasED-Seq detected all of these with nearly identical tumor fractions (Spearman rho = 0.97). However, PhasED-Seq also detected MRD in an additional 5 samples containing tumor fractions as low as 0.000094% (median 0.0004%). We analyzed serial samples from a patient with stage III LUAD treated with chemoradiotherapy (CRT) and durvalumab. SNV-based ctDNA and PhasED-Seq detected similar MRD levels (0.8%) prior to therapy. However, 3 samples collected during CRT, as well as before and during immunotherapy, were undetectable by SNVs. SNV-based ctDNA then re-emerged at disease recurrence. PhasED-Seq detected MRD in all 3 samples not detected by SNVs with tumor fractions as low as 0.00016%, including prior to immunotherapy (8 months prior to progression). Similar improvements were seen in samples not detected by SNVs from 2 additional patients. **Conclusions:** Personalized ctDNA monitoring via PVs is feasible and improves MRD detection in localized NSCLC. PhasED-Seq allows clinical studies testing personalized treatment based on MRD. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

8519 **Poster Discussion Session**

Early detection of lung cancer using cfDNA fragmentation. *First Author: Dimitrios Mathios, The Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Lung cancer incidence and mortality are increasing worldwide despite more effective treatments. This is primarily due to the late stage of diagnosis when treatments are less effective. Although large randomized trials have demonstrated a significant decrease in lung cancer mortality through screening of high-risk individuals with chest low dose computed tomography (LDCT), LDCT has made little impact in the community, mainly due to lack of accessibility. There is therefore an unmet clinical need for development of cost-effective and easily implemented tests for early lung cancer detection. **Methods:** We have previously shown that altered genome-wide fragmentation of cell free DNA (cfDNA) is a common characteristic of many cancers. In this study, we leverage this knowledge to increase the sensitivity of lung cancer detection by interrogating characteristics of the size distribution of cfDNA fragments across the genome using machine learning methods. The approach we present, called DELFI (DNA evaluation of fragments for early interception) generates a score that reflects the presence of tumor-derived DNA in plasma based on a multi-feature genomic analysis that assesses millions of cfDNA fragments for tumor-derived genomic and epigenomic changes in a small amount of blood (2-4 mls) via inexpensive low coverage (1-2x) whole genome sequencing. We applied this methodology in a prospectively collected cohort of 365 individuals under investigation for lung cancer and we prospectively validated it in a separate case-control cohort of patients with newly diagnosed early stage lung cancer as well as individuals without cancer (n=427). **Results:** These analyses revealed high performance for detection of early and late stage disease (Table). When DELFI was used as a prescreen for LDCT it increased specificity from 58% with CT imaging alone to 80% using the combined approach. The DELFI score was significantly associated with T and N stage in lung cancer cases (p<0.0001) as well as with overall survival (p=0.003). In a multivariable analysis including age, histology and stage, DELFI score was an independent prognostic factor of overall survival (HR=2.53; p=0.0003). Finally, we determined that genome-wide fragmentation profiles can be used to distinguish small cell lung cancer from non-small cell lung cancer with high accuracy (AUC 0.98). **Conclusions:** These findings provide key insights into cfDNA fragmentation in patients with cancer and a new and easily accessible avenue for non-invasive diagnosis and molecular profiling of lung cancer. Research Sponsor: Dr. Miriam and Sheldon G. Adelson Medical Research Foundation, SU2C in-Time Lung Cancer Interception Dream Team Grant, Other Foundation, Pharmaceutical/Biotech Company, U.S. National Institutes of Health.

Sensitivity of DELFI followed by LDCT for lung cancer detection*.

	Sensitivity	
	DELFI	**DELFI, LDCT**
Stage		
Stage I (n=8)	88%	100%
Stage II (n=7)	86%	86%
Stage III (n=30)	93%	93%
Stage IV (n=49)	92%	98%
Histology		
Adenocarcinoma (n=46)	87%	94%
Squamous (n=25)	96%	100%
Small cell (n=8)	100%	100%
Other (n=15)	93%	93%

*Sensitivities refer to the fraction of cases detected at single or combined test specificities of 80%.

8520 **Poster Session**

Updated overall survival (OS) and exploratory analysis from the randomized, phase II EVAN study of erlotinib (E) versus vinorelbine plus cisplatin (NP) as adjuvant therapy in Chinese patients with stage IIIA EGFR+ NSCLC. *First Author: Dongsheng Yue, Tianjin Medical University Cancer Institute and Hospital, Tianjin, China*

Background: The EVAN study of E vs NP in stage III EGFR+ NSCLC has met its primary endpoint and been previously published: 2-year disease-free survival was 81.4% (95% CI, 69.6–93.1) in E group vs 44.6% (95% CI, 26.9-62.4) in NP group (HR, 1.823; 95% CI, 1.194–2.784; P=0.0054). We report 5-year OS and exploratory results from EVAN with a further 43 month follow up (cutoff date: Jan 6, 2021). **Methods:** Patients with stage IIIA EGFR+ NSCLC were randomized assigned (1:1) into either E arm (n=51, 150mg/day) or NP arm (n=51, vinorelbine 25mg/m^2 on day 1, 8 and cisplatin 75mg/m^2 on day 1 of a 21-day cycle). In order to explore the relationship between patient benefits and co-occurring variants, 47 patients received whole exome sequencing (WES) analysis (E, n=24; NP, n=23). **Results:** Median follow-up time was 54.8 months for E and 63.9 months for NP. E improved OS and 5-year survival rate compared with NP in ITT population. The median OS was 84.2m (95% CI, 78.1,-) with E vs 61.1m (95% CI, 39.6-82.1) with NP (HR, 0.318; 95% CI, 0.151-0.670). The 5-year survival rates were 84.8% (95%CI, 72.0-97.6) and 51.1% (95% CI, 34.7-67.5), respectively. In the WES analysis, we found that the most frequent genes with co-occurring variants at baseline were TP53, MUC16, FAM104B, KMT5A and DNAH9, and additional EGFR variants, each with similar prevalence regardless of EGFR-activating mutation subgroup. Moreover, in the erlotinib-treated patients, the SNP mutation of UBXN11 was associated with significantly worse DFS (P=0.0111). **Conclusions:** This is the first randomized study of EGFR-TKI to demonstrate a clinically meaningful improvement in OS vs chemotherapy in stage III EGFR+ NSCLC (5-year survival rate 84.8% in E vs 51.1% in NP). The co-occurring variants at baseline may be associated with reduced DFS. Further studies are required to confirm our results (EVAN, NCT01683175). Clinical trial information: NCT01683175. Research Sponsor: None.

8521 **Poster Session**

Different exposure duration of adjuvant icotinib in stage II-IIIA non-small cell lung cancer patients with positive EGFR mutation (ICOMPARE study): A randomized, open-label phase 2 study. *First Author: Chao Lyu, Thoracic Surgery II, Peking University Cancer Hospital, Beijing, China*

Background: EGFR-TKI has been widely used in the treatment for advanced non-small cell lung cancer (NSCLC). Previous studies, such as the EVIDENCE study and the ADAURA study, have confirmed that patients with EGFR-mutated NSCLC could benefit from adjuvant EGFR-TKI treatment. However, the optimal duration time of adjuvant EGFR-TKIs has not been clearly defined. **Methods:** In this multicenter, randomized, phase 2 trial, eligible patients with II-IIIA stage EGFR mutation-positive NSCLC after R0 resection were randomized in 1:1 to receive adjuvant icotinib for 1 year (group A) or 2 years (group B). The primary endpoint was disease-free survival (DFS). **Results:** Between September 2013, and September 2018, 109 patients from 8 centers were enrolled in this study, among whom 55 were randomized to group A and 54 to B. As of August 24, 2020 (data cutoff), the median follow-up was 44.1 months (95%CI 37.1-49.9), 31 (56%) of 55 patients in the 1-year group and 25 (46%) of 54 patients in the 2-year group had DFS events. The median DFS was 48.92 months (95%CI 33.15, 70.11) in 2-year group and 32.89 month (95%CI 26.61, 44.78) in 1-year group, respectively. 2-year icotinib significantly prolonged DFS (HR 0.521, 95%CI 0.278, 0.976; p = 0.039). OS events were observed in 20 patients, the OS was not mature yet. Icotinib was re-given for 32 patients with disease recurrence or metastasis as first-line treatment, objective response occurred in 66.7% of 30 patients with measurable disease. Treatment-related adverse events were recorded in 41 of 55 (75%) patients in 1-year group and 36 of 54 (67%) patients in 2-year group, and grade 3 or 4 treatment-related adverse events occurred in 4 (7%) of 55 patients in the 1-year group versus 3 (6%) of 54 in the 2-year group, respectively. No treatment-related deaths or interstitial lung disease were reported. **Conclusions:** 2-year adjuvant treatment with icotinib resulted in a significantly lower risk of recurrence than 1-year adjuvant icotinib in patients with stage II-IIIA NSCLC positive EGFR mutations and was not associated with increased toxic effects. Clinical trial information: NCT01929200. Research Sponsor: Betta pharmaceuticals.

8522 **Poster Session**

Two-year follow-up of single PD-1 blockade in neoadjuvant resectable NSCLC. *First Author: Shugeng Gao, Thoracic Surgery Department, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Early stage non-small-cell lung cancer (NSCLC) could benefit from anti-programmed cell death-1 (PD-1) monotherapy; however, the survival profiles remain to be disclosed. Here, we presented the two-year follow-up outcomes from a phase 1b study of sintilimab, an anti-PD-1 inhibitor in the neoadjuvant setting of NSCLC. **Methods:** Treatment-naive pts with resectable NSCLC (stage IA–IIIB) received two cycles of sintilimab followed by surgical resection. Postoperative treatment of sintilimab was at the discretion of investigator. The primary endpoint was AE, and key secondary endpoints included major pathological response (MPR), disease free survival (DFS) rate of 1 year and 2 years, and overall survival (OS) rate of 2 years. **Results:** Among 40 enrolled pts, 36 (90%) underwent R0 resection and were included in the R0 resection population. By data cutoff (January 20, 2021), the median follow-up for DFS and OS for all the enrolled pts was 23.9 (IQR 20.5–24.4) months and 26.4 (IQR 24.2–29.0) months. A total of 12 (33.3%) pts experienced relapse, and 6 pts died. The 1-yr and 2-yr DFS rate was 91.7%/73.3%. The 2-yr OS rate for overall population and R0 population was 87.5%/91.7%, respectively. In the R0 resection population, the median DFS and OS were both not reached. Superior 2-year DFS rates were observed in pts who achieved MPR (MPR vs. Non-MPR: 86.7% vs. 63.8%). DFS of pts with non-squamous cell carcinoma tended to be shorter than that of pts with squamous cell carcinoma (HR 2.71 [95%CI 0.67–11.0], p=0.1479). Pts with tumor mutation burden (TMB) ≥10 mutations/Mb and PD-L1 tumor proportion score (TPS)≥50% tended to have a better 2-yr DFS rate compared to those with TMB<10 and TPS<50. [table] For the post-hoc event free survival (EFS) analysis, the same trend was observed with DFS among different subgroups, and patients with TMB ≥10 mutations/Mb had a significant improved EFS (HR 0.125[95% CI 0.02,1.03], P=0.0222). **Conclusions:** Anti-PD-1 monotherapy emerged to be a promising neoadjuvant therapeutic strategy for resectable NSCLC with improved clinical outcomes. MPR could serve as a surrogate efficacy biomarker in this setting. Clinical trial information: ChiCTR-OIC-17013726. Research Sponsor: None.

DFS for R0 resection population.

Groups	N (Event)	Median, mo, (95%CI)	HR (95%CI)	P	1-yr rate, %	2-yr rate, %
Total	36 (9)	NR (NE–NE)	NA	NA	91.7	73.3
non-squamous	6 (3) 30	NR (16.9–NE)	2.71 (0.67–11.0)	0.1479	100 90.0	50.0
squamous	(6)	NR (NE–NE)				78.7
non-MPR MPR	21 (7) 15	NR (19.2–NE)	2.58 (0.535–12.45)	0.2202	95.2	63.8
	(2)	NR (NE–NE)			86.7	86.7
PD-L1 TPS≥50	10 (1) 20	NR (10.4–NE)	0.253 (0.03–2.06)	0.1653	90.0	90.0
TPS <50	(7)	NR (18.3–NE)			95.0	61.0
TMB≥10	10 (1) 11	NR (23.4–NE)	0.156 (0.018–1.348)	0.0534	100 90.9	83.3
TMB<10	(5)	NR (15.9–NE)				52.0
non-responder	28 (8) 8	NR (NE–NE) NR	2.31 (0.29–18.48)	0.4179	92.9	69.7
responder*	(1)	(10.4–NE)			87.5	87.5
Stage I/II Stage III	14 (2) 16	NR (NE–NE) NR	—	—	95.0	79.3
	(5)	(18.3–NE)			87.5	67.5

*, assessed by investigator per RECIST v1.1.

8523 **Poster Session**

Statewide rates of adjuvant checkpoint inhibitor use after definitive chemoradiation for stage III non-small cell lung cancer. *First Author: Alex K. Bryant, Department of Radiation Oncology, Rogel Cancer Center, University of Michigan, Ann Arbor, MI*

Background: In the landmark PACIFIC trial, adjuvant durvalumab after definitive chemoradiation for unresectable stage III non-small-cell lung cancer (NSCLC) produced a 11% absolute overall survival benefit at two years compared to placebo, and the US Food and Drug Administration approved durvalumab for this indication in February 2018. We investigated the real-world use of adjuvant durvalumab and other immune checkpoint inhibitors (ICI) in a contemporary cohort of patients. **Methods:** We identified patients with unresectable stage III (AJCC 8th edition) NSCLC treated with definitive chemoradiation from February 2018 to March 2020 from a statewide radiation oncology quality consortium, representing a mix of community (n=22 centers, 336 patients) and academic practice settings (n=5 centers, 64 patients) across the state of Michigan. Use of adjuvant durvalumab or other ICI (atezolizumab, nivolumab, or pembrolizumab) was ascertained at the time of routine three- or six-month follow-up after completion of chemoradiation. Baseline characteristics of patients treated with or without adjuvant ICI were compared with the Chi-squared test for categorical variables and a two-sided t-test for continuous variables. **Results:** Of 400 patients with unresectable stage III NSCLC treated with definitive chemoradiation, 268 (67%) received adjuvant ICI. Of these, the majority received durvalumab (86%) followed by pembrolizumab (7.5%) and nivolumab (6.0%). The proportion of patients receiving ICI remained stable throughout the study period with no discernable time trends. Eight-five percent of white patients received ICI compared with 77% of black patients (p=0.04), but there were no differences in gender (54.5% male in ICI vs 52.3% no ICI), current smoking (42.2% ICI vs 37.9% no ICI, p=0.68), number of comorbidities (29.5% with 3 or more comorbidities in ICI vs. 26.5% in no ICI, p=0.86), baseline oxygen use (8.9% ICI vs 10.6% no ICI, p=0.59), age (median 66.4 years [IQR 60.3-73.4] for ICI vs. 66.9 years [IQR 61.1-72.2] no ICI, p=0.89), treatment at an academic center (16.0% ICI vs 15.9% no ICI, p=0.97), or ECOG performance status (59.3% ECOG 0 in ICI vs 62.8% no ICI). **Conclusions:** In a broad range of academic and community-based practices across a state including 27 sites, only two-thirds of potentially eligible stage III NSCLC patients received adjuvant durvalumab or other ICI agents despite a proven overall survival benefit. Receipt of ICI was not strongly associated with baseline demographic or comorbidity variables. Further work will seek to clarify the patient-level reasons behind non-initiation of adjuvant ICI. Research Sponsor: None.

8524 **Poster Session**

Osimertinib as neoadjuvant treatment for resectable stage II-IIIB EGFR mutant lung adenocarcinoma (NEOS). *First Author: Chao Lyu, Thoracic Surgery II, Peking University Cancer Hospital, Beijing, China*

Background: Neoadjuvant treatment has demonstrated efficacy in several types of cancer and is increasingly used for the treatment of early-stage cancers with the potential of cancer downstaging to enhance complete surgical resection and to improve clinical outcomes. Recent evidences have demonstrated that the neoadjuvant use of first/second-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) may provide clinically meaningful improvement in EGFRm non-small cell lung cancer (NSCLC) patients, however, limited data were reported on osimertinib, the third-generation EGFR-TKI, in the neoadjuvant setting. Here we present an interim analysis of osimertinib as neoadjuvant treatment for resectable EGFRm NSCLC. **Methods:** NEOS is a prospective, multi-center, single-arm study to evaluate the efficacy and safety of osimertinib as neoadjuvant treatment in resectable EGFRm (19del/L858R) lung adenocarcinoma. Eligible patients were treated with osimertinib 80 mg orally per day for six weeks followed by surgery. Assessment of response to neoadjuvant therapy was performed according to RECIST 1.1. The primary endpoint was response rate. Secondary endpoints included safety, R0 surgical resection rate, quality of life, major pathologic response (MPR) rate, pathological complete response (pCR) rate, and N2 downstaging rate. **Results:** As of Dec. 17, 2020, 18 eligible patients (median age 61 [range 46-73], 27.8% male, 22.2% ECOG PS 1) have been enrolled. Patients with clinical stages IIa, IIb, and IIIa (8th AJCC) accounted for 16.7%, 22.2% and 61.1%, respectively. Half (9/18) of the patients had EGFR exon 21 L858R mutations and the other half (9/18) had EGFR exon 19del mutations. Amongst all 15 patients who completed efficacy assessment after neoadjuvant osimertinib, the response rate (RR) was 73.3% (11/15) and the disease control rate (DCR) was 100% (15/15). R0 surgical resection was performed in 93.3% (14/15) patients. Pathological downstaging occurred in 53.3% (8/15) patients. 42.9% (3/7) of the patients with confirmed N2 lymph nodes experienced downstaging to N0 disease after receiving neoadjuvant osimertinib. One patient was identified with a pCR. Adverse events (AEs) were reported in 66.7% (12/18) of patients, with the most common AE being rash (8/18, 44.4%), oral ulceration (8/18, 44.4%), and diarrhea (5/18, 27.8%). No grade 3-5 AEs or serious AEs were reported. **Conclusions:** Interim analysis from this study indicated neoadjuvant osimertinib as an effective and feasible treatment in patients with resectable stage II-IIIB EGFRm NSCLC. The trial is ongoing and the final results will be provided in the future. Clinical trial information: ChiCTR1800016948. Research Sponsor: astrazeneca.

8525 **Poster Session**

Cost evaluation of adjunctive osimertinib use in resected epidermal growth factor receptor-positive non-small cell lung cancer. *First Author: Briana Choi, University of Arizona College of Pharmacy, Tucson, AZ*

Background: About 30% of patients with epidermal growth factor receptor positive (EGFR+) non small cell lung cancer (NSCLC) are eligible for surgical resection. Osimertinib, a first line therapy for advanced EGFR+ NSCLC (stages 1B, 2, 3A), has shown clinical efficacy compared to placebo as an adjunctive therapy post resection. We evaluated the cost effectiveness/utility of this regimen. **Methods:** A two health state Markov model was built (disease free vs. disease recurrence or death). Disease free survival (DFS) curves were digitized and fitted to exponential function. 3 year timeline as patients received osimertinib for 3 years in published data. US payer perspective and 3% discount rate were applied. Drug costs were per Redbook whole acquisition cost and monitoring costs were from published data (US$ 2020). No adverse events $> 5\%$ were reported hence none were included. Life years (LY) and quality adjusted life years (QALY) were estimated for each stage. Incremental cost-effectiveness and utility ratios (ICER/ICUR) for LY and QALY gained were estimated in base case (BCA) and probabilistic sensitivity analyses (PSA). **Results:** Shown in the table are BCA and (PSA) results. Using LY as outcome, for stage 1B, incremental DFSLY of 0.40 (0.39) and incremental cost of $500,782 ($501,034) yielded an ICER/DFSLYG of ~$1.3 million (M) (~$1.2 M). For stage 2, incremental DFSLY of 0.79 (0.79) and incremental cost of $503,144 ($503,092) resulted in an ICER/DFSLYG of $636,913 ($638,278). For stage 3A, incremental of DFSLY of 0.18 (0.07) and incremental cost of $322,356 ($293,377) yielded an ICER/DFSLYG of ~$1.2 M (~1.2 M). The incremental costs are the same for QALY outcomes. Using QALY as outcome, for stage 1B, incremental of DFSQALY of 0.26 (0.27) yielded an ICUR/DFSQALY of ~$1.9 M. In stage 2, incremental DFSQALY of 0.53 (0.53) resulted in an ICUR/DFSQALY of $950,616 ($952,654). For stage 1C, incremental DFSQALY of 0.18 (0.07) yielded an ICUR/DFSQALY of ~$1.8 M (~$3.7 M). **Conclusions:** The ICERs and ICURs indicate that cost effectiveness varies markedly across stages of disease. Stage 2 showed the lowest cost to outcome association. In general, the cost burden of adjunctive maintenance therapy with osimertinib in resected EGFR+ NSCLC is substantial relative to the observed clinical benefit. The incremental benefit of osimertinib in stage 2b is more evident than the ones in 1B and 3A. Research Sponsor: None.

BCA (PSA).

	1B		2		3A	
	Placebo	Osimertinib	Placebo	Osimertinib	Placebo	Osimertinib
Cost	$7,128 ($7,142)	$507,910 ($508,176)	$6,189 ($6,195)	$509,333 ($509,287)	$5,048 ($5,046)	$327,404 ($298,425)
DFS LY	2.31 (2.32)	2.71 (2.71)	1.93 (1.93)	2.72 (2.72)	1.47 (1.47)	1.74 (1.59)
DFS QALY	1.55 (1.55)	1.81 (1.82)	1.29 (1.29)	1.82 (1.82)	0.99 (0.99)	1.17 (1.06)
ICER/ DFSLYG	-	$1,263,917 ($1,283,518)	-	$636,913 ($638,278)	-	$1,186,058 ($2,496,044)
ICUR/ DFSQALYG	-	$1,886,443 ($1,915,699)	-	$950,616 ($952,654)	-	$1,770,236 ($3,725,439)

8526 **Poster Session**

Minimal residual disease (MRD) in patients with resected stage I NSCLC: Results of the prospective adjuvant IFCT-0703 trial. *First Author: Damien Vasseur, Gustave Roussy, Villejuif, France*

Background: MRD aims to detect circulating biomarkers of micrometastatic disease and ultimately predict recurrences. The IFCT-0703 randomized phase II trial failed to show a benefit of 6 months adjuvant pazopanib (P) vs. placebo after resection of stage I NSCLC (7th TNM edition). The outcome of pts based on their MRD status has been evaluated. **Methods:** Blood samples were collected in EDTA tubes (Becton Dickinson Company) after surgery (T0), after 3 months (T3) of P or placebo and at the end of treatment (T6). Plasmas were obtained after double centrifugation of total blood. Total nucleic acid was extracted using the Maxwell RSC LV plasma kit (Promega) according to the manufacturer's protocol. Samples were quantified using the QuBit dsDNA HS Assay kit on a QuBit 3.0 flurometer (Thermo Fisher Scientific). Molecular analysis was performed by next generation sequencing using the Oncomine Lung cfDNA Assay (ThermoFisher Scientific). Two MRD definitions were tested : 1) high level of DNA in the blood or 2) any mutation detected by the standard bioinformatic pipeline was considered present, whatever the allelic fraction. **Results:** 143 pts were randomized in 29 centers between March 2009 and August 2012, 71 and 72 in the placebo and P arms respectively. Among the 119 pts with evaluable T0 samples, 27 pts recurred and 14 died. Median DNA concentration ([DNA]) was 6.6 ng/ml and an increase of [DNA] of 10 ng/ml was found prognostic of poor DFS and OS, HR=1.4, 95%CI [1.14-1.72], p=0.0016 and HR=1.62, 95%CI [1.15-2.30], p=0.0057 respectively. In 81 pts with available T0-T6 samples, [DNA] variation had no different impact on DFS and OS, in the P arm and the placebo arm. ctDNA mutations (ctDNA+) were detected in 31/119 pts. ctDNA+ were more frequent in samples with high DNA quantity (p=0.0002). Genes mutated at T0 were *TP53* in 16, *NRAS* in 6, *MAP2K1* in 2, *KRAS* in 1, *EGFR* in 5, *BRAF* in 1, *ALK* in 2. 29 pts had 1 mutation, 2 had 2 mutations. DFS and OS were similar between pts with or without ctDNA+ : HR= 1.038 (95%CI 0.438-2.456, p=0.93) and 1.193 (95% CI 0.367-3.882, p=0.77) respectively. Among 27 pts with ctDNA+ at T0 and available sample at T6, 23 had no more mutations at T6. Two pts had a ctDNA+ only at T6 (not at T3), one of them had a recurrence at 7 months. **Conclusions:** Post-operative ctDNA mutations are found in 26.0% of the pts but their positivity had no impact on DFS or OS. In contrast, DFS and OS were poorer in pts with increased plasma DNA concentration. ctDNA mutations status do not recapitulate the complexity of MRD characterization. NGS will be performed on matched tissues in order to refine MRD definition. Clinical trial information: NCT00775307. Research Sponsor: Fondation ARC.

8527 **Poster Session**

Modeling the cost-effectiveness of adjuvant osimertinib in resected EGFR-mutant non-small cell lung cancer patients. *First Author: Christopher Lemmon, Cleveland Clinic, Cleveland, OH*

Background: Adjuvant Osimertinib (Osi) was recently approved for resected EGFR-mutant non-small cell lung cancer (NSCLC) based on disease free survival (DFS) benefits from the ADAURA trial. Prior studies of adjuvant EGFR inhibitors yielding DFS benefits have lacked an overall survival (OS) benefit, leading to debate over early clinical implementation given the associated drug costs. This study aims to evaluate the cost-effectiveness (CE) of Osi in this setting. **Methods:** We constructed Markov models using post-resection health state transitions with digitized DFS data from the ADAURA trial to compare cost and quality-adjusted life years (QALYs) of the use of 3 years of adjuvant Osi versus placebo in the ADAURA patient population of stage IB to IIIA NSCLC patients over a 10-year time horizon. All patients entering the progressive disease (PD) state were assigned for re-treatment with Osi. Cost and utility values were derived from Medicare reimbursement data and literature (Table). A CE threshold of 3 times the GDP per capita was used. Deterministic sensitivity analyses were performed to assess the impact of a range of OS benefit, as the impact of adjuvant Osi on OS has not yet been reported. **Results:** The incremental cost-effectiveness ratio (ICER) for adjuvant Osi was $317,119.90 per QALY gained. Initial costs of Osi are higher in the first 3 years, but become lower than the placebo group in year 4 onward, with similar costs after year 7. Costs due to PD are higher in the placebo group through the first 6.5 years. Average pre-PD, post-PD, and total costs were $2,388, $379,047, and $502,937, respectively in the placebo group, compared to $505,775, $255,638, and $800,697, respectively in the Osi group. QALYs were higher in the Osi arm throughout. Sensitivity analysis using incremental OS gains reaches the CE threshold of $195,000 between 25-30% OS benefit of Osi over placebo. A 50% discount to the Osi annual cost yielded an ICER of $115,419. **Conclusions:** 3 years of adjuvant Osi is more cost-effective than placebo if one is willing to pay $317,119 more per QALY gained, with most costs accruing in the first 3 years as drug cost. This strategy became cost-effective with an OS benefit between 25-30% over placebo. Discount to Osi annual costs improves the ICER significantly. True cost-effectiveness of adjuvant Osi will require further study due to immaturity of ADAURA OS data and model limitations. Research Sponsor: None.

Model QALY utility an cost inputs.

QALY Utilities	NED state (osi/placebo)	0.81/0.83
	PD state (CNS+/CNS-)	0.55/0.71
Annual Costs	EGFR testing	$324.58
	Osimertinib cost	$222,196
	NED state healthcare costs	1914.83
	PD diagnostic costs	$7,202.88
	PD state healthcare costs	$1,186.76
	Average CNS+ PD lifetime costs	$45,081.39
	Palliative/end of life cancer costs	$78,571.06
	Adverse event costs and disutilities also incorporated	

8528 **Poster Session**

Driver mutations to predict for poorer outcomes in non-small cell lung cancer patients treated with concurrent chemoradiation and consolidation durvalumab. *First Author: Yufei Liu, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The use of durvalumab after chemoradiation in locally advanced non-small cell lung cancer (NSCLC) patients significantly improves overall survival. However, it is unclear whether this benefit applies to all genetic subtypes of lung cancer. We hypothesize that patients with driver mutation NSCLC may derive less benefit from consolidation durvalumab. **Methods:** Using the Genomic Marker-Guided Therapy Initiative (GEMINI) database at MD Anderson, we identified 134 patients who were treated with chemoradiation followed by durvalumab for NSCLC. We segregated patients with driver mutations to targetable (EGFR, ALK translocation, ROS1 fusion, MET exon 14 skipping, RET fusion, and/or BRAF) (N = 24) and those driven by canonical KRAS mutations (N = 26). The rest (N = 84) had none of these mutations. We gathered demographic, treatment, and outcome data and compared progression-free survival (PFS) and overall survival (OS) using the Kaplan-Meier method. We used multivariate regression analysis to account for demographic and treatment variables. **Results:** For our cohort, median age at diagnosis was 64.8, 52% were female (n = 70), and median follow up was 1.5 years. 86% of patients have a history of smoking (n = 115). 21% had squamous cell histology (n = 28). 2 patients had stage IIA disease, 6 had stage IIB, 48 had stage IIIA, 56 had stage IIIB, 13 had stage IIIC, and 9 had stage IV. 73 patients had progression after durvalumab and 37 patients died. Patients with driver mutations had significantly worse median PFS compared to those without driver mutations (8.9 mo vs 26.6 mo; HR 2.62 $p < 0.001$). Patients with KRAS mutations had particularly poor PFS (Median 7.9 mo, HR 3.34, $p < 0.001$), while patients with targetable driver mutations trended to worse PFS (Median 14.5 mo, HR 1.96, p = 0.056). The median OS for the cohort was 4.8 yrs with no significant differences based on driver mutation status. On multivariate analysis, only driver mutation status was associated with PFS, but not OS. For patients with first progression, we found the targetable driver group to have significantly improved time to second objective progression (PFS2) compared to the KRAS (HR 0.28, p = 0.011) or non-mutated group (HR 0.38, p = 0.025). All patients in the targetable driver group received targeted therapy after first progression. **Conclusions:** Our results suggest that patients with driver mutations have worse PFS compared to patients without these mutations after chemoradiation. However, patients with targetable oncogene driver mutations have significantly improved prognosis after initial progression compared to the other groups, likely due to targeted therapy, suggesting that these therapies, including novel approaches towards KRAS mutants, should be further explored in this setting. Research Sponsor: None.

8529 **Poster Session**

Natural history of curatively resected stage IB-IIIA EGFR mutation (+) NSCLC: Clinicopathologic and molecular prognostic factors (ROOT-EGFR-ADJ). *First Author: Hyun Ae Jung, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Surgery is the primary therapy for patients with early-stage NSCLC. However, five-year recurrence rates were 45%, 62%, and 76% for pathologic stage (pStage) IB, II, and III respectively. In the ADARUA study, adjuvant osimertinib significantly improved DFS in patients with completely resected EGFR mutation (+) NSCLC. Though marked improvement of DFS is encouraging, OS is not mature yet and several questions remain unanswered; Does this DFS benefit translate to cure? Do all patients need to receive adjuvant Osiemrtinib? In order to address these questions we reviewed the clinical records of pStage IB-IIIA EGFR mutant NSCLC. **Methods:** From January 2008 and August 2020, total 2,340 patients with pStage IB-IIIA, non-SQ NSCLC underwent curative surgery at Samsung Medical Center. Using innovative in-house algorithm to retrieve medical big data-based cohort called ROOT (Realtime autOmetically updated data warehOuse in healTh care) detailed clinical data were analyzed to investigate any prognostic factors of recurrence. In order to identify any molecular prognostic factors, we did a comprehensive genomic analysis (WTS/WES)in a subset of patients with matched case-control. **Results:** Total 1,811 patients with pStage IB-IIIA, non-SQ EGFR mutation (+) NSCLC were included (367 patients : no EGFR mutation test) . Median follow-up duration was 38.8 (range: 0.5 -156.2). Patient demographics; Deletion 19 was 52.7%, L858R was 47.3%. Female was 64.7% and never smoker was 72%. Stage IB, IIA, IIIA was 50.4%, 26.5%, and 23.2%. Among them, 6.7% of pStage IB, 72.8% of pStage II, and 88.7% of pStage IIIA received adjuvant chemotherapy. Median DFS were 74.0 months (95% CI 63.2-84.8), 48.6 months (95% CI: 40.2-57.0), and 22.4 months (95%: 19.5-25.3) for pStage IB, II, and IIIA, respectively. The median OS were 132.1 months (95% CI: 101.3-162.8), 124.3 months (95% CI: 61.8-186.9), and 82.1 months (95% CI: 71.2-93.1) for pStage IB, II, and IIIA, respectively. In univariate analysis, pStage, poorly differentiation, histologic subtype (micropapillary, solid), lymphatic invasion, vascular invasion, and pleural invasion were related with high recurrence rate statistically. In multivariate analysis, pStage, vascular invasion, and pleural invasion were related with recurrence statistically. To detect molecular factors, 76 patients performed the matched case -control (included pStage, type of EGFR mutation, and sex) analysis (WES/WTS). **Conclusions:** This study showed that the median DFS of pStage II-IIIA EGFR mutation (+) NSCLC was 31.9 months. With approximately 55% of patients with pStage II-IIIA EGFR mutation (+) NSCLC experienced recurrence at the 3rd year, we need to find the appropriate subset who need 3-year adjuvant osimertinib by comprehensive predictive marker for cure. Updated and detail exploratory biomarker outcome will be presented at the annual meeting. Research Sponsor: None.

8530 **Poster Session**

Molecular characteristics of EGFR exon 19 deletion subtypes in NSCLC patients. *First Author: Weiquan Gu, The Thoracic Surgery Department, Foshan First People's Hospital, Foshan , China*

Background: EGFR exon 19 deletion mutations are well characterized, known to be activating, and are associated with responses to EGFR tyrosine kinase inhibitors (TKIs). A variety of methods have been developed to identify EGFR mutations. Deletions of EGFR exon 19 are more complex compare to the other because they consist of different subtypes. **Methods:** In this study, we retrospectively analyzed the different subtypes of EGFR exon 19 deletions using next-generation sequencing(NGS). From May 2019 to December 2020, 3275 patients who were diagnosed with Non-small cell lung cancer (NSCLC)were detected. **Results:** In this analyzed cohort, the average age of patients was 62 years (range, 24-92 years). Most of the patients were female (61.07%) and were diagnosed with lung adenocarcinoma (82.60%). It is worth noting that the deletions in exon 19 of EGFR were also detected in 35 patients (1.07%) with squamous cell carcinoma and 1 patient (0.03%) with sarcomatoid. The most frequent EGFR exon 19 deletions were delE746-A750 (63.4%), followed by delL747-P753insS (9.7%) and L747-T751 (6.9%). The characteristics of the patients in this study are presented. Significantly, three samples with compound EGFR exon 19 deletions were detected: 1) S1:E746_A750delinsFP+E746_A750del; 2) S2: E746_S752delinsV+L747_P753delinsS; 3) S3:E746_P753delinsVS + L747_P753delinsS. **Conclusions:** EGFR exon 19 starting at codon 729 to 761, our data showed the deletions occur throughout almost the entire exon 19 amino acid. As our integrated data results, EGFR exon 19 has many different deletions and insertion subtypes could be defined as 79 subtypes. Among those subtypes,70 were complex with an accompanying insertion. The most frequent deletions were starting at E746 and L747. Based on several clinical researches, different deletion subtypes may have significantly different clinical responses after TKI treatment. However, more clinical research is needed to support this finding. Research Sponsor: None.

8531 **Poster Session**

Seroprevalence and immunological memory against SARS-CoV-2 in lung cancer patients (p): SOLID study. *First Author: Mariano Provencio, Puerta de Hierro Majadahonda University Hospital, Madrid, Spain*

Background: Coronavirus disease 2019 (COVID-19) is diagnosed by detecting the virus by reverse transcription polymerase chain reaction (RT-PCR). The majority of p go on to develop antibodies (Ab) against viral proteins. However, it is not known how long these antibodies last nor whether cancer treatments could affect the duration of immune response. The prognosis and greater or lesser vulnerability of the oncological population are also unknown. **Methods:** This prospective, longitudinal, multicenter serological study in the setting of SARS-CoV-2 was carried out in 50 Spanish hospitals. Eligibility criteria was a diagnosis of any thoracic cancer. The first determinations were performed between April 21, 2020 and June 3, 2020, either for p in follow up or in active treatment. Between September 10, 2020, and November 20, 2020, the second antibody (Ab) determination was performed in all previously seropositive p. Clinical and treatment data were collected, as was their clinical situation at study end. Study objectives were to prospectively determine seroprevalence in unselected lung cancer p during the first wave of the pandemic; the natural history of these p; the persistence of immunity more than 4 months after first determination; protection or lack thereof against reinfection after this period, and the nature of such protection; and the influence of treatments on maintenance or loss of immunity. **Results:** Of 1,500 p studied, 128 were seropositive, representing an overall prevalence of 8.5% seropositivity [95% confidence interval [CI], 7.2%, 10.1%]. Seventy-five percent were in active cancer treatment. COVID-19 infection was suspected in 47.7% [95% CI, 38.8%, 56.6%]. A second determination was performed on average 4.5 months later [IQR: 4; 5] and obtained for 104 of the initially seropositive p (81%). A second determination could not be obtained in 24 p, the majority due to death caused by disease progression (73%). In the second determination, IgG was not detected in 30.8% (32/104) of p. The severity of the infection, the need for hospitalization *(p: 0.032)* and the presence of symptoms at diagnosis *(p: 0.02)*, including fever *(p: 0.005)* and nasal congestion *(p: 0.005),* were associated with persistence of immunity in the second determination. No variables or treatments received were associated with Ab loss. At time of last follow-up among those p for whom a second determination was performed, 89% (93 p) had completely recovered from the virus, with no lasting after effects. Only 1 of the 128 (0.78%) seropositive p had died from COVID-19. **Conclusions:** The prevalence of infection in lung cancer p is similar to that of the general population. Immunity against SARS-CoV-2 does not appear to be compromised by treatment, persisting beyond 4 months. Neither do mortality rates appear to be particularly high in this unselected population. Research Sponsor: Roche.

8532 **Poster Session**

Association of high level of plasma tissue factor activity with venous thromboembolism and early death in lung cancers. *First Author: Helene Doubre, Pneumology, Hopital Foch, Suresnes, France*

Background: Venous thromboembolism (VTE) is associated with tumor aggressiveness and mortality in cancers. Tissue Factor is the main activator of the coagulation but its variations in lung cancers (LC) have been less studied than D-dimers (DDi). We assessed plasma Tissue Factor Activity (TFa) and DDi and VTE events and mortality in patients with LC. **Methods:** This prospective study included patients, from 5 hospitals, recently diagnosed LC, without prior VTE or anticoagulant therapy within the last 2 months. Clinical and tumor data, Khorana score (KS), VTE events and overall survival (OS) were assessed (follow up 2 years). Blood samples were collected before any cancer treatment (V1): DDi (HemosIL) and TFa (chromogenic assay, Diagnostica Stago) were analyzed in a central lab. Independent nonparametric tests were used for group comparisons. A relevant clinical threshold of both markers was determined :1500 μg/ml for DDi and 1.2 ng/ml for TFa. Early death was compared using Cox model and Kaplan Meier curves and logrank tests. All tests were two-tailed tests and 0.05 was considered as significant. **Results:** Between 12/2014 and 01/2017, 302 consecutive patients (pts) were included (mean age 64 years, 61% males, 89% smokers, 85% NSCLC, 67% stage IV). At V1, TFa levels increased with cancer stage (p = 0.004) but not DDi. VTE incidence was 13,9%: 39 events (62% incidental and 51% pulmonary embolism) with 33 events within 6 months. KS failed to predict VTE (KS $>$ 3 in 23% of the pts in VTE group vs 21% of the 302 pts, p = 0.42). DDi and TFa levels were not significantly different in VTE pts than in no VTE pts. But, a TFa $>$ 1.2 ng/ml was significantly predictive in occurrence of VTE within the first 6 months (57.6% of the VTE pts vs 38.8% of no VTE pts, p = 0.04), and also within the first year (p = 0.03). Median OS was 17,6 months (m) in VTE pts and 19.5 m in no VTE pts (p = 0,97). Compared to survivors, higher levels of DDi and TFa were observed for the 38 pts who died within 6 months : 1.82 vs 0.67 μg/ml ($p < 0.001$) and 1.95 vs 0.33 ng/ml ($p < 0.001$) respectively. These differences were observed for the 97 pts who died during the first year, too. With thresholds of TFa $>$ 1.2 ng/ml and DDi $>$ 1500 μg/ml, median OS was significantly shorter: 14.4 m vs $>$ 29.8 m (p $<$ 0,001) and 13.8 m vs 22.6 m ($p < 0.001$), respectively. **Conclusions:** High TFa level discriminates a population with high risk to VTE and early death in LC. This biomarker could take place in a predictive score. Clinical trial information: NCT02853188. Research Sponsor: None.

8533 **Poster Session**

Noninvasive identification of emergent mutations following cytotoxic therapy for lung cancer. *First Author: Everett James Moding, Stanford University, Stanford, CA*

Background: Lung cancer is the leading cause of cancer death world-wide, and chemotherapy and radiation remain backbones of therapy for patients with locoregionally advanced and metastatic disease. However, the genetic mechanisms that mediate resistance to chemotherapy and radiation are largely unclear due to a lack of available tissue at the time of relapse. We hypothesized that circulating tumor DNA (ctDNA) analysis could identify emergent mutations after chemotherapy and radiation that may lead to treatment resistance. **Methods:** To identify emergent mutations at the time of progression following an initial response to chemotherapy and/or radiation therapy for lung cancer, we utilized CAncer Personalized Profiling by deep Sequencing (CAPP-Seq) to analyze plasma samples and matched leukocytes collected pre-treatment and at the time of relapse. We analyzed a targeted panel enriched for lung cancer drivers and recurrently mutated genes for 27 patients treated with chemoradiation therapy for locoregionally advanced lung cancer. In addition, we performed ultra-deep whole exome sequencing ($>$ 2000X deduped depth) of pre-treatment and relapse cell-free DNA for 5 patients treated with combination chemotherapy for metastatic lung cancer. Functional enrichment analysis was performed on emergent mutation gene lists to identify significantly enriched pathways. **Results:** We identified emergent variants in 6 out of 27 patients using targeted sequencing after chemoradiation therapy. Emergent mutations after chemoradiation were enriched for plasma membrane adhesion molecules such as *PCDH17*, *PCDH10,* and *FAT3* (adjusted P = 0.03). Using ultra-deep whole exome sequencing, we observed emergent mutations in 3 out of 5 patients treated with combination chemotherapy. After combination chemotherapy, there was a trend towards enrichment in mutations in ATP-binding cassette transporters, including *ABCA13* and *ABCB4* (adjusted P = 0.057). Notably, there were no recurrent emergent mutations within our cohort. **Conclusions:** Our results suggest that ultra-deep whole exome sequencing can non-invasively identify emergent mutations at the time of progression. Resistance to cytotoxic therapy is likely multi-factorial and analysis in expanded cohorts will be helpful to identify recurrently mutated pathways that may contribute to disease progression after an initial response to therapy. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Pharmaceutical/Biotech Company.

8534 **Poster Session**

Sequential monitoring of PD-L1 on circulating stromal cells in blood predicts PFS in NSCLC patients undergoing immunotherapy after definitive chemoradiation. *First Author: Daniel L Adams, Creatv MicroTech, Inc., Monmouth Junction, NJ*

Background: Cancer Associated Macrophage-Like cells (CAMLs) are circulating stromal cells in the blood of patients (pts) with solid tumors that are phagocytic macrophages that may represent the inflammatory state of the tumor microenvironment. Previously, we demonstrated CAMLs ≥50μm after chemo-radiation therapy (CRT) in NSCLC is associated with worse progression free survival (PFS) and overall survival (OS). We also showed that PDL1 expression in CAMLs is dynamic & can change with CRT, difficult to assess with repeat biopsies, but possible with liquid biopsy. For this study we evaluated whether CAML properties can predict response to CRT with/without immunotherapy (IMT) agents in unresectable NSCLC. **Methods:** A single blind multi-year prospective study was undertaken to test the relationship of PDL1 expression and ≥50μm CAML size to PFS/OS in NSCLC, pre and post CRT with (n = 96) and without (n = 72) anti-PDL1/PD1 IMT. This included atezolizumab (prospective single arm NCT02525757) n = 39, durvalumab n = 52 or pembrolizumab n = 5 both after 2018 FDA approval. We recruited 168 pts with pathologically confirmed unresectable NSCLC prior to CRT. Blood samples 15 mL were taken at baseline (BL), CRT completion (T1), and ~1 month after CRT (T2) (with n = 96 or without n = 72 IMT). Blood was filtered by CellSieve filtration and CAMLs quantified for size ($<$ 49 μm or ≥50 μm) and PDL1 expression to evaluate PFS and OS hazard ratios (HRs) by censored univariate and multivariate analysis at 24 months. **Results:** CAMLs were found in 90% of all samples, average 5.8 CAMLs/15mL. At BL, ≥50μm CAMLs did not predict PFS in CRT/IMT pts (HR 1.6, p = 0.220) nor CRT alone (HR 1.3, p = 0.593). However, after completion of CRT (T1) ≥50μm CAMLs predicted PFS in CRT/IMT pts (HR 2.7, p = 0.003) and CRT alone (HR 2.5, p = 0.015). In primary tumor biopsies, PDL1 expression $>$ 1% did not predict CRT/IMT response (PFS HR 1.8, p = 0.262 & OS HR 2.3, p = 0.158). At BL, high CAML PDL1 did not predict PFS in CRT/IMT pts (HR 1.4, p = 0.427) nor CRT alone (HR 1.1, p = 0.982). Further, at CRT completion (T1), high CAML PDL1 only trended for better PFS in CRT/IMT pts (HR 1.7, p = 0.137), but not CRT alone (HR 1.1, p = 0.972). At T2, however, pts with continuously high CAML PDL1 had significantly better PFS with IMT (HR 3.2, p = 0.002) vs CRT alone (HR 1.4, p = 0.616). While ≥50μm CAMLs at BL did not predict 24 month progression, ≥50 μm CAMLs after CRT (with or without 1 cycle of anti-PDL1 IMT) was 84% accurate at predicting progression. Further subtyping and analysis is ongoing to evaluate OS and PDL1 in the CAML populations. **Conclusions:** Our data suggests that in unresectable NSCLC, ≥50 μm CAMLs after completion of CRT is prognostic regardless of IMT use. PDL1 expression in CAMLs also appears to predict for response to consolidated IMT after CRT. Additional studies are needed to validate these findings. Research Sponsor: U.S. National Institutes of Health.

8535 **Poster Session**

Genomic and immunologic characterization of large-cell neuroendocrine carcinoma of the lung. *First Author: Chul Kim, Georgetown University, Department of Hematology and Oncology, School of Medicine, Washington, DC*

Background: Large-cell neuroendocrine carcinoma (LCNEC) is a rare type of lung cancer with a poor prognosis. Due to its rarity, molecular characterization of LCNEC is not well elucidated. We aim to understand the genomic and immunologic landscape of LCNEC to identify molecular alterations and relevant biological pathways with potential therapeutic value. **Methods:** Comprehensive profiling including whole exome sequencing (WES), next-generation sequencing (NGS), whole transcriptome sequencing (WTS), and immunohistochemistry (IHC) for PD-L1 was performed (Caris Life Sciences, Phoenix, AZ). Tumor mutational burden (TMB) was calculated based on somatic nonsynonymous mutations. LCNEC was categorized as small cell lung cancer (SCLC)-like LCNEC (*TP53*/*RB1* co-mutated) and non-small-cell lung cancer (NSCLC)-like LCNEC (wild type for one or both of *TP53*/*RB1*). Molecular features of LCNEC were compared among the subgroups and with those of SCLC using the χ^2 test with Benjamini & Hochberg correction. **Results:** A total of 467 cases of LCNEC were included. Commonly altered genes (≥ 5%) included *TP53* (79.1%), *RB1* (36.8%), *SMARCA4* (10.4%), *ARID1A* (10.3%), *KRAS* (9.7%), *KEAP1* (9.2%), *KMT2D* (8.7%), *STK11* (8.4%), *NF1* (7.1%), *PTEN* (6.1%), and *CDKN2A* (5.9%). The prevalence of potentially actionable mutations was as follows: *EGFR* exon 19 deletion (0.48%), *EGFR* L858R (0.48%), *ALK* fusion (1.7%), *KRAS* G12C (2.9%). *EGFR* exon 19 deletion, *EGFR* L858R, and *ALK* fusion were exclusive to NSCLC-like LCNEC tumors. *RET* fusion, *NTRK* fusion and $BRAF^{V600E}$ were not detected. Copy number alterations (CNAs) were found in *MYC* (8.8%), *ZNF703* (4.1%), *FOXA1* (4.0%), *FGFR1* (4.0%), *ATK2* (3.9%), *CCNE1* (3.7%), *FGF19* (3.4%), *TNFRSF14* (3.4%), and *CCND1* (2.7%). Over-expression of cMET was noted in 10% and PD-L1 expression (by 22C3 pharmDx) of $>$ 1% was noted in 21.5% of samples. WTS detected cMET exon 14 skipping mutations in 2.4% of samples. High tumor mutation burden (TMB; ≥ 10 Mut/MB) was seen in 40.6%. Among the 467 cases of LCNEC, 112 (24%) were SCLC-like LCNEC and 335 (76%) NSCLC-like LCNEC. Mutations in *KRAS* (12%), *STK11* (11%), *CDKN2A* (9%), and *SMARCA4* (14%) were more common in NSCLC-like LCNEC, compared with SCLC-like LCNEC (p value $<$ 0.05). 442 cases of SCLC were compared with LCNEC tumors. *SLFN11:SLFN12* fusion events, detected by WTS, were exclusively seen in SCLC and were not seen in any of the LCNEC cases. Gene expression profiles revealed that 1) B cell infiltration was higher in SCLC-like LCNEC, compared with SCLC, and 2) NK and T cell infiltration was lower, but B-cell infiltration was higher in NSCLC-like LCNEC, compared with SCLC. **Conclusions:** LCNEC displays a broad pattern of genomic alterations that overlap in the SCLC-like subset with the classic alterations in SCLC. The distinct genomic alterations and transcriptomic profiles present opportunities for therapeutic targeting and inform a future framework for development of therapeutics for LCNEC. Research Sponsor: None.

8536 **Poster Session**

Deep learning to predict subtypes of poorly differentiated lung cancer from biopsy whole slide images. *First Author: Gouji Toyokawa, Department of Thoracic Surgery, Clinical Research Institute, National Hospital Organization, Kyushu Medical Center, Fukuoka, Japan*

Background: Lung cancer is the leading cause of cancer-related death in many countries, and its prognosis remains unsatisfactory. Since treatment approaches differ substantially based on the subtype, such as adenocarcinoma (ADC), squamous cell carcinoma (SCC) and small cell lung cancer (SCLC), an accurate histopathological diagnosis is of great importance. However, if the specimen is solely composed of poorly differentiated cancer cells, distinguishing between histological subtypes can be difficult. The present study developed a deep learning model to classify lung cancer subtypes from whole slide images (WSIs) of transbronchial lung biopsy (TBLB) specimens, in particular with the aim of using this model to evaluate a challenging test set of indeterminate cases. **Methods:** Our deep learning model consisted of two separately trained components: a convolutional neural network tile classifier and a recurrent neural network tile aggregator for the WSI diagnosis. We used a training set consisting of 638 WSIs of TBLB specimens to train a deep learning model to classify lung cancer subtypes (ADC, SCC and SCLC) and non-neoplastic lesions. The training set consisted of 593 WSIs for which the diagnosis had been determined by pathologists based on the visual inspection of Hematoxylin-Eosin (HE) slides and of 45 WSIs of indeterminate cases (64 ADCs and 19 SCCs). We then evaluated the models using five independent test sets. For each test set, we computed the receiver operator curve (ROC) area under the curve (AUC). **Results:** We applied the model to an indeterminate test set of WSIs obtained from TBLB specimens that pathologists had not been able to conclusively diagnose by examining the HE-stained specimens alone. Overall, the model achieved ROC AUCs of 0.993 (confidence interval [CI] 0.971-1.0) and 0.996 (0.981-1.0) for ADC and SCC, respectively. We further evaluated the model using five independent test sets consisting of both TBLB and surgically resected lung specimens (combined total of 2490 WSIs) and obtained highly promising results with ROC AUCs ranging from 0.94 to 0.99. **Conclusions:** In this study, we demonstrated that a deep learning model could be trained to predict lung cancer subtypes in indeterminate TBLB specimens. The extremely promising results obtained show that if deployed in clinical practice, a deep learning model that is capable of aiding pathologists in diagnosing indeterminate cases would be extremely beneficial as it would allow a diagnosis to be obtained sooner and reduce costs that would result from further investigations. Research Sponsor: None.

8537 **Poster Session**

A new model using artificial intelligence to predict recurrence after surgical resection of stage I-II non-small cell lung cancer. *First Author: Natalie Lui, Stanford University, Stanford, CA*

Background: Five-year survival for stage I-II lung cancer is quite low even after complete surgical resection. Current guidelines recommend adjuvant treatment only for selected patients with stage II or higher disease. A prediction model that identifies patients at high risk of recurrence who may benefit from adjuvant treatment is greatly needed. Many existing prediction models include a small number of genes that were found to be significant in previous studies. We propose using artificial intelligence to analyze a microarray of $>$ 20,000 well-annotated genes to create a model that predicts recurrence after surgical resection of stage I-II lung cancer. **Methods:** We identified 275 patients who underwent surgical resection for pathologic stage I-II lung adenocarcinoma or squamous cell carcinoma from 2009 to 2019 in our institution's prospective surgical database. We excluded patients who had follow up time less than 3 years or received adjuvant therapy and had not had a recurrence, as well as patients with missing specimen blocks. Patient characteristics and recurrence information were obtained from chart review. The patients were divided into training (192 patients) and validation (83 patients) cohorts, and the recurrence status for the validation cohort was initially blinded. Gene expression levels were generated using Clariom S human array (ThermoFisher) from 10um sections cut from the formalin-fixed, paraffin-embedded surgical specimen blocks. The artificial intelligence algorithm Support Vector Machine (SVM) was used to create a prediction model for recurrence using the gene expression and recurrence status of the patients in the training cohort. The model was then tested on the validation cohort using Kaplan-Meier analysis and the area under the receiver operator curve (AUROC). **Results:** The recurrence prediction model separated the validation cohort into 15 (18.1%) patients in the high-risk group and 68 (81.9%) patients in the low-risk group. Kaplan-Meier analysis showed the five-year disease-free survival was significantly higher in the low-risk group compared to the high-risk group (86 vs. 50%, HR = 4.41, p = 0.0025). The AUROC for predicting recurrence was 0.744. **Conclusions:** Our model uses artificial intelligence to successfully predict recurrence after surgical resection for stage I-II non-small cell lung cancer. With an AUROC of 0.744, our model outperforms previously described models with AUROC up to 0.6. Our model separates patients into high-risk and low-risk groups, which will make management decisions clearer compared to other models that also include an intermediate-risk group. Patients in the low-risk group had 86% five-year disease-free survival; patients in the high-risk group had 50% five-year disease-free survival and may benefit from increased postoperative surveillance or adjuvant therapy. Research Sponsor: Auspex Diagnostics.

8538 **Poster Session**

Surgical outcomes for early-stage non-small cell lung cancer at facilities with stereotactic body radiation therapy programs. *First Author: Yusef Syed, Emory University, Atlanta, GA*

Background: Patients undergoing surgery for early-stage non-small cell lung cancer (NSCLC) may be at high-risk for post-operative mortality. Access to stereotactic body radiation therapy (SBRT) offers a less invasive alternative for this population that may facilitate more appropriate patient selection for surgery. **Methods:** An analysis of all patients with early-stage NSCLC reported to the National Cancer Database between 2004-2015 was performed. Post-operative mortality rates were derived using vital status data. Utilization of SBRT was defined by each facility's SBRT Experience in years and SBRT-to-Surgery volume ratios, defined by quartiles. Multivariable logistic regression with backward elimination was used to test for independence of associations between exposures of interest and post-operative mortality. Interaction testing was performed to assess the statistical relationship of covariates found to have independent associations. **Results:** The study cohort consisted of 202,542 patients who underwent surgical resection of clinical stage T1-T2 NSCLC (AJCC 7th edition). The 90-day post-operative mortality rate declined significantly during the study period from 4.6% to 2.6% ($p < 0.001$). During this period, the proportion of facilities that utilized SBRT increased from 3.3% to 77.5% ($p < 0.001$) and the proportion of patients treated with SBRT increased significantly from 0.7% to 15.4% ($p < 0.001$). Lower 90-day post-operative mortality rates were observed at facilities with greater than six years of SBRT experience (OR 0.84, CI 0.76-0.94, p = 0.003) and SBRT-to-Surgery volume ratios above 17% (OR 0.85, CI 0.79-0.92, $p < 0.001$). Additional covariates associated with 90-day mortality included higher surgical volume, geographic region, year of diagnosis, age, sex, race, insurance status, facility type, Charlson-Deyo score, clinical T stage, histology, anatomic location, surgery type, and prior malignancy. Interaction testing between these covariates was negative, demonstrating that higher SBRT Experience and SBRT-to-Surgery volume ratios were independently associated with lower 90-day surgical mortality. **Conclusions:** Patients who underwent surgery for early-stage NSCLC at facilities with higher SBRT Experience and SBRT-to-Surgery volume ratios had lower rates of post-operative mortality. These findings suggest that the availability of SBRT may be a surrogate for a more comprehensive and safer approach to matching patients to surgery or SBRT. The observation of higher post-operative mortality rates at facilities without an SBRT program deserves further study. Research Sponsor: None.

8539 **Poster Session**

Prognostic value of SUVmax on FDG-PET/CT before and after stereotactic body radiotherapy (SBRT) on recurrence and survival in early-stage non-small cell lung cancer (NSCLC). *First Author: Saarang Deshpande, Case Western Reserve University School of Medicine, Cleveland, OH*

Background: Stereotactic body radiotherapy (SBRT) is the standard of care in medically inoperable early-stage non-small cell lung cancer (NSCLC). Assessment of FDG-PET/CT before and after SBRT may stratify risk of disease recurrence and survival outcomes. **Methods:** Patients with T1-2N0M0 NSCLC who underwent PET/CT prior to SBRT (50-60 Gy over 3-5 fractions) between 2012 and 2019 were retrospectively identified. Pre-SBRT SUVmax and change in SUVmax at 3 and 6 months after SBRT were assessed as predictors of local control (LC), progression-free survival (PFS), and overall survival (OS). Optimal cutoff points for comparison were determined by receiver operator characteristic (ROC) analysis. Survival analyses were performed with Kaplan-Meier estimates with log rank testing, and Cox proportional hazards models including age, sex, T stage, histology, and performance status. **Results:** Out of 163 patients identified, 71 (43.6%) underwent repeat PET/CT within 6 months of SBRT completion. Median follow-up was 19 months (range 1 – 94 months). For the whole cohort, 1-year and 2-year LC, PFS, and OS were 95.0% and 80.3%, 75.9% and 47.7%, and 87.1% and 67.0%, respectively. Pre-SBRT SUVmax greater than 12.3 had an aHR of 2.80 (95% CI 1.3 – 6.2, p = 0.011) for PFS. A cutpoint of 12.6 for pre-SBRT SUVmax had an aHR of 3.00 (95% CI 1.6 – 5.8, p = 0.003) for OS. Pre-SBRT SUVmax did not significantly predict LC. A 3-month SUVmax decrease of at least 45% was associated with improved LC (aHR = 0.15, 95% CI 0.02 – 0.91, p = 0.018). At 6 months following SBRT, a cutoff point of a 53% decrease in SUVmax was associated with better LC (p = 0.038). Change in SUVmax was not significantly associated with PFS or OS at either time point. Performance status significantly predicted PFS and OS in all models. No other factors were significant. **Conclusions:** Pre-treatment SUVmax cutoffs can predict PFS and OS in early-stage NSCLC. At both the 3- and 6-month time points following SBRT, cutoff values for change in SUVmax can stratify risk of local recurrence. Research Sponsor: None.

	Outcome	Cutoff value	p-value
Pre-SBRT SUVmax	LC	14.8	0.097
Pre-SBRT SUVmax	PFS	12.3	0.011
Pre-SBRT SUVmax	OS	12.6	0.003
3-mo SUVmax change	LC	-45%	0.018
3-mo SUVmax change	PFS	-50%	0.936
3-mo SUVmax change	OS	-72%	0.245
6-mo SUVmax change	LC	-53%	0.038
6-mo SUVmax change	PFS	-78%	0.317
6-mo SUVmax change	OS	-40%	0.089

8540 **Poster Session**

Multiomics analysis reveals high-immune infiltration in tumor-adjacent lung tissues affects the prognosis of stage I NSCLC. *First Author: Lisa Ying, Department of Pathology, Cancer Hospital of the University of Chinese Academy of Sciences (Zhejiang Cancer Hospital);Institute of Basic and CancerMedicine (IBMC), Chinese Academy of Sciences, Hangzhou, China*

Background: Along with the wide application of low-dose spiral CT in lung cancer screening, a large number of resectable patients with lung cancer are identified, especially stage I Non-Small Cell Lung Cancer (NSCLC). However, their prognosis varies greatly and 5-year recurrence rate of stage I NSCLC is around 30%. Therefore, it is crucial to explore the potential mechanism of recurrence of early NSCLC. **Methods:** Eighty-seven patients with stage I NSCLC were enrolled from April 2008 to July 2015, including 79 squamous carcinoma and 28 adenocarcinoma. Frozen tumor tissues and paired tumor-adjacent lung tissues were collected to employ targeted panel sequencing, RNA sequencing and TCR repertoire sequencing. **Results:** Ninety-five non-silent mutations were detected in tumor-adjacent lung tissues with a median tumor mutation burden of 1.5/Mb, significantly lower than that in tumor tissues (11/Mb), $p < 0.05$. 42 mutations were specifically detected in the adjacent normal tissues, enriching in the immune response pathways. Comparing with paired tumors, tumor-adjacent lung tissues were found more favorable immune infiltration including higher immune cell activity like CD8+ T cell (0.50 vs 0.43, $p < 0.0001$), up-regulated immune-associated pathways, higher TCR clonality (0.19 vs 0.18, $p < 0.05$), less loss of heterozygosity (LOH) of human leukocyte antigen (HLA) (6.25% vs 50%, $p < 0.0001$) and observed predicted neoantigens expression (1 vs 128, $p < 0.01$). However, more shared viral-associated TCRs in tumor and tumor-adjacent tissues were found using the GLIPH algorithm. Prognostic analysis showed patients with higher overlap of TCR in tumors and tumor-adjacent lung tissues were prone to recur in five years. Furthermore, patients with higher immune infiltration in tumor-adjacent lung tissues had favorable outcomes than those with lower immune infiltration (HR: 0.37 for DFS, $p < 0.05$, HR: 0.31 for OS, $p < 0.05$), irrelevant of the infiltration level in tumor tissues. **Conclusions:** Immune microenvironment in tumor-adjacent lung tissues plays important roles in progress of stage I NSCLC. Research Sponsor: Major Science and Technology Project of Zhejiang Province of China Grants 2020C03023, Public Welfare Technology Foundation of Zhejiang Province of China Grant 2017C34001 and Zhejiang high-level innovative talent program.

8541 **Poster Session**

Phase II trial of toripalimab plus chemotherapy as neoadjuvant treatment in resectable stage III non-small cell lung cancer (NeoTPD01 Study). *First Author: Zerui Zhao, Department of Thoracic Surgery, Sun Yat-Sen University Cancer Center, Guangzhou, VA, China*

Background: Multi-modality treatment provides modest survival benefits for locally advanced non-small-cell lung cancer (NSCLC) patients. Preoperative immunotherapy has continuously been shown to be promising in treating resectable NSCLC. The current study aimed to investigate the activity and safety of the PD-1 inhibitor, toripalimab, with chemotherapy given as neoadjuvant treatment for resectable stage III NSCLC in Asian population. **Methods:** Eligible patients recruited were aged 18 years or older with histologically confirmed AJCC-defined stage IIIA or T3-4N2 IIIB NSCLC who deemed surgically resectable. Patients received 3 cycles of neoadjuvant treatment with intravenous toripalimab (240 mg), carboplatin (area under curve 5), and pemetrexed (500 mg/m^2 for adenocarcinoma) or nab-paclitaxel (260 mg/m^2 for others) on day 1 of each 21-day cycle. Surgical resection was performed 4-5 weeks following the first day of the last cycle of treatment. The primary endpoint was major pathological response (MPR; ≤10% viable tumor cells). Secondary endpoints included pathological complete response (pCR), R0 resection rate, disease-free survival and safety. Paired primary tumor +/- lymph node and blood samples at baseline and surgery were obtained for exploratory study. This study is registered with ClinicalTrials.gov, NCT04304248. **Results:** Between August 2019 and July 2020, 33 patients (median age: 61, IQR: 56-66; female: 6, 18.2%) were enrolled and received neoadjuvant treatment. 18 (54.5%) patients had squamous cell lung cancer, and 13 (39.4%) had T3-4N2 stage IIIB disease. Two patients refused surgery and one had progressive disease after treatment. 30 (91.9%) patients underwent resection (median interval between neoadjuvant treatment and surgery: 36.5 days, IQR 30-42.5) and all except one achieved R0 resection (29/30, 96.7%). 20 patients (20/30, 66.7%) had an MPR, including 15 patients (15/30, 50.0%) had a pCR in the per-protocol population. Surgical complications included three arrhythmias, one prolonged air leak, and one chylothorax. 24 patients (80.0%) had pathological downstaging following treatment, and complete lymph node clearances (ypN0) were seen in 70.0% (21/30) of patients. The most common grade 3-4 treatment-related adverse events in the intention-to-treat population were anemia (2, [6.0%]). Severe treatment-related adverse event included one (3.0%) patient with grade 3 peripheral neuropathy (Guillain-Barré syndrome) and resulted in surgery cancellation. At the time of data cutoff (Feb 7, 2021), the median duration of follow-up was 4.13 months, and there were no treatment-related deaths. **Conclusions:** Toripalimab plus platinum-based doublet yields a high MPR rate, manageable treatment-related toxicity, and feasible surgical resection in resectable stage III NSCLC. Ongoing analysis of biomarker will be available at the meeting. Clinical trial information: NCT04304248. Research Sponsor: None.

8542 **Poster Session**

Impact of genomic aberrations and additional therapies on survival outcomes of patients with operable non-small cell lung cancer (NSCLC) from the NEOSTAR study. *First Author: Nicolas Zhou, Thoracic and Cardiovascular Surgery, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The NEOSTAR study compared nivolumab (N) vs. nivolumab plus ipilimumab (NI) with major pathological response (MPR; ≤10% viable tumor) as primary outcome. We report updated rates of treatment failure (TF), including in patients whose tumors harbored genomic aberrations, and outcomes of additional treatments. **Methods:** Patients (pts) with stage I-IIIA resectable NSCLC (AJCC 7th) were randomized to either neoadjuvant N or NI followed by surgery (n = 44). TF was defined as radiographic and/or biopsy-proven recurrence from primary lung cancer and/or death (treatment or cancer-related). Additional systemic therapy at recurrence included immuno-oncology (IO)-based therapy (IO or chemo-IO), targeted therapy (TT), or chemotherapy. Disease control rate (DCR) was defined as the proportion of pts with radiographic objective responses and stable disease at first restaging. Cox proportional hazards model was used to associate baseline characteristics and time to TF. **Results:** A total of 44 randomized pts were evaluated, the median follow-up was 35 months (mts) as of February 4, 2021. Among the 12 TF pts (12/44, 27%), 42% (5/12) did not undergo surgery on trial, 9 (9/44, 20%) experienced recurrence and 6 (6/44, 14%) died (1 non-cancer-related, 5 cancer-related). TF was less likely in smokers vs. never smokers (hazard ratio = 0.20, 95% confidence interval = 0.06-0.65, p = 0.007). Among pts with pathological specimen resected on trial, MPR was achieved in 40% (12/30) of non-TF pts. Only 1 (1/7, 14%) TF pt achieved MPR, but died of a non-cancer related cause. TF-free survival rate at 2 years was 92% in MPR and 78% in non-MPR pts. Eight (8/9, 89%) pts had tumors with canonical oncodriver aberrations (5 *EGFR mutations*, 1 with *STK11+ KRAS Q61H* mutations, 1 *ALK* translocation and 1 *RET* fusions). Of the 9 recurrences, 44% (4/9) were treated with IO therapy, and all 7 pts with targetable aberrations were treated with TT (3 after retreatment with IO therapies). Of the 4 pts retreated with IO therapy, duration between end of neoadjuvant and retreatment were 20, 17, 23, and 19 mts. Duration from retreatment until progression (PD) were 1, 1, and 2 mts, respectively. Last pt was treated without PD for 2 mts but switched to TT due to discovery of genomic aberration. IO retreatment achieved 25% DCR (1/4). In comparison, the DCR for TT treated pts was 71% (5/7, p = 0.242). Median time to treatment was 21 mts, and median time to PD was not reached. Among 32 non-TF pts, 12 had genomic analysis and 7 aberrations were found in 6 pts (2 *STK11*, 2 *ERBB2*, 1 *STK11* + 1 *KRAS G12C*, and 1 *KRAS G12C* mutation). **Conclusions:** A 27% TF rate was observed after neoadjuvant IO. TF was less likely to occur in smokers and MPR pts, and 42% of TF pts did not undergo curative-intent surgery on trial. Genomic aberrations were common in pts with recurrence (89%), and treatment with TT achieved 71% DCR vs. 25% DCR with IO-based retreatment. Clinical trial information: NCT: 03158129. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation, U.S. National Institutes of Health, The University of Texas MD Anderson Cancer Center Lung Cancer Moon Shot Program, The University of Texas MD Anderson Cancer Center Physician Scientist Program .

8543 **Poster Session**

PIT-2: A multicenter phase II trail of S-1 plus cisplatin with concurrent radiotherapy followed by surgery in stage IIIA (N2) lung squamous cell carcinoma. *First Author: Kazuya Takamochi, Department of General Thoracic Surgery, Juntendo University School of Medicine, Tokyo, Japan*

Background: A multicenter phase II study, PIT-2 (Personized Induction Therapy-2), was performed to investigate the efficacy and safety of S-1 plus cisplatin and concurrent thoracic radiation therapy (TRT) followed by surgery in patients with stage IIIA (N2) lung squamous cell carcinoma (LSCC). To date, no clinical trials on the use of induction therapy prior to surgery have focused solely on the treatment of N2 LSCC. **Methods:** Eligible patients were 20 to 75 years old and had stage IIIA (pathologically proven N2) LSCC, performance status of 0-1, and no prior treatment. The patients received induction therapy consisting of three cycles of S-1 and cisplatin plus concurrent TRT (45 Gy in 25 fractions) followed by surgery. S-1 was administered orally at 40 mg/m^2 twice per day, on days 1 through 14 along with an intravenous infusion of cisplatin (60 mg/m^2) on day 1. The treatment cycles were repeated every four weeks. The primary endpoint was 2-year progression-free survival (PFS) rate and key secondary endpoints included overall survival (OS), the objective response rate (ORR) as defined by the Response Evaluation Criteria in Solid Tumors version 1.1, pathological complete remission (pCR) rate, feasibility, and toxicity. **Results:** Of the 45 patients registered between December 2013 and September 2018, 43 received induction therapy. Of the 43 patients, 39 (91%) underwent surgery (25 lobectomies, 10 bilobectomies, three pneumonectomies, and one wedge resection). The complete resection rate was 95% (37/39). Median follow-up time was 35.7 months. The 2-year PFS and OS rates were 67% (90% CI: 54-78%) and 70% (95% CI: 53-81%), respectively. The ORR and pCR rates were 86% (37/43, 95% CI: 76-96%) and 39% (15/39, 95% CI: 23-54%), respectively. Grade (G) 3 or 4 toxicities during the induction therapy in 43 patients included neutropenia (40%), anemia (9%), thrombocytopenia (7%), and hyponatremia (7%). Severe surgical complications in 39 patients included G3/4 pneumonia (5%), G3 bronchopleural fistula (5%), and G3 pleural effusion (5%). No G3/4 intraoperative adverse events occurred. There was no 30-day postoperative mortality and one 90-day postoperative mortality in a patient who underwent right pneumonectomy and developed pneumonia after discharge. **Conclusions:** Induction therapy using S-1 plus cisplatin and concurrent TRT followed by surgery is a promising treatment for patients with stage IIIA (N2) LSCC. Clinical trial information: 000012413. Research Sponsor: None.

8544 **Poster Session**

Impact of society and national guidelines on patient selection for lung cancer surgery in the United Kingdom. *First Author: Aina Pons, Royal Brompton and Harefield Hospitals, London, United Kingdom*

Background: In 2010 the British Thoracic Society (BTS) guidelines introduced clinical decision based on patient perception of risk to make surgery more permissive and revised recommendations for broader oncologic criteria such as surgery for N2 disease to improve surgical resection rates. In 2011 the National Institute for Health and Care Excellence (NICE) guidelines were updated with similar recommendations, but notable disagreement on surgery for N2 disease. We sought to conduct one of the largest cross-sectional studies to ascertain the impact of national clinical guidelines (with conflicting recommendations) on clinician behaviour. **Methods:** We analysed data from the UK national registry (National Lung Cancer Audit) comprising all patients diagnosed with lung cancer between 2008 to 2013 within England and Wales. Categorical data was summarised as frequency (%) and continuous data was summarised as mean (SD). Linear and logistic regression analyses were used with each year as an independent categorical outcome to determine global and year specific changes in FEV1 and proportions with N2 undergoing surgery respectively. **Results:** From January 2008 to December 2013, data from 167,192 patients with primary lung cancers were submitted to the NLCA. In 2008, 23,293 new lung cancers were diagnosed in England and Wales increasing annually by 2013 to 29,224. The most common presentation was advanced disease stage IV (49.7%), IIIB (13.2%) and IIIA (12.0%) and early-stage disease was less frequent with presentations IA (7.0%), IB (6.7%), IIA (2.9%) and IIB (4.27%). Lung function tests were undertaken in a subset of 53,905 of all diagnosed patients from 2008 to 2013. The mean FEV_1 (SD) increased annually from 67 (22)% in 2008 to 71 (24)% in 2013 ($p < 0.001$). Overall, 28% (n = 46,742) of the patients were preoperatively staged as N2 disease at diagnosis. The proportion of patients with N2 disease increased from 24 to 29% in this timeframe (P = 0.003). The proportion of patients undergoing surgery for lung cancer increased from 9.5% in 2008 to 20.5% in 2013 ($p < 0.001$). Mean FEV_1 of surgical patients were higher at 79 (22)% than the population average of 69 (23)%, an accepted reflection of surgical selection. Over time, mean FEV_1 of surgical patients increased from 76 (22)% in 2008 to 81 (22)% in 2013 ($p < 0.001$). Of the patients undergoing surgery, the proportion of patients across the 6-year interval were broadly consistent between 8 to 11% without any evidence of trend (P = 0.125). **Conclusions:** Within 3 years of new clinical guidelines, we did not observe any overall change in selection based on lower levels of lung function and when presented with conflicting recommendation no observable change in attitudes of clinicians on surgery for N2 disease. The observed increase in surgical resection rates is more likely due to (greater access to surgery by) increasing number of surgeons rather than any impact of guideline recommendations. Research Sponsor: None.

8545 **Poster Session**

The efficacy of PD-1 antibody sintilimab on ground glass opacity lesions in patients with early-stage multiple primary lung cancer (CCTC-1901, NCT04026841). *First Author: Bo Cheng, Department of Thoracic Surgery and Oncology, The First Affiliated Hospital of Guangzhou Medical University, State Key Laboratory of Respiratory Disease & National Clinical Research Center for Respiratory Disease, Guangzhou, China*

Background: Immune checkpoint inhibitors (ICIs) targeting programmed cell death protein 1 (PD-1) have been proven its significant efficacy on advanced non-small cell lung cancer (NSCLC). However, it remains unknown and is of great interest whether the PD-1 antibody affects early-stage lung cancer. Here, we reported the preliminary efficacy and safety outcomes of sintilimab on these early-stage GGO lesions in patients (pts) with multiple primary lung cancer in the CCTC-1901 study, the first trial evaluating PD-1 antibody in preinvasive or low invasive lung cancer worldwide. **Methods:** This single-center, phase II, Simon's two-stage design trial included pts who had a pathological diagnosis of resected lung cancer and at least one unresectable GGO lesion suspicious malignant which evaluated by a multidisciplinary team's consensus. The enrolled pts received 4 cycles of intravenous sintilimab 200 mg every 3 weeks. The primary endpoint is the objective response rate (ORR) of unresectable GGO lesions. For persistent GGO lesions that did not respond to treatment, either observation or second operation was taken. Also, immune biomarkers (T/B/NK subpopulation etc.) were monitored during treatment to validate the immune activity. **Results:** A total of 36 pts were included, with median age 59.5 (53.5-69), 66.7% females, 80.6% never smokers. All resected lesions were adenocarcinomas, of which 52.8% were EGFR mutated. 49 unresected GGOs (pure 11[22.4%], mixed 38[77.6%]) were defined as target lesions from 36 enrolled pts, with a mean size of 13.20±5.06 mm. The ORR (RECIST v1.1) was 5.6% (2/36, 1 PR and 1 CR); none of the pts had PD. Additionally, 3 non-target lesions (unresected solid lesions) from 3 included pts showed PR after the treatment of sintilimab, and the rest lesions (target or non-target) of 31 pts performed SD. Grade 1-2 fatigue (13, 36%), rash (13, 36%) and arthralgia (8, 22%) were the most common treatment-related adverse events (TrAEs), and no grade 3-5 TrAEs occurred. The proportion of $CD8^+$ T-cell and the ratio of $CD8^+/CD4^+$ in 5 patients who showed PR of unresected lesions were significantly higher compared to those with SD lesions at baseline ($CD8^+$ 36.6% vs 24.6%, $p < 0.01$; $CD8^+/CD4^+$ 1.09±0.18 vs 0.64±0.22, $p < 0.01$). **Conclusions:** This study is the first to confirm that PD-1 antibody sintilimab has immune-related antitumor activity on GGO-featured lung cancer and could be well tolerated among pts with early-stage lung cancer. Clinical trial information: NCT04026841. Research Sponsor: China National Science Foundation (Grant No. 81871893).

8546 **Poster Session**

Doubling of median overall survival in a nationwide cohort of veterans with stage III non-small cell lung cancer in the durvalumab era. *First Author: Kamya Sankar, Division of Hematology and Oncology, Department of Internal Medicine, University of Michigan, Ann Arbor, MI*

Background: The standard of care for patients with unresectable stage III non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy followed by durvalumab maintenance based on outcomes from the PACIFIC trial. However, PACIFIC did not include Veterans, a unique population with significant co-morbidities; thus, the impact of durvalumab on survival of Veterans with stage III NSCLC is unknown. **Methods:** Using the U.S. Department of Veterans Affairs Corporate Data Warehouse, patients with stage III non-small cell lung cancer who received chemoradiotherapy and at least one dose of durvalumab were selected. Kaplan-Meier survival analysis and univariate Cox proportional hazards modeling were used to determine progression-free survival (PFS), overall survival (OS) and independent predictors of PFS and OS. PFS was manually extracted by review of serial surveillance scans. All statistical computations were performed using SAS 9.4 software. **Results:** 1106 Veterans met our inclusion criteria. The median age was 69. 95.1% (n = 1052) were male. The median Charlson Comorbidity Index was 1. 86.4% (n = 956) reported current or former tobacco use. 48.1% (n = 532) had adenocarcinoma histology, 48.4% (n = 535) squamous cell, 0.5% (n = 5) large cell, 0.3% (n = 3) neuroendocrine, and 0.1% (n = 1) sarcomatoid. 60% (n = 619) had AJCC 8^{th} edition stage IIIA disease, 34.5% (n = 382) stage IIIB, and 3.3% (n = 36) stage IIIC. Median PFS was 19.9 months (95% CI: 16.9 – 23.6) and median OS was 34.9 months (95% CI: 29.7 – not reached). In univariate survival analyses, adenocarcinoma histology (HR 1.14, $p = 0.03$) predicted progression. Older age (HR 1.03, $p < 0.0001$) and stage IIIB/IIIC disease (HR 1.05, $p = 0.008$) predicted inferior OS. 18.4% (n = 204) of patients completed all planned cycles of adjuvant durvalumab. The median number of durvalumab infusions received was 6 (range: 1 – 38). Among evaluable patients, 175 (19.4%) discontinued durvalumab for progression, 211 (23.4%) discontinued for suspected immune-related toxicity and 17 (1.9%) died during treatment. **Conclusions:** While several factors have led to the improvement of OS in patients with stage III NSCLC over time, we report a doubling of median OS in Veterans with stage III NSCLC who received chemoradiotherapy plus durvalumab as compared to historical cohorts who received chemoradiotherapy alone (1). Veterans in our study received a lower median number of durvalumab infusions as compared to patients in the PACIFIC trial (6 vs. 14), and a significant proportion discontinued durvalumab due to suspected immune-mediated toxicity (23.4%). If further analyses confirm our findings, investigation of alternative dosing regimens and/or dosing intervals of durvalumab in order to balance safety and efficacy of durvalumab therapy in Veterans is warranted. (1) Santana-Davila R et al. J Clin Oncol. 2015 Feb 20;33(6):567-74. Research Sponsor: None.

8547 **Poster Session**

Elderly patients with unresectable stage 3 NSCLC treated with definitive chemoradiation with or without durvalumab: Safety and outcomes. *First Author: Malcolm Isaiah Ryan, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Recently, it has been demonstrated that the addition of durvalumab after chemoradiation (CRT) in unresectable stage 3 non-small cell lung cancer (NSCLC) significantly improves overall survival (OS). The benefit of CRT in elderly patients is considered controversial given its increased toxicity. As such, CRT followed by durvalumab in elderly patients may be underutilized despite its demonstrated superiority. The practice pattern at our center is to offer curative treatment unless clearly contraindicated. We sought to investigate the outcomes of elderly patients treated with CRT +/- durvalumab at our center. **Methods:** We conducted a review of all stage 3 NSCLC patients treated with CRT between 2018 and 2020. Patients were analyzed based on age: < 70 years, ≥ 70 years. Endpoints evaluated were treatment patterns, toxicity, progression free survival (PFS) and overall survival (OS). **Results:** We identified 115 stage 3 patients: 44 patients ≥ 70 years (70-89) and 71 patients < 70 years (34-69). Patients were fit: ECOG 0-1 (98%/97%), mean Charlson comorbidity index (CCI) (1.1/0.9) in elderly vs young patients; $p > 0.05$. All other baseline characteristics including PD-L1 expression were similar. The chemotherapy regimens (platinum in combination with etoposide, paclitaxel or pemetrexed), dose intensity (97% vs 97%) and percentage of planned cycles received (91% vs 96%) were similar. There were 2 treatment related deaths from CRT among the younger cohort and none in the elderly patients. At the completion of CRT, 75% of elderly and 72% of young patients received durvalumab. Clinician/patient preference was the most common reason for not receiving consolidation durvalumab in older patients (55% vs 25%). The median time to starting durvalumab was 43 days in the elderly and 37 days in young patients (p = 0.19). Durvalumab was well tolerated in the elderly and incidence of grade ≥ 3 immune-related adverse events was 9% compared to 6% in young patients; p = 0.68. The durvalumab completion rates were 30% in elderly and 24% in young patients; p = 0.22. Median PFS was similar between elderly and young patients (17.9 vs 10.6 months respectively; p = 0.07), even after adjusting for the CCI (HR 0.60; p = 0.07). The 24- and OS rates are also similar (p = 0.93): 77% in elderly and 77% in young patients. **Conclusions:** Definitive CRT followed by durvalumab can be safely delivered in elderly patients ≥ 70 years with comparable outcomes. The non-significant trend towards better PFS in elderly patients suggests that only select fit patients are being referred for treatment. In conclusion, all patients should undergo comprehensive oncologic assessment to determine if curative intent treatment can be delivered to avoid undertreatment of elderly patients. Research Sponsor: None.

8548 **Poster Session**

NRG-RTOG 1106/ACRIN 6697: A phase IIR trial of standard versus adaptive (mid-treatment PET-based) chemoradiotherapy for stage III NSCLC—Results and comparison to NRG-RTOG 0617 (non-personalized RT dose escalation). *First Author: Feng-Ming Spring Kong, Clinical Oncology Department, The University of Hongkong-Shenzhen Hospital, Shenzhen, China*

Background: NRG-RTOG 0617 (R0617) found that non-personalized dose escalation of radiotherapy (RT) with concurrent chemotherapy was deleterious. NRG-RTOG 1106/ACRIN 6697 (R1106) studied adaptive chemoradiotherapy, using tumor and patient individualized RT dose intensification simultaneously with field reduction, based upon mid-treatment FDG-PET. **Methods:** The control arms of both studies used 60 Gy (+ weekly carboplatin/paclitaxel). The investigational arm of R0617 used 74 Gy in 37 fractions, with no field/dose adaptation, while R1106 used mid-treatment FDG-PET (after ~40 Gy) to design an individualized dose adaptive RT plan with daily-fraction size 2.2 to 3.8 Gy (up to 80.4 Gy/30 fractions), based upon a model of isotoxic lung risk. Nearly all (93%) patients had IMRT. No patients had consolidation immunotherapy. The primary endpoint for R1106 was local-regional-progression freedom (LRPF) assessed by central review. Other endpoints reported here were survival, toxicity, and institution-defined local/regional control. **Results:** From 2012-2017, 127 patients were enrolled to R1106 (43 in the standard and 84 in the adaptive arms), with a median follow-up of 3.6 years. The median actual RT dose in the adaptive arm was 71 Gy (Q1-Q3 68-76 Gy). The 2-year LRPF was 59.5% versus 54.6% (p=0.66) for standard versus adaptive RT; the 3-year survival rates were 49.1% versus 47.5% (p=0.80). An exploratory analysis of 2-year in-field local primary tumor control and local-regional tumor control (institution-assessed) were 58.5% and 55.6% for standard RT, and 75.6% and 66.3% for adaptive RT, respectively. As shown in the table, there were no significant differences in cardiac or esophageal adverse events between the two arms; the adaptive RT arm had more Grade 3+ respiratory events (23.8% versus 14.3%). **Conclusions:** NRG-RTOG1106 did not meet its primary endpoint of demonstrating improved LRPF. Unlike R0617, there was no suggestion of a detrimental effect of adaptive dose-intensified RT on survival and cardiac events. Studies to refine personalized RT, especially in the immunotherapy era, should be considered. Outcome comparison between R0617 and R1106. Clinical trial information: NCT01507428. Research Sponsor: This project was supported by grants UG1CA189867 (NCORP), U10CA180822 (NRG Oncology SDMC), U10CA180868 (NRG Oncology Operations), and U24CA180803 (IROC) from the National Cancer Institute (NCI).

	R0617 Control Arm	R0617 High-dose Arm	R1106 Control Arm	R1106 Adaptive Arm
3-yr OS	44.5%	31.1%	49.1%	47.5%
3-yr Local-regional failure (institution reported)	47.1%	50.9%	30.0%	30.2%
2-yr In-field primary tumor local control (institution reported)	NS	NS	58.5%	75.6%
2-yr In-field local-regional control (institution reported)	NS	NS	55.6%	66.3%
Cardiac event Grade 3+ (crude %)	17.9%	19.8%	2.6%	1.3%
Pulmonary toxicity Grade 3+ (crude %)	20.6%	19.3%	14.3%	23.8%
Esophagitis Grade 3+ (crude %)	5.0%	17.4%	7.9%	3.8%

8549 **Poster Session**

The impact of a genomic sequencing classifier (GSC) on clinical decision making in patients with a high-risk lung nodule. *First Author: Sonali Sethi, Cleveland Clinic, Cleveland, OH*

Background: Current guidelines recommend that patients who have lung nodules with high risk of malignancy (ROM) ($>$ 65%) should undergo surgical and other ablative therapies. However, prior studies have shown that clinicians may opt for more conservative management in these high-risk patients. Percepta Genomic Sequencing Classifier (GSC), a RNA-seq based classifier derived from bronchial epithelial cells to assess risk of lung cancer, was designed to risk stratify lung nodules by both down classifying ROM as a "rule -out" test with high sensitivity as well as up-classifying ROM as a "rule- in" test with high specificity for malignancy. This study assesses the impact of up-classification of high ROM to very high- risk (ROM $>$ 90%) by Percepta GSC in increasing the number of ablative therapies recommended for high-risk lung nodules. **Methods:** This prospective randomized decision impact survey included 37 patients from the AEGIS I/ II cohorts and the Percepta Registry who were undergoing work up of a lung nodule and had a high ROM that was up-classified to very high ROM by Percepta GSC. 97 physicians assessed 10 randomly assigned patient cases. They then responded to a survey designed to test the hypothesis that including a Percepta GSC result will increase the recommendation for surgical or other ablative therapy in very high- risk patients as well as their level of confidence of this recommendation. Physicians were first presented with the patient's clinical information without Percepta GSC and then with Percepta GSC. **Results:** 97 physicians provided a total of 682 evaluations of 37 patients. In this study, the recommendation for surgical or other ablative therapy increased from 19/341 (5.6%) prior to the Percepta GSC result to 157/341 (46%) after the Percepta GSC result (odds ratio of 4.76, p-value $<$ 0.001). The number of extremely confident recommendations increased from 72/341 (21%) without Percepta GSC to 106/341 (31%) with Percepta GSC. Significantly more physicians had increased confidence in their recommended next step post-Percepta GSC when collapsing the confidence level responses into increased confidence (n = 93) and decreased confidence (n = 44) (p-value = 0.002). **Conclusions:** Percepta GSC had a quantifiable impact on clinical decision making. It increased the number of surgical and other ablative therapies recommended when patients were re-classified from high to very high- risk of lung cancer with a higher confidence in the recommended next step. By up-classifying nodules from high to very high ROM, Percepta GSC will improve the likelihood and timeliness of appropriate therapies and assist clinicians more effectively manage patients to improve patient outcomes. Research Sponsor: Veracyte, Inc.

8550 **Poster Session**

Patients with early-stage (T1-2N0) adenosquamous lung cancer have worse long-term survival compared to patients with early-stage lung adenocarcinoma or squamous cell histology. *First Author: Larisa Shagabayeva, Harvard Medical School, Boston, MA*

Background: Survival outcomes for patients with adenosquamous carcinoma of the lung are not well understood by virtue of reduced prevalence. The objective of this study is to compare the long-term survival among patients with adenocarcinoma, squamous cell carcinoma and adenosquamous carcinoma of the lung. **Methods:** Overall survival of all patients with adenosquamous carcinoma, squamous cell carcinoma, and adenocarcinoma who received guideline-concordant treatment for T1-2N0M0 from 2004-2017 in the National Cancer Data Base was assessed using Kaplan-Meier analysis, multivariable Cox proportional hazard analysis, and propensity score-matched analysis. **Results:** Among patients who met study criteria (N = 88,983), there were 2,469 (2.77%) patients with adenosquamous, 60,148 (67.59%) with adenocarcinoma and 26,366 (29.63%) with squamous cell carcinoma histology. In patients who had T1-T2 N0 M0 disease, adenosquamous carcinoma was associated with significantly worse 5-year overall survival (58.9% [95%CI:56.6%-61.1%]) when compared with adenocarcinoma (72.4% [95% CI:72.0%-72.8%]) and squamous cell carcinoma (62.6% [95% CI:61.9%-63.3%]). In multivariable Cox proportional hazards analysis, adenocarcinoma (HR 0.81 [95% CI:0.76-0.87], p $<$ 0.001) and squamous cell carcinoma (HR 0.86 [95% CI:0.80-0.92], p $<$ 0.001) continued to be associated with significantly better survival when compared to adenosquamous carcinoma histology. A propensity score-matched analysis of 1,854 adenocarcinoma and 1,854 adenosquamous patients who were well matched by 17 common prognostic covariates (including tumor size and comorbidities) found that adenosquamous histology (57.2% [95% CI:54.7%-59.6%]) was associated with worse survival when compared to adenocarcinoma (63.0% [95% CI:60.6%-65.4%]). An additional propensity score-matched analysis of 1,852 squamous cell carcinoma and 1,852 adenosquamous patients matched by the same covariates demonstrated that adenosquamous carcinoma (57.1% [95%CI:54.6%-59.6%]) was associated with worse survival when compared with squamous cell carcinoma (64.0% [95% CI:61.5%-66.4%]). **Conclusions:** Early stage adenosquamous carcinoma of the lung is associated with worse overall survival compared to its individual histologic components of adenocarcinoma or squamous cell carcinoma. These observations in both the unmatched and propensity matched patient cohorts invoke consideration of multimodality therapy for these early tumors. Research Sponsor: Departmental Funding.

8551 **Poster Session**

Early candidate nasal swab classifiers developed using machine learning and whole transcriptome sequencing may improve early lung cancer detection. *First Author: Peter J. Mazzone, Cleveland Clinic, Cleveland, OH*

Background: The goal of lung nodule management is to make an early diagnosis in patients with lung cancer while avoiding unnecessary, costly and potentially harmful procedures in patients with benign lesions. Increased implementation of low dose CT screening will lead to increased numbers of both benign and malignant nodules that will require effective management. We have previously described the feasibility of detecting gene expression changes associated with lung cancer ("field of injury") in nasal epithelium utilizing whole transcriptome RNA sequencing from non-invasive nasal brush samples. Using this approach, we now report the performance of candidate nasal classifiers that combine both genomic and clinical features to risk stratify lung nodules from ever-smokers to aid in the diagnosis of lung cancer. **Methods:** Patients from several clinical cohorts who were ever-smokers with a lung nodule $<$ 30 mm and without a history of prior cancer underwent nasal epithelium sampling. All patients had at least one year of follow up or until a final diagnosis of benign or malignant nodule was made. Candidate classifiers were developed using whole-transcriptome RNA sequencing and machine learning. Training of these classifiers included genomic and clinical information (age, sex, pack-years, years-since-quit, nodule size and nodule spiculation). Two decision boundaries were chosen to maximize sensitivity and specificity for low and high-risk nodules, respectively. The performance of these classifiers was evaluated using cross-validation (CV). **Results:** All candidate nasal classifiers underwent CV assessment on over 700 patients with lung nodules. All candidate classifiers achieved CV performance of $>$ 40% specificity at 95% sensitivity in low- risk nodules and all candidate classifiers achieved CV performance of $>$ 60% sensitivity at 90% specificity in high-risk nodules. The classifiers stratified benign nodules as low- risk with $>$ 95% negative predictive value (NPV), intermediate risk nodules were stratified as 5-65% risk and malignant nodules were stratified as high- risk with $>$ 65% positive predictive value (PPV) in a population with estimated 25% prevalence. This performance was robust across subgroups of age ($<$ 65 year vs. $>$65 year), sex, and current versus former smokers. **Conclusions:** The nasal genomic-clinical candidate classifiers have a high NPV effectively identifying benign nodules when calling them low- risk, thereby, informing decisions to more safely avoid a diagnostic workup. Additionally, the high PPV of these classifiers identifies malignant nodules when calling them high- risk and informs decisions regarding the urgency of a further diagnostic work-up. A nasal genomic-clinical classifier has the potential to serve as a non-invasive tool for lung cancer risk-stratification to help inform decision making in patients with lung nodules. Research Sponsor: Veracyte, Inc.

8552 **Poster Session**

A comparative analysis of mortality between black and white stage III non–small cell lung cancer patients in the United States. *First Author: Elizabeth Blessing Elimimian, Cleveland Clinic Fl, Weston, FL*

Background: Lung cancer remains the leading cause of cancer death in the United States (U.S.). For stage III non-small cell lung cancer (NSCLC), concurrent chemotherapy (CT) plus radiotherapy (RT) within 30 days (CCRT) confers a survival benefit. The proportion of Black and White NSCLC patients not receiving CCRT and their outcomes have not been explored. **Methods:** Stage III NSCLC in Black and White patients diagnosed between 2004 and 2015 from the U.S. NCDB were included. Those with multiple tumors and who received surgery were excluded. Six groups were analyzed: CCRT (0-30 days between CT and RT), SCRT (31-120 days between CT and RT), RT (only RT), CT (only CT), No-RT-nor-CT (didn't receive RT nor CT), and other (uncategorized). Univariate, multivariate, and Kaplan-Meier analyses were utilized ($p<0.05$). **Results:** A total of 22,459 Black (CCRT 42.3%, SCRT 7.6%, RT 13.8%, CT 15.1%, and No-RT-nor-CT 21.2%) and 138,477 White (CCRT 43.9%, SCRT 7.0%, RT 12.7%, CT 14.9%, and No-RT-nor-CT 21.5%) stage III NSCLCs were analyzed. Male gender and White race were positive predictive factors for receiving CCRT (Table). In Black patients SCRT (HR 1.1; 95% CI 1.04-1.17), RT only (HR 1.2; 95% CI 1.81-1.99), CT only (HR 1.4; 95% CI 1.36-1.49), and No RT or CT (HR 2.6; 95% CI 2.49-2.69) was associated with decreased overall survival (OS) compared to CCRT. In White patients, SCRT (HR, 1.0; 95% CI, 0.99-1.03) did not decrease OS compared to CCRT, whereas RT only (HR 1.8; 95% CI, 1.74-1.80), CT only (HR 1.3; 95% CI, 1.29-1.34), and No RT or CT (HR 2.6; 95% CI, 2.59-2.67) were associated with decreased OS. Median OS with CCRT was 18 months for Black patients, versus 16 months for White patients ($p<0.0001$). **Conclusions:** OS was highest when CCRT was given. A lower proportion of Black cases were managed with CCRT, but Black patients benefit more from CCRT and had improved OS than White patients. Despite the known benefits of CT and RT in stage III NSCLC, the second largest management cohort received neither RT nor CT. Research Sponsor: None.

Factors associated with receiving CCRT versus other treatments [a] in NSCLC.

	Gender		Race		Age		Comorbidity			
Variable	**Male**	**Female**	**White**	**Black**	**< 65**	**> 65**	**0**	**1**	**2**	**3**
CCRT N (%)	40753 (56.9)	29591 (54.0)	60841 (56.0)	9503 (53.7)	32493 (63.2)	37851 (50.5)	43470 (57.1)	18703 (55.0)	6103 (51.5)	2068 (46.8)
Other Treatments[a] N (%)	30863 (43.1)	251999 (46.0)	47858 (44.0)	8204 (46.3)	18945 (36.8)	37117 (49.5)	32649 (42.9)	15306 (45.0)	5753 (48.5)	2354 (53.2)
Odds Ratio (95%CI)	1.121 (1.095-1.148)	1	1.158 (1.119-1.199)	1	1	0.637 (0.617-0.658)	1	0.921 (0.897-0.946)	0.809 (0.777-0.842)	0.661 (0.620-0.704)
Multivariate p-value	0.0001		0.0001			0.0001		0.0001	0.0001	0.0001

[a]All other treatments = SCRT + RT Only + CT Only (No-RT-nor-CT excluded).

8553 **Poster Session**

Early detection of lung cancer with an incidental lung nodule program (ILNP). *First Author: Matthew Smeltzer, University of Memphis, School of Public Health, Memphis, TN*

Background: Lung cancer early detection improves survival, but risk-based low-dose CT screening (LDCT) only identifies a minority of patients. We implemented an ILNP in a community healthcare system, and evaluated its risks and benefits. **Methods:** Patients with lung lesions on routinely-performed radiologic studies were flagged by radiologists and triaged using evidence-based guidelines. We tracked demographics, clinical characteristics, procedures, complications, and health outcomes. We analyzed ILNP subjects' eligibility for LDCT by National Lung Screening Trial (NLST), Center for Medicaid Services (CMS), NEderlands Leuvens Screening ONderzoek (NELSON), National Comprehensive Cancer Network (NCCN) Risk Groups 1 and 2 (screening recommended), NCCN Risk Group 3 (screening not currently recommended), and US Preventive Services Task Force (USPSTF) criteria from 2013 and 2020. Statistical analysis used the chi-square test and Kaplan Meier method. **Results:** From 2015-2020, 13,710 patients were evaluated in the ILNP program: median age, 64 years; 42% male; 65% White, 29% Black; 667 (4.9%) were diagnosed with lung cancer. Lung cancers diagnosed from ILNP were 39% adenocarcinoma / 20% Squamous Cell with clinical stage distribution 49% I, 8% II, 17% III, and 16% IV. 832 (6.1%) had invasive diagnostic testing- CT-guided biopsy (50%), bronchoscopy (30%), and/or EBUS (26%); 11% of the 832 had >1 invasive diagnostic test. The most common complications from invasive testing were pneumothorax and chest tube placement. Only 11%-20% of all ILNP patients would have been eligible for LDCT. In ILNP patients diagnosed with lung cancer, only 33% were eligible for screening by NLST criteria; the proportion increased substantially when USPSTF 2020 or NCCN Group 2 criteria were applied (Table). Compared to NLST, NCCN Group 2 criteria increased screening eligibility among cancer patients by 22% (from 33% to 55%), while only increasing screening eligibility by 6% (from 8% to 14%) in non-cancer patients. Aggregate 1-year and 3-year survival rates for lung cancer patient diagnosed through ILNP were 76% (95% CI: 73, 80) and 64% (95% CI: 59, 69). **Conclusions:** The ILNP identified early-stage lung cancer more frequently than most LDCT programs, with promising survival rates. The majority of subjects with lung cancer were not eligible for LDCT, we still need to optimize risk-based screening criteria. Even with new, expanded criteria for LDCT, structured ILNP is necessary to expand early detection of lung cancer. Research Sponsor: None.

Screening Criteria	**%ILNP Lung Cancer Patients Eligible for LDCT Screening**
NLST Criteria	33%
CMS Criteria	39%
NELSON Criteria	41%
USPSTF 2013	41%
USPSTF 2020	47%
NCCN Group 1	39%
NCCN Group 2	55%
NCCN Group 3	64%

8554 **Poster Session**

Radical surgery in malignant pleural mesothelioma (MPM): An analysis of SEER database. *First Author: Qian Wang, Department of Medicine, Icahn School of Medicine at Mount Sinai St Luke's and West, New York, NY*

Background: MPM is an aggressive malignancy with poor overall prognosis. A combined treatment approach involving radical surgery (RS), radiation (RT) and chemotherapy (CT) provide improved survival compared to systemic treatment alone. Selecting patients who may benefit from RS is challenging. The NCCN guidelines recommend that up to T3N1M0 (Stage IIIA) epithelioid or biphasic MPM should be considered for multimodality therapy incorporating RS. However, the impact of clinical and pathologic features within each histologic subtype of MPM on RS outcomes is unknown. **Methods:** MPM patients from the SEER 18 program from 2004-2015 were identified. Cox proportional hazard regression models were used to examine the independent contribution of several clinical and pathologic features on overall survival (OS) in patients who received RS vs those that did not. **Results:** A total of 5,498 MPM patients were identified, of which 531 underwent RS. Overall, RS was associated with improved OS in the multivariate model adjusting for important clinical and pathological characteristics (Table). When stratifying according to histology, epithelioid subtype was linked to improved OS with RS despite of the presence male gender, age > 60 years old, T3, T4 or N2 or above disease; and the OS improved among those who also underwent CT ± RT with RS. Patients with sarcomatoid histology also had OS benefit from RS (HR=0.59, 95%CI: 0.37-0.93), even those that were > 60 years old, but not among those with more advanced disease (T3/4, N2/3). Sarcomatoid patients who received CT ± RT (HR = 0.52, 95%CI: 0.30-0.90) also experienced OS benefit. Among biphasic histology, no OS benefit was found overall (P = 0.11) or within other high-risk clinical features except for those who were treated CT ± RT (HR = 0.64, 95%CI: 0.45-0.90). **Conclusions:** Our findings demonstrate that the presence of high-risk clinical and pathologic features does not impact OS benefit of RS in epithelioid MPM, however should be considered when deciding on RS in sarcomatoid and biphasic histologies. Poor prognostic histology especially sarcomatoid subtype may experience improved survival with RS if in conjunction with other treatment modalities. Research Sponsor: None.

OS associated with vs without RS by patho-clinical features.

	All participants	**Epithelioid**	**Sarcomatoid**	**Biphasic**
Overall	0.71 (0.64-0.79)	0.70 (0.60-0.81)	0.59 (0.37-0.93)	0.78 (0.57-1.06)
Male	0.73 (0.65-0.82)	0.75 (0.63-0.89)	0.65 (0.41-1.04)	0.77 (0.54-1.09)
Age > 60	0.67 (0.60-0.76)	0.65 (0.55-0.76)	0.57 (0.34-0.98)	0.95 (0.68-1.33)
T3	0.77 (0.62-0.94)	0.70 (0.52-0.94)	1.31 (0.28-6.09)	1.49 (0.67-3.31)
T4	0.71 (0.57-0.88)	0.55 (0.41-0.74)	0.55 (0.25-1.20)	1.02 (0.52-1.99)
N2 or N3	0.54 (0.41-0.71)	0.44 (0.30-0.66)	3.58 (0.07-173.5)	2.10 (0.001-NA)
CT± RT	0.65 (0.58-0.74)	0.64 (0.54-0.76)	0.52 (0.30-0.90)	0.64 (0.45-0.90)

8555 **Poster Session**

Comprehensive molecular profiling of pleural mesothelioma according to histologic subtype. *First Author: Ibiayi Dagogo-Jack, Massachusetts General Hospital, Boston, MA*

Background: Malignant pleural mesothelioma (MPM) is an aggressive malignancy with limited therapeutic options. Immunotherapy has emerged as an effective therapeutic strategy, particularly in the non-epithelioid MPM subgroup. An improved understanding of the molecular profile of MPM may inform targeted therapeutic approaches and provide insights into factors underlying differential sensitivity to therapies. **Methods:** We performed comprehensive genomic profiling of MPMs from 980 patients, with histologic subtyping on a subset (n = 340; n = 235 epithelioid, n = 48 sarcomatoid, n = 57 biphasic). Analyses included quantifying tumor mutational burden (TMB), assessing microsatellite instability (MSI), and evaluating PD-L1 expression (Dako 22C3). **Results:** Median TMB of MPM was 1.74 (0.87-2.61) mutations per megabase (mut/mb). Median TMB was comparable for non-epithelioid (biphasic, sarcomatoid) vs epithelioid MPM (1.25 mut/mb vs 1.25 mut/mb, p = 0.43). In the overall cohort, inactivating alterations in the following genes were most prevalent: *CDKN2A* (49%), *BAP1* (44%), *CDKN2B* (42%), *MTAP* (35%), and *NF2* (33%). *MTAP* loss co-occurred with *CDKN2A* and *CDKN2B* loss in > 99% and 94% of cases, respectively. *MTAP* loss was observed in 28% of epithelioid vs 46% of non-epithelioid MPMs (p = 0.03). *BAP1* alterations were detected in 51% of epithelioid vs 36% of non-epithelioid MPMs (p = 0.81). PD-L1 expression was assessed in 308 MPMs, among which 153 (49%) had PD-L1 ≥1%, including 35 (11%) with PD-L1 ≥50%. Among 164 specimens that underwent histologic subtyping and PD-L1 evaluation, PD-L1 was expressed in 46 (71%) non-epithelioid MPMs compared to 49 (51%) epithelioid MPMs (p = 0.03). Given the high prevalence of alterations involving the two genes, we evaluated impact of *BAP1* and *MTAP* status on PD-L1 and TMB. TMB (1.74 mut/mb vs 1.74 mut/mb) and PD-L1 expression (50% vs 54%) were comparable in *BAP1*-altered vs wildtype specimens. Although TMB was comparable in *MTAP*-deficient and *MTAP*-intact tumors (1.25 mut/mb vs 1.74 mut/mb), more tumors with *MTAP* loss expressed PD-L1 (68% vs 44%, p = 0.0004). **Conclusions:** Compared to epithelioid MPM, non-epithelioid tumors demonstrate comparable TMB, higher PD-L1 expression, and enrichment for *MTAP* loss. As *MTAP* is frequently altered in MPM, further study is indicated to explore the relationship between *MTAP* status and MPM biology, including sensitivity to therapeutics such as immunotherapy and synthetic lethal approaches. Research Sponsor: Foundation Medicine.

8556 **Poster Session**

Improved survival among patients with malignant pleural mesotheliomas who develop immune-related adverse events on immunotherapy. *First Author: Michael Offin, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: While immune checkpoint inhibitors (ICI) are a standard option for patients with malignant pleural mesotheliomas (MPM), there is limited data on the rate of immune related adverse events (irAEs) and effects on clinical outcomes. **Methods:** 61 patients with MPM who received ICI between January 2016 and October 2020 were assessed and followed through November 2020. irAEs (CTCAE v5.0) were noted along with the time from ICI start to irAE onset. Patients were grouped into irAE ever versus never. Clinicopathologic characteristics, prior treatments, and investigator assessed clinical benefit rate (CBR; partial response [PR] + stable disease [SD]) were compared by Fisher's Exact and Mann-Whitney Tests. Overall survival (OS) and investigator assessed progression free survival (PFS) from ICI start were compared using Kaplan Meier. In consented patients (n = 56), next generation sequencing (MSK-IMPACT) was performed with HLA genotyping analysis by POLYSOLVER software and alleles for the three major MHC class I (HLA-A, -B, -C) genes were obtained from whole exome recapture. **Results:** Most patients were male (72%), smokers (55%), > 70 years old (median 72, range 34-90), and had epithelioid histology (67%). No patients had baseline autoimmune disease. The median line of prior systemic therapies to ICI start was 2 (range 1-5). 17 patients (28%) developed an irAE on therapy including 7 (11%) with grade 3 to 5 events (pneumonitis, myositis, pancreatitis, nephritis, encephalitis and adrenal insufficiency). The median time from ICI start to irAE was 2.5 months (range 2 days – 5.8 months). There was no association with dual ICI (n = 6) vs single agent (n = 11) and sooner onset (2.1 vs 4.0 months; p = 0.10) nor higher grade (median grade 2 vs 3; p = 0.31) of irAEs. 1 patient developed grade 5 pneumonitis with onset 2 days after initial dose of dual-ICI. Comparing patients with irAEs to those without, there was no difference in distribution of epithelioid histology (n = 10 vs 31; p = 0.54), median age (71 vs 72 years old; p = 0.43), nor prior thoracic radiation (n = 5 vs 11; p = 0.75).There was no difference in HLA type nor the fraction of HLA alleles of individual genes amongst the groups. Patients who had an irAE were on ICI longer than those that did not (median time on ICI 5.4 vs 0.9 months, respectively; p = 0.02). OS was higher in patients with irAEs compared to those without (21.1 vs 4.7 months; p = 0.003) as was PFS (6.8 vs 1.7 months; p = 0.01). There was a significant increase in the CBR between those that had an irAE (65%; 5 PR, 6 SD) and those that did not (27%; 2 PR, 10 SD; p = 0.006). **Conclusions:** 28% of patients with MPM who received ICIs developed an irAE and onset tended to be early in the course of treatment. There was no clear predictive clinicopathologic feature that correlated with the occurrence of irAE. There was a significant increase in OS, PFS, and CBR in patients that had an irAE compared to those that did not. Research Sponsor: National Cancer Institute Cancer Center Support Grant to Memorial Sloan Kettering Cancer Center [P30 CA008748].

8557 **Poster Session**

Comprehensive genomic profiling of malignant peritoneal mesothelioma (MPeM) reveals key genomic alterations (GAs) distinct from malignant pleural mesothelioma (MPM). *First Author: Lynne O. Chapman, Baylor College of Medicine, Houston, TX*

Background: MPeM is a rare and aggressive cancer with very limited treatment options. Lack of dedicated research has impeded improvements in outcomes. Defining prevalent GAs is a critical unmet need for use of targeted therapies in these patients. Although MPeM is notably distinct from MPM vis-à-vis epidemiologic and clinical attributes, the genomic underpinings of these differences have yet to be established. We aimed at describing a comprehensive genomic profile (CGP) of MPeM in comparison to MPM. **Methods:** We performed a retrospective comparative analysis between 89 patients with MPeM and 241 patients with MPM (N = 330) who underwent CGP using CLIA certified next-generation sequencing assays. The cohort was generated using mesothelioma patients at MD Anderson Cancer Center (N = 223) and supplemented by additional mesothelioma patients (N = 107) from a publicly available database from Memorial Sloan Kettering Cancer Center, the MSK-IMPACT database. Essential clinicopathological variables were collected. Descriptive statistics, Fisher's exact and Mann-Whitney tests were used for comparison. Kaplan-meier method and log rank tests were used for overall survival (OS) estimates. **Results:** MPeM cohort (vs. MPM) had more women (54% vs. 31%, $P < 0.001$) and younger age at diagnosis (56 vs. 69 years, $P < 0.001$). Histology was epithelioid, biphasic and sarcomatoid in 86%, 7% and 7% cases, a distribution similar to MPM cohort. At least 1 GA was found in 64 (72% vs. 82% in MPM, P = 0.044) of MPeM patients with a median of 1 (range 1 – 12) (vs. a median of 2, range 1 – 24, $P < 0.001$) GA per patient. A significantly lower proportion of MPeM patients had ≥ 3 mutations (14% vs. 26%, OR 2.1, P = 0.028) per patient. The most frequent mutations were present in the following genes: *TP53* (24%), *BAP1* (16%), *NF2* (15%), *MET* (9%) and *TRAF7*, *KIT* and *PIK3CA* (each 6%). MPeM patients harbored more mutations in *MET* (9% vs. < 1%, $P < 0.001$) and *TRAF7* (6% vs. < 1%, P = 0.02) but fewer mutations in *BAP1* (16% vs. 32%, P = 0.003) and *CDKN2B* (0% vs. 5%, P = 0.041). The most common copy number variations (CNVs: amplifications or deletions) were seen in *BAP1*, *MCL1*, *SETD2*, *WT1* (each 2%) and *AURKA* (1%) genes. Among genes with CNVs, MPeM had a lower rate of deletions in *CDKN2A* (1% vs. 6%, P = 0.040). Among more common GAs, only *BAP1* mutations appeared to be associated with poor OS (45.7 vs. 127.1 months, HR 2.5, 95%CI: 0.6 – 10.1, P = 0.050) in patients with MPeM. **Conclusions:** In this large cohort with CGP, we identified potential molecular drivers in MPeM and demonstrated key genomic differences between MPeM and MPM. MPeM is frequently driven by GAs involved in cell cycle control, a potentially targetable pathway. Despite this insight from CGP, a large subset of patients do not have actionable GAs and for these patients, further collaborative trans-"omic" research efforts are needed to advance potential therapeutic options. Research Sponsor: U.S. National Institutes of Health.

8558 **Poster Session**

A phase II trial of abemaciclib in patients with p16ink4a negative, relapsed mesothelioma. *First Author: Dean Anthony Fennell, University of Leicester and University Hospitals of Leicester, Leicester, United Kingdom*

Background: Genetically stratified therapy for malignant mesothelioma (MM) is lacking. MMs frequently harbour loss of chromosome 9p21.3 locus (CDKN2A) associated with shorter survival. CDKN2A encodes the tumour suppressor p16ink4a, an endogenous suppressor of CDK4 and CDK6. Genetic reconstitution of p16ink4a into CDKN2A suppresses MM in preclinical models, underpinning the rationale for targeting of CDK4/6 in p16ink4a negative MM. We therefore developed a multi-centre molecularly stratified phase IIa trial to test this hypothesis as arm 2 of the Mesothelioma Stratified Therapy umbrella trial (NCT03654833, MiST2). **Methods:** Patients with histologically confirmed MM (pleural or peritoneal) were molecularly screened by immunohistochemistry for p16ink4a, BAP1, BRCA1, and PDL1 (Dako 22C3). Patients with p16ink4a negative MM were eligible. Key inclusion factors: histological confirmation of MM with an available archival tissue block, ECOG performance status 0-1, prior platinum-based 1st line chemotherapy (any line allowed), evidence of disease progression with measurable disease by CT (RECIST 1.1), and adequate haematological/organ function. Patients received Abemaciclib (Ab) 200mg bd po daily in q21 day cycles. Primary endpoint was disease control rate at 12 weeks (DCR12w). The null hypothesis was rejected if ≥ 11 patients had disease control (A'Hern design). Secondary endpoints: DCR at 24 weeks (DCR24w), best objective response rate and toxicity (NCI CTCAE 4.03). Patients could undergo an optional re-biopsy upon disease progression. **Results:** Between November 2019 and March 2020, 26 patients with p16ink4a negative MM received at least one dose of Ab. The median age of pts was 67 (range, 64-74) years, 89% were male, 80.8% epithelioid, 84.6% ECOG PS1, > 1 prior systemic therapy 62%. All patients received at least one cycle with 27% completing 6 cycles. No dose reductions occurred in 53.9% of pts. DCR12w: 54% (95% confidence limit (CI), 36% – 71%), DCR24w: 23% (95%CI, 9% – 44%). Best responses (within 24w): partial - 15% (95%CI, 4-35%), one occurring after 18 weeks; stable disease - 53.8% (33.4 – 73.4%); progression - 7.7% (0.9 – 25.1%). Adverse events (any cause): ≥ grade 3 toxicities affected 5.7% of pts. **Conclusions:** MiST2 met its primary endpoint, warranting further clinical evaluation of Ab. Whole exome sequencing of the cohort is ongoing to explore genomic correlates of *de novo* and acquired resistance. Clinical trial information: NCT03654833. Research Sponsor: Mesothelioma Stratified Therapy 2.

8559 **Poster Session**

Genomic landscape of malignant mesothelioma by site and histology. *First Author: Elio Adib, The Lank Center for Genitourinary Oncology, Dana-Farber Cancer Institute and Brigham and Women's Hospital, Boston, MA*

Background: Malignant mesothelioma (MM) is a highly lethal tumor that can develop in the pleura, the peritoneum, the pericardium or the testes. While the genomic features of pleural MM have been well-described overall, less is known about the distribution of genetic alterations (GAs) according to histology. In addition, few reports comparing genetic features according to disease site are available. **Methods:** We identified patients with pleural or peritoneal mesothelioma with mutational analysis through the GENIE registry. Patient tumor genetic data were provided by Memorial Sloan-Kettering Cancer Center (MSK)-IMPACT and Dana-Farber Cancer Institute (DFCI)-Oncopanel NGS initiatives. Patients with more than one sequenced sample were excluded. We limited our analysis to genes common to all versions of both panels and that were significantly mutated in the TCGA mesothelioma cohort. Mutation and copy number variant (CNV), collectively called GAs, were determined, and were compared using the Fisher's Exact test and Kruskal-Wallis Test. Comparisons were made both by disease site (pleural vs. peritoneal) and histology for the pleural samples (epithelioid vs. biphasic vs. sarcomatoid). Nominal *p*-values were obtained, and FDR correction was employed ($q<0.1$). **Results:** We identified 439 patients with MM in the GENIE registry who fit the inclusion criteria. The median age was 70.5 years for pleural MM and 60 years for peritoneal MM (Wilcoxon-rank sum test *p*-value = 3e-9). 72% of patients were male. *CDKN2A/CDKN2B* GAs (97% and 100% being deletions in *CDKN2A* and *CDKN2B* respectively), a described prognostic marker in MM, were more common in pleural than in peritoneal MM. Among pleural MMs, tumors of epithelioid histology had less *NF2* GAs than biphasic or sarcomatoid tumors, whereas sarcomatoid tumors had the lowest frequency of *BAP1* GAs (Table). **Conclusions:** Malignant mesotheliomas of different disease sites and/or histologies display distinct patterns of GAs. These findings may contribute in part to differences in response to treatment and survival among these subsets of MM. Research Sponsor: None.

Gene	Pleural MM (all histologies) N=366	Peritoneal MM N=73	q-value	Epithelioid Pleural MM N=266	Biphasic Pleural MM N=76	Sarcomatoid Pleural MM N=24	q-value
BAP1	162 (44%)	25 (34%)	0.117	120 (45%)	39 (51%)	3 (13%)	0.072
CDKN2A	98 (27%)	7 (10%)	0.004	61 (23%)	25 (33%)	6 (25%)	0.276
CDKN2B	92 (25%)	6 (8%)	0.004	65 (24%)	26 (34%)	7 (29%)	0.276
NF2	96 (26%)	12 (16%)	0.15	54 (20%)	30 (40%)	12 (50%)	0.0005
SETD2	39 (11%)	9 (12%)	0.68	33 (12%)	5 (7%)	1 (4%)	0.276
TP53	30 (8%)	8 (11%)	0.588	22 (8%)	6 (8%)	2 (8%)	0.99

8560 **Poster Session**

Efficacy and safety analysis of anlotinib combined with etoposide plus cisplatin/carboplatin as first-line therapy for extensive-stage small cell lung cancer (SCLC): The final results from a phase II single-arm trial. *First Author: Tiandong Kong, Cancer Hospital of Henan University/the Third People's Hospital of Zhengzhou City, Zhengzhou, China*

Background: In recent years, the therapeutic regimens of extensive-stage small cell lung cancer (ES-SCLC) have progressed a lot. The most significant clinical studies include IMpower133 and CASPIAN**.** However, the relevant results showed that the combination of PD-L1 monoclonal antibody and EC regimen chemotherapy as first-line treatment of small cell lung cancer have a median PFS (progession-free survival) of about 5 months, which is comparable to that of simple chemotherapy. Therefore, the EP/EC is still the standard treatment for extensive-stage small cell lung cancer. Meanwhile, we noticed that anlotinib (multi-target small molecule oral VEGF inhibitor) has a curative effect on patients with extensive-stage SCLC as a third-line or above treatment in the ALTER 1202 study in China. Therefore, we tried to add anlotinib to the first-line treatment with EP/EC regimen in patients with ES-SCLC to observe the efficacy and safety. **Methods:** Eligible ES-SCLC pts (18~75 years old, initial treatment, no obvious heart, liver and kidney dysfunction) were received anlotinib (12mg QD from day 1 to 14 of a 21-day cycle) + etoposide(100mg/m^2, d1~3 of a 21-day cycle)+CBP (AUC = 4~5 ,d1,Q3W) or DDP (70~75mg/m^2, d1,Q3W) for 4~6 cycles, then anlotinib maintenance (12mg QD from day 1 to 14 of a 21-day cycle) until the disease progresses or intolerable adverse reactions occur. During the treatment, dose reduction of anlotinib was permitted, which could be reduced to 10mg or 8mg if it was intolerable. The main observation endpoints were ORR, PFS and adverse events. **Results:** Between January 2019 and August 2020, a total of 20 patients with extensive-stage SCLC were enrolled in the study, with an average age of 66.2 ± 8.1(45-75) years old, 17 males (85%) and 3 females (15%). The median PFS was 10 months (95% CI: 7.809-12.191), median OS was 15 months (95%CI:10.639-19.361), ORR (objective remission rate) was 90% and DCR (disease control rate) was 100%. The most common grade 3 or 4 adverse events related to the trial regimen included: neutropenia was 10/20 (50.0%), thrombocytopenia was 5/20 (25.0%), anemia, nausea and fatigue were all 2/20 (10%), hypertension, transaminase elevation and hoarseness were all 1/20 (5%). **Conclusions:** Anlotinib combined with EP/EC regimen has better PFS, OS, ORR and DCR for the initial treatment of extensive-stage SCLC, and a manageable safety profile. A randomized, controlled phase III clinical study will be conducted to confirm this conclusion. Clinical trial information: ChiCTR2000035043. Research Sponsor: Tianqing Pharmaceutical Group Co. Ltd.

8561 **Poster Session**

Real-world evidence of cancer immunotherapy (CIT) combination treatment in first-line (1L) extensive-stage small cell lung cancer (ES-SCLC). *First Author: Eric S. Nadler, Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX*

Background: Atezolizumab plus chemotherapy was the first CIT combination regimen approved for 1L treatment of ES-SCLC in 2019. This study investigated patient characteristics and treatment patterns for patients with ES-SCLC receiving this regimen in the real-world community oncology setting. **Methods:** This was a retrospective study including adult patients diagnosed with ES-SCLC between 01-Oct-2018 (after IMpower 133 publication in NEJM Sep-2018) and 31-Dec-2019, with follow-up through 31-March-2020 using The US Oncology Network electronic health records data. Descriptive analyses of patient characteristics and treatment patterns were conducted, with Kaplan-Meier (K-M) methods used to assess time to treatment discontinuation (TTD) and time to next treatment/death (TTNT). **Results:** Of the 408 patients included in this study, 267 (71.4%) received atezo+carboplatin+etoposide (Atezo+Chemo), 80 (21.4%) received carboplatin+etoposide (Chemo only) and the rest received other regimens. The Atezo+-Chemo patients in the real-world cohort compared with the IMpower 133 trial (n = 201) were older (median age 68 vs. 64 years) and included fewer males (45% vs. 64%), fewer white race (73% vs. 81%), more patients with brain metastases at baseline (23% vs. 9%), and more patients with worse ECOG (2/3) performance-status score (24% vs. 0%). The median follow-up, TTD, and TTNT in months (mo) for the real-world cohort are presented in the table alongside the best comparable measures reported for the trial. **Conclusions:** Most patients in this real-world ES-SCLC cohort received the Atezo+Chemo regimen in the 1L setting. While the follow-up was much shorter and patients had worse baseline characteristics (age, brain metastases, ECOG) in the real-world setting compared to the IMpower 133 trial, the real-world median TTD in this descriptive analysis was found to be in line with the median duration of treatment in the trial. Further research with longer follow-up comparing the real-world effectiveness of the CIT and chemo regimens is needed. Research Sponsor: Genentech.

Real-world Cohort: Atezo+Chemo (n = 267)	IMpower 133: Atezo+Chemo (Reference) (n = 201)
Median follow-up (FU): 5.45mo (range 0.72, 14.36)	Median FU 13.9mo (Data cut-off April 24, 2018)
K-M median TTD*: 4.9mo (95% CI 4.2, 5.3)	Median duration of treatment: 4.7mo (range:0, 21)†
% still on treatment at 6mo (K-M): 35.1% (95% CI 28.4, 41.9)	% still on treatment 6mo: 31.3%†
K-M median TTNT: 6.9m0 (95% CI 6.4, 8.2)	K-M Median progression-free survival (PFS): 5.2mo (95%CI 4.4, 5.6)
% not initiated on 2L at 6mo: 64.5% (95% CI 56.7, 71.3)	PFS (RECIST criteria) at 6mo: 30.9% (95% CI 24.3, 37.5)

*From 1L treatment initiation to discontinuation for any cause (including death). Patients who did not discontinue treatment during the study period were censored on the study end date or the last visit date available in the dataset, whichever occurred first.
†Not based on K-M.

8562 **Poster Session**

The clinical efficacy of olaparib monotherapy or combination with ceralasertib (AZD6738) in relapsed small cell lung cancer. *First Author: Sehhoon Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: The molecular profiling of small cell lung cancer (SCLC) has demonstrated a high incidence of genomic alterations in cell cycle-related genes and DNA damage and response (DDR) pathways, which correlates with devastating clinical outcomes of SCLC. Using two small molecules targeting the DNA repair pathway, olaparib (PARP inhibitor) and ceralasertib (ATR inhibitor), we evaluated their clinical efficacy in monotherapy or in combination, in relapsed SCLC. **Methods:** As part of the phase II biomarker-driven umbrella study in SCLC (SUKSES), patients who failed prior platinum-based regimen were enrolled and allocated based on their genomic alterations. Patients with mutations harboring HR pathway gene mutation not limited to BRCA 1 or 2, ATM deficiency or MRE11A mutations were allocated to the olaparib monotherapy (SUKSES-B, NCT03009682). As an biomarker non-matched arm, biomarker unselected patients were also allowed to receive olaparib and ceralasertib arm (SUKSES-N2, NCT0328607). The primary endpoint was objective response rate (ORR), and two-stage Simon's design was used. **Results:** Based on pre-defined protocol criteria, both arms terminated at stage 1. In the olaparib monotherapy arm (SUKSES-B, n = 15), ORR was 6.7%, and disease control rate (DCR) was 26.7%, 1 partial response (PR), and 3 stable diseases (SD). Median progression-free survival (PFS) was 1.25 months (95% confidential interval [CI] 1.18–NA), and median overall survival (OS) was 8.56 months (95% CI, 6.62–NA). Adverse events that led to treatment discontinuation (n = 2 total, 13.3%) were drug related grade 3 renal impairment, thrombocytopenia, and grade 2 anemia. A patient with confirmed PR showed a tumor volume decrease of 37% compared to the baseline, and a splicing site mutation in BRCA2 was identified from deep target sequencing. In the olaparib and ceralasertib treatment arm (SUKSES-N2, n = 26), ORR was 3.8% (n = 1) and DCR was 42.3% (n = 11). Median PFS was 2.75 months (95% CI 1.77–5.44), and OS was 7.18 months (95% CI 5.97-10.79). Three patients discontinued treatment due to drug related grade 5 pneumonia, grade 3 drug-induced pneumonitis and grade 2 anemia. The most common adverse events for the combination were anemia (n = 11, 42.3%), followed by thrombocytopenia (n = 6, 23.1%). A patient with confirmed PR with a 43% decreases in tumor volume compared with baseline had a mutation in TP53. **Conclusions:** Targeting the DDR pathways with olaparib as single agent or in combination with ceralasertib demonstrated early signal of efficacy in relapsed SCLC patients with a tolerable safety profile. Clinical trial information: NCT03009682, NCT0328607. Research Sponsor: AstraZeneca.

8563 **Poster Session**

Analysis of homologous recombination DNA repair gene mutation status in patients with metastatic small cell lung cancer treated with cediranib and olaparib on NCI 9881 study. *First Author: Joseph W. Kim, Yale Cancer Center, Yale School of Medicine, New Haven, CT*

Background: Cediranib, a pan-vascular endothelial growth factor receptor tyrosine kinase inhibitor, suppresses expression of homologous recombination DNA repair (HRR) genes and increases sensitivity of tumors to a poly-(ADP-ribose) polymerase (PARP) inhibitor *in vitro* and *in vivo* models of breast and ovarian cancer. Olaparib, a PARP inhibitor, demonstrated clinical efficacy in patients with advanced solid tumor with a deleterious mutation in HRR genes. We hypothesized that cediranib induces HRR deficient phenotype by suppressing expression of HRR genes and cediranib and olaparib combination (C+O) results in an objectives response in patients with HRR proficient (HRP) advanced solid tumors. Herein, we report the biomarker data from analyses of targeted sequencing of 84 DNA repair (DR) genes with BROCA-HR assay in patients with metastatic small cell lung cancer (mSCLC). **Methods:** This multi-institutional phase 2 trial enrolled patients with mSCLC previously treated with a platinum-based chemotherapy. Patients received cediranib 30mg orally (po) daily plus olaparib 200mg po twice daily until disease progression or unacceptable toxicity. The primary endpoint was objective response rate (ORR) by RECIST v1.1. A tumor biopsy was obtained from the patients with safely accessible metastatic tumor. HRR deficiency (HRD) was defined as presence of a deleterious mutation in any of the 10 key HRR-related genes per BROCA-HR assay including: ATM, BARD1, BRCA1, BRCA2, BRIP1, CDK12 (somatic mutations only), NBN, PALB2, RAD51C, or RAD51D. Otherwise, the tumors were defined as HRR proficiency (HRP). **Results:** A total of 25 patients with SCLC received the study treatment. Fourteen patients had available tumor biopsy samples and/or germline available for BROCA-HR. One patient (7%) was determined to have a HRD tumor by a presence of PALB2 mutation. This patient had stable disease as a best overall response but came off study due to unequivocal clinical progression. Thirteen patients (93%) had a HRP tumor. Six of these (46%) patients had PR. Median PFS in patients with HPR tumors was 122 days. The most common gene alterations detected by BROCA-HR assay was TP53 (93%) and RB1 (79%). Other DR gene alterations noted from our study samples were MRE11, CKD12 PALB2, ERCC4, FANCB, and BAP1. **Conclusions:** HRD was infrequent in our mSCLC samples. C+O resulted in objective responses in 46% of mSCLC patients with HRP tumors. Mutations in *TP53* and *RB1* were the most common gene alterations. Further investigation in warranted to confirm this observation. Clinical trial information: NCT02498613. Research Sponsor: U.S. National Institutes of Health.

8564 **Poster Session**

Circulating tumor DNA (ctDNA) mutations may predict treatment response in extensive-stage small cell lung cancer (ES-SCLC) treated with talazoparib and temozolomide (TMZ). *First Author: Matthew Mulroy, UCLA Medical Center, Los Angeles, CA*

Background: Poly (ADP-ribose) polymerase (PARP) inhibition in combination with TMZ is a promising treatment strategy for ES-SCLC. In SCLC models, talazoparib, a potent PARP inhibitor, exhibits cytotoxic effects by inhibiting PARP proteins 1/2 and trapping PARP on DNA while TMZ potentiates antitumor response by contributing to genomic instability (Wainberg 2016). Prior ctDNA studies in SCLC have suggested that treatment precipitates the appearance of DNA repair alterations (Nong 2018), but it is unknown whether homologous recombination deficiency (HRD) predicts for treatment response with this combination. **Methods:** Patients (pts) with relapsed or refractory ES-SCLC were treated with oral talazoparib 0.75 mg daily on 28-day cycles and oral TMZ 37.5 mg/m2 on days 1-5 in a phase 2 clinical trial (UCLA/TRIO-US L-07, NCT03672773). ctDNA was collected and assessed based on allele frequency and plasma copy number at baseline and every 8 weeks during treatment with the Guardant360 assay (Redwood City, CA). HRD was defined as a deletion or missense mutation known or likely to result in aberrant expression of *ATM* or *BRCA1/2* (other HRD genes not detected by assay). Response to treatment was defined by RECIST 1.1 criteria. Fisher's exact tests were used to compare proportions of patients with P-values < 0.05 considered statistically significant (www.r-project.org, Vienna, AU). **Results:** For 15 evaluable pts in the first Simon stage of this trial, 45 ctDNA samples were collected. The most common baseline genetic alterations were mutations in *TP53* (14 pts), *BRCA2* (5 pts), *ATM* (4 pts), and *RB1* (3 pts). Of those with > 1 ctDNA timepoint collected, 10/11 (90.9%) pts had $\geq$1 new mutation (range 1-19) detected after receiving treatment (range 8-35 weeks), most commonly in *ATM* (5 pts). Overall, 5 pts had confirmed partial responses (PR), 7 had stable disease, and 3 had progressive disease. Disease control (DC) was associated with the presence of new mutations ($P = 0.022$) and was more common in those with HRD, with DC in 9/10 (90.0%) HRD pts vs 3/5 (60.0%) pts without HRD. All those with PRs experienced a ctDNA nadir at 8 weeks of treatment with nearly all (4/5, 80.0%) exhibiting HRD, 2 at baseline and 2 at 8 weeks of treatment. **Conclusions:** Mutations in DNA repair genes occur on treatment with talazoparib and TMZ and may associate with disease control. With a response rate of 33% in the first Simon stage of this trial, the TRIO-US L-07 trial exploring the combination of talazoparib and TMZ will be assessed in 13 additional patients, after which additional ctDNA analyses will be performed on the cohort as a whole. Clinical trial information: NCT03672773. Research Sponsor: Pfizer, U.S. National Institutes of Health.

8565 **Poster Session**

Cisplatin versus carboplatin for the treatment of limited-stage small cell lung cancer (LS-SCLC). *First Author: Ibrahim Azar, Albany Medical College, Albany, NY*

Background: Standard of care therapy for LS- SCLC is concurrent chemo-radiation (CRT) with a platinum-etoposide backbone. Cisplatin is traditionally the preferred platinum agent in the curative intent setting. Data comparing the efficacy of the less toxic carboplatin to cisplatin in LS-SCLC are lacking. **Methods:** Data from the National VA Cancer Cube were collected. Pathologically confirmed cases of LS-SCLC that received concurrent CRT with platinum-based multiagent chemotherapy were included. Interval-censored Weibull and Cox proportional hazard regression models were used to estimate median overall survival (OS) and hazard ratio (HR), respectively. Survival curves were compared by a Wald test. **Results:** 801 LS-SCLC patients who received carboplatin-based therapy (Carbo-SCLC) and 1018 who cisplatin-based therapy (Cis-SCLC) were included in the analysis. Median OS with Carbo-SCLC and Cis-SCLC were 2.13 years (95% CI 1.97-2.31) and 2.24 years (95% CI 2.09-2.4), respectively (HR=1.04;95% CI, 0.94-1.16; p=0.46). Subset analysis showed similar median OS for Carbo-SCLC and Cis-SCLC in patients with ECOG-PS of 0, 1 and 2, as well as patients in their 50s, 60s and >70. Multivariable regression analysis accounting for age and ECOG-PS shows a HR of 0.99 (95% CI 0.86-1.14; p=0.91). **Conclusions:** Concurrent CRT with carboplatin-etoposide was associated with similar OS compared to cisplatin-etoposide in LS-SCLC, irrespective of PS and age. Carboplatin's advantageous toxicity profile and comparable OS indicate that it is an acceptable choice of platinum for LS- SCLC. Research Sponsor: None.

	Median OS in years (95% CI)	
	Carboplatin	Cisplatin
Total population	2.13 (1.97-2.31)	2.24 (2.09-2.40)
ECOG-PS 0	2.60 (2.18-3.11)	2.74 (2.35-3.16)
ECOG-PS 1	2.15 (1.86-2.48)	2.15 (1.88-2.43)
ECOG-PS 2	1.62 (1.28-2.05)	1.95 (1.51-2.47)
Age 50-59	2.75 (2.15-3.52)	2.89 (2.44-3.39)
Age 60-69	2.32 (2.07-2.59)	2.22 (2.02-2.42)
Age>70	1.78 (1.57-2.01)	1.82 (1.56-2.10)
Stage I	2.35 (1.88-2.93)	2.85 (2.28-3.49)
Stage II	2.48 (2.05-3.01)	2.70 (2.25-3.17)
Stage III	2.04 (1.85-2.24)	2.09 (1.92-2.27)

8566 **Poster Session**

Application value of plasma exosomal long RNA in SCLC diagnosis and prognosis. *First Author: Chang Liu, Fudan University Shanghai Cancer Center, Shanghai, China*

Background: Little research has focused on blood exosomal transcription profile in small cell lung cancer (SCLC). The aim of this study is to identify plasma exosomal specific transcriptional profile in SCLC and explore the application value of plasma exosomal long RNA (exLR) in SCLC diagnosis and prognosis. **Methods:** This study included 81 healthy people and 40 SCLC patients receiving standard first-line chemotherapy with etoposide and carboplatin/cisplatin. The efficacy was evaluated by progression-free survival (PFS), objective response rate (ORR) and disease control rate (DCR). 19 Patients who achieved complete response (CR) or partial response (PR) as best response during the first-line therapy and had not progressed within the following 90 days after the end of first-line therapy were defined as chemosensitive. 21 Patients who achieved stable disease (SD) as best response or received progressive disease during the first-line therapy or within the following 90 days after the end of first-line therapy were defined as chemoresistant. Baseline plasma samples were collected from 40 SCLC patients (17 patients' samples after 2 courses were collected) and 81 healthy people. Plasma exosomes were isolated and purified; exosomal RNA were extracted for high-throughout sequencing analysis. **Results:** We obtained plasma exLRs profiles from 81 healthy control samples and 57 SCLC samples (baseline samples from 40 patients plus samples collected by 17 patients after 2 courses). Bioinformatics analysis found that exLRs were significantly different between the SCLC and the healthy control group; between the chemosensitive and the chemoresistant group; between the baseline samples and the paired samples after 2 courses. For 40 SCLC patients receiving first-line chemotherapy, ORR was 65.0%, DCR was 90.0% and mPFS was 6.0 months (95% CI, 4.3-7.7 months). Multivariate analysis showed that baseline brain metastases and baseline bone metastases were independent predictors of poor PFS; and 223 genes were independent predictors of PFS. There were 10 genes (AC107954.1, H2AFZP2, CALB2, IFITM9P, GFPT2, PLA1A, CHST10, AC021231.2, SETP20, HILPDA) intersected in differentially expressed genes between the SCLC and the healthy control group, differentially expressed genes between the chemosensitive and the chemoresistant group and independent predictors of PFS. These 10 genes were highly expressed in both the SCLC group and the chemoresistant group, and their high expression was an independent risk factor for poor PFS. **Conclusions:** This study firstly identified the plasma exLRs profiles in SCLC patients, verified the feasibility and value of identifying biomarkers based on exLRs profiles in SCLC diagnosis and prognosis. Research Sponsor: None.

8567 **Poster Session**

Imfirst: A phase IIIb, safety, single arm study of carboplatin (CB) or cisplatin (CP) plus etoposide (ET) with atezolizumab (ATZ) in patients with untreated extensive-stage small cell lung cancer (ES-SCLC) in Spain—Primary safety results of the induction phase. *First Author: Maria Rosario García Campelo, Complejo Hospitalario Universitario A Coruna Hospital Teresa Herrera-Materno Infantil, A Coruna, Spain*

Background: Clinical trial (CT) IMpower133 met both primary endpoints and is the first CT to show significant clinical improvement over standard chemotherapy (C) with a good safety profile in first line (1L) ES-SCLC. The addition of ATZ to CB + ET resulted in an OS landmark of 34% and 22% compared to 21% and 16.8% of patients alive at 18 and 24 months respectively versus C. IMfirst evaluates ATZ + CB or CP + ET in a broader patient population than the pivotal study. ECOG Performance status (PS) 2, asymptomatic untreated brain metastases, underlying stable autoimmune diseases and HIV+ pts are eligible. IMfirst also includes the possibility of 6 C induction cycles according to investigator's choice and consolidation radiotherapy. **Methods:** To evaluate the safety and efficacy of ATZ added to CB or CP + ET as 1L treatment in an interventional real world setting of ES-SCLC. Exploratory endpoints include tumor biomarker analysis related to ATZ. **Results:** As of Oct 2020, 117 pts had been enrolled, 105 treated with ATZ + CB + ET and 12 with ATZ + CP + ET. The median age was 65 years (Y) (range 35-89); 84 males; 14 pts (12%) had CNS metastases and 66 pts were current smokers and 50 former smokers, one had never smoked. The PS was 0 in 28 pts (24%), 1 in 75 (64%) and 2 in 14 (12%). The median of cycles of ATZ received was 4 for all the pts (range 1-12) and 2 for the pts (40) in maintenance phase (range 1-8). Number of pts with adverse events (AEs) was 109, 36 with Serious Adverse Events (SAEs) and 63 with AEs. 8 pts had SAEs related to treatment, 4 had adverse events of special interest and 13 pts discontinued the treatment due to AEs: 6 to ATZ, 12 to CB or CP and 10 to ET, 1 patient discontinued ATZ due to a related AE. Table shows the treatment related AEs (TRAEs). No grade 5 TRAEs were reported. **Conclusions:** IMfirst induction phase analysis confirms the safety profile of ATZ plus C in a broader population of patients. Efficacy, biomarker and further safety analyses will be presented in the future with longer follow up. Research Sponsor: Roche Farma S.A.

Treatment related AEs	Grade 1-2	Grade 3-4
Neutropenia	5 (4.3%)	6 (5.1%)
Thrombocytopenia	3 (2.6%)	4 (3.4%)
Platelet Count Decreased	3 (2.6%)	3 (2.6%)
Anaemia	11 (9.4%)	2 (1.7%)
Febrile Neutropenia	0 (0%)	2 (1.7%)
Alanine Aminotransferase Increased	7 (6.0%)	2 (1.7%)
Gamma-Glutamyltransferase Increased	4 (3.4%)	2 (1.7%)

Regarding the immune-mediated AEs (IMAEs), there were two pts (2.6%) with grade 1 and 2 hyperthyroidism. One patient had a grade 2 increase in Alanine Aminotransferase. One patient presented grade 4 hepatotoxicity and another one had grade 3 pneumonitis. All patients with IMAEs were treated accordingly.

8568 **Poster Session**

Penpulimab plus anlotinib as second-line treatment for the small cell lung cancer after failure of platinum-based systemic chemotherapy. *First Author: Changgong Zhang, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing Key Laboratory of Clinical Study on Anticancer Molecular Targeted Drugs, Beijing, China*

Background: Combined therapy of an immune checkpoint inhibitor with a targeted anti-angiogenic agent had been proved to be effective for lung cancer. Penpulimab (AK105) was engineered to eliminate FcγR binding and antibody-dependent cell-mediated cytotoxicity (ADCC)/ antibody-dependent celluar phagocytosis (ADCP) completely, where ADCC/ADCP effects could induce T-cell apoptosis and clearance and therefore compromise anti-tumor activity. Penpulimab demonstrated a slower programmed death-1(PD-1) antigen binding off-rate, which resulted in better cellular activity and higher receptor occupancy. Penpulimab also showed numerous contacts with N58 glycosylation on the BC loop of PD-1. These structural differentiations enhance the anti-tumor activity of penpulimab and improve its safety. Anlotinib is a multi-targeted tyrosine kinase inhibitor selective for VEGF receptors 1/2/3, FGF receptors 1-4, PDGF receptors α and β, and c-kit. Anlotinib has been approved by National Medical Products Administration as the treatment for small cell lung cancer (SCLC) patients, who had progressed/relapsed on or after at least two regimens of chemotherapy. Here we report the results of one cohort which received penpulimab plus anlotinib in a Phase II study. **Methods:** In Cohort 4 of an open-label, multi-center, multi-cohort Phase II study evaluating the efficacy and safety of penpulimab plus anlotinib in pts with advanced head, neck or chest tumors(NCT04203719), the SCLC patients, who failed to platinum-based systemic chemotherapy treatment, received penpulimab (200 mg IV Q3W) and anlotinib (12/10 mg PO 2 weeks on/1 week off). Primary endpoint was objective response rate (ORR) per RECIST v1.1. Secondary endpoints were disease control rate (DCR), duration of response, progression-free survival (PFS) and overall survival. **Results:** 20 patients (median age was 61 [range:37–75] years old, Eastern Cooperative Oncology Group performance status 0/1 [5%/95%], male/female [65%/35%]) were enrolled and received combination therapy (17 received 12 mg anlotinib, 3 received 10 mg anlotinib; and all received 200 mg penpulimab). At data cut-off (Jan 25, 2021), the confirmed ORR was 50.0% (10/20, 1 complete response and 9 partial response) and DCR was 75.0% (15/20). 9 PFS events (45%) had occurred, and the median PFS was 4.7 months (95% CI: 3.6-not reached). Grade 3 treatment-related adverse events (TRAEs) occurred in 30% (6/20, 2 hypertension, 1 hypertriglyceridaemia, 1 gamma-glutamyltransferase increased, 1 palmar-plantar erythrodysaesthesia syndrome and 1 hyponatraemia) of patients, No Grade 4 or 5 TRAEs had occurred. **Conclusions:** Penpulimab plus anlotinib showed favorable antitumor activity and an acceptable safety profile in SCLC patients who failed to platinum-based systemic chemotherapy. This new combination therapy warrants further evaluation for the treatment of SCLC. Clinical trial information: NCT04203719. Research Sponsor: Chia Tai Tianqing Pharmaceutical Group Co., Ltd.

8569 **Poster Session**

Chemoimmunotherapy for the treatment of extensive-stage small cell lung cancer (ES-SCLC) in patients with an Eastern Cooperative Group (ECOG) performance status (PS) of two or greater. *First Author: Daniel Almquist, Mayo Clinic, Phoenix, AZ*

Background: Immune checkpoint inhibitor (atezolizumab or durvalumab) combined with platinum-etoposide is the standard first-line therapy for patients with extensive-stage small cell lung cancer (ES-SCLC). The phase III clinical trials that led to the approval of chemoimmunotherapy in ES-SCLC, excluded patients with an Eastern Cooperative Group (ECOG) Performance Status (PS) of Two or Greater. Therefore, data on efficacy of this combination in this subgroup of ES-SCLC patients whose performance status two or greater is limited. **Methods:** A retrospective analysis was performed of patients diagnosed with ES-SCLC who received chemoimmunotherapy (atezolizumab or durvalumab) within the Mayo Clinic Health System between January 2016 and January 2021. Cases were identified from clinical databases at Mayo Clinic. Data on demographics, ECOG-PS, date of diagnosis, date of progression, whole brain radiation, CNS involvement, liver involvement, stereotactic body radiation, chest consolidation, platinum sensitivity, lines of therapy and last follow up date were extracted. Overall Survival (OS) and progression free survival (PFS) for ECOG-PS 2-3 were compared to patients with an ECOG-PS 0-1. **Results:** A total of 84 patients were identified with a median age of 68.2 (48-88) years old. Of these, 54 patients were identified with an ECOG-PS 0-1 and 30 patients with an ECOG-PS 2-3. The median PFS for the ECOG PS 0-1 cohort was 5.2 months (95% CI 4.6-6.1) while the median PFS for the ECOG-PS 2-3 cohort was 6.0 months (95% CI 4.2-7.7; logrank p = 0.93). The median OS for the ECOG-PS 0-1 cohort was 10.8 months (95% CI 8.5-12.9) while the median OS for the ECOG-PS 2-3 cohort was 10.3 months (95% CI 6.0-14.1; logrank p = 0.39). Hazard ratios of ECOG-PS 0-1 versus 2-3 showed no tendency of increased PFS or OS for either group within cox proportional hazards models. Forty-three percent of ECOG-PS 0-1 achieved a partial response (PR) and 57% of patients who had ECOG-PS 2-3 also achieved a PR (Fisher's exact p = 0.23). A complete response was found in 4% of ECOG-PS 0-1 compared to 3% in the ECOG-PS 2-3 cohort. For patients who responded to initial therapy, 46% of ECOG-PS 2-3 patients had a platinum sensitive relapse while only 33% of ECOG-PS 0-1 were still platinum sensitive at the time of relapse. Five ECOG-PS 2-3 patients were able to receive a second-line therapy. **Conclusions:** To our knowledge, this is the first study to evaluate chemoimmunotherapy in the subgroup of ES-SCLC patients with an ECOG-PS 2 or greater. This retrospective study demonstrated no significant difference in PFS, OS, and ability to achieve a least a PR in ECOG-PS 2-3 cohort when compared to ECOG-PS 0-1. Therefore, chemoimmunotherapy should not be reserved for only an ECOG-PS of 0-1 but should be considered for all treatment eligible patients. Research Sponsor: None.

8570 **Poster Session**

A phase I trial of plinabulin in combination with nivolumab and ipilimumab in patients with relapsed small cell lung cancer (SCLC): Big Ten Cancer Research Consortium (BTCRC-LUN17-127) study. *First Author: Jyoti Malhotra, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Plinabulin (BPI-2358) is a vascular disrupting agent with immune-enhancing function by inducing dendritic cell maturation and decreasing regulatory T cells. Preclinical studies report that plinabulin potentiates the cytotoxicity of dual checkpoint inhibition (CPI) with nivolumab and ipilimumab. Plinabulin may also reduce immune-related AEs from CPI through its phosphodiesterase-4 (PDE4) inhibitory activity which is associated with anti-inflammatory effects. We report initial results from a Phase I study assessing plinabulin in combination with nivolumab and ipilimumab. **Methods:** In this dose-escalation phase I study, patients with extensive-stage SCLC who had progressed on or after prior platinum-based chemotherapy (±CPI) were enrolled using a 3+3 design. The primary objective was to determine dose-limiting toxicities (DLT's) and recommended Phase 2 dose (RP2D). Patients received nivolumab (1 mg/kg), ipilimumab (3 mg/kg) and plinabulin (as per dose escalation schema) IV on day 1 of each 21 day cycles. After completion of 4 cycles, patients continued therapy with nivolumab (240 mg) and plinabulin every 2 weeks till progression or intolerable toxicity. Patients were evaluable for DLT if they received at least 2 cycles of therapy; DLT period was defined as the first 6 weeks from C1D1. Secondary endpoints were ORR, PFS and frequency of irAEs. Correlative analysis included inflammatory biomarkers: hsCRP, ESR, SAA and haptoglobin. **Results:** Between 9/2018 and 11/2020, 17 patients were enrolled (1 patient withdrew consent before treatment, 16 were evaluable for safety). Median age was 59 years (range 43 to 78); 9 patients were male and 10 had received prior CPI. Eight patients were treated at dose-level 1 of plinabulin (20 mg/m2) and 8 patients at 30 mg/m2 of plinabulin (level 2); dose-level 2 was determined to be RP2D. There were 2 DLTs; 1 at dose-level 1 (grade 3 altered mental status lasting $<$ 24 hours) and 1 at dose-level 2 (grade 3 infusion reaction). The most common treatment-related AEs (all grades) were nausea (10; 63%), infusion reaction (8; 50%), vomiting (7; 44%), diarrhea (7; 44%) and fatigue (6, 32%). Seven patients (44%) had at least one grade 3 or higher treatment-related AE; there were no treatment-related deaths. Two patients (13%) had grade 3 or higher irAE requiring steroids (1 colitis, 1 transaminitis); both at dose-level 1. At data cutoff (12/30/20), there were 3 PRs in CPI naïve patients (3/6; 50%) and 2 PRs in evaluable CPI-resistant patients (2/7; 29%). In the two CPI-resistant patients with confirmed response, the tumor reduction was 68% and 52%. **Conclusions:** Plinabulin in combination with nivolumab and ipilimumab was safe and well tolerated. A phase 2 study in CPI-experienced patients with relapsed SCLC is planned to confirm the preliminary signals of clinical activity and reduced immune toxicity. Clinical trial information: NCT03575793. Research Sponsor: BeyondSpring Pharmaceuticals, Bristol Myers Squibb.

8571 **Poster Session**

A randomized phase II/III study comparing carboplatin and irinotecan with carboplatin and etoposide for the treatment of elderly patients with extensive-disease small cell lung cancer (JCOG1201/TORG1528). *First Author: Tsuneo Shimokawa, Department of Respiratory Medicine, Yokohama Municipal Citizen's Hospital, Yokohama-Shi, Japan*

Background: Carboplatin and etoposide is the current standard treatment for elderly extensive-disease small-cell lung cancer (ED-SCLC). The purpose of this study is to evaluate the efficacy and safety of carboplatin and irinotecan compared with carboplatin and etoposide in elderly Japanese patients with ED-SCLC in a randomized phase II/III design. **Methods:** Eligibility included histologically or cytologically proven SCLC, no previous systemic chemotherapy, performance status of 0 to 2, and aged 71 years or older. Patients received carboplatin (AUC 5 mg/ml/min on day 1) and etoposide (80 mg/m^2 on day 1 to 3) (CE) every 3 weeks for 4 cycles or carboplatin (AUC 4 mg/ml/min on day 1) and irinotecan (50 mg/m^2 on day 1 and 8) (CI) every 3 weeks for 4 cycles. In the phase II part, the primary endpoint was the objective response rate of the CI arm and the secondary endpoint was adverse events. In the phase III part, the primary endpoint was overall survival, and the secondary endpoints were progression-free survival, objective response rate, adverse events, and symptom score. This study was designed to confirm the superiority of CI arm in terms of overall survival over CE arm. The median survival time with CI arm was expected to be increased by 3.5 months with hazard ratio (HR) of 0.750 (10.5 vs. 14.0 months). The sample size was set at 250 to observe the required number of events of 227 with one-sided alpha level of 0.05, a power of 70%, an accrual period of 6.5 years, and a follow-up period of 1.5 years. **Results:** Between December 2013 and June 2019, 258 patients were randomized (CE arm, 129 patients; CI arm, 129 patients). The median age was 75 (range, 71-90). The characteristics of the patients were well balanced between CE arm and CI arm. Overall survival, progression-free survival, and objective response rate of CE arm vs. CI arm were 12.0 (95% CI, 9.3-13.7) vs. 13.2 (95% CI, 11.1-14.6) months (HR, 0.848 (95% CI, 0.650-1.105)) (one-sided P=0.11), 4.4 (95% CI, 4.0-4.7) vs. 4.9 months (95% CI, 4.5-5.2) (HR, 0.851 (95% CI, 0.664-1.090)) (two-sided P=0.21), and 59.7% (77 of 129) vs. 64.3% (83 of 129), respectively. Symptom score showed no significant difference between the arms. Higher incidences of myelosuppression of grade 3 or worse occurred with CE arm, whereas higher incidences of gastrointestinal toxicity of grade 3 or worse occurred with CI arm. Three treatment-related deaths including lung infection in CE arm and lung infection and sepsis in CI arm were observed. **Conclusions:** Efficacy tended to be favorable in carboplatin and irinotecan arm, but there was no statistically significant difference. These results indicate that carboplatin and etoposide is a still standard treatment in elderly Japanese patients with ED-SCLC. Clinical trial information: 000012605. Research Sponsor: None.

8572 **Poster Session**

Combination of quantitative features from H&E biopsies and CT scans predicts response to chemotherapy and overall survival in small cell lung cancer (SCLC). *First Author: Cristian Barrera, Case Western Reserve University, Cleveland, OH*

Background: Small Cell Lung Cancer (SCLC) is an aggressive malignancy with a rapid growth, and Chemotherapy remains mainstay of treatment. Identifying therapeutic targets in SCLC presents a challenge, partially due to a lack of accurate and consistently predictive biomarkers. In this study we sought to evaluate the utility of a combination of computer-extracted radiographic and pathology features from pretreatment baseline CT and H&E biopsy images to predict sensitivity to platinum-based chemotherapy and overall survival (OS) in SCLC. **Methods:** Seventy-eight patients with extensive and limited-stage SCLC who received platinum-doublet chemotherapy were selected. Objective response to chemotherapy (RECIST criteria) and overall survival (OS) as clinical endpoints were available for 51 and 78 patients respectively. The patients were divided randomly into two sets (Training (Sd), Validation (Sv)) with a constraint (equal number of responders and nonresponders in Sd)—Sd comprised twenty-one patients with SCLC. Sv included thirty patients. CT scans and digitized Hematoxylin Eosin-stained (H&E) biopsy images were acquired for each patient. A set of CT derived (46%) and tissue derived (53%) image features were captured. These included shape and textural patterns of the tumoral and peritumoral regions from CT scans and of tumor regions on H&E images. A random forest feature selection and linear regression model were used to identify the most predictive CT and H&E derived image features associated with chemotherapy response from Sd. A Cox proportional hazard regression model was used with these features to compute a risk score for each patients in Sd. Patients in Sv were stratified into high and low-risk groups based on the median risk score. Kaplan-Meier survival analysis was used to assess the prognostic ability of the risk score on Sv. **Results:** The risk score comprised nine CT (intra and peri-tumoral texture) and six H&E derived (cancer cell texture and shape) features. A linear regression model in conjunction with these 15 features was significantly associated with chemo-sensitivity in Sv (AUC = 0.76, PRC = 0.81). A multivariable model with these 15 features was significantly associated with OS in Sv (HR = 2.5, 95% CI: 1.3-4.9, P = 0.0043). Kaplan-Meier survival analysis revealed a significantly reduced OS in the high-risk group compared to the low-risk group. **Conclusions:** A combined CT and H&E tissue derived image signature model predicted response to chemotherapy and improved OS in SCLC patients. Image features from baseline CT scans and H&E tissue slide images may help in better risk stratification of SCLC patients. Additional independent validation of these quantitative image-based biomarkers is warranted. Research Sponsor: U.S. National Institutes of Health.

8573 **Poster Session**

Myasthenia gravis-associated thymoma and myasthenia gravis-free thymoma have distinct somatic mutation and gene expression profiles. *First Author: Yi Zhang, Thoracic Surgery Department, Xuanwu Hospital, Capital Medical University, Beijing, China*

Background: A significant proportion of thymoma patients have concurring autoimmune diseases such as myasthenia gravis (MG). However, the molecular signature of myasthenia gravis-associated thymoma (MGT) is largely unknown. Genomic and transcriptomic profiling of MGT may provide valuable insight to the etiology of MGT and facilitate the development of effective therapeutic approaches. **Methods:** To study the molecular signature of MGT, 26 thymoma patients were divided into two subgroups according to their clinical presentations. One group included 16 thymoma patients associated with MG (MGT) and the other group had 10 patients without MG (MGF). We profiled the genomic and transcriptomic changes of tumor samples from both subgroups with whole exome sequencing (WES) and RNA sequencing (RNA-seq). **Results:** The WES results indicated that more genes were mutated in the MGF subgroup than the MGT group, although the difference between two subgroups was not statistically significant. There were only five mutated genes (*NBPF1*, *HRAS*, *ATAD3B*, *IFITM3* and *MUC4*) appeared total mutation frequency exceeded 10%. *NBPF1* is the most frequently mutated gene, seen in 25% of the MGTs (4/16) and 10% (1/10) of the MGFs. Neuroblastoma breakpoint family member 1 encoded by *NBPF1* was involved in several cancer types including gastric cancer and neuroblastoma, but there is no report on the link of *NBPF1* with thymoma or MG. Recent studies showed that NBPF1 is a negative regulator of Akt-p53-Cyclin D and PI3K/mTOR signal pathways. Recurrent mutations in *HRAS* was only observed in MGFs but not MGTs. Genes mutated in more than one patient were *NBPF1*, *ATAD3B*, *RPDM9*, *LOC642131*, *ADAM21*, *CGNL1*, *MUC4* and *MUC2* in the MGT subgroup, while only three genes *HRAS*, *CSPG4* and *IFITM3* were mutated in more than one patient in the MGF subgroup. Moreover, RNA-seq data identified 106 significantly differentially expressed genes, including 54 upregulated and 52 downregulated genes in the MGT subgroup, further pathway enrichment analysis revealed that the Hippo, Wnt, TGF-β and focal adhesion signaling pathways were significantly downregulated in the MGT subgroup compared with the MGF subgroup. **Conclusions:** Our findings provide new insights for the etiology of thymoma with and without MG. mTOR signaling pathway is a key regulator of immune response. Importantly, the protein level of some components in the mTOR pathway was reduced in MG caused-atrophic muscle. Further investigation is warranted to examine the functional roles of *NBPF1* in mTOR signaling regulation and the etiology of MG-associated thymoma. Research Sponsor: None.

8574 **Poster Session**

First long-term results on efficacy and safety of long-acting pasireotide in combination with everolimus in patients with advanced carcinoids (NET) of the lung/thymus: Phase II LUNA trial. *First Author: Eric Baudin, Department of Nuclear Medicine and Endocrine Oncology, Gustave Roussy Cancer Campus, Villejuif, France*

Background: Everolimus (EVE) improves progression-free survival (PFS) in patients (pts) with progressive non-functioning thoracic and digestive advanced neuroendocrine tumors (NET). The LUNA trial aimed to assess the efficacy and safety of long-acting pasireotide (PAS) and EVE alone or in combination in pts with progressive bronchial or thymic carcinoids. Core phase results for primary endpoint (PFS) and secondary endpoints at 9 and 12 months (mo) were previously published. Cumulative data results at the end of the extension phase are presented here. **Methods:** LUNA was a prospective, multicenter, randomized, open-label, 3-arm, phase II trial. Adult pts with carcinoids of lung/thymus were randomized (1:1:1) to receive either PAS (60 mg/mo i.m.) or EVE (10 mg/day orally) or PAS + EVE. The key secondary endpoints assessed in this extension phase, including all the patients who were still not progressing at 12 months, were PFS, duration of biochemical response (DBR), and biochemical PFS (BPFS). **Results:** Of the total 124 pts included in the core phase, 41 pts with a median age of 61 years entered the extension phase including PAS (12), EVE (14) and PAS + EVE (15). Lung was the primary site of cancer in 95.1% and 82.9% had non-functioning tumors. Surgery/local or regional therapy was the preferred prior treatment in 63.4% pts. Disease progression was the primary reason for discontinuation among 3 arms with 65.9% in overall extension phase; no pts in PAS arm discontinued due to adverse events (AEs). Mean relative dose intensity (RDI) was higher for PAS (95.6% alone and 90.4% in combination) when compared to EVE (76.6% alone and 72.4% in combination); 38.1% pts in the EVE arm and 43.9% pts in the combination arm with EVE had RDI <70%. PAS +EVE combination showed clinical benefit in terms of PFS and BPFS compared to PAS and EVE alone as shown in Table. At least one dose reduction of PAS or EVE was reported in >50% pts. Most common AEs of any grade regardless of the study drug in PAS +EVE arm were hyperglycemia (87.8%), diarrhea (80.5%), and weight loss (58.5%), while stomatitis was reported in 34.1%. Twelve deaths were reported during the study and up to 56 days from last study treatment dose. Duration of exposure and efficacy. **Conclusions:** Mature median PFS and BPFS data suggest a benefit of PAS+EVE combination. The safety and tolerability profile of PAS and EVE alone or in combination were consistent with prior experience of these treatments in the oncology setting, with no new safety signals being reported during the study. Post-hoc prognostic studies are ongoing. Clinical trial information: NCT01563354. Research Sponsor: None.

	PAS N=41	EVE N=42	PAS + EVE N=41
Duration of exposure, weeks (range)	38.9 (4.0-295.6)	26.9 (1.0-224.1)	49.0 (4.0-307.9)
Median PFS, mo, (95% CI)	8.51 (5.68-14.03)	12.48 (5.55-20.21)	16.53 (11.10-23.26)
Median BPFS, mo, (95% CI)	2.89 (2.79-5.49)	2.86 (2.79-3.52)	5.62 (3.19-8.31)

8575 **Poster Session**

Cancer activation pathways of thymic epithelial tumors (TETs) by targeted gene expression analysis. *First Author: Jose Carlos Benitez, Gustave Roussy, Villejuif, Paris, YT, France*

Background: TETs are rare malignancies of the anterior mediastinum. Clinical behavior varies from mild thymoma (T) A to aggressive thymic carcinoma (TC). The biology of TETs is poorly understood and knowledge of the transcriptomic fingerprint of T and TC is limited. Additionally, up to 30% of patients (pts) will develop associated autoimmune disorders (AIDs). We aimed to characterize the main cancer activation pathways of the TET subgroups. **Methods:** We selected a representative balanced set of Ts and TCs to analyze 24 main cancer activation pathways using HTG Oncology biomarkers panel (2562 genes) by RNA sequencing. Tumor representative paraffin-embedded blocks were macrodissected for gene expression analysis. We analyzed epidemiologic, clinical and pathological characteristics of pts with TET's and correlated with genes expression based on cancer Hallmarks. **Results:** From January 2010 to December 2019, 219 pts were included in the cohort. Molecular results of 194 pts were available. Median age at diagnosis was 56 (9-83) years. 54.1% were women. 65/194 (33.5%) reported AIDs. T B2 was the most frequent (n=41, 21.1%), followed by B1, AB, B3, TC and A. RNA expression analysis identified 2 main clusters, corresponding mainly to T (cluster 2) and TC (cluster 1) respectively ($p<0.0001$) (Table). Tumors of cluster 1 (TCs predominant) shown activated pathways (MYC [gene ratio= 0.5]; $p<0.0001$). In cluster 2 (T predominant), activated pathways differed among subgroups: B1 (E2F[0.5], G2M checkpoint [0.45]; $p<0.001$), B2 (E2F [>0.4]; $p<0.0001$). Routes were mostly suppressed: A (MYC [>0.5], E2F[>0.4], G2M checkpoint[>0.45], mitotic spindle[>0.35], MTOR [<0.35]; $p<0.001$), AB (INFα [>0.5], inflammatory response [>0.45], INTγ [0.45], NFkb [>0.4], MTOR[>0.4]; $p<0.001$), B1 (EMT [0.6], angiogenesis [>0.5], INFα [0.5], homeostasis [0.5], NFkb [0.5], INTγ [>0.45], myogenesis [<0.4]; $p<0.0001$), B2 (INFα [>0.65], INTγ [>0.5], NFkb [0.5], EMT [0.45], inflammatory response [<0.4]; $p< 0.0001$), B3 (EMT [0.6], MYC [0.45]; $p<0.001$). Among pts reporting AIDs 61 and 4 were associated to cluster 2 and 1, respectively ($p=0.017$). **Conclusions:** We describe differential molecular characteristics among histological subgroups in 2 clusters. The analysis suggests new therapeutic venues. Additional analysis will be presented on outliers and response to treatment. Research Sponsor: None.

Correlation between histological subgroups and molecular clusters (K means used for all subgroups).

Histological subtype	Cluster (n)	
Thymoma A	1	2
Thymoma AB	1	16
Thymoma B1	1	34
Thymoma B2	2	34
Thymoma B3	1	40
Thymoma B1/B2	4	29
Thymoma B2/B3	2	6
Thymic Carcinoma	0	2
p-value < 0.01	16	4

8576 **Poster Session**

A phase II study of palbociclib for recurrent or refractory advanced thymic epithelial tumor (KCSG LU17-21). *First Author: Myung-Ju Ahn, Samsung Medical Center, Seoul, South Korea*

Background: Thymic epithelial tumors (TETs) are rare but the most common tumor of the anterior mediastinum. Platinum-based combination chemotherapy is standard of care which is associated with a 50%-90% overall response rate (ORR) in metastatic disease. However, there is no standard chemotherapeutic option after failure of platinum-based combination chemotherapy. Genetic alterations associated with cell cycle including pRB, $p16^{INK4A}$, and cyclin D1 are commonly observed in TETs. Based on these results, we conducted a phase II trial to evaluate the efficacy and safety of palbociclib in patients with recurrent or refractory advanced TETs. **Methods:** This is a phase II multicenter, open-label, single arm study of palbociclib monotherapy in patients with recurrent or metastatic advanced TETs who failed one or more cytotoxic chemotherapy. Patients receive oral palbociclib 125mg daily for 21 days followed by a 7-day break. The primary endpoint was the progression-free survival (PFS) rate at 6 months (H0 = 30% vs H1 = 48%). **Results:** Between August 2017 and October 2019, 48 patients were enrolled. The median number of previous chemotherapy was 1 (range: 1-4) and 21 (43.7%) of 48 patients received thymectomy. By WHO classification, Type A (n = 1), Type B1 (n = 2), Type B2 (n = 8), Type B3 (n = 13), Type C (n = 23), and unknown (n = 1). With medial follow-up of 14.5 months (range 0.8-38.2), the median cycle of palbociclib was 10 (range 1-40). The PFS at 6 months was 60% and the median PFS was 11.0 months (95% CI: 4.6-17.4). Six of 48 patients (12.5%) achieved partial response. The median overall survival was 26.4 months (95% CI: 17.4-35.4). The most common adverse events of any grade included neutropenia (62.5%), anemia (37.5%) and thrombocytopenia (29.1%). **Conclusions:** Palbociblib monotherapy is well tolerable and encouraging efficacy in patients with TETs who failed platinum-based combination chemotherapy. Updated results will be presented. Clinical trial information: NCT03219554. Research Sponsor: None.

8577 **Poster Session**

Cell-free circulating tumor DNA (cfDNA) analysis of advanced thymic epithelial tumors (TETs). *First Author: Hiba I. Dada, Guardant Health, Inc., Redwood City, CA*

Background: Thymic epithelial tumors (TETs) are rare tumors originating from the epithelial cells of the thymus. Thymomas tend to be slowly growing, whereas thymic carcinomas are more aggressive and often metastasize wildly. TETs have a very low tumor mutational burden (TMB). cfDNA has been used in several tumor types to describe the molecular characteristics and select treatment options, especially in absence of tissue availability. There is no information on the cfDNA detected in TETs. The purpose of this study was to identify common genomic alterations occurring in circulating tumor DNA (ctDNA) in patients with advanced TETs, detected using a cfDNA assay. **Methods:** We retrospectively evaluated 157 TET samples from the Guardant Health database between November 2017 – November 2020. The cfDNA analysis interrogated single nucleotide variants (SNV), fusions, indels and copy number variations (CNV) of up to 83 genes using a commercially available liquid biopsy assay (Guardant360; Guardant Health, Redwood City, CA). We evaluated the frequency of genomic alterations based on diagnosis, age, and sex. **Results:** In this cohort, 66% of the patients had thymic carcinoma and 34% had thymoma. The median age was 60 years, and 59% of patients were male. 126 patients (80%) of this cohort had ≥1 somatic alteration detected. The most prevalent mutations detected are TP53 (55%), KIT (13%), EGFR (12%), BRCA2 (11%), PIK3CA (10%), ARID1A (10%), ATM (10%), KRAS (9%), APC (9%), and BRAF (9%). Mutations were more commonly observed in thymic carcinomas than thymomas, but statistical significance was not reached due to the small sample size. Frequencies of the observed genomic alterations are shown in the table below. **Conclusions:** This study confirms that advanced stage TETs shed tumor DNA into the circulation that can be picked up in the majority of patients, using a solid tumor platform, despite the low TMB typically observed in these tumors. This assay can potentially be used to monitor response to therapy. A more targeted gene panel, enriched for genes commonly mutated in TETs (e.g. GTF2I, BAP1, CYLD) might provide further insights in the future in the management of TETs. Research Sponsor: None.

	Thymic Carcinoma	Thymoma
Amp	12.7%	10.7%
Fusion	0.4%	0.0%
Indel	9.2%	5.3%
Missense	59.4%	58.7%
Nonsense	2.8%	6.7%
Splice	2.8%	2.7%
Synonymous	12.7%	16.0%

8578 **Poster Session**

Outcomes of thymic epithelial tumors (TETs) with pleural metastases: Real-world insight from RYTHMIC. *First Author: Jean-Michel Maury, Department of Thoracic Surgery Lung and Heart Lung Transplantation, Lyon, France*

Background: TETs are rare and potentially aggressive malignancies with high associated prevalence of autoimmune disorders (AIDs). The pleura is the main metastatic site at relapse, referred as Masaoka-Koga stage (MK) IVa. The benefit of surgical management is unknown, so we have collected outcomes of patients with MK IVa TETs in a large prospective database. **Methods:** RYTHMIC (Réseau tumeurs THYMiques et Cancer) is a French nationwide network mandated to systematically discuss every case of TETs. The database, hosted by IFCT (Intergroupe Francophone de Cancérologie Thoracique), prospectively includes all consecutive pts with a diagnosis of TET discussed in RYTHMIC national or regional tumor boards. We analyzed epidemiologic, clinical and pathological characteristics of patients (pts) with MK IVa TETs. **Results:** From January 2012 to December 2019, 2909 pts were included in the database, including 182 MK IVa (6.2%). The median age at diagnosis was 63.5 (range 9 to 91). 58/182 (32%) pts reported AIDs, 76% myasthenia gravis. 129/182 pts had synchronous pleural metastasis. 118/182 (65%) tumors were resected, of them 10 (8.4%) had only pericardial metastases. Thymoma (T) B2 rate was 35.6%, B3 17.8% and thymic carcinoma (TC) 13.5%. Induction chemotherapy (CT) was given in 46 (39%) T and 10 (8%) TC with response rate of 50% and 70% respectively. Thymectomy was performed in addition to pleurectomy in 44 pts (37.2%), pericardiectomy in 68 (57.6%), lung resection in 80 (67.8%) or pneumonectomy in 15 (12.7%). Node resection was performed in 57.6% (n = 67), 12 (18%) were positive. The complete resection rate assessed by surgeons was 57% with a median of 15 (0 to 28) resected pleural metastasis. Intrapleural chemotherapy was added for 19 (16%) pts. No mortality was reported 90 days after surgery procedure. Median follow-up was 36 months. Pleural recurrence was seen in 47 (72%) pts. Median disease-free survival (DFS) was 39 vs 16 months in resected vs not resected tumors ($p < 0.0001$), 5-years overall survival (OS) was 88 vs 66% ($p = 0.28$), respectively. Risk of relapse decreased by 60% with surgery (HR = 0.4, 95CI (0.25-0.62); $p < 0.0001$). **Conclusions:** The prevalence of MK IVa in our cohort was 6.2%. Surgery appears to be a safe and valid option for pts with MK IVa TET at diagnosis. Research Sponsor: None.

8579 **Poster Session**

Clinicogenomic characterization of metastatic thymic epithelial tumors. *First Author: Fatemeh Ardeshir-Larijani, Indiana University, Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Thymic epithelial tumors (TET) are one of the rarest adult malignancies. Overall, patients have favorable survival outcomes, however a small subset develop metastatic disease. Genomic characterization of this very rare, clinically aggressive TET subset is lacking. Herein, we evaluated the clinical and genomic characteristics of metastatic TET (mTET) compared to a large cohort (n = 117) of primary TET (pTET) from The Cancer Genome Atlas (TCGA). **Methods:** From 2015 to 2020, 52 pts with mTET underwent clinical CLIA-based sequencing using either whole-exome (n = 35), panel-based testing (n = 13) and/or liquid biopsy (n = 22). The specimen was taken from a metastatic organ (n = 34) or relapsed primary mediastinal mass (n = 14); 4 pts had liquid bx only. Data on pTET was derived from the TCGA. Kaplan-Meier and log-rank test was used for assessment of PFS, OS. **Results:** The median age was 56 yrs in mTET (range 32-74) vs. 60 yrs (range 17-84) in TCGA data. The M/F (%) was 40/60 in mTET and 48/52 in TCGA, respectively. Of note, 13 mTET pts had other types of cancer prior or concurrent with TET diagnosis (4-breast, 2-bladder, 5-other) in which radiotherapy (n = 4) and/or chemotherapy (n = 3) was administered prior to TET diagnosis. In our cohort, 19 pts had stage IVA and 33 pts had stage IVB (most common metastatic site was liver in 17 pts). WHO histologic classification was: A = 1, A/B = 3, B1 = 4, B2 = 10, B3 = 12, TC = 18, TC with neuroendocrine feature = 3, and lymphoepithelial carcinoma = 1. WHO B3 and TC histologies were more common in our cohort of mTET than in the TCGA cohort (63% (33/52) vs. 17% (20/117), respectively). Pts with TC had worse mOS compare to thymoma (109m vs. 163m, HR = 2.78, P = 0.04). The most common genomic alteration in mTET was TP53 (n = 17, 33%) compared to 3% in TCGA. This was followed by CDKN2A (n = 5, 10%), PIK3CA (n = 4, 8%), CDKN2B (n = 3, 6%) and NF1 (n = 3, 6%). All TP53 missense mut functionality was analyzed with polyphen-2 software and 91.6% (22/24) had 98-100% damaging probability. 70% of pts that harbored TP53 muts were TC (41%) or B3 (29%) histology. Clinically actionable genomic alterations targetable with available or investigational agents (e.g. high TMB; gain-of-function mutations in PIK3CA, CDK4, and mTOR; loss-of-function mutations in NF1) were seen in 23% (12/52) of pts. **Conclusions:** Patients with mTET are associated with more aggressive WHO histology (B3 and TC). Greater frequency of TP53 mutations are observed in mTET compared to pTET. Clinically actionable genomic alterations are frequently seen in mTET suggesting value in the routine sequencing of these patients. Research Sponsor: None.

TPS8580 **Poster Session**

Phase 3 study of pembrolizumab with concurrent chemoradiation therapy followed by pembrolizumab with or without olaparib versus concurrent chemoradiation therapy followed by durvalumab in unresectable, locally advanced, stage III non-small cell lung cancer: KEYLYNK-012. *First Author: Salma K. Jabbour, Rutgers Cancer Institute of New Jersey, Robert Wood Johnson Medical School, Rutgers University, New Brunswick, NJ*

Background: Pembrolizumab, an anti–PD-1 antibody is standard of care therapy for metastatic non–small-cell lung cancer (NSCLC) as monotherapy and in combination with chemotherapy. Durvalumab, an anti–PD-L1 antibody, is approved for unresectable, stage III NSCLC without disease progression following concurrent chemoradiation therapy (CCRT). Early trials of pembrolizumab in combination with chemoradiotherapy, either concurrently or as consolidation, showed acceptable tolerability and promising PFS in patients with unresectable stage III NSCLC. Early data suggest the combination of poly(ADP-ribose) polymerase (PARP) plus anti–PD-(L)1 inhibition can enhance treatment effects. KEYLYNK-012 (NCT04380636) is evaluating pembrolizumab plus CCRT followed by pembrolizumab with/without the PARP inhibitor olaparib vs CCRT followed by durvalumab in patients with unresectable, locally advanced, stage III NSCLC. **Methods:** This global phase 3, randomized, placebo- and active-controlled, double-blind study is enrolling patients aged ≥18 y with previously untreated, pathologically confirmed, stage IIIA–C NSCLC, an ECOG PS of 0 or 1, and a tumor sample available for PD-L1 evaluation. Patients are randomized 1:1:1 to CCRT (platinum-doublet chemotherapy [cisplatin plus pemetrexed or etoposide; or carboplatin plus paclitaxel] plus radiotherapy 60 Gy over 6 wks [cycles 2–3]) with pembrolizumab 200 mg Q3W (groups A and B) or CCRT alone (group C) for 3 cycles. This is followed by pembrolizumab 200 mg Q3W for 17 cycles plus placebo (group A) or olaparib 300 mg BID (group B); or durvalumab 10 mg/kg Q2W for 26 cycles (group C). Randomization is stratified by disease stage (IIIA vs IIIB/IIIC), tumor histology (squamous vs nonsquamous), PD-L1 tumor proportion score (≥50% vs < 50%) and region (East Asia vs North America/Western Europe/UK vs other). PFS (RECIST v1.1 by blinded independent central review [BICR]) and OS are dual primary endpoints. Secondary endpoints include ORR, duration of response, safety and tolerability, and quality-of-life outcomes. Tumor response will be evaluated per RECIST v1.1 by BICR after CCRT and at regular intervals throughout the study until disease progression, new cancer therapy, study withdrawal, or death. AEs will be graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0. Enrollment began July 6, 2020 and is ongoing at 204 sites in 24 countries. Clinical trial information: NCT04380636. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS8581 **Poster Session**

A phase III clinical trial of adjuvant chemotherapy versus chemoimmunotherapy for stage IB-IIIA completely resected non-small cell lung cancer (NSCLC) patients nadim-adjuvant: New adjuvant trial of chemotherapy versus chemoimmunotherapy. *First Author: Virginia Calvo, Instituto Investigacion Sanitaria Puerta de Hierro-Segovia de Arana, Hospital Universitario Puerta de Hierro-Majadahonda, Madrid, Spain*

Background: The results of current studies are considered acceptable evidence to support the hypothesis of efficacy of the proposed combination of immunotherapy with chemotherapy (CT-IO) in patients with NSCLC stages Ib-IIIA candidates for adjuvant treatment. **Methods:** This is an open-label, randomised, two-arm, phase III, multi-centre clinical trial. Primary objective and endpoint: The primary objective is disease free survival (DFS) defined time from randomization to the earliest event defined as disease recurrence, any new lung cancer (even in the opposite lung), or death from any cause at any known point in time Sample size: 210 patients NSCLC stages Ib-IIIA (Experimental Arm (Adjuvant Chemotherapy-Inmunotherapy + maintenance adjuvant Inmunotherapy): 105 patients, Control Arm (Adjuvant Chemotherapy): 105 patients Treatment Patients randomised to the experimental arm will receive Nivolumab 360mg + Paclitaxel 200mg/m2 + Carboplatin AUC5 for 4 cycles every 21 days (+/- 3 days) as adjuvant treatment followed by maintenance adjuvant treatment for 6 cycles with Nivolumab 480 mg Q4W (+/- 3 days). Patients randomized to the control arm will receive Paclitaxel 200mg/m2 + Carboplatin AUC5 for 4 cycles every 21 days (+/- 3 days) followed by 2 observation visits. Total trial duration: 6.5 years, 3.5 years of recruitment, 1 year of adjuvant treatment or observation and 2 years of follow up. The start date was January 2021. The estimated primary completion date is June 2027. Clinical trial information: NCT04564157. Research Sponsor: BMS.

TPS8583 **Poster Session**

A randomized phase II trial of adjuvant pembrolizumab versus observation following curative resection for stage I non-small cell lung cancer (NSCLC) with primary tumors between 1-4 cm: Big Ten Cancer Research Consortium BTCRC-LUN18-153. *First Author: Greg Andrew Durm, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: There are approximately 35,000 cases of stage I lung cancer in the United States each year. While these patients have better 5-year overall survival (OS) rates than their counterparts with locally advanced and metastatic disease, there is still considerable room for improvement. Based on a recent publication validating the 8th edition of the TNM classification, the 5-year OS for node-negative pathologically-staged NSCLC between 1-4cm ranges from 73-86%, and recurrence rates for resected stage I NSCLC can range from 18-38%. Previous studies looking at adjuvant chemotherapy in this setting have shown no benefit for stage IA tumors, and the current standard of care is observation alone. Checkpoint blockade with PD-1/PD-L1 inhibitors has shown considerable activity in NSCLC including in metastatic disease, as consolidation in stage III disease after chemoradiation, and in studies evaluating neoadjuvant immunotherapy. Given this activity and their favorable safety profile, we designed a study of adjuvant PD-1 inhibition following resection in stage I NSCLC. **Methods:** This study is a randomized phase II multicenter trial of adjuvant Pembrolizumab versus observation alone following complete resection of stage I NSCLC with tumors between 1-4cm. The trial will enroll 368 patients randomized 1:1 to either Pembrolizumab 400mg IV every 6 weeks for up to 9 cycles or observation alone with scheduled CT scans and routine clinical follow-up. Stratification factors include PD-L1 ≥50% vs. < 50% and tumor size of 1-2cm vs. > 2-4cm. The lead site is Indiana University, and the trial will be conducted through the Big Ten Cancer Research Consortium. The primary endpoint is disease free survival (DFS), and secondary endpoints include OS, DFS at 1-, 2-, and 3-year time points, and toxicity. The trial opened to accrual at the lead site in May 2020, and there are currently 6 patients enrolled. Clinical trial information: NCT04317534. Research Sponsor: Merck.

TPS8584 **Poster Session**

Randomized phase III Trial of MEDI4736 (durvalumab) as concurrent and consolidative therapy or consolidative therapy alone for unresectable stage 3 NSCLC: A trial of the ECOG-ACRIN Cancer Research Group (EA5181). *First Author: John M. Varlotto, Edwards Comprehensive Cancer Center, Huntington, WV*

Background: Platinum-based concurrent chemoradiation(CRT) followed by one year of the human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody, durvalumab, which blocks the interaction of PD-L1 with its receptors PD-1 and CD80, is the standard of care for locally advanced, unresectable non-small cell lung cancer (NSCLC). Early studies have noted the feasibility of concomitant administration of radiotherapy and immune checkpoint inhibition in NSCLC. EA5181 will evaluate the use of concomitant durvalumab with chemo-radiotherapy for locally advanced NSCLC. **Methods:** EA5181 is a randomized, multi-center, phase III study for patients with unresectable Stage III NSCLC comparing the efficacy of CRT with concomitant durvalumab to CRT, followed by one year of durvalumab. Eligibility criteria include: an ECOG PS of 0-1, adequate pulmonary function (FEV1 and DLCO both > 40%), no history of auto-immune disease and no past chemotherapy or RT for this lung cancer. Stratification factors include age, sex, stage, and planned concurrent chemotherapy type. Eligible patients with be randomized 1:1 to receive 60Gy RT (2Gy fractions) CRT and durvalumab (Arm A) or 60Gy CRT (Arm B). Investigators will be allowed to choose from three different chemotherapy options: cisplatin/etoposide q 28 days, Pemetrexed/cisplatin q 21 days, and weekly paclitaxel/Carboplatin. Arm A will use 750mg fixed of durvalumab (considered equivalent to 10mg/kg) on days 1, 11, and 21 of RT. Assuming no disease progression, patients in both arms will be followed by monthly (q28 days) fixed dose of 1500mg durvalumab for one year which will be given optimally within 14 days of radiation or when (non)hematologic toxicity is < Grade 2. The primary endpoint is overall survival. Secondary endpoints include progression-free survival, incidence of local/distant progression and toxicity. The target sample size is 660 patients, anticipated to recruit over 55 months, with follow up for an additional 42 months. This provides approximately 82% power if the true hazard ratio for overall survival was 0.75 or less, with 2-sided alpha of 0.05, and assuming a median survival of 42.5 months in the control arm. The study was activated on 04/09/20 and has currently accrued 90 patients on 02/03/21. Clinical trial information: NCT04092283. Research Sponsor: Astra Zeneca.

TPS8585 **Poster Session**

Thoracic radiotherapy PLUS durvalumab in elderly and/or frail NSCLC stage III patients unfit for chemotherapy: Employing optimized (hypofractionated) radiotherapy to foster durvalumab efficacy—The TRADE-hypo trial. *First Author: Farastuk Bozorgmehr, Thoraxklinik at University Hospital Heidelberg, Heidelberg, Germany*

Background: Non-small cell lung cancer (NSCLC) is the most common cause of cancer death worldwide highlighting the importance of improving current therapeutic options. In particular, elderly and frail patients are not only underrepresented in clinical trials, but also frequently do not receive standard treatment regimens due to comorbidities. For example, patients with unresectable stage III NSCLC who are unfit for chemotherapy (CHT) do not benefit from the recent seminal therapy algorithm change for this disease, i.e. consolidation therapy with the immune checkpoint inhibitor (ICI) durvalumab after combined radiochemotherapy (RChT). Instead, these patients are treated with radiotherapy only, raising the serious concern of undertreatment. This issue is addressed by the TRADE-hypo clinical trial that investigates a novel therapy option for NSCLC stage III patients not capable of receiving CHT. To this end, thoracic radiotherapy (TRT) is administered together with durvalumab, employing the synergism created by the combination of restoring anti-tumor immune response by the ICI with the induction of immunogenicity by irradiation. The latter effect has been suggested to be further boosted by hypofractionated radiotherapy, which could also be more practicable for the patient. Taken these considerations into account, the TRADE-hypo trial addresses safety and efficacy of durvalumab therapy combined with either conventional or hypofractionated TRT. **Methods:** The TRADE-hypo trial is a prospective, randomized, open-label, multicentric phase II trial. Eligible patients are diagnosed with unresectable stage III NSCLC and not capable of receiving sequential RChT due to high vulnerability as reflected by a poor performance status (ECOG 2 or ECOG1 and CCI$\geq$ 1) and/or high age ($\geq$ 70)]. Two treatment groups are evaluated: Both receive durvalumab (1,5000 mg, Q4W) for up to 12 months. In the CON-group this is combined with conventionally fractionated TRT (30 x 2 Gy), while in the HYPO-group patients are treated with hypofractionated TRT (20 x 2.75 Gy). In the HYPO-arm, a safety stop-and-go lead-in phase precedes full enrollment. Here, patients are closely monitored with regard to toxicity (i.e., pneumonitis grade $\geq$ 3 within 8 weeks after TRT) in small cohorts of 6. The primary objective of the trial is safety and tolerability. As a primary efficacy endpoint, the objective response rate after 3 months will be evaluated. Further endpoints are additional parameters of safety and efficacy, as well as the comprehensive collection of biomaterials to be analyzed regarding treatment-induced changes and potential novel biomarkers. As of February 10, 2021, 9 patients of planned 88 patients have been enrolled in the TRADE-hypo trial. Clinical trial information: NCT04351256. Research Sponsor: AstraZeneca.

TPS8586 **Poster Session**

DREAM3R: Durvalumab with chemotherapy as first-line treatment in advanced pleural mesothelioma—A phase 3 randomized trial. *First Author: Patrick M. Forde, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: Standard first line treatment for unresectable malignant pleural mesothelioma (MPM) is platinum-based chemotherapy with pemetrexed. Two recent, single-arm, phase 2 trials (DREAM1 and PrE05052) combining the PD-L1 inhibitor durvalumab and standard first line cisplatin and pemetrexed (CP) exceeded pre-specified criteria for proceeding to phase 3. DREAM3R aims to determine the effectiveness of adding durvalumab to first line CP chemotherapy in advanced MPM. **Methods:** Treatment-naïve patients with advanced MPM will be randomised (2:1) to EITHER durvalumab 1500 mg every 3 weeks plus doublet chemotherapy (cisplatin 75 mg/m2 and pemetrexed 500 mg/m2) every 3 weeks for 4-6 cycles, followed by durvalumab 1500 mg every 4 weeks until disease progression, unacceptable toxicity or patient withdrawal; OR doublet chemotherapy alone for 4-6 cycles, followed by observation. The target sample size is 480 patients (320 durvalumab, 160 control) recruited over 27 months, with follow up for an additional 24 months. This provides over 85% power if the true hazard ratio for overall survival is 0.70, with 2-sided alpha of 0.05, assuming a median survival of 15 months in the control group. Key inclusion criteria: MPM of any histological subtype; measurable disease as per RECIST 1.1 modified for mesothelioma (mRECIST 1.1) without prior radiotherapy to these sites; ECOG PS 0-1; and, adequate hematologic, renal, and liver function tests. Key exclusion criteria: prior systemic anticancer treatment for MPM; diagnosis based only on cytology or fine needle aspiration biopsy; contraindication to immunotherapy; and conditions requiring immunosuppressives or corticosteroids. Stratification: Age (18-70 years vs. $>$ 70), sex, histology (epithelioid vs. non-epithelioid), and region (USA vs. ANZ). The primary endpoint is overall survival. Secondary endpoints include progression-free survival; objective tumour response (by mRECIST 1.1 and iRECIST); adverse events; health-related quality of life; and healthcare resource use. Tertiary correlative objectives are to explore and validate potential prognostic and/or predictive biomarkers (including features identified in the DREAM and PrE0505 studies, PD-L1 expression, tumour mutation burden, nuanced genomic characteristics, and HLA subtypes) in tissue and serial blood samples. An imaging databank will be assembled for validation of radiological measures of response, and studies of possible radiomic biomarkers in mesothelioma. Clinical trial information: NCT04334759. and ACTRN 12620001199909. Research Sponsor: AstraZeneca.

TPS8587 **Poster Session**

KEYLYNK-013: A phase 3 study of pembrolizumab in combination with concurrent chemoradiation therapy followed by pembrolizumab with or without olaparib versus concurrent chemoradiation therapy in patients with newly diagnosed limited-stage SCLC. *First Author: Andreas Rimner, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Concurrent chemoradiotherapy with etoposide and platinum (carboplatin/cisplatin) plus the anti–PD-1 antibody pembrolizumab (pembro) has shown antitumor activity and acceptable safety in patients with limited-stage small-cell lung cancer (LS-SCLC). The poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib, has shown clinical activity in combination with checkpoint inhibitors in patients with SCLC. KEYLYNK-013 (NCT04624204) is a randomized, placebo-controlled, double-blind phase 3 trial of pembro plus concurrent chemoradiation therapy followed by pembro with or without olaparib in patients with newly diagnosed LS-SCLC. **Methods:** Eligible patients are those aged $\geq$18 years with previously untreated LS-SCLC, ECOG PS 0/1, and adequate pulmonary function. Patients are randomized 1:1:1 to receive pembro 200 mg Q3W (groups A and B) or pembro placebo (saline) Q3W (group C) during the chemoradiation phase. All patients also receive 4 cycles of chemotherapy (etoposide 100 mg/m^2 on days 1, 2, and 3 of each cycle and investigator's choice of carboplatin AUC 5 mg/mL/min or cisplatin 75 mg/m^2 on day 1 of each cycle) with definitive thoracic radiotherapy (total dose of 45 Gy in 30 fractions twice daily over 3 weeks or 66 Gy in 33 fractions once daily over 6.5 weeks starting on day 1 of cycle 2). After chemoradiation, prophylactic cranial irradiation is strongly recommended for patients with CR/PR or at investigator's discretion for patients with SD. Postchemoradiation patients receive pembro 400 mg Q6W plus olaparib placebo (group A), or pembro 400 mg Q6W plus olaparib 300 mg BID (group B), or pembro placebo plus olaparib placebo (group C) for 9 cycles/12 months. Randomization is stratified by ECOG PS (0 vs 1), SCLC stage (I/II vs III), radiation fractionation (twice vs once daily), and region (east Asia vs North America/western Europe/UK/Australia vs rest of world). Tumor imaging occurs at baseline, within 12 weeks of cycle 1 day 1, followed by Q9W to the end of year 2, Q12W in year 3, Q16W in year 4, every 6 months in year 5, and annually thereafter. Imaging is assessed per RECIST v1.1 by blinded independent central review. AEs are monitored from randomization to 30 days after cessation of study treatment (90 days for serious AEs) and graded per NCI-CTCAE v5.0. Health-related quality of life is assessed using EORTC-QLQ-C30 and QLQ-LC13. Primary endpoints are OS and PFS per RECIST v1.1 by blinded independent central review. OS and PFS are estimated by the Kaplan-Meier method. Between-group differences will be evaluated with stratified log-rank tests and Cox proportional hazard models with Efron's method of tie handling. Secondary endpoints include ORR, duration of response, safety, and patient-reported outcomes. The study began enrollment in December 2020. Clinical trial information: NCT04624204. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

TPS8588 **Poster Session**

A phase I, open-label, dose-escalation trial of BI 764532, a DLL3/CD3 bispecific antibody, in patients (pts) with small cell lung carcinoma (SCLC) or other neuroendocrine neoplasms expressing DLL3. *First Author: Martin Wermke, Department of Thoracic Oncology, Carl-Gustav-Carus Dresden University Hospital, Dresden, Germany*

Background: First-line standard of care for pts with metastatic SCLC and neuroendocrine carcinoma (NEC) is platinum-based chemotherapy ± immunotherapy. While the addition of anti-PD1 antibodies has improved outcomes, nearly all pts relapse and prognosis is poor. There is a major unmet need for additional treatment (tx) options. BI 764532 is a delta-like ligand 3 (DLL3)/CD3 T cell engaging bispecific antibody. DLL3 is expressed on the cell surface of many SCLC and NEC tumors, but not on normal cells. In preclinical studies, BI 764532 induced cytotoxicity of DLL3-positive cells and showed anti-tumor activity in animal models. **Methods:** NCT04429087 is a first-in-human, open-label, dose-escalation trial of BI 764532 in adults with locally advanced/metastatic SCLC, large cell neuroendocrine lung carcinoma, NEC or small cell carcinoma of any other origin. Pts must have failed on or be ineligible for available standard therapies (including $\geq$1 line of platinum-based chemotherapy). Tumors must be positive for DLL3 expression (archived tissue/in-study fresh biopsy) according to central review. Pts must have $\geq$1 evaluable lesion (modified RECIST 1.1) outside of CNS and adequate liver, bone marrow and renal organ function. Main exclusion criteria: previous tx with T cell engagers or DLL3-targeted therapies; persistent toxicity from previous tx that has not resolved to $\leq$ CTCAE grade 1; immunodeficiency or receiving immunosuppressive therapy $\leq$7 days, prior anti-cancer therapy $\leq$3 wks/5 half-life periods or extensive field radiotherapy $\leq$2 wks of first dose of BI 764532. The main objective of phase Ia is to determine the maximum tolerated dose (MTD) or recommended dose for expansion of BI 764532, based on dose-limiting toxicities during the MTD evaluation period. Further objectives are to evaluate safety, tolerability, PK/PD and preliminary efficacy. The phase Ib objectives, endpoints and design will be specified after availability of phase Ia results. The trial will assess $\leq$3 dosing regimens: Regimen A (fixed iv dose once every 3 wks); Regimen B1 (fixed iv dose once every wk); Regimen B2 (step-in dose[s] followed by fixed-dose weekly doses; optional). Tx will continue until confirmed progressive disease, unacceptable toxicity, other withdrawal criteria or a maximum tx duration of 36 mos, whichever occurs first. For Phase Ia, ~160 pts will be screened and 110 pts accrued. As of Feb 2021, pts are being recruited and treated in early dose escalation cohorts. Clinical trial information: NCT04429087. Research Sponsor: Boehringer Ingelheim.

TPS8589 **Poster Session**

Trial in progress: A multicenter phase Ib/II study of pelcitoclax (APG-1252) in combination with paclitaxel in patients with relapsed/refractory small-cell lung cancer (R/R SCLC). *First Author: Angel Qin, University of Michigan, Ann Arbor, MI*

Background: Increased expression of BCL-2, BCL-xL, and MCL-1 allows certain tumors to evade apoptosis. Pelcitoclax is a novel, dual BCL-2/BCL-xL inhibitor with strong single-agent antitumor activity against tumor cells addicted to BCL-2, BCL-xL, and BCL-w, and exhibits even broader antitumor activity when administered with chemotherapy. Pelcitoclax reduces tumor growth in SCLC and other human cancer xenograft models, with manageable effects on platelet counts. Preliminary findings from the first-in-human study suggested promising antitumor activity and a favorable safety profile. **Methods:** This open-label study is evaluating the safety and preliminary efficacy of pelcitoclax combined with paclitaxel in adults with R/R SCLC that has progressed on or after initial treatment. Prior treatments may include platinum-based therapy (± thoracic radiation), immunotherapy, or chemotherapeutic agents other than paclitaxel. Eligible patients have an ECOG performance status of 0-2; adequate organ function; no known bleeding diathesis, immune thrombocytopenic purpura, autoimmune hemolytic anemia, serious gastrointestinal bleeding, or concomitant use of most anticoagulants; and no residual grade ≥ 2 adverse events from previous treatment. In the phase Ib study, the pelcitoclax maximum tolerated dose is being determined using a time-to-event continual reassessment method. In this phase, pelcitoclax is administered by IV infusion over 30 minutes on Days 1, 8, and 15 at dose levels of 80, 160, and 240 mg per week, with fixed-dose paclitaxel 80 mg/m^2 on Days 1 and 8 of a 21-day cycle. In addition to a baseline scan within 4 weeks before study entry, computed tomography will be performed every two cycles to evaluate antitumor response. Treatment will continue until disease progression, unacceptable toxicity, consent withdrawal, or administrative discontinuation. The primary endpoint of this phase includes dose-limiting toxicity by NCI CTCAE v5.0 over 21 days. After determination of the recommended phase II dose of pelcitoclax in the phase Ib study, the efficacy of pelcitoclax with paclitaxel will be determined in the phase II study using a Simon two-stage design, with overall response rate as the primary endpoint. Other study endpoints in the phase II study include pharmacokinetics of pelcitoclax with paclitaxel, as well as progression-free and overall survival. As of February 8, 2021, 15 of 58 patients had been enrolled. Internal study identifier APG1252SU101. Clinical trial information: NCT04210037. Research Sponsor: Ascentage Pharma Group Corp Limited (Hong Kong).

9000 **Oral Abstract Session**

First-line nivolumab (NIVO) plus ipilimumab (IPI) plus two cycles of chemotherapy (chemo) versus chemo alone (4 cycles) in patients with advanced non-small cell lung cancer (NSCLC): Two-year update from CheckMate 9LA.

First Author: Martin Reck, Airway Research Center North, German Center for Lung Research, LungClinic, Grosshansdorf, Germany

Background: In the randomized phase 3 CheckMate 9LA trial (NCT03215706), first-line NIVO + IPI combined with 2 cycles of chemo significantly improved overall survival (OS), progression-free survival (PFS), and objective response rate (ORR) vs chemo alone (4 cycles). Clinical benefit was observed regardless of programmed death ligand 1 (PD-L1) expression level and histology. Here we report data with 2 years' minimum follow-up from this study. **Methods:** Adult patients (pts) with stage IV / recurrent NSCLC, ECOG performance status ≤ 1, and no known sensitizing *EGFR/ALK* alterations were stratified by PD-L1 (< 1% vs ≥ 1%), sex, and histology (squamous vs non-squamous) and were randomized 1:1 to NIVO 360 mg Q3W + IPI 1 mg/kg Q6W + chemo (2 cycles; n = 361) or chemo alone (4 cycles; n = 358). Pts with non-squamous NSCLC in the chemo-alone arm could receive pemetrexed maintenance. The primary endpoint was OS. Secondary endpoints included PFS and ORR by blinded independent central review, and efficacy by different PD-L1 levels. Safety was exploratory. **Results:** At a minimum follow-up of 24.4 months for OS (database lock: Feb 18, 2021), pts treated with NIVO + IPI + chemo continued to derive OS benefit vs chemo, with a median OS of 15.8 months vs 11.0 months, respectively (HR, 0.72 [95% CI, 0.61–0.86]); 2-year OS rates were 38% vs 26%. Median PFS with NIVO + IPI + chemo vs chemo was 6.7 months vs 5.3 months (HR, 0.67 [95% CI, 0.56–0.79]); 8% and 37% of pts who had disease progression received subsequent immunotherapy, respectively. ORR was 38% with NIVO + IPI + chemo vs 25% with chemo. Similar clinical benefit with NIVO + IPI + chemo vs chemo was observed in all randomized pts and across the majority of subgroups, including by PD-L1 expression level (Table) or histology. Any grade and grade 3–4 treatment-related adverse events were reported in 92% and 48% of pts in the NIVO + IPI + chemo arm vs 88% and 38% in the chemo arm, respectively. **Conclusion:** With 2 years' minimum follow-up, first-line NIVO + IPI + chemo demonstrated durable survival and benefit versus chemo in pts with advanced NSCLC; no new safety signals were identified. Clinical trial information: NCT03215706. Research Sponsor: Bristol Myers Squibb.

9001 **Oral Abstract Session**

Outcomes of anti-PD-(L1) therapy in combination with chemotherapy versus immunotherapy (IO) alone for first-line (1L) treatment of advanced non-small cell lung cancer (NSCLC) with PD-L1 score 1-49%: FDA pooled analysis.

First Author: Oladimeji Akinboro, U.S. Food and Drug Administration, Silver Spring, MD

Background: IO + chemotherapy ± anti-angiogenics comprise FDA-approved 1L regimens for metastatic NSCLC, with IO-only therapy approved only for PD-L1-positive NSCLC. Patients with PD-L1 scores 1-49% have many therapeutic options, and little is known about how subgroups of patients experience benefit across treatment regimens. **Methods:** Data was pooled from 8 randomized controlled trials investigating anti-PD-(L)1 therapy as IO-only or in chemo-IO regimens for the 1L treatment of patients with advanced NSCLC. PD-L1 score was defined as the proportion of tumor cells stained by the assay, and analysis was conducted for patients whose tumors had PD-L1 score 1-49%. Tumor-infiltrating immune cell staining was not considered. OS and PFS were compared between chemo-IO and IO alone via a pooled analysis. Median survival times were estimated using Kaplan-Meier methods. Hazard ratios were estimated using Cox proportional hazards models stratified by trial and adjusted for age, sex, race, ECOG, histology and smoking status. **Results:** A total of 2108 patients with NSCLC and PD-L1 score 1-49% were identified for this analysis. Baseline characteristics were: 37% aged 65-74 years and 12% aged ≥75; 67% male; 79% white; 65% ECOG ≥ 1; and 85% smokers. Median follow-up was 12.1 months. This pooled analysis showed that patients receiving chemo-IO (N=639) had longer PFS and OS compared to patients treated with IO alone (N=529), with median PFS 7.7 vs 4.2 months (HR 0.60; 95% CI 0.48, 0.76) and median OS 21.4 vs 14.5 months (HR 0.68; 95% CI 0.52, 0.90). All results presented are considered exploratory and hypothesis generating. **Conclusions:** This exploratory pooled analysis suggests that chemo-IO may improve efficacy outcomes over IO alone in most subgroups of patients with advanced NSCLC with PD-L1 score 1-49%. Patients 75 and over experienced similar outcomes across therapeutic options. Research Sponsor: None.

Efficacy outcomes of Chemo-IO vs. IO alone by subgroup.

	Subgroup	N[1]	Median OS in months	OS HR[2] (95% CI)	Median PFS in months	PFS HR[2] (95% CI)
Age	<65	580	23.7 vs 16.1	0.63 (0.43, 0.92)	7.1 vs 4.0	0.55 (0.40, 0.76)
	65-74	443	22.5 vs 14.8	0.61 (0.38, 0.97)	9.5 vs 4.5	0.60 (0.40, 0.88)
	≥75	132	13.9 vs 10.3	0.95 (0.42, 2.14)	6.4 vs 4.9	0.85 (0.42, 1.71)
ECOG	0	415	25.2 vs 20.0	0.65 (0.38, 1.10)	9.6 vs 5.8	0.57 (0.38, 0.86)
	1+	751	16.8 vs 11.0	0.68 (0.50, 0.94)	7.0 vs 4.0	0.65 (0.49, 0.86)
Smoking	Never	160	28.2 vs 18.0	0.57 (0.22, 1.46)	8.1 vs 4.1	0.44 (0.21, 0.92)
	Ever	1005	20.8 vs 13.5	0.68 (0.51, 0.91)	7.6 vs 4.2	0.62 (0.49, 0.80)

[1]Number of patients in the chemo-IO and IO-only arms of all trials [2]Comparisons utilized chemotherapy as the control arm.

9002 **Oral Abstract Session**

Pooled analyses of immune-related adverse events (irAEs) and efficacy from the phase 3 trials IMpower130, IMpower132, and IMpower150.

First Author: Mark A. Socinski, AdventHealth Cancer Institute, Orlando, FL

Background: PD-L1/PD-1 inhibitors have transformed the treatment (tx) of advanced NSCLC. Evidence suggests that the occurrence of irAEs with these agents may predict improved outcomes in cancers such as NSCLC. Atezolizumab (atezo; anti–PD-L1) has shown efficacy and tolerability in NSCLC and is currently approved in the 1L and 2L+ settings. The Ph 3 IMpower130, IMpower132 and IMpower150 trials evaluated atezo + chemo ± bevacizumab (bev) as 1L tx of NSCLC. We explore the association between irAEs and efficacy in these trials. **Methods:** Each trial enrolled tx-naive patients (pts) with nonsquamous stage IV NSCLC. Pts were randomized to: carboplatin (carbo) + *nab*-paclitaxel alone or with atezo in IMpower130; carbo or cisplatin alone or with atezo in IMpower132; atezo (A) + bev (B) + carbo + paclitaxel (CP), ACP or BCP in IMpower150. Data were pooled (data cutoffs: Mar 15 2018 [IMpower130]; May 22 2018 [IMpower132]; Sep 13 2019 [IMpower150]) and analyzed by tx (atezo-containing vs control) and irAE status. A time-dependent Cox model and landmark analyses at 1, 3, 6 and 12 mo were used to control for immortal bias. Study protocols required atezo tx interruption/discontinuation for grade (Gr) ≥3 irAEs. **Results:** 2503 pts were included in the analysis (atezo, n = 1577; control, n = 926). In both arms, baseline characteristics were generally balanced between pts with irAEs (atezo, n = 753; control, n = 289) and without irAEs (atezo, n = 824; control, n = 637). Any-Gr irAEs occurred in 48% (atezo) and 32% (control) of pts; Gr 3-5 irAEs occurred in 11% (atezo) and 5% (control). The most common irAEs (atezo vs control) were rash (28% vs 18%), hepatitis (lab abnormalities; 15% vs 10%) and hypothyroidism (12% vs 4%). Median time to onset of first irAE was 1.7 (atezo) vs 1.4 mo (control). OS HRs (95% CI) from the time-dependent Cox model between pts with vs without irAEs were 0.69 (0.60, 0.78) in the atezo arm and 0.82 (0.68, 0.99) in the control arm; after excluding rash (perceived as the least specific irAE), OS HRs (95% CI) were 0.75 (0.65, 0.87) and 0.90 (0.71, 1.12), respectively. OS landmark data are in the Table. **Conclusions:** In this exploratory pooled analysis, pts with irAEs had longer OS vs pts without irAEs in the atezo-containing and control arms per the time-dependent Cox model and landmark analyses; this trend remained for the atezo arm after excluding rash. Landmark analyses suggest that in the atezo arm, pts with Gr 1/2 irAEs had the longest OS and pts with Gr ≥3 irAEs had the shortest OS, potentially due to tx interruption/discontinuation. Clinical trial information: NCT02367781; NCT02657434; NCT02366143. Research Sponsor: F. Hoffmann-La Roche, Ltd.

Landmark	Atezo with irAE	Atezo with Gr 1/2 irAE	Atezo with Gr 3-5 irAE	Atezo without irAE	Control with irAE	Control without irAE
	n mOS, mo	n mOS, mo	n mOS, mo	n mOS, mo	n mOS, mo	n mOS, mo
1 mo	305	247	58	1210	116	764
	22.2	23.8	11.3	18.9	19.3	14.3
3 mo	451	370	81	963	180	625
	23.1	24.8	16.6	19.6	19.1	16.0
6 mo	532	431	101	736	197	498
	25.6	26.6	21.5	22.4	21.8	19.3
12 mo	519	428	91	455	175	329
	32.7	33.4	29.9	27.5	31.8	25.5

9003 **Oral Abstract Session**

Overall survival and exploratory subgroup analyses from the phase 2 CodeBreaK 100 trial evaluating sotorasib in pretreated *KRAS* p.G12C mutated non-small cell lung cancer.

First Author: Ferdinandos Skoulidis, The University of Texas MD Anderson Cancer Center, Cambridgeshire, United Kingdom

Background: In the registrational phase 2 CodeBreaK 100 trial, sotorasib demonstrated an objective response rate (ORR) of 37.1% (95% CI: 28.6, 46.2) and a median progression-free survival (PFS) of 6.8 months (95% CI: 5.1, 8.2) in patients with pretreated *KRAS* p.G12C mutated non-small cell lung cancer (NSCLC). Tumor response was observed in patients bearing co-mutations in *STK11*, a driver of poor clinical outcomes with standard of care. Here, we report efficacy across an extended set of patient subgroups by key baseline characteristics and biomarkers. **Methods:** Sotorasib was given orally at 960 mg once daily to eligible patients who had advanced NSCLC harboring *KRAS* p.G12C and received prior standard therapies. Primary endpoint was ORR assessed by central review. Key secondary endpoints included PFS, overall survival, and safety. *KRAS* p.G12C mutant allele frequency (MAF) and tumor mutational burden (TMB) were analyzed by next-generation sequencing (NGS) using tissue samples. Mutational status of individual genes was determined by NGS using tissue and/or plasma samples. Correlations between response and *KRAS* p.G12C MAF, TMB, or co-mutations were analyzed in subsets of patients who had available respective results. Association between MAF and response was reported by odds ratio (95% CI), from a logistic regression with dependent variable of log odds of being a responder and an independent variable of MAF in a unit of 10%. **Results:** ORR across subgroups is presented in the Table. Response was independent of *KRAS* p.G12C MAF in the study population (odds ratio [95% CI]: 1.11 [0.88, 1.39]). OS remained immature. **Conclusions:** In the exploratory analyses of the phase 2 CodeBreaK 100 trial, the clinical benefit of sotorasib was observed across patient subgroups. Overall survival and updated exploratory analyses will be presented. Clinical trial information: NCT03600883. Research Sponsor: Amgen Inc.

Subgroups (n)	ORR % (95% CI)
Total patients evaluable (N = 124)	37.1 (28.6, 46.2)
Age	
< 65 years (65)	30.8 (19.9, 43.4)
≥ 65 years (59)	44.1 (31.2, 57.6)
ECOG PS status	
0 (37)	43.2 (27.1, 60.5)
1 (87)	34.5 (24.6, 45.4)
Metastatic disease	
Yes (120)	36.7 (28.1, 45.9)
No (4)	50.0 (6.8, 93.2)
Prior lines of therapy	
1 (53)	39.6 (26.5, 54.0)
≥2 (71)	35.2 (24.2, 47.5)
Prior anti-PD-1 or PD-L1	
Yes (113)	36.3 (27.4, 45.9)
No (11)	45.5 (16.7, 76.6)
***TP53* co-mutation**	
Wild-type (20)	40.0 (19.1, 63.9)
Mutant (84)	39.3 (28.8, 50.5)
***STK11* co-mutation**	
Wild-type (69)	39.1 (27.6, 51.6)
Mutant (35)	40.0 (23.9, 57.9)
***KEAP1* co-mutation**	
Wild-type (84)	44.0 (33.2, 55.3)
Mutant (20)	20.0 (5.7, 43.7)
TMB level	
Low, < 10 Mut/Mb (69)	42.0 (30.2, 54.5)
High, ≥ 10 Mut/Mb (15)	40.0 (16.3, 67.7)

9004 **Oral Abstract Session**

Biomarker tissue journey among patients (pts) with untreated metastatic non-small cell lung cancer (mNSCLC) in the U.S. Oncology Network community practices. *First Author: Nicholas J. Robert, Ontada, Irving, TX*

Background: Given the importance of molecular testing and targeted therapy for mNSCLC, the MYLUNG (Molecularly Informed Lung Cancer Treatment in a Community Cancer Network) consortium pragmatic study assessed real-world biomarker testing rates and turnaround times (TAT) within The US Oncology Network of over 1,000 providers across the United States. **Methods:** This was a retrospective observational chart review study of pts with mNSCLC initiating first-line (1L) systemic therapy between 04/01/2018 and 03/31/2020. iKnowMed electronic health records were used to examine timing of biomarker testing: before 1L therapy (cohort 1), after 1L therapy (cohort 2) or no testing (cohort 3). We assessed testing rates for ALK, BRAF, EGFR, ROS1, and PD-L1; use of full next-generation sequencing panel (NGS); time from mNSCLC diagnosis (dx) to 1L therapy; TAT from biomarker orders to results; and time from mNSCLC dx to test results. **Results:** We identified 3474 adults. Median age was 69 years (range 23-90), 51% female, 74% with adenocarcinoma and 76% with a documented ECOG performance status of 0 or 1. Testing rates are shown in table: 90% of pts had at least one biomarker test and 46% received all 5 biomarker tests. Changes in testing rates from 2018 to 2020 were 51% to 59% for BRAF, 71% to 71% for EGFR, 71% to 70% for ALK, 69% to 67% for ROS1, 82% to 84% for PD-L1, and 42% to 49% for pts tested for all 5 biomarkers. NGS testing increased from 33% to 44% ($p<0.0001$). The median (interquartile range [IQR]) time from mNSCLC dx to 1L therapy for all pts was 35 (22, 55) days. Median (IQR) TAT from biomarker testing orders to results ranged from 10 (6, 17) to 15 (10, 22) days for the individual biomarkers; and time from mNSCLC dx to biomarker results ranged from 14 (7, 26) to 21 (12, 36) days by biomarker. **Conclusions:** This real-world study showed that most pts received at least one biomarker test prior to 1L, but <50% received all 5 tests. NGS testing occurred in <50% of pts but increased over the periods examined. Median time from dx to 1L therapy was about 5 weeks and TAT from orders to results about 2 weeks. Analyses by histology and other trends will be reported. These data will be compared to the next phase of the MYLUNG study, which will evaluate contemporary ordering practices and TATs prospectively Research Sponsor: Amgen Inc.; Mirati Therapeutics, Inc.; Eli Lilly and Company.

	Total Patients	Cohort 1 biomarker test result received prior to 1L	Cohort 2 biomarker test result received during/after 1L	Cohort 3 no biomarker test
Overall n (%)[a]	3474	2752 (79)	371 (11)	351 (10)
Any biomarker test[b]	3123	2752 (88)	371 (12)	NA
All 5 biomarker tests[b]	1602	1230 (77)	372 (23)	NA
Biomarker testing, n (%)[a]				
ALK	2446	1986 (57)	460 (13)	1028 (30)
BRAF	1912	1489 (43)	423 (12)	1562 (45)
EGFR	2443	1979 (57)	464 (13)	1031 (30)
PD-L1	2882	2526 (73)	356 (10)	592 (17)
ROS1	2348	1897 (55)	451 (13)	1126 (32)

[a]Row percentage denominator: 3474 [b]Row percentage denominator: total patients with test.

9005 **Oral Abstract Session**

Racial disparities in biomarker testing and clinical trial enrollment in non-small cell lung cancer (NSCLC). *First Author: Debora S. Bruno, The MetroHealth System, Cleveland, OH*

Background: Cancer racial disparities may exist at many levels in the health care system, from screening to timely diagnosis and treatments received, as well as clinical trial enrollment. This study investigated differences in black versus white race among patients with NSCLC undergoing biomarker testing and clinical trial enrollment in the US. **Methods:** This retrospective observational study utilized the Flatiron Health database, which includes longitudinal data of patients with advanced/metastatic NSCLC. Patients were eligible if they had evidence of systemic therapy in the database from 1/1/2017 through 10/30/2020. Descriptive analyses summarized differences by race in biomarker testing and trial enrollment. Multivariable regression examined the relationship between these factors. **Results:** A total of 14,768 patients were eligible: 9,793 (66.3%) were white and 1,288 (8.7%) were black. 76.4% of white patients and 73.6% of black patients underwent at least one single molecular test or comprehensive genomic analysis ($p = 0.03$). Next-generation sequencing (NGS) was performed among 50.1% of white patients and 39.8% of black patients ($p < 0.0001$. Trial participation was observed among 3.9% of white and 1.9% of black patients ($p = 0.0002$). There was a statistically significant association between race (white vs black) and both biomarker testing (ever vs never) and trial participation (yes vs no) (both $p < 0.001$, unadjusted chi square). Differences in NGS testing, baseline biomarker testing, and race were retained as statistically significant ($p < 0.01$) in adjusted regression analyses. The receipt of first-line targeted therapy was comparable between white and black patients (10.2% and 9.2%, respectively, $p = 0.24$); however, this summary did not consider biomarker test results. First line use of pembrolizumab+carboplatin+pemetrexed was observed among 19.8% of white and 22.6% of black patients; carboplatin+paclitaxel was observed among 16.5% and 18.6%, and single-agent pembrolizumab was observed among 14.8% and 11.5%, respectively. **Conclusions:** The use of NGS-based testing, which is recommended by the National Comprehensive Cancer Network Clinical Guidelines in Oncology for patients with advanced/metastatic NSCLC, is the most notable disparity among black patients, with more than a 10 percentage-point difference in receipt of this testing versus white counterparts. This may in part contribute to the more than double the rate of participation in clinical trials observed among white patients, as many second line and beyond trials utilize molecular targets as inclusion criteria. While multiple factors are known to impact health care disparities, access to and receipt of appropriate biomarker testing may be an attenable goal in order to ensure equal access to quality care. Research Sponsor: None.

9006 **Oral Abstract Session**

Amivantamab in combination with lazertinib for the treatment of osimertinib-relapsed, chemotherapy-naïve EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC) and potential biomarkers for response. *First Author: Joshua Bauml, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA*

Background: Preliminary efficacy was observed with the combination of amivantamab, an EGFR-MET bispecific antibody, and lazertinib, a 3rd-generation tyrosine kinase inhibitor, in both treatment-naïve and osimertinib (osi)-relapsed patients (pts) with EGFRm NSCLC (Cho *Ann Oncol* 2020;31:S813). We present updated results of the combination in osi-relapsed pts, including an analysis of potential biomarkers of response. **Methods:** Pts with EGFR exon 19 deletion or L858R mutation NSCLC, who had progressed on osi without intervening chemotherapy, were enrolled in the combination cohort of the ongoing CHRYSALIS study (NCT02609776). With pre-treatment tumor biopsies and ctDNA collected prospectively, pts received the combination dose of 1050/1400 mg amivantamab + 240 mg lazertinib to assess safety and efficacy in the osi-relapsed population. Response was assessed by investigator per RECIST v1.1. Osi-resistance mutations or amplifications in EGFR/MET identified by next-generation sequencing (NGS) in either ctDNA or tumor biopsy (biomarker-positive [pos]), were evaluated for enriching response. Immunohistochemistry (IHC) staining for EGFR and MET expression was also explored as a potential biomarker for response. **Results:** Of the 45 osi-relapsed pts, 36% (95% CI, 22–51) had a confirmed response (1 complete response and 15 partial responses [PR]). At a median follow-up of 8.2 mo (1.0–11.8), 20/45 pts (44%) remain on treatment. With 11/16 pts (69%) continuing in response (2.6–9.6+ mo), median duration of response has not been reached (NR). The median progression-free survival (mPFS) was 4.9 mo (95% CI, 3.7–8.3). In total, 44/45 pts were evaluable by ctDNA and 29/45 by tumor NGS. Genetic testing identified 17 biomarker-pos pts, of whom 8 (47%) responded. Of the remaining 28 pts, 8 (29%) responded. Among these 28 pts, 18 had unknown mechanisms of osi-resistance (8 PR) and 10 had non-EGFR/MET mechanisms of resistance identified (none responded). The mPFS (95% CI) for biomarker-pos and remaining pts was 6.7 mo (3.4–NR) and 4.1 mo (1.4–9.5), respectively. Adequate tissue was available for 20 pts to perform IHC testing for EGFR and MET–9/10 (90%) IHC high (combined EGFR+MET H score>400) pts responded to treatment, while 1/10 IHC low pts responded to treatment. **Conclusions:** Treatment with the combination of amivantamab and lazertinib yielded responses in 36% of chemotherapy-naïve pts who progressed on osi. Among these pts, genetic EGFR and MET-based biomarkers of resistance identified a subgroup of pts more likely to respond to amivantamab and lazertinib, although additional pts lacking identified resistance markers also responded. An IHC-based approach may identify pts most likely to benefit from the combination regimen, but further investigation is warranted. Clinical trial information: NCT02609776. Research Sponsor: Janssen R&D, LLC.

9007 **Oral Abstract Session**

Efficacy and safety of patritumab deruxtecan (HER3-DXd) in EGFR inhibitor-resistant, *EGFR*-mutated (*EGFR*m) non-small cell lung cancer (NSCLC). *First Author: Pasi A. Janne, Dana-Farber Cancer Institute, Boston, MA*

Background: Patients (pts) with advanced *EGFR*m NSCLC have limited treatment options after failure of EGFR TKI and platinum-based chemotherapy (PBC). HER3-DXd is an antibody drug conjugate consisting of a fully human monoclonal antibody to HER3 attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. We previously presented efficacy/safety data (median follow-up, 5.4 mo) from an ongoing study of HER3-DXd in *EGFR*m NSCLC after failure of EGFR TKI therapy. We now present extended follow-up of pts receiving the recommended dose for expansion (5.6 mg/kg IV Q3W). **Methods**: This Ph 1 dose-escalation/expansion study included pts with locally advanced or metastatic *EGFR*m NSCLC with prior EGFR TKI therapy (NCT03260491). Pts with stable brain metastases (BM) were allowed. The primary endpoint was confirmed ORR by blinded independent central review (BICR) per RECIST v1.1; secondary endpoints included DOR, PFS and safety. **Results**: At data cutoff (Sept 24, 2020), 57 pts were treated with HER3-DXd 5.6 mg/kg IV Q3W; median follow-up, 10.2 mo (range, 5.2-19.9 mo). Median number of prior anticancer regimens was 4 (range, 1-10). 100% had prior EGFR TKI (86% prior osimertinib [OSI]) and 91% had prior PBC. 47% had a history of BM. Median treatment duration was 5.5 mo (range, 0.7-18.6 mo); treatment was ongoing in 18 pts (32%). Confirmed ORR by BICR was 39% (22/57; 95% CI, 26.0%-52.4%; 1 CR, 21 PR, 19 SD) with 14/22 responses occurring within 3 mo of starting HER3-DXd. DCR was 72% (95% CI, 58.5%-83.0%). Median DOR was 6.9 mo (95% CI, 3.1 mo-NE), and median PFS was 8.2 mo (95% CI, 4.4-8.3 mo). Antitumor activity was observed across diverse mechanisms of EGFR TKI resistance, including those not directly related to HER3 (*EGFR* C797S, MET or HER2 amp, and BRAF fusion). Among pts with prior PBC, ORR was 37% (19/52; 95% CI, 23.6%-51.0%); in pts with prior OSI and PBC, ORR was 39% (17/44; 95% CI, 24.4%-54.5%). Among 43 pts evaluable for HER3 expression, nearly all expressed HER3; median membrane H-score by IHC was 180 (range, 2-280). Median H-score (range; N) was 195 (92-268; 15) in pts with CR/PR, 180 (4-280; 15) with SD, 126.5 (2-251; 6) with PD, and 180 (36-180; 7) in pts unevaluable for best overall response. The most common grade ≥3 adverse events (AEs) were thrombocytopenia (30%), neutropenia (19%), and fatigue (14%). Drug-related interstitial lung disease by central adjudication occurred in 4 pts (7%; 1 grade ≥3 [2%]; no grade 5). 6/57 pts (11%) had AEs associated with treatment discontinuation (none were due to thrombocytopenia). **Conclusions**: HER3-DXd 5.6 mg/kg IV Q3W demonstrated antitumor activity across various EGFR TKI resistance mechanisms in heavily pretreated metastatic/locally advanced *EGFR*m NSCLC. The safety profile was consistent with previous reports. A Ph 2 study of HER3-DXd in pts with *EGFR*m NSCLC after failure of EGFR TKI and PBC has been initiated (NCT04619004). Clinical trial information: NCT03260491. Research Sponsor: Daiichi Sankyo, Inc.

9008 **Oral Abstract Session**

Preliminary safety and efficacy results from phase 1 studies of DZD9008 in NSCLC patients with EGFR Exon20 insertion mutations. *First Author: James Chih-Hsin Yang, National Taiwan University Hospital and National Taiwan University Cancer Center, Taipei, Taiwan*

Background: There are no approved targeted therapies for EGFR exon20 insertion (exon20ins) mutant NSCLC. DZD9008 is a rationally designed selective, irreversible EGFR exon20ins inhibitor being studied in two ongoing phase 1/2 studies (NCT03974022 and CTR20192097). **Methods:** The objectives of the studies are to assess the safety, tolerability, pharmacokinetics, and preliminary anti-tumor efficacy of DZD9008 in NSCLC with EGFR or HER2 mutations. Both studies include dose escalation and expansion cohorts. Pooled analysis is applied to define recommended phase 2 dose (RP2D). **Results:** Between July 9, 2019 and February 5, 2021, 97 NSCLC patients with EGFR or HER2 mutations were dosed with DZD9008 (dose range: 50 mg to 400 mg, once daily). M/F: 44/53; 59 with EGFR exon 20. DZD9008 was well tolerated up to 400 mg (MTD) once daily. The DLTs were diarrhea and cardiac arrhythmia. The most common TEAEs were diarrhea (grade 3, 5.2%) and skin rash (grade 3, 1%). DZD9008 showed approximately dose-proportional PK, with a half-life of around 50 hours. Fifty-six patients with $>$ 16 different EGFR exon20ins mutations had $>$ 1 post-treatment efficacy assessment. Prior therapies: median 2 (range 1 - 10), prior chemotherapy 92.9% (52/); prior TKI 44.6% (25/56) including 1 patient had poziotinib treatment; 42.9% (24/56) with brain metastasis. Partial response was observed at $\geq$ 100 mg dose levels. At the RP2D dose of 300 mg once daily, the objective response rate was 48.4% (15/31), and disease control rate (DCR) was 90.3% (28/31). Responses were observed in 2 patients with prior JNJ-61186372 treatment. Anti-tumor activity was observed across different EGFR exon20ins mutation subtypes. By data cut-off, the median treatment duration was 100 days (range 1 – 422). The longest duration of response was over 6 months, and 18 out of 22 responders are still responding. **Conclusions:** DZD9008 showed a favorable safety profile and promising anti-tumor efficacy in pre-treated NSCLC with EGFR exon20ins mutations. The updated data will be presented at the meeting. DZD9008 is currently in phase II clinical development (NCT03974022). Clinical trial information: NCT03974022. Research Sponsor: Dizal pharma.

9009 **Clinical Science Symposium**

Overall survival with circulating tumor DNA-guided therapy in advanced non-small cell lung cancer. *First Author: Justin Jee, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The effectiveness of circulating tumor DNA (ctDNA) at matching patients to life prolonging therapy has been studied mostly in small cohorts with limited follow up. The prognostic value of ctDNA alterations, particularly those absent on tissue, is also unclear. To address these questions, we studied survival outcomes in a prospective cohort of patients (N = 1002) with non-small cell lung cancer (NSCLC). **Methods:** Adults with metastatic or recurrent NSCLC were eligible if they had no known driver mutation or a known driver with progression following targeted therapy. Patients were enrolled at Memorial Sloan Kettering Cancer Center (New York, NY) starting October 21, 2016; analysis here is from a snapshot November 1, 2020. All patients had ctDNA sequenced via the Resolution ctDx Lung platform. To reduce inclusion of incidental germline mutations, we excluded non-functionally significant mutations with an allele frequency 35-65% that were present in gnomAD. Patients could also receive, at their provider's discretion, tissue sequencing with MSK-IMPACT, which filters germline and clonal hematopoietic (CH) mutations with matched white blood cell sequencing. We performed survival analyses using Cox proportional hazards models from time of diagnosis of advanced disease to death, left truncating at time of study entry. **Results:** Of 1002 patients, 348 (35%) were treated with targeted therapy; in 181 of these (52%) the targetable alteration was detected in ctDNA. Patients treated with targeted therapy had prolonged survival whether matched by tissue-based methods (HR 0.39, 95%CI 0.30-0.51) or ctDNA (HR 0.47, 95%CI 0.37-0.61). These benefits persisted across multiple subgroups. ctDNA alterations themselves were associated with worse survival (HR 2.2, 95%CI 1.8-2.8), in a manner that scaled with allele fraction and burden. Of 401 patients with time-matched tissue sampling, 62 (15%) had ctDNA alterations that were absent on IMPACT ("unique" ctDNA alterations). Three such patients had unique ctDNA EGFR T790M mutations leading to changes in therapy. However, unique ctDNA alterations were generally associated with worse survival than no ctDNA alterations (HR 2.5, 95%CI 1.7-3.7) and even tissue-matched ctDNA alterations (HR 1.7, 95%CI 1.1-2.4). Of 98 unique ctDNA mutations, 48 (49%) were detectable in tissue at subthreshold levels, 12 (12%) were filtered by IMPACT as CH or germline, and 38 mutations (39%) were absent even at subthreshold levels. ctDNA alteration burden correlated with radiographic disease extent. In multivariate models with radiographic disease extent and other clinical variables, ctDNA alterations were the strongest independent predictor of worse survival. **Conclusions:** Our results show that ctDNA may match patients to life-prolonging targeted therapy and have prognostic importance. ctDNA may provide data about a patient's cancer missed by spatially restricted tissue sequencing. Clinical trial information: NCT01775072. Research Sponsor: U.S. National Institutes of Health.

9010 **Poster Session**

Concordance of tissue- and plasma-derived genomic profiling in CheckMate 9LA, using the FoundationOne CDx and GuardantOMNI assays. *First Author: Jonathan F. Baden, Bristol Myers Squibb, Princeton, NJ*

Background: Blood-based profiling of genomic features including tumor mutational burden (TMB) has generally demonstrated positive correlations with tissue-derived assessments from paired tumor samples. However, both technical and biological factors contributing to discordance between these measurements and underlying sequence alterations need further investigation for the successful adoption of noninvasive tumor profiling. We explored the genomic landscape, including the association between tissue TMB (tTMB) and blood TMB (bTMB), in samples from patients with stage IV non-small cell lung cancer (NSCLC) enrolled in CheckMate 9LA (NCT03215706), a phase 3, randomized clinical trial of nivolumab + ipilimumab in combination with 2 cycles of chemotherapy (chemo) vs 4 cycles of chemo as first-line treatment for NSCLC. **Methods:** Tissue- (FoundationOne CDx [F1CDx]) and blood-based (GuardantOMNI [OMNI]) genomic data obtained from both treatment arms were utilized for our retrospective analysis of genomic variants and complex biomarkers, including tTMB and bTMB. In total, 692 tissue and 646 plasma samples were analyzed. **Results:** Following the established criteria for the validated F1CDx and OMNI platforms, 464 tissue and 537 plasma samples passed quality control, resulting in ascertainment levels of 67% for tTMB and 83% for bTMB. Across 344 paired tissue and plasma samples, tTMB and bTMB scores were found to be moderately correlated (Spearman's $r = 0.56$; $P < 0.001$); median tTMB score was 7.7 mutations per megabase (mut/Mb) and median bTMB score was 13.5 mut/Mb. For the prespecified cutoffs of 10 mut/Mb for tTMB and 16 mut/Mb for bTMB, the positive, negative, and overall percentage agreements between assays were 65%, 79%, and 73%, respectively. Interestingly, 2 discordant sample pairs had considerably higher bTMB than tTMB (76.1 vs 3.8 and 172.6 vs 5.0 mut/Mb for bTMB and tTMB, respectively) and both had high microsatellite instability from blood-based assessments. OMNI and F1CDx data from 477 patients were evaluable for the analysis of short sequence variants (single nucleotide variations and indels). OMNI detected 4557 variants, F1CDx detected 4620, and 2903 (46% of total reported variants) were detected by both assays. **Conclusions:** In CheckMate 9LA, data from paired samples revealed the complementary nature of TMB assessments from tissue and blood and suggest that both approaches may have the potential to identify genomic alterations that may be useful in the management of patients with NSCLC. Further interrogation of the biological and analytical factors affecting tumor- and blood-derived genomic profiling is warranted to support their implementation in clinical settings. Clinical trial information: NCT03215706. Research Sponsor: Bristol Myers Squibb.

9011 **Clinical Science Symposium**

Early circulating tumor (ct) DNA dynamics and efficacy of lorlatinib: Analysis from the CROWN study. *First Author: Ross A. Soo, National University Cancer Institute, Singapore, Singapore*

Background: Lorlatinib, a third-generation ALK tyrosine kinase inhibitor, significantly improved progression-free survival (PFS) and overall/intracranial responses vs crizotinib in patients (pts) with previously untreated *ALK*-positive advanced non-small cell lung cancer (NSCLC) in the ongoing randomized Phase 3 CROWN study (NCT03052608). To identify whether additional molecular biomarker analysis correlated with efficacy, we evaluated early ctDNA dynamics compared with clinical outcomes. **Methods:** Plasma samples were prospectively collected at screening (SC), week 4 (cycle 2, day 1 [C2D1]), week 24 (C7D1), and end of treatment for ctDNA analysis. ctDNA was analyzed using Guardant360CDx (Guardant Health, Inc., Redwood City, CA, USA). Mean variant allele fraction (VAF) of *ALK* alterations (fusions and/or mutations) and overall detected alterations at each time point and longitudinal mean change (dVAF) as (VAF_{C2D1}) – (VAF_{SC}) were calculated; dVAF $<$0 indicated decreased ctDNA at week 4. Objective tumor response and PFS were evaluated according to dVAF. These analyses were repeated vs ctDNA results at week 24. Additional correlation analyses between depth of molecular response and/or ctDNA clearance and clinical outcomes are ongoing. **Results:** Paired samples were available at SC and week 4 from 232 of 255 pts included in the ctDNA analysis: 118/130 (90.8%) in the lorlatinib arm and 114/125 (91.2%) in the crizotinib arm. *ALK* alterations were detected in 122/232 (52.6%) pts at SC (62/118 [52.5%] from the lorlatinib arm) but only 19/232 (8.2%) at week 4 (8/118 [6.8%] from the lorlatinib arm). Mean VAF of *ALK* alterations at week 4 was significantly decreased compared with SC in both treatment arms (lorlatinib -1.54, crizotinib -1.25; both $P<0.0001$; $P=0.4239$ between arms). In the lorlatinib arm, mean VAF at week 4 was significantly decreased compared with SC in pts with a complete or partial response (dVAF -1.53; n=47; $P<0.0001$), or stable disease (dVAF -1.37; n=12; $P=0.0304$). Similar results were observed in the crizotinib arm. In pts with dVAF $<$0 for *ALK* alterations, mean percent change from screening in tumor size was -40.8% with lorlatinib (n=59) and -38.7% with crizotinib (n=58). Only 2 pts had dVAF $\geq$0, both from the crizotinib arm. Median PFS for pts with dVAF $<$0 for *ALK* alterations was not reached in the lorlatinib arm (n=62), and was 7.4 months (95% CI, 7.2–9.3) in the crizotinib arm (n=58). Similar response and PFS data were observed in the analysis of dVAF for *ALK* alterations at week 24. **Conclusions:** Early ctDNA dynamics may predict lorlatinib efficacy in pts with previously untreated *ALK*-positive NSCLC. The magnitude of reduction in ctDNA at 4 weeks may be associated with better responses and potentially longer PFS. These findings further support the utility of dynamic ctDNA monitoring in *ALK*-positive NSCLC. Reference: Shaw AT, et al. N Engl J Med. 2020;383:2018-2029. Clinical trial information: NCT03052608. Research Sponsor: Pfizer Inc.

9012 **Clinical Science Symposium**

*MET*ex14 ctDNA dynamics & resistance mechanisms detected in liquid biopsy (LBx) from patients (pts) with *MET*ex14 skipping NSCLC treated with tepotinib. *First Author: Paul K. Paik, Memorial Sloan-Kettering Cancer Center, New York, NY*

Background: In the VISION study, tepotinib in *MET*ex14 skipping NSCLC pts (Cohort A) had robust and durable clinical activity. Serial LBx samples were collected for biomarker analyses, presented herein. **Methods:** LBx samples taken at baseline (BL), Week 6, 12, & end of treatment (EOT) were analyzed using Guardant360® CDx (73 genes). Investigator (INV)-assessed clinical outcome was evaluated per BL biomarker profiles and by molecular response (MR; defined as > 75% depletion from BL in *MET*ex14 variant allele frequency [VAF] ctDNA confirmed in 2 consecutive samples) or molecular progression (MP; defined as VAF increase > 0 from BL). Acquired resistance was investigated in EOT samples, following progression per INV. **Results:** LBx pts (n = 99) had a median age of 72 yrs (range 49–88), 53% were male, 44% never smokers, 85% had adenocarcinoma. INV ORR was 53% (95% CI 42, 63); ORR in 1L (n = 44) was 59% (43, 74) & ≥2L (n = 55) was 47% (33, 61). 94 pts had BL biomarker profiles; these were similar in 1L and ≥2L pts, except *EGFR* amp: 1/43 1L [2%] vs 8/51 ≥2L [16%]. Outcomes were not impacted by location/type of *MET*ex14 alteration. 1 pt with concomitant *MET* M1250T mutation had a PFS of 17.3 months. A trend towards better efficacy was seen in pts with concomitant *MET* amp (6 responses in 8 pts). Response to tepotinib occurred both in pts with wt or mutant *TP53*; however, there was a trend for longer mDOR in pts with wt *TP53* (18.3 [95% CI 9.7, ne] vs 7.1 [4.7, 10.9] months) and mPFS (9.5 [6.7, 19.7] vs 5.1 [2.8, 6.9] months). Concomitant oncogenic mutations were rare, with no responses in 3 pts with *KRAS*, *NRAS* alterations and 3 responses in 5 pts with *PI3K/AKT* alterations. 65 pts had 2 consecutive on-treatment samples: 46 (71%) had confirmed MR, 5 (8%) had confirmed MP, 14 (22%) had no change in VAF or lacked confirmation. MR was associated with clinical response and MP was associated with no response/short PFS (Table). 52 pts with progression had EOT LBx samples. Emerging *MET* resistance mutations (Y1230H/C & D1228H/N) occurred in 7 (13%) pts, all responders and 5/7 had PFS > 10 months. Analyses on non-MET-driven resistance mechanisms will be presented. **Conclusions:** LBx biomarker analysis from the largest on-treatment data set for a MET inhibitor in *MET*ex14 skipping NSCLC, showed that ctDNA depletion in *MET*ex14 VAF is associated with improved clinical response in pts treated with tepotinib. This suggests serial LBx could help us to monitor response/non-response, understand resistance, and guide trials that test escalation/de-escalation strategies to improve outcomes and maximize QOL. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA, Darmstadt, Germany.

	All		1L		≥2L	
N	65		30		35	
Confirmed molecular status	MR	MP	MR	MP	MR	MP
n (%)	46 (71)	5 (8)	20 (67)	4 (11)	26 (74)	1 (3)
ORR, n (%)	35 (76)	0	18 (90)	0	15 (58)	0
mDOR, months (95% CI)	14 (9.8, ne)	0	18 (7.23, ne)	0	14 (9.69, ne)	0
DCR, n (%)	42 (91)	3 (60)	18 (90)	2 (50)	24 (92)	1
mPFS, months (95% CI)	11.0 (8.6, 17.7)	5.5 (2.8, ne)	19.7 (9.67, ne)	4.8 (2.8, ne)	9.9 (6.9, 13.8)	5.8

9013 **Poster Discussion Session**

Randomized phase III trial of aumolertinib (HS-10296, Au) versus gefitinib (G) as first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) and EGFR exon 19 del or L858R mutations (EGFRm). *First Author: Shun Lu, Shanghai Lung Cancer Center, Shanghai Chest Hospital, Shanghai JiaoTong University, Shanghai, China*

Background: Au is a novel, irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR TKI) with favorable pharmacologic properties that selectively inhibits both EGFR sensitizing and resistance mutations. Au has been approved in China for treatment of patients (pts) with EGFR mutant NSCLC with EGFR T790M upon progression of disease on previous EGFR TKIs (Proc. AACR 2020, Abstract CT190). This Phase III trial assessed the efficacy and safety of Au versus G as initial treatment of patients with advanced NSCLC with EGFRm. **Methods:** Pts with previously untreated metastatic or locally advanced NSCLC and EGFR exon 19 deletion or L858R were randomly assigned in a 1:1 ratio to receive either Au (110 mg once daily) or G (250 mg once daily). The primary endpoint was progression-free survival (PFS) by RECIST v1.1 per investigator assessment. At 262 PFS events, the study had 90% power to detect a PFS HR = 0.67. Secondary endpoints included overall survival (OS), objective response rate (ORR), duration of response (DoR) and safety. **Results:** Between Nov 30, 2018 and Sept 6, 2019, 429 patients across 53 sites in China were enrolled and randomized. Pt. characteristics were well-balanced. At the planned final event-driven PFS analysis, Au significantly prolonged PFS (median 19.3 vs 9.9 months, HR 0.46, p-value <0.0001). DoR was also significantly prolonged with Au. Median OS has not been reached. Efficacy and relevant safety results are summarized in Table. Despite a significantly longer duration of treatment (median 463 vs 254 days), Au was associated with a lower incidence of rash, diarrhea, AST/ALT increase, and treatment related serious adverse events (SAEs) (4.2% vs 11.2%). Au was associated with more frequent events of CPK increased, platelet count decreased, and neutrophil count decreased, which were predominantly low grade. **Conclusions:** Au significantly prolonged PFS and DoR compared to G as first-line therapy in pts with advanced NSCLC with EGFRm. Au demonstrated a favorable safety profile, especially regarding toxicities mediated by wild-type EGFR. These results establish Au as a promising option for advanced NSCLC with EGFRm. Clinical trial information: NCT03849768. Research Sponsor: Hansoh Pharma.

	Au (N=214)	G (N=215)	Hazard ratio (95% CI)	P-value
Efficacy				
Median PFS (95% CI), mo	19.3 (17.8, 20.8)	9.9 (8.3, 12.6)	0.46 (0.36, 0.60)	<0.0001
Median DoR (95% CI), mo	18.1 (15.2, NA)	8.3 (6.9, 11.1)	0.38 (0.28, 0.51)	<0.0001
Selected AEs , n (%)				
Alanine aminotransferase increased	63 (29.4)	120 (55.8)		
Aspartate aminotransferase increased	64 (29.9)	116 (54.0)		
Rash	50 (23.4)	89 (41.4)		
Diarrhea	35 (16.4)	77 (35.8)		
Creatine phosphokinase increased	76 (35.5)	20 (9.3)		

9014 **Poster Discussion Session**

Mobocertinib (TAK-788) in *EGFR* exon 20 insertion (ex20ins)+ metastatic NSCLC (mNSCLC): Additional results from platinum-pretreated patients (pts) and EXCLAIM cohort of phase 1/2 study. *First Author: Suresh S. Ramalingam, Emory University, Atlanta, GA*

Background: No approved targeted therapies are available for *EGFR* ex20ins+ mNSCLC. Mobocertinib, a first-in-class, potent, oral TKI targeting *EGFR* ex20ins mutations, has Breakthrough Therapy Designation in the US and China for post-platinum-based chemotherapy pts with *EGFR* ex20ins+ mNSCLC. **Methods:** This 3-part, open-label, multicenter study (NCT02716116) has dose-escalation/expansion and extension (EXCLAIM) cohorts. Pts with *EGFR* ex20ins+ mNSCLC, ECOG status 0–1, and ≥1 prior line of therapy for locally advanced/metastatic disease received mobocertinib 160 mg QD. Primary endpoint was confirmed objective response rate (ORR; RECIST v1.1) assessed by independent review committee (IRC). We present additional efficacy and safety data for 114 platinum-pretreated pts (PPP) and 96 pts from EXCLAIM safety cohort. **Results:** Results are from Nov 1, 2020, data cutoff. Among PPP pts (n=114; median age 60 y [27–84 y]), 66% were female, 60% were Asian, and 59% had ≥2 prior systemic anticancer lines. Confirmed ORR per IRC was 28%, including 1 complete response (CR); disease control rate (DCR) was 78% [95% CI: 69–85]; median duration of response (DOR) was 17.5 mo (Table). In EXCLAIM (n=96; median age 59 y [27–80 y]), 65% were female, 69% were Asian, and 49% had ≥2 prior lines. Confirmed ORR per IRC was 25%, with 1 CR; DCR was 76% [95% CI: 66–84]; median DOR was not reached (Table). In EXCLAIM, baseline brain metastases were present in 33/96 pts (34%); the first site of disease progression by IRC was the brain in 40% of all pts and 73% of pts with baseline brain metastases. Confirmed responses were seen in all prespecified subgroups in PPP and EXCLAIM. Efficacy by *EGFR* ex20ins mutation variant will be presented. Treatment-related adverse events (TRAEs; >20%) in PPP were diarrhea (91%), rash (45%), paronychia (38%), decreased appetite (35%), nausea (34%), dry skin (31%), vomiting (30%), increased blood creatinine (25%), stomatitis (24%), and pruritus (21%); the only grade ≥3 TRAE in ≥5% was diarrhea (22%). AEs leading to discontinuation in >2% were diarrhea (4%) and nausea (4%). A similar safety profile was observed in EXCLAIM. **Conclusions:** Mobocertinib demonstrated clinically meaningful benefit for pts with *EGFR* ex20ins+ mNSCLC in PPP and EXCLAIM cohorts, with a manageable safety profile.Clinical trial information: NCT02716116. Research Sponsor: Millennium Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

	PPP(n=114)	EXCLAIM(n=96)
Median follow-up, mo	14.2	13.0
Confirmed ORR, n (%) [95% CI] Per IRC	32 (28) [20–37]	24 (25) [17–35]
Per investigator	40 (35) [26–45]	31 (32) [23–43]
Median DOR, mo [95% CI] Per IRC	17.5 [7.4–20.3]	NE [5.6–NE]
Per investigator	11.2 [5.6–NE]	11.2 [7.0–NE]
Median progression-free survival, mo [95% CI] Per IRC*	7.3 [5.5–9.2]	7.3 [5.5–9.1]
Median OS, mo [95% CI]	24.0 [14.6, 28.8]	NE [13.1, NE]
6 mo OS rate, %	87%	87%
12 mo OS rate, %	70%	69%

*Investigator-assessed median PFS was similar in both cohorts.

9015 **Poster Discussion Session**

Combination of trastuzumab, pertuzumab and docetaxel in patients with advanced non-small cell lung cancer (NSCLC) harboring HER2 mutation: Final results from the IFCT-1703 R2D2 trial. *First Author: Julien Mazieres, Thoracic Oncology Department, CHU Toulouse–Hôpital Larrey, Toulouse, France*

Background: Human epidermal growth factor receptor 2 (*HER2)* exon 20 insertions and mutations are oncogenic drivers found in 1-2% of NSCLC. However, there are no approved therapies for these patients. Many studies suggest that the use of HER2 inhibitors developed for breast cancer patients might be of interest in this setting. The aim of this trial was to prospectively evaluate the interest of a combination of two antibodies against HER2 (trastuzumab and pertuzumab) with docetaxel. **Methods:** IFCT-1703 R2D2 trial is a multicenter, non-randomized phase 2 study with a two-stage design, a power of 90% and an alpha risk at 5% (one-sided). *HER2* mutational status was assessed locally in certified molecular genetic centers. Main other inclusion criteria were advanced NSCLC, progression after ≥ 1 platinum-based chemotherapy, asymptomatic brain metastases, left ventricular ejection fraction (LVEF) ≥ 50%, and PS 0-2. Patients were treated every 3 weeks with pertuzumab at a loading dose of 840 mg, and 420 mg thereafter; plus trastuzumab at a loading dose of 8 mg/kg and 6 mg/kg thereafter; and docetaxel at 75 mg/m^2. Treatment was given until toxicity or disease progression. The primary outcome was overall response rate (ORR). Other endpoints included duration of response, progression-free survival and safety. NCT number: NCT03845270. **Results:** From May 2019 to October 2020, 45 patients were enrolled in 17 centers and received study treatment. Median age was 64.5 years (range 31–84), 72% females, 35% smokers, 100% non-squamous histology and 15% with ECOG PS 2. 31.1% patients had brain metastases. PD-L1 was expressed ≥ 1% and ≥ 50% in 36% and 7% of the patients, respectively. No other oncogene driver was found associated with HER2 exon 20 mutation. With a median follow-up of 12 months, 44 (98%) patients were evaluable for the primary endpoint. Overall response rate was 29% (n = 13), stable disease 56% (n = 26). Median PFS was 6.8 months (95% CI[4.0-8.5]). Median duration of treatment in patients with confirmed response (n = 13) was 10 months (95% CI[2.7-14.9]). At the time of data cut-off, 15 patients (33%) were still under treatment. Grade 3/4 treatment-related adverse events (AEs) were observed in 64% of patients. No patient experienced treatment discontinuation because of toxicity. One sudden death was possibly related to treatment. Most frequent grade ≥ 3 AEs were neutropenia (33%), diarrhea (13%) and anaemia (9%). Grade 1/2 dyspnea was observed in 3 (6.7%) patients. No ILD were reported. Variation LVEF was -1.72% on average (min: -18 %; max: 10 %). **Conclusions:** The triplet trastuzumab, pertuzumab and docetaxel is feasible and active in *HER2* pretreated advanced NSCLC. These results confirm the activity of *HER2* antibodies-based strategy which should be considered in these patients. Clinical trial information: NCT03845270. Research Sponsor: Intergroupe Francophone de Cancerologie Thoracique, Pharmaceutical/Biotech Company.

9016 **Poster Discussion Session**

Nivolumab (NIVO) plus ipilimumab (IPI) versus chemotherapy (chemo) as first-line (1L) treatment for advanced non-small cell lung cancer (NSCLC): 4-year update from CheckMate 227. *First Author: Luis G. Paz-Ares, Hospital Universitario 12 de Octubre, CNIO-H12o Lung Cancer Clinical Research Unit, Universidad Complutense & CiberOnc, Madrid, Spain*

Background: 1L NIVO + IPI was shown to provide durable long-term overall survival (OS) benefit vs chemo regardless of tumor programmed death ligand 1 (PD-L1) expression in patients (pts) with advanced NSCLC in CheckMate 227 Part 1 (NCT02477826); 3-year OS rates were 33% vs 22% in pts with PD-L1 ≥ 1% (HR, 0.79 [95% CI, 0.67–0.93]) and 34% vs 15% in pts with PD-L1 < 1% (HR, 0.64 [95% CI, 0.51–0.81]). Here we report updated results from the study with 4 years' minimum follow-up. **Methods:** Adults with previously untreated stage IV / recurrent NSCLC, no known *EGFR*/*ALK* alterations, and ECOG performance status ≤ 1 were enrolled; pts were stratified by squamous (SQ) and non-squamous (NSQ) histology. Pts with PD-L1 ≥ 1% (n = 1189) were randomized 1:1:1 to receive NIVO (3 mg/kg Q2W) + IPI (1 mg/kg Q6W), NIVO alone (240 mg Q2W), or chemo. Pts with PD-L1 < 1% (n = 550) were randomized 1:1:1 to receive NIVO + IPI, NIVO (360 mg Q3W) + chemo, or chemo. OS with NIVO + IPI vs chemo in pts with PD-L1 ≥ 1% was the primary endpoint. **Results:** With minimum follow-up of 49.4 months (database lock, Feb 18, 2021), pts were at least 2 years beyond the protocol-specified end of immunotherapy treatment. Pts with PD-L1 ≥ 1% continued to show durable benefit with NIVO + IPI vs chemo (HR, 0.76 [95% CI, 0.65–0.90]); 4-year OS rates were 29% (NIVO + IPI), 21% (NIVO), and 18% (chemo). At 4 years, 14% (NIVO + IPI), 10% (NIVO), and 4% (chemo) remained progression free. Among responders, 34%, 30%, and 7% remained in response, respectively. In an exploratory analysis in pts with PD-L1 ≥ 50%, 4-year OS rates were 37% (NIVO + IPI), 26% (NIVO), and 20% (chemo). In pts with PD-L1 < 1%, OS HR for NIVO + IPI vs chemo was 0.64 (95% CI, 0.51–0.81); 4-year OS rates were 24% (NIVO + IPI), 13% (NIVO + chemo) and 10% (chemo). At 4 years, 12% (NIVO + IPI), 7% (NIVO + chemo), and 0% (chemo) remained progression free. Among responders, 31%, 13%, and 0% remained in response, respectively. Among pts who progressed on NIVO + IPI vs chemo, 7% vs 40% (PD-L1 ≥ 1%), and 9% vs 33% (PD-L1 < 1%), received subsequent immunotherapy. Benefit with NIVO + IPI vs chemo was observed for both SQ and NSQ histology (Table). With long-term follow-up, no new safety signals were identified. **Conclusions:** With 4 years' minimum follow-up, 1L NIVO + IPI continued to provide durable, long-term OS benefit vs chemo in pts with advanced NSCLC regardless of PD-L1 expression or histology. Clinical trial information: NCT02477826. Research Sponsor: Bristol Myers Squibb and Ono Pharmaceutical.

OS with NIVO + IPI vs chemo by PD-L1 expression and histology.

PD-L1	≥ 1%	≥ 1%	< 1%	< 1%
Histology	NSQ	SQ	NSQ	SQ
	NIVO + IPI (n = 278) vs chemo (n = 279)	NIVO + IPI (n = 118) vs chemo (n = 118)	NIVO + IPI (n = 141) vs chemo (n = 140)	NIVO + IPI (n = 46) vs chemo (n = 46)
Median OS, months	19.4 vs 17.2	14.8 vs 9.2	17.5 vs 13.1	15.9 vs 8.5
HR (95% CI)	0.81 (0.67–0.99)	0.68 (0.51–0.89)	0.69 (0.53–0.89)	0.53 (0.34–0.84)
4-year OS rate, %	32 vs 23	20 vs 6	25 vs 12	22 vs 7

9017 **Poster Discussion Session**

Effect of antibiotic therapy on immunotherapy outcomes for non-small cell lung cancer: Analysis from the Veterans Health Administration Database. *First Author: William A. Stokes, Emory University School of Medicine, Atlanta, GA*

Background: Dysregulation of the gut microbiota induced by antibiotic therapy (Abx) may alter the anticancer immune response. Multiple small studies have associated Abx use with inferior immune checkpoint inhibitor (ICI) efficacy in patients with non-small cell lung cancer (NSCLC). We aimed to study the impact of Abx in a larger population of NSCLC patients treated with ICI within the Veterans Health Administration. **Methods:** We conducted a nested cohort study of Veterans who were diagnosed with NSCLC between 2010 & 2018 and treated with ICI. Two exposures to Abx were specified and separately analyzed: prior Abx (pAbx) was defined as receipt of an Abx prescription within 30 days prior to initiation of ICI, and concurrent Abx (cAbx) was defined as receipt of an Abx prescription within 60 days following ICI initiation. A landmark analysis of 2 months from ICI start was applied to the cAbx analysis to exclude any Veterans with an OS event before that time point. OS was measured from start of ICI using Cox proportional hazard multivariate analyses (MVA). **Results:** 3,634 Veterans received ICI, mostly nivolumab (59.3%) or pembrolizumab (35.1%). Their median age was 69, and a plurality had male gender (97.0%), white race (73.0%), comorbidity count ≥1 (60.4%), adenocarcinoma (47.8%), and stage IV disease at diagnosis (40.9%). Of the 762 (21.0%) Veterans prescribed pAbx, beta-lactams, quinolones, and macrolides were the most common classes. These patients had shorter OS than those without pAbx (median 7 versus 10 months). Receipt of pAbx was also associated with lower OS on MVA (HR 1.31, $p<0.01$). In the propensity-matched cohort analysis, Veterans receiving pAbx had lower OS (HR 1.27, $p<0.01$) (Table top). For the cAbx analysis, 3,223 Veterans survived to the 2-month landmark, of whom 970 (30.1%) received cAbx. These Veterans had shorter OS than those without cAbx (median 7 versus 10 months). Lower OS with cAbx was also observed both on Cox MVA (HR 1.33, $p<0.01$) and in the matched cohort (HR 1.32, $p<0.01$) (Table bottom). **Conclusions:** In the largest analysis to date of Abx use in NSCLC patients receiving ICI, receipt of Abx within either 30 days before or 60 days after start of ICI was associated with lower OS. These findings suggest Abx therapy may have a detrimental effect on immunotherapy outcomes. Research Sponsor: Morningside Center for Innovative and Affordable Medicine, Emory Woodruff Health Sciences Center, Other Government Agency.

	No. of Pts	Median OS	Cox MVA HR	Cox MVA 95%CI	Matched No. of Pts	Matched median OS	Matched UVA HR	Matched UVA 95%CI
pAbx								
no	2,872	10 m	-	-	760	9 m	-	-
yes	762	7 m	1.31	1.20-1.44	760	7 m	1.27	1.14-1.41
cAbx								
no	2,253	10 m	-	-	968	10 m	-	-
yes	970	7 m	1.33	1.21-1.45	968	7 m	1.32	1.19-1.46

9018 **Poster Discussion Session**

Association of a very high tumor mutational load with increased CD8+ and PD-1+ T-cell infiltration and improved clinical outcomes to PD-(L)1 blockade across different PD-L1 expression levels in non-small cell lung cancer. *First Author: Biagio Ricciuti, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Although high TMB correlates with improved outcomes to immune checkpoint inhibitors (ICI) in patients (pts) with non-small cell lung cancer (NSCLC), an optimal TMB cutoff to discriminate cancers most likely to respond to ICI has not been identified. Whether TMB impacts outcomes to ICI in different PD-L1 levels subgroups is also unclear. **Methods:** Unbiased recursive partitioning (URP) was used to identify an optimal TMB cutoff for objective response rate (ORR) in two independent cohorts of pts with NSCLC treated with ICI at DFCI and MSKCC. TCGA was interrogated to find differences in tumor immune cell subsets according to the TMB cutoff identified. Multiplexed immunofluorescence (IF) for CD8, PD-1, PD-L1, Foxp3, and CK7 was also performed on NSCLC samples at the DFCI. **Results:** In the DFCI (N=686) and MSKCC (N=672) cohorts, URP found an optimal TMB cutoff for ORR at 19 mutations/megabase (mut/Mb), corresponding to the ~90th percentile in each cohort. Median progression-free (PFS) and overall survival (OS) were significantly longer in NSCLCs with TMB ≥19 mut/Mb vs <19 mut/Mb, in both cohorts (Table). After harmonizing TMB between DFCI OncoPanel and MSK-IMPACT NGS platforms, URP confirmed an optimal TMB cutoff for ORR at the 90th percentile in the combined cohort, which also associated with longer PFS/OS to ICI (Table). A TMB ≥90th percentile correlated with longer PFS/OS to ICI among NSCLCs with PD-L1 levels ≥50% and 1-49%, and longer PFS among those with PD-L1 <1% (Table). Cell subset transcriptome analysis from the TCGA showed higher proportions of CD8+ T cells (P=0.02) and M1 macrophages (P<0.01) among NSCLCs with a TMB ≥ vs <90th percentile. IF confirmed increased CD8+, CD8+ PD1+ T-cell infiltration (P<0.01), and increased CD8+/Foxp3+ ratio in NSCLC with very high TMB **Conclusions:** A very high TMB is associated with better outcomes to ICI and a distinct immunophenotype in NSCLC. Rational integration of TMB and PD-L1 expression may identify NSCLCs most likely to respond to ICI. Research Sponsor: None.

Cohort	PD-L1 expression	PFS TMB ≥ vs <90th percentile HR [95%CI], P	OS TMB ≥ vs <90th percentile HR [95%CI], P
DFCI N=686	0-100	0.48 [0.36-0.65], P<0.01	0.57 [0.41-0.78], P<0.01
MSKCC N=672	0-100	0.38 [0.28-0.52], P<0.01	0.46 [0.33-0.65], P<0.01
DFCI+MSKCC	0-100	0.44 [0.35-0.54], P<0.01	0.50 [0.39-0.64], P<0.01
DFCI+MSKCC	≥50%	0.52 [0.34-0.81], P<0.01	0.54 [0.32-0.94], P=0.03
	1-49%	0.33 [0.19-0.57], P<0.01	0.36 [0.19-0.69], P<0.01
	<1%	0.40 [0.25-0.65], P<0.01	0.72 [0.34-1.18], P=0.19

9019 **Poster Discussion Session**

Intestinal *Akkermansia muciniphila* predicts overall survival in advanced non-small cell lung cancer patients treated with anti-PD-1 antibodies: Results a phase II study. *First Author: Lisa Derosa, Department of Cancer Medicine, Gustave Roussy Cancer Campus, Paris-Sud University, Francepartment of Cancer Medicine, Gustave Roussy Cancer Campus, Paris-Sud University, Villejuif, France*

Background: The gut microbiome, most specifically centered on one of the most prevalent anaerobic bacterium *Akkermansia muciniphila (Akk),* has emerged as a potential hallmark of clinical benefit to ICI. The goal of this study was to validate the prognostic significance of *Akk* in advanced NSCLC patients amenable to ICI. **Methods:** The multicentric prospective observational study enrolled patients with advanced NSCLC amenable to single agent ICI in first and second line. Stool sample was collected at study entry. Primary end-point was investigator-assessed objective response rate (ORR). We considered that a meaningful clinical difference would correlate to a 10% ORR increase in the Akk-Pos group compared to the Akk-Neg group. At least 292 patients equally divided each in each group would be required for a power at 80% and a two-sided alpha level of 5%. **Results:** From Dec 2015 to Nov 2019, a total of 409 patients were screened and 311 patients enrolled across 12 academic centers in France and Canada. Median age was 64yr, 32% were female, 77% had non-squamous NSCLC and PD-L1 was ≥1% in 70% of the 213 assessable samples. *Akk* was detectable in 158 (51%) and absent in 153 (49%) patients. Baseline characteristics were well balanced between the two groups. When considering Akk-Pos *vs* Akk-Neg groups the primary endpoint ORR was 27% and 17% respectively ($p = 0.04$). Rates of partial response, stable disease and progressive disease (PD) were 62%, 50% and 46% respectively in the Akk-Pos group compared to 38%, 50% and 54% in the Akk-Neg group ($p = 0.04$). Moreover, 57% of patients were still alive after 12 months in the Akk-Pos group *vs* 43% in the Akk-Neg group ($p = 0.04$). Microbiome profiling demonstrated that Akk-Pos group was associated with increase bacterial diversity and enrichment of *Ruminococcus, Alistipes* and *Eubacterium.* When considering the variations of the relative abundance of *Akk* within the Akk-Pos group, we obtained a large interval ranging from 0.0022% up to 64.78% with a 75th percentile at 4.42%. The relative abundance of *Akk* within > 0% to < 4.42% range in stools at diagnosis was associated with increased ORR, overall survival (OS) in multivariate analysis, independent of PD-L1 expression and ECOG. This sub-group was associated with more inflamed tumors with upregulation of CD3e, *Ifng*TH1 and Vcam-1. Conversely, patients with overrepresentation of *Akk* > 4.42% experienced more PD and shorter OS. Antibiotic use was associated with a shift in favor of Gammaproteobacteria, enrichment of *Akk* (> 4.42%) and shorter OS. **Conclusions:** We validated the prognostic role of *Akk* in patients with NSCLC. Stratification based on *Akk* relative abundance represents a more accurate independent predictor than the binary modality. Our study provides the rationale to develop microbiome-based approach to study gut dysbiosis in routine clinical oncology care. Clinical trial information: NCT04567446. Research Sponsor: Torino Lumiere.

9020 **Poster Discussion Session**

Capmatinib in *MET* exon 14-mutated, advanced NSCLC: Updated results from the GEOMETRY mono-1 study. *First Author: Juergen Wolf, Department of Internal Medicine, Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany*

Background: Capmatinib, a selective MET inhibitor, is approved in the USA and Japan for the treatment of patients (pts) with *MET* exon 14 skipping mutation (*MET*ex14) advanced non-small-cell lung cancer (NSCLC) based on the multi-cohort phase II GEOMETRY mono-1 study. This is the first report on expansion Cohort 7 in first line (1L) *MET*ex14 NSCLC pts, with updates to previously reported results (Wolf et al, *NEJM* 2020) for *MET*ex14 pts. **Methods:** In GEOMETRY mono-1, pts were assigned to cohorts based on previous lines of therapy and *MET* status (*MET*ex14 or *MET* amplification). This efficacy analysis includes patients with *MET*ex14 NSCLC who were treatment-naive (Cohort 5b and 7) and those who had previously received 1L or 2L of therapy (expansion Cohort 6 and Cohort 4) for their advanced disease (data cutoff: Sep 18, 2020). Evaluated outcomes included overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS), all by BIRC; and overall survival (OS). The safety analysis includes all patients enrolled. **Results:** In total, 160 pts with *MET*ex14 who received capmatinib 400 mg BID were analyzed. ORR of 65.6% (95% CI 46.8-81.4) for the treatment-naive expansion Cohort 7 was in line with that previously reported for Cohort 5b (Table). Though Cohort 7 data are still immature, median PFS was 10.8 mo (95% CI 6.87-not estimable [NE]). Mature median OS was 20.8 mo (95% CI 12.4-NE) in Cohort 5b and 13.6 mo (95% CI 8.6-22.2) in Cohort 4. Median OS for Cohorts 6 and 7 and DOR for Cohort 7 are not yet reached. The safety profile remained unchanged across all study cohorts (N = 373): 98.4% of pts reported AEs (68.6% Grade [G] 3/4) regardless of causality and 16.1% reported AEs leading to discontinuation (10.5% G3/4). The most common AEs (≥20% all G) were peripheral edema (54.2%), nausea (45.0%), vomiting (28.2%), increased blood creatinine (26.5%), dyspnea (23.3%), fatigue (22.3%), and decreased appetite (21.2%). **Conclusions:** Results of Cohort 7 confirm those previously reported for Cohort 5b showing higher efficacy of capmatinib when used as 1L in *MET*ex14 NSCLC pts. A clinically meaningful median OS of 20.8 mo in 1L (Cohort 5b) and of 13.6 mo in relapse (Cohort 4) was also observed and, together with the continued manageable toxicity profile, the data support capmatinib as a valuable targeted treatment option for *MET*ex14 NSCLC pts. Clinical trial information: NCT02414139. Research Sponsor: Novartis Pharmaceuticals.

	Treatment-naive N = 60		Previously treated N = 100	
	Cohort 5b N = 28	Expansion cohort 7 N = 32	Cohort 4 (2/3L) N = 69	Expansion cohort 6 (2L) N = 31
ORR by BIRC* % (95% CI)	67.9 (47.6-84.1)	65.6 (46.8-81.4)	40.6 (28.9-53.1)	51.6 (33.1-69.8)
Median DOR by BIRC† mo (95% CI)	12.6 (5.6-NE)	NE‡ (5.5-NE)	9.7 (5.6-13.0)	8.4 (4.2-NE)
Median PFS by BIRC mo (95% CI)	12.4 (8.2-23.4)	10.8‡ (6.9-NE)	5.4 (4.2-7.0)	6.9 (4.2-13.3)
Median OS mo (95% CI)	20.8 (12.4-NE)	NE‡ (10.6-NE)	13.6 (8.6-22.2)	NE‡ (13.5-NE)

Data cutoff: Sep 18, 2020; *Primary endpoint; †Key secondary endpoint; ‡Not yet mature.

9021 **Poster Discussion Session**

Tepotinib in patients (pts) with advanced non-small cell lung cancer (NSCLC) with *MET* amplification (*MET*amp). *First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: *MET*amp is an oncogenic driver occurring in 1–5% of NSCLCs that confers a poor prognosis and lacks approved targeted therapies. Tepotinib, a highly selective MET inhibitor, provided durable response in NSCLC with *MET* exon 14 (*MET*ex14) skipping in Cohort A of the Phase II VISION trial (NCT02864992). VISION Cohort B evaluated tepotinib in pts with advanced NSCLC and *MET*amp, as detected by a convenient and minimally invasive liquid biopsy assay, in the absence of *MET*ex14 skipping. **Methods:** Pts with locally advanced or metastatic NSCLC, Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, 0–2 prior lines of therapy, *EGFR*/*ALK* wild-type status, no *MET*ex14 skipping, and *MET*amp by liquid biopsy (Guardant360®; *MET* gene copy number ≥2.5) received oral tepotinib 500 mg QD (450 mg active moiety). The primary endpoint was objective response (RECIST v1.1) by independent review committee (IRC). Secondary endpoints included duration of response (DOR), progression-free survival (PFS) and safety. The data cut-off was July 1, 2020. **Results:** Among 24 enrolled pts, median age was 63.4 years (range: 38–73), 21 pts (88%) were male, 21 (88%) had ECOG PS 1 and 21 (88%) were smokers. Tepotinib was given to 7 pts (29%) in first line (1L), 10 pts (42%) in second line (2L) and 7 pts (29%) in third line (3L). As of November 2020, treatment was ongoing for > 1 year in 5 pts (1L, n = 2; 2L, n = 2; 3L, n = 1). Objective response rate (ORR) by IRC was 42% (10/24 pts) overall, 71% (5/7 pts) in 1L, 30% (3/10 pts) in 2L and 29% (2/7 pts) in 3L (Table). Median DOR by IRC was not estimable (NE; 95% confidence interval [CI]: 2.8 months–NE). Investigator-assessed outcomes were similar. Five pts (20.8%) discontinued due to adverse events (AEs), which were considered unrelated to tepotinib. Treatment-related AEs were reported in 16 pts (67%; Grade 3/4, 7 pts [29%]) and included peripheral edema (9 pts [38%]; Grade 3/4, 2 pts [8%]), generalized edema (4 pts [17%]; Grade 3/4, 2 pts [8%]) and constipation (4 pts [17%]; Grade 3/4, 0 pts). **Conclusions:** In the first study of a MET inhibitor in NSCLC with *MET*amp prospectively detected by liquid biopsy, tepotinib showed high and clinically meaningful activity, especially in 1L, and was generally well tolerated. Tepotinib warrants further evaluation in NSCLC with *MET*amp. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA, Darmstadt, Germany.

Endpoints by IRC		Overall (n = 24)	1L (n = 7)	2L (n = 10)	3L (n = 7)
Best overall response, n (%)	Partial response	10 (42)	5 (71)	3 (30)	2 (29)
	Stable disease	1 (4)	0	1 (10)	0
	Progressive disease	5 (21)	1 (14)	2 (20)	2 (29)
	Not evaluable	8 (33)	1 (14)	4 (40)	3 (43)
ORR	n, % [95 CI]	10 (42) [22–63]	5 (71) [29–96]	3 (30) [7–65]	2 (29) [4–71]
DOR	9-month event-free rate, % (95% CI)	67 (28–88)	60 (13–88)	100 (NE–NE)	NE (NE–NE)
	Median, months (95% CI)	NE (2.8–NE)	NE (2.8–NE)	NE (NE–NE)	NE (3.2–NE)
PFS	9-month event-free rate, % (95% CI)	40 (19–61)	51 (12–81)	58 (18–84)	NE (NE–NE)
	Median, months (95% CI)	4.2 (1.4–NE)	NE (1.4–NE)	NE (1.0–NE)	1.4 (0.6–4.5)

9022 **Poster Discussion Session**

Final OS analysis from the phase III j-alex study of alectinib (ALC) versus crizotinib (CRZ) in Japanese ALK-inhibitor naïve *ALK*-positive non-small cell lung cancer (*ALK*+ NSCLC). *First Author: Hiroshige Yoshioka, Department of Thoracic Oncology, Kansai Medical University Hospital, Osaka, Japan*

Background: The primary analysis of the J-ALEX (JapicCTI-132316) study for the ALK-inhibitor naïve *ALK*+ NSCLC demonstrated superior progression-free survival (PFS) in Japanese patients randomized to the ALC, compared with those assigned in the CRZ (HR 0.34, 99.7% CI 0.17–0.71, stratified log-rank p<0·0001) by the Independent Review Facility (IRF) (Hida et al., Lancet 2017). The final PFS and 2nd overall survival (OS) interim analysis (IA) data were subsequently reported (Nakagawa et al., Lung cancer 2020). Here, we report the final OS data. **Methods:** *ALK*+ NSCLC (by IHC and FISH or RT-PCR) patients were randomized 1:1 either to receive ALC (Japanese approved dose 300 mg BID, n = 103) or CRZ (250 mg BID, n = 104). Stratification factors included ECOG PS, treatment line, and clinical stage. The primary endpoint was PFS according to the blinded IRF. Secondary endpoints included OS, objective response rate, and safety. **Results:** After a median follow-up of 68.6 months in the ALC arm and 68.0 months in the CRZ arm, death events occurred in 40.8% and 39.4% in the ALC and the CRZ arms, respectively. Five-year survival rates for patients in the ALC and CRZ arm were 60.85% and 64.11%, respectively. The final OS HR was 1.03 (95%CI 0.67-1.58), however, median OS was not reached in either arm. Of note, patients in the CRZ arm tended to have their treatment switched earlier than those in the ALC arm (median time to treatment-switch: 12.3 months vs. NE). Most of the patients (78.8%) in the CRZ arm received ALC as a 1st subsequent therapy, whereas only 10.7% of patients in the ALC arm received CRZ. **Conclusions:** In this final J-ALEX OS analysis, prolongation of OS in the ALC arm was not observed compared to the CRZ arm. However, OS result may be substantially confounded since 78.8% of the patients in the CRZ arm received ALC as initial, subsequent therapy. Clinical trial information: 132316. Research Sponsor: Chugai pharmaceutical.

9023 **Poster Discussion Session**

Clinicogenomic real-world data analysis of patients (pts) with *KRAS G12C*-mutant advanced non-small cell lung cancer (aNSCLC) from the natural history cohort of the Blood First Assay Screening Trial (BFAST). *First Author: Rafal Dziadziuszko, Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland*

Background: BFAST (NCT03178552) is a global, multicohort trial of targeted therapies or cancer immunotherapy (CIT) in treatment (tx)-naive aNSCLC. Pts are screened for the study using comprehensive blood-based next-generation sequencing (NGS). In the BFAST natural history cohort, data were collected for pts who received tx or care outside the study's interventional cohorts. Here, we analyzed the subset of pts whose tumors have *KRAS G12C* mutations (mut). **Methods:** Pts eligible for blood-based NGS screening had unresectable aNSCLC, ECOG PS 0-2 and no prior systemic tx for aNSCLC. Pts without tissue samples were eligible. Key genomic and molecular features, including bTMB, PD-L1 and ctDNA concentration; cancer tx; tx response and survival data were collected and analyzed in an exploratory analysis. **Results:** In the full BFAST screening population through December 2020 (N = 5917), 23% of pts had tumors with any *KRAS* mut; 9% were *KRASG12C*. Pts were enrolled in the natural history cohort from October 2018 to October 2020 (n = 1017); 63 pts had tumors with *KRAS G12C* mut. Median age was 68 y, 59% were male, 86% had ECOG PS 0-1 and 84% had non-squamous histology. Co-mut in *TP53* (60%) and *STK11* and/or *KEAP1* (25%) were detected; 8% of pts had bTMB ≥16. High PD-L1 expression per local testing was reported in 32% of pts; 38% were not tested. Among pts with 1L tx (n = 50), 50%, 28% and 20% received chemo, CIT or CIT + chemo, respectively, with real-world response rates (CR/PR per physician assessment) of 20%, 29% and 30%, respectively. Of the 13 pts (21%) without documented 1L tx, 7 died ≤3 mo from enrollment. Median OS was 14 mo overall, with differences found between key genomic subsets (Table). **Conclusions:** BFAST is the first study to identify *KRAS G12C* mut using blood-based NGS and describe the natural history, clinical characteristics and genomic landscape of this pt subset. Up to 21% of pts may not receive 1L tx. Pts with *TP53* co-mut appear to have favorable outcomes, while those with *STK11* and/or *KEAP1* co-mut appear to have inferior outcomes vs pts without these mut. The lack of PD-L1 testing in many pts indicates a lack of tissue for comprehensive tissue testing, highlighting a potential benefit of blood-based detection of biomarkers, including *KRASG12C*. Clinical trial information: NCT03178552. Research Sponsor: F. Hoffmann-La Roche, Ltd.

Pt subset by mut status[a]	n	mOS (from aNSCLC diagnosis), 95% CI, mo	n	mOS (from 1L tx start), 95% CI, mo	n	1L CIT[b] mOS (from 1L tx start), 95% CI, mo
All pts	63	14.0 9.8, 41.6	49	16.8 10.3, NE	24	17.9 13.1, NE
***TP53* mut–**	27	9.8 8.0, NE	22	7.9 6.0, NE	9	9.6 4.1, NE
***TP53* mut+**	36	19.6^ 12.7, NE	27	17.9** 16.8, NE	15	17.9* NE, NE
***STK11* and *KEAP1* mut–**	47	19.6 14.0, NE	38	19.1 13.1, NE	–	–
***STK11* and/or *KEAP1* mut+**	16	5.2** 3.5, 11.4	11	6.0** 3.0, NE	–	–

NE, not estimable [a] Known/likely function per Foundation Medicine [b] Monotherapy or combination therapy * $P < 0.05$; ** $P < 0.001$; ^ $P < 0.1$ (comparing pts with mut+ tumors vs those with mut– tumors).

9024 **Poster Discussion Session**

A phase II study of rucaparib in patients with high genomic LOH and/or BRCA 1/2 mutated stage IV non-small cell lung cancer (Lung-MAP Sub-Study, S1900A). *First Author: Jonathan W. Riess, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: While prior studies have shown robust efficacy leading to FDA approval of PARP inhibitors (PARPi) in BRCA-associated cancers, data in NSCLC are much less clear. S1900A, a LUNG-MAP substudy, evaluated the PARPi rucaparib in advanced stage NSCLC harboring BRCA1/2 mutations or genomic loss of heterozygosity (LOH) as a phenotypic marker of homologous recombination deficiency (HRD). **Methods:** Eligible patients (pts) were required to have a deleterious mutation in BRCA1/BRCA2 and/or high (≥21%) genomic LOH. Key eligibility criteria: advanced NSCLC patients (pts) with progression on or after platinum based chemotherapy and/or PD-(L)1 antibody and progressed on most recent line of systemic therapy, a Zubrod performance status of 0-1, adequate organ function, no ≥ grade 3 hypercholesterolemia, no previous PARPi exposure and no systemic therapy within 21 days of registration. Pts stratified by histology into two cohorts (squamous [sq] and non-squamous/mixed histology [nsq]). With 40 eligible pts per cohort, the design had 91% power to rule out an ORR of 15% if the true ORR was at least 35% at the 1-sided 5% level. A planned interim analysis on the first 20 pts evaluable for response per cohort required ≥ 3 responses to proceed to full enrollment. **Results:** 64 pts enrolled (27 sq cohort; 37 nsq cohort) of whom 59 are eligible. Median age 65.7 yrs; M/F 33/26 (56/44%); 98% of the pts received at least 1 prior line of treatment for stage IV disease. Biomarker selection included 36 pts (61%) LOH only, 4 pts (7%) BRCA1 only, 11 pts (19%) BRCA2 only, 4 pts (7%) BRCA1 + LOH high and 4 pts (7%) BRCA2 + LOH high. Both cohorts were closed for futility with insufficient responses in the interim analysis populations. In the full study, 4 responses (3 nsq/1 sq) were reported. ORR was 7% (95% CI: 0-13) (9% nsq/4% sq) and DCR was 62% (95% CI: 50-75) (62% nsq/64% sq); 3 of the 4 responders harbored BRCA1/2 mutations and 1 of 4 high LOH; ORR in BRCA1/2+ pts 3/23 (13%). Median PFS was 3.2 months (95% CI: 1.6-4.6) in nsq cohort and 2.9 months (95% CI 1.6-6.2) in sq cohort. Median OS was 7.8 months in nsq cohort and 7.9 months in sq cohort. The most frequent grade ≥3 adverse events were anemia (22%), lymphopenia (8%), fatigue (8%) and transaminitis (5%). **Conclusions:** S1900A failed to show the requisite level of efficacy for rucaparib in advanced NSCLC pts with high genomic LOH and/or a BRCA1/2 mutation. There were no new safety signals and hematologic toxicities were the most frequent adverse events. Genomic LOH as a phenotypic marker of HRD does not predict sufficient activity of rucaparib in NSCLC. These results stand in contrast to the high level of efficacy of PARPi in patients with BRCA-associated or high LOH cancers of other tumor types. Underlying biologic differences in the genomic characteristics of these cancers vs. NSCLC may be responsible. Studies examining this premise are ongoing. (NCT03845296). Clinical trial information: NCT03845296. Research Sponsor: U.S. National Institutes of Health.

9025 **Poster Session**

Anti PD-(L)1 in KRAS mutant advanced nsclcs: A meta-analysis of randomized controlled trials. *First Author: Thierry Landre, UCOG-HUPSSD-APHP, Paris, France*

Background: KRAS comprise the most frequently found oncogene driver mutation in non-small cell lung cancer (NSCLC), accounting for 20-25% of these patients. Single-agent Anti PD-(L)1 clinical efficacy against KRAS mutant NSCLC is a topic of debate. **Methods:** This meta-analysis examined randomized-trial data comparing first-or second line Anti PD-(L)1 +/- chemotherapy (CT) vs CT alone for KRAS mutant advanced NSCLCs. Outcome measures included overall survival (OS) and progression-free survival (PFS). Analyses were computed using the Cochrane method of collaboration for meta-analyses, with Review Manager software (RevMan version 5.3; Oxford, UK). **Results:** We analyzed 3 trials in first line (IMPOWER-150, KEYNOTE-189 and KEYNOTE-042), as well as 3 trials in second line (OAK, POPLAR and CHECKMATE-057) including 1313 NSCLCs (386 KRAS mutant and 927 KRAS wild-type tumor). Anti PD-(L)1 +/- CT was significantly associated (hazard ratio [95% confidence interval]) with prolonged OS (0.59 [0.49-0.72]; $p < 0.00001$) and PFS (0.58 [0.43-0.78]; $p = 0.0003$) compared to CT alone in KRAS mutant NSCLCs. Survival benefits occured in both first and second line. Survival benefits observed in KRAS wild-type NSCLCs were (0.87 [0.76-0.99]; $p = 0.03$) and (0.79 [0.56-1.11]; $p = 0.17$) respectively. OS benefit in KRAS mutant was significantly superior compared to OS benefit in KRAS wild-type (p = 0,001). **Conclusions:** Anti PD-(L)1 (+/- CT) appears superior to CT alone both for mutant and wild-type KRAS in advanced NSCLCs for OS and PFS with higher magnitude of benefit in KRAS mutated group for OS. Research Sponsor: None.

9026 **Poster Session**

Clinical performance of artificial intelligence-powered annotation of tumor cell PD-L1 expression for treatment of immune-checkpoint inhibitor (ICI) in advanced non-small cell lung cancer (NSCLC). *First Author: Hyojin Kim, Department of Pathology, Seoul National University Bundang Hospital, Seongnam, South Korea*

Background: Programmed death ligand 1 (PD-L1) expression is the standard biomarker for first line ICI in advanced NSCLC. However, manual evaluation of tumor proportion score (TPS) by pathologists has practical limitations including intra/inter-observer bias, variation in subjectivity on area of interest and intensive labor. We developed an artificial intelligence (AI)-powered TPS analyzer, namely Lunit SCOPE PD-L1, for objective annotation of tumor cell PD-L1 expression for prediction of ICI response in advanced NSCLC. **Methods**: Lunit SCOPE PD-L1 was developed by a total of 393,565 tumor cells annotated by board-certified pathologists for PD-L1 expression in 802 whole-slide images (WSI) stained by 22C3 pharmDx immunohistochemistry. A After excluding the in-house control tissue regions, the WSI were divided into patches, from which a deep learning-based model detected the location and PD-L1 positivity of tumor cells. The patch-level cell predictions were aggregated for TPS estimation. Clinical performance of the model was validated in an external cohort of 430 NSCLC tumor slides from patients treated with ≥ ICI at Seoul National University Bundang Hospital and Samsung Medical Center. Independent control TPS annotation of this external validation cohort was performed by three pathologists, and their consensus TPS was calculated by mean value of such. **Results**: AI-model (Lunit SCOPE PD-L1) predicts PD-L1-positive tumor cell with the area under the curves of 0.889 and PD-L1-negative tumor cells with that of 0.809 at cell-level analysis. At WSI-level, significant positive correlation was observed between TPS by AI model and control TPS by pathologists (Spearman coefficient = 0.9247, $P < 0.001$). Concordance rate between AI-model and control TPS by pathologists according to expression level of PD-L1 ≥ 50%, 1-49%, and < 1% status was 85.7%, 89.3%, and 52.4%, respectively. Median progression-free survival (mPFS) according to TPS by AI model ≥ 1% vs. < 1% were 2.8 vs. 1.7 months (hazard ratio, HR, 0.52, 95% confidence interval, CI, 0.38-0.71, $P < 0.001$). In contrast, mPFS according to control TPS was 2.8 vs. 2.1 months (HR 0.70, 95% CI 0.55-0.91, $P < 0.001$). Forty out of 84 patients (47.6%) annotated as control TPS < 1% by pathologists were considered as TPS ≥ 1% by AI-model and mPFS of this subgroup was 2.7 months. **Conclusions**: PD-L1 expression by AI-model correlates with PD-L1 expression by pathologists. Clinical performance of AI-model in WSI-level is comparable with assessment by pathologists. The AI-model can accurately predict tumor response and progression-free survival of ICI in advanced NSCLC. Research Sponsor: Lunit Inc.

9027 **Poster Session**

Clinical outcomes for plasma-based comprehensive genomic profiling versus tissue testing in advanced lung adenocarcinoma. *First Author: Ray D. Page, The Center for Cancer and Blood Disorders, Fort Worth, TX*

Background: Somatic genomic testing is recommended by numerous expert guidelines to inform targeted therapy treatment for patients with advanced lung adenocarcinoma (aLUAD). The NILE study was a prospective observational study that demonstrated non-inferiority of cell-free circulating tumor DNA (cfDNA)-based tumor genotyping compared to tissue-based genotyping to find targetable genomic alterations in patients with newly diagnosed aLUAD. As the cohort has matured, clinical outcomes data can now be reported. **Methods:** This prospective, multicenter North American study (NCT03615443) enrolled patients with previously untreated aLUAD who had standard of care (SOC) tissue genotyping performed and concurrent comprehensive cfDNA analysis using the commercially available Guardant360 assay (Guardant Health, Redwood City, CA). After 12 months of study enrollment, objective response rates, disease control rate, and time to treatment data were collected for patients with targetable genomic alterations, as defined by NCCN guidelines, who were treated with physician's choice of therapy. **Results:** Among 282 patients on the study, 89 (31.6%) had an actionable biomarker detected by tissue (21.3%) and/or cfDNA (27.3%) analysis. Sixty-one (68.5%) of these patients were treated with an FDA-approved targeted therapy guided by somatic genotyping results (*EGFR*, *ALK*, *ROS1*). Thirty-three patients were eligible for clinical response evaluation and demonstrated an objective response rate of 58% and disease control rate of 94%. Twenty-five (76%) achieved a durable response > 6 months; 17 (52%) achieved a durable response > 12 months. Patients responded to targeted therapy regardless of the variant allele frequency of the target alteration. The time to treatment (TtT) was significantly faster for cfDNA-informed biomarker detection as compared to tissue genotyping (median 18 vs 31 days, respectively; p = 0.0008). **Conclusions:** This is the first prospective community-based study to find that cfDNA detects guideline-recommended biomarkers at a rate similar to tissue genotyping, and therapeutic outcomes based on plasma-based comprehensive genomic profiling are comparable to published tissue-based targeted therapy clinical outcomes. The NILE study complements and confirms findings in the prospective FLAURA and SLLIP studies, which exclusively enrolled at academic sites. Clinical trial information: NCT03615443. Research Sponsor: Guardant Health.

9029 **Poster Session**

Changes in PD-L1 tumor proportion score are associated with *CD274* gene (encoding PD-L1) copy number variation in non-small cell lung cancer. *First Author: Stephanie Leigh Alden, Harvard Medical School, Boston, MA*

Background: PD-L1 tumor proportion score (TPS) is often used to determine eligibility for first line therapy with immune checkpoint inhibitors (ICIs) in advanced non-small cell lung cancer (NSCLC). However, PD-L1 expression can vary over time and between tumor sites, potentially leading to inaccurate patient stratification. Therefore, it is critical to understand the clinicopathologic and genomic factors that are associated with PD-L1 changes in NSCLC. **Methods:** Clinicopathologic and genomic data were collected from patients with NSCLC and quantitative PD-L1 immunohistochemistry (IHC) on at least two different biopsies. NSCLC biopsies were categorized as PD-L1 negative, low, and high if they had a PD-L1 TPS $<$ 1%, 1-49%, and $\geq$50%, respectively. Intrapatient changes in PD-L1 TPS between samples (DPD-L1) were defined as follows: major decrease (decrease in PD-L1 TPS from $\geq$50% to $<$ 50% or from $\geq$1% to $<$ 1%), major increase (increase in PD-L1 TPS from $<$ 1% to $\geq$1% or $<$ 50% to $\geq$50%), and non-major change (all other cases). Next-generation sequencing (NGS) was used to evaluate copy number (CN) variations at the *CD274* locus, which encodes PD-L1. Wilcoxon and Kruskal-Wallis rank sum tests were used to analyze continuous variables and Fisher's exact test was used to analyze categorical variables. **Results:** Among 250 patients with NSCLC with PD-L1 IHC assays performed on at least two distinct tissue samples, PD-L1 TPS of the first biopsy was $<$ 1% in 104 (41.6%), 1-49% in 80 (32.0%), and $\geq$50% in 66 (26.4%) samples, for a median PD-L1 TPS of 2% (range: 0% to 100%). When intrapatient DPD-L1 was examined, there were major decreases and major increases in PD-L1 TPS in 49 (19.6%) and 65 (26.0%) cases, respectively, and non-major changes were observed in the remaining 136 samples (54.4%), with a median DPD-L1 of 0% (range: -90% to +90%). Baseline PD-L1 TPS and DPD-L1 were not significantly affected by histology, smoking status, sex, or treatment. Among 219 NSCLC samples that underwent tissue NGS and had full CN data available, the median PD-L1 TPS differed significantly based on *CD274* CN: PD-L1 TPS 1% with single copy deletion vs. 5% with copy neutral vs. 42.5% with low amplification vs. 97.5% with high amplification ($p < 0.01$). Among 56 patients with paired PD-L1 TPS and NGS on both samples, there was a significant difference in median DPD-L1 according to *CD274* CN change: DPD-L1 TPS -49% with acquired *CD274* CN loss vs. 0% with no major change in *CD274* CN vs. +1.75% with acquired *CD274* CN gain ($p = 0.01$). **Conclusions:** PD-L1 TPS varies within the same patient in almost half of NSCLC cases, with few clinicopathologic correlates of change in expression. Variation in PD-L1 TPS correlates with changes in *CD274* CN across biopsies. These findings suggest a genomic correlate to predict PD-L1 TPS across samples, as well as a potential complementary method in determining in ICI initiation. Research Sponsor: None.

9030 **Poster Session**

The combination of EGFR-TKIs and anlotinib as a first-line therapy for EGFR-mutant advanced non-small cell lung cancer: A multicenter, single-arm, phase II clinical trial. *First Author: Zhiyong He, Fujian Cancer Hospital & Fujian Medical University Cancer Hospital, Fuzhou, China*

Background: Currently,EGFR-TKIs are widely accepted as the standard treatment for EGFR-mutant advanced non-small-cell lung cancer (NSCLC); however, acquired resistance is inevitable. Combination therapy is considered as a strategy to overcome the resistance to EGFR-TKIs. Anlotinib, a novel multi-targeting, small-molecule TKI, has shown active to suppress tumor angiogenesis and growth. However, there is still a lack of evidence supporting the use of EGFR-TKIs in combination with anlotinib for the treatment of NSCLC until now. A multi-center, single-arm, phase II clinical trial was therefore designed to examine the efficacy and safety of EGFR-TKIs combined with anlotinib for treatment-naïve, advanced NSCLC patients, and unravel the possible mechanisms. **Methods:** This study was conducted in 14 research centers in Fujian, China. The main eligibility criteria were stage IV or relapsed nonsquamous NSCLC with EGFR mutations (exon 19 deletion, and L858R), ECOG score 0-2,and age 20 to 75 years and no previous systemic treatment. Patients with asymptomatic brain metastases were admitted.Eligible patients were given gefitinib (250 mg QD) or icotinib (125 mg TID) in combination with anlotinib (10 mg per day, on days 1–14; 21 days per cycle) until disease progression. The primary endpoint is progression-free survival (PFS) and safety, and the secondary endpoint is overall survival (OS), objective response rate (ORR) and disease control rate (DCR).Peripheral blood was sampled pre-treatment, once every two months during treatment and after disease progression, and T790M mutation was detected in plasma ctDNA using a droplet digital PCR (ddPCR) assay. **Results:** Of 60 patients enrolled (August 2, 2018 to May 28, 2020). As of February 1, 2021, 37 patients (61.7%) experienced PFS events and 10 (16.7%) died. The ORR was 78.3%, and the DCR was100%.Median PFS was 13.0 months (95%CI,10.7-15.3).The 5 most common treatment-related adverse events included rash (63.3%), fatigue (55.0%), hypertension (48.3%), diarrhea (33.3%) and hand-foot syndrome (30.0%), and grade 3 adverse events included hypertension (5.0%), rash (1.67%), hypertriglyceridemia (1.67%), vomiting (1.67%) and elevated ALT (1.67%); no grade 4 adverse events or drug-related deaths were observed. Peripheral blood samples were collected from 36 patients pre-treatment, and 30.6% were identified with low-frequency de novo T790M mutations, with the mutation-allele frequency (MAF) ranging from 0.01% to 0.28%. **Conclusions:** The combination of the first-generation EGFR-TKIs and anlotinib shows impressive ORR and DCR, and acceptable toxicity in treatment-naïve advanced NSCLC patients with activating EGFR mutations, and we observed a high proportion of patients harboring de novo EGFR T790M mutations in this study. Clinical trial information: NCT03720873. Research Sponsor: None.

9031 **Poster Session**

A randomized phase III study comparing carboplatin with nab-paclitaxel versus docetaxel for elderly patients with squamous-cell lung cancer: Capital study. *First Author: Yoichiro Hamamoto, National Hospital Organization Nishisaitama-Chuo National Hospital, Tokorozawa, Japan*

Background: Cytotoxic monotherapy is one of the standard treatments for elderly patients with advanced non-small cell lung cancer (NSCLC). Carboplatin plus nab-paclitaxel demonstrated significantly higher objective response rate (ORR) than carboplatin plus paclitaxel in patients with squamous histology and could improve overall survival (OS) in patients aged $\geq$70 years. Here, we compared carboplatin plus nab-paclitaxel with docetaxel in elderly patients with squamous NSCLC. **Methods:** The CAPITAL study is a multicenter, open-label, phase 3, randomized trial at 92 institutions in Japan. Eligible patients had advanced squamous NSCLC with no prior systemic chemotherapy, aged $\geq$70 years, and had an ECOG performance status of 0 or 1. Patients were randomized 1:1 to docetaxel 60 mg/m^2 (D arm) or carboplatin AUC 6 mg/mL/min plus nab-paclitaxel 100 mg/m^2 weekly (nab-PC arm) for each 21-day cycle. The primary endpoint was OS. This trial is registered with the UMIN Clinical Trials Registry (UMIN000019843) and the Japan Registry of Clinical Trials (jRCTs041180110). **Results:** Between December 2015 and August 2020, 196 patients were randomly assigned to the two treatment arms (D arm, n=98; nab-PC arm, n=98). The median follow-up and age were 11.5 months and 76 years (range: 70–88 years), respectively, and 87% of the patients were male. After the planned interim analysis, the independent data monitoring committee confirmed that the study met the primary endpoint of improved OS in August 2020, and this report represents the final analysis. The nab-PC arm showed significant superiority in OS versus the D arm (hazard ratio [HR], 0.52; 90% CI, 0.38-0.70; median, 16.9 vs. 10.9 months; $p<0.001$). There were also significant improvements in progression-free survival (median, 5.8 vs. 4.0 months; HR, 0.42; 95% CI, 0.30-0.58; $p<0.001$) and objective response rate (66.3 vs. 28.0 %; $p<0.001$) in the nab-PC arm versus the D arm. The most common grade 3 or 4 adverse events were leukopenia (46.3 %), neutropenia (63.2 %), and anemia (38.9 %) in the nab-PC arm, and leukopenia (56.7 %), neutropenia (77.3 %), and febrile neutropenia (17.5 %) in the D arm. As notable adverse events, grade $\geq$2 sensory peripheral neuropathy was observed in 15 (15.8%) and 1 (1.0%) patient in the nab-PC and D arms, respectively. Moreover, serious treatment-related adverse events and treatment-related deaths occurred in 14 (14.7%) and 12 (12.4%) patients and in two and one patient in the nab-PC and D arms, respectively. **Conclusions:** The nab-PC arm had a significantly improved OS than the D arm among elderly patients with squamous NSCLC. Carboplatin plus nab-paclitaxel became a new standard treatment for these patients. Clinical trial information: UMIN000019843. Research Sponsor: Taiho Pharmaceutical.

9032 **Poster Session**

Response to selpercatinib versus prior systemic therapy in patients (pts) with *RET* fusion+ non-small-cell lung cancer (NSCLC). *First Author: Alexander E. Drilon, Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY*

Background: Selpercatinib, a first-in-class highly selective, potent, CNS-active RET kinase inhibitor, is approved in multiple countries for treatment of *RET* fusion+ lung or thyroid cancers. Selpercatinib demonstrated durable antitumor activity in previously treated pts with *RET* fusion+ NSCLC in an ongoing Phase 1/2 trial, LIBRETTO-001 (Besse et al., ASCO 2021). **Methods:** Pts with *RET* fusion+ NSCLC enrolled in the global, multicenter, LIBRETTO-001 trial (NCT03157128; 16 countries, 89 sites). Primary endpoint was objective response rate (ORR). Secondary endpoints included progression-free survival, duration of response, and safety. This post-hoc intrapatient analysis was based on a 30 March 2020 data cutoff date. Historical physician-reported best overall response (BOR) from last systemic therapy received prior to enrollment was compared with selpercatinib BOR by independent review committee per RECIST v1.1, with each patient serving as his/her own control. **Results:** In efficacy-evaluable pts (N = 218) who previously received platinum-based chemotherapy (chemo), median pt age was 61 years, the majority with ECOG of 0/1 (37%/61%), with a median of 2 (range: 1-15) prior systemic therapies. Overall, 57% of patients responded to selpercatinib while 16% responded to the immediate prior therapy. ORR improvements with selpercatinib were observed regardless of prior therapy: chemotherapy + immune checkpoint inhibitor (ICI) (57% vs 14%), single-agent ICI (48% vs 3%), or chemotherapy (58% vs 15%). A total of 108 patients (49%) did not respond to immediate prior therapy but responded to selpercatinib. Fewer patients had progressive disease as their BOR with selpercatinib (2%) compared to the immediate prior therapy (28%). The median duration of therapy for selpercatinib was notably extended compared with that of the immediate prior therapy (11.8 vs. 3.4 months, respectively). **Conclusions:** In pts with *RET* fusion+ NSCLC treated on LIBRETTO-001, systemic therapies administered prior to enrollment achieved less meaningful clinical benefit than selpercatinib. Selpercatinib demonstrated consistent efficacy regardless of the type of prior therapy. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

9033 **Poster Session**

Second-line nintedanib plus docetaxel for patients with lung adenocarcinoma after failure on first-line immune checkpoint inhibitor combination therapy: Initial efficacy and safety results from VARGADO Cohort C. *First Author: Christian Grohé, Department of Pneumology, ELK Berlin, Berlin, Germany*

Background: The treatment landscape in advanced non-small cell lung cancer (NSCLC) has undergone significant changes, with immune checkpoint inhibitor (ICI) +/- chemotherapy now the preferred first-line (1L) regimen for metastatic, non-mutated NSCLC. However, only limited clinical data are available to guide subsequent treatment selection. Nintedanib (Vargatef), an oral triple angiokinase inhibitor targeting the vascular endothelial growth factor receptor (VEGFR), platelet-derived growth factor receptor (PDGFR), and fibroblast growth factor receptor (FGFR) pathways, is approved in the EU and other countries in combination with docetaxel for the treatment of advanced adenocarcinoma NSCLC after failure on 1L chemotherapy. **Methods:** This analysis is part of the ongoing, prospective, non-interventional VARGADO study (NCT02392455) of nintedanib + docetaxel. Here, we present initial efficacy and safety results from 100 patients (pts) with adenocarcinoma NSCLC in Cohort C, who received second-line (2L) nintedanib + docetaxel after failure on prior 1L ICI in combination with chemotherapy. **Results:** In Cohort C, the median age was 63 years (range: 43–84); 58 pts (58.0%) were men, and 71 pts (71.0%) had ECOG PS 0/1. Ninety-five pts (95.0%) had received prior 1L pembrolizumab-based combination therapy. Thirty-nine pts (39.0%) had progressed within 6 months after the start of 1L therapy, and 66 pts (66.0%) had progressed within 9 months. Objective response rate with 2L nintedanib + docetaxel was 37.3% (22/59 pts), disease control rate was 67.8% (40/59 pts), and median progression-free survival (PFS) was 4.4 months (95% confidence interval [CI]: 2.6–6.6). Among pts who had experienced disease progression $<$ 9 months after the start of 1L therapy (n = 66), median PFS from the start of 2L nintedanib + docetaxel was 4.1 months (95% CI: 2.5–6.6). Among pts with disease progression $\geq$9 months after the start of 1L therapy (n = 34), median PFS from the start of 2L nintedanib + docetaxel was 8.5 months (95% CI: 2.4–not estimable). Grade $\geq$3 treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to treatment discontinuation were observed in 47 pts (47.0%), 37 pts (37.0%) and 28 pts (28.0%), respectively. **Conclusions:** Initial data from VARGADO Cohort C provide the first evidence that 2L nintedanib + docetaxel has encouraging and clinically meaningful efficacy, and a manageable safety profile in pts with advanced adenocarcinoma NSCLC following progression on 1L ICI in combination with chemotherapy. Clinical trial information: NCT02392455. Research Sponsor: Boehringer Ingelheim Pharma GmbH & Co. KG.

9034 **Poster Session**

Phase II trial of atezolizumab (A) + carboplatin (C) + pemetrexed (P) + bevacizumab (B) in pts with stage IV non-squamous non-small cell lung cancer (NSq-NSCLC): Big Ten Cancer Research Consortium Study LUN 17-139. *First Author: Fatemeh Ardeshir-Larijani, Indiana University, Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: The addition of A to C+ Paclitaxel (Pac) + plus B improved progression free survival (PFS) and overall survival (OS) compared with C + Pac + B alone in pts with metastatic NS-NSCLC. However, C + Pem is more commonly used for this patient population with a shorter infusion time and favorable toxicity profile compared with Pac. **Methods:** Multicenter single arm phase II clinical trial of chemo and immunotherapy-naïve pts with stage IV NSq-NSCLC. All pts received A (1200 mg, D1) + C (AUC 5, D1) + P (500 mg/m2, D1) + B (15mg/kg D1) q3 week x4. If non-PD, pts could receive maintenance APB until PD or intolerable side effects. The primary endpoint was 1 yr. PFS. Sample size of 42 planned with 87% power and two-sided type I error of 0.05 for 1 yr PFS. Secondary endpoints included ORR, disease control rate (DCR) [defined by CR + PR + SD], and toxicity. **Results:** 30 pts were enrolled from 11/15/2018 to 10/5/2020. The study was closed early due to 3 patient deaths, possibly related to treatment (VTE, Febrile neutropenia, colonic perforation). Median age 64 (range 38-83); M/F 20/10; mutations in EGFR/ALK/KRAS/BRAF (5/1/4/2); PD-L1 TPS $<$ 1%/ 1-49%/ $>$ 50% (9/14/6) and one pt did not have PDL-1 status. Median f/u was11.6 mos (range 1-20). ORR 35.71% (95% CI: 18.64%-55.95%), DCR 92.85% (95% CI: 83%-100%). 1yr PFS and OS were 55.27% and 82.90% respectively. The most common G III and G II toxicity were HTN (20%) and fatigue (33.3%).3 pts had G IV toxicity (Anemia, Febrile neutropenia and colonic perforation) and 2 pts had Grade (G) V toxicity (VTE, Hypoxia/Sepsis). **Conclusions:** Atezolizumab + Carboplatin + Pemetrexed + Bevacizumab was associated with longer DCR, PFS, and OS than historical controls. 3 on-treatment deaths, possibly related to therapy (more likely bevacizumab), prompted early closure. A phase 3 study evaluating this regimen is ongoing by another group NCT03786692. Clinical trial information: NCT03713944. Research Sponsor: Genentech.

9035 **Poster Session**

Efficacy and safety of pan-ErbB inhibitor pyrotinib combined with antiangiogenic agent apatinib for HER2-mutant or amplified metastatic NSCLC: A phase II clinical study. *First Author: Guangjian Yang, Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Tumor angiogenesis could be induced by activation of HER2 receptor, and currently, there is lack of clinical evidence of anti-HER2 tyrosine kinase inhibitors (TKIs) combined with antiangiogenic therapy for HER2-mutant or amplified non-small cell lung cancer (NSCLC). We conducted a study to explore the efficacy and safety of a pan-ErbB inhibitor pyrotinib combined with apatinib for metastatic NSCLC patients harboring HER2 amplification or activating mutations. **Methods:** This was a single-center, single-arm phase II study with Simon's optimal two-stage design. Metastatic NSCLC patients with ECOG scores of 0-1 and harboring primary HER2 amplification, exon 20 insertion or activating missense mutations who had failed to prior chemotherapies or anti-HER2 TKIs were eligible to be enrolled. All patients received oral pyrotinib (400mg once daily) combined with apatinib (250mg once daily) therapy. The primary endpoint was objective response rate (ORR), and second endpoints included progression-free survival (PFS), duration of response (DoR), disease control rate (DCR), overall survival (OS) and safety. **Results:** Between March 5, 2019, and December 1, 2020, 33 metastatic NSCLC patients with HER2 alterations were enrolled, including exon 20 insertions (A775_G776insYVMA, 20/33; P780_Y781insGSP, 6/33; other variants, 2/33), missense mutations (3/33), and primary HER2 amplification (2/33). Seventeen patients (51.5%) were pretreated with first-line platinum-based chemotherapies or anti-HER2 TKIs, and the remaining had received at least 2 lines of prior therapies (range, 2-6). At the last follow-up time January 23, 2021, the overall ORR and DCR were 45.5% (15/33) and 93.9% (31/33), respectively. The median PFS was 6.8 (95%CI: 5.4-8.2) months. The median DoR and OS were 5.3 (95%CI: 0-11.8) and 12.9 (95%CI: 8.6-17.2) months, respectively. The mPFS was significantly longer in patients who received second-line pyrotinib combined with apatinib therapy than those in third- or above-line settings (9.8 *vs.* 5.3 months, P = 0.018, HR = 0.281 [95%CI: 0.098-0.807]). Although pyrotinib combined with apatinib therapy showed similar ORRs in patients with presence (46.2%, 6/13) or absence (45.0%, 9/20) of brain metastases, and those in second-line (47.1%, 8/17) or above-line settings (43.8%, 7/16). Common treatment-related adverse events (AEs) were grade 1-2, mainly including diarrhea (90.9%), hypertension (72.7%), asthenia (63.6%), anorexia (54.5%) and nausea (51.5%). Grade 3 AEs were diarrhea (3.0%) and hypertension (9.1%). No grade 4 or 5 AE or treatment-related deaths were reported. **Conclusions:** Pyrotinib combined with apatinib showed potent anti-tumor activity and acceptable safety profile in metastatic NSCLC with HER2 amplification or activating mutations. Clinical trial information: ChiCTR1900021684. Research Sponsor: None.

9036 **Poster Session**

Treatment outcome and functional characterization of uncommon EGFR mutations in the German National Network Genomic Medicine Lung Cancer (nNGM). *First Author: Melanie Janning, Personalized Medical Oncology, German Cancer Research Center (DKFZ), Heidelberg, Personalized Oncology, University Hospital Mannheim, Department of Oncology, Hematology and BMT, University Medical Center Hamburg Eppendorf, Heidelberg, Germany*

Background: The nNGM centralizes molecular diagnostics, treatment recommendations and follow-up reporting in NSCLC in Germany. Uncommon EGFR mutations pose a clinical challenge because they comprise a heterogenous group and analyses of treatment outcome are still scarce. Here, we analyzed follow-up data of patients with rare EGFR mutations and performed functional characterization of recurrent mutations with unknown function. **Methods:** This multicenter, retrospective analysis of uncommon EGFR mutations (excluding L858R-, T790M mutations and exon 19 deletions) includes stage IV patients with NSCLC from 12 nNGM centers. We categorized EGFR-mutations into 3 groups: uncommon EGFR mutations with known driver function, for instance E709X, G719X, S768I and L861Q (group 1), exon 20 insertions (group 2) and all other very rare mutations (group 3). Functional characterization of unknown mutations was performed by insertion mutagenesis in Ba/F3 cells and monitoring of growth factor-independent proliferation. **Results:** In total, 834 cases with uncommon EGFR mutations were reported. Follow-up data after EGFR-TKI (Erlotinib, Gefitinib, Afatinib and Osimertinib), chemotherapy and/or mono-PD(L)1 blockade was available for 252 patients. Mean progression free survival (mPFS) on EGFR-TKIs vs. chemotherapy was 6.6 months vs. 5.0 months (HR 0.54, 95%CI 0.35 to 0.81, P = .003) in group 1 (n = 84), and 6.7 months vs. 3.4 months (HR 0.66, 95%CI 0.47 to 0.92, P = .015) in group 3 (n = 104). Mono-anti-PD(L1) blockade was not superior to chemotherapy (group 1, mPFS 3.0 months, HR 1.32, 95% 0.55 – 3.15, P = .535 and group3, mPFS 4.3 months, HR 1.02, 95% CI 0.64 – 1.62, P = 0.951). Exon 20 insertions (group 2, n = 63) did not benefit from EGFR-TKIs or anti-PD(L1) blockade vs. chemotherapy. Overall survival (OS) analysis (n = 218) following chemotherapy (56%) or EGFR-TKI treatment (44%) showed median OS (mOS) of 18.0 months vs. 13.9 months in patients treated with EGFR-TKI and chemotherapy, respectively in group 1 (HR 0.97, 95%CI 0.54 to 1.75, P = .929). In group 3 patients treated with EGFR-TKI and chemotherapy had a mOS of 35.4 months vs. 12.0 months, respectively (HR 0.59, 95%CI 0.35 to 1.01, P = .056). In the Ba/F3 system we could identify 8 recurrent driver and 12 non-driver mutations with a clinically applicable assay turnaround time of 4 weeks to inform clinical decision-making in the future. **Conclusions:** This real-world dataset confirms that patients with group 1(uncommon) EGFR mutations benefit from EGFR-TKIs and indicates that mono-anti PD(L)1 blockade is not superior to chemotherapy. Furthermore, patients with very rare EGFR mutations (group 3) also experienced a PFS benefit from EGFR-TKI compared to chemotherapy while immune therapy was not beneficial. Research Sponsor: Deutsche Krebshilfe, Hector Stiftung, Margarete Clemens Stiftung.

9037 **Poster Session**

A randomized phase II study comparing nivolumab (NIVO) with carboplatin-pemetrexed (CbPEM) for patients (pts) with EGFR mutation-positive non-small cell lung cancer (NSCLC) who acquire resistance to tyrosine kinase inhibitors (TKIs) not due to a secondary T790M mutation (WJOG8515L). *First Author: Hidetoshi Hayashi, Kindai University Faculty of Medicine, Osaka, Japan*

Background: Although the efficacy of antibodies to programmed cell death–1 (PD-1) appears to be less pronounced in patients with NSCLC harboring epidermal growth factor receptor gene (*EGFR*) mutations, patients who develop disease progression (PD) to TKIs due to mechanisms other than secondary T790M mutation of *EGFR* might be more likely to benefit from NIVO. Here, we report the results of first randomized phase II trial to compare NIVO with the CbPEM in those population. **Methods:** Pts with advanced *EGFR* mt NSCLC who experienced PD after EGFR-TKIs were randomized 1:1 to NIVO or CbPEM. Eligibility criteria included the treatment history with TKIs as follow; no evidence of T790M after PD on 1st/2nd generation (gen) TKIs (A) after PD on 3rd gen TKIs as a 2nd line for T790M positive tumor (B) or 3rd gen TKIs as a front-line (C). The primary end point is progression-free survival (PFS) and biomarker analysis were included for exploratory analysis. **Results:** A total of 102 patients was randomized. Median PFS and overall survival (OS) were 1.7 and 20.7 months (mo), respectively, for NIVO arm (n = 52) versus 5.6 and 19.9 months for CbPEM (n = 50) (Hazard ratio [HR] = 1.92 and 0.88, respectively). Overall response rate and duration of response were 9.6% and 5.3 months for NIVO and 36.0% and 5.5 months for CbPEM. PD-L1 expression on tumor cells and tumor mutation burden (TMB) were evaluated in 77 (TPS 0%. 1-49%, > 50%, n = 46, 20, and 11) and 50 (Median TMB 6.2mt/mb). Immune-related gene expression profiling was under evaluation and the results will be demonstrated in the meeting. The efficacy of NIVO in PD-L1 strong positive (>50%, n = 8) and no evidence of T790M after PD on 1st/2nd gen TKIs (n = 29) was tended to be better than their counterparts. There was no significant correlation between TMB and the efficacy of NIVO. Pneumonitis was observed in one patient (1.0%) for NIVO arm and no new safety signals were noted. **Conclusions:** NIVO was not associated with longer PFS than CbPEM in selected pts with advanced *EGFR* mt NSCLC. OS was similar between groups. Baseline PD-L1 status and genetic alteration features may be relevant predictive markers to select pts who would benefit from NIVO. Clinical trial information: jRCTs051180133. Research Sponsor: Ono Pharmaceutical Co. Ltd.

	PFS for entire population	OS for entire population	PFS by PD-L1 (0%, 1-49%, 50%)	OS by PD-L1 (0%, 1-49%, 50%)	PFS by TMB (Low, High cutoff 6.2mt/mb)	OS by TMB (High, Low cutoff 6.2mt/mb)	PFS by resistance mechanisms (A, B, C)	OS by resistance mechanisms (A, B, C)
NIVO (Median, months)	1.7	20.7	1.4/2.2/4.6	17.9/18.0/NR	2.1/1.7	19.1/15.3	2.7/1.3/NR	19.9/22.7/NR
CbPEM (Median, months)	5.6	19.9	3.6/5.3/5.6	20.7/19.9/NR	2.9/2.5	12.2/9.5	5.8/4.9/3.2	19.0/17.9/13.3
Hazard ratio (NIVO vs CbPEM)	1.92	0.88	1.67/2.10/1.49	0.90/2.50/0.72	1.06/1.22	0.59/0.32	1.62/13.3/0.43	0.99/0.79/0.29

9038 **Poster Session**

Health-related quality of life for pembrolizumab (pembro) plus ipilimumab (ipi) versus pembro plus placebo in patients with metastatic NSCLC with PD-L1 tumor proportion score ≥ 50%: KEYNOTE-598. *First Author: Mehmet Nahit Sendur, Ankara Yõldõrõm Beyazõt University, Faculty of Medicine and Ankara City Hospital, Ankara, Turkey*

Background: In the phase 3 KEYNOTE-598 study (NCT03302234), OS (HR, 1.08; 95% CI, 0.85–1.37; $P = 0.74$) and PFS (1.06; 95% CI, 0.86–1.30; $P = 0.72$) were not improved for pembro + ipi vs pembro + placebo in patients (pts) with previously untreated metastatic NSCLC with PD-L1 tumor proportion score (TPS) ≥50% and without *EGFR/ALK* genomic alterations. Incidence of treatment-related grade 3–5 AEs, fatal AEs, and AEs leading to discontinuation was higher with pembro + ipi vs pembro + placebo. We present prespecified patient-reported outcome (PRO) analyses from KEYNOTE-598. **Methods:** Pts (n = 568) with previously untreated stage IV NSCLC with PD-L1 TPS ≥50% were randomized 1:1 to pembro 200 mg Q3W for up to 35 cycles + ipi 1 mg/kg or placebo Q6W for up to 18 cycles. The EORTC QLQ-C30, QLQ-LC13, EQ-5D-5L, and NSCLC-SAQ were administered at cycles 1–7, then every 3 cycles through cycle 19, and every 4 cycles until PD or a maximum of 35 cycles. Change from baseline in global health status (GHS)/quality of life (QoL) score from the QLQ-C30 and the time to true deterioration (TTD) in the composite endpoint of cough (LC13), chest pain (LC13), or dyspnea (C30) were secondary objectives in KEYNOTE-598. Change from baseline in GHS/QoL was analyzed using a constrained longitudinal data analysis model with missing at random assumption. Difference in TTD was evaluated using a Cox proportional hazards model and stratified log-rank test. PROs were analyzed in all pts who completed ≥1 PRO assessment and received ≥1 dose of study treatment. *P* values are two-sided and nominal. **Results:** As of data cutoff (Sept 1, 2020), PRO analyses included 280 pts in the pembro + ipi group and 280 pts in the pembro + placebo group. QLQ-C30 completion rates were 95.7% in the pembro + ipi group vs 96.1% in the pembro + placebo group at baseline and 63.6% vs 70.0% at week 18. QLQ-LC13 completion rates were 95.4% vs 96.4% at baseline and 63.6% vs 69.6% at week 18. Mean QLQ-C30 GHS/QoL scores at baseline were 62.8 in the pembro + ipi group and 64.2 in the pembro + placebo group and were similar between the groups across the follow-up period. Least squares (LS) mean (95% CI) change from baseline to week 18 in GHS/QoL scores was improved in both groups (pembro + ipi: 3.7 [0.9–6.5]; pembro + placebo: 4.1 [1.4–6.9]), with no significant difference between groups (LS mean difference −0.4 [−4.0 to 3.1], $P = 0.82$). Median TTD in composite of cough, chest pain, or dyspnea was not reached (NR; 95% CI, 13.0 mo–NR) in the pembro + ipi group vs 20.0 (95% CI, 12.7–NR) mo in the pembro + placebo group (hazard ratio, 0.98 [95% CI, 0.74–1.30]; $P = 0.91$). **Conclusions:** There was no difference in health-related QoL or TTD in lung cancer symptoms between pembro + ipi and pembro + placebo in pts with previously untreated metastatic NSCLC with PD-L1 TPS ≥50%. Clinical trial information: NCT03302234. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

9039 **Poster Session**

Whole-exome sequencing in advanced-stage sensitizing *EGFR* mutation non-small cell lung cancer: Explore resistance biomarkers to EGFR TKI treatment. *First Author: Chanida Vinayanuwattikun, Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Background: Despite the development of predictive biomarkers to shape treatment paradigms and outcomes, 10-20% of *de novo* EGFR TKI resistance advanced non-small cell lung cancer (NSCLC) in the presence of *EGFR* mutation remains the issue of concern. **Methods:** We explored clinical factors in 332 advanced NSCLC who received EGFR TKI and molecular characteristics through 65 whole exome sequencing of various EGFR TKI responses including; *de novo* (progression within 3 months), intermediate response (IRs) and long-term response (LTRs) (durability > 2 year). **Results:** Uncommon *EGFR* mutation subtype was a significant variable in *de novo* resistance vs. IRs and LTRs with odd ratios of 6.83 ([95% CI 2.36 – 19.80], p-value < 0.001) and 16.84 ([95%CI 1.66 – 171.45, p-value 0.02), respectively. The remaining sensitizing *EGFR* mutation subtype (exon 19 del and L858R) accounted for 75% of *de novo* resistance. Genomic landscape analysis was conducted, focusing in 10 frequent oncogenic signaling pathways with functional contributions; cell cycle, Hippo, Myc, Notch, Nrf2, PI-3-Kinase/Akt, RTK-RAS, TGF-β, p53 and β-catenin/Wnt signaling. Cell cycle pathway was the only significant alteration pathway among groups with the FDR p-value of 6×10^{-4}. We found only significant q-values of < 0.05 in 7 gene alterations; *CDK6, CCNE1, CDK4, CCND3, MET, FGFR4* and *HRAS* which enrich in *de novo* resistance [range 36-73%] compared to IRs/LTRs [range 4-22%]. Amplification of *CDK4/6* was significant in *de novo* resistance, contrary to IRs and LTRs (91%, 27.9% and 0%, respectively). The presence of co-occurrence *CDK4/6* amplification correlated with poor disease outcome with HR of progression-free survival of 3.63 [95% CI 1.80-7.31, p-value < 0.001]. **Conclusions:** The presence of *CDK4/6* amplification in pretreatment specimen serve as a predictive biomarker for *de novo* resistance in sensitizing *EGFR* mutation. Research Sponsor: Chulalongkorn Academic Advancement into Its 2nd Century (CUAASC) Project .

9040 **Poster Session**

Phase II study of brigatinib in ROS1 positive non-small cell lung cancer (NSCLC) patients previously treated with crizotinib: Barossa cohort 2. *First Author: Haruko Daga, Department of Medical Oncology, Osaka City General Hospital, Osaka, Japan*

Background: Brigatinib is a next-generation tyrosine kinase inhibitor targeting ALK and ROS1. Crizotinib is the first drug approved for the treatment of ROS1 fusion-positive NSCLC. Standard treatment for crizotinib-resistant ROS1 positive NSCLC is not established. Barossa is a multicenter, phase II basket, study of brigatinib in patients with ROS1 positive solid tumors. This study is composed of three cohorts. ROS1 inhibitor-naïve ROS1 positive NSCLC patients were enrolled in the cohort 1, and ROS1 positive NSCLC patients previously treated with crizotinib were enrolled in the cohort 2. Patients with ROS 1 positive solid tumors other than NSCLC were enrolled in the cohort 3. This time we report the cohort 2 results. **Methods:** Patients with advanced, previously treated with crizotinib, ROS1 positive NSCLC received brigatinib at a dose of 180 mg once daily with a 7-day lead-in period at 90 mg. The primary end point was objective response rate (ORR; RECIST 1.1) by independent review. Key secondary endpoint was PFS, OS, and safety. The sample size was set at 19 patients, with a one-sided alpha of 0.05, beta of 0.2, and threshold and expected values for primary endpoint of 20% and 50%, respectively. **Results:** From July 2019 and Jan 2020, 19 patients were enrolled from 9 institutions. Baseline characteristics as follows: median age (range): 60 (31-75) years; women, n = 10 (53%); ECOG PS of 0 to 1, n = 18 (95%); never smoker, n = 11 (58%); tumor histopathological type: adenocarcinoma, n = 18 (95%). Five and 6 patients achieved PR and SD, respectively at data cutoff date of 30 Oct 2020. The ORR was 26.3% (90%CI, 11.0-47.6), and the disease control rate was 57.9% (95%CI, 33.5-79.7). The median duration of follow-up for PFS was 12.0 months. The median PFS was 7.3 months (95% CI, 1.3-9.3), and the 1-year PFS rate was 26.9% (95%CI, 9.2-48.6). Grade ≥3 TRAEs were CPK increased (21.1%), infection (5.3%), AST and/or ALT increased (5.3%), hypercalcemia (5.3%), anorexia (5.3%), hypoxia (5.3%), erythema (5.3%), hypertension (5.3%). Pneumonitis was observed in one patient (5.3%, Grade 2). No treatment-related death was observed. **Conclusions:** Brigatinib has modest activity for ROS1 positive NSCLC patients previously treated with crizotinib. The safety profile of brigatinib was consistent with previous studies. Enrollment of the cohort 1 for ROS1 inhibitor-naïve NSCLC patients is ongoing, and the data will be presented at a future congress. Clinical trial information: JapicCTI-194851. Research Sponsor: AMED.

9041 **Poster Session**

Determination of clinical benefit among patients with radiological stable disease to immune checkpoint inhibitors. *First Author: Jia Luo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: SD is a common but ambiguous outcome in patients receiving immune checkpoint inhibitors (ICIs) and likely represents a heterogenous mix of responders and non-responders. This study aimed to characterize SD and identify the subset of patients with SD who are benefiting from treatment. The ability to distinguish whom among patients with SD is actually benefiting from treatment would facilitate drug development and improve precision in correlative research. **Methods:** A systematic review was performed to characterize SD in ICI trials. SD and objective response was compared to proliferation index using TCGA gene expression data. To identify a subgroup of SD with outcomes mirroring responders, we examined a discovery cohort of NSCLC treated with ICIs and had RECIST assessment. In patients with best overall response (BOR) of SD, serial cutpoints of two variables, % BOR and PFS, were tested to define a subgroup with similar survival as PR-minor (patients with partial response [PR] and % shrinkage $<$ median among responders). Results were then tested in two external validation cohorts (n = 326, n = 381). **Results:** Among trials of ICIs (59 studies, 14,280 patients), SD ranged from 16-42% in different tumor types and was associated with disease-specific proliferation index (Spearman rho = -0.75, p = 0.03), a proxy of tumor kinetics, rather than relative response to ICIs. In a discovery cohort of 1220 patients with NSCLC who were treated with ICIs, 26% had SD, 19% had PR/CR, and 55% had PD. Outcomes among those with SD ranged widely (OS range 0.5-76 months, PFS range 0.2-49 months). The subset of SD with PFS $>$ 6 months and no tumor growth mirrored PR-minor (OS HR 1.0) and was proposed as the definition of "SD-responder". SD-responders (n = 87) represented 7% (95% CI 6-9%) of the overall population and 28% (95% CI 23-33%) of the SD population. This definition was confirmed in two validation cohorts from trials of NSCLC treated with durvalumab. **Conclusions:** RECIST-defined SD to immunotherapy is common, heterogenous, and may largely reflect tumor growth rate rather than ICI response. In patients with NSCLC and SD to ICIs, PFS $>$ 6 months and no tumor growth (~1/3 of SD) may be considered "SD responders." This definition may improve the efficiency of and insight derivable from clinical and translational research. Research Sponsor: NIH.

9042 **Poster Session**

Brigatinib in Japanese patients with anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer (NSCLC): First results from the J-ALTA tyrosine kinase inhibitor (TKI)-naive expansion cohort. *First Author: Masashi Kondo, Department of Respiratory Medicine, Nagoya University Graduate School of Medicine, Nagoya, Japan*

Background: Brigatinib is a next-generation ALK inhibitor with demonstrated activity against ALK mutations. We report primary analysis results with brigatinib in Japanese patients with ALK-positive NSCLC who have not previously been treated with an ALK TKI in the phase 2 J-ALTA study (NCT03410108). **Methods:** J-ALTA, a multi-cohort study, included a TKI-naive expansion cohort. Patients in the TKI-naive cohort received brigatinib 180 mg qd with 7-day lead-in at 90 mg. Primary endpoint was 12-month progression-free survival (PFS) as assessed by an independent-review committee (IRC). Secondary endpoints included confirmed objective response rate (ORR; IRC- and investigator-assessed); IRC-assessed PFS and duration of response (DoR); overall survival (OS); intracranial PFS (iPFS by IRC); and safety. **Results:** A total of 104 patients were enrolled in the whole study; of these, 32 patients had TKI-naive NSCLC (median age, 60.5 y; 94% had adenocarcinoma; 22% had baseline brain metastases; 25% received prior chemotherapy). As of September 29, 2020, median follow-up was 14.2 months and 27 patients remained on treatment. IRC-assessed 12-month PFS was 93% (90% CI, 79–98). Confirmed ORR was 97% (90% CI, 84–100) by IRC, with 2 complete responses and 29 partial responses. Median DoR as assessed by the IRC was not mature; median PFS, iPFS, and OS were not reached. In the TKI-naive cohort, treatment-emergent adverse events (TEAEs) were reported in all 32 patients (most common: increased creatine phosphokinase, 81%; hypertension, 59%; diarrhea, 47%). Grade $\geq$3 TEAEs were reported in 91% of patients in this cohort (most common: increased creatinine phosphokinase, 44%; hypertension, 34%; increased lipase, 19%) and 75% of all patients. Three cases (9.4%) of interstitial lung disease/pneumonitis were reported in the TKI-naive cohort; all were grade 1 and occurred after day 15 of brigatinib treatment. Dose discontinuations/interruptions/reductions due to AEs in the TKI-naive cohort were 0%/94%/66%, respectively, and in the total study population were 5%/72%/41%. AE frequency and profile were similar in the TKI-naive and overall cohorts. **Conclusions:** In the J-ALTA TKI-naive cohort, brigatinib demonstrated substantial efficacy and manageable safety in the Japanese patient population. Brigatinib remains one of the treatment options in Japanese patients. Clinical trial information: NCT03410108. Research Sponsor: ARIAD Pharmaceuticals, Inc., a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

9043 **Poster Session**

A large real-world study on the effectiveness of the combined inhibition of *EGFR* and *MET* in *EGFR*-mutant advanced non-small cell lung cancer (NSCLC). *First Author: Liu Li, Hunan Cancer Hospital, Changsha, China*

Background: *MET* amplification is an important mechanism mediating acquired resistance to EGFR tyrosine kinase inhibitors (TKI). Until now, no consensus exists on the standard treatment strategy for this subset of patients due to the lack of clinical data from large cohort or controlled trials. In our clinical practice, three regimens were commonly administered to patients after *MET* amplification-mediated EGFR-TKI progression: EGFR-TKI and MET-TKI combination therapy, MET-TKI monotherapy, or chemotherapy. Our study aimed to compare the effectiveness of these three regimens. **Methods:** Seventy patients with *EGFR*-mutant advanced NSCLC who progressed from prior EGFR-TKI through the acquisition of *MET* amplification and received treatment between March 2015 and March 2020 were included in this study. Of them, 38 received EGFR-TKI plus crizotinib, 10 received crizotinib monotherapy, and 22 received platinum-based doublet chemotherapy. Somatic mutation profiling was performed on blood and tissue biopsy samples. Resistance mechanisms to the combination targeted therapy were also explored in 12 patients. **Results:** The objective response rate (ORR) and disease control rate (DCR) were 47.5% and 84.0% for EGFR-TKI+crizotinib group, 40.0% and 70.0% for crizotinib monotherapy group, and 18.2% and 50.0% for chemotherapy group, respectively. The EGFR-TKI+crizotinib group had significantly better ORR (P = 0.026) and DCR (P = 0.016) than the chemotherapy group but was not statistically different from the crizotinib monotherapy group (ORR, P = 0.73; DCR, P = 0.39). Progression-free survival (PFS) was significantly longer for the EGFR-TKI+crizotinib group than those who received crizotinib monotherapy (5.0 vs 2.3 months, P = 0.004) or chemotherapy (5.0 vs 2.9 months, P = 0.036), but overall survival was comparable (10.0 vs 4.1 vs 8.5 months, P = 0.088). *TP53* mutation (58.5%) and *EGFR* amplifications (42.9%) were the two common concurrent mutations in the three cohorts. PFS was significantly longer for patients with either concurrent *TP53* mutation (n = 17) (6.0 vs 2.3 vs 2.9 months, P = 0.009) or concurrent *EGFR* amplification (n = 13) (5.0 vs 1.2 vs 2.4 months, P = 0.016) who received EGFR-TKI+crizotinib. Potential molecular mechanisms of acquired resistance to EGFR-TKI+crizotinib therapy included *EGFR* T790M (n = 2), *EGFR* L718Q (n = 1), *EGFR* S645C (n = 1), *MET* D1228H (n = 1), *BRAF* V600E (n = 1), *NRAS* Q61H (n = 1), and amplifications in *KRAS* (n = 2), *ERBB2* (n = 1), *CDK4* (n = 1), and *MYC* (n = 2). **Conclusions:** Our study provides real-world clinical evidence, in the largest cohort to date, that simultaneous inhibition of *EGFR* and *MET* improves clinical outcomes of patients with *EGFR*-mutant NSCLC who acquired *MET* amplification from prior EGFR-TKI therapy, indicating that combinatorial regimen of EGFR-TKI and MET-TKI could be a more effective therapeutic strategy in this subset of patients. Research Sponsor: National Natural Science Foundation of China, Other Foundation.

9044 **Poster Session**

Differential immune-related microenvironment determines PD-1/PD-L1 blockade efficacy in advanced non-small cell lung cancer patients. *First Author: Masayuki Shirasawa, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: Programmed death ligand-1 (PD-L1) expression is not a completely reliable predictive marker of the efficacy of anti-programmed cell death protein-1 (PD-1)/anti-PD-L1 therapy in advanced non-small cell lung cancer patients (NSCLC). Immune-related tumor microenvironment (TME) is classified into four different types based on the status of tumor-infiltrating lymphocytes (TILs) and PD-L1 expression. **Methods:** We retrospectively reviewed advanced NSCLC patients treated with anti-PD-1/anti-PD-L1 therapy between 2015 and 2019, and investigated the association between the efficacy of anti-PD-1/anti-PD-L1 therapy, the types of TME based on PD-L1 (clone: 22C3) expression, and the density of CD8-positive TILs by immunohistochemistry (/mm^2), and mutational profiles assessed by next-generation sequencing. **Results:** Overall, 228 patients without driver mutation (*EGFR*, *ALK*, *ROS1,* and *RET*) were included in the analysis. The patients were classified into four following groups: Type I: PD-L1$_{High}$ (tumor proportion score [TPS]$\geq$50%)/TIL$_{High}$ ($\geq$85/mm^2; n = 73), Type II: PD-L1$_{Low}$ (TPS $<$ 50%)/TIL$_{Low}$ ($<$ 85/mm^2; n = 70), Type III: PD-L1$_{High}$/TIL$_{Low}$ (n = 37), and Type IV: PD-L1$_{Low}$/TIL$_{High}$ (n = 48). The progression-free survival (PFS) and objective response rate (ORR) of anti-PD-1/anti-PD-L1 therapy clearly differed according to the different tumor microenvironment (TME) types (ORR and median PFS; Type I: 64%, 14.5 months, Type II: 12%, 2.1 months, Type III: 24%, 3.6 months, Type IV: 41%, 10.8 months). In patients with PD-L1$_{High}$ tumors, Type I tumors had significantly better ORR and PFS than Type III(ORR: p $<$ 0.001, and PFS: p $<$ 0.001) tumors. Regarding the association between mutational profiles, histology and the TME types, the presence of *TP53* mutation and *KRAS* mutation significantly related to TIL$_{High}$ (Type I and IV) and PD-L1$_{High}$ tumors (Type I and III), respectively. Pleomorphic and NSCLC- not otherwise specified histology were associated with Type I tumors, while LCNEC was associated with PD-L1 low tumors (Type II and IV). **Conclusions:** Various factors (mutational profile and histology) are related to TME classification based on the status of TILs and PD-L1 expression. Differential types of TME, including PD-L1 expression and TILs status, can accurately predict the efficacy of anti-PD-1/anti-PD-L1 therapy. Research Sponsor: None.

	ORR (95% CI) (%)	PFS (95% CI) (months)
All patients (n = 228)	36 (30-43)	5.5 (3.7-7.3)
Type I (PDL-1$_{High}$CD8$_{High}$, n = 73)	64 (52-75)	14.5 (8.3-NA)
Type II (PDL-1$_{Low}$CD8$_{Low}$, n = 70)	12 (5-21)	2.1 (1.8-2.4)
Type III (PDL-1$_{High}$CD8$_{Low}$, n = 37)	24 (12-41)	3.6 (2.3-4.9)
Type IV (PDL-1$_{Low}$CD8$_{High}$, n = 48)	41 (27-57)	10.8 (8.1-13.5)

9045 **Poster Session**

Predicting response to pembrolizumab in non-small cell lung cancer, by analyzing the spatial arrangement of tumor infiltrating lymphocytes using deep learning. *First Author: Efrat Ofek, Department of Pathology, Sheba Medical Center, Ramat Gan, Israel*

Background: Immune checkpoint inhibitors (ICI) have become the standard treatment for metastatic NSCLC, although only a small proportion of patients derive durable benefit. PDL1 expression is the only approved biomarker to select NSCLC patients for treatment with single-agent pembrolizumab, however its predictive value is limited and better predictive biomarkers are needed. The spatial arrangement of immune cells in the tumor microenvironment (TME), namely tumor infiltrating lymphocytes (TILs), emerges as a potential biomarker for ICI efficacy. In this work, we utilized deep-learning (DL) models to extract TME features from digitized H&E slides and evaluated their predictive and prognostic role in patients with mNSCLC treated with Pembrolizumab. **Methods:** NSCLC patients (n=90) treated with single-agent 1st line pembrolizumab in two centers were identified. 47 patients from one center were used to train the model, and 43 patients from another center were used for validating the model. Pre-treatment H&E whole slide images (WSI) were analyzed using a deep-learning model to identify and classify tumor cells, TILs, tumor and stromal areas, and spatial features were calculated. Spatial features were correlated with clinical outcome data to train a binary classifier that identifies patients with a favorable clinical outcome. The resulting classifier combined three spatial features and three clinical features. The classifier was then applied to the validation set and differences in duration of treatment (DOT), and overall survival (OS) between patients with positive and negative scores were assessed. **Results:** The classifier identified patients in the validation set to have either positive (n=18) or negative (n=25) scores. Baseline patient characteristics and PDL1 score were similar between the positive and negative groups. In a Kaplan-Meier (KM) analysis, OS was significantly higher in patients with a positive score compared to patients with a negative score (HR=0.35, 95% CI 0.13-0.98; $p<0.05$). Positive patients had a significantly higher median OS (NR vs.17.8m, $p<0.05$) and 2-year OS (70.8% vs. 33%, p=0.02) than negative patients. Median DOT was also higher in positive patients compared to negative patients (10.1m vs. 6.5m). **Conclusions:** Deep-learning models that analyze the TME from H&E whole-slide images can identify NSCLC patients with durable benefit on Pembrolizumab. Identifying NSCLC patients who are exceptionally sensitive to anti-PD-1 therapy as monotherapy may improve clinical decision making and spare patients the unnecessary adverse effects associated with the addition chemotherapy or another IO agent. Research Sponsor: Nucleai.

9046 **Poster Session**

Results from a phase II study of eftilagimod alpha (soluble LAG-3 protein) and pembrolizumab in patients with PD-L1 unselected metastatic non-small cell lung carcinoma. *First Author: Timothy Dudley Clay, St. John of God Hospital, Perth, Australia*

Background: Eftilagimod alpha (efti) is a soluble LAG-3 protein that binds to a subset of MHC class II molecules to mediate antigen presenting cell (APC) activation and CD8 T-cell activation. The stimulation of the dendritic cell network and subsequent T cell recruitment with efti may lead to stronger anti-tumor responses in combination than observed with pembrolizumab alone. We hereby report results of the 1st line non-small cell lung carcinoma (NSCLC) part of the phase II trial (NCT03625323). **Methods:** Patients (pts) with untreated, immunotherapy naïve, advanced NSCLC unselected for PD-L1 expression were recruited into part A. The study used a Simon's 2-stage design (17 pts planned for stage 1 and 19 pts for stage 2), with objective response rate (ORR) by iRECIST as the primary endpoint (EP). Secondary EPs include tolerability, disease control rate (DCR), progression free survival (PFS), overall survival (OS), PK, PD and immunogenicity. Efti is administered as 30 mg subcutaneous injection every 2 wks for 8 cycles and then every 3 wks for 9 cycles with pembrolizumab (200 mg intravenous infusion every 3 wks for up to 2 yrs). Imaging was performed every 8 weeks locally and with blinded independent central review (BICR) retrospectively. The study was approved by ethic committees and institutional review boards. **Results:** In total 36 pts were enrolled. At data cut-off (Jan 2021; median FU of 14 months), the median age was 69 yrs (range 53-84) and 69 % were male. The ECOG PS 0 and 1 was 42% and 58% respectively. Patients had squamous (42%) and non-squamous (58%) NSCLC and 95% presented with metastatic disease. All PD-L1 subgroups (TPS < 1 %, ≥ 1 % to ≤ 49 %; ≥ 50 %) were represented with 36% pts having ≥ 50% TPS. Pts received a median of 7.0 (range 1 – 31) pembrolizumab and 11.5 (range 1-22) efti administrations. Responses as per BICR and local read are shown in the table. ORR (local, iRECIST) by different PD-L1 subgroups was 27% for pts with TPS<1%, 39 % for TPS ≥ 1 %and 54% for ≥ 50 % TPS. Median PFS (n=36) was 8.2 months while median OS was not yet reached. The most common (> 20 %) treatment emergent adverse events (AEs) were asthenia (47 %), cough (36 %), decreased appetite (36 %), dyspnea (32 %), pruritus (31 %), fatigue (28 %), diarrhea (25 %), anemia (25 %), constipation (25 %) and back pain (22%). Two patients discontinued treatment due to adverse reactions (Grade 4 immune-mediated hepatitis, Grade 3 AST+ALT increase). **Conclusions:** Efti in combination with pembrolizumab is safe and shows encouraging antitumor activity in 1st line advanced NSCLC patients across all PD-L1 (TPS) levels. Clinical trial information: NCT03625323. Research Sponsor: Immutep S.A.

N=36	iRECIST (BICR)	iRECIST (local read)
CR	2 (6 %)	2 (6%)
PR	13 (36%)	11 (31%)
SD	10 (28 %)	10 (28%)
PD	6 (17%)	9 (25%)
NE/NA	5 (14%)	4 (11%)
ORR (95 % CI)	42% (95 % CI 25.5-59.2)	36 % (95 % CI 20.8-53.8)
DCR	69 %	64 %

9047 **Poster Session**

Safety and efficacy of the anti-CD73 monoclonal antibody (mAb) oleclumab ± durvalumab in patients (pts) with advanced colorectal cancer (CRC), pancreatic ductal adenocarcinoma (PDAC), or EGFR-mutant non-small cell lung cancer (EGFRm NSCLC). *First Author: Johanna C. Bendell, Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN*

Background: Upregulation of CD73 in multiple cancers increases adenosine production, leading to local immunosuppression. Oleclumab, a human IgG1λ mAb, inhibits CD73 function and may increase antitumor immunity. Initial data from a Phase I, first-in-human, dose-escalation and expansion study showed that oleclumab ± durvalumab had manageable safety and encouraging clinical activity in pts with advanced CRC or PDAC. We report updated safety and activity in these cohorts and the first results in an expansion cohort of pts with advanced EGFRm NSCLC. **Methods:** Previously treated pts with histologically or cytologically confirmed microsatellite stable CRC, PDAC, or EGFRm NSCLC received oleclumab 5–40 mg/kg (escalation) and 40 mg/kg (expansion) IV Q2W, alone (escalation only) or with durvalumab 10 mg/kg IV Q2W. The primary objective was safety; secondary efficacy objectives included objective response (OR) per RECIST v1.1 and duration of response (DoR). **Results:** 66 pts were enrolled in the escalation phase (35 CRC, 31 PDAC) and 126 in the expansion phase (42 CRC, 42 PDAC, 42 EGFRm NSCLC). At data cutoff (DCO; June 9, 2020), the median number of oleclumab doses was 4 in pts on monotherapy (range 1–26) and 4 in pts on combination therapy across both phases (range 1–76). In the escalation phase, there were no DLTs in pts on monotherapy or combination therapy; treatment-related adverse events (TRAEs) occurred in 54.8% of pts on monotherapy (Grade 3–4 in 7.1%) and 54.2% of pts on combination therapy (Grade 3–4 in 20.8%); fatigue was the most common TRAE with both regimens. No TRAEs resulted in death. In previous interim analyses before this DCO, no ORs were reported in the escalation phase. In the expansion phase, 5 pts were treated for ≥ 12 mos; 6 pts were ongoing at DCO. TRAEs occurred in 54.0% (Grade 3–5 in 15.1%); the most common TRAEs were fatigue (15.1%), diarrhea (9.5%), and rash (7.1%). One pt had a TRAE resulting in death (systemic inflammatory response syndrome). ORs were seen in 1 CRC pt (DoR 35.9+ mos [+ = ongoing response]), 2 PDAC pts (DoR 22.1+ and 28.6+ mos), and 4 EGFRm NSCLC pts (DoR range 5.6 to 15.7+ mos, median not reached; only 1 of the 4 pts had $\geq 25\%$ programmed cell death ligand-1 [PD-L1]+ tumor cells). Nine CRC pts, 8 PDAC pts, and 9 EGFRm NSCLC pts had SD. Of 6 pts with matched biopsies who received combination therapy, 5 had increases in CD8+ T cells, PD-L1, and granzyme B. Baseline tumor CD73 expression and association with clinical response will be presented. **Conclusions:** Oleclumab ± durvalumab had a tolerable safety profile and combination therapy showed promising antitumor activity in EGFRm NSCLC. ORs and SD were durable, even in tumor types that are generally immunotherapy-resistant. Clinical trial information: NCT02503774. Research Sponsor: AstraZeneca.

9048 **Poster Session**

Phase 1b/2 study of capmatinib plus gefitinib in patients with EGFR-mutated, MET-dysregulated non-small cell lung cancer who received prior therapy: Final overall survival and safety. *First Author: Yi-Long Wu, Guangdong Lung Cancer Institute, Guangdong Provincial Peoples Hospital & Guangdong Academy of Medical Sciences, Guangzhou, China*

Background: Primary findings from the phase 1b/2 study (NCT01610336) demonstrated clinical activity of combination therapy with capmatinib, a potent and selective MET inhibitor, and gefitinib, an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) in heavily pre-treated patients with EGFR-mutated and MET dysregulated non-small cell lung cancer (NSCLC). The objective response rate (ORR) was 27% in patients across phase 1b/2 of the study. At the recommended phase 2 dose (R2PD) of capmatinib 400 mg twice-daily (bid) and gefitinib 250 mg once-daily (qd), the ORR was 47% in patients with high *MET*-amplified tumors (*MET* gene copy number ≥ 6). Here, we report the updated data on the efficacy and safety from the NCT01610336 study. **Methods:** Patients with locally advanced or metastatic NSCLC harboring *EGFR* exon 19 deletion or L858R mutation with a recorded clinical benefit on prior single-agent EGFR-TKI before progression and confirmed dysregulated MET pathway after progression on EGFR TKIs were included. Patients in phase 1b received capmatinib 100 to 800-mg capsules qd or 200 to 600-mg capsules or tablets bid, plus gefitinib 250 mg qd. Patients in phase 2 received the R2PD dose. Data on the overall survival (OS) and cumulative safety endpoints are reported in this final analysis. **Results:** Overall, 161 patients received the combination treatment in this study; phase 1b (n = 61) and phase 2 (n = 100). The median age of patients was 60.0 years, mostly Asian (67.1%) with an Eastern Cooperative Oncology Group performance status of 0/1: 18.0%/78.3%. At data cut-off on May 27, 2020, all patients had discontinued the study; 82 out of the 100 patients in phase 2 had died and 18 were censored (mostly lost to follow-up [n = 15]). One patient was still on treatment with a partial response and rolled over to another study. The median (range) follow-up time for OS was 12.2 (0.9-70.2) months. The median OS was 13.9 months (95% confidence interval, 11.6-15.7 months). The median (range) duration of exposure for capmatinib plus gefitinib was 16 weeks (0.4-209.7 weeks) during phase 1b and 18.5 weeks (0.4-268.0 weeks) during phase 2. Majority of the patients (98.8%) experienced ≥ 1 adverse event (AE); 87% of the patients had treatment-related AEs. Most common treatment-related AEs (reported in $\geq 20\%$) were nausea (28.0%), peripheral edema (23%), rash (21.7%), and decreased appetite (21.1%). Grade 3 or 4 treatment-related AEs occurred in 51 patients (31.7%) across both phases, of which, the most frequent (reported in $\geq 5\%$) were increased amylase and increased lipase (6.2% each) and peripheral edema (5%). **Conclusions:** Capmatinib 400 mg bid in combination with gefitinib 250 mg qd was well-tolerated and showed encouraging clinical activity in patients with EGFR-mutant and MET-dysregulated NSCLC. Clinical trial information: NCT01610336. Research Sponsor: Novartis.

9049 **Poster Session**

Response to immune checkpoint inhibition as monotherapy or in combination with chemotherapy in metastatic *ROS1*-rearranged lung cancers. *First Author: Noura J. Choudhury, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *ROS1* fusions are oncogenic drivers in various cancers types, including 1-3% of non-small cell lung cancers (NSCLCs). Immunotherapy approvals for NSCLC include *ROS1*-rearranged carcinomas, but the activity of immune checkpoint inhibition (ICI) as monotherapy or in combination with chemotherapy (chemo-ICI) therapy, as well as the immunophenotypic characteristics of these tumors, have not been described in a large data set. **Methods:** In this multi-institutional study, patients with *ROS1*-rearranged NSCLC were identified retrospectively. Tumor PD-L1 expression and tumor mutational burden (TMB) were assessed as part of routine clinical care. In patients who received ICI monotherapy or chemo-ICI in the metastatic setting, time to treatment discontinuation (TTD) and objective response rate (ORR; RECIST v. 1.1) were calculated. TTD was assessed with Kaplan-Meier methods; patients remaining on treatment were censored at last follow up. **Results:** 184 patients with *ROS1*-rearranged NSCLC were identified. Among 146 PD-L1 evaluable cases, PD-L1 expression was $<$ 1% in 60 (41%), 1-49% in 35 (24%) and $\geq$50% in 51 (35%) tumors. Ninety-two of 100 (92%) TMB-evaluable tumors had $<$ 10 mutations/megabase (mut/Mb). TMB was significantly lower for *ROS1*-rearranged NSCLCs (n = 97) vs. *ROS1*-wild type tumors (n = 5,380) evaluated with next-generation sequencing using MSK-IMPACT (median 2.6 vs. 5.9 mut/Mb, p $<$ 0.001). Twenty-eight patients received ICI monotherapy and 11 patients received chemo-ICI. The median TTD was 2.1 months (95% CI: 1.0-4.2; n = 28) for single-agent ICI therapy and 10 months (95% CI: 4.7-14.1; n = 11) for chemo-ICI therapy. The ORR was 13% (2/16 RECIST-evaluable; 95% CI: 2-38%) for ICI monotherapy and 83% (5/6 RECIST-evaluable; 95% CI: 36-100%) for chemo-ICI therapy. There was no difference in PD-L1 tumor expression (p = 0.9) or TMB (p = 0.8) between responders and non-responders and no correlation between PD-L1 tumor expression (rho = 0.16, p = 0.6) or TMB (rho = 0.03, p = 0.9) and maximum change in sum of target lesions. **Conclusions:** Most *ROS1*-rearranged NSCLCs have low or no PD-L1 expression and low TMB. The activity of checkpoint inhibitor monotherapy is disappointing in ROS1-driven NSCLC. In contrast, combination chemoimmunotherapy can achieve clinically meaningful activity. Research Sponsor: None.

9050 **Poster Session**

Complete metabolic response in advanced non-small cell lung cancer patients with prolonged response to immune checkpoint inhibitor therapy. *First Author: Daniel Christian Christoph, Evang. Kliniken Essen-Mitte, Essen, Germany*

Background: Recently reported, extended follow-up data from KEYNOTE-024 or -010 indicates that non-small-cell lung cancer (NSCLC) patients can experience long-term benefit from immunotherapy irrespective of discontinuation (per protocol: 35 cycles ~24 months) or type of response in computed tomography (CT). Similar results were observed in the pooled analysis of 5-year follow-up data from CheckMate-017 and -057. This raises the question, whether patients may safely discontinue immunotherapy after achieving durable response. However, recently published results from CheckMate-153 demonstrated inferior survival rates in patients ceasing immunotherapy after one year, therefore optimal treatment duration of immunotherapy in advanced NSCLC remains unknown. Protocols from published Phase-III trials implemented treatment for a period of approximately 24 months or until evidence of disease progression or unbearable toxicity. Therefore, the ideal duration of immunotherapy remains unclear, and finding markers of beneficial outcome is of great importance. Here, we determine the proportion of complete metabolic responses (CMR) in patients that have not progressed after 24 months of immunotherapy. **Methods:** This is a retrospective analysis of forty-five patients with positron emission tomography using 2-[18F]fluoro-2-deoxy-D-glucose (FDG-PET) imaging for assessment of residual metabolic activity after at least 24 months of immunotherapy. Lesion-uptake in FDG PET on or below background level (using mediastinum as reference) was considered as CMR. Time until best objective morphological response including disease stabilization was measured from start of immunotherapy until first stable CT-scan (i.e. no progression or further response compared to previous scan) using RECIST 1.1. **Results:** Out of 45 patients, 29 patients had a CMR (64%). CMR was observed more frequently in non-first line patients. Patients with CMR were younger (median 65.7 vs. 75.5, P = 0.03). Fourteen patients with CMR have discontinued therapy and have not progressed until time of analysis; however median follow-up was only 5.6 (range 0.8-17.0) months. **Conclusions:** After a minimum of 24 months of palliative immunotherapy for NSCLC, CMR occurred in almost two thirds of patients. Potentially, achievement of CMR might identify patients, for whom palliative immunotherapy may be safely discontinued. Research Sponsor: None.

9051 **Poster Session**

Comprehensive investigation of mutational features of adenocarcinoma in situ and invasive adenocarcinoma among Chinese lung cancer patients. *First Author: Chan Xiang, Department of Pathology, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China*

Background: Lung adenocarcinoma (LUAD) is further classified into several histological subtypes with adenocarcinoma in situ (AIS), minimally invasive adenocarcinoma (MIA), and invasive adenocarcinoma (IAC) as the three major subtypes according to the extent of invasion. AIS has been considered as a precursor of IAC. Considering the significantly higher mutation burden among IAC tumors than AIS tumors, it seems likely that AIS tumors undergo a process of accumulating various somatic mutations to gain invasive ability. To understand the gene mutations involved in this transformation, we compared the mutational features of AIS and IAC tumors. **Methods:** This retrospective study included 2,769 Chinese patients diagnosed with stage 0-IIIA LUAD. Targeted sequencing was performed on tissue DNA isolated from 246 AIS tumors and 2,523 IAC tumors using 68 lung cancer-related genes (Lung Core, Burning Rock Biotech). **Results:** Analysis of mutation profiles revealed that mutation count was significantly lower for AIS ($P<$ 0.01) as compared to IAC tumors. Moreover, AIS tumors had significantly higher mutation detection rates for *ERBB2* exon 20 insertion (20ins) ($P\leq$0.05), *EGFR* 20ins ($P\leq$0.05), non-V600E *BRAF* mutations ($P\leq$0.05), and *MAP2K1* small insertion-deletion variants ($P\leq$0.05). These 4 gene mutations were grouped and referred to as AIS-like mutations for further analysis. Detection rates of AIS-like mutations were 54.9% for AIS tumors and 7.8% for IAC tumors. Patients with AIS-like mutation-positive AIS tumors were significantly younger than those with AIS tumors without AIS-like mutations (P =0.018), while age were similar for IAC tumors with or without AIS-like mutations. Mutation count was similar between AIS tumors with or without AIS-like mutations. Interestingly, IAC tumors harboring AIS-like mutations had a significantly higher mutation count than those harboring known oncogenic drivers (P= 0.045). Further investigation of the molecular profiles of IAC tumors harboring AIS-like mutations (n = 198) revealed the presence of various concurrent mutations in 8 genes including *TP53* (39.4%), *EGFR* (non-20ins) (16.7%), *RB1* (7.1%), *PIK3CA* (6.6%), *MET* (5.1%), *ROS1* (4.0%), *FLT3* (4.0%), and *PTEN* (3.5%), which were absent among AIS tumors, particularly those that harbor AIS-like mutations. In addition to *TP53* (35.8%), *PIK3CA* (4.5%), and *RB1* (4.0%), IAC tumors without AIS-like mutations (n = 2,324) had additional concurrent mutations in 2 other genes *CDK4* (5.7%) and *STK11* (3.9%) as compared to AIS tumors. **Conclusions:** Our data suggest that AIS-like mutations could be involved in the early stages of tumorigenesis by initiating the accumulation of other gene mutations that are required for the transformation of AIS tumors into IAC tumors. Our study contributes to a deeper understanding of the distinct gene mutations between AIS and IAC tumors among Chinese LUAD patients. Research Sponsor: Shanghai Municipal Health Commission Intelligent Medical Research Project, Other Foundation.

9052 **Poster Session**

Amivantamab compared with real-world therapies in patients with NSCLC with EGFR Exon 20 insertion mutations who have progressed after platinum doublet chemotherapy. *First Author: Anna Rachel Minchom, Drug Development Unit, Royal Marsden/Institute of Cancer Research, Sutton, United Kingdom*

Background: Amivantamab is an epidermal growth factor receptor (EGFR)-MET bispecific antibody with immune cell-directing activity. Amivantamab has demonstrated efficacy and safety in patients (pts) with EGFR exon 20 insertion (Exon20ins) in the ongoing CHRYSALIS phase 1 study in advanced non-small cell lung cancer (aNSCLC). Because CHRYSALIS is a non-randomized, single arm study, external controls (EC) can add valuable context in interpreting amivantamab's efficacy and appreciating the unmet needs given real-world therapies. A protocol-driven treatment comparison was conducted of amivantamab vs real-world therapies in pts with Exon20ins aNSCLC who progressed after platinum chemotherapy. **Methods:** Custom curated, real-world data abstracting clinically relevant measures that are not typically available from off-the-shelf datasets were obtained from 3 US-based companies: Flatiron, COTA, and ConcertAI. Datasets were de-duplicated via a tokenization procedure, analyzed separately and as a single pooled database. Key eligibility for the EC included: Exon20ins aNSCLC, prior platinum chemotherapy, $\geq$1 line after platinum therapy, and ECOG PS 0 or 1. Propensity score weighting (average treatment effects on the treated) was used to adjust for differences in age, brain metastases, ECOG PS, and number of prior lines of therapy (LOT). **Results:** The amivantamab-treated population (N = 81) included post-platinum pts with EGFR Exon20ins aNSCLC treated at the recommended phase 2 dose (Sabari WCLC 2020 Abs #3031). After de-duplication of the custom real-world datasets, 126 unique pts formed the EC. Most frequent treatments after platinum doublet chemotherapy in the EC group were checkpoint inhibitors (CPI; 25%), single-agent, non-platinum chemotherapies (25%), and EGFR tyrosine-kinase inhibitors (TKIs; 16%). Baseline demographics were generally similar between amivantamab and the EC pts; notable differences included a higher percentage of Asian pts (56% vs 9%) and more prior LOT (median 2 vs 1) among the amivantamab compared to the EC pts. Median overall survival (OS) among amivantamab pts was 22.8 months and EC pts was 13.1 months (HR = 0.53 [95% CI, 0.33, 0.86]). Similarly, amivantamab pts had longer progression-free survival (8.3 vs 2.9 months; HR = 0.46 [95% CI, 0.33, 0.63]) and time to next treatment (14.8 vs 4.8 months; HR = 0.42 [95% CI, 0.29, 0.6]) compared to the EC pts. Confirmed overall response rate was 40% among amivantamab pts and 10% for the EC pts (odds ratio = 4.44 [95% CI 2.42, 8.14]). **Conclusions:** Amivantamab demonstrated a 10-month higher OS than real-world therapies in the post-platinum setting. The poor performance of the EC, frequently treated with CPI, single chemotherapies, and EGFR TKI, highlights the ineffectiveness of these agents and the urgent need to find more alteration-specific treatments in aNSCLC. Research Sponsor: Janssen R&D.

9053 **Poster Session**

Totality outcome of afatinib sequential treatment in patients with EGFR mutation-positive NSCLC in Korea: KCSG LU-19-22. *First Author: Hyun Ae Jung, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: While osimertinib showed impressive efficacy and safety profile in 1st-line setting for EGFR mutation-positive (EGFR M+) NSCLC patients, there are no standard targeted therapy following progression. Thus, interest has been growing on sequential treatment of osimertinib as 2nd-line treatment for patients acquiring T790M resistance mutation after 2nd generation EGFR TKIs. We did a retrospective study to support the hypothesis that sequential approach of afatinib followed by osimertinib represents a practical treatment option in 'real-world' practice. **Methods:** In this non-interventional, multicenter study, EGFR M+ NSCLC patients had to start 1st-line afatinib treatment ≥ 13 months prior to data entry. They were categorized into 4 cohorts according to 2nd-line treatments with retesting results: T790M+ patients sequentially treated with osimertinib in cohort A, T790M patients treated with chemotherapy or other treatments in cohort B, and patients with unknown mutation status in cohort C. Cohort D included patients who were still ongoing with afatinib. Primary outcome was the time on treatment (TOT) of patients receiving 1st-line afatinib (TOT-1) followed by 2nd-line treatments (TOT-2). Secondary endpoints were acquisition rate of T790M after progression, objective response rates of afatinib (ORR-1) and 2nd-line treatments (ORR-2), and overall survival (OS). **Results:** Among a total of 761 enrolled patients, 737 patients excluding 24 screening failures were allocated into cohort A (n=116), B (n=143), C (n=111), and D (n=367). Median age was 62 years (22 - 90) with 53.05% of female proportion. Brain metastasis was discovered in 38.94% at initial diagnosis. Regarding genotypes of EGFR mutations, del19 was 57.53%, 31.48% for L858R, 7.33% for uncommon mutations, and 3.66% for compound mutation. Median TOTs in cohort A, B, C, and D were 35.09 months (95% CI, 30.09 to 43.53), 18.76 months (95% CI, 16.92 to 20.20), 12.02 months (95% CI, 10.22 to 14.98), and 42.61 months (95% CI, 30.95 to 59.23), respectively. Particularly, in cohort A, median TOT-1 and TOT-2 were 17.43 months (95% CI, 15.21 to 19.32) and 11.04 months (95% CI, 7.10 to 14.13), respectively. Retesting was attempted in 262 of 370 patients (70.81%) with 44.27% of T790M detection rate. ORR-1 and -2 in cohort A, B, and C were 84.48% and 56.03%, 82.52% and 29.08%, 54.95% and 21.70%, respectively and 68.94% of ORR for cohort D. Median OS has was not reached. **Conclusions:** These data suggest that, in real-world practice, sequential afatinib followed by osimertinib be a feasible and effective therapeutic strategy for EGFR M+ NSCLC patients acquiring T790M during the period of afatinib treatment. Of note, median TOT in cohort D is over 3.5 years, suggesting that 1st-line afatinib potentially allow certain patients to maintain long-term, chemotherapy-free state. Further analysis is currently being undertaken and will be presented. Research Sponsor: Boehringer Ingelheim.

9054 **Poster Session**

Clinico-pathological and genomic features of *NRAS*- or *HRAS*-mutated non-small cell lung cancer (NSCLC) identified in large-scale genomic screening project (LC-SCRUM-Asia). *First Author: Yutaro Tamiya, National Cancer Center Hospital East, Kashiwa, Japan*

Background: *RAS* (*KRAS*, *NRAS* and *HRAS*) is a targetable oncogene family in several cancers, including NSCLC, and the clinical development of various RAS-targeted therapies are ongoing. However, the clinical relevance of uncommon *RAS* mutations, such as *NRAS* and *HRAS* mutations, in NSCLC patients (pts) remains unclear. **Methods:** In a large-scale genomic screening project (LC-SCRUM-Asia), we have prospectively analyzed lung cancer pts for genomic alterations by a targeted next-generation sequencing (NGS) system, Oncomine Comprehensive Assay. We evaluated clinico-pathological and genomic characteristics in *NRAS*- or *HRAS*-mutated NSCLC pts comparing with those in *KRAS*-mutated pts based on the LC-SCRUM-Asia database. **Results:** Since March 2015 to December 2020, 9131 NSCLC pts were enrolled in the LC-SCRUM-Asia, and 8374 of them (92%) were successfully analyzed by NGS. The *RAS* mutation frequencies were 1134 *KRAS* (14%), 50 *NRAS* (0.6%), and 15 *HRAS* (0.2%). The most frequent variant of *NRAS* and *HRAS* mutations was Q61X (78%) and G13X (80%), respectively, whereas that of *KRAS* was G12X (84%). Patient characteristics were summarized in Table. Male was significantly frequent in *NRAS*- than in *KRAS*-group (p=0.03), and smokers were frequent in all the three groups (overall, 79%). The majority of *NRAS* (70%) and *KRAS* mutations (89%) were detected in adenocarcinoma (Ad), whereas 60% of *HRAS* mutations were in squamous cell carcinoma (Sq). Tumor mutation burden (TMB) was significantly higher in *NRAS*-mutated tumors than in *KRAS*-mutated tumors (p=0.03). Concomitant *TP53* mutations were significantly frequent in *HRAS*-mutated pts than in *KRAS*-mutated pts (53% vs. 30%, p=0.05), and *STK11* mutations were also tended to be frequent in *HRAS*-mutated pts than in *KRAS*-mutated pts (20 vs. 7%, p=0.10). Therapeutic efficacy of PD-1/PD-L1 inhibitors was not different among the three groups in the current follow-up data, but *HRAS*-mutated tumors did not respond to PD-1/PD-L1 inhibitors (response rate, 0%; median PFS, 1.6 months). **Conclusions:** *NRAS*- or *HRAS*-mutated NSCLCs were different from *KRAS*-mutated NSCLCs in clinicopathological and genomic profiles. In particular, the immunotherapies were not effective for *HRAS*-mutated NSCLCs. Research Sponsor: Japan Agency for Medical Research and Development.

		KRAS	***NRAS***		***HRAS***	
		N=1134 (%)	N=50 (%)	p-value(vs. *KRAS*)	N=15 (%)	p-value(vs. *KRAS*)
Age	Median [range]	69 [25-91]	69 [36-87]	0.67	67 [30-84]	0.64
Sex	Male	737 (65)	40 (80)	0.03	13 (87)	0.10
Smoking status	Ever	895 (79)	41 (82)	0.72	13 (87)	0.75
Histology	Ad	1008 (89)	35 (70)	<0.01	4 (27)	<0.01
	Sq	42 (4)	1 (2)		9 (60)	
	Other	84 (7)	14 (28)		2 (13)	
TMB (N=477)	Mean [SD]	6.2 [9.4]	9.4 [11.6]	0.03	7.4 [8.4]	0.70

9055 **Poster Session**

SHR-1701, a bifunctional fusion protein targeting PD-L1 and TGF-β, for advanced NSCLC with *EGFR* mutations: Data from a multicenter phase 1 study. *First Author: Meiqi Shi, Department of Oncology, Jiangsu Cancer Hospital, Nanjing, China*

Background: Despite the development of targeted therapies for advanced NSCLC harboring *EGFR* mutations (*EGFR*+), acquired resistance remains inevitable. Immune checkpoint inhibitor as monotherapy has limited efficacy. Blockade of the TGF-β pathway which plays a key role in immune suppression may enhance the tumor response to anti-PD-1/PD-L1 antibodies. Here, we assessed SHR-1701, a novel bifunctional fusion protein composed of a mAb against PD-L1 fused with the extracellular domain of TGF-β receptor II, in advanced NSCLC pts including one separate *EGFR+* cohort. **Methods:** This phase 1 study includes a 3+3 dose-escalation and dose-expansion period of pretreated advanced NSCLC and multiple clinical expansion cohorts of different tumor types, genetic aberrations, or prior therapies. During the dose-escalation and dose-expansion period, pathologically confirmed pts received SHR-1701 at 3, 10, or 20 mg/kg Q3W or 20 mg/kg Q2W by intravenous infusion. The primary objectives were to determine the safety profile, maximum tolerated dose (MTD), and recommended phase 2 dose (RP2D) of SHR-1701. In the *EGFR*+ NSCLC clinical expansion cohort, histologically or cytologically confirmed advanced pts after at least 1L standard EGFR TKI received SHR-1701 at RP2D, and the primary endpoint was objective response rate (ORR). Treatment beyond progression was allowed. **Results:** During the dose-escalation and dose-expansion period, 30 pts were recruited: all stage IV; 83.3% had ≥2 metastasis sites; 76.7% had received ≥2L prior systemic therapy. One dose-limiting toxicity (immune-mediated pneumonitis) in the 20 mg/kg Q2W group was observed, and the MTD was not reached. Population pharmacokinetics and exposure-response analysis of SHR-1701 based on this study and another phase 1 study for advanced solid tumors (NCT03710265) demonstrated 30 mg/kg Q3W as the RP2D. In the *EGFR*+ NSCLC cohort, 27 pts were enrolled: all stage IV; 77.8% had ≥2 metastasis sites; 70.4% had received ≥2L prior systemic therapy; 29.6% had 19-Del, 14.8% 19-Del and T790M, 7.4% 20-ins, 29.6% L858R, 18.5% L858R and T790M. With a median SHR-1701 exposure of 8.7 weeks (range, 3.0-24.0), 4 of the 24 pts who had at least one post-baseline radiographic assessment achieved objective responses, including 3 ongoing confirmed and 1 unconfirmed partial response. ORR was 16.7% (95% CI, 4.7%-37.4%), and disease control rate was 50.0% (95% CI, 29.1%-70.9%). Grade 3 treatment-related adverse events (TRAEs) occurred in 2 (7.4%) pts, including anemia, hypokalemia, and asthenia (1 [3.7%] for each). There were no grade 4 or 5 TRAEs. No pts discontinued treatment due to TRAEs. **Conclusions:** SHR-1701 monotherapy shows a manageable safety profile and encouraging antitumor activity in advanced *EGFR*+ NSCLC pts after failure of at least 1L standard EGFR TKI. Further investigation of SHR-1701 combination therapy for *EGFR+* NSCLC is warranted. Clinical trial information: NCT03774979. Research Sponsor: Jiangsu Hengrui Medicine Co., Ltd.

9056 **Poster Session**

Patient-reported outcomes in capmatinib-treated patients with *MET*ex14-mutated advanced NSCLC: Results from the phase II GEOMETRY mono-1 study. *First Author: Juergen Wolf, Department of Internal Medicine, Center for Integrated Oncology, University Hospital of Cologne, Cologne, Germany*

Background: Capmatinib, a potent, selective MET inhibitor, showed substantial antitumor activity and manageable tolerability in patients with *MET*ex14-mutated advanced non-small cell lung cancer (aNSCLC) in the GEOMETRY mono-1 trial (NCT02414139). Patient-reported outcomes (PROs) from this study are reported here. **Methods:** GEOMETRY mono-1 enrolled patients ≥18 years with *MET*ex14-mutated or *MET*-amplified, *ALK*-negative and *EGFR* wild-type, treatment-naïve (1L) or pre-treated (2L+) aNSCLC, to receive capmatinib orally 400 mg bid during 21-day treatment cycles. Here we report results for patients with *MET*ex14 mutations. PROs (EORTC QLQ-C30, QLQ-LC13 and EQ-5D-5L) were collected at baseline (BL) and every 6 weeks (Wks) until end of treatment. Key PROs (in patients with BL and ≥1 post-BL value) included change from BL in QLQ-C30 global health status (GHS), QLQ-LC13 symptoms (cough, chest pain and dyspnea), and EQ-5D-5L visual analogue scale (VAS), with a ≥10-point change from BL considered clinically meaningful. Time to definitive deterioration (TTDD) in QLQ-LC13 symptoms (time from treatment initiation to first date of ≥10% symptom change from BL with no later reduction) was assessed using Kaplan-Meier. QLQ-LC13 symptoms over time were explored by BIRC-assessed clinical response to capmatinib. **Results:** By Jan 6, 2020 cut-off, median capmatinib exposure was 48.2 (4.0 117.4) Wks and 22.1 (0.4 136.0) Wks for 1L and 2L+ patients, respectively. A total of 27/28 1L patients and 65/69 2L+ patients completed PROs at BL, and completion rate remained high (mostly > 70%) through treatment cycles. Mean [SD] BL PRO scores were moderate-to-high in 1L and 2L+ patients (GHS: 64.7 [21.6] and 58.8 [21.0.]; cough: 35.9 [32.6] and 28.7 [28.2]; chest pain: 12.8 [23.2] and 17.2 [22.7]; dyspnea: 23.5 [23.4] and 22.2 [20.8]; VAS: 67.7 [20.8] and 61.9 [18.8], respectively). Overall change from BL in PROs was maintained over time. Cough improved early, with meaningful improvements observed through cycles, notably in 1L patients (mean change from BL [SD] at Wk 7: 1L -13.0 [39.9], 2L+ -8.2 [28.4]; Wk 25: 1L -15.6 [33.0], 2L+ -6.0 [31.5]; Wk 43: 1L -28.2 [26.7], 2L+ -10.5 [27.3]). Median TTDD in GHS was 16.6 months (95% CI: 9.7, NE [not estimated]) and 12.4 months (95% CI: 4.2, 19.4) in 1L and 2L+ patients, respectively. Median TTDD for cough and chest pain was NE in both 1L and 2L+ patients, and for dyspnea was 19.4 months (95% CI: 12.4, NE) and 22.1 months (95% CI: 9.9, NE), respectively. QLQ-LC13 symptoms improved at all cycles in patients achieving clinical complete response or partial response, while symptom worsening was seen in those with no clinical response. **Conclusions:** Capmatinib was associated with clinically meaningful improvements in cough, delayed time to lung symptom deterioration, and preserved QoL, supporting its use as a treatment option in patients with *MET*ex14-mutated aNSCLC. Clinical trial information: NCT02414139. Research Sponsor: Novartis.

9057 **Poster Session**

Patient-reported outcomes (PRO) from the phase 2 CodeBreaK 100 trial evaluating sotorasib in *KRAS* p.G12C mutated non-small cell lung cancer (NSCLC). *First Author: Alexander I. Spira, US Oncology Research/Virginia Cancer Specialists, Fairfax, VA*

Background: In the registrational phase 2 CodeBreaK 100 trial, sotorasib demonstrated a response rate of 37.1% with median duration of 10.0 months, a median progression-free survival of 6.8 months, and a tolerable safety profile in patients with pretreated *KRAS* p.G12C mutated NSCLC. Patients received a median of 2 prior lines of therapy. Here, we report PRO measures of health-related quality of life (QoL), physical functioning, and key lung cancer symptoms from this trial. **Methods:** Eligible patients had *KRAS* p.G12C mutated advanced NSCLC and received prior standard therapies. Sotorasib was given at an oral daily dose of 960 mg with 21-day treatment cycles until disease progression. Disease-related symptoms and health-related QoL were evaluated as exploratory endpoints on day 1 of each cycle from baseline to discontinuation, using the European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire Core 30 (EORTC QLQ-C30) and its lung cancer module, EORTC QLQ-LC13. The single item, 5-point scale GP5, of the Functional Assessment of Cancer Therapy-General version was used to evaluate the impact of side effects. Predefined analyses included change from baseline using descriptive statistics and mixed model for repeated measures for global health status/QoL, physical functioning, and key lung cancer symptoms of cough, dyspnea and chest pain. **Results:** Of 126 patients enrolled, compliance rates for each of the questionnaires were high throughout the study ($>$ 70%). Data up to cycle 11 (where n $>$ 20) are presented. EORTC QLQ-C30 global health status/QoL and physical functioning were maintained over time (least-square mean changes ranged from -3.5 to 0.2 and 0.1 to 3.9, respectively). EORTC QLQ-C30 symptoms of fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, and constipation were stable or improved. Similarly, key lung cancer-related symptoms, as measured by EORTC QLQ-LC13, remained stable or improved from baseline, with the greatest least-square mean change of -11.2 (95% CI: -16.2, -6.1) for cough, -4.9 (95% CI: -10.3, 0.4) for chest pain, and -3.4 (95% CI: -7.8, 1.0) for dyspnea. Most patients reported on the GP5 that they were "not at all" (54.2%-79.2%) or "a little bit" (8.3%-33.3%) bothered by side effects from sotorasib, with 0%-7.4% reporting being bothered as "quite a bit" and 0% as "very much". **Conclusions:** In patients from the single-arm phase 2 trial of sotorasib, PRO measures suggested maintenance or improvement of global health status/QoL, physical functioning, and the severity of key lung cancer-related symptoms, including cough, dyspnea, and chest pain. Self-reported side effect bother was minimal. These data, together with the encouraging efficacy and safety profiles, strongly support the use of sotorasib in this population. Clinical trial information: NCT03600883. Research Sponsor: Amgen Inc.

9058 **Poster Session**

TROPION-PanTumor01: Dose analysis of the TROP2-directed antibody-drug conjugate (ADC) datopotamab deruxtecan (Dato-DXd, DS-1062) for the treatment (Tx) of advanced or metastatic non-small cell lung cancer (NSCLC). *First Author: Funda Meric-Bernstam, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Datopotamab deruxtecan (Dato-DXd; DS-1062) is an ADC composed of a humanized anti-TROP2 IgG1 monoclonal antibody conjugated to a topoisomerase I inhibitor via a tetrapeptide-based cleavable linker. **Methods:** TROPION-PanTumor01 (NCT03401385) is a multicenter dose-escalation/expansion study evaluating Dato-DXd administered Q3W in patients (pts) with advanced NSCLC (since expanded to other tumor types, excluded from this analysis). Efficacy and safety were evaluated in 175 pts for dose analysis. Pharmacometric analyses (population pharmacokinetics [popPK] and exposure-response modeling) were conducted across doses to inform dose selection for further development. **Results:** At data cutoff (Sept 4, 2020), median follow-up was 7.4 mo (range, 0.10-21.7 mo). Select all-grade TEAEs were 1.5- to 2-fold higher in the 8 mg/kg vs 4 and 6 mg/kg cohorts: vomiting (34% vs 12% and 18%), anemia (28% vs 4% and 16%), diarrhea (20% vs 6% and 11%), and mucositis (29% vs 6% and 13%). Rates of grade $\geq$3 drug-related TEAEs and serious drug-related TEAEs were $\geq$2-fold higher with the 8 mg/kg dose (n = 80; 34% and 20%) relative to the 4 mg/kg (n = 50; 10% and 8%) and 6 mg/kg (n = 45; 16% and 9%) doses. Rates of drug-related interstitial lung disease (ILD), as determined by an independent adjudication committee, were higher in the 8 mg/kg cohort (15% vs 2% and 2% in the 4 and 6 mg/kg cohorts); 3 pts in the 8 mg/kg cohort experienced grade 5 ILD. Dose interruptions and reductions due to TEAEs increased with dose (4 mg/kg: 4% and 2%; 6 mg/kg: 20% and 9%; 8 mg/kg: 20% and 31%). More pts in the 8 mg/kg cohort discontinued Tx early due to AEs (15%) compared with those in the 4 mg/kg (4%) and 6 mg/kg (7%) cohorts. ORRs determined by blinded independent central review were similar: 8 mg/kg, 25% (20/80); 6 mg/kg, 21% (8/39); and 4 mg/kg, 23% (9/40). Preliminary median PFS (95% CI) was 5.4 mo (4.1-7.1 mo) in the 8 mg/kg cohort, 8.2 mo (1.5-11.8 mo) in the 6 mg/kg cohort, and 4.3 mo (2.0 mo-NE) in the 4 mg/kg cohort. PFS was limited by early censoring due to immature duration of follow-up, with the majority of pts having $\leq$3 mo of follow-up in the 4 (66%) and 6 mg/kg (67%) cohorts vs 8 mg/kg (46%) cohort. In pharmacometric analyses, tumor-size change from baseline and probability of complete response/partial response positively correlated with exposure (AUC) of Dato-DXd. Incidences of dose reduction and grade $\geq$2 stomatitis/mucositis were also positively correlated with exposure; projected probabilities in a virtual population bootstrapped from pts with NSCLC in the popPK data confirmed these trends. Updated results will be presented. **Conclusions:** A Dato-DXd dose of 6 mg/kg was selected for the randomized, phase 3, TROPION-Lung01 trial (NCT04656652) based on better tolerance and improved efficacy, including a trend toward increased PFS. Clinical trial information: NCT03401385. Research Sponsor: Daiichi Sanko Co., Ltd.

9059 **Poster Session**

The role of chemotherapy plus immune checkpoint inhibitors in oncogenic driven non-small cell lung cancer: A University of California Lung Cancer Consortium retrospective study. *First Author: Karen Kelly, University of California Davis Comprehensive Cancer Center, Sacramento, CA*

Background: Immune checkpoint inhibitors (ICIs) have demonstrated limited efficacy in patients (pts) with actionable oncogenic drivers. As a result, pts with the prototypic oncogenic drivers (EGFR and ALK) have purposefully been excluded from many NSCLC ICI trials although ICI is commonly used in combination with chemotherapy for these pts. Data from one randomized trial that included pts with known EGFR and ALK alterations did not show a survival benefit with an ICI plus a platinum doublet. We sought to gain further insight into the role of chemotherapy plus ICI in pts with oncogenic driven tumors. **Methods:** We conducted a retrospective analysis of pts with oncogenic drivers (EGFR, ALK, ROS1, BRAF, MET, RET, HER2 and KRAS) who were treated with chemotherapy (C) or chemotherapy plus ICI (C+ICI) between 2018 and 2019 at the five University of California (UC) NCI Designated Cancer Centers (UC Irvine, UC Davis, UC Los Angeles, UC San Diego and UC San Francisco). Descriptive statistics were used. Kaplan-Meier plots and confidence intervals summarize PFS and OS in the overall cohort and oncogenic subgroups. **Results:** 125 pts were identified. Median age 64.1 years; M/F (45%/55%); White/Asian (59%/33%); Current/Former/Never Smokers (4%/39%/57%); PS 0/1/2(22%/68%/10%); prior number of tyrosine kinase inhibitors 0/1/2/ $>$ 3 (46%/23%/19%/11%); Oncogenic driver: EGFR mutations (60%), KRAS mutations (23%), ALK fusions (8%), MET mutations (2.4%), RET fusions (1.6%), ROS1 fusions (1.6%), HER2 mutations (1.6%), and BRAF mutations (0.8%). The table below displays the efficacy outcomes. **Conclusions:** There was no survival benefit for pts with oncogenic drivers treated with chemotherapy plus an immune checkpoint inhibitor in the overall cohort or any of the subsets. Pts with KRAS mutations treated with C+ICI had a numerically longer median PFS than their counterparts treated with C. Updated data and additional analyses including PD-L1, TMB, co-mutations and toxicity will be presented. Research Sponsor: None.

Cohort	# of Pts (C/C+ICI)	PFS (HR)	Median PFS (C/C+ICI)	OS (HR)	Median OS (C/C+ICI)
All patients	70/55	1.07 (0.72, 1.59) P = 0.72574	225 days/219 days	0.80 (0.48, 1.33) P = 0.38655	555 days/653 days
EGFR	50/25	1.13 (0.67, 1.91) P = 0.64177	213 days/178 days	0.77 (0.40, 1.49) P = 0.44319	496 days/574 days
KRAS	8/22	0.85 (0.33, 2.19) P = 0.73898	176 days/249 days	0.82 (0.21, 3.21) P = 0.77742	NR/NR
Non-EGFR/KRAS	12/8	1.37 (0.50, 3.71) P = 0.53906	285 days/200 days	1.34 (0.35, 5.13) P = 0.66511	944 days/653 days
Never smoker	41/30	1.14 (0.68, 1.90) P = 0.62813)	246 days/232 days	0.77 (0.40, 1.48) P = 0.43269	555 days/599 days
Current/Former smoker	29/25	1.00 (0.54, 1.85) p = 0.99526	206 days/214 days	0.83 (0.36, 1.92) P = 0.66541	546 days/NR

PFS – Progression Free Survival; HR – Hazard Ratio; OS – Overall Survival; NR – Not Reached.

9060 **Poster Session**

A phase 2, open-label, multicenter study to evaluate the efficacy, safety, and tolerability of KN046 in combination with chemotherapy in subjects with advanced non-small cell lung cancer. *First Author: Yunpeng Yang, Department of Medical Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center of Cancer Medicine, Guangzhou, China*

Background: Dual blockade of PD-1 and CTLA-4 has shown improved overall survival (OS) in combination with a short course of chemotherapy. KN046 is a novel bispecific antibody that blocks both PD-L1 interaction with PD-1/CD80 and CTLA-4 interaction with CD80/CD86. We hypothesized that KN046 could be combined with a full course of chemotherapy and build more durable clinical benefit. **Methods:** This study enrolled systemic treatment naive, stage IV NSCLC patients (pts). Eligible pts received KN046 plus platinum doublet chemotherapy until progressive disease, unacceptable toxicity, withdrawal of informed consent or death. Efficacy evaluation was performed by investigators per RECIST 1.1. Safety and tolerability were assessed per NCI-CTCAE v5.0. **Results:** As of the Jan. 19, 2021, 87 pts [Cohort 1 (n = 51), Cohort 2 (n = 36)] have been enrolled with 83 pts having tumor PD-L1 expression data (PD-L1 $\geq$1%: 55.4%; PD-L1 $<$ 1%: 44.6%). 33.3% pts remained on the study treatment and 66.7% pts discontinued treatment due to disease progression (27.6%), TEAE (13.8%), death (9.2%) and other reasons (16%). The median treatment duration of KN046 was 21 weeks (range: 1.6~68.7 weeks). Treatment related TEAE (TRAE) occurred in 92% pts. 25.3% pts experienced Grade$\geq$3 TRAE [diarrhoea (5.7%), alanine aminotransferase increased (4.6%), infusion related reaction (3.4%), rash (3.4%), aspartate aminotransferase increased, dermatitis allergic and immune-mediated pneumonitis (2.3%, respectively), anaphylactoid reaction, autoimmune hepatitis, back pain, bilirubin conjugated increased, hypertension, neutrophil count decreased, platelet count decreased, pneumonitis, rash maculo-papular, septic shock and white blood cell count decreased (1.1%, respectively). In 81 efficacy evaluable pts, the overall objective response rate (ORR) was 50.6% (95% CI: 39.3%,61.9%) and disease control rate (DCR) was 87.7% (95% CI: 78.5%-93.9%). The ORR and DCR in pts with non-squamous NSCLC (n = 48) were 45.8% (95% CI: 31.4%, 60.8%) and 89.6% (95% CI: 77.3%, 96.5%). The ORR and DCR in pts with squamous NSCLC (n = 33) were 57.6% (95% CI: 39.2%, 74.5%) and 84.8% (95% CI: 68.1%, 94.9). Progression free survival (PFS) and OS events have occurred in 53% and 18% patients. Median PFS was 5.9 (95%CI: 5.3, 8.7) months. Median OS was not reached. OS rate at 12 and 15 months were both 74.9%. Similar OS curves have been observed in PD-L1 $\geq$1% and PD-L1 $<$ 1% pts. In PD-L1 $\geq$1% patients, median PFS was 6.7 months (10.8 months for PD-L1 $\geq$1% squamous NSCLC pts). **Conclusions:** KN046 combined with platinum doublet chemotherapy is tolerated and has shown promising clinical benefit as IL treatment for stage IV NSCLC particularly in PD-L1$\geq$1% tumors and squamous histology. Pivotal Phase III trial in advanced unresectable or metastatic squamous NSCLC is currently ongoing. Clinical trial information: NCT04054531. Research Sponsor: Alphamab oncology.

9061 **Poster Session**

Comparison of time to failure of pembrolizumab plus chemotherapy versus pembrolizumab monotherapy: A consecutive analysis of NSCLC patients with high PD-L1 expression. *First Author: Hiroshi Takumida, Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*

Background: There are two types of pembrolizumab-containing strategies for patients with non-small cell lung cancer (NSCLC) exhibiting a high expression level of programmed death-ligand 1 (PD-L1) (tumor proportion score [TPS] ≥50%): the early combination of pembrolizumab plus chemotherapy, and chemotherapy after pembrolizumab failure. Which strategy is superior, however, remains unclear. Comparing progression-free survival (PFS) or progression after the next therapy line (PFS2) in previous clinical trials has not allowed any conclusions regarding superiority to be made. Instead, the time to failure of strategy (TFS), which represents the time until disease exacerbation when the same number of drugs has been used, should be used to compare the two strategies. **Methods:** We consecutively reviewed the efficacy and safety of first-line, pembrolizumab-containing regimens administered between December 2017 and November 2020. We divided the patients who received pembrolizumab as a first-line treatment into two groups according to whether they received chemotherapy: a pembrolizumab plus chemotherapy group (combo group), and a pembrolizumab monotherapy group (mono group). TFS was defined as the PFS in the combo group and the PFS2 in the mono group. We used the propensity score matching (PSM) method to reduce the bias. **Results:** Of the 964 patients with advanced NSCLC who underwent first-line treatment, 126 with a PD-L1 TPS ≥50% were eligible for inclusion in this analysis (89 in mono group, 37 in combo group). PSM matched 36 people from each of the two groups. The median follow-up period was 16.2 months (range, 0.1-34.3 months). The patient backgrounds were similar. The overall response rate (ORR) of the combo group was higher than that of the mono group (69.4% vs. 50.0%). The median PFS (mPFS) in the combo group was longer (11.4 months vs. 6.0 months). However, the median TFS (mTFS) of the two groups was almost the same (11.4 months vs. 11.7 months). At the time of the analysis, the median overall survival had not been reached. The frequency of all immune-related serious adverse events (irSAE) was similar, however, that of all SAE and AE leading to treatment discontinuation were larger in the combo group. **Conclusions:** The ORR of the combo group was higher than that of the mono group; however, the TFS was similar. We suggest that pembrolizumab plus chemotherapy, which can increase toxicity, might be of value in patients, producing a clinically meaningful increase in the ORR. Research Sponsor: None.

Characteristics, efficacy, and safety of two groups after PSM.

	Combo group (n = 36)	Mono group (n = 36)
Age in years, median (range)	64 (46-78)	66 (45-80)
PS over 2, n	5	3
ORR, % (95% CI)	68.8 (50.0-83.9)	50.0 (32.9-67.1)
mPFS in months, n (95% CI)	11.4 (7.0-NR)	6.0 (3.2-10.7)
mTFS in months, n (95% CI)	11.4 (7.0-NR)	11.7 (9.1-21.5)
SAE, n	12	6
irSAE, n	11	12
Treatment discontinuation, n	18	11

9062 **Poster Session**

EGFR Exon 20 insertion: Prognostic and predictive values in advanced non-small cell lung cancer, a real-world study. *First Author: Christos Chouaid, Pneumology, Centre Hospitalier Intercommunal (CHI) Creteil, Créteil, France*

Background: In Europe, 10-15% of non-squamous non-small cell lung cancer (nsqNSCLC) have EGFR mutations of which 5-12% are an Exon 20 insertion (20ins). **Methods:** Analysis of Epidemio-Strategy and Medical Economics (ESME) Advanced and Metastatic Lung cancer (AMLC) Data Platform (NCT03848052), a multicenter real-life database using a supervised, retrospective data collection process. The database includes 13737 advanced nsqNSCLC treated from January 2015 at participating centres. The cut-off date for patient follow-up for this analysis was June 30, 2020. The aim of the study was to assess real-world patient characteristics, treatment patterns and clinical outcomes of advanced nsqNSCLC EGFR 20ins. Overall survival (OS) of EGFR cohorts (20ins, 19del/L858R without 20ins, other EGFR mutations) and EGFR wild-type/not tested cohort were assessed. **Results:** 1549 (11.3%) nsqNSCLC had an EGFR mutation, 61 (3.9%) of whom being an EGFR 20ins. These 61 patients (pts) are mainly female (68.9%), non-smoker (55.7%), with de novo stage IIIB/IV disease (78.6%), PS 0-1 (76.9%). Median age was 68.0 years (q1-q3: 54-74). PD-L1 status was assessed in 34 (55.7%) pts, mainly (n = 20) before first line and 22 (64.7%) had negative result. Most (63.9%) pts had EGFR 20ins positive result available before first line. Almost all pts (95.1%, n = 58) received a systemic therapy with a median number of 3 (q1-q3: 1-4) lines. In first line setting, 74% of the pts received chemotherapy (mainly chemotherapy combination), 13.7% received EGFR TKI (mainly as monotherapy) and 8.6% received immunotherapy only. Median treatment duration for pts treated with CarboPem (n = 19), CisplatinPem (n = 16) and CarboTaxol (n = 6) were 4.7 (q1-q3: 2.6-6.6), 7.4 (q1-q3: 5.0-12.8) and 3.3 (q1-q3: 2.8-3.8) months, respectively. For afatinib (n = 3), erlotinib (n = 2) and gefitinib (n = 1), median treatment durations were 1.6 (q1-q3: 0.5-2.8); 1.8 (q1-q3: 1.4-2.1) and 2.3 months, respectively. After a median follow up of 36.3 (95%CI: 34.1-39.8) months, median OS was 24.3 (95%CI: 19.1-32.6) months; 1 and 2-years OS rates were 82.5% (95%CI: 69.7-90.2) and 52.6% (95%CI: 37.3-65.9), respectively. For pts with 19del/L858R without 20ins (n = 1049) and those with other EGFR mutations (n = 439) median OS were 35.4 (95%CI: 32.6-37.5) and 41.7 (95%CI: 31.9-53.5), respectively compared to 20.7 (95%CI: 20.0-21.8] months for pts EGFR wild type/not tested (n = 12188). **Conclusions:** This large, national real-world analysis based on medical chart data's confirm that EGFR 20ins is a rare disease (0.4% of advanced nsqNSCLC). Currently available EGFR TKIs appear to have low efficacy and response to chemotherapy seems identical to that of EGFR wild-type/not tested pts. Prognosis for NSCLC pts with EGFR 20ins mutations was in line with that of EGFR wild type/not tested but worse than common EGFR mutations highlighting the need for advancements for this rare population. Research Sponsor: This work was supported by UNICANCER. The ESME AMLC database is supported by an industrial consortium (AstraZeneca, MSD, BMS, Janssen, Amgen and Roche). Data collection, analysis and publication are fully managed by UNICANCER independently of the industry.

9063 **Poster Session**

Features in genomics and tumor immune microenvironment in NSCLC treated with neoadjuvant PD-1 blockade. *First Author: Shuhang Wang, Clinical Cancer Center, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China*

Background: Results from several clinical trials have preliminarily demonstrated the safety and effectiveness of single PD-1 inhibitors in neoadjuvant setting for resectable non-small cell lung cancer (NSCLC). However, only around 40% patients could achieve Major Pathological Response. How to select patients who could benefit from single PD-1 blockade remains elusive. **Methods:** In this study, we aimed to assess the association of PD-L1 expression, tumor mutation burden (TMB), copy number alteration (CNA, including copy number gain and loss) burden with the pathological response to neoadjuvant PD-1 blockade. We also evaluated the dynamic changes of tumor immune microenvironment (TIME) by analyzing pre-immunotherapy treatment tumor biopsy samples from twenty-nine NSCLC patients as well as the matched post-surgery samples after neoadjuvant sintilimab treatment and resection. Targeted DNA sequencing (543 genes), PD-L1 immunochemistry staining (22C3) and multiplex immunofluorescence (CD4, CD8, CD9) were applied. **Results:** The degree of pathological regression and major pathological response (MPR), were positively correlated with tumor proportion score (TPS) of PD-L1 ($R = 0.40$, $p = 0.04$) and negatively correlated with copy number gain (CNgain) burden ($R = -0.44$, $p = 0.04$). Of note, the combination of CNgain burden and TPS can better stratify MPR patients compared to CNgain or TPS alone. Whereas, TMB only had a marginal association with pathological response ($R = 0.32$, $p = 0.15$). Additionally, PD-1 blockade led to an increase in $CD8^+$PD-1-T cells in the tumor region ($p = 0.04$, Mann-Whitney U test for paired samples) and a reduction in Tregs and M2 macrophages in the stromal region ($p < 0.05$, Mann-Whitney U test for paired samples). Further investigation showed that the degree of $CD8^+$PD-1-T cell increase was significantly associated with MPR ($p < 0.05$, Mann-Whitney U test). Intriguingly, we also observed a substantial reduction in $CD19^+$ cells in the non-MPR group but not in the MPR group, indicating the involvement of B cells in improving neoadjuvant immunotherapy response in NSCLC patients. **Conclusions:** TPS and CNgain burden were correlated with pathological response to neoadjuvant immunotherapy in NSCLC patients. This may provide potential selective indicators for future clinical trials of neoadjuvant immunotherapy. The dynamic changes of components in the tumor immune microenvironment may provide novel insight into the immune responses induced by neoadjuvant PD-1 blockade therapy. Research Sponsor: Chinese Academy of Medical Sciences (grants 2016-I2M-1-001, 2017YFC0907903, 2016-12M-1-005, and 2016-12M-1-001).

9064 **Poster Session**

Subgroup-level network meta-analysis for efficacy of first-line immunotherapy-based treatments in advanced non-small cell lung cancer. *First Author: Fang Wu, Department of Oncology, The Second Xiangya Hospital, Central South University, Changsha, China*

Background: Immunotherapy has unequal efficacies in populations with different clinical or histological features. This study aims to explore inter-subgroup differences in responses to immunotherapy in patients with advanced non-small cell lung cancer (NSCLC) and find the optimal treatments for each subgroup. **Methods:** We performed (network) meta-analyses of phase III random controlled trials, in which efficacies of 10 immunotherapy-based treatments were compared, including anti-programmed death receptor-1 (PD-1) (+chemotherapy), anti-programmed death ligand-1 (PD-L1) (+chemotherapy), anti-PD-L1+anti-cytotoxic T-lymphocyte protein 4 (CTLA-4), anti-PD-1+anti-CTLA-4 (+chemotherapy), anti-CTLA-4+chemotherapy, anti-PD-1+anti-angiogenic therapy (AT)+chemotherapy, and anti-PD-L1+AT+chemotherapy, for 19 subgroups by sex, age, smoking status, metastatic site (liver/brain/bone), histological type (squamous/non-squamous cancer), and PD-L1 expression, using hazard ratios (HRs) for overall survival (OS) and progression-free survival (PFS) and their 95% confidence intervals (CIs). **Results:** 22 studies comprised of 12678 patients with advanced NSCLC were included in our study. The results showed OS and PFS advantages of immunotherapy-based treatments in 16 out of 19 subgroups comparing with chemotherapy. Never-smokers (OS-HR 0.81, 95% CI 0.55-1.18; PFS-HR 0.73, 95% CI 0.51-1.07), ¡Ý75-year-old patients (OS-HR 0.9, 95% CI 0.71-1.13), and patients with liver metastases (OS-HR 0.88, 95% CI 0.77-1) showed indisposed responses to immunotherapy. In patients with PD-L1 tumor proportion score (TPS)<1%, anti-CTLA-4+anti-PD-1 and anti-PD-1+anti-CTLA-4+chemotherapy had significant OS benefit comparing with anti-PD-L1 monotherapy (HR 0.6, 95% CI 0.44-0.81; HR 0.6, 95% CI 0.41-0.87; respectively) and anti-PD-L1+AT+chemotherapy (HR 0.66, 95% CI 0.48-0.92; HR 0.66, 95% CI 0.45-0.98; respectively). In patients with liver metastases, anti-PD-L1+AT+chemotherapy showed significant PFS advantage comparing with anti-PD-L1+chemotherapy (HR 0.51, 95% CI 0.33-0.77). As for other populations, anti-PD-1+chemotherapy showed wide-ranging promising efficacies in multiple subgroups. **Conclusions:** Patients with advanced NSCLC generally benefit from immunotherapy. Specific immunotherapy treatments should be applied according to different clinical or histological features. Meanwhile, we expect more preclinical and clinical studies to focus on therapeutic strategies for populations with impaired responses towards immunotherapy. Funding: CSCO-BMS Oncologic Research Foundation (Grant No. Y-BMS2019-100); Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2017B030314120) and Guangdong Association of Clinical Trials (GACT); Changsha Science and Technology Bureau (Grant No. kq1907077). Research Sponsor: CSCO-BMS Oncologic Research Foundation (Grant No. Y-BMS2019-100), Other Foundation.

9065 **Poster Session**

Updated overall efficacy and safety of selpercatinib in patients (pts) with *RET* fusion+ non-small cell lung cancer (NSCLC). *First Author: Benjamin Besse, Department of Medicine and Thoracic Pathology Committee, Gustave Roussy, Villejuif, France*

Background: Selpercatinib, a first-in-class highly selective and potent, CNS-active RET kinase inhibitor, is approved in multiple countries for treatment of *RET* fusion+ lung or thyroid cancers. Here we report an update of efficacy and safety results which provide a longer follow up and increased number of patients (safety population: N = 345 vs N = 329). **Methods:** Pts with *RET* fusion+ NSCLC enrolled in the global, multicenter, ongoing LIBRETTO-001 trial (NCT03157128; 16 countries, 89 sites) were included in this analysis. Pts with the opportunity to be followed ≥6 months from their first dose were included in the efficacy-evaluable population for these analyses. Integrated analysis set (IAS) included 218 NSCLC pts with prior platinum-chemotherapy. Primary analysis set (PAS) was a subset of the IAS and included the first 105 consecutively enrolled pts. The treatment-naïve population included 48 efficacy-evaluable pts. Primary endpoint was objective response rate (ORR, RECIST v1.1) by independent review committee (IRC). Secondary endpoints included ORR by investigator, duration of response (DoR), progression-free survival (PFS), clinical benefit rate (CBR; CR+PR+SD ≥16 weeks), and safety. Safety population (N = 345) included all pts with NSCLC who received ≥1 selpercatinib dose by data cutoff (30 Mar 2020). **Results:** In pts with prior treatment (N = 218) and treatment-naïve (N = 48) pts, 56% and 60% were female, with a median pt age of 61 and 64 years, respectively. The ORR with selpercatinib was 57% in the IAS, 64% in the PAS, and 85% in the treatment-naïve population (Table). In both the IAS and PAS, the median DoR was 17.5 months, median PFS was 19.3 months at median follow-up of 12.0 and 15.7 months, respectively (Table). The most common treatment-emergent adverse events (TEAEs) reported in ≥25% of pts were dry mouth, diarrhea, hypertension, increased ALT/AST, edema peripheral, and fatigue. Twenty-five pts (7%) permanently discontinued due to TEAEs, with 10 pts (3%) discontinuing selpercatinib due to treatment-related AEs as per investigator. **Conclusions:** In this updated data set, selpercatinib continued to demonstrate durable antitumor activity in pts with *RET*-fusion+ NSCLC. Selpercatinib was well-tolerated with a safety profile consistent with previous reports. A global, randomized, phase 3 trial (LIBRETTO-431) evaluating selpercatinib compared with standard frontline therapy is ongoing. Clinical trial information: NCT03157128. Research Sponsor: Eli Lilly and Company.

	IAS (N = 218)	PAS (N = 105)	Treatment-naive (N = 48)
Best response by IRC, n (%)			
ORR, % (95% CI), n	57 (50.0, 63.6), 124	64 (53.9, 73.0), 67	85 (72.2, 93.9), 41
CBR% (95% CI), n	84 (78.9, 89.0), 184	85 (76.4, 91.0), 89	94 (82.8, 98.7), 45
DoR, median (95% CI), months	17.5 (12.1, NE)	17.5 (12.1, NE)	NE (12.0, NE)
PFS, median (95% CI), months	19.3 (16.5, NE)	19.3 (13.9, NE)	NE (13.8, NE)
Duration of follow-up, median (25^{th}, 75^{th} percentiles), months	12.0 (7.4, 15.9)	15.7 (12.1, 18.2)	9.8 (7.0, 13.1)

9066 **Poster Session**

Taletrectinib (AB-106; DS-6051b) in metastatic non-small cell lung cancer (NSCLC) patients with ROS1 fusion: Preliminary results of TRUST. *First Author: Caicun Zhou, Department of Medical Oncology, Shanghai Pulmonary Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China*

Background: Taletrectinib (AB-106; DS-6051b) is a potent, selective ROS1/NTRK inhibitor. In two phase I trials, NSCLC patients (pts) with ROS1 fusion who received taletrectinib as first line ROS1 TKI had an objective response rate (ORR) of 66.7% (6/9) and median progression-free survival (PFS) of 29.1 mo (Sai-Hong Ignatius Ou et al., *JTO Clinical and Research Reports*, 2020). TRUST (NCT04395677) is an ongoing, multicenter, phase II study of taletrectinib in Chinese NSCLC pts with ROS1 fusion. **Methods:** The ROS1 TKI naïve or crizotinib pre-treated NSCLC patients with ROS1 fusion were treated with taletrectinib 400 or 600 mg QD. ROS1 testing was performed in each center and confirmed by central lab using RT-PCR. The primary endpoint was ORR (complete response [CR] + partial response [PR]) by IRC assessment. Secondary endpoints were disease control rate (DCR; CR + PR + stable disease), PFS and safety, etc. The pharmacokinetics (PK) of taletrectinib following 400 or 600 mg QD regimen was also evaluated. **Results:** As of the data cutoff (15 Jan 2021), 22 pts had received taletrectinib treatment. Median age was 54.5 years (range, 32-77 years;); 18.2% (4/22) had central nervous system metastases; ECOG performance status was 0 in 13.6% (3/22) of pts and 1 in 86.4% (19/22) of pts. Most pts (54.5%, 12/22) had prior systematic chemotherapy; 31.8% (7/22) of pts had prior crizotinib treatment. ORR by investigator among the crizotinib naïve pts with tumor assessment (N = 11) was 100% (95% CI, 72%-100%); 81.8% (18/22) of pts had treatment-emergent adverse events (TEAEs), including nausea, vomiting, diarrhea, transaminase elevation, white blood cell count decrease/neutrophil count decrease, etc. 13.6% (3/22) were grade ≥ 3, including fatigue (4.5%, 1/22), white blood cell decrease (4.5%, 1/22) and transaminase elevation (4.5%, 1/22).TEAEs led to dose interruption in 3 pts (13.6%), including dose reduction in 2 pts (9.1%). Taletrectinib in plasma approximately reached steady state on Cycle 1 Day 8 with 2- to 3- fold accumulations of exposure, which was consistent with results observed in the phase I trials. **Conclusions:** Taletrectinib demonstrated promising clinical activity with high ORR and good tolerability in ROS1 fusion positive NSCLC patients. The safety and PK profiles following taletrectinib treatment was generally consistent with the phase I trials. Clinical trial information: NCT04395677. Clinical trial information: NCT04395677. Research Sponsor: AnHeart Therapeutics.

9067 **Poster Session**

Physician concern about delaying lung cancer treatment while awaiting biomarker testing: Results of a survey of U.S. oncologists. *First Author: Kathryn Finch Mileham, Levine Cancer Institute/Atrium Health, Charlotte, NC*

Background: With rapid advancements in biomarker testing informing lung cancer treatment decisions, clinicians are challenged to maintain knowledge of who, what and when to test and how to treat based on test results. An ASCO taskforce including representatives from the American Cancer Society National Lung Cancer Roundtable and patient advocates conducted a study to assess biomarker testing and treatment practices for patients with advanced non-small cell lung cancer (aNSCLC) among U.S. oncologists. **Methods:** A survey was sent to 2374 ASCO members – lung cancer specialists and general oncologists. Eligibility required treating ≥1 lung cancer patient/month. Proportions were estimated across groups and compared using chi-square tests. **Results:** 170 responses were analyzed. 59% of respondents work at an academic center (i.e., have a fellowship program), while 41% work at a community (non-academic hospital/health system/private practice). Nearly all (98%) believe biomarker results should be received within 1 or 2 weeks of ordering, yet 37% wait an average of 3 or 4 weeks for results. Of respondents who usually wait 3 or 4 weeks, 37% initiate a non-targeted systemic treatment while waiting. Respondents from community practices were more likely to initiate non-targeted systemic treatment if results were not available after 2 weeks (59% compared to 40% of academic respondents; p = 0.013).). When asked about reasons for not testing, respondents <5 years since training were more likely to report that delaying treatment while waiting for results was always/often a concern compared to those >6 years from training (41% vs 19%). Respondents reported high testing rates in both non-squamous and squamous aNSCLC. Roughly equal representation of generalists/specialists and academic/community respondents helps mitigate potential concerns about external validity. **Conclusions:** Respondents indicated that treatment decisions are impacted by delays in biomarker test results. Clinicians should be informed about when it is safe and appropriate to defer treatment while biomarker testing is pending. Respondents suggest that diagnostic biomarker testing companies should strive to expedite results. Research Sponsor: ASCO.

Respondents Characteristics (N=170) N(%).

	All	Academic Setting	Community Setting
1-50% / 51-100% lung cancer pts (row %)	7 (51) / 82 (49)	35 (35) / 65 (65)	52 (75) / 17 (25)
Order multigene panel aNSCLC squamous	154 (91)	96 (62)	58 (38)
Order multigene panel aNSCLC non-squamous	160 (95)	97 (61)	63 (39)
Access to Molecular Tumor Board	142 (84)	91 (64)	51 (36)
Time Since Training (column %)			
<5 yrs	32 (19)	20 (20)	12 (17)
6-15	63 (38)	44 (45)	19 (28)
16+	72 (43)	34 (35)	38 (55)
Avg Time – Biomarker Results			
1 or 2 wks	107 (63)	60 (60)	47 (68)
3 or 4 wks	62 (37)	40 (40)	22 (32)

9068 **Poster Session**

Neratinib efficacy in a subgroup of patients with *EGFR* exon 18-mutant non-small cell lung cancer (NSCLC) and central nervous system (CNS) involvement: Findings from the SUMMIT basket trial. *First Author: Jonathan Wade Goldman, University of California, Los Angeles, Los Angeles, CA*

Background: The phase 2 SUMMIT basket trial (NCT01953926) demonstrated efficacy of neratinib in patients with *EGFR* exon 18-mutant NSCLC [Boni et al. WCLC 2020]. Neratinib also has documented activity in HER2+ metastatic breast cancer with CNS metastases [Saura et al. SABCS 2020 & J Clin Oncol 2020]. Here we report neratinib efficacy in a subgroup of patients with *EGFR* exon 18-mutant NSCLC and CNS involvement from SUMMIT. **Methods:** Patients with *EGFR* exon 18-mutant NSCLC were treated with single-agent neratinib (240 mg po daily). Prior EGFR tyrosine kinase inhibitors (TKIs), chemotherapy, and checkpoint inhibitors (IO) were allowed. Patients with stable, asymptomatic CNS metastasis were enrolled. Study endpoints: objective response rate (ORR) at week 8 (±1 week); ORR (RECIST 1.1 confirmed); duration of response (DOR); clinical benefit rate (CBR); progression-free survival (PFS); safety; biomarkers. **Results:** Baseline characteristics of 11 patients with *EGFR* exon 18-mutant NSCLC: median age 67 (range 56–83) years; ECOG PS 0/1 (45%/55%). Prior lines of therapies: 2 (range 1–3): EGFR TKIs (91%); chemotherapy (55%); IO (27%). 3/11 patients had baseline CNS metastasis and received radiation 8–22 months prior to study enrollment. Best CNS response in these 3 patients was stable disease with overall individual PFS of 1.9 (censored), 6.9 and 9.1 months and OS of 2.6 (censored), 17.7 (censored), and 17.9 months. Efficacy is summarized in Table. Efficacy summary: TKI-pretreated *EGFR* exon 18-mutant NSCLC cohort receiving neratinib monotherapy. **Conclusions:** Activity of single-agent neratinib was observed in prior TKI-exposed patients with *EGFR* exon 18-mutant NSCLC. Despite the small sample size of only 3 patients with baseline CNS metastases, findings suggest a potential role for neratinib as a systemic treatment option for patients with NSCLC and difficult-to-treat uncommon mutations with CNS involvement. The SUMMIT trial continues to enroll patients with *EGFR* exon 18-mutant NSCLC. Clinical trial information: NCT01953926. Research Sponsor: Puma Biotechnology Inc.

	TKI-pretreated subgroup (n=10)[a]
ORR (confirmed)$_{Rb,\dagger}$, n	4
CR	0
PR	4
ORR, % (95% CI)	**40** (12–74)
Best overall response, n	6
CR	0
PR	6
Best overall response rate, % (95% CI)	60 (26–88)
Median DOR,[c] months (95% CI)	7.5 (4.0–NE) (1.9*, 4.0, 7.5, 9.2*)
CBR,[d] n	8
CR or PR	4
SD ≥16 weeks	4
CBR, % (95% CI)	80 (44–97)
Overall median PFS,[c] months (95% CI)	**9.1** (3.7–NE)
Overall median OS,[c] months (95% CI)	**17.9** (5.7–NE)
PFS in patients with CNS metastases, months	**1.9#, 6.9, 9.1**
OS in patients with CNS metastases, months	**2.6#,17.7#, 17.9**

Data cut: Aug 2020. [a]10/11 patients had prior EGFR TKIs. [b]ORR = CR/PR (confirmed ≥4 weeks after criteria for response initially met). [c]KM analysis in safety population. [d]CBR = confirmed CR/PR + SD for ≥16 weeks ±7 day. [†]ORR at week 8 (ORR$_{first}$) and ORR (RECIST 1.1 confirmed) are identical and only presented once. *Response ongoing; #Censored.

9069 **Poster Session**

The effects of tislelizumab treatment on the health-related quality of life of non-small cell lung cancer patients who progressed on a prior platinum-containing regimen. *First Author: Cai Zhou, Shanghai Pulmonary Hospital, Shanghai, China*

Background: Anti-PD-1/L1 therapies have improved overall survival (OS) by 2-4 months vs docetaxel in patients with advanced non−small cell lung cancer (NSCLC) who progressed after receiving a platinum regimen. Tislelizumab, an anti-PD-1 antibody, has been tested as monotherapy in the RATONALE (NCT 03358875) trial, which found that tislelizumab prolonged OS (median OS difference 5.3 months in ITT population) as compared to docetaxel, improved progression-free survival (median 4.1 vs 2.6 months), as well as overall response rate (ORR difference = 14.9%).Here we report health-related quality of life (HRQoL) of patients receiving tislelizumab vs docetaxel in this clinical trial. **Methods:** NSCLC patients in this open-label, multicenter Phase 3 study were randomized to either the tislelizumab or docetaxel. HRQoL was measured using the QLQ-C30 global health status/quality of life score (GHS/QoL) from EORTC QLQ-C30 as well as the lung cancer specific subscales of the EORTC QLQ-LC13. Descriptive analysis for the GHS/QoL score was performed for baseline through cycle 10; changes from baseline to cycle 12 were examined for the symptom subscales. **Results:** 805 patients were randomized to tislelizumab (n = 535) or docetaxel (n = 270). Patients were 77% male with an average age of 60 years (range 28-88 years). The compliance rates were mostly $>$ 98% and were similar across arms. The GHS/QoL score in the tislelizumab arm improved relative to baseline from cycles 5 through 10 while declining in cycles 6 through 10 in the docetaxel arm. The tislelizumab arm showed a reduction from baseline at cycle 12 in the symptom scores of coughing, chest pain, and dyspnea while patients in the docetaxel arm experienced an increase in symptoms. **Conclusions:** The study results show that tislelizumab monotherapy improved HRQoL in patients who previously failed treatment with a platinum containing chemotherapy; this is especially important as the NSCLC patients treated with tislelizumab not only experienced improvements in OS, but also reductions in their symptomology. Clinical trial information: NCT 03358875. Research Sponsor: BeiGene LTD.

9071 **Poster Session**

Brigatinib (BRG) in ALK+ crizotinib (CRZ)-refractory non-small cell lung cancer (NSCLC): Final results of the phase 1/2 and phase 2 (ALTA) trials. *First Author: Scott N. Gettinger, Yale School of Medicine and Smilow Cancer Center, Yale New Haven Hospital, New Haven, CT*

Background: BRG is a kinase inhibitor approved for the treatment of patients (pts) with ALK+ metastatic NSCLC; specific details for BRG use vary by indication and country. We report long-term efficacy and safety results of the Phase 1/2 and Phase 2 (ALTA) trials of BRG. **Methods:** The Phase 1/2 study was a single-arm, open-label trial (NCT01449461) of BRG 30–300 mg/d in pts with advanced malignancies. ALTA (NCT02094573) randomized pts with CRZ-refractory ALK+ NSCLC to receive BRG at 90 mg qd (arm A) or 180 mg qd with 7-d lead-in at 90 mg (arm B). For the Phase 1/2 study, investigator assessments of confirmed objective response rate (cORR; RECIST v1.1), duration of response (DoR), progression-free survival (PFS), overall survival (OS), and safety in pts with ALK+ NSCLC are reported. The primary endpoint of ALTA was cORR per investigator; secondary endpoints included cORR per independent review committee (IRC), DoR, PFS, and OS. **Results:** In the Phase 1/2 study, 137 pts received BRG; of these, 79 pts had ALK+ NSCLC (71/79 had prior CRZ; 28/79 received 180 mg qd [7-d lead-in at 90 mg]; 14/79 received 90 mg qd). In ALTA, 222 pts with CRZ-refractory ALK+ NSCLC were randomized (n = 112/110, arm A/B). At the end of the Phase 1/2 study (Feb 18, 2020), with median 27.7 mo follow-up (~67 mo after last pt enrolled), 4 pts remained on BRG. At the end of ALTA (Feb 27, 2020), with median 19.6/28.3 mo follow-up in arm A/B (~53 mo after last pt enrolled), 10/17 pts in arm A/B were still on treatment. Table shows efficacy results from final analyses with long-term follow-up. In ALTA, the IRC-assessed intracranial cORR in pts with measurable baseline brain metastases was 50% (13/26) in arm A and 67% (12/18) in arm B; Kaplan-Meier (KM) estimated median intracranial DoR was 9.4 mo (95% CI, 3.7, not reached [NR]) in arm A and 16.6 mo (3.7, NR) in arm B. With long-term follow-up, no new safety signals were identified. Treatment-emergent adverse events led to dose interruption (Phase 1/2: 59%; ALTA arm A/B: 49%/61%), dose reduction (13%; 8%/33%), or discontinuation (10%; 4%/13%). **Conclusions:** BRG showed sustained long-term activity, PFS, and manageable safety in pts with CRZ-refractory ALK+ NSCLC. The 180 mg/d dose after 7-d lead-in at 90 mg/d led to numerically higher median PFS and OS. Final results are similar to those reported for other approved ALK tyrosine kinase inhibitors in this setting. Clinical trial information: NCT01449461, NCT02094573. Research Sponsor: ARIAD Pharmaceuticals, Inc., Cambridge, MA, USA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited.

	Phase 1/2 (n = 79)	ALTA: A (n = 112)	ALTA: B (n = 110)
cORR, n (%) [95% CI] Per investigator	53 (67) [56, 77]	51 (46) [36, 55]	63 (57) [48, 67]
Per IRC	—	58 (52) [42, 61]	62 (56) [47, 66]
Median DoR (95% CI),[a] mo Per investigator	14.9 (9.9, 29.5)	12.0 (9.2, 19.4)	13.8 (10.8, 17.6)
Per IRC	—	19.4 (9.2, 24.9)	15.7 (13.6, 22.1)
Median PFS (95% CI),[a] mo Per investigator	14.5 (10.8, 21.2)	9.2 (7.4, 11.1)	15.6 (11.1, 18.5)
Per IRC	—	9.9 (7.4, 12.8)	16.7 (11.6, 21.4)
Median OS (95% CI),[a] mo	47.6 (28.6, NR)	25.9 (18.2, 45.8)	40.6 (32.5, NR)
OS at 5 years[a]	42%	31%	43%

[a]KM estimates.

9072 **Poster Session**

Activity of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) in patients (pts) with NSCLC with uncommon *EGFR* mutations: A real-world cohort study (UpSwinG). *First Author: Satoru Miura, Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan*

Background: EGFR TKIs are an established treatment (tx) option for pts with *EGFR* mutation-positive NSCLC with common mutations (Del19 or L858R); however, 7–23% of NSCLC tumors harbor uncommon *EGFR* mutations, where EGFR TKI efficacy is less established. These mutations are highly heterogeneous, and developments in detection by NGS are helping to identify mutations with little or no clinical data. **Methods:** In this non-interventional, global, multi-center study (NCT04179890), existing medical or electronic health records were identified for consecutive EGFR TKI-naïve pts with uncommon *EGFR* mutations (T790M, ex20ins, major uncommon [G719X, L861Q or S768I], 'other' or compound mutations) treated with erlotinib, gefitinib, afatinib, osimertinib or other systemic therapy. Endpoints were time to tx failure (TTF), ORR, OS and duration of response (DoR). **Results:** Overall, 246 pts (median age: 69.5 yrs; Asian: 84%; brain metastases: 8%; ECOG PS $\geq$2: 16%) were recruited from 9 countries. Most pts (n=226; 92%) received an EGFR TKI as 1st-line therapy; 132 (54%), 105 (43%) and 7 (3%) received afatinib, 1st-gen TKIs and osimertinib, respectively. 57% of pts received $>$1 line of therapy. Most pts (73%) had a major uncommon mutation, 9% had other mutations and 33% had a compound mutation; these were detected using PCR (75%) or sequencing (25%), mainly based on tissue biopsy (86%). Pathology reports varied in quality, often lacking detail on specific mutations e.g. 21% of ex18 and 72% of ex20ins were undefined. Median TTF and OS with EGFR TKIs were 9.9 and 24.4 mos; ORR was 42%. In pts treated with 1st-line chemotherapy (n=20), median TTF and ORR were 6.6 mos and 41%. Outcomes were most favorable in major uncommon and compound mutations (Table). TTF appeared to be higher with afatinib vs 1st-gen EGFR TKIs. In most mutation categories, median OS was $>$2 yrs, possibly reflecting high subsequent therapy uptake. **Conclusions:** In a real-world setting, EGFR TKIs were the preferred tx option in pts with uncommon *EGFR* mutations; strongest outcomes were seen in major uncommon and compound mutations, and in pts treated with afatinib. Data were in line with recent analyses of afatinib in uncommon mutations. Tx with an EGFR TKI should be considered as standard for most pts with uncommon mutations. Optimal tx for pts with uncommon mutations requires improvements in pathology reports, with more emphasis on NGS methodology and precise definition of mutations. Clinical trial information: NCT04179890. Research Sponsor: Boehringer Ingelheim.

Pts treated with afatinib	Median TTF, mos	Median OS, mos	ORR, %	Median DoR, mos
All (n=132)	11.3	24.5	44	12.0
Major uncommon (n=94)	14.3	24.5	51	12.0
Compound (n=46)	12.6	23.4	53	10.0
Other (n=9)	10.8	20.2	29	10.5
Ex20ins (n=18)	8.4	22.5	19	5.5
Pts treated with 1st-gen EGFR TKI				
All (n=106)	8.8	24.2	44	6.0
Major uncommon (n=80)	9.8	28.5	47	6.5
Compound (n=32)	12.4	31.3	48	6.0
Other (n=12)	7.3	12.8	56	4.5
Ex20ins (n=10)	5.2	21.0	17	33.0

9073 **Poster Session**

A phase II trial of chemotherapy plus pembrolizumab in patients with advanced NSCLC previously treated with a PD-1 or PD-L1 inhibitor: Big Ten Cancer Research Consortium BTCRC-LUN15-029. *First Author: Nikhil Shukla, Indiana University Melvin and Bren Simon Cancer Center, Indianapolis, IN*

Background: Chemoimmunotherapy with a platinum doublet plus a checkpoint inhibitor (CPI) is a standard of care for pts with advanced NSCLC. While some pts experience prolonged responses to initial CPI therapy, the majority of pts will eventually experience PD. It is unknown if continuing CPI treatment beyond progression has any advantages in this setting. We report the results of a phase 2 trial of chemotherapy plus pembrolizumab in pts with advanced NSCLC previously treated with a PD-1 or PD-L1 inhibitor. **Methods:** Pts experiencing PD after clinical benefit to CPI (PFS $>$ 3 months) were enrolled. Pts received pembrolizumab 200 mg q3wks plus next-line chemotherapy (gemcitabine 1000 mg/m^2 IV D1 and D8 q3wks, or docetaxel 60-75 mg/m^2 IV D1 q3wks, or pemetrexed 500 mg/m^2 IV D1 q3wks [non-squamous histology only]). The primary endpoint was PFS by RECIST 1.1. Key secondary endpoints included ORR, OS, and toxicity. The null hypothesis was median 3-month PFS with pembrolizumab plus next-line chemotherapy and the alternative hypothesis was median 6-month PFS with pembrolizumab plus chemotherapy. **Results:** 35 pts were enrolled. Median follow-up was 18.1 months and median age 63 (44-80). 51.4% male and 48.6% female. 82.9% were current or former smokers. Histology included 74.3% with adenocarcinoma, 20% with squamous cell carcinoma, 5.7% with NSCLC NOS. Treatment regimens included pembrolizumab/docetaxel (40%), pembrolizumab/gemcitabine (45.7%), or pembrolizumab/pemetrexed (14.3%). Median number of cycles of pembrolizumab was 6 (1-31). Median PFS using RECIST 1.1 and irRECIST was 5.2 months (95% CI 3.6-11.2, p $<$ 0.05) and 6.9 months (95% CI 3.8-12), respectively. Median OS was 26.8 months (95% CI 13.4-30.9). Best response using RECIST 1.1 was PR (23.5%) and SD (53%). 45.7% of pts experienced G3 or higher treatment-related AEs (TRAEs). Most common TRAEs were fatigue (60%), anemia (51.4%), and nausea (42.9%). There were no treatment related deaths. **Conclusions:** Pembrolizumab plus next-line chemotherapy in pts with advanced NSCLC who experienced PD after clinical benefit to CPI was associated with prolonged PFS compared with historical controls of single agent chemotherapy. Further investigations into which pts would benefit from continued CPI treatment after progression is warranted. Clinical trial information: NCT03083808. Research Sponsor: Merck.

9074 **Poster Session**

Phase I study of the aurora kinase A inhibitor alisertib in combination with osimertinib in EGFR-mutant lung cancer. *First Author: Collin M. Blakely, UCSF Helen Diller Comprehensive Cancer Center, San Francisco, CA*

Background: The 3rd generation EGFR tyrosine kinase inhibitor (TKI) osimertinib is effective for the treatment of advanced EGFR-mutant (mt) lung adenocarcinoma (LUAD). However, tumor resistance to osimertinib monotherapy invariably occurs. Activation of Aurora Kinase A (AURKA) drives resistance to osimertinib treatment in preclinical models of EGFR-mutant LUAD and is associated with TKI resistance in patients. Alisertib is a selective AURKA inhibitor with an acceptable safety profile established in early phase clinical trials. **Methods**: We performed a single institution phase Ia clinical trial of alisertib in combination with the 3rd generation EGFR inhibitor osimertinib in patients with metastatic EGFR-mutant LUAD who had experienced disease progression on osimertinib monotherapy (NCT04085315). The primary objective of the study was to determine the safety and tolerability of alisertib in combination with osimertinib in order to define the maximum tolerated dose (MTD) and to identify a recommended phase 2 dose (RP2D). Secondary efficacy endpoints included objective response rate (ORR), disease control rate (DCR) and progression-free survival (PFS). Utilizing a 3+3 trial design, patients receiving osimertinib 80 mg daily were treated with alisertib using an intermittent dosing strategy of 20-50 mg twice daily (BID) oral alisertib on days (d) 1-3, 8-11, and 15-17 of a 28-day cycle. **Results:** A total of 10 patients were treated with osimertinib 80 mg and received at least one dose of alisertib. 6 patients were treated at the 30 mg BID and 4 patients at the 40 mg BID intermittent dosing schedule of alisertib. The most commonly reported adverse events (AEs) were diarrhea (70%), fatigue (60%), alopecia (50%) and neutropenia (50%). All AEs, except neutropenia, were grade 1 or 2. Two patients (20%) experienced grade 3 or grade 4 neutropenia; both patients were treated at the 40 mg BID intermittent dose of alisertib. Intermittent alisertib 30 mg BID was identified as the MTD and RP2D in combination with osimertinib 80 mg daily. The ORR was 10% (1/10) and DCR 70% (7/10), with the majority of patients, 60% (6/10), achieving stable disease (SD). 30% (3/10) experienced progressive disease (PD) as their best response. The median PFS was 9.4 months (2.0 months - N.R.). **Conclusions:** Intermittent dosing of alisertib 30 mg BID on d1-3, 8-11, and 15-17 of a 28-day cycle in combination with osimertinib 80 mg daily demonstrates an acceptable toxicity profile. Preliminary efficacy analysis suggests that alisertib + osimertinib may result in clinically meaningful disease control in EGFR-mt LUAD patients whose disease is resistant to osimertinib monotherapy. Clinical trial information: NCT04085315. Research Sponsor: Takeda, Other Foundation.

9075 **Poster Session**

Phase II randomized study of ramucirumab plus pembrolizumab versus standard of care for advanced non-small cell lung cancer previously treated with a checkpoint inhibitor: Toxicity update (Lung-MAP non-matched substudy S1800A). *First Author: Karen L. Reckamp, Cedars-Sinai Medical Center, Los Angeles, CA*

Background: The therapeutic landscape in metastatic NSCLC has dramatically changed with approvals of immunotherapy agents in both treatment-naïve and previously treated cancer patients (pts) and irrespective of histology. Pts with tumors that develop resistance is a significant area of unmet need. Vascular endothelial growth factor (VEGF) has been shown to modulate the tumor immune microenvironment and combination immune checkpoint and VEGF/VEGF receptor inhibition have shown benefit in multiple tumor types. Lung-MAP is a master protocol for pts with stage IV, previously treated NSCLC. Pts who were not eligible for a biomarker-matched substudy enrolled in S1800A. The adverse event profile will be presented. **Methods:** S1800A is a phase II randomized trial for pts who previously received PD-1 or PD-L1 inhibitor therapy for at least 84 days and platinum-based doublet therapy with ECOG 0-1 stratified by PD-L1 expression, histology and intent to receive ramucirumab in the standard of care (SOC) arm. Pts were randomized 1:1 to pembrolizumab and ramucirumab P+R or SOC (docetaxel +R [SOC w R]; docetaxel, pemetrexed or gemcitabine [SOC wo R]). The primary endpoint was overall survival. Secondary endpoints included response, duration of response, investigator assessed-progression free survival and evaluation of toxicity. **Results:** From May 17, 2019 to November 16, 2020, 166 pts enrolled and 140 determined eligible [69 (49%) P+R; 46 (33%) SOC w R; 25 (18%) SOC wo R]. Treatments for those who received SOC wo R included 3 on docetaxel (19%); 12 on gemcitabine (75%); and on 1 on pemetrexed (6%). 131 were eligible for adverse event (AE) assessment. The most common AE were fatigue (38%), proteinuria (28%), hypertension (23%), diarrhea (22%) and hypothyroidism (22%) on P+R; fatigue (61%), anemia (48%), diarrhea (41%) and neutropenia (39%) on SOC w R and anemia (56%), leukopenia (56%), fatigue (44%) and neutropenia (44%) on SOC wo R. Grade $\geq$ 3 treatment-related AEs occurred in 32% of pts on P+R, 54% of pts on SOC w R and 56% of pts on SOC wo R. Cardiac and thromboembolic events occurred in 12% of pts on P+R, 11% of pts on SOC w R and 0% of pts on SOC wo R. Grade 5 AE occurred in 2 pts on P+R (respiratory failure and cardiac arrest), 3 pts on SOC w R (2 respiratory failure and sepsis) and 1 pt on SOC wo R (sepsis). Four patients were diagnosed with COVID-19 (1 on P+R and 3 on SOC) and 3 died (1 on P+R and 2 on SOC). **Conclusions:** Grade 3 toxicities were lower in P+R compared to SOC arms with or without R. Cardiac and thromboembolic events were similar in arms that included R. P+R was generally well-tolerated. Efficacy outcomes will be presented when data matures. Clinical trial information: NCT03971474. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Eli Lilly and Company and MSD International GmbH.

9076 **Poster Session**

PD-(L)1 inhibitors as monotherapy for the first-line treatment of non-small cell lung cancer patients with high PD-L1 expression: A network meta-analysis. *First Author: Margarita Majem, Department of Medical Oncology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain*

Background: PD-L1 has emerged as a potential biomarker for predicting responses to immunotherapy and as a prognostic factor in non-small cell lung cancer (NSCLC). In this network meta-analysis, we aimed to evaluate the efficacy of first-line PD-(L)1 monotherapy in advanced NSCLC patients with high PD-L1 expression. **Methods:** We conducted a systematic search in PubMed to identify all eligible trials from inception until 1 November 2020, with no start date limit applied. Only phase III trials evaluating the efficacy of first-line (1L) PD-(L)1 monotherapy in patients with stage IIIB/stage IV NSCLC and high PD-L1 expression were included. **Results:** Six clinical trials (KEYNOTE-024, KEYNOTE-042, EMPOWER Lung-01, IMpower110, MYSTIC and CheckMate-026) with 2,111 patients were included. In head-to-head comparisons, immunotherapy showed a significant improvement in progression-free survival (PFS: HR_{pooled} = 0.69, 95% CI: 0.52-0.90, p = 0.007), overall survival (OS: HR_{pooled} = 0.69, 95% CI: 0.61-0.78; $p <$ 0.001) and overall response rate (ORR) (Risk ratio $[RR]_{pooled}$ = 1.354, 95% CI: 1.04-1.762, p = 0.024) compared to chemotherapy (CT). In the assessment of relative efficacy for PFS through indirect comparisons, pembrolizumab (results from KEYNOTE-024) ranked highest followed by cemiplimab and atezolizumab, with statistical significance determined across some of the drugs. In terms of OS, cemiplimab ranked highest followed by atezolizumab and pembrolizumab, although non-significant OS was determined across these drugs. Overall, 1L PD-(L)1 monotherapy improved OS in almost all subgroups, reaching statistical significance in men (HR_{pooled} = 0.624, 95% CI: 0.51-0.72, $p <$ 0.001), non-Asian patients (HR_{pooled} = 0.66, 95% CI: 0.55-0.79, $p <$ 0.001), all patients regardless of age ($<$ 65 years [HR_{pooled} = 0.72, 95% CI: 0.57-0.90, p = 0.005]; $\geq$65 years [HR_{pooled} = 0.61, 95% CI: 0.48-0.77, $p <$ 0.001]), ECOG PS status (ECOG PS = 0 [HR_{pooled} = 0.68, 95% CI: 0.56-0.82, $p <$ 0.001; ECOG PS = 1 [HR_{pooled} = 0.59, 95% CI: 0.43-0.82, p = 0.001) and histological tumour type (Squamous [HR_{pooled} = 0.49, 95% CI: 0.37-0.67, $p <$ 0.001; Non-squamous [HR_{pooled} = 0.67, 95% CI: 0.52-0.87, p = 0.003). In the case of smokers and NSCLC stage, only current/former smokers (HR_{pooled} = 0.623, 95% CI: 0.47-0.83, p = 0.001) and patients with stage IV disease* (HR_{pooled} = 0.687, 95% CI: 0.59-0.81, $p <$ 0.001) benefited from single PD-(L)1 monotherapy over CT. **Conclusions:** PD-(L)1 inhibitor monotherapy improves efficacy outcomes in the 1L setting of advanced NSCLC patients with high PD-L1 expression. Current/former smokers $\geq$65 years, with ECOG PS = 1 and squamous NSCLC benefited most from this therapy. *KEYNOTE-042 was the only study including patients with stage IIIB NSCLC. Research Sponsor: ROCHE FARMA.

9077 **Poster Session**

Safety and activity of CLN-081 (TAS6417) in NSCLC with EGFR Exon 20 insertion mutations (Ins20). *First Author: Zofia Piotrowska, Massachusetts General Hospital, Boston, MA*

Background: NSCLC with EGFR ins20 represents a significant area of unmet need, with no approved targeted therapies. While several agents targeting EGFR ins20 are in development, wild-type (WT) EGFR-related adverse events (AEs) have been common and challenging to manage. CLN-081 is a novel oral EGFR TKI with broad activity against clinically relevant EGFR mutations, including ins20, and has attenuated activity against WT EGFR relative to EGFR ins20 *in vitro*, suggesting that CLN-081 may have a more favorable clinical therapeutic window. We present interim results of a multicenter, Phase (Ph) 1/2a trial evaluating CLN-081 in advanced, EGFR ins20 NSCLC (NCT04036682). **Methods:** Patients (pts) with EGFR ins20 previously treated with platinum-based therapy (tx) were eligible to enroll. Ph 1 dose escalation in this adaptive trial began with an accelerated titration (AT) design, and converted to a rolling six design based upon prespecified safety criteria or at clinically active doses. Cohort expansion in Ph 1 occurred at any dose where responses were seen. Transition from Ph 1 to 2a was based on a Simon-Two Stage design. Prior tx with EGFR ins20-specific inhibitors was allowed in AT cohorts only. CLN-081 was dosed twice daily (BID) in 21-day cycles. **Results:** As of 10 November 2020, 37 pts [median age 64 years (44-82); median 2 (1-9) prior lines of tx] received CLN-081 at doses of 30 mg (n = 8), 45 mg (1), 65 mg (12), 100 mg (13), and 150 mg (3) BID. The most common all-grade (gr) treatment-related AEs (TRAEs) were rash (49%), diarrhea (24%), paronychia (16%), nausea (14%), stomatitis (14%), and dry skin (11%). Gr 3 TRAEs included anemia (5%), diarrhea (3%), and increased alkaline phosphatase (ALP) (3%). There was 1 DLT, gr 3 diarrhea at 150 mg BID. No gr $\geq$ 3 rash or gr 4/5 TRAEs were reported. Four pts (11%) required dose reductions for rash (2), diarrhea (1), and increased ALP (1). Two pts (5%) discontinued tx due to TRAEs of gr 2 hypersensitivity reaction (1) and gr 2 pneumonitis (1); the latter also experienced pneumonitis while receiving prior osimertinib. Among the 25 response evaluable pts (RECIST 1.1), 10 (40 %) had a partial response (PR) (6 confirmed, 2 pending confirmation, 2 unconfirmed), 14 (56%) had stable disease (SD), and 1 (4%) had progressive disease as best response. Of the 4 pts that received prior EGFR ins20 inhibitors, 2 had PR and 2 SD. Of pts with SD or PR as best response, 20/24 (83 %) experienced tumor regression [median regression: -18 % (-100 to +3)]. Enrollment is ongoing and updated data will be presented. **Conclusions:** CLN-081 has an acceptable safety profile, including diarrhea in $<$ 25% of pts treated to date. CLN-081 has demonstrated encouraging preliminary anti-tumor activity across the full dose range tested, in multiple distinct EGFR ins20 variants, and in heavily pre-treated pts that are either naïve or refractory to other EGFR ins20 inhibitors. Since the time of the data cut, a Ph 2a expansion has been initiated at 100 mg BID. Clinical trial information: NCT04036682. Research Sponsor: Cullinan-Pearl.

9078 **Poster Session**

Patient-reported symptoms, functioning, and quality of life (QoL) in patients treated with cemiplimab monotherapy for first-line treatment of advanced NSCLC with PD-L1 ≥ 50%: Results from EMPOWER-Lung 1 study. *First Author: Mahmut Gumus, Istanbul Medeniyet University, Istanbul, Turkey*

Background: Cemiplimab, a PD-1 inhibitor, improved survival and progression-free survival vs platinum doublet chemotherapy (chemo) in patients (pts) with advanced NSCLC and PD-ligand(L)1 expression ≥50% in the EMPOWER-Lung 1 Phase 3 study (NCT03088540). Since pts with advanced NSCLC have a high symptom burden that adversely impacts QoL and functioning, these outcomes were evaluated as secondary endpoints in the clinical trial. **Methods:** Pts with advanced NSCLC with PD-L1 expression ≥50% and ECOG performance status ≤1 were randomized to IV cemiplimab 350 mg Q3W (n=356) or platinum doublet chemo (n=354). At baseline (BL) and day 1 of each treatment cycle (C) to C15, pts were administered the EORTC core questionnaire (QLQ-C30) and its lung cancer specific module (QLQ-LC13) to assess symptoms, functioning, and Global Health Status (GHS)/QoL. In the intent-to-treat population, mixed-effects repeated measures models were used to estimate least squares (LS) mean change from BL on all scales. Kaplan–Meier analysis estimated time to definitive deterioration, defined as worsening ≥10 points from BL observed at all subsequent time points or patient withdrawal after worsening; hazard ratios (HR) with 95% CIs estimated the likelihood of definitive deterioration. **Results:** BL scores showed moderate to high levels of functioning and low symptom burden. Cemiplimab-treated pts had lower likelihood of definitive deterioration vs chemo on key symptoms of dyspnea, cough, pain in chest, pain in other body parts, fatigue, nausea/vomiting, appetite loss, constipation, and diarrhea vs chemo (all $P<.05$). Treatment-related symptoms of peripheral neuropathy and alopecia had a lower likelihood of definitive deterioration with cemiplimab vs chemo (both $P<.05$). Cemiplimab resulted in significantly greater improvements vs chemo on all functioning scales and reduced the likelihood of definitive deterioration as indicated by HR <1 (Table). GHS/QoL improvements with cemiplimab at C2 were maintained to C15; LS mean change (SE) from BL across all timepoints was 7.1 (1.0) for cemiplimab vs 1.7 (1.2) for chemo ($P<.0001$). **Conclusions:** In pts with advanced NSCLC and PD-L1 expression ≥50%, cemiplimab significantly improved GHS/QoL, functioning, and most symptoms vs chemo. Over 1 year of treatment, cemiplimab delayed worsening of key lung cancer symptoms and functioning. Clinical trial information: NCT03088540. Research Sponsor: Regeneron Pharmaceuticals, Inc, and Sanofi.

	Difference in LS mean change from BL (95% CI)[a]	HR (95% CI) for definitive deterioration
GHS/QoL	5.4 (2.7–8.1)*	0.73 (0.52–1.03)
Physical functioning	4.2 (1.6–6.7)*	0.59 (0.42–0.84)*
Role functioning	3.3 (0.2–6.3)*	0.65 (0.46–0.92)*
Emotional functioning	3.4 (1.0–5.9)*	0.49 (0.30–0.79)*
Cognitive functioning	2.5 (0.4–4.5)*	0.64 (0.44–0.93)*
Social functioning	5.2 (2.5–7.9)*	0.50 (0.35–0.72)*

[a]Cemiplimab minus chemo.
*$P<.05$.

9079 **Poster Session**

Real-world patterns of biomarker testing and targeted therapy in metastatic non-small cell lung cancer (mNSCLC) in the community oncology setting. *First Author: Eric S. Nadler, Texas Oncology-Baylor Charles A. Sammons Cancer Center, Dallas, TX*

Background: National guidelines recommend biomarker testing in mNSCLC, and targeted therapy is associated with improved outcomes. The aim of this study was to understand the real-world biomarker testing and treatment patterns in the community setting. **Methods:** This was a retrospective study of adult patients diagnosed with de novo mNSCLC between 01-Jan-2016 and 30-Sep-2019, with follow-up through 31-Dec-2019 using The US Oncology Network structured electronic health records data. Patients who received systemic treatment for mNSCLC were included. **Results:** A total of 3213 patients were identified with median age 68 years (24, 90+); 52.7% were male and 10% were current smokers. ECOG score was 0-1 in 55.2%; 60% had adenocarcinoma, 16% had squamous cell carcinoma, and the rest had other/unknown histology. Since most of the biomarker-guided therapies were approved after 2016, testing patterns are described for 2017-2019 (n=2257). Overall, 23.6% were not tested for any biomarker (PD-L1 or driver mutation [DM]) at any time during the study period, and only 49% had a biomarker test result prior to 1L treatment. We observed similar patterns when assessing DM specifically; 35.8% were never tested for DM, and only 39.3% had a DM test result prior to 1L treatment. As an example, out of 42 ALK+ patients in this study population, only 5 had test results prior to 1L treatment and only 3 received an ALK inhibitor as their 1L treatment (Table). Similar patterns were observed for the other biomarkers. **Conclusions:** Despite availability of promising biomarker-based therapies, the lack of adequate testing in the community oncology setting means that not all eligible patients are receiving the most effective therapies upfront. Nearly 61% of patients had no DM test reported before 1L treatment in this mNSCLC cohort (all histologies), and some were determined to be DM positive at a later time, highlighting a missed opportunity to employ the most effective biomarker-directed front-line treatment. Next steps in this study will include assessing patterns by histology. Structured data, which are recorded for clinical management, might have gaps; future research with chart reviews could provide a more comprehensive assessment. Research Sponsor: Genentech.

N=2257	PD-L1		ALK		EGFR		BRAF		ROS1	
	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L	Study observation period	Before/ at 1L
Tested (n, %)	1481 (65.6)	982 (43.5)	1300 (57.6)	801 (35.5)	1316 (58.3)	794 (35.2)	634 (28.1)	385 (17.1)	1187 (52.6)	750 (33.2)
Results positive (n, % of tested)	586 (39.6)	516 (52.5)	42 (3.2)	5 (0.6)	503 (38.2)	230 (28.9)	25 (3.9)	10 (2.6)	15 (1.3)	6 (0.8)
Biomarker-directed treatment (n, % of positive)	532 (90.8)	394 (76.4)	40 (95.2)	3 (60.0)	206 (40.9)	33 (14.3)	6 (24)	0	6 (40)	1 (16.7)

9080 **Poster Session**

Identification of recurrence-associated gene signature and tumor immune microenvironment features in resected stage I NSCLC. *First Author: Fang Wu, Hunan Key Laboratory of Early Diagnosis and Precision Therapy in Lung Cancer, The Second Xiangya Hospital, Central South University, Changsha, China*

Background: Surgery is the primary treatment for stage I NSCLC, but postoperative recurrence leads to poor prognosis. Alterations of tumor genes and immune microenvironment may be crucial factors for tumor recurrence; however, the detailed mechanisms remain unclear. **Methods:** A total of 130 resected stage I NSCLC patients were enrolled, 69 developed recurrence within three years and 61 without recurrence over five years. Whole exome sequencing (WES) was performed to evaluate genomic alterations. Immunohistochemistry was carried out to assess the expression of PD-L1, CD3 and CD8. We calculated density of CD3+ and CD8+ T cells in the center of tumors (CT) and invasive margins (IM), defined six immunoscore types based on the location and density of both cells, and performed ROC analysis to evaluate prognostic value of them. We further verified our results using stage I NSCLC cohorts from the Cancer Genome Atlas (TCGA) and Tumor immune estimation resource (TIMER) database. **Results:** In univariate analysis, lung adenocarcinoma (LUAD) patients showed significantly higher risk of recurrence (p = 0.008). There was no statistically significant correlation between recurrence and other clinical factors, including TNM stage. Although driver gene mutations, such as those of EGFR, had no correlation with recurrence, *MUC4* mutation and high tumor mutation burden (TMB) were significantly associated with higher risk of recurrence (p = 0.001 and 0.0032, respectively). Enrichment analysis of KEGG pathways showed that Ras pathway mutations were significantly enriched in *MUC4* mutant group and recurrence group (p = 0.02 and 0.05, respectively). 9.6% patients had PD-L1 positive expression (TPS≥1%), but showed no association with recurrence. Recurrence group had much lower density of $CD8_{CT}$, $CD8_{IM}$ and $CD3_{CT}$ +T cells(p = 0.0026, 0.0022 and 0.0308, respectively). Immunoscore type V, based on the average of $CD8_{CT}$, $CD8_{IM}$ and $CD3_{CT}$ + T cells, had the highest prognostic value (AUC = 0.764) and was used as the final immunoscore in our study. In multivariate analysis, we found *MUC4* mutation and low immunoscore were independent predictors of higher risk of recurrence. Smoking history was also an independent prognostic factor in LUAD. While in LUSC, only immunoscore correlated with recurrence. In TCGA cohort, *MUC4* mutation rate was significantly lower (3.6% vs. 24.3%, p < 0.001) and had no correlation with risk of recurrence (p = 0.765). Besides, the tumor infiltrating CD8+ T cells also had no correlation with risk of recurrence (p = 0.469). **Conclusions:** In this study, we established a refined immunoscore with high prognostic value for tumor recurrence in stage I NSCLC. In addition, we showed for the first time a strong association between *MUC4* mutation and recurrence, which might be mediated by the Ras pathway. Finally, the recurrence mechanisms might vary among different histological subtypes. Research Sponsor: 1) The Health Commission of Hunan Province (Grant No. 202103100948); 2) CSCO-BMS Oncologic Research Foundation (Grant No. Y-BMS2019-100) and 3) Guangdong Provincial Key Lab of Translational Medicine in Lung Cancer (Grant No. 2017B030314120) and Guangdong As.

9081 **Poster Session**

Update analysis of NEJ009: Gefitinib alone (G) versus gefitinib plus chemotherapy (GCP) for non-small cell lung cancer with mutated EGFR. *First Author: Eisaku Miyauchi, Department of Respiratory Medicine, Tohoku University Hospital, Sendai, Japan*

Background: NEJ009 study is the first randomized phase III trial that compared gefitinib plus chemotherapy with gefitinib in patients with untreated NSCLC harboring EGFR mutations. We report an updated OS and long-term tolerability analysis, including subgroup analyses focusing on a type of EGFR mutation and metastatic sites. **Methods:** Patients were randomly assigned to gefitinib (gefitinib 250 mg PO, QD) and GCP regimen (gefitinib 250 mg PO, QD combined with carboplatin AUC 5 and pemetrexed 500 mg/m2 in a 3-week cycle for up to six cycles, followed by concurrent gefitinib and pemetrexed maintenance). This study tested multiple primary endpoints, PFS, PFS2, and OS, which were analyzed using a preplanned hierarchical sequential testing method. **Results:** Three hundred forty-five patients were randomly assigned (gefitinib, n = 172; GCP, n =170). At latest data cut-off (May 22, 2020), although there was no significant difference in OS between the groups (HR, 0.82; 95% CI, 0.64 to 1.06; P=0.13), GCP still demonstrated significantly better PFS and PFS2 compared to G. The updated median PFS, PFS2, and OS was 11.2 months, 18.0 months, and 38.5 months in the gefitinib group and 20.9 months, 20.9 months, and 49.0 months in the GCP group, respectively. No severe adverse events occurred in the period since the first report. **Conclusions:** This updated analysis confirmed that the GCP regimen achieved significantly better PFS and PFS2 with an acceptable safety profile compared with gefitinib alone. The efficacy outcome of GCP is more favorable than gefitinib monotherapy as first-line treatment of NSCLC with EGFR mutation. Clinical trial information: UMIN000006340. Clinical trial information: UMIN000006340. Research Sponsor: grant-in-aids from the Japan Society for Promotion of Science and Japanese Foundation for the Multidisciplinary Treatment of Cancer.

	GCP	Gefitinib	HR(95% CI)
Median PFS(95% CI), mo	20.9(18.0-24.0)	11.2(9.0-13.4)	0.50(0.40-0.63)
Median PFS2(95% CI), mo	20.9(18.0-24.0)	18.0(16.3-20.7)	0.77(0.62-0.97)
Median OS(95% CI), mo	49.0(41.8-56.7)	38.5(31.1-47.1)	0.82(0.64-1.06)

9082 **Poster Session**

Discontinuation of immune checkpoint inhibitor (ICI) above 18 months of treatment in real-life patients with non-small cell lung cancer (NSCLC): INTEPI, a multicentric retrospective study. *First Author: Geoffroy Bilger, Centre Hospitalier Universitaire de Grenoble, Grenoble, France*

Background: The optimal treatment duration of ICIs for patients with NSCLC remains uncertain. In phase 3 clinical trials, treatment continued for two years or until disease progression, and results from CheckMate 153 trial suggest to continue beyond one year. Real life data are missing. **Methods:** This multi-centric retrospective study presents data on real-life patients who discontinued treatment after at least 18 months of ICI monotherapy, their tumour being still controlled. Their characteristics, the causes of discontinuation of ICI, and their outcome are described. **Results:** Between July 2015 and May 2018, 107 patients had their tumour controlled after at least 18 months of treatment. Among them, 54 (50%) patients discontinued ICI: 76% male, median age 63, 91% PS 0-1, 54% adenocarcinoma, 20% with brain metastases, PD-L1 expression level available for 18 (33%) patients (2 $<$ 1%, 8 btw 1-50% and 8 $>$ 50%), 93% treated after 1st line. The median duration of treatment was 26 months. Treatment was stopped by choice of the prescriber and toxicity in 46% and 22% respectively. With a median follow up of 21 months from ICI discontinuation, 18 (33%) patients had a tumor progression with a median time of 10 months (2-33). From discontinuation, overall survival (OS) and progression free survival (PFS) were 90% and 71% respectively at 12 months and 84% and 63% respectively at 24 months. Duration of disease control after ICI cessation seemed to be correlated to the best tumor response at treatment discontinuation, with a PFS rates at 12 months of 73% for complete response (CR n = 11), 77% for partial response (PR n = 37), 22% for patients with stable disease (SD n = 6), 80% for CR and/or complete metabolic response with 18F-FDG PET/CT (CMR) and 65% for others. Fourteen patients out of the 18 in the relapse group received a subsequent treatment : 7 were retreated with ICI (with best response 14% PR and 86% SD) and 5 received a localized therapy with 60% CR. **Conclusions:** Our study in real life provides new insight into the long-term outcomes of patients treated with ICI for at least 18 months before discontinuation in the absence of PD. CR and CMR with FDG-PET before therapy discontinuation may be a positive factor for a prolonged disease control upon discontinuation. Research Sponsor: None.

9084 **Poster Session**

Intracranial activity of tepotinib in patients (pts) with *MET* exon 14 (*MET*ex14) skipping NSCLC enrolled in VISION. *First Author: Jyoti D. Patel, Lurie Cancer Center, Northwestern University-Feinberg School of Medicine, Chicago, IL*

Background: Brain metastases (BMs) are reported in 20–40% of pts with *MET*ex14 skipping NSCLC and present a high unmet need with poor prognosis. Tepotinib is a highly selective MET inhibitor that has demonstrated intracranial activity in preclinical MET-driven lung cancer orthotopic BM models, and has high binding in brain tissue with 25% of free tepotinib levels in brain, relative to plasma. In VISION Cohort A (N = 152), tepotinib had robust and durable clinical activity in pts with *MET*ex14 skipping NSCLC, with an objective response rate (ORR) of 45% and a median duration of response (mDOR) of 11.1 months. Here, we report the intracranial activity of tepotinib. **Methods:** In the Phase II VISION study, pts with *MET*ex14 skipping NSCLC received 500 mg QD (450 mg active moiety) oral tepotinib. Study eligibility allowed for pts with BM (neurologically stable on symptomatic therapy with stable steroids, and pts with asymptomatic BM). Primary endpoint: systemic OR per RECIST v1.1; subgroup analysis in pts with BM (determined by RECIST v1.1) was predefined. An *ad hoc* retrospective analysis of brain lesions determined by CT/MRI was conducted by an IRC using Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria, which accounts for pts' clinical status and steroid use. Responses were determined in pts with $\geq$1 evaluable post-baseline tumor assessment (due to the retrospective nature and resulting incomplete data, confirmation was not required). For pts with non-measurable lesions per RANO-BM (enhancing and non-enhancing non-target lesions [NTL]), disease control in the brain was defined as non-complete response/non-progressive disease. Data cut-off: July 1, 2020. **Results:** Based on RECIST v1.1, 23 pts in Cohort A had BM at baseline. Systemic efficacy in pts with BM (ORR 47.8% [95% CI: 26.8, 69.4], mDOR 9.5 months [95% CI: 5.5, not estimable]) was consistent with the overall population. 15 pts were evaluable by RANO-BM; 12 received prior radiotherapy for BM (median 6.4 weeks before tepotinib initiation [range 2.6–44]). Systemic best objective responses (BORs) were partial response (PR, n = 9), stable disease (SD, n = 3), and progressive disease (PD; n = 3). Of 7 pts with measurable CNS disease per RANO-BM (all of whom received prior radiotherapy), intracranial BORs were PR (n = 5; including 3 with complete disappearance of target lesions), SD (n = 1) and PD (n = 1). Of 8 pts with NTL only, 7 achieved intracranial disease control and 1 had PD. Of the 7 pts with disease control, 3 had CR of the enhancing NTL. **Conclusions:** Tepotinib demonstrated robust systemic activity in pts with *MET*ex14 skipping NSCLC with BM; this is complemented by intracranial activity in an *ad hoc* analysis using RANO-BM. Small pt numbers, a large proportion of pts with prior radiotherapy for BM, and the retrospective nature of analysis should be considered. Prospective evaluation of intracranial activity data from VISION Cohort C is ongoing. Clinical trial information: NCT02864992. Research Sponsor: Merck KGaA, Darmstadt, Germany.

9085 **Poster Session**

Cemiplimab monotherapy as first-line (1L) treatment of patients with brain metastases from advanced non-small cell lung cancer (NSCLC) with programmed cell death-ligand 1 (PD-L1) $\geq$ 50%: EMPOWER-Lung 1 subgroup analysis. *First Author: Mustafa Ozguroglu, Cerrahpaşa Medical Faculty, Istanbul University-Cerrahpaşa, Istanbul, Turkey*

Background: In the Phase 3, EMPOWER-Lung 1 study, cemiplimab monotherapy provided significant survival benefit and an acceptable safety profile vs chemotherapy in patients with advanced NSCLC and PD-L1 $\geq$50%. EMPOWER-Lung 1 included patients with brain metastases at baseline who are typically underrepresented in clinical trials. Other published exploratory analyses in single-cohort studies suggest benefit from immunotherapy in this patient population. Here, we present subgroup analysis of patients with brain metastasis from EMPOWER-Lung 1. **Methods:** Patients were randomized 1:1 to cemiplimab 350 mg IV every 3 weeks or investigator's choice of chemotherapy (NCT03088540). Patients with treated, clinically stable brain metastases (radiological stability not required) were eligible to enroll and are the focus of this subgroup analysis from the PD-L1 $\geq$50% population (n=563) of the EMPOWER-Lung 1 study. **Results:** A total of 68 of 563 (12.1%) cases had treated stable brain metastases at time of randomization. Patients were evenly distributed between cemiplimab (n=34) and chemotherapy (n=34), with similar median duration of follow-up (Table). Baseline characteristics were generally similar; median (range) age: 60.0 (45–76) vs 62.0 (48–77); male: 97.1% vs 85.3%; and non-squamous histology: 85.3% vs 76.5%; between cemiplimab vs chemotherapy, respectively. Per independent review committee, median overall survival (OS, 18.7 vs 11.7 months), median progression-free survival (PFS, 10.4 vs 5.3 months), and objective response rate (ORR, 41.2% vs 8.8%) were superior with cemiplimab vs chemotherapy (Table). After baseline, central nervous system (CNS) disease progression occurred in 2 (5.9%) patients with cemiplimab vs 4 (11.8%) patients with chemotherapy; extra-CNS disease progression occurred in 9 (26.5%) patients with cemiplimab vs 15 (44.1%) patients with chemotherapy. **Conclusions:** 1L cemiplimab monotherapy improved OS, PFS, and ORR vs chemotherapy, in patients with advanced NSCLC with PD-L1 $\geq$50%, and clinically stable brain metastases at baseline. Cemiplimab monotherapy represents a suitable option for this subgroup of patients. Clinical trial information: NCT03088540. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

Clinical outcomes in patients with advanced NSCLC and brain metastases.

	Cemiplimab (n=34)	Chemotherapy (n=34)	HR (cemiplimab vs chemotherapy)
Median duration of follow-up, weeks (IQR)	9.2 (3.7–16.3)	9.3 (6.1–13.3)	
OS, median, months (95% CI)	18.7 (17.3–NE)	11.7 (7.0–NE)	0.17 (0.04–0.76); P=0.0091
PFS, median, months (95% CI)	10.4 (4.2–NE)	5.3 (2.2–6.5)	0.45 (0.22–0.92); P=0.0231
ORR, %, (95% CI)	41.2% (24.6–59.3)	8.8% (1.9–23.7)	

HR, hazard ratio; IQR, inter-quartile range; NE, not evaluable.

9086 **Poster Session**

Real-world outcomes and clinical characteristics of patients with brain metastases from EGFR mutated non-small cell lung cancer: Data from a large retrospective study (REFLECT). *First Author: Urska Janzic, University Clinic of Respiratory and Allergic Diseases Golnik, Golnik, Slovenia*

Background: Brain metastases (BM) frequently occur in patients (pts) with epidermal growth factor receptor mutated non-small cell lung cancer (EGFRm NSCLC) and represent a poor prognostic marker. This study aimed to describe the clinical characteristics, treatment patterns and survival outcomes in EGFRm NSCLC pts treated with 1st or 2nd generation tyrosine-kinases inhibitors (TKIs) in first-line (1L). **Methods:** The retrospective real-world study REFLECT (NCT04031898) collected data from 896 pts initiating 1L TKI between 1 January 2015-30 June 2018 in Europe and Israel. Descriptive statistics were used to assess demographic and clinical characteristics in subgroups of patients with and without BM. Kaplan-Meier methods were used to estimate median real world progression free survival (mPFS) and overall survival (mOS) from start of 1L. **Results:** Out of 896 pts, 198 (22.1%) had BM at start of 1L, 134 (15%) developed BM later (any time), and 564 (62.9%) had no sign of BM at the time of data collection. Among pts who later developed BM the median time between the start of 1L and first diagnosis of BM was 13.5 months. Median duration of follow-up was 21.5 months. Of 332 pts with BM at any time 64.2% were female, similar to the ratio in pts without BM (64.0%). At diagnosis, median age was 65 years in pts with BM vs. 70 in those who never developed BM. Of pts with BM at any time, 50.9% had exon 19 deletion, 30.4% L858R point mutation and 18.7 % uncommon EGFR mutations at baseline, compared to 56.6%, 31.7% and 11.7% in pts without BM, respectively. At data collection, 94.9% of the pts with BM at diagnosis had progressed compared to 79.8% among those with no BM. Overall, whole brain radiation was the most frequently used treatment for BM (31.0%) followed by stereotactic radiosurgery (18.1%) and targeted therapies (13.3%). T790M testing rates were highest among pts developing BM later (85.7%) and lowest among those with BM from start (66.1%). The T790M positivity rate was highest in pts developing BM later (65.7%) and lowest among those with BM from start (50.4%). More pts received osimertinib in later lines among those with BM at any time compared to those without BM (51.3% vs 43.8%). Median real world PFS and OS (95% CI) were shorter among pts with BM at baseline compared to those never developing BM: 10.2 (8.8, 11.5) vs 15.2 (13.7, 16.1) months, and 19.4 (17.1, 22.1) vs 30.3 (27.1, 33.8) months, respectively. At the time of data collection, 77.3% of pts with BM at baseline were deceased compared to 52.5% pts with no BM. **Conclusions:** More than one third of pts included in REFLECT had BM at any time. Uncommon EGFR variants at baseline were observed more frequently in pts with BM. mPFS and mOS were shorter in pts with BM at baseline compared to those never developing BM. These data highlight the need for improved treatment and CNS control in pts with EGFRm NSCLC. Clinical trial information: NCT04031898. Research Sponsor: AstraZeneca.

9087 **Poster Session**

STK11/_TP53_ co-mutated non-small cell lung cancer (NSCLC) to display a unique tumor microenvironment (TME) and metabolic profile. *First Author: Abdul Rafeh Naqash, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD*

Background: Recent data suggest inferior responses to immune checkpoint inhibitors (ICIs) in *STK11*-mt NSCLC. *TP53* is a critical tumor suppressor gene regulating DNA repair by arresting cells in the G1 phase in response to critical double strand breaks. We hypothesized that accumulated DNA damage from mutations in the *TP53* gene might increase immunogenicity and potentially enhance benefit of ICIs in *STK11-mt* NSCLC. **Methods:** A total of 16,896 NSCLC tumors submitted to Caris Life Sciences (Phoenix, AZ) for targeted NGS (DNA-Seq, 592 genes) were analyzed. A subset (N = 5034 tumors) had gene expression profiling (RNA-Seq, whole transcriptome). PD-L1 (TPS) was tested with 22c3 antibody (Dako). Exome-level neoantigen load for *STK11*-mt NSCLC was obtained from published TCGA Pan-immune analysis (Thorsson et al. 2018). Non-parametric tests were used for comparing differences in tumor mutational burden (TMB) and neoantigen load. Transcriptomic analysis included differential gene expression and hierarchical clustering. Tumor immune cell content was obtained from transcriptome using Microenvironment Cell Population-counter (MCP). Publicly available data from the POPLAR/OAK trials of atezolizumab in advanced NSCLC were used to model PFS and OS for *STK11*-mt with *TP53*-mt (n = 14) and without *TP53*-mt (n = 20). **Results:** Of 16,896 NSCLC samples, 12.6% had an *STK11*-mt with the proportions of TMB-high (≥10 Mut/Mb), PD-L1 ≥ 50% and MSI-high being 55.9%, 11.8%, and 0.72%, respectively. *STK11*-mt vs. *STK11*-wt NSCLC did not differ in median TMB (Caris:10 vs. 10 Mut/Mb; $p > 0.1$) or neoantigen load (TCGA: 154.5 vs. 165; $p > 0.1$). Median TMB (13 vs. 9 Mut/Mb; $p < 0.001$) and neoantigen load (263 vs. 134; $p < 0.001$) were higher in *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*-wt. MCP analysis showed higher CD8, NK-cell and lower myeloid dendritic cell infiltration in *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*-wt ($p < 0.01$) . Expression of *MYC* and *HIF-α* were increased in the *STK11*-mt/*TP53*-mt vs. *STK11*-mt/*TP53*-wt ($p < 0.01$) along with higher expression ($p < 0.01$) of genes associated with both glycolysis (*HK2, LDHA, ALDOA*) and glutamine metabolism (*GOT2, PPAT2*). Hierarchical clustering of *STK11*-mt adenocarcinomas (n = 463) for STING pathway genes (CCL5, CXCL10, cGAS) identified a STING-high and a STING low cluster. The STING high cluster was significantly enriched in *TP53*-mt (48 vs. 32%; $p < 0.01$).In the OAK/POPLAR cohort, median OS (HR is 1.14, 95% CI 0.53 - 2.48); $p > 0.1$) and PFS (HR 1.88, 95% CI 0.89-3.97, $p = 0.098$) were not statistically different between *STK11*-mt/*TP53*-mt vs. *STK*-mt/*TP53*-wt. However, the 15-months PFS was 21% in the *STK11*-mt/*TP53*-mt vs 0% in the *STK11*-mt/*TP53*-wt. **Conclusions:** *STK11*-mt NSCLC with *TP53*-mt are associated with an immunologically active TME with metabolic reprogramming. These intrinsic properties could be exploited to improve outcomes to ICIs in combination with metabolically directed agents. Research Sponsor: None.

9088 **Poster Session**

Chemo-immunotherapy outcomes of KRAS-G12C mutant lung cancer compared to other molecular subtypes of KRAS-mutant lung cancer. *First Author: Kathryn Cecilia Arbour, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: *KRAS* mutations are identified in approximately 30% of NSCLC, with G12C mutations being the most common subtype and representing 12% of all non-small cell lung cancer cases. Novel direct inhibitors are in clinical development and have shown promising activity, although the efficacy of these agents compared to other standard therapies for lung cancer is not yet known. We hypothesized that patients with *KRAS*-G12C mutations may have distinct responses to chemo-immunotherapy regimens both with respect to STK11 and KEAP1 co-mutation status and compared to patients with non-G12C subtypes. **Methods:** Patients with KRAS-mutant lung cancers at Memorial Sloan Kettering Cancer Center and Dana Farber Cancer Institute treated with chemo-immunotherapy regimens as first line therapy for advanced/metastatic disease were identified. Subset with KRAS G12C mutations non-G12C subtypes were compared and response to therapy was assessed by investigator. Baseline characteristics were compared with the Chi-square and Fisher's exact test for categorical data and Wilcoxon rank-rum test for continuous data. Response evaluations where performed by investigators and compared between groups with the Fisher's exact test. Progression free survival and overall survival was calculated from start of therapy to date of progression or death/last follow up, respectively and compared between groups using the Cox proportional-hazards model. **Results:** We identified 137 patients with KRAS-mutant NSCLC treated with chemo-immunotherapy: 45% (62/137) had mutations in *KRAS*-G12C and 55% harbored non-G12C mutations (17% G12V, 15% G12D, 4% G12A, 4% G12S, 3% G13D). The median OS was 21 and 14 months for G12C and non-G12C patients, respectively ($p = 0.24$). ORR to chemo-immunotherapy for patients harboring a *KRAS*-G12C mutation was 40% (25/62) compared to 31% (23/75) in non-G12C subtypes ($p = 0.3$). Median PFS was similar for both G12C and non-G12C subtypes (7.3 vs 6.1 months, respectively, $p = 0.12$). Concurrent *STK11* mutation was identified in 40% of patients with *KRAS*-G12C and *KEAP1* alterations were observed in 32% of patients. In patients with *KRAS*-G12C, co-mutation in *STK11* and/or *KEAP1* was associated with shorter PFS (15.8 vs 5.1 months, $p = 0.01$). **Conclusions:** *KRAS*-G12C mutations are present in 12% of patients with NSCLC and represent a relevant subtype of NSCLC given KRAS G12C inhibitors now in clinical development. Treatment outcomes to chemo-immunotherapy are similar in patients with G12C and non-G12C subtypes. Outcomes are poor for patients with concurrent *STK11* and/or *KEAP1* mutations representing a significant unmet need. Research Sponsor: None.

9089 **Poster Session**

Safety and efficacy of pralsetinib in patients with advanced _RET_ fusion-positive non-small cell lung cancer: Update from the ARROW trial. *First Author: Giuseppe Curigliano, European Institute of Oncology, IRCCS and University of Milano, Milan, Italy*

Background: *RET* fusions are targetable oncogenic drivers in 1–2% of non-small cell lung cancer (NSCLC). ARROW (NCT03037385) supported the US FDA approval of pralsetinib, a highly potent oral selective RET inhibitor for *RET*-altered NSCLC and thyroid cancer. Here, we present updated results for a larger population of patients with *RET* fusion–positive NSCLC enrolled in ARROW. **Methods:** ARROW is a phase 1/2 open-label study conducted at 84 sites in 13 countries. Phase 2 expansion cohorts included patients with *RET* fusion–positive NSCLC. Initially, all treatment-naïve patients were not candidates for platinum-based therapy, a requirement removed by protocol amendment in July 2019. Primary objectives are overall response rate (ORR; blinded independent central review [BICR] per RECIST v1.1), assessed for patients with baseline measurable disease, and safety. **Results:** Updated analyses were completed as of Nov 6, 2020 (data cut-off), for patients who initiated pralsetinib 400 mg QD by May 22, 2020 (enrollment cut-off). Efficacy results, including analyses for treatment-naïve patients enrolled after eligibility criteria were revised to allow candidates for platinum-based therapy, are shown in the Table. **Conclusions:** Pralsetinib showed rapid, potent, and durable clinical activity in patients with *RET* fusion-positive NSCLC (regardless of prior therapies), including poor prognosis patients not eligible for platinum-based therapy. Overall, pralsetinib was well-tolerated. These data highlight the need for *RET* testing early in the course of disease to identify candidates who may benefit from treatment with pralsetinib.Clinical trial information: NCT03037385. Research Sponsor: Blueprint Medicines Corporation.

	Prior Platinum[a] (n = 126)	Treatment-Naïve[a] (n = 68)	Treatment-Naïve: Subset Enrolled After Eligibility Revision[a] (n = 25)
ORR, % (95% CI)	62 (53–70)	79 (68–88)	88 (69–98)
Clinical benefit rate, % (95% CI)[b]	74 (65–81)	82 (71–91)	88 (69–98)
Disease control rate, % (95% CI)	91 (85–96)	93 (84–98)	96 (80–100)
Median duration of response, mo (95% CI)	22.3 (15.1–NE)	NR (9.0–NE)	NR (NE–NE)
Median time to response, mo (95% CI)	1.8 (1.3–11.4)	1.8 (0.9–6.1)	1.8 (1.7–6.1)
Median PFS, mo (95% CI)[c]	16.5 (10.5–24.1)[d]	13.0 (9.1–NE)[e]	NR (NE–NE)[f,g]

CI, confidence interval; mo, months; NE, not estimable; NR, not reached; PFS, progression-free survival. [a]Measurable disease population. [b]Confirmed response or stable disease of ≥16 weeks. [c]Assessed in full efficacy population. [d]n = 136. [e]n = 75. [f]n = 28. [g]Median follow-up for PFS in this population was 8.2 mo. In all patients enrolled in ARROW who received pralsetinib 400 mg QD by May 22, 2020 irrespective of tumor type (n = 471; data cut-off Nov 6, 2020), the most common (≥25%) treatment-related adverse events (TRAEs) were increased aspartate aminotransferase (39%), anemia (35%), increased alanine aminotransferase (27%), constipation (26%) and hypertension (25%). Overall, 6% of patients discontinued treatment due to TRAEs.

9090 **Poster Session**

Association between improvements in survival of metastatic NSCLC patients and targeted- and immuno-therapy. *First Author: Sreeram Ramagopalan, F. Hoffmann-La Roche Ltd., Basel, Switzerland*

Background: Significant improvements in mortality among NSCLC cancer patients in the US over the past two decades have recently been reported based on SEER data. The timing of these improvements led to suggestions that they are primarily a result of the introduction of new and innovative treatments, however few studies have directly investigated this. **Methods:** We utilised the US Flatiron Health database to identify a cohort of non-biomarker (EGFR/ALK/ROS1/BRAF) positive metastatic NSCLC (mNSCLC) patients and a separate cohort of ALK positive (ALK+) patients diagnosed between 2012 and 2019. Multivariable Cox models adjusting for baseline characteristics and receipt of targeted and immunotherapy were utilised to explore the relationship between these variables and changes in the hazard of death by calendar year in each cohort. **Results:** We identified cohorts of 30,076 (54.7% Males) non-biomarker positive and 652 (45.4% males) ALK+ mNSCLC cancer patients in the database eligible for the analysis. Survival in both cohorts improved over time. After adjustment for differences in baseline characteristics the hazard of death in non-biomarker positive patients diagnosed in 2015, 2016, 2017, 2018 and 2019 was observed to be 14%, 13%, 16% 19% and 21% lower respectively than that in those diagnosed in 2012. Upon additionally adjusting for receipt of first line or second line immunotherapy the decrease in the hazard of death by calendar year was no longer observed, suggesting improvements in survival observed over time may be explained by the introduction of these innovative treatments. Similarly, decreases in the hazard of death were only observed in ALK+ patients diagnosed in 2018 and 2019 relative to 2012 and were no longer observed following adjustment for the use of ALK inhibitors. **Conclusions:** Our findings expand on the SEER data and provide direct evidence linking improvements in survival of NSCLC patients over the past decade with the introduction of innovative therapies. Research Sponsor: F. Hoffmann-La Roche AG.

Hazard ratios for death in metastatic NSCLC patients in years 2013 to 2019 relative to 2012, adjusting only for differences in baseline characteristics (model 1) and adjusting for baseline characteristics and treatment (model 2).

	Non-biomarker positive mNSCLC	Non-biomarker positive mNSCLC	ALK+ mNSCLC	ALK+ mNSCLC
	Model 1	Model 2	Model 1	Model 2
2012 vs 2013	0.95 (0.89 – 1.00)	0.94 (0.89 – 1.00)	1.06 (0.68 - 1.65)	1.13 (0.71 - 1.79)
2012 vs 2014	0.95 (0.89– 1.00)	0.93 (0.87 - 0.99)	0.98 (0.62 - 1.57)	1.34 (0.84 - 2.13)
2012 vs 2015	0.86 (0.81 - 0.91)	0.92 (0.86 - 0.98)	0.98 (0.63 - 1.52)	1.40 (0.88 - 2.25)
2012 vs 2016	0.87 (0.83 - 0.92)	0.93 (0.88 - 0.99)	1.12 (0.72 - 1.73)	1.45 (0.90 - 2.34)
2012 vs 2017	0.84 (0.79 - 0.89)	0.97 (0.90 - 1.03)	0.71 (0.45 - 1.10)	1.19 (0.69 - 2.04)
2012 vs 2018	0.81 (0.77 - 0.86)	1.01 (0.94 - 1.08)	0.51 (0.29 - 0.87)	1.15 (0.56 - 2.37)
2012 vs 2019	0.79 (0.74 - 0.85)	0.97 (0.89 - 1.05)	0.51 (0.28 - 0.95)	1.15 (0.56 - 2.38)

9091 **Poster Session**

First-line pembrolizumab monotherapy for PD-L1-positive (TPS ≥ 50%) advanced non-small cell lung cancer (aNSCLC) in the real world: A national French bispective multicentric cohort—ESCKEYP trial (GFPC 05-2018). *First Author: Renaud Descourt, Thoracic Oncology Department, Hospital Morvan, Brest, France*

Background: To determine real-world outcomes with first line pembrolizumab monotherapy, for aNSCLC with PD-L1 TPS ≥50%. **Methods:** Bispective, national and multicentric study including consecutively aNSCLC patients who initiated first-line pembrolizumab monotherapy from May 5, 2017 (marketing authorization of pembrolizumab monotherapy in France) to Nov 22, 2019 (marketing authorization of pembrolizumab-chemotherapy for non-squamous aNSCLC). Data were collected on medical charts. Responses were locally assessed according to RECIST v1.1; overall survival (OS) and real-world progression-free survival (rwPFS) were assessed by Kaplan-Meier method. **Results:** 845 patients (pts) were included by 33 centres: 67.8% were men, PS 0/1/≥2: 25.5%/46.9%/27.6%, active/former/non-smokers: 39.1%/51.7%/6.4%, adenocarcinoma: 70.8%; stage IV at diagnosis: 91.6%; median number of metastatic sites at baseline: 2±1 (brain (20.8%), liver (13.9%) and bone (35%)); KRAS mutated: 27.7%, PDL1 TPS > 75%: 53.7% At the cut off date (31 December 2020), on the 783/845 (92.7%) evaluable pts, CR, PR, disease stabilization and progression were reported on 4.7%, 42.6%, 24.1% and 28.6% of cases, respectively; 588 (69.6%) pts had discontinued pembrolizumab, 390 (66.4%) had a first disease progression; 320/390 (82.1%) received a second line treatment, mainly platinum-based chemotherapy (90.6%). With a median follow up of 25,8 [95%CI: 24,8-26,7] months, median rwPFS and median OS were 8,2 [95%CI: 6,9-9,5] and 22,6 [95%CI: 18,5-27,4] months, respectively; 6, 12, 18-months survival rates were 76,8%, 64,8% and 54,3%. 835 adverse events were reported in 48% of the patients, grade ≥3 in 13.8% of cases, mainly asthenia, colitis, pneumonitis. For evaluable patients receiving a platinum-based doublet in second line (266/290, 89%), CR, PR, disease stabilization and progression were reported on 1.9%, 41%, 35.3% and 21.8% of cases, respectively. Uni and multivariate analysis of factors related to OS will be presented at the congress. **Conclusions:** Despite a less stringent selection of patients, pembrolizumab as a single agent achieves similar tumor shrinkage, rwPFS and OS than those of pivotal clinical trials. Research Sponsor: GFPC.

9092 **Poster Session**

Beyond steroids: Immunosuppressants in steroid-refractory/resistant immune related adverse events. *First Author: Jia Luo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: The optimal management for immune related adverse events (irAEs) in patients who do not respond or become intolerant to steroids is unclear. Guidelines suggest additional immunosuppressants based on case reports and expert opinion. **Methods**: We examined patients with advanced lung cancers at MSK treated with immune checkpoint blockade (ICB) from 2011-2020. Pharmacy records were queried to identify patients who received systemic steroids as well as an additional immunosuppressant (eg TNFα inhibitor, mycophenolate mofetil). Patient records were manually reviewed to examine baseline characteristics, management, and outcomes. **Results**: Among 2,750 patients with lung cancers treated with ICB, 51 (2%) received both steroids and an additional immunosuppressant for a severe irAE (TNFα inhibitor (73%), mycophenolate mofetil (20%)). The most common events were colitis (53%), pneumonitis (20%), hepatitis (12%), and neuromuscular (10%). At 90 days after start of an additional immunosuppressant, 57% were improved from their irAE, 18% were unchanged, and 25% were deceased. Improvement was more common in hepatitis (5/6) and colitis (18/27) but less common in neuromuscular (1/5) and pneumonitis (3/10). All patients with hepatitis received mycophenolate mofetil 500-1000mg BID for a median of 3 months, range 2-5 months. Of the 18 patients with colitis who improved with a TNFα inhibitor, 10 needed just one dose. Of 13 patients who died, 4 were related to toxicity from immunosuppression (3, infection-related deaths; 1, drug-induced liver injury leading to acute liver failure). Those who died from immunosuppressive therapy received higher amounts of systemic steroids than those who did not (max median 525 vs 132 mg prednisone equivalent, Mann Whitney U p = 0.004, total median 5.9k vs 2.3k mg prednisone equivalent, p = 0.004). Of 31 patients who received at least 3 weeks of prednisone ≥ 20mg, most (90%, 28/31) had at least one side effect that was brought to clinical attention (most commonly altered mood/ sleep, 52%, increase in BMI > 1kg/m2, 45%, and infection, 32%). **Conclusions**: Steroid-refractory/resistant immune related adverse events are rare. While existing treatments help patients with hepatitis and colitis, most patients with other irAEs remain refractory and/or experience toxicities from immunosuppression. Systemic steroid use likely contributed to side effects and mortality. A more precise understanding of the pathophysiology of specific irAEs is needed to guide biologically informed treatment regimens for severe irAEs to realize the true benefit of ICB therapy. Research Sponsor: U.S. National Institutes of Health.

9093 **Poster Session**

CNS activity of poziotinib in NSCLC with exon 20 insertion mutations. *First Author: Xiuning Le, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Treatment addressing non-small cell lung cancer (NSCLC) harboring EGFR or HER2 exon 20 insertion mutations remains an unmet need. These tumors are associated with a high incidence of CNS metastases and unfavorable survival rates. Poziotinib is a potent, irreversible, tyrosine kinase inhibitor (TKI) with a structure that can overcome the steric hindrance of the exon 20 limited binding pocket. Preclinical data suggest poziotinib CNS penetration, and here we show meaningful poziotinib CNS activity in patients with NSCLC harboring exon 20 insertion mutations in an ongoing multi-cohort, multi-center Phase 2 study (ZENITH20; NCT03318939). **Methods:** ZENITH20 enrolled previously treated and naïve patients with advanced/metastatic NSCLC and EGFR or HER2 exon 20 insertion mutations in several cohorts: Cohort 1 (C1) EGFR previously treated; Cohort 2 (C2) HER2 previously treated and Cohort 3 (C3) EGFR treatment-naïve. All patients with stable CNS metastases at baseline were included. Poziotinib (16 mg) was administered orally QD, with follow-up for up to 24 months. The primary endpoint was Objective Response Rate (ORR) evaluated centrally using RECIST v1.1 by an independent image review committee. Secondary endpoints included Disease Control Rate (DCR), Duration of Response (DOR), Progression-Free Survival (PFS) and safety. Primary efficacy results have been previously released. Intracranial response was determined based on the modified RECIST criteria. **Results:** A total of 284 patients across 3 cohorts (C1 n=115; and C2 n=90; and C3 n=79) with a median age of 60.5 years were enrolled. The median follow-up was 7.3, 8.3, and 9.2 months for all patients in C1, C2, and C3, respectively. In NSCLC patients that had baseline CNS lesions (N=36), the analysis showed a patient-based ORR of 22.2% (8/36) and a DCR of 88.9% (32/36). One patient in each cohort had a complete intracranial response and stable disease was 80.6% across 3 cohorts and 92.9% in C2. Two patients each in C1 and C3 had progressive disease (PD) and none had CNS progression in C2 (Table). **Conclusions:** Poziotinib exhibited clinically meaningful CNS activity in patients with EGFR or HER2 exon 20 mutations in ZENITH20 Cohorts 1-3. The majority of the patients had no CNS progression and 3/36 patients had intracranial complete responses. The preliminary data suggest that poziotinib may provide a meaningful treatment alternative for patients with NSCLC that harbor EGFR or HER2 exon 20 mutations and who present with CNS metastases that have poor prognosis. Clinical trial information: NCT03318939. Research Sponsor: Spectrum Pharmaceuticals, Inc.

	Cohort 1 n=115	Cohort 2 n=90	Cohort 3 n=79	Total N=284
Patients with CNS Metastases at Baseline	12	14	10	36
ORR in CNS patients	1 (8.3)	4 (28.6)	3 (30.0)	8 (22.2)
Best Evaluable intracranial Response, n (%)				
Complete Response [a]	1 (8.3)	1 (7.1)	1 (10.0)	3 (8.3)
Stable Disease	9 (75.0)	13 (92.9)	7 (70.0)	29 (80.6)
Progressive Disease	2 (16.7)	0	2 (20.0)	4 (11.1)

a) ≥2 consecutive MRI scans with negative finding.

9094 **Poster Session**

Impact of rapid multigene assays with short turnaround time (TAT) on the development of precision medicine for non-small cell lung cancer (NSCLC). *First Author: Shingo Matsumoto, National Cancer Center Hospital East, Kashiwa, Japan*

Background: A variety of oncogene drivers have been identified in NSCLC and molecularly-stratified precision medicine has led to improved survival in advanced NSCLC. Next-generation sequencing (NGS)-based testing is utilized to detect actionable gene alterations; however, the TAT of NGS is often too long to translate into clinical decision making. Thus, rapid multi-gene testing alternatives are needed. **Methods:** A lung cancer genomic screening project (LC-SCRUM-Asia) capturing clinical outcome was established in 2013 to identify patients with oncogene drivers and to support the development of novel targeted therapies. Since February 2013 to May 2019 (LC-SCRUM-Asia 1st-phase), single gene testing and/or a targeted NGS assay, Oncomine Comprehensive Assay (OCA), were used for the genomic screening. Since June 2019 to December 2020 (2nd-phase), a multi-gene PCR assay (Amoy 9-in-1 test) and a rapid NGS assay (Genexus/Oncomine Precision Assay [OPA]) were also implemented as rapid multi-gene testing. **Results:** A total of 10667 Japanese NSCLC patients, including 6826 in the 1st-phase and 3841 in the 2nd-phase, were enrolled in the LC-SCRUM-Asia. Success rate for OCA: 93%, for 9-in-1 test: 98%, for Genexus/OPA: 96%. Median TAT for OCA: 21 days, for 9-in-1 test: 3 days, for Genexus/OPA: 4 days. The frequencies of genetic alterations detected in the 1st-/2nd-phase were *EGFR*: 17/24%, *KRAS*: 15/16%, *HER2* ex20ins: 4/3%, *ALK* fusions: 3/3%, *RET* fusions: 3/2%, *ROS1* fusions: 3/2%, *MET* ex14skip: 2/2%, *BRAF* V600E: 1/1%, *NRG1* fusions: 0/0.2% and *NTRK3* fusions: 0.05/0.04%. Overall percent agreement of 9-in-1 test compared with OCA for *EGFR/KRAS/HER2/BRAF/MET/ALK/ROS1/RET/NTRK3* alterations was 98%, and that of OPA compared with OCA was 95%. The rate of patients who received targeted therapies as 1st-line treatment was significantly elevated in the 2nd-phase compared with the 1st-phase (510/3841 [13%] vs. 567/6826 [8%], p < 0.001). Through the genomic screening, 1410 (37%) and 1269 (18%) candidate patients for clinical trials of KRAS, HER2, BRAF, MET, ALK, ROS1, RET or TRK-targeted drugs were identified in the 2nd-phase and in the 1st-phase, respectively. The rate of patients who were actually enrolled into the genotype-matched clinical trials were also significantly higher in the 2nd-phase than in the 1st-phase (222 [6%] vs. 186 [3%], p < 0.001). In 1st-line treatments for advanced NSCLC patients, the median progression-free survival was 8.5 months (95% CI, 7.7−9.4) in the 2nd-phase (n = 1839) versus 6.1 months (95% CI, 5.9−6.3) in the 1st-phase (n = 4262) (p < 0.001). **Conclusions:** Both the 9-in-1 test and Genexus/OPA had short TATs (3−4 days), high success rates (96−98%) and good concordance (95−98%) compared with another NGS assay (OCA). These rapid multi-gene assays highly contributed to enabling precision medicine and the development of targeted therapies for advanced NSCLC. Research Sponsor: AMED (Japan Agency for Medical Research and Development), Pharmaceutical/Biotech Company.

9095 **Poster Session**

Maintenance targeted therapy compared to standard of care (SoC) in patients (pts) with metastatic non-small cell lung cancer (NSCLC): Results from the phase II randomized UNICANCER/IFCT1301- SAFIR02-LUNG intergroup trial. *First Author: Benjamin Besse, Department of Medicine and Thoracic Pathology Committee, Gustave Roussy, Villejuif, France*

Background: Targeted therapies (TT) are approved in NSCLC based on a limited number of oncogenic drivers. Numerous additional TT can be matched to other molecular alterations found in comprehensive profiles. We investigated the effect of 8 TT compared to SoC as a maintenance strategy after chemotherapy in pts with metastatic NSCLC. **Methods:** In SAFIR02-LUNG trial (NCT: 02117167), open-label multicentric phase II randomized trials, PS 0-1 pts with *ALK/EGFR* WT NSCLC after a CR/PR/SD to 4 cycles of platinum-based chemotherapy were selected. All pts underwent a fresh biopsy, followed by targeted sequencing on 70 genes and SNP-array when > 30% cancer cells were present on HES slides. In case of genomic alteration (including *KRAS*, *ERBB2*, *BRAF, BRCA* mutations), pts were randomized 2:1 between 8 TT and SoC. TT allocation was decided during weekly national tumor board, based on predefined guidelines. The primary endpoint was Progression-Free Survival (PFS) and the secondary endpoint was Overall Survival (OS). **Results:** 999 patients were enrolled and 394 had a molecular alteration eligible for the study. Among the 175 randomized pts (between July 2014 and May 2019), 116 received TT (65 selumetinib, 18 vistusertib, 9 capivasertib, 8 AZD4547, 5 AZD8931, 5 vandetanib, 4 olaparib, 1 savolitinib) and 59 SoC (54 pemetrexed, 4 gemcitabine and 1 erlotinib). Median age was 60, 40.6% were female, 4.6% never-smoker, 44% were PS 0, 88.6% had a non-squamous NSCLC and 26.9% a PR to chemotherapy. At data cut-off, 168 pts had progressed or died. With a median follow-up of 42.0 months (mo), median PFS was 2.7 mo (95% confidence interval (CI) 1.6 to 2.7) with TT vs. 2.7 mo (95%CI 1.6-4.1) with SoC (HR for disease progression or death 1.00; 95%CI = 0.73 to 1.38; p = 0.978). There was no significant PFS differences among the molecular subgroups; in the cohort with *KRAS* or *BRAF* mutation without *STK11* mutations the HR for disease progression or death was 0.76; 95%CI = 0.52 to 1.13; p = 0.17. Median OS was 14.3 mo (95%CI 11.0-18.3) with TT vs. 14.1 mo (95% CI 8.0-30.9) with SoC (HR for death 1.12; 95%CI = 0.75-1.65; p = 0.581). Grade 3 or 4 treatment-related adverse events occurred in 31 pts (26.7%) on TT (G3: 30 pts (25.9%), G4: 1 pt (0.8%)) and in 13 (22%) on SoC (G3 8 pts, G4 5 pts). **Conclusions:** The SAFIR02-LUNG trial demonstrated the feasibility of a routine precision medicine for advanced NSCLC. However, the monotherapy TT used as maintenance therapy after platinum-based chemotherapy failed to improve PFS or OS in this advanced *ALK/EGFR* WT NSCLC pts population. Newly available therapeutic options (ex. for *KRASG12C, RET, NTRK, ERBB2, NRG1*, etc) need to be evaluated. Clinical trial information: 2013-001653-27. Research Sponsor: Astrazeneca.

9096 **Poster Session**

Time-dependent efficacy of checkpoint inhibitor nivolumab in metastatic lung cancer patients. *First Author: Abdoulaye Karaboué, Medical Oncology Unit, GHT Grand Paris Est, Montfermeil Hospital, Montfermeil, France*

Background: Nivolumab (NIV) is a Programmed-cell-Death-1 inhibitor approved as 2nd line treatment for metastatic Non-Small Cell Lung Cancer (NSCLC). NIV mainly targets T(CD8) cells, whose functions and trafficking are regulated by circadian clocks (Nobis et al. PNAS 2019), hence suggesting possible dosing time-dependent changes in NIV efficacy. **Methods:** Consecutive metastatic NSCLC patients (pts) received single agent NIV (240 mg iv q 2 weeks) at a single institution. NIV timing slots were randomly allocated for each course by the day hospital coordinator on a logistics basis and recorded. The median NIV timing and its intra-pt coefficient of variation (CVar) were computed over the whole treatment span. The study population was split into two NIV timing groups based upon the median value of the median treatment times of all the pts. CTCAE-toxicity rates were compared between groups with c2 or Fisher exact. Progression free survival (PFS) and overall survival (OS) were compared between both NIV timing groups with Log Rank. **Results:** From 9/2015 to 11/2020, the study accrued 95 stage 4 NSCLC pts (males, 83%; PS 0-1, 96%), aged 41-83 years (median, 67). Primary histological types were adenocarcinoma (55 pts, 58%), squamous cell carcinoma (37 pts, 39%) or unspecified (3 pts, 3%). The pts had a median of 4 metastatic sites, including bone (52% of the pts), pleura (41%), liver (25%), brain (24%) and adrenal gland (20%). A total of 1818 NIV courses were given as 2nd line for 72 pts (76%), or as 3rd or later line for 22 pts (23%). Median PFS and OS (months, mo.) were 3.9 mo. [95% CL, 2.1 – 5.8], and 14.0 mo. [9.5 – 18.4] respectively, for the 95 pts. The majority of NIV administrations occurred between 9:27 and 12:54 for 48 pts ('morning' group) and between 12:55 and 17:14 for 47 pts ('afternoon' group), with intra-pt NIV timing CVar ranging from 2% to 21% (median, 10%). Main pts characteristics were similar for both groups, except for fewer females (8% vs 26%) and younger age (median, 66 vs 69 years) in the 'morning' group compared to the 'afternoon' one. Grade 3-4 fatigue, anorexia or myalgias were less in the 'morning' group compared with the "afternoon' one (6% vs 15%; 2% vs 6%; 0% vs 4%, respectively). Strikingly, median PFS [95% CI] were 11.3 mo. [5.5 - 17.1] for the 'morning' group as compared to 3.1 mo. [1.5 - 4.6] for the 'afternoon' one ($p<0.001$). Median OS were 34.2 mo. [15.1 - 53.3] for the 'morning' group *vs* 9.6 mo. [4.9 - 14.4] for the 'afternoon' group ($p<0.001$). Multivariate analyses identified NIV 'morning' timing and 2nd line administration, as significant independent predictors of longer PFS and OS. **Conclusions:** NIV was both less toxic and four times as effective following 'morning' as compared to 'afternoon' dosing in this study in Stage 4 NSCLC pts, possibly as a result of dosing time-dependent pharmacology. Translational and clinical nivolumab timing validation studies are needed, in order to optimize pts benefits from cancer immunotherapy. Research Sponsor: None.

9097 **Poster Session**

Optimal next-generation sequencing (NGS) panel for estimating tumor mutation burden (TMB) and its clinical implication for non-small cell lung cancer (NSCLC). *First Author: Takaya Ikeda, National Cancer Center Hospital East, Kashiwa, Japan*

Background: TMB estimation using targeted NGS panels is widely performed in clinical practice. The objective of this study was to determine the optimal NGS panel for estimating TMB and to evaluate its clinical implications for NSCLC. **Methods:** Two NGS panels, Oncomine Tumor Mutation Load Assay (OMLA) and FoundationOne (F1), were compared to select the most accurate TMB prediction panel. From February 2017 to May 2018, 350 lung cancer patients were analyzed by whole-exome sequencing (WES), and the concordance rate of OMLA and F1 to WES was examined. In addition, its clinical utility as a biomarker for immune checkpoint inhibitors (ICIs) was evaluated in our international genome screening network (LC-SCRUM-Asia). From June 2019 to December 2020, 3141 patients with NSCLC from 185 institutions were enrolled, and genomic analysis was successful. The clinico-genomic database of LC-SCRUM-Asia was used for this analysis. **Results:** The linear correlation with WES was 0.80 for OMLA and 0.78 for F1. This indicated that OMLA was more strongly correlated with WES. The cutoff value of F1 was 10 mut/Mb, which corresponded to 9 mut/Mb (OMLA) and 194 mutations (WES). The sensitivity of the OMLA for WES was 79%, and the specificity was 85%. Meanwhile, the sensitivity of the F1 was 74%, and the specificity was 80%. OMLA more accurately predicted TMB, and its clinical utility was evaluated. 3141 NSCLC patients, consisting of 2282 adenocarcinomas, 593 squamous cell carcinomas, and 266 others, were analyzed for TMB, estimated using OMLA. The median number of mutations was 4.2 mut/Mb (range, 0-718.4/Mb). High TMB (≥9 mut/Mb) was observed in 17.2% (393/2282) of adenocarcinoma cases and 25.8% (153/593) in squamous cell carcinoma cases. 778 patients were treated with ICI or ICI plus chemotherapy as the first-line treatment. Patients' characteristics were as follows: male/female; 595/183, median age (range); 67 (25-90), stage II/III/VI/recurrence; 11/90/649/28, TMB high/low; 177/601, ICI/ICI plus chemotherapy; 114/664. The progression-free survival (PFS) was significantly longer in patients with high TMB than in those with low TMB (median PFS, 7.5 vs. 5.9 months, p = 0.0314). The overall survival (OS) was significantly longer in patients with high TMB than in those with low TMB (median OS, 27.4 vs. 20.4 months, p = 0.006). **Conclusions:** The TMB estimated by OMLA correlated more strongly with the WES-derived TMB comparing with F1. TMB estimated by OMLA was correlated with PFS and OS in NSCLC patients treated with ICIs. Prospective clinical trials are needed to determine whether TMB estimated by OMLA is a biomarker for ICI. Research Sponsor: Ono Pharmaceutical Co., Ltd.

9098 **Poster Session**

Real-world response and outcomes in NSCLC patients with EGFR exon 20 insertion mutations. *First Author: Sai-Hong Ignatius Ou, Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA*

Background: There is currently no targeted therapy approved for patients with EGFR exon 20 insertion mutations (exon20ins) in NSCLC. Real world treatment outcome evidence for this rare population is limited. This study describes treatment patterns and outcomes in US patients with advanced NSCLC with EGFR exon20ins. **Methods:** The nationwide Flatiron Health electronic health record-derived deidentified database (cut-off 29 Feb 2020) was used to select 4 separate cohorts: (1) first-line (1L): patients receiving 1L therapy after documented exon20ins (1L start date as index date); (2) second or later line (≥2L): patients receiving ≥2L therapy after documented exon20ins (start date of ≥2L as index date); (3) ≥2L trial-aligned: ≥2L patients with baseline characteristics aligned with the key eligibility criteria of mobocertinib Trial NCT02716116 Part 3; and (4) ≥2L post platinum: ≥2L trial-aligned patients previously treated with platinum-based chemotherapy. Real-world endpoints were: confirmed overall response rate (cORR), PFS, and OS. Additional analyses were conducted for patients treated with immune-oncology therapy (IO). **Results:** Of 237 EGFR exon20ins patients, 129 patients were included in 1L cohort and 114 were in ≥2L cohort, including 63 ≥2L trial-aligned and 50 ≥2L post platinum patients. In 1L patients, EGFR TKI (28.7%) and platinum-based chemotherapy ± IO (56.6%) were the most common 1L regimens. In ≥2L patients, 28.1% received IO monotherapy, 17.5% received EGFR TKI, and 23.7% received platinum-based chemotherapy ± IO as index treatment. In the 1L setting, median PFS (mPFS) was 5.7 months for platinum-based chemotherapy and 4.5 months for IO + platinum-based chemotherapy. In the ≥2L setting, mPFS was 3.7 months for any therapy and 2.3 months for IO monotherapy. Full effectiveness data are provided in the accompanying table. **Conclusions:** This real world study provided a benchmark on the treatment outcome in patients with advanced NSCLC with EGFR exon20ins. Platinum-based chemotherapy was the most common 1L therapy and provided the longest mPFS. Immunotherapy, either as monotherapy or in combination with chemotherapy, appeared less effective for treatment of NSCLC with EGFR exon20ins. There is an unmet medical need for improved therapeutic options. Research Sponsor: Takeda Pharmaceutical Company Limited.

Cohort	N	cORR (95% CI)	Median OS (95% CI), months	Median PFS (95% CI), months
1L: any therapies	129	18.6% (12.3%, 26.4%)	17.0 (11.2, 19.5)	5.2 (3.1, 6.9)
1L: IO monotherapy	11	9.1% (0.2%, 41.3%)	11.0 (1.2, n/r)	3.1 (1.1, 5.2)
1L: IO + Platinum	16	18.8% (4.0%, 45.6%)	11.3 (5.6, n/r)	4.5 (1.2, 10.3)
1L: Platinum	41	19.5% (8.8%, 34.9%)	17.0 (10.5, 33.2)	5.7 (3.0, 10.9)
≥2L: any therapies	114	9.6% (4.9%, 16.6%)	13.6 (8.2, 15.4)	3.7 (2.7, 5.2)
≥2L: IO monotherapy	32	3.1% (0.1%, 16.2%)	8.1 (2.9, 15.0)	2.3 (1.9, 3.7)
≥2L post platinum: any therapies	50	14.0% (5.8%, 26.7%)	11.5 (7.9, 16.6)	3.3 (2.3, 5.9)
≥2L post platinum: IO monotherapy	20	5.0% (0.1%, 24.9%)	7.1 (2.5, 10.1)	2.2 (1.7, 3.0)

9099 **Poster Session**

Impact of immune checkpoint inhibitor (CPI) and EGFR tyrosine kinase inhibitor (TKI) sequence on time to treatment failure (TTF) among EGFR plus NSCLC treated in a community-based cancer research network.

First Author: Carissa Jones, Sarah Cannon Research Institute, Nashville, TN

Background: The development of CPIs and driver-targeted TKIs has transformed the treatment of NSCLC and increased survival rates. However, the role of CPIs in patients with oncogenic-driven NSCLC remains an area of investigation. We sought to examine the impact of CPI sequence on treatment response among patients with oncogenic-driver mutation-positive NSCLC. **Methods**: Patients with NSCLC being treated within the Sarah Cannon Research Institute network were identified through Genospace, Sarah Cannon's clinico-genomic analytics platform. Advanced stage oncogenic-driven tumors (driver+) were defined as those with a record of receiving an FDA-approved TKI targeting EGFR, ALK, RET, ROS1, NTRK, MET, or BRAF. Kaplan-Meier estimates were used to examine TTF (defined as time from therapy start to start of next therapy, death, or loss to follow-up) and overall survival (OS). **Results**: We identified 12,352 patients with lung cancer and available therapy data (2005-2020), including 2,270 (18%) driver+ patients. Eleven percent (N=245) of driver+ patients received a CPI, including 120 (49%) with CPI prior to TKI, 122 (50%) with CPI post TKI, and 3 (1%) who received CPI both pre and post TKI. The CPI TTF was significantly longer for those who received CPI post TKI compared to those who received it prior (Table). EGFR+ tumors accounted for 82% (N=1,867) of driver+ patients, 10% of whom (N=188) received a CPI. Of the EGFR+/CPI+ patients, 78 patients (41%) received CPI prior to TKI, 107 (57%) received CPI post TKI, and 3 (2%) received CPI both pre and post TKI. EGFR+ tumors exposed to a CPI post TKI had a longer CPI TTF compared to patients who received it prior (Table). In contrast, there was no difference in length of benefit from TKI if it was received pre vs. post CPI (Table). There was also no difference in OS based on sequence of TKI and CPI (p=0.88). Larger sample sizes are needed for analysis of additional driver-stratified cohorts. **Conclusions**: Patients with oncogenic-driven NSCLC benefited from CPI longer when it was administered after TKI compared to before. Importantly, therapy sequence only affected length of benefit from CPIs and did not affect length of benefit from TKIs. This effect was present in EGFR+ NSCLC, but sample sizes were too small to determine if the same is true for other oncogenic-drivers. Therapy sequence had no impact on OS, indicating the presence of additional clinical, therapeutic, and/or genomic factors contributing to disease progression. Continued research is needed to better understand markers of CPI response in driver+ NSCLC. Research Sponsor: None.

Median TTF (mTTF) for driver+ NSCLC based on therapy sequence.

	mTTF (days)	P-value
Driver+		
CPI pre TKI	189	<0.005
CPI post TKI	280	
TKI pre CPI	418	0.40
TKI post CPI	486	
EGFR+		
CPI pre TKI	210	<0.005
CPI post TKI	280	
TKI pre CPI	450	0.88
TKI post CPI	436	

9100 **Poster Session**

Interim results of viagenpumatucel-L (HS-110) plus nivolumab in previously treated patients (pts) with advanced non-small cell lung cancer (NSCLC) in two treatment settings.

First Author: Roger B. Cohen, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

Background: Viagenpumatucel-L (HS-110) is an allogeneic cell therapy derived from a human lung adenocarcinoma cell line incorporating multiple cancer testis antigens and transfected with a gp96-Ig fusion protein. **Methods:** We report interim results of cohort A (previously treated pts who had not received a checkpoint inhibitor [CPI]) and cohort B (pts who progressed after CPI treatment) in an ongoing phase 2 trial evaluating HS-110 plus nivolumab (NIVO) in advanced NSCLC pts (NCT02439450). Pts received HS-110 (1×10^7 cells) intradermally QW for 18 wk and NIVO Q2W until tumor progression. Stratified analyses were performed by injection site reaction (ISR), yes (+) or no (–); baseline blood tumor mutational burden (bTMB), bTMB-L (<10 mutations/ megabase [mut/Mb]) or bTMB-H (≥10 mut/Mb) by FoundationACT test; and baseline PD-L1 expression, – (<1%) or + (≥1%). **Results:** As shown in the Table, median progression-free survival (PFS) in cohort A (n=47) was 1.8 mo (95% CI 1.8-7.8) and median overall survival (OS) was 24.6 mo (95% CI 11.7-36.0) after a median follow-up (MFU) of 19.5 mo. We observed significantly longer PFS and OS in ISR+ pts (hazard ratio [HR] 0.43, p=0.01; HR 0.23, p<0.001) and longer OS in PD-L1+ pts (HR 0.25, p=0.02). In cohort B (n=68), median PFS was 2.8 mo (1.8-3.9) and median OS was 11.9 mo (9.7-16.3) after a MFU of 11.9 mo. We observed significantly longer OS in ISR+ pts (HR 0.48, p=0.03) and a trend toward extended OS in bTMB-L pts (HR 0.58, p=0.20). HS-110 TEAEs were reported in 21 (44.7%) pts in cohort A and 18 (26.5%) pts in cohort B. TEAEs in >5% of pts included fatigue, maculopapular rash, nausea, diarrhea, and pruritus. Few HS-110–related TEAEs led to discontinuation of treatment [cohort A, 5 (10.6%); cohort B, 3 (4.4%)], and no serious AEs were considered related to HS-110. **Conclusions:** HS-110 was well tolerated when administered in combination with NIVO. In previously treated pts with advanced NSCLC, we observed (1) significantly longer PFS and OS in ISR+ pts in both CPI naïve and CPI progressor cohorts; (2) significantly longer OS in PD-L1+ patients in the CPI naïve cohort; and (3) a trend of improved OS in bTMB-L pts in the CPI progressor cohort. Further clinical evaluation of HS-110 is warranted in both CPI naïve and CPI progressor NSCLC patients. Clinical trial information: NCT02439450. Research Sponsor: HEAT Biologics.

	All	ISR+	ISR–	Adj HR or OR; p	bTMB-L	bTMB-H	Adj HR or OR; p	PD-L1+	PD-L1-	Adj HR or OR; p
Cohort A, n	47	28	19	-	2	2	-	9	22	-
ORR, %	21.3	28.6	10.5	3.91†; 0.12	-	-	-	44.4	9.1	8.10†; 0.04
PFS‡	1.8	5.4	1.5	0.43; 0.01	-	-	-	4.8	1.8	0.46; 0.11
OS‡	24.6	36.0	4.5	0.23; <0.001	-	-	-	40.5	20.7	0.25; 0.02
Cohort B, n	68	52	16	-	32	11	-	23	29	-
ORR, %	10.3	11.5	6.3	1.99†; 0.60	15.6	9.1	2.25†; 0.50	13.0	10.3	1.27†; 0.80
PFS‡	2.8	3.0	1.7	0.63; 0.14	3.7	2.7	0.94; 0.90	3.2	2.9	1.11; 0.80
OS‡	11.9	12.1	6.4	0.48; 0.03	18.2	12.2	0.58; 0.20	12.1	12.3	0.99; 0.90

† OR. ‡median, mo. OR, odds ratio; ORR, objective response rate.

9101 **Poster Session**

Incidence and heterogeneity of C797S and other EGFR resistance mutations on routine comprehensive genomic profiling (CGP).

First Author: Pasi A. Janne, Dana-Farber Cancer Institute, Boston, MA

Background: The emergence of osimertinib (osi) as standard of care therapy for *EGFR*-mutant NSCLC has led to investigations into understanding and overcoming drug resistance. There are now a number of therapeutic approaches aimed at overcoming *EGFR* resistance mutations (muts). We sought to understand the biology of *EGFR* C797S and other *EGFR* resistance muts through querying our clinico-genomic database (CGDB). **Methods:** CGP results from tissue (n = 60,889) or circulating tumor DNA (ctDNA; [n = 9,922]) samples from 70,811 NSCLC patients (pts) were queried for known osi resistance muts in *EGFR* (C797, L792, G796, L718, G724). Clinical outcomes were evaluated for a cohort of NSCLC pts with osi resistance from the Flatiron Health-Foundation Medicine CGDB, a nationwide de-identified EHR-derived database linked to CGP data. **Results:** Between 12/2014 and 11/2020, 261 osi resistance mutations in *EGFR* were detected in 228 samples. The most common were C797S (66%), L718X (14%), G724S (11%), and others (9%). 173 C797S muts were detected in 155 samples (123 ex19del, 30 L858R, 2 other *EGFR* muts); 100 tissue, 55 ctDNA (median VAF = 7.6%). *EGFR* T790M co-occurred with C797S muts (96% cis, 3.7% trans) in 118 (76%) samples and decreased over time, occurring in 92% (24/26) of C797S samples tested in 2017 vs 56% (20/36) of samples tested in 2020 (p = 0.002). In 19/155 (12%) samples with C797S (14 ctDNA), multiple changes resulting in *EGFR* resistance muts were present: 16 samples had > 1 nucleotide changes resulting in C797S (100% trans), 3 samples had other resistance muts (L718Q/V, L792H, L792F) and 3 samples had multiple C797S changes with other resistance muts (C797G, L792H/F + G796S, L718Q + G796S+C797G). 29 pts (14 ctDNA) had C797S with potential off-target resistance (17 *PIK3CA* muts, 4 *BRAF* muts, 3 *CCDC6-RET* fusions, 3 *KRAS* muts, 2 *ERBB2* amplifications (amps), 1 *ERBB2* ex16 del, 1 *STRN-ALK* fusion, 1 *FGFR3-TACC3* fusion). In the CGDB, 527 *EGFR*-mut NSCLC pts had documented receipt of osi. Pre and post osi-treated specimens were available for 19 of these pts (12 ex19del, 6 L858R, 1 G719A/S768I). Heterogeneous acquired resistance mechanisms were observed in the post-osi specimen, including 2 *CCDC6-RET* fusions, 2 *MET* amps, 2 *BRAF* fusions, *BRAF* V600E, and secondary *EGFR* muts (C797S, L704F, L718V). 161/527 pts had a documented line of therapy after osi discontinuation and most frequently received platinum doublet + immunotherapy (27%) or platinum doublet alone (23%); 17 (11%) pts received another *EGFR* tyrosine kinase inhibitor. 214/527 had documented osi progression and median post-progression survival was 11.8 months. **Conclusions:** Osi resistance in *EGFR*-mutant NSCLC is a poor prognosis condition. *EGFR* C797S is a recurring resistance mut which, in a minority of cases, can co-occur with alternate on and off target resistance muts detected with tissue and liquid biopsy. Research Sponsor: Foundation Medicine.

9102 **Poster Session**

RATIONALE-307: Tislelizumab plus chemotherapy versus chemotherapy alone as first-line treatment for advanced squamous NSCLC in patients aged ≥ 65.

First Author: Jie Wang, State Key Laboratory of Molecular Oncology, Department of Medical Oncology, National Cancer Center/ National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

Background: Tislelizumab is a humanized, monoclonal antibody with high affinity and specificity for the programmed cell death protein 1 (PD-1). It has demonstrated antitumor activity in advanced lung cancers. We conducted a Phase 3, multicenter, randomized open-label study (NCT03594747) to assess the safety and efficacy of tislelizumab plus chemotherapy in patients (pts) with advanced squamous NSCLC. As previously reported, tislelizumab (TIS) significantly improved progression free survival (PFS) and reduced the risk of progression. Here, we report results from a sub-group of pts aged ≥ 65 years. **Methods:** Eligible pts (aged 18-75 years) enrolled in China were treatment-naive for locally advanced or metastatic squamous NSCLC. Pts were stratified by disease stage (IIIB vs IV), and programmed death-ligand 1 (PD-L1) expression (<1% vs 1-49% vs 50% tumor cells), and randomized 1:1:1 to Arm A: TIS 200 mg + paclitaxel (P) 175 mg/m^2 and carboplatin (C) area under the plasma concentration 5 (every 3 weeks [Q3W] on day 1); Arm B: TIS + *nab*-paclitaxel (*nab*-P) 100 mg/m^2 (Q3W on days 1, 8 and 15) + C (Q3W on Day 1); or Arm C: P + C (Q3W on day 1). P, *nab*-P and C were administered for 4 to 6 cycles. TIS was administered until loss of benefit, withdrawal of consent or start of a new anticancer therapy. In this sub-group analysis, pts aged ≥ 65 years were evaluated according to the primary endpoint (PFS) and key secondary endpoints (objective response rate and safety). **Results:** Overall, 127 pts aged ≥ 65 years were randomized to receive treatment. Median age of pts aged ≥ 65 was 68.0 years and 120 pts (94.5%) were male. In total, 18 (46.2%), 20 (38.5%), and 34 (94.4%) pts in Arms A, B and C, respectively, had discontinued treatment. In Arm C 22/34 pts had completed chemotherapy. The primary and secondary endpoints, PFS and ORR, were longer and higher, respectively, in Arms A and B, compared with Arm C (Table). Grade ≥ 3 treatment related adverse events (TRAEs) occurred in 33 (84.6%), 44 (84.6%) and 28 (82.4%) pts aged ≥ 65 years in Arms A, B and C, respectively, compared with 103 (85.8%), 99 (83.9%) and 94 (80.3%) pts aged ≥ 18 years enrolled in the study. The most commonly reported TRAEs in pts aged ≥ 65 years were anemia, decrease in neutrophil count, and alopecia. **Conclusions:** In this sub-group analysis, PFS and ORR were longer and higher, respectively, with TIS in pts aged ≥ 65 years with advanced squamous NSCLC. The safety profile of TIS in pts aged ≥ 65 years was similar to the safety profile for all aged pts aged ≥ 18 years. Clinical trial information: NCT03594747. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Tamsin Grewal, MSc, of Ashfield Medcomms, an Ashfield Health Company, and funded by BeiGene, Ltd.

	Arm A (N = 39)	Arm B (N = 52)	Arm C (N = 36)
Median PFS, months (95% CI)	9.7 (5.59, NE)	9.7 (6.87, NE)	5.2 (4.14, NE)
HR (95% CI)	0.602 (0.309, 1.175)	0.564 (0.302, 1.052)	
ORR, % (95% CI)	69.2 (52.4, 83.0)	75.0 (61.1, 86.0)	50.0 (32.9, 67.1)

CI, confidence interval; HR, hazard ratio; NE, not estimable; ORR, objective response rate; PFS, progression free survival.

9103 **Poster Session**

Chronic immune checkpoint inhibitor (ICI) pneumonitis in patients (pts) with non-small cell lung cancer (NSCLC). *First Author: Jessica Stuart, Brigham and Women's Hospital, Boston, MA*

Background: ICI pneumonitis is an immune-related adverse event (irAE) of the lung and often requires discontinuation of ICI. While some pneumonitis cases resolve within the recommended 4-6-week period of corticosteroid therapy, others either fail to improve or have multiple flares necessitating longer or repeated courses of steroids. We investigated the clinical features and courses of pts with chronic pneumonitis. **Methods:** We analyzed 869 pts with NSCLC initiated on ICIs at our institution between 2011 and 2019 for development of ICI pneumonitis. Chronic pneumonitis was defined as any pneumonitis requiring a total of ≥12 weeks of steroids, given either continuously or over multiple courses of treatment. Cases of chronic pneumonitis in which the initial course of steroids lasted ≥12 weeks without interruption were termed "primary refractory pneumonitis". Subsequent episodes of pneumonitis were categorized as either "recurrent pneumonitis" from ICI rechallenge or "pneumonitis flare" after steroid taper without ICI rechallenge. Chest CT scans were analyzed to classify the imaging patterns. **Results:** Of the 869 pts analyzed, 44 developed ICI pneumonitis (5.1%) and 22 of the 44 (50%) experienced chronic pneumonitis (Grade 2 in 11, Grade 3 in 9, and Grade 4 in 2). A cryptogenic organizing pneumonia (COP) pattern was the most common CT pattern among all pneumonitis cases (30/44) and in chronic pneumonitis cases (14/22). Among chronic pneumonitis cases, the median number of total weeks on corticosteroid therapy was 25.9 (range: 12.4 – 114.4 weeks). Four pts required additional immunosuppressive agents including mycophenolate or infliximab. Fourteen of 22 pts with chronic pneumonitis had primary refractory pneumonitis, while the remaining 8 pts were weaned off of steroids within 12 weeks but later developed additional episode(s) of pneumonitis, ultimately resulting in a total steroid duration of ≥12 weeks. The 14 pts with primary refractory pneumonitis had significantly shorter time to pneumonitis onset compared to the other 8 pts (median time to onset: 1.8 vs. 5.5 months, Wilcoxon ranksum p = 0.04). Seventeen of 22 patients had their ICI permanently discontinued; of these, 9 pts subsequently experienced pneumonitis flare after steroid taper, necessitating additional course(s) of steroid therapy. 5 of the 22 patients were rechallenged with ICI, and 4 of them had recurrent pneumonitis with ICI rechallenge. **Conclusions:** Half of the pts diagnosed with pneumonitis developed chronic pneumonitis requiring at least 12 weeks in aggregate of glucocorticoid therapy. Some patients had an initial prolonged steroid course while others initially improved and then flared, even after ICI discontinuation. Recognition of chronic pneumonitis as a distinct and common clinical entity is important in management of pts with ICI pneumonitis. Research Sponsor: None.

9105 **Poster Session**

Genomic markers associated with hyperprogression in patients with lung cancer treated with immune checkpoint inhibitors. *First Author: Eyob ale Tadesse, Aurora Cancer Care, Advocate Aurora Health, Milwaukee, WI*

Background: Immune checkpoint inhibitor (ICI) therapy has become a mainstay of non-small cell lung cancer (NSCLC) treatment. However, not all patients (pts) benefit with a subset paradoxically experiencing accelerated tumor growth while on ICI. Hyperprogression (HP) refers to accelerated tumor growth on ICI with worsening clinical status. Various gene alterations may be associated with HP including MDM2/MDM4 amplifications, EGFR alterations, and STK11/LKB1 mutations. Kato et al. (doi: 10.1158/1078-0432.CCR-16-3133) showed HP in 6/6 pts with MDM2/MDM4 amplification and in 2/10 pts with EGFR alterations. This report describes HP in pts with NSCLC treated with ICIs in a large health system. **Methods:** Pts with NSCLC treated with ICIs from Jan 2012 to Jan 2021 at Advocate Aurora Health were reviewed after IRB approval. Pts with NSCLC histology (ICD diagnosis codes and/or manual chart review), ICI treatment, and molecular testing were identified via the real world data integrated within the Syapse Learning Health Network platform. Additional chart review to ascertain HP was performed, and molecular results were analyzed. HP criteria include: 1) time-to-treatment failure < 2 months (from start to discontinuation of ICI for any reason), 2) > 50% increase in tumor burden by RECIST, 3) spread of the disease to a new organ between baseline and first radiologic evaluation or clinical deterioration, and 4) ECOG PS ≥ 2 during the first 2 months of treatment. Based on the number of criteria fulfilled, HP = > 3, Progression = 1-2, and non-progressor = 0. Pts with and without HP were compared using Chi-squared and Fisher Exact tests. T-tests were performed for continuous variables. **Results:** Out of 7,078 NSCLC pts, 1,389 (20%) were treated with ICI including atezolizumab (40 pts, 3%), durvalumab (17 pts, 1%), nivolumab (167 pts, 12%), pembrolizumab (190 pts, 14%), and multiple ICIs (12 pts, 1%). Of those pts treated with ICIs, molecular testing was performed in427 (31%). 98 of 427 pts (23%)had HP and an additional 86 pts (20%) had progressive disease without meeting the definition of HP. Biomarker associations with HP are shown in the table. By tumor gene alterations, HP was seen in pts with: EGFR (20/60), STK11/LKB1 (16/25); and MDM2/4 (4/7). **Conclusions:** EGFR, STK11/LKB1, and MDM2/4 gene alterations were all statistically significantly associated with HP. Clinical and molecular predictors of HP need to be explored in order to optimize selection of pts for ICI therapy. Research Sponsor: None.

	Hyperprogression Status						
	No HP		+HP				
Molecular Alteration	N	%	N	%	N	%	P-Value*
EGFR							
No	367	86	289	88	78	80.59	
Yes	60	14	40	12	20	20	0.04
STK11/LKB1							
No	402	94	320	97	82	84	
Yes	25	6	9	3	16	16	< 0.0001
MDM2/4							
No	420	98	326	99	94	96	
Yes	7	2	3	1	4	4	0.03

*P-values were calculated using Chi-squared tests.

9106 **Poster Session**

Impact of *STK11* mutation on first-line immune checkpoint inhibitor (ICI) outcomes in a real-world KRAS G12C mutant lung adenocarcinoma cohort. *First Author: Rebecca Suk Heist, Massachusetts General Cancer Center, Boston, MA*

Background: The introduction of KRAS G12C inhibitors into clinical trials has demonstrated promise and may provide a new therapeutic option for patients (pts) harboring *KRAS* G12C mutations. Recent data has also indicated that immune checkpoint inhibitors (ICI) have shown benefit in *KRAS* G12C mutant lung adenocarcinoma (LUAD); however, data on the impact of co-occurring *STK11* mutations on outcomes are conflicting. We utilized the Guardant INFORM real-world clinical-genomic database to assess the impact of co-occurring *STK11* mutations on outcomes in pts with *KRAS* G12C mutant LUAD treated with a first-line ICI containing regimen. **Methods:** This retrospective matched cohort observational study was conducted in a nationally representative clinical-genomic database covering over 137,000 pts with comprehensive ctDNA results and associated clinical information. Adult pts with metastatic LUAD who received ≥ 1 dose of first-line anti-PD1/PD-L1 ± chemotherapy and had at least 90 days follow-up after first *KRAS* G12C detection were included. A cohort of pts without *KRAS* G12C, including *KRAS* wildtype pts and pts with other *KRAS* mutations, were matched 3:1 for age, gender, year of index and baseline comorbidity. Time to next treatment (TTNT), time to discontinuation (TTD), real-world overall survival (rwOS) were compared with vs. without *STK11* mutations for both cohorts using cox proportional-hazards model. **Results:** Among 330 pts in the *KRAS* G12C cohort, 21% (n = 70) had an *STK11* mutation. Among the matched cohort (n = 938), 754 pts were *KRAS* wildtype, of whom 6% (n = 49) had *STK11* mutations. Within the *KRAS* G12C cohort, pts with *STK11* mutations had statistically significant shorter TTNT (hazard ratio [HR] 2.7, 95% confidence internal [CI] 1.8-4.0, p < 0.0001), TTD (HR 1.4, 95% CI 1.0-2.0, p < 0.04) and rwOS (HR 3.2, 95% CI 2.0-5.1, p < 0.0001) than pts without *STK11* mutations. Within the matched *KRAS* wildtype cohort, the differences in TTD (HR 1.4, 95% CI = 1.0-2.0, p = 0.08) and rwOS (HR 1.4, 95% CI = 0.8-2.4, p = 0.3) in patients with vs. without *STK11* mutation did not reach statistical significance (Table). **Conclusions:** This study provides real-world evidence that *STK11* co-mutations are associated with worse outcomes among pts with *KRAS* G12C mutant LUAD treated with first-line ICI. These inferior outcomes indicate a high unmet medical need among LUAD pts harboring co-occurring *KRAS* G12C and *STK11* mutations and demonstrate the need for effective targeted and/or combination therapies in this patient population. Research Sponsor: Mirati Therapeutics.

Cohort	Endpoints	HR (95% CI) No *STK11* vs *STK11*	P-value
***KRAS* G12C (N = 331)**			
	TTNT	2.7 (1.8, 4.0)	< .0001
	TTD	1.4 (1.0, 2.0)	< 0.03
	rwOS	3.2 (2.0, 5.1)	< .0001
Matched *KRAS* wildtype cohort* (N = 754)			
	TTNT	1.7 (1.1, 2.6)	0.02
	TTD	1.4 (1.0, 2.0)	0.08
	rwOS	1.4 (0.8, 2.4)	0.3

*Data on the full matched cohort to be presented.

9107 **Poster Session**

Association of concomitant NSAID and immunotherapy on outcomes in patients with non-small cell lung cancer: Analysis of the National Veterans Health Administration Database. *First Author: Drew Moghanaki, Atlanta Veterans Affairs Health Care System, Decatur, GA*

Background: Preclinical data suggests the efficacy of immune checkpoint inhibitors (ICI) may be enhanced with concomitant nonsteroidal anti-inflammatory (NSAID) medications. Real-world evidence to support investigating this hypothesis in prospective randomized trials are needed. **Methods:** A retrospective cohort study queried the VA Corporate Data Warehouse (VA-CDW) to identify patients diagnosed with NSCLC who were treated with ICI between 2010-18. Exposure to concomitant NSAID was determined whenever NSAID prescriptions were released from the VA pharmacy within 90 days of the first ICI infusion. Chi-square and ANOVA tests were used to compare baseline characteristics. The outcome of overall survival (OS) was measured from the start of ICI. Cox proportional hazard regression was used to adjust for demographic, clinical, tumor, and treatment characteristics. **Results:** The study cohort consisted of 3,415 patients with NSCLC treated with ICI, and 2,336 (64%) were exposed to concomitant NSAID. The median age was 69, male 97%, race: white 73%, black 21%, and 66% lived in urban areas. Most patients were initially diagnosed with stage III or IV disease (68%); tumor histology: adenocarcinoma 48% and squamous cell 38%. Comorbidity counts were 0 in 40%, 1-3 in 30%, and 4+ in 30%. Chemotherapy was delivered before ICI in 54% and concurrently with ICI in 31%. The most commonly used NSAIDs were aspirin (35%), ketorolac (11%), and ibuprofen (7%); 44% were exposed to more than one NSAID. With a median follow-up of 8 months, exposure to concomitant NSAIDs was associated with a longer OS (HR = 0.90; 0.83-0.98, p = 0.01) after adjusting for all available potential confounders on multivariable analyses. Longer OS persisted following propensity score matching (HR = 0.89; 0.82-0.97 p = 0.007). Other factors significant for OS on multivariable testing included use of chemotherapy after ICI (HR = 0.53 [0.40-0.69], p < 0.001), concurrent chemotherapy during ICI (HR = 0.68 [0.62-0.74], p < 0.001), younger age, black race, female gender, and adenocarcinoma histology. Among the various NSAIDs analyzed on the multivariable analyses, only diclofenac approached statistical significance (HR = 0.78 [0.59-1.03], p = 0.08). Limiting the comparison to patients exposed to diclofenac (n = 101) versus no NSAIDs (n = 1,298), the comparison demonstrated a similar trend for OS (HR = 0.79 [0.60-1.04], p = 0.094), although the association was attenuated after propensity-score matching (HR = 0.90 [0.63-1.29], p = 0.57). **Conclusions:** This retrospective cohort study of Veterans with NSCLC who were treated with ICI identified that concomitant receipt of NSAIDs is associated with longer OS. Research Sponsor: Morningside Center for Innovative and Affordable Medicine, Emory Woodruff Health Sciences Center, Other Government Agency.

9108 **Poster Session**

Genomic landscape differences in patients with advanced non-small cell lung cancer by sex and age. *First Author: ErinMarie Kimbrough, Mayo Clinic, Jacksonville, FL*

Background: Non-small cell lung cancer (NSCLC) remains a leading cause of cancer-related death in the U.S. The median age at diagnosis is 70 years, and NSCLC is uncommon among younger individuals (< 50 years).Overall, outcomes in NSCLC have improved significantly with targeted therapy. A prior study demonstrated patients < 50 are more likely to have targetable alterations including EGFR, ALK, ERBB2, and ROS1. Another study reported an increased prevalence of EGFR mutations in females and KRAS mutations in males with NSCLC. The comprehensive genomic landscape of NSCLC patients in different age groups and genders remains largely unknown. In our study, we aim to investigate the genomic alterations in patients with advanced NSCLC according to age and sex. Efforts that are focused on identifying targetable alterations in NSCLC will likely help personalize treatment and improve outcomes. **Methods:** We performed a retrospective review of de-identified data from the Guardant Health database from March 2018 through October 2020. We reviewed 34,237 profiles from patients with NSCLC who underwent molecular profiling using the plasma-based circulating-tumor DNA (ctDNA) Next-Generation Sequencing (NGS) assay Guardant360. Single nucleotide variants (SNV), fusions, indels and copy number variations (CNV) of up to 83 genes were analyzed. We assessed for genomic differences among patients with advanced NSCLC by both sex and age (≥70 and < 70). We conducted two-tailed tests of equality of proportions comparing males to females and ≥70 to < 70. **Results:** Of the 34,237 profiles reviewed, somatic alterations were seen in 81.7% (n = 27,972) of the patients. The median age was 70 (range 16-102) and 55% were female. Our study demonstrated that the most common genomic alterations in both age groups and genders were TP53, EGFR, KRAS, ATM, and MET. Patients ≥70 were more likely to have ATM (21% versus 14%, $p < 0.0001$) and MET (12% versus 10 %, $p < 0.0001$) mutations than those < 70. Patients < 70 were more likely to have EGFR (30% versus 27%, $p < 0.0001$), STK11 (14% versus 11%, $p = 0.0056$), and KRAS (26% versus 24%, $p < 0.0001$) alterations. EGFR was seen more frequently in females (33% versus 26%, $p < 0.0001$). ATM (11% versus 6%, $p < 0.0001$) and MET (8% versus 5%, $p = 0.0050$) were seen more frequently in males. **Conclusions:** Significant differences in the distribution of targetable genomic alterations were identified among different age groups and genders in patients with advanced NSCLC. These findings highlight the importance of taking personalized approaches to diagnostic testing and treatment of advanced NSCLC. Research Sponsor: None.

9109 **Poster Session**

Long-term efficacy and safety of larotrectinib in patients with TRK fusion-positive lung cancer. *First Author: Jessica Jiyeong Lin, Department of Medicine, Massachusetts General Hospital and Harvard Medical School, Boston, MA*

Background: Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions have been identified as oncogenic drivers in a diverse array of tumor types including lung cancer. Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor approved for the treatment of adult and pediatric patients (pts) with TRK fusion cancer, with an objective response rate (ORR) of 78% across multiple non-CNS cancers (McDermott et al, ESMO 2020). Here, we report the updated data on pts with lung cancer treated with larotrectinib. **Methods:** Pts with lung cancer harboring a *NTRK* gene fusion enrolled in two clinical trials (NCT02576431 and NCT02122913) were identified for this analysis. Larotrectinib 100 mg PO BID was administered on a continuous 28-day schedule until disease progression, withdrawal, or unacceptable toxicity. Response was assessed by the investigator per RECIST v1.1. **Results:** As of July 20, 2020, a total of 20 pts with TRK fusion-positive lung cancer (19 with non-small cell lung cancer and 1 with small cell lung cancer) were enrolled. Median age was 48.5 years (range 25.0–76.0). The gene fusions involved *NTRK1* (n = 16; 80%) or *NTRK3* (n = 4; 20%). Pts were heavily pre-treated with a median of 3 systemic therapies (range 0–6). Among 15 evaluable pts, the confirmed ORR was 73% (95% CI 45–92): 1 complete response, 10 partial responses (PR), 3 stable disease (SD) and 1 progressive disease (PD). The median time to response was 1.8 months. Among 8 evaluable pts with baseline measurable and non-measurable CNS metastases, the ORR was 63% (95% CI 25–91): 5 PR, 2 SD, and 1 PD. In all evaluable pts, the 12-month rates for duration of response and progression-free survival were 81% and 65%, respectively. Median overall survival was 40.7 months (95% CI 17.2 to not estimable) at a median follow-up of 16.2 months. Duration of treatment ranged from 0.03+ to 51.55+ months. Adverse events (AEs) were predominantly Grade 1–2. Treatment-related AEs were reported in 16 pts, of which 2 experienced Grade 3 events (myalgia, hypersensitivity, weight increase). There were no treatment discontinuations due to AEs. **Conclusions:** These data confirm that larotrectinib is highly active with rapid and durable responses, extended survival benefit, and a favorable long-term safety profile in pts with advanced lung cancer harboring *NTRK* gene fusions, including in pts with CNS metastases. These results underscore the importance of screening for *NTRK* gene fusions in pts with lung cancer. Clinical trial information: NCT02576431 and NCT02122913. Research Sponsor: Bayer HealthCare and Loxo Oncology.

9110 **Poster Session**

Ph I/II study of oral selective AXL inhibitor bemcentinib (BGB324) in combination with erlotinib in patients with advanced EGFRm NSCLC: End of trial update. *First Author: Lauren Averett Byers, MD Anderson Cancer Center, Houston, TX*

Background: AXL, a receptor tyrosine kinase, is over-expressed in many cancers, and has been identified as a marker of poor prognosis in NSCLC. AXL overexpression is implicated in development of resistance to EGFR inhibitors including erlotinib (Erl) and osimertinib. AXL inhibition by bemcentinib (Bem), a first-in-class, oral, selective and potent AXL kinase inhibitor, abrogates resistance to EGFR inhibitors *in vivo*. Bem is currently under evaluation as a monotherapy and in combination with EGFRi, CPIs and chemotherapy across several PhII trials. **Methods:** Phase I of this study was designed to confirm safety/tolerability of Bem in NSCLC pts as monotherapy and in combination with Erl in pts previously progressing on Erl (arm A). In Phase II, pts who had progressed on an approved EGFRi (arm B) or who were responding/stable on Erl in the 1L setting (arm C) were treated with Bem 200mg and Erl 150mg od to evaluate the safety and activity of the combination, assessing reversal or prevention of resistance to EGFR inhibition in these 2 groups, respectively. Plasma protein biomarker levels were sequentially measured using the DiscoveryMap v3.3 panel (Myriad RBM). **Results:** As of 7 Oct 2020, all arms have completed recruitment. Median exposure to Bem was 63d (mean: 200d, range: 2d-1175d). Treatment was generally well-tolerated. Common TRAEs (>20% pts) were diarrhea (70%; G3 20%), nausea (50%; G3 0%), QTc prolongation (35%; G3 3%), vomiting (35%; G3 0%), and fatigue (25%; G3 5%). 1 unrelated G4, 0 G5 reported. In the run-in arm (5 female, median age 61 yrs [57-76]), 2/8 pts achieved SD for ~1 yr, including 19% tumor shrinkage in 1 pt. In arm A (5 female, median age 58 yrs [38-67]), 1/8 pts (68 F) achieved tumor shrinkage of 38%, with treatment duration of 2 yrs until progression. A further 5 pts reported SD. In arm B, 11 pts (7 female, median age 63 yrs [49-78]) had received a median of 1 (0 - 4) prior lines of chemotherapy and a median of 2 prior lines of EGFRi. One achieved a PR (51M) and one a SD (62F) on the combination (CBR of 18%); durations on treatment were 1 yr, and 6 mos, respectively. Neither had EGFR T790M. mPFS was 1.4 mos. In arm C, 13 pts (10 female, median age 66 yrs [32-80]) were enrolled. 11/13 pts were evaluable for efficacy. 1 PR (58M) was reported with 47% tumor shrinkage, duration of treatment was 315d. 9 other pts achieved SD (CBR of 91%), including 4 (3 F/1 M, age range 64-71yrs) who continued on trial for 772+ to 1008+ d. mPFS is currently 12.2 mos. Protein biomarkers predictive of pt benefit upon Bem treatment are being explored. **Conclusions:** Bem with Erl combination is feasible and tolerable in NSCLC pts, with benefit was seen in a subset of pts who either progressed on an EGFRi or were receiving Erl concurrently in remission in the first line. Further studies of Bem + EGFRi are warranted to explore the potential benefits of this combination. Clinical trial information: NCT02424617. Research Sponsor: Privately.

9111 **Poster Session**

Capmatinib efficacy in patients with NSCLC identified as *MET*ex14 using an NGS-based liquid biopsy assay: Results from the GEOMETRY mono-1 study. *First Author: Rebecca Suk Heist, Massachusetts General Cancer Center, Boston, MA*

Background: Capmatinib, a highly selective and potent MET inhibitor, was approved for patients (pts) with advanced MET exon 14 skipping mutation (METex14) NSCLC in the US and Japan, with the FoundationOne CDx (tissue NGS assay), based on results of the ongoing GEOMETRY mono-1 study (NCT02414139). Here, we report efficacy findings in pts from GEOMETRY mono-1, who were identified as *MET*ex14 using a next-generation sequencing (NGS)-based liquid biopsy test (LDx), which detects *MET*ex14 in circulating tumor (ct)DNA. **Methods:** During the GEOMETRY mono-1 study, pts were screened for *MET*ex14 status using a *MET*ex14 RT-PCR clinical trial assay (CTA) on FFPE tissue. Clinical validation of the LDx was performed using plasma samples from pts enrolled in the GEOMETRY mono-1 study, which include *MET*ex14-positive samples from Cohort (C)4 (pretreated) and C5b (treatment-naïve), in addition to *MET*ex14-negative samples from C1b, C2, and C3, and 21 tissue-matched NSCLC plasma samples from commercial sources to supplement the total number of *MET*ex14 deletion negative patients. Concordance of the CTA and LDx were evaluated by positive percent agreement (PPA) and negative percent agreement (NPA). This retrospective analysis reports overall response rate (ORR), duration of response (DOR), and progression-free survival (PFS), all by BIRC, and overall survival (OS) in pts identified as *MET*ex14 by the LDx (data cutoff: Sep 18, 2020). **Results:** Of the 97 pts with *MET*ex14 NSCLC in C4 (n = 69) and C5b (n = 28), 88 pts had plasma volume ≥2.5 mL and cell free DNA ≥20 ng (minimum input); of these 57 were LDx positive (C4, n = 41; C5b, n = 16), 26 were negative; 5 had invalid sequencing results. Of the 97 CTA *MET*ex14-negative patients who met minimum input requirements, 88 were LDx negative and 9 had invalid sequencing results; none of the CTA *MET*ex14-negative pts (N = 97) were reported as positive by the LDx. The PPA and NPA for these were 68.7% (95% CI: 57.6%, 78.4%) and 100% (95% CI: 95.9%, 100%), respectively, when excluding LDx invalid results. In pts identified as *MET*ex14 positive by LDx, the ORR (95% CI) was 81.3% (54.4–96.0; n = 16) in C5b and 48.8% (32.9–64.9; n = 41) in C4; median DOR (95% CI) was 20.3 (4.2, NE; n = 13) months in C5b and 9.8 (4.2–19.5; n = 20) months in C4; median PFS (95% CI) was 12.4 (4.5–NE; n = 16) months in C5b and 5.4 (4.0–6.6; n = 41) months in C4; median OS was 17.9 (9.8–NE; n = 16) months in C5b and 13.6 (6.6–23.3; n = 41) months in C4. Clinical findings in those identified as *MET*ex14 positive by LDx were comparable with those identified by the CTA. **Conclusions:** Current findings from the GEOMETRY mono-1 study support the activity of capmatinib in advanced NSCLC pts with *MET*ex14 identified using LDx. For pts identified as *MET*ex14-negative by the LDx, further testing should be performed on tissue samples, as a negative LDx result does not preclude a positive result by tissue biopsy. Clinical trial information: NCT02414139. Research Sponsor: Novartis.

9112 **Poster Session**

Interim results of a phase II single arm trial combining afatinib with cetuximab in patients with EGFRex20ins positive NSCLC. *First Author: Bianca van Veggel, Antoni van Leeuwenhoek Hospital, Amsterdam, Netherlands*

Background: Epidermal growth factor receptor exon 20 insertions (EGFRex20ins) are identified in 4-10% of all EGFR mutations in non-small cell lung cancer (NSCLC) and are associated with primary resistance to EGFR tyrosine kinase inhibitors (TKIs). Treatment options are limited. A case series showed that dual EGFR blockade with afatinib and cetuximab can induce tumor responses with manageable toxicity. We report on the first seventeen EGFRex20ins patients treated with afatinib in combination with cetuximab. **Methods:** In this Simon's two stage, single-arm, phase II trial, patients with advanced NSCLC harboring an EGFRex20ins mutation were treated with afatinib 40 mg once daily, in combination with cetuximab 500 mg/m^2, every two weeks, in five institutions in the Netherlands. Supportive medication consisted of minocycline, loperamide and skin creams. No previous line of treatment was required and asymptomatic brain metastases were allowed. The primary endpoint was disease control rate (DCR) after 18 weeks of treatment. Secondary endpoints included safety, response rate (RR), duration of response (DOR) and progression-free survival (PFS). Patients were treated until progression or unacceptable toxicity. A Simon's two stage optimal design was used in order to minimize the number of patients being treated in the event that the regimen proves to be inactive. The estimated sample size of the first stage was 17 patients. At least four successes were required to enter stage 2 of the trial (alpha = 0.10; power = 0.90). **Results:** Eighteen patients were enrolled between Jan 2019 and Aug 2020; one patient did not meet the eligibility criteria due to absence of measurable disease. Median age was 66.0 years, 65% female, 53% never smoker. 47% of patients were treated as first-line therapy. Median prior lines of treatment was 1 (range 0-6). 53% received prior platinum-based chemotherapy. The primary endpoint was met as disease control was achieved by 10 patients (59%) after 18 weeks of treatment. Median PFS was 5.5 months. Best responses were partial (n = 8, RR 47%), stable (n = 7) or progressive disease (n = 2). Four patients were still on treatment at the cut-off date (Feb 2021). Most common treatment-related adverse events (TRAEs) were diarrhea (71%), rash (65%), paronychia (59%) and dry skin (53%). Grade III TRAEs were reported in 59% of all patients. Grade III TRAEs $\geq$ 10% included rash (n = 3; 18%) and diarrhea (n = 3; 18%). No grade IV toxicity was observed. One patient died due to respiratory failure after infusion of study medication, probably related to disease progression, possibly treatment related. 82% of patients required a dose reduction. Rate of treatment discontinuation due to AEs was 12% (n = 2). **Conclusions:** Combination treatment with afatinib and cetuximab demonstrated antitumor activity with a DCR of 59% at 18 weeks and a 47% RR, with manageable toxicity. Clinical trial information: NCT03727724. Research Sponsor: Merck Healthcare, Schiphol-Rijk, Netherlands, an affiliate of Merck KGaA, Darmstadt, Germany, and Boehringer Ingelheim.

9113 **Poster Session**

***DNMT3A* mutation to identify a subset of non-small cell lung cancers with increased sensitivity to PD-(L)1 blockade.** *First Author: Biagio Ricciuti, Lowe Center for Thoracic Oncology, Dana-Farber Cancer Institute, Boston, MA*

Background: Despite significant improvements in overall survival with PD-(L)1 inhibition, the majority of patients with metastatic NSCLC do not respond to immune checkpoint inhibition (ICI). Growing evidence suggests the importance of genomic alterations in modulating anti-cancer immune response and predicting ICI efficacy in solid tumors. However, the genomic correlates of response and resistance to ICI in NSCLC are still largely unknown. **Methods:** Patients with advanced NSCLC treated with PD-(L)1 blockade whose tumors underwent comprehensive genomic profiling were included. Mutation enrichment analysis was performed to identify genomic alterations enriched in responders versus (vs) non-responders to ICI. Loss-of function mutations annotated as oncogenic by OncoKB, and missense mutations predicted to be deleterious by SIFT/Polyphen-2 were considered. Cox proportional hazards models was used to estimate hazard ratios (HRs) in univariable and multivariable models. **Results:** : Among 600 NSCLCs, we identified deleterious mutations in the DNA methyltransferase 3A (*DNMT3A*) gene as the most significant alteration enriched in responders versus non-responders to PD-(L)1 blockade (q-Value $<$ 0.05). *DNMT3A*^{MUT} (7.3%, N = 44) and *DNMT3A* wild-type (*DNMT3A*^{WT}) cases (92.7%, N = 556) were well balanced in terms of baseline clinicopathologic features, including PD-L1 expression, sex, performance status, age, concurrent genomic alterations, and smoking history. *DNMT3A*^{MUT} tumors had a significantly higher median TMB compared to *DNMT3A*^{WT} cases (12.1 vs 9.8 mutations/megabase, P = 0.03). *DNMT3A* loss was associated with significantly higher objective response rate (ORR, 50% vs 20.5%, P $<$ 0.001), longer median progression-free (mPFS, 9.2 vs 2.9 months, HR 0.60, P $<$ 0.01) and overall survival (mOS, 23.1 s 12.1 months, HR 0.59, P = 0.01) among *DNMT3A*^{MUT} compared to *DNMT3A*^{WT} NSCLCs. Loss-of function mutation in *DNMT3A* was confirmed be an independent predictor of improved PFS (HR 0.61, P = 0.01) and OS (HR 0.62, P = 0.04) at multivariable analysis. *DNMT3A* mutation had no impact on OS among patients with advanced NSCLC who did not receive ICI (HR 1.18, P = 0.22), nor among those with early-stage resected NSCLC (HR 1.17, P = 0.48), suggesting that *DNMT3A* mutation is predictive, rather than prognostic, of ICI efficacy. Although a subset of *DNMT3A* mutations could have potentially arisen from tumor-associated hematopoietic cells, the *DNMT3A* allele fraction-to-tumor purity ratio was $\geq$0.5 in more than 50% of cases, suggesting that a proportion of these mutations were derived from lung cancer cells. **Conclusions:** Loss-of-function mutation in DNMT3A may identify a new genomically defined subset of NSCLC with increased sensitivity to PD-(L)1 blockade. Additional studies are ongoing to determine the exact source of DNMT3A mutation (clonal hematopoiesis vs tumor) and their relative contribution to ICI efficacy. Research Sponsor: None.

9114 **Poster Session**

Nitroglycerin (NTG) plus whole intracranial radiotherapy for brain metastases (BM) in non-small cell cancer patient (NSCLC): A randomized open label, phase II clinical trial. *First Author: Oscar Gerardo Arrieta Rodriguez, Instituto Nacional de Cancerologia (INCan), Mexico City, Mexico*

Background: Hypoxia has been associated with chemo-radioresistance secondary to Vascular Endothelial Growth Factor Receptor induced by Hypoxia Induced Factor (HIF). Nitroglycerin (NTG) can reduce HIF-1 in cell lines, and this may have anti-angiogenic, pro-apoptotic, and anti-efflux effects. Particularly, *EGFR* mutated (EGFRm) tumor cell lines have been shown to overexpress both VEGF and HIF. In this phase II study, we evaluated the effect of transdermal NTG on intracranial objective response rate (iORR), intracranial progression-free survival (ICPFS), and overall survival (OS) of NSCLC patients with BM. **Methods:** We performed an open-label, phase II clinical trial among ninety-six histologically confirmed NSCLC patients with BM. Patients were randomized 1:1 to receive NTG plus WBRT (30 Gy in 10 fractions) or WBRT alone. iORR and ICPFS were evaluated by MRI by two independent, blinded radiologists. Nitroglycerin was administered using a transdermal 36 mg patch, which released 10 mg in 24 hours with a rest interval of 12 hours from Monday-Friday throughout WBRT administration (10 days). **Results:** Fifty patients were allocated to the control group, while 46 were allocated to the experimental group (NTG); among these 26 (55.3%) had *EGFR*m in the control group and 21 (44.7%) had *EGFR*m in the NTG arm. In terms of the iORR, patients in the NTG group had a significantly higher response when compared to controls (56.6% vs. 43.5%; p = 0.024). Additionally, patients who received NTG in addition to WBRT had an independently prolonged ICPFS compared with those who received WBRT alone (27.7 vs. 9.6; HR: 0.470 [95%CI: 0.24-0.89]; p = 0.021). PFS was also positively impacted (HR: 0.519 [95%CI: 0.27-0.98]; p = 0.043). The benefit in terms of iORR and ICPFS (HR: 0.38 [95%CI: 0.16-0.91]; p = 0.030) was particularly important in the *EGFRm* patient subgroup. No differences were observed in OS. A significantly higher rate of vomiting presented in the NTG arm of the study (p= 0.016). **Conclusions:** The concurrent administration of NTG and chemo-radiotherapy improves iORR and ICPFS among NSCLC patients with BM. The benefit is particularly significant in the *EGFR*m patient subgroup. Clinical trial information: NCT04338867. Research Sponsor: Consejo Nacional de Ciencia y Tecnología (CONACyT).

9115 **Poster Session**

Stereotactic body radiation therapy and in situ oncolytic virus therapy followed by immunotherapy in metastatic non-small cell lung cancer. *First Author: Carlo Guerrero, Houston Methodist Hospital, Houston, TX*

Background: The introduction of immunotherapy has altered the treatment paradigm for metastatic non-small cell cancer (mNSCLC). Unfortunately, many patients with mNSCLC have limited or no benefit from immune checkpoint inhibitors (ICIs). A variety of approaches have been explored to augment the efficacy of ICIs. Our study's aim was to determine whether the addition of stereotactic body radiation therapy (SBRT) and intratumoral injection of the oncolytic virus ADV/HSV-tk (adenovirus-mediated expression of herpes simplex virus thymidine kinase) to a monoclonal antibody targeting programmed cell death-1 (PD-1) would improve the ICI's efficacy in the treatment of mNSCLC. **Methods:** In this single-arm, open-label phase II study, patients with mNSCLC (squamous or non-squamous) who were ICI-naive or who were previously treated with a maximum of one line of therapy that included an ICI received an intratumoral injection of ADV/HSV-tk (5 x 10^{11} vp) followed by SBRT (30 Gy in 5 fractions) to the same tumor. An anti-PD-1 agent (pembrolizumab 200 mg IV every 3 weeks or nivolumab 240 mg IV every 2 weeks) was then given for up to 24 months (pembrolizumab) or 12 months (nivolumab), or until disease progression or intolerable toxicity. The primary endpoint was objective response rate (ORR) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. A secondary endpoint was clinical benefit rate (CBR). **Results:** A total of 35 patients were enrolled, with 28 (80%) receiving pembrolizumab and 7 (20%) receiving nivolumab; 14 (40%) had previous ICI therapy while 21 (60%) were ICI-naive. The ORR and CBR were 28.5% and 61.9% in the ICI-naive group, and 14.2% and 64.2% in the group that previously received an ICI, respectively. Grade 3 or higher toxicity was seen in five patients (26.3%) in the ICI-naive group and in one patient (7.1%) in the previously ICI-treated group. No treatment-related deaths were observed. **Conclusions:** The addition of SBRT and intratumor injection of ADV/HSV-tk to anti-PD-1 therapy in mNSCLC resulted in a CBR of over 60% for both ICI-naive and previously ICI-treated patients without the use of chemotherapy. The combination was able to reinstitute sensitivity to ICIs in patients previously treated with an ICI, and also benefited some patients whose tumors did not express PD-L1. These findings should be further explored in a larger study population. Clinical trial information: NCT03004183. Research Sponsor: Merck.

PD-L1 expression and treatment response.

	ICI-naïve (N = 21)	Previous ICI (N = 14)	Total (N = 35)
Tumor PD-L1 - no. (%)	13 (61.9)	6 (42.8)	19 (54.3)
< 1%	7 (33.3)	6 (42.8)	13 (37.1)
1-49%	1 (4.8)	2 (14.3)	3 (8.6)
≥ 50%			
Best overall response – no. (%)	2 (9.5)	0 (0)	2 (5.7)
Complete response (CR)	4 (19.0)	2 (14.3)	6 (17.1)
Partial response (PR)	7 (33.3)	7 (50.0)	14 (40.0)
Stable disease (SD)	8 (38.1)	5 (35.7)	13 (37.1)
Progressive disease (PD)			
CBR	13 (61.9)	9 (64.2)	22 (62.8)

CBR = CR + PR + SD; PD-L1 = Programmed death-ligand 1.

9116 **Poster Session**

Genomic landscape of non-small cell lung cancer (NSCLC) with methylthioadenosine phosphorylase (*MTAP*) deletion. *First Author: Stephen L. Graziano, Regional Oncology Center, Syracuse, NY*

Background: NSCLC remains a major cause of cancer-associated mortality despite major advancements in treatments. In addition to immune checkpoint inhibitors (ICPI), new strategies for clinically advanced NSCLC now include the development of new synthetic lethality targets focused on protein arginine methyl transferases such as PRMT5 that exploit the impact of tumor cell genomic loss of *MTAP*. **Methods:** 29,379 advanced/metastatic NSCLC cases underwent hybrid-capture based comprehensive genomic profiling to evaluate all classes of genomic alterations (GA). Tumor mutational burden (TMB) was determined on up to 1.1 Mb of sequenced DNA and microsatellite instability (MSI) was determined on up to 114 loci. PD-L1 tumor cell expression was determined by DAKO 22C3 immunohistochemistry (IHC); low positive was a tumor proportion score (TPS) 1-49% and high positive was a TPS ≥50%. **Results:** 3,928 NSCLC exhibited *MTAP* homozygous loss. Cases had the following subtypes: adenocarcinoma (59%), squamous cell ca (22%), NSCLC NOS (16%), and large cell neuroendocrine, sarcomatoid, adenosquamous ca (all 1%). GA/tumor were similar when *CDKN2A/B* losses associated with 9p21 co-deletion with *MTAP* loss are excluded. Significant differences in currently targetable GA included *KRAS* G12C higher in *MTAP*-intact NSCLC (P = .0003) and *EGFR* short variant mutations higher in *MTAP*-deleted NSCLC (P < .0001). *MTAP*-intact NSCLC had higher frequencies of GAs in *TP53* (P < .0001) and *RB1* and a lower frequency of *SMARCA4* (P < .0001). GAs frequencies in *ERBB2, MET, ALK, ROS1* and *NTRK1* were similar. Biomarkers for potential ICPI efficacy were higher in *MTAP*-intact including TMB ≥10mut/Mb (P = .0002) and low and high PD-L1 IHC staining (P = .01). Biomarkers potentially predictive of ICPI resistance (*STK11* and *KEAP1*) were similar in both groups. **Conclusions:** *MTAP* loss occurs in 13% of NSCLC, supporting the development of novel targeted therapies designed to exploit PRMT5 hyper-dependence in these tumors. *MTAP* loss in NSCLC is accompanied by differences in targeted and ICPI options for these patients which may impact future combination strategies. Further study of anti-PRMT5 drugs that are enabled by *MTAP* loss in NSCLC appears warranted. Research Sponsor: Foundation Medicine Inc.

	NSCLC *MTAP* Intact	NSCLC *MTAP* Loss	P Value
Number of Cases	25,843	3,928	
% Male	50%	50%	NS
Median age (range) yrs	68 (12-89+)	69 (18-89+)	NS
GA/tumor	5.5	8.2	NS*
CDKN2A	20%	98%	< .0001
CDKN2B	6%	95%	< .0001
TP53	70%	63%	< .0001
***KRAS* (all)**	31%	29%	NS
***KRAS* (G12C)**	12%	10%	= .0003
***EGFR* short variants only**	10%	13%	< .0001
ALK	3%	4%	NS
ROS1	1%	1%	NS
NTRK1	1%	1%	NS
STK11	15%	16%	NS
KEAP1	7%	7%	NS
PIK3CA	11%	12%	NS
SMARCA4	7%	10%	< .0001
PTEN	6%	6%	NS
MET	5% (3% amp)	6% (3% amp)	NS
ERBB2	4% (2%amp)	4% (2% amp)	NS
BRAF	5%	5%	NS
RB1	10%	2%	< .0001
MSI High	0.4%	0.2%	NS
Mean TMB	9.4	8.6	= .001
TMB>10 mut/Mb	35%	32%	= .0002
TMB>20 mut/Mb	10%	8%	< .0001
PD-L1 Low Positive	30% (13,931)	28% (2125)	= .01
PD-L1 High Positive	32%	30%	= .01

*when *CDKN2A/B* GA are excluded.

9117 **Poster Session**

Superior overall survival (OS), progression-free survival (PFS), and clinical response (CR) predictions for patients with non-small cell lung cancer (NSCLC) using Cellworks Singula: myCare-022-05. *First Author: Vamsidhar Velcheti, Cleveland Clinic Foundation, Cleveland, OH*

Background: The Cellworks Singula Therapeutic Response Index (TRI) has been developed to assist clinicians and NSCLC patients in choosing between competing therapeutic options. In contrast to approaches that consider single aberrations, which often yield limited benefit, Cellworks utilizes an individual patient's next generation sequencing results and a mechanistic multi-omics biology model, the Cellworks Omics Biology Model (CBM), to biosimulate downstream molecular effects of cell signaling, drugs, and radiation on patient-specific *in silico* diseased cells. For any individual patient and alternative therapy, Cellworks integrates this biologically modeled multi-omics information into a continuous Singula TRI Score, scaled from 0 (low therapeutic benefit) to 100 (high therapeutic benefit). We demonstrate that Singula is strongly associated with overall survival, progression-free survival and relative therapeutic benefit beyond standard clinical factors, including patient age, gender, and physician prescribed treatments (PPT). **Methods:** In this study, Singula's ability to predict response was evaluated in a retrospective cohort of 446 NSCLC patients with OS, PFS, and CR data from The Cancer Genome Atlas (TCGA) project, treated with PPT. As a primary analysis of the CBM and TRI Score, Cox Proportional Hazards (PH) regression and likelihood ratio (LR) tests were used to assess the hypothesis that Singula is predictive of OS, PFS, and CR above and beyond standard clinical factors. A p-value < 0.05 for the corresponding likelihood ratio statistic was required to be considered significant. **Results:** Multivariate analyses were performed to assess the performance of the Singula Therapy Response Index above and beyond physician's choice of treatment. The same Singula TRI algorithm and clinical cutoffs were used for all clinical outcome measures. For OS the median survival times for the high and low benefit groups were 60.16 and 28.57 months respectively, based on the median Singula value. Also, the hazard ratio per 25 Singula units for OS was 0.5103 (95% CI: 0.3337 - 0.7804) and the odds ratio for CR was 1.6161. These and further analyses, shown in Table, suggest that Singula TRI provides predictive value of OS, PFS, and CR above and beyond standard clinical factors. **Conclusions:** The Singula TRI Score provides a continuous measure for alternative NSCLC therapeutic options. In this retrospective cohort, Singula was strongly predictive of OS, PFS, and CR and provided predictive value of OS beyond PPT, patient age and gender. These results will be further validated in prospective clinical studies. Research Sponsor: None.

	OS	OS	PFS	PFS	CR	CR
LR Test	χ^2_1	**p-value**	χ^2_1	**p-value**	χ^2_1	**p-value**
Singula TRI	10.0120	0.0016	3.8579	0.0495	6.9185	0.0085

LR Analysis for TRI; OS and CR multivariate analysis; PFS univariate analysis.

9118 **Poster Session**

Use of brain radiotherapy as part of first course of treatment for NSCLC with de novo brain metastasis. *First Author: Rafael Arteta-Bulos, Cleveland Clinic Florida, Weston, FL*

Background: Loco-regional management of brain metastases from non-small cell lung cancer (NSCLC) are surgery and/or brain radiotherapy, either whole brain (WBRT) or stereotactic (SRS). We used a national registry to evaluate trends in the use of brain radiotherapy as part of the first course of management in patients diagnosed with de novo brain metastasis. **Methods:** We retrospectively analyzed the National Cancer Database (NCDB) to identify patients with NSCLC and de novo brain metastasis diagnosed from 2004-2016. We described the socio-demographic and clinical characteristics of this population, then used chi-squared testing to evaluate for an association between these variables and the use of brain radiotherapy (either SRS or WBRT). Significant variables ($p < 0.05$) were included in a multiple logistic regression model. **Results:** Of n = 41,454 patients with NSCLC and de novo brain metastasis, n = 27,949 (67.4%) received either SRS or WBRT as part of their first course of treatment, while n = 13,505 (32.6%) did not receive primary brain radiation. Of those that did not receive radiation: n = 9,927 (73.5%) were < 70 years old while n = 3,578 (26.5%) were ≥70. N = 11,081 (82.7%) were White, n = 1,550 (11.6%) were Black and n = 768 (5.7%) were Asian. Variables significantly associated with the use of primary brain radiotherapy at the multivariate level were: treatment facility type (p = 0.004), tumor histology (p < 0.001), clinical T-staging (p < 0.001), and clinical N-staging (p < 0.001). Age, sex, race, comorbidity, grade, insurance status, and setting (metro vs. rural vs. urban) were not significantly associated with the use of radiotherapy. Compared to patients treated at community cancer programs (CPs), those treated at comprehensive community CPs (OR 1.152, 95% CI 1.027-1.291, p = 0.015) and academic CPs (OR 1.242, 95% CI 1.104-1.398, p < 0.001) were more likely to receive primary brain radiotherapy. Patients with squamous NSCLC were less likely (OR 0.680, 95% CI 0.619-0.747, p < 0.001) to receive brain radiotherapy compared to those with adenocarcinoma. Finally, patients with advanced T-staging (p < 0.001) and N-staging (p < 0.001) were less likely (OR < 1) to receive brain radiotherapy as part of the first course of treatment. **Conclusions:** While insurance status and setting were not significantly associated with the use of brain radiotherapy, facility type was. Further research is needed to evaluate whether this is a true disparity in medical practice, or the differences can be explained by characteristics of the patient population undocumented by the NCDB (e.g. severity of brain metastasis). Additionally, patients with larger primary tumors were less likely to receive brain radiation as part of the first course of treatment, which may reflect the need for local therapy prior to treating metastatic sites. Research Sponsor: None.

9119 **Poster Session**

Clinicopathologic, genomic, and tumor microenvironment correlates of aneuploidy and immunotherapy outcomes in NSCLC. *First Author: Joao Victor Machado Alessi, Dana-Farber Cancer Institute, Boston, MA*

Background: Cancer aneuploidy, an unbalanced number of chromosomes, is associated with somatic mutation rate, expression of proliferative genes, and altered immune signaling. Whether aneuploidy correlates to a distinct immunophenotype or impacts clinical outcomes to immune checkpoint inhibitors (ICIs) in NSCLC is unclear. **Methods:** In NSCLCs which underwent targeted next-generation sequencing, we retrospectively analyzed the aneuploidy score (AS), defined as the sum of the number of altered chromosome arms. An unbiased recursive partitioning (URP) algorithm was used to investigate an AS cutoff to discriminate responders from non-responders to ICIs. Multiplexed immunofluorescence to quantify CD8+, Foxp3+, PD-1+, and PD-L1 expression was performed to determine differences in tumor immune cells subsets according to AS cutoff. **Results:** Among 436 NSCLCs identified, stage I tumors (median AS 1) had significantly lower median AS (mAS) than stage IV cancers (mAS 7, P < 0.001), stage III (mAS 4, P = 0.03), and numerically lower compared to stage II cancers (mAS 3, P = 0.18). We found no difference in the mAS across tumors with a PD-L1 tumor proportion score of ≥50%, 1-49%, or < 1% (mAS 5 vs 7 vs 6, respectively, P = 0.26), nor was there any correlation between aneuploidy and TMB when taken as continuous variables (Spearman R: 0.074, P = 0.12). A total of 279 advanced NSCLCs with available aneuploidy scores were treated with ICIs. An URP analysis identified an AS of 2 as the strongest discriminator of objective response to ICI. Compared to pts with an AS > 2 (N = 207, 74.2%), pts with AS ≤2 (N = 72, 25.8%) had a significantly higher objective response rate (ORR 43.0% vs 19.8%, P < 0.001), a significantly longer median progression-free survival (mPFS 6.2 vs 2.9 months, HR: 0.70 [95% CI: 0.52-0.94], P = 0.02), and a significantly longer median overall survival (mOS 19.8 vs 13.8 months, HR: 0.66 [95% CI: 0.47-0.94], P = 0.02) to treatment with ICIs. After adjusting for other variables such as performance status, presence of oncogenic driver mutation, PD-L1, TMB, and line of treatment, AS was significantly associated with improved mPFS (HR: 0.72 [95% CI: 0.52-0.99], P = 0.04) and mOS (HR: 0.64 [95% CI: 0.44-0.94], P = 0.02). By contrast, among pts who received first-line platinum doublet chemotherapy without ICI, an AS ≤2 (N = 29), when compared to an AS > 2 (N = 56), did not correlate with improved ORR (55.2% vs 44.6%, P = 0.4) or PFS (5.3 vs 4.8 months, HR 0.83 [95% CI: 0.5-1.3], P = 0.43). Among 179 NSCLCs profiled by multiplex immunofluorescence, compared to cancers with an AS > 2, those with low aneuploidy had significantly higher numbers of CD8+, Foxp3+, PD-1+ immune cells, and PD-1+ CD8+ T cell, both intratumorally and when looking at the total numbers of cells within the tumor and at the tumor-stroma interface. **Conclusions:** NSCLCs with low aneuploidy have a distinct immune microenvironment and more favorable outcomes to ICIs. Research Sponsor: None.

9120 **Poster Session**

Population-based impacts of new therapies on outcomes for stage IV non-small cell lung cancer. *First Author: Rebekah Rittberg, CancerCare Manitoba, Winnipeg, MB, Canada*

Background: Over 15 years, diagnostic and therapeutic algorithms for Stage IV non-small cell lung cancer (NSCLC) have dramatically progressed. While clinical trials demonstrate overall survival (OS) advantages, population level impact remains uncertain. Here we evaluate real world, population-based outcomes for Stage IV NSCLC to assess impact of changing therapies on referral, treatment patterns and OS, which may help explain ongoing stigma/nihilism. **Methods**: A retrospective cohort analysis was completed to evaluate *de novo* Stage IV NSCLC diagnosed in Manitoba from 2006 to 2015. We evaluated treatment received (not seen by specialist, saw a specialist but did not receive therapy, radiation therapy (RT) only, and systemic therapy (mutation unknown and known)) and treatment era of diagnosis (2006-2009, 2010-2013 and 2014-2015). Multivariable logistic regression assessed systemic therapy predictors. Kaplan-Meier curve and Cox proportional hazard models evaluated OS. **Results**: 3,601 patients were diagnosed with Stage IV NSCLC, 53% male. Only 21% received systemic therapy, mean age of 62. Within the cohort, 973 (27%) patients did not see a specialist, 610 (17%) saw a specialist but did not receive therapy, 1248 (35%) only received RT, and 771 (21%) received systemic therapy (17% mutation status unknown and 4% known). Younger patients and those with confirmed histology were more likely to see a specialist and receive treatment, each ($p < 0.001$). Patients who received systemic therapy had lower comorbidity and higher income quintile, each ($p < 0.001$). Median OS did not differ between treatment era with median OS of 3.0, 2.9 and 2.8 months for 2006-2009, 2010-2013 and 2014-2015 respectively, $p = 0.082$. When survival analysis was restricted to patients who received systemic therapy, median OS improved by era to 10.9, 11.2 and 15.6 months respectively, $p = 0.001$. Variables found to be independently associated with survival included treatment type, age, sex and comorbidity. **Conclusions**: Improved systemic therapy and molecular testing has improved OS for patients who receive systemic therapy. However, due to the large proportion of Stage IV NSCLC patients who never receive systemic therapy we do not see improved survival at a population level between treatment eras. Research Sponsor: CancerCare Manitoba Foundation.

9121 **Poster Session**

Clinicopathologic and genomic correlates of tumor-infiltrating immune cells and immunotherapy efficacy in NSCLC. *First Author: Joao Victor Machado Alessi, Dana-Farber Cancer Institute, Boston, MA*

Background: Tumor-infiltrating immune cells and PD-L1 expression are associated with improved clinical outcomes in patients (pts) with NSCLC treated with immune checkpoint inhibitors (ICIs). However, as tumor-infiltrating immune cells are not a well-established biomarker for NSCLC, further data are needed to integrate and identify clinicopathological and genomic factors that influence the tumor microenvironment. **Methods:** We collected clinicopathologic and genomic data from pts with NSCLC who underwent multiplexed immunofluorescence. Uniform Manifold Approximation and Projection (UMAP) was used to identify distinct immunophenotypic clusters according to the number of intratumoral PD-1+ immune cells (ICs), CD8+, and Foxp3+ T cells, as well as PD-L1 on tumor and immune cells. An unbiased recursive partitioning (URP) algorithm was used to investigate an optimal cluster with respect to objective response rate (ORR) in the subset of pts treated with ICIs. **Results:** Among 304 pts, UMAP identified 5 clusters: PD-L1-high with high vs low CD8+ and PD-1+ ICs (clusters A & B, respectively); PD-L1-low with high vs low CD8+ and PD-1+ ICs (clusters C & D respectively); PD-L1-low and moderate levels of CD8+ and PD-1+ ICs (cluster E). Clinicopathological characteristics of the clusters shown in Table. URP analysis identified immune rich clusters A and C as optimal responders to ICIs. From the start of ICIs, we observed a significantly higher ORR (53.3% vs 4.3%; $P<0.001$), a significantly longer median progression-free survival (mPFS 25.6 vs 3.7 months; HR: 0.12 [95% CI: 0.05-0.32]; $P<0.001$), and longer median overall survival (mOS 45.1 vs 22.3 months; HR: 0.25 [95% CI: 0.1-0.68]; $P=0.006$) in clusters A + C (N=15) vs other clusters (N=23). After adjusting for other variables such as performance status, histology, presence of oncogenic driver mutation, and line of treatment, clusters A + C were significantly associated with improved mPFS (HR: 0.08 [95% CI: 0.03-0.24], $P<0.001$) and mOS (HR: 0.11 [95% CI: 0.03-0.40], $P<0.001$). **Conclusions:** Incorporation of multiplex immunofluorescence may improve prediction of response and resistance to immunotherapy in NSCLC. Research Sponsor: None.

	Clusters					
Clinical Characteristics	A N=54	B N=53	C N=64	D N=67	E N=69	P
PD-L1 expression	High	High	Low	Low	Low	
CD8+, PD-1+	High	Low	High	Low	Moderate	
Smoking status	50 (92.6)	39 (73.6)	58 (90.6)	45 (67.2)	46 (67.7)	**<0.001**
Current/Former	4 (7.4)	14 (26.4)	6 (9.4)	22 (32.8)	23 (33.3)	
Never						
TMB, median (mut/Mb)	9.6	8.4	9.1	6.1	6.8	0.06
Oncogene Driver	14 (41.2)	10 (28.5)	22 (48.8)	9 (20.5)	14 (29.8)	**<0.001**
KRAS	4 (11.8)	9 (25.7)	3 (6.7)	9 (29.5)	21 (44.7)	
EGFR	4 (11.8)	0 (0.0)	3 (6.7)	0 (0.0)	2 (4.2)	
BRAF	4 (11.8)	8 (22.9)	4 (8.9)	8 (18.2)	4 (8.5)	
Other drivers	8 (23.4)	8 (22.9)	13 (28.9)	14 (31.8)	6 (12.8)	
None identified						
Stages	30 (55.6)	18 (34.0)	45 (70.3)	24 (35.8)	39 (56.5)	**0.02**
I/II	24 (44.4)	35 (66.0)	19 (29.7)	43 (64.2)	30 (43.5)	
III/IV						

9122 **Poster Session**

Patterns of survival in NSCLC with de novo brain metastasis: SRS, WBRT, and no radiotherapy cohorts. *First Author: Diana Saravia, Cleveland Clinic Florida, Weston, FL*

Background: Prognostic determinants in metastatic non-small cell lung cancer (mNSCLC) include numerous sociodemographic and clinical characteristics. We provide granular, real-world survival data in different cohorts of this heterogeneous population, stratifying by: age, Charlson/Deyo scoring (CDS) of comorbidity, tumor histology, and use of immunotherapy. **Methods**: This retrospective analysis uses the National Cancer Database (NCDB) to explore patterns of survival in patients diagnosed between 2010-2016 with mNSCLC involving the brain. Kaplan-Meier (KM) modeling was used to evaluate for differences in overall survival (OS) between 3 cohorts of patients: those undergoing 1) stereotactic radiosurgery (SRS), 2) whole-brain radiotherapy (WBRT), and 3) those not undergoing brain radiotherapy (NR) as part of the first course of treatment. As per Table, we ran 8 KM models to generate median OS (mOS) data across stratifications for age (<70 vs. ≥ 70), CDS (0-1 vs. 2-3), tumor histology (adenocarcinoma vs. squamous), and use of immunotherapy (yes vs. no). We provide a ranked order of these 3 cohorts by mOS ('survival sequence', or 'SS'), as well as differences in mOS ('ΔmOS') between NR and WBRT – the two cohorts most comparable in life expectancy. **Results:** A total of n=38,119 patients were included in this study. Most received WBRT (n=18,052, 47.4%), n=6,562 (17.2%) received SRS, while n=13,505 (35.4%) did not receive brain radiation as part of their first course of treatment. In all subgroups, patients treated with SRS for brain metastasis had the highest mOS. Survival for those receiving WBRT was better or comparable (difference in mOS <0.5 months) to those that did not receive radiotherapy, except in patients aged ≥ 70 (SS: NR > WBRT; KM p-value <0.05; ΔmOS of 1.6 months), those with Charlson-Deyo comorbidity scores of 2-3 (SS: NR > WBRT; KM p-value <0.05; ΔmOS: 0.6 months), those with squamous carcinoma (SS: NR > WBRT; KM p-value <0.05; ΔmOS: 0.7 months), and those already receiving immunotherapy (SS: NR > WBRT; KM p-value <0.05; ΔmOS: 0.6 months). **Conclusions:** SRS for de novo brain metastases is associated with improved OS in mNSCLC. In contrast, the burden of WBRT may outweigh the survival benefit it affords in patients ≥ 70, and those with comorbidities. Squamous cell carcinomas may be associated with more radio-resistance than adenocarcinomas to WBRT. Finally, as previously described in melanoma, the survival benefit afforded by brain radiotherapy may be lower in patients on immunotherapy. Research Sponsor: None.

Stratifications	Kaplan Meier Models	NR mOS	SRS mOS	WBRT mOS	SS	ΔmOS (WBRT-NR)
Age	1) <70	8.9	14.5	9.2	SRS > WBRT > NR	0.3
	2) ≥ 70	7.7	11.7	6.1	SRS > NR > WBRT	-1.6
CDS	3) 0-1	8.8	13.8	8.7	SRS > NR = WBRT	-0.1
	4) 2-3	7.1	10.6	6.5	SRS > NR > WBRT	-0.6
Histology	5) Adenocarcinoma	9.9	15.5	9.5	SRS > NR > WBRT	-0.4
	6) Squamous	6.9	9.3	6.2	SRS > NR > WBRT	-0.7
Immunotherapy	7) None	8.5	13.3	8.4	SRS > NR = WBRT	-0.1
	8) Received	11.5	15.7	10.9	SRS > NR > WBRT	-0.6

9123 **Poster Session**

Analysis of patterns of care and benefit of thoracic radiotherapy for patients with stage IV NSCLC in the immunotherapy-era from a national hospital-based registry. *First Author: Michael Kharouta, University Hospitals, Case Medical Center - Seidman Cancer Center, Cleveland, OH*

Background: Metastatic non-small cell lung cancer (mNSCLC) has classically been treated with platinum-doublet chemotherapy. Recent studies have established immunotherapy as an integral part of therapy for mNSCLC without targetable mutations. There are limited data on the role of consolidative thoracic radiotherapy (TRT) for patients with mNSCLC in the immunotherapy-era. A secondary analysis of KEYNOTE-001 showed significant improvement in overall survival in patients who received radiotherapy with pembrolizumab compared to patients not previously receiving radiotherapy. **Methods:** We queried the National Cancer Database (NCDB) for patients with metastatic presentation, stage IVA/IVB non-small cell lung cancer between the ages of 18-90 years treated between 2012-2017 with a combination of chemotherapy, immunotherapy, and thoracic radiotherapy. Patients with unknown treatment status, follow up time, or vital status were excluded. Overall survival (OS) was estimated using the Kaplan-Meier method and compared between treatment groups utilizing log-rank testing. A 3:1 nearest-neighbor propensity-score matching was performed utilizing clinical and demographic covariates to reduce the impact of potential confounders of overall survival on the probability of receipt of TRT. Cox proportional hazards regression was used to identify predictors of overall survival. **Results:** A total of 81,382 patients were identified that met inclusion criteria. The median age was 68 (18-90) years. The majority of patients (n = 51,681, 64%) had chemotherapy, while 7,929 (10%) patients received immunotherapy, and 15,984 (20%) received TRT. The median follow-up was 6.18 (range 0-76.9) months. For the entire cohort of patients receiving immunotherapy, 2 year OS was 29.4% with TRT compared to 32.7% without. Following propensity matching by age, sex, race, and comorbidity score, a total number of 4,264 patients receiving immunotherapy were matched. The 2 year OS was 27.7% in patients receiving TRT and immunotherapy vs. 22.2% in patients with immunotherapy alone ($p = 0.004$). On multivariable analysis receipt of TRT was a significant predictor of OS after adjustment for age, race, comorbidity score, sex, and median income ($p = 0.0003$, HR 0.87, 95% CI 0.80 - 0.94). For patients receiving BED10 $>$ 39 Gy (equivalent to 30 Gy in 10 fractions), 2 year OS was significantly improved at 37.0% vs 18.1% ($p < 0.0001$). **Conclusions:** In patients with mNSCLC, the addition of TRT to immunotherapy is associated with improved overall survival at 2 years. Receipt of a higher BED10 is associated with further improved survival. Selection of mNSCLC patients receiving immunotherapy for TRT approaching definitive doses warrants further investigation. Data from prospective, randomized trials may better elucidate this benefit and identify a potential mechanism. Research Sponsor: None.

9124 **Poster Session**

Effect of continuing osimertinib with chemotherapy in the post-progression setting on progression-free survival among patients with metastatic epidermal growth factor receptor (EGFR) positive non-small cell lung cancer. *First Author: Tejas Patil, University of Colorado Cancer Center, Aurora, CO*

Background: Continuing a 1st generation EGFR TKI with chemotherapy upon TKI progression was not shown to be beneficial in the IMPRESS trial. However, the validity of this approach with osimertinib remains under explored. We attempted to characterize the efficacy of continuing osimertinib with chemotherapy in the post-progression setting. **Methods:** A single-center retrospective review of patients with metastatic EGFR mutant NSCLC who had progressed on osimertinib was performed. Clinical characteristics and treatment outcomes were noted. Progression free survival (PFS), duration of treatment (DOT), overall survival (OS) and rates of intracranial progression were captured. ANOVA or a Fisher exact test were used to identify associations between cohort characteristics and treatment outcomes. Differences in PFS, DOT and OS were assessed using a log-rank test. A Cox proportional hazard model was used to adjust for potential confounders. **Results:** 73 patients with EGFR mutant NSCLC with post-osimertinib treatment outcomes were identified. Cohort characteristics are summarized in Table. Median duration of follow up was 41 months. Upon progression, osimertinib was discontinued in 34 patients (Cohort A) and continued with next line of therapy in 39 patients (Cohort B). Survival analyses were adjusted for prior lines of therapy, use of platinum doublet chemotherapy, and use of immune checkpoint inhibitors in the post-progression setting. After adjusting for covariates, continuing osimertinib post-progression was associated with an improved PFS (7 vs 4 months; HR 0.58; 95% CI 0.34 – 1.00; p = 0.003) and DOT (7 vs 4 months; HR 0.52; 95% CI 0.31 – 0.87; p = 0.006). There was no difference in OS between Group A and B (52 vs 41 months; HR 0.73; 95% CI 0.43 – 1.24; p = 0.234). Rates of intracranial progression were similar between Group A and B (28% vs 23%; p = 0.649). **Conclusions:** After adjusting for covariates, continuing osimertinib with chemotherapy in the post-progression setting was associated with a significant difference in PFS and DOT, but with no differences in OS. Continuing osimertinib does not appear to influence the rate of subsequent intracranial progression. Prospective studies are needed to identify the optimal practice pattern. Research Sponsor: International Association for the Study of Lung Cancer (IASLC).

Variables	Values	Osimertinib discontinued (%)	Osimertinib continued (%)	P-value
Sex	Female	22 (64%)	27 (69%)	0.803
	Male	12 (35%)	12 (30%)	
Age (years)		61 (36 – 86)	61 (30 – 78)	0.512
Smoking Status	Never	28 (82%)	29 (74%)	
	Former	6 (18%)	10 (26%)	0.317
EGFR	Drug-sensitizing	32 (94%)	33 (85%)	0.110
	Atypical	2 (6%)	6 (15%)	
Prior lines of therapy		2 (1 – 6)	2 (1 - 8)	0.934
ECOG	0-1	32 (94%)	31 (79%)	0.468
	>2	2 (6%)	8 (21%)	
Brain metastases upon osimertinib progression	Present	6 (18%)	6 (15%)	0.704
	Absent	16 (47%)	15 (38%)	
	Not evaluated	12 (35%)	18 (46%)	

9125 **Poster Session**

Lung cancer in HIV versus non-HIV population: Nationwide analysis of mortality, morbidity, demographics, and healthcare utilization. *First Author: Muhammad Junaid Tariq, Department of Internal Medicine, John H. Stroger Jr. Hospital of Cook County, Chicago, IL*

Background: Lung cancer (LC) is the most common non-AIDS defining cancer with a high cancer-related mortality in patients with HIV. With improving survival in HIV patients, the incidence of LC is increasing. We attempted to evaluate the characteristics and outcomes, including healthcare utilization in patients with HIV-LC compared to non-HIV-LC using a national sample. **Methods:** Healthcare Cost and Utilization Project National Inpatient Sample (HCUP-NIS) was queried to identify HIV and non-HIV-LC admissions between 2016-2018. We studied socio-demographic differences, medical comorbidities (including hypertension (HTN), diabetes (DM), Coronary artery disease (CAD), Chronic kidney disease (CKD), Heart failure (HF), dialysis (HD), COPD), all-cause mortality, mean length of stay (LOS), mean total hospital charges (THC). Secondary outcomes included sepsis, septic shock, acute kidney injury (AKI), influenza, pneumonia, respiratory failure, lung collapse, ICU care, hemoptysis, anemia, pain, and protein energy malnutrition (PEM). Statistics were performed using the t-test, univariate and multinomial logistic regression. **Results:** A total 4,105 HIV-LC and 1,204,365 non-HIV-LC admissions were identified. HIV-LC were younger (mean age 48.7 vs 53.4 $p<0.05$), male (67% vs 51%, $p<0.01$), African American (52% vs 12% $p<0.01$), on Medicaid (35% vs 10% $p<0.01$), from lowest quartile income zip codes (51% vs 30% $p<0.01$). HIV-LC had significantly high rates of CKD and HD ($p<0.05$) while non-HIV-LC had significantly higher rates of HTN, DM, Dyslipidemia, CAD, COPD, obesity, HF and smoking (all $p<0.05$). Odds of adjusted all-cause mortality were significantly lower in HIV-LC (aOR 0.47 CI 0.36-0.63 $p<0.001$). HIV-LC had higher LOS (8.1 vs 6 days $p<0.001$) and higher THC ($83,328 vs $65,642 $p<0.001$), amounting to over $72 million over 3 years. Significantly different secondary outcomes between the two groups are shown in Table, the rest were similar between the groups. **Conclusions:** HIV-LC patients were younger, minority with a significantly lower all-cause mortality despite higher rates of complications and significantly higher LOS and THC compared to non-HIV-LC cohort. A higher comorbidity burden may be responsible for higher mortality in the non-HIV group while higher rates of secondary complications, CKD, HD may be driving up healthcare utilization in HIV-LC. More studies are needed to clarify these findings. Research Sponsor: None.

	HIV-LC	non-HIV-LC	p-value
Sepsis	18.5%	12.6%	0.00
Septic shock	19%	14.2%	0.00
AKI	16.5%	3.2%	0.00
Pneumonia	27.8%	21.1%	0.00
Hemoptysis	5%	3.4%	0.01
Anemia	42.4%	35.6%	0.00
ICU care	7.7%	5.9%	0.049
PEM	37.2%	23.2%	0.00

TPS9126 **Poster Session**

Blood-based biomarker analysis in high PD-L1 expressing NSCLC treated with PD-1/PD-L1 based therapy with or without the addition of platinum-based chemotherapy. *First Author: Mary J. Fidler, Rush University Medical Center, Chicago, IL*

Background: Immunotherapy directed against the programmed death-1 / ligand-1 (PD-1/L1) axis has revolutionized the treatment of advanced non-small cell lung cancer (aNSCLC). Tumor PD-L1 is currently the only biomarker validated for predicting patient response to front line PD-1/L1 directed immunotherapy, yet 20% of patients with ≥50% PD-L1 expression die within six months of starting therapy (Reck et al. 2016). Blood-based agents such as autoantibodies and circulating inflammatory biomarkers have stratified patient outcomes on anti-PD-1/L1 immunotherapy in preliminary studies (Tarhoni, Kollipara et al. 2019; Tarhoni, Fidler et al. 2019). Moreover, a serum-based proteomic test that uses mass spectrometry and machine learning to provide three classifications (Good, Intermediate and Poor) has stratified non-treatment naïve aNSLCC patients treated with nivolumab based on their outcomes (Mueller et al. 2020) and identified a subset of patients who progressed rapidly. This study will evaluate these blood-based biomarkers as predictors of response and early progression in patients with >50% PD-L1 positive aNSCLC treated with immunotherapy regimens. **Methods:** This is a prospective, observational, multicenter study (NCT04676386) designed to assess biomarkers (serum and plasma) as predictive of early progression in 390 patients with aNSCLC treated with anti-PD 1/PD-L1 immunotherapy with or without platinum-based chemotherapy. Key eligibility criteria are treatment naïve aNSCLC with tumor biopsy PD-L1 tumor proportion score > 50%, Eastern Cooperative Oncology Group performance status (ECOG PS) 0-2, and ability to consent to participate. Prior to enrollment, tumor specimens will be tested for PD-L1 expression according to participating centers' standard operating procedures. For each treatment cohort of 195 patients, enrollment will proceed in sub-cohorts to ensure a population with 20% patients with ECOG PS2 and a total of 40 patients with squamous cell carcinoma per treatment arm. Patients will be followed for a maximum of 3 years. Blood draw for biomarker assessment will be performed prior to treatment initiation, start of 3rd cycle and investigator assessed progression. Biomarker analysis will be performed retrospectively. As a secondary objective, this study will evaluate proteomic test performance in predicting early overall survival (OS) and rapid progression, and in stratifying patient survival and response. Exploratory analyses will correlate baseline and serial circulating protein analytes and autoantibodies with the proteomic test, response measures (RECIST 1.1) and toxicities. Enrollment opened in February 2021. Clinical trial information: NCT04676386. Research Sponsor: Biodesix, Inc.

TPS9127 **Poster Session**

A randomized, phase 3 study of datopotamab deruxtecan (Dato-DXd; DS-1062) versus docetaxel in previously treated advanced or metastatic non-small cell lung cancer (NSCLC) without actionable genomic alterations (TROPION-Lung01). *First Author: Kiyotaka Yoh, Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa-Shi, Chiba, Japan*

Background: Treatment options are limited for patients with advanced/metastatic NSCLC without driver genomic alterations after failure of a platinum-based chemotherapy and immunotherapy; median survival is < 1 year. Datopotamab deruxtecan (Dato-DXd; DS-1062) is an antibody-drug conjugate consisting of a humanized anti-TROP2 IgG1 monoclonal antibody attached to a topoisomerase I inhibitor payload via a tetrapeptide-based cleavable linker. Results from the ongoing phase 1 study (TROPION-PanTumor01; Spira, WCLC 2020) demonstrated an overall response rate (ORR) of 21%, a disease control rate (DCR) of 67%, and a preliminary median progression-free survival (PFS) of 8.2 months (all by blinded independent central review [BICR]), with a manageable safety profile, in patients with NSCLC who were treated with 6 mg/kg of Dato-DXd. This phase 3 study (NCT04656652) will compare the efficacy of Dato-DXd with that of docetaxel as 2/3L therapy in patients with advanced/metastatic NSCLC. **Methods:** TROPION-Lung01 is an open-label, phase 3, randomized study of Dato-DXd vs docetaxel in patients with advanced/metastatic NSCLC without *EGFR*, *ALK*, or other actionable genomic alterations. Patients must have been previously treated with platinum-based chemotherapy and a PD-(L)1 monoclonal antibody in combination or sequentially and have radiographic disease progression on or after the most recent therapy. Those with asymptomatic and stable/treated brain metastases are eligible. A tumor specimen is required for biomarker analyses. Patients (N = 590) are randomized 1:1 to either Dato-DXd 6 mg/kg or docetaxel 75 mg/m^2 given intravenously on day 1 of each 3-week cycle. Randomization is stratified by histology (squamous vs nonsquamous), immunotherapy in last regimen (yes vs no), and region (US/Japan/Western Europe vs rest of world). Treatment continues until disease progression or intolerance or other discontinuation criteria are met. The study will be conducted globally at approximately 184 study sites. Dual primary endpoints are PFS by BICR and overall survival. Secondary outcome measures include PFS by investigator, ORR, duration of response, DCR, and time to response (all assessed by BICR and by investigator per RECIST version1.1), patient-reported outcomes, safety, pharmacokinetics, and proportion of patients who develop antidrug antibodies. Biomarkers will be evaluated for potential associations with efficacy. Clinical trial information: NCT04656652. Research Sponsor: Daiichi Sankyo, Inc.

TPS9128 **Poster Session**

AdvanTIG-302: Anti-TIGIT monoclonal antibody (mAb) ociperlimab (OCI) plus tislelizumab (TIS) versus pembrolizumab (PEM) in programmed death ligand-1 (PD-L1) selected, previously untreated, locally advanced, unresectable or metastatic non-small cell lung cancer (NSCLC). *First Author: Mark A. Socinski, Advent Health Hematology and Oncology, Orlando, FL*

Background: Monotherapy with programmed death 1 (PD-1)/PD-L1 antibodies has improved clinical outcomes for patients (pts) with non-oncogenic driven NSCLC but clinical responses are limited by primary and secondary resistance, and improvements in durability of response are required. T-cell immunoreceptor with immunoglobulin and immunoreceptor tyrosine-based inhibition motif domain (TIGIT) is a co-inhibitory, immune checkpoint receptor upregulated on T-cells and natural killer cells in multiple solid tumors, which can inhibit anticancer immune responses. OCI (BGB-A1217) is a novel, humanized mAb that binds to TIGIT with high affinity and specificity, which has demonstrated competent binding with C1q and all Fcγ receptors while inducing antibody-dependent cellular cytotoxicity. Preclinical and clinical studies suggest that dual targeting with anti-TIGIT and anti-PD-1 antibodies produces synergistic immune cell activation and enhanced antitumor activity. **Methods:** AdvanTIG-302 is a Phase 3, multicenter, international, randomized, double-blind study (NCT04746924) investigating OCI in combination with TIS compared with PEM in adult pts ($\geq$ 18 years of age) with PD-L1 selected, previously untreated, locally advanced, unresectable or metastatic NSCLC without oncogenic *EGFR* or *ALK* mutation. Approximately 605 pts will be randomized 5:5:1 to receive: OCI 900 mg intravenously (IV) plus TIS 200 mg IV every three weeks (Q3W; Arm A), PEM 200 mg IV plus placebo IV Q3W (Arm B) or TIS 200 mg IV plus placebo IV Q3W (Arm C). Pts will be treated until disease progression, loss of clinical benefit, intolerable toxicity or withdrawal of consent. Stratification factors include histology (squamous vs non-squamous) and region (Asian vs non-Asian). Crossover is not permitted. Key eligibility criteria include histologically confirmed disease, PD-L1 expression $\geq$ 50%, no known *EGFR* or *ALK* mutations and no prior checkpoint inhibitor therapy. Dual primary endpoints are investigator-assessed progression-free survival (PFS; RECIST v1.1) and overall survival (Arms A and B) in the Intention-to-Treat population. Secondary endpoints include PFS (assessed by Blinded Independent Review Committee), investigator-assessed overall response rate and duration of response, safety and tolerability, and patient-reported health-related quality of life (EORTC-QLQ-C30, QLQ-LC13 and EQ-5D-5L; Arms A and B). Exploratory endpoints include disease control rate, clinical benefit rate and time to response. This study will also evaluate the association between biomarkers and response or resistance. Study enrollment has begun and recruitment is ongoing. Clinical trial information: NCT04746924. Research Sponsor: This study was sponsored by BeiGene, Ltd. Medical writing support, under the direction of the authors, was provided by Jessica Jones, PhD, of Ashfield Medcomms, an Ashfield Health company, and funded by BeiGene, Ltd.

TPS9129 **Poster Session**

KRYSTAL-12: A randomized phase 3 study of adagrasib (MRTX849) versus docetaxel in patients (pts) with previously treated non-small-cell lung cancer (NSCLC) with KRAS^{G12C} mutation. *First Author: Tony S. K. Mok, State Key Laboratory of Translational Oncology, Chinese University of Hong Kong, Hong Kong, China*

Background: Despite significant advances in chemotherapy and immunotherapy for advanced NSCLC, the majority of pts ultimately develop progressive disease associated with poor outcomes. KRAS is a key mediator of the RAS/MAPK signaling cascade that promotes cell growth and proliferation. KRAS^{G12C} mutations occur in 14% of NSCLC (adenocarcinoma), and mutations in KRAS are associated with a poor prognosis. Although KRAS has historically been undruggable, recent research into the development of agents that specifically bind mutant KRAS has led to the development of direct inhibitors of KRAS^{G12C}. Adagrasib, an investigational agent, is a potent, covalent inhibitor of KRAS^{G12C} that irreversibly and selectively binds to and locks KRAS^{G12C} in its inactive state. Adagrasib was optimized for favorable pharmacokinetic (PK) properties, including oral bioavailability, long half-life (~24 h), and extensive tissue distribution. Initial results have demonstrated encouraging antitumor activity and tolerability of adagrasib monotherapy in pts with NSCLC harboring a KRAS^{G12C} mutation. **Methods:** KRYSTAL-12 is a multicenter, randomized Phase 3 study evaluating the efficacy of adagrasib (600 mg BID) vs docetaxel in pts with advanced NSCLC harboring a KRAS^{G12C} mutation who have progressed during or after treatment with a platinum-based regimen and an immune checkpoint inhibitor. The study is designed to demonstrate improvement in the dual primary endpoints of progression-free survival (PFS) and overall survival (OS). Secondary endpoints include safety, objective response rate (ORR) per RECIST 1.1, duration of response (DOR), plasma PK parameters of adagrasib, and patient-reported outcomes (PROs). The study will also explore correlations between gene alterations (at baseline and upon development of treatment resistance) and efficacy. Approximately 450 patients will be randomized in a 2:1 ratio to receive adagrasib or docetaxel and will be stratified by region (United States/Canada vs other countries) and sequential vs concurrent administration of prior platinum-based chemotherapy and anti–PD-1/PD-L1 antibody. The planned sample size is sufficiently powered for the hypothesized treatment effect of the endpoints. Pts will receive study treatment until disease progression, unacceptable adverse events, investigator decision to terminate treatment, or patient withdrawal. This study is currently enrolling and will be open at sites in the United States, Europe, and Asia. Clinical trial information: NCT04685135. Research Sponsor: Mirati Therapeutics, Inc.

TPS9130 **Poster Session**

Camrelizumab monotherapy or in combination with apatinib for PD-L1-positive advanced pulmonary sarcomatoid carcinoma: A multicenter, open-label, single-arm, phase II study. *First Author: Mingfang Zhao, Department of the Second Medical Oncology, The First Hospital of China Medical University, Shenyang, China*

Background: Pulmonary sarcomatoid carcinoma (PSC) is a rare subtype of non-small cell lung cancer (NSCLC) with a fairly poor prognosis. As a highly aggressive malignancy, PSC is insensitive to conventional chemotherapy or radiotherapy and no optimal treatment for PSC has been established yet. Immune checkpoint inhibitors (ICIs) were documented to possess encouraging therapeutic efficacy in PSC patients, which is demonstrated to be associated with high expression of programmed death-ligand 1 (PD-L1) in PSC. However, because of the rarity of PSC, most of the existed data were derived from case repots which could not reflect the true clinical efficacy of ICIs for PSC treatment. This clinical trial was designed to investigate the clinical outcomes of camrelizumab in treating PD-1-positive PSC. Apatinib may be used simultaneously based on the expression level of PD-L1 in PSC as the combination of camrelizumab and apatinib exhibited treatment potential in NSCLC in previous researches. **Methods:** In this multicenter, open-label, single-arm, phase II study conducted in 44 sites in China, 30 patients with an age of 18-80 years old, an Eastern Cooperative Oncology Group (ECOG) performance score of 0–2, positive PD-L1 expression, no EGFR, ALK, ROS1, and MET gene mutations, and histologically or cytologically confirmed stage IIIB-IV PSC regardless of prior lines of standard therapy will be enrolled. Patients with PD-L1 expression 1-49% will receive Camre (200 mg, IV, Q3W) and Apa (250mg, QD). Patients with PD-L1 expression$\geq$50% receive Camre (200 mg IV Q3W) alone. The treatment will continue until a maximum treatment duration of 36 months, disease progression, intolerable toxicity, death or consent withdrawal. The primary endpoint is objective response rate (ORR). The secondary endpoints are progression-free survival (PFS), overall survival (OS), disease control rate (DCR), time to objective response (TTR), duration of response (DOR) and safety. This study is ongoing. Clinical trial information: ChiCTR2000032649, China. Research Sponsor: None.

TPS9131 **Poster Session**

A multicenter, randomized, double-blind study of gefitinib in combination with anlotinib or placebo in previously untreated patients with EGFR mutation-positive advanced non-small cell lung cancer (FL-ALTER). *First Author: Li Zhang, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Department of Medical Oncology, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Preclinical and clinical evidence has demonstrated that the dual blockade of the EGFR and VEGF pathways is a viable strategy in the EGFR-mutated advanced NSCLC population. Anlotinib is an oral multi-targeted tyrosine kinase inhibitor (TKI) that effectively inhibits VEGFRs, FGFRs, PDGFRs, c-kit and MET. It has been proved to be safe and effective in advanced lung cancer after second-line standard chemotherapy failure. A cohort study of Anlotinib plus Erlotinib has shown a favorable safety profile and promising antitumor activity with an objective response rate (ORR)92.6%. This phase III study aims to evaluate the efficacy and safety of Anlotinib or placebo plus Gefitinib in patients(pts) with untreated EGFR-mutated metastatic NSCLC. **Methods:** Eligible pts were aged 18~75 years old, had stage IIIB or IV NSCLC, with an EGFR 19del or 21L858R mutation, an ECOG PS of 0 or 1, measurable lesion according to RECIST v1.1 and adequate organ function. We randomly assigned eligible pts in a 1:1 ratio to receive oral Gefitinib (250 mg QD) plus either Anlotinib (12 mg QD from day 1 to 14 of a 21-day cycle) or matching placebo until progressive disease or unacceptable toxicity. Randomization was done by an interactive web response system with a computer-generated sequence and stratified by EGFR mutation status, gender, ECOG PS and pathological type . The primary endpoint is progression-free survival(PFS). Secondary endpoints include overall survival, ORR, disease control rate, time to progression, duration of response, quality of life and the safety profile. The peripheral blood of the pts will be detected three times by polygenic detection to monitor the resistance mechanism (before treatment, during the first evaluation, during tumor progression, each time 10ml peripheral blood). Independent Data Monitoring Committee and Independent Review Committee will be used in this study. According to previous report (Erlotinib plus Bevacizumab vs. Erlotinib alone: 16.0 vs. 9.7 mos, HR 0.54, *Lancet Oncol, 15(11):1236-1244*), the sample size was determined based on a median PFS of 15 months for the Anlotinib + Gefitinib group and median PFS of 10 months for the Placebo + Gefitinib group. To achieve 80% power at a two-sided α = 0.05 and an anticipated dropout rate of 20%, 310 patients (with 192 events required for the analyses) were needed. In total, 310 patients will be enrolled in this trial at 16 sites in China. From April 2019, 224 patients have been enrolled. Clinical trial information: NCT04028778. Research Sponsor: None.

TPS9132 **Poster Session**

CHRYSALIS-2: A phase 1/1b study of lazertinib as monotherapy and in combination with amivantamab in patients with EGFR-mutant NSCLC. *First Author: Catherine A. Shu, Columbia University Medical Center, New York, NY*

Background: Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) have improved clinical outcomes for patients with EGFR mutant (EGFRm) non-small cell lung cancer (NSCLC); however, patients will inevitably progress due to acquired resistance mutations. Lazertinib is a potent, brain-penetrant, 3rd-generation EGFR TKI with efficacy against activating EGFR and resistance T790M mutations. Amivantamab is an EGFR-MET bispecific antibody with immune cell-directing activity that targets activating EGFR and MET mutations. Synergistic inhibition of the EGFR by targeting the receptor's extracellular domain with amivantamab and the kinase domain with lazertinib, may lead to more potent inhibition of the EGFR pathway and potentially delay resistance. In the ongoing CHRYSALIS phase 1 study (NCT02609776), preliminary antitumor activity has been demonstrated with the combination of lazertinib and amivantamab in patients with treatment-naïve and osimertinib-relapsed EGFRm NSCLC (Cho *Ann Oncol* 2020;31:S813). **Methods:** CHRYSALIS-2 is an ongoing phase 1/1b open-label study of lazertinib as monotherapy and in combination with amivantamab in patients with advanced EGFRm NSCLC (NCT04077463; https://clinicaltrials.gov/ct2/show/NCT04077463). Phase 1 of the study has confirmed the safety and tolerability of lazertinib monotherapy in Japanese patients. The objective of phase 1b is to characterize the preliminary efficacy of lazertinib in combination with amivantamab in subpopulations of patients with EGFRm NSCLC (Phase 1b Expansion Cohorts) at the recommended combination dose of 1050 mg (1400 mg, ≥80 kg) IV amivantamab dosed weekly in cycle 1 (28-day cycle), every other week thereafter, and 240 mg oral lazertinib QD. Global enrollment in Phase 1b Expansion Cohorts is currently ongoing. Expansion Cohort A is enrolling patients who have progressed on 1st or 2nd-line osimertinib followed by platinum chemotherapy; Expansion Cohort B is enrolling patients with EGFR exon 20 insertion (Exon20ins) mutation who have progressed on prior therapy; and Expansion Cohort C is enrolling patients with uncommon non-Exon20ins EGFR mutations (i.e., S768I, L861Q, G719X) who are treatment-naïve or received 1st or 2nd-generation EGFR TKI as last therapy. The primary endpoints of the study are frequency of dose-limiting toxicity for phase 1 and 1b combination cohorts, and overall response rate for phase 1b expansion cohorts. Key secondary endpoints include safety (adverse events), pharmacokinetics, duration of response, clinical benefit rate, progression-free survival, and overall survival. Safety assessments will include monitoring AEs, clinical laboratory tests, ophthalmologic examination, ECG, and ECHO/MUGA. Blood samples will be collected to access PK. Tumor response will be assessed every 6 weeks by the investigator using RECIST, v1.1. Clinical trial information: NCT04077463. Research Sponsor: Janssen R&D.

TPS9134 **Poster Session**

CONTACT-01: A phase III, randomized study of atezolizumab plus cabozantinib versus docetaxel in patients with metastatic non-small cell lung cancer (mNSCLC) previously treated with PD-L1/PD-1 inhibitors and platinum-containing chemotherapy. *First Author: Joel W. Neal, Stanford Cancer Institute, Stanford, CA*

Background: Patients with mNSCLC who progress on anti–PD-L1/PD-1 therapy administered in combination with or after platinum-based chemotherapy (PBC) are mainly treated with docetaxel or pemetrexed monotherapy. These therapies only have modest clinical activity, leaving a high unmet medical need. Cabozantinib, a tyrosine kinase inhibitor (TKI), promotes an immune-permissive environment and may enhance the efficacy of PD-L1/PD-1 inhibitors, offering a promising second/third-line therapeutic opportunity for patients with mNSCLC. In a Phase Ib multi-cohort study (COSMIC-021; NCT03170960), cabozantinib plus atezolizumab (anti–PD-L1) showed an acceptable safety profile and promising efficacy (ORR: 27%; mDOR: 5.7 mo [range: 2.6-6.9]; disease control rate [CR + PR + SD]: 83%) in 30 patients with mNSCLC who had progressed after prior anti–PD-L1/PD-1 therapy plus chemotherapy (Neal et al. J Clin Oncol 2020). The Phase III CONTACT-01 study will further evaluate the efficacy and safety of atezolizumab plus cabozantinib versus docetaxel monotherapy in patients with mNSCLC who have progressed during or after prior treatment with anti–PD-L1/PD-1 therapy and PBC. **Methods:** CONTACT-01 (NCT04471428) is a Phase III, multi-center, randomized, open-label study that will enroll ≈350 patients from 150 to 200 sites internationally. Key eligibility criteria include histologically or cytologically confirmed mNSCLC, disease progression with concurrent or sequential anti–PD-L1/PD-1 treatment and PBC, measurable disease (RECIST 1.1), ECOG PS of 0-1 and the availability of tissue specimens for centralized PD-L1 testing or known PD-L1 status using a health authority–approved PD-L1 assay. Patients with NSCLC previously treated with cabozantinib, docetaxel or anti–PD-L1/PD-1 + VEGFR TKIs are excluded. Patients with known sensitizing *EGFR/ALK* mutations and active or untreated CNS metastases are also excluded. Patients will be randomized 1:1 to receive either atezolizumab (1200 mg IV every 3 weeks) + cabozantinib (40 mg orally once daily) or docetaxel (75 mg/m^2 IV every 3 weeks). The primary endpoint is OS. Secondary endpoints include investigator-assessed PFS, ORR and DOR per RECIST 1.1; TTD in patient-reported physical function and global health status (EORTC QLQ-C30); investigator-assessed PFS rates at 6 months and 1 year; OS rates at 1 and 2 years; safety and PK. Clinical trial information: NCT04471428. Research Sponsor: F. Hoffmann-La Roche.

TPS9135 **Poster Session**

Phase I trial of *in situ* vaccination with autologous *CCL21*-modified dendritic cells (CCL21-DC) combined with pembrolizumab for advanced NSCLC. *First Author: Aaron Elliott Lisberg, University of California, Los Angeles, Los Angeles, CA*

Background: Effective immunotherapy options are lacking for patients with advanced non-small cell lung cancer (NSCLC) who progress on a programmed cell death-(ligand)1 [PD-(L)1] inhibitor and for those that are epidermal growth factor receptor (EGFR) mutation or anaplastic lymphoma kinase (ALK) rearrangement positive after progression on tyrosine kinase inhibitor (TKI) therapy. One potential approach to improve immune checkpoint efficacy in these patient populations is to promote cytolytic T cell infiltration into tumors. This can be accomplished via *in situ* vaccination with functional antigen presenting cells (APCs) which can take advantage of the full repertoire of tumor antigens and convert the tumor into a lymph node-like environment promoting both local and systemic T cell activation. The chemokine CCL21 promotes co-localization of naive T cells and antigen-experienced dendritic cells (DCs) to facilitate T cell activation. Our preclinical studies and phase I trial of intratumoral (IT) administration of DC genetically modified to overexpress CCL21 (CCL21-DC) revealed augmentation of tumor antigen presentation *in situ*, resulting in systemic antitumor immunity. However, increased PD-L1 expression was observed in some patient tumors, suggesting that tumor-mediated impairment of T cell function may be forestalling a more robust CCL21-DC mediated antitumor response. Similarly, improved PD-(L)1 inhibitor efficacy may be possible with enhanced T cell infiltration and augmented APC function following IT CCL21-DC. Therefore, we are conducting a phase I trial, combining IT CCL21-DC with pembrolizumab in patients with advanced NSCLC that are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. **Methods:** Phase I, dose-escalating, multi-cohort trial followed by dose expansion. Maximum of 24 patients (9-12 escalation + 12 expansion) with stage IV NSCLC will be evaluated who have tumors accessible for IT injection and are either (1) EGFR/ALK wild-type after progression on a PD-(L)1 inhibitor or (2) EGFR/ALK mutant after progression on TKI therapy. Three IT injections of autologous CCL21-DC (days 0, 21, 42) will be concurrently administered with pembrolizumab, followed by q3wk pembrolizumab up to 1 year. Primary objective of dose escalation is safety and determination of maximum tolerated dose (MTD) of IT CCL21-DC ($5x10^6$, $1x10^7$, or $3x10^7$) when combined with pembrolizumab. Primary objective of dose expansion is objective response rate at MTD. Secondary objectives include adverse event profiling and determination of drug target activity by immune monitoring studies. This trial, NCT03546361, is currently open for enrollment. Clinical trial information: NCT03546361. Research Sponsor: California Institute for Regenerative Medicine (CIRM).

TPS9136 **Poster Session**

Phase II two-arm study of tepotinib plus osimertinib in patients with *EGFR*-mutant NSCLC and acquired resistance to first-line osimertinib due to *MET* amplification: INSIGHT 2. *First Author: Viola Weijia Zhu, Chao Family Comprehensive Cancer Center, University of California Irvine, Orange, CA*

Background: *MET*amp is a mechanism of acquired resistance to EGFR tyrosine kinase inhibitors (TKIs). *MET*amp occurs in ~30% of patients who progress on EGFR TKI therapy as measured using fluorescence in situ hybridization (FISH). There is an unmet need for targeted treatment options in these patients. Combination treatment with a MET TKI may overcome *MET*-related osimertinib resistance. Tepotinib is an oral, once daily (QD), highly selective, potent MET TKI. In the INSIGHT study (NCT01982955), the combination of tepotinib and the EGFR TKI gefitinib improved outcomes in patients with *EGFR*-mutant *MET*amp NSCLC and EGFR TKI resistance compared to chemotherapy (INSIGHT). Median progression-free survival (PFS) was 16.6 vs 4.2 months (hazard ratio [HR] = 0.13; 90% confidence interval [CI]: 0.04, 0.43) and median overall survival (OS) was 37.3 vs 13.1 months (HR = 0.08; 90% CI: 0.01, 0.51). **Methods:** INSIGHT 2 is a global, open-label, Phase II trial of tepotinib + osimertinib in patients with advanced *EGFR*-mutant NSCLC. Following a protocol amendment in Apr 2020, the study is enrolling patients with acquired resistance to 1L osimertinib (radiological documentation of disease progression following previous objective clinical benefit) due to *MET*amp by FISH (GCN ≥5 or MET/CEP7 ratio ≥2). Patients must be ≥18 years old, have an Eastern Cooperative Oncology Group performance status of 0/1, and normal organ function. Both tissue and liquid biopsy, obtained at the time of progression to osimertinib, will be sent for central confirmation of *MET*amp. Liquid biopsy samples will also be used for exploratory biomarker evaluation. Enrollment is allowed based on local FISH testing while awaiting central confirmation of *MET*amp. Patients will receive 500 mg QD (450 mg active moiety) tepotinib + 80 mg QD osimertinib until disease progression, unacceptable toxicity, or consent withdrawal. The study is anticipated to enroll 120 patients. The primary endpoint is objective response rate (ORR) by independent review (RECIST v1.1) in patients with *MET*amp, centrally confirmed by FISH. Secondary endpoints include ORR by investigator assessment, duration of response, disease control, PFS, OS, pharmacokinetics, health-related quality of life, tolerability, and safety. An exploratory tepotinib monotherapy arm will enroll 12 patients to assess the contribution of tepotinib to the activity of the combination. At progression (determined by independent review committee), monotherapy patients can switch to combination treatment. These patients will be analyzed separately. Recruitment is ongoing, with > 300 patients prescreened. Approximately 100 sites in 17 countries in Europe, Asia, and North America are expected to participate. Approximately 15 sites will recruit patients in the US. Clinical trial information: NCT03940703. Research Sponsor: Merck KGaA, Darmstadt, Germany.

TPS9137 **Poster Session**

Phase 2 study of PD-1 inhibitor JTX-4014 alone and in combination with vopratelimab, an ICOS agonist, in biomarker-selected subjects with metastatic NSCLC after one prior platinum-containing regimen (SELECT). *First Author: Oleh Kobziev, Communal Non-profit Enterprise Regional Center of Oncology, Kharkiv, Ukraine*

Background: Immune checkpoint inhibitors have led to durable remissions for some patients with advanced malignancies, including NSCLC; however, only a minority of patients benefit. The field of oncology is addressing this via the development of novel therapies, combinations and identification of biomarkers to select patients most likely to derive clinical benefit. ICOS, a novel therapeutic target, is a costimulatory molecule upregulated on activated T cells. Vopratelimab is an investigational IgG1 ICOS agonist monoclonal antibody that results in activation and proliferation of primed CD4 T effector cells. The preliminary efficacy of vopratelimab +/- nivolumab was assessed in the phase 1/2 ICONIC study in which durable responses were observed in a subset of patients who demonstrated on treatment emergence of peripheral ICOS hi CD4 T effector cells. Patients with peripheral ICOS hi CD4 T cells achieved significantly greater clinical benefit than patients whose CD4 T cells remained ICOS lo. An RNA based tumor inflammation signature (TIS) comprised of 18 genes associated with immune cell infiltration was previously identified as a predictive biomarker of response to anti-PD-1 therapy (Ayers et al, 2017); it was also associated with ICOS hi CD4 T cell emergence in ICONIC (ASCO-SITC 2020). The pre-treatment tumor TIS score, coupled with a specific threshold established by Jounce, referred to as TIS^{vopra}, was predictive of ICOS hi CD4 T cell emergence. TIS^{vopra} positive patients had improved RECIST response, PFS, and OS compared to those with a TIS^{vopra} negative score. Therefore, we hypothesize that patient selection by TIS^{vopra} will identify those who will display emergence of ICOS hi CD4 T cell populations and importantly, improved clinical outcomes when treated with vopratelimab in combination with JTX-4014 (a novel PD-1 inhibitor in development by Jounce) vs JTX-4014 alone. **Methods:** This Phase 2 open-label multicenter study is investigating JTX-4014 alone and in combination with vopratelimab in TIS^{vopra} selected patients with metastatic NSCLC after one prior platinum-containing regimen (NCT04549025). Patients must be PD-1/L1 inhibitor naïve and negative for activating EGFR mutations. TIS^{vopra} eligibility is determined using RNA isolated from a tumor sample. Eligible patients will be randomized to receive either JTX-4014 as monotherapy or in combination with one of two dose levels of vopratelimab. The primary endpoint is mean percent change from baseline tumor size of all measurable existing and new lesions averaged over 9 and 18 weeks. Secondary endpoints include ORR and PFS according to RECIST v1.1, OS, safety, and association of baseline TIS score with clinical outcomes. The study has a target enrollment goal of approximately 75 patients; the first patient was dosed October 2020. Clinical trial information: NCT04549025. Research Sponsor: Jounce Therapeutics.

TPS9138 **Poster Session**

An open-label, multicenter phase I/IIa study evaluating the safety and clinical activity of clonal neoantigen reactive T cells in patients with advanced non-small cell lung cancer (CHIRON). *First Author: Mariam Jamal-Hanjani, University College London, London, United Kingdom*

Background: Lung cancer is the most common cause of cancer-related death worldwide with over 1.6 million deaths per year. Non-small cell lung cancer (NSCLC) accounts for 80% of cases, the majority of which are adenocarcinomas. 75% of patients present with inoperable tumours and/or with distant metastatic spread, with 5-year survival for stage IV disease as low as 5%. Treatment options include chemotherapy, targeted therapies for specific mutations, and - increasingly - immune checkpoint inhibitors (CPI). Adoptive cell therapies (ACT) can produce durable responses in pre-treated NSCLC. Evidence also suggests potential benefit of combining ACT with CPIs, even after acquired resistance. Efforts to improve efficacy include the expansion of T cells able to recognise patient-specific clonal tumour neoantigens. Clonal tumour neoantigens arise early in cancer evolution and represent a subset of patient-specific mutations present in all cancer cells. Developing ACTs that target clonal neoantigens represents a personalised approach to treating all cancer cells concurrently, minimising the risk of tumour escape and reducing potential for off-target toxicities. Insights gained from applying the PELEUS bioinformatic platform (developed using UK TRACERx study data) to matched tumour and blood samples from NSCLC patients – as part of a tissue acquisition study (NCT03517917) – has enabled the manufacture of a personalized clonal neoantigen-reactive T cell (cNeT) product (ATL001), which is now in clinical development. **Methods:** The CHIRON Study (NCT04032847), is a first-in-human, open-label, multi-centre, phase I/IIa study to characterise the safety and clinical activity of ATL001 administered intravenously in up to 40 adults with advanced unresectable or metastatic NSCLC. Following consent and screening, patients enter the study for procurement of tumor tissue and blood to manufacture ATL001. Tissue may be procured during treatment with standard systemic therapies. Patients in Cohort A receive cyclophosphamide/fludarabine on days -6 to -4, followed by a single dose of ATL001 and 10 daily doses of subcutaneous IL-2; Patients in Cohort B will additionally receive one dose of pembrolizumab between days -13 and -6 before receiving ATL001, then restart pembrolizumab 2 weeks after receiving ATL001 and continue for up to 12 months. Key eligibility criteria include treatment with at least one prior systemic therapy (including a PD-1 inhibitor). Primary endpoints are the safety and tolerability of ATL001 as a monotherapy and in combination with pembrolizumab. Secondary endpoints include change in tumor size and response rate by RECIST 1.1 and imRECIST. Correlative studies will investigate the effects of cNeT dose and engraftment kinetics on clinical activity. The study began enrolling patients in Cohort A in August 2019. Clinical trial information: NCT04032847. Research Sponsor: Achilles Therapeutics.

TPS9139 **Poster Session**

HERTHENA-Lung01: A randomized phase 2 study of patritumab deruxtecan (HER3-DXd) in previously treated metastatic *EGFR*-mutated NSCLC. *First Author: Pasi A. Janne, Dana-Farber Cancer Institute, Boston, MA*

Background: Few treatment options have demonstrated therapeutic benefit in epidermal growth factor receptor–mutated (*EGFR*m) non–small cell lung cancer (NSCLC) that has progressed after treatment with EGFR tyrosine kinase inhibitors (TKIs) and platinum-based chemotherapy. HER3, a member of the human epidermal growth factor family, is detectable in most *EGFR*m NSCLC, and its expression has been linked to worse clinical outcomes. There are no approved HER3 directed therapies for the treatment of NSCLC. HER3-DXd is a novel, potentially first-in-class HER3 directed antibody drug conjugate that has demonstrated preliminary evidence of safety and antitumor activity in patients (pts) with *EGFR*m TKI–resistant NSCLC in an ongoing Phase 1 study, providing proof of concept of HER3-DXd. The Phase 2 study (HERTHENA-Lung01) is further evaluating HER3-DXd in pts with previously treated metastatic or locally advanced *EGFR*m NSCLC. **Methods:** This randomized, open-label Phase 2 study will enroll up to 420 pts at approximately 135 study sites in North America, Europe and the Asia-Pacific region. Eligible pts will have metastatic or locally advanced NSCLC with an activating *EGFR* mutation (exon 19 deletion or L858R), progression during or after systemic treatment with $\geq$1 EGFR TKI and $\geq$1 platinum-based chemotherapy regimen, and $\geq$1 measurable lesion confirmed by blinded independent central review (BICR) per RECIST v1.1. Pts with an *EGFR* T790M mutation must have received and progressed on prior osimertinib. Pts with stable brain metastases are eligible. Exclusion criteria include evidence of previous small cell or combined small cell/non–small cell histology or any history of interstitial lung disease. Tumor tissue will be assessed retrospectively for HER3 expression and molecular mechanisms of TKI resistance. HER3 expression will not be used to select pts for enrollment. Pts will be randomized 1:1 to receive 1 of 2 HER3-DXd Q3W dose regimens that will be independently evaluated: a 5.6 mg/kg fixed-dose regimen (Arm 1) or an up-titration dose regimen (Arm 2: Cycle 1, 3.2 mg/kg; Cycle 2, 4.8 mg/kg; Cycle 3 and beyond, 6.4 mg/kg). After review of data from an ongoing Phase 1 study with similar patients treated with either of these dose regimens, a decision could be made to continue enrollment into 1 or both arms. The primary objective is to evaluate the efficacy of HER3-DXd as measured by objective response rate (ORR) by BICR. Secondary objectives are to evaluate the efficacy and safety/tolerability of HER3-DXd and to assess the relationship between efficacy and HER3 expression. Secondary endpoints include duration of response, progression-free survival, ORR by investigator, disease control rate, time to response, best percentage change in the sum of diameters of measurable tumors, and overall survival. The study is enrolling and is planned to finish in 2023. Clinical trial information: NCT04619004. Research Sponsor: Daiichi Sankyo.

9500 **Oral Abstract Session**

Crossover and rechallenge with pembrolizumab in recurrent patients from the EORTC 1325-MG/Keynote-054 phase 3 trial, pembrolizumab versus placebo after complete resection of high-risk stage III melanoma. *First Author: Alexander M. Eggermont, Princess Máxima Center, Utrecht, Netherlands*

Background: The phase 3 double-blind EORTC 1325/KEYNOTE-054 trial evaluated pembrolizumab (pembro) vs placebo in stage III cutaneous melanoma patients (pts) with complete resection of lymph nodes. Pembro improved RFS (hazard ratio [HR] 0.57) and DMFS (HR 0.60) (Eggermont, NEJM 2018, TLO 2021). In the pembro group, the incidence of immune related AE (irAE) grade 1-5 was 37%, and of grade 3-5 was 7%. We present the safety profile, response rate and PFS for the subset of pts who had a recurrence and crossed over or were rechallenged with pembrolizumab, within protocol. **Methods:** Pts were randomized to receive iv. pembro 200 mg (N=514) or placebo (N=505) every 3 weeks for a total of 18 doses (~1 year). Upon recurrence with no brain metastases, pts with an ECOG PS 0-2 were eligible to enter part 2 of the study, i.e. to receive pembro 200 mg iv. every 3 weeks for a maximum of 2 years, for crossover (those who received placebo) or rechallenge (those who recurred ≥6 months after completing one year of pembro therapy). Treatment was stopped in case of disease progression (RECIST 1.1) or unacceptable toxicity. **Results:** At the clinical cut-off (16-Oct-2020), 298 (59%) pts had a disease recurrence in the placebo group; 155 pts participated in the crossover part 2 of the trial. A total of 297 (58%) pts completed the 1-yr pembro adjuvant treatment, of whom 47 had a recurrence ≥6 mths from the stop of treatment and 20 entered in the rechallenge part of the trial. Among 175 pts who started pembro in Part 2, 160 discontinued due to completion of therapy (N=24), disease progression (N=88), toxicity (N=20), investigator's decision (N=21), or other reason (N=7); 15 pts were still on-treatment. Results for the 2 groups are provided in the table. The median number of doses was 12 and 5.5, respectively (resp), and the median follow-up was 41 and 19 mts, resp. Among the 175 pts, 51 (29%) had a grade 1-4 irAE (by group: 47 [30%] and 4 [20%] resp) and 11 (6%) a grade 3-4 irAE. **Conclusions:** Pembrolizumab treatment after crossover yielded a 39% ORR in evaluable pts and an overall 3-yr PFS of ~32%, but after rechallenge the efficacy was lower. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA The median PFS (95% CI) from start of Part 2 was 14 (5-27) and 8 (5-15) mts for stage III-resected and III/IV various, resp. Among the 80 stage IV crossover pts with evaluable disease, 31 (39%) had an objective response: 14 (18%) CR, 17 (21%) PR. The 2-yr PFS rate from response was 69% (95% CI 48-83%). For these 80 pts, the median PFS was 6.1 mts and the 3-yr PFS rate was 31% (95% CI 21-41%). Among 9 stage IV rechallenged pts with an evaluable disease, 1 (11%) reached CR, 3 had SD and 5 PD.Clinical trial information: NCT02362594.

	Crossover (N=155)	Rechallenge (N=20)
Stage at baseline of Part 2, n		
III-resected	50	7
III/IV various	105	13
IV unresected	83	9
III-C unresected	10	
IV resected	12	4
PFS events in Part 2, n	103	12
Median PFS (95% CI), mts	8.5 (5.7-15.2)	4.1 (2.6-NE)
3-yr PFS rate (95% CI), %	32 (25-40)	NE

9501 **Oral Abstract Session**

Final analysis of overall survival (OS) and relapse-free-survival (RFS) in the intergroup S1404 phase III randomized trial comparing either high-dose interferon (HDI) or ipilimumab to pembrolizumab in patients with high-risk resected melanoma. *First Author: Kenneth F. Grossmann, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT*

Background: We assessed whether or not adjuvant pembrolizumab given over 1 year would improve OS and RFS in comparison to high dose ipilimumab (ipi10) or HDI - the two FDA-approved adjuvant treatments for high risk resected melanoma at the time of study design. **Methods:** Patients age 18 or greater with resected stages IIIA(N2), B, C and IV were eligible. Patients with CNS metastasis were excluded. At entry, patients must have had complete staging and adequate surgery to render them free of melanoma including completion lymph node dissection for those with sentinel node positive disease. Prior therapy with PD-1 blockade, ipilimumab or interferon was not allowed. Two treatment arms were assigned based on stratification by stage, PD-L1 status (positive vs. negative vs. unknown), and intended control arm (HDI vs. Ipi10). Patients enrolled between 10/2015 and 8/2017 were randomized 1:1 to either the control arm [(1) interferon alfa-2b 20 MU/m2 IV days 1-5, weeks 1-4, followed by 10 MU/m2/d SC days 1, 3, and 5, weeks 5-52 (n=190), or (2) ipilimumab 10 mg/kg IV q3w for 4 doses, then q12w for up to 3 years (n=465)], or the experimental arm [pembrolizumab 200 mg IV q3w for 52 weeks (n=648)]. The study had three primary comparisons: 1) RFS among all patients, 2) OS among all patients, 3) OS among patients with PD-L1+ baseline biopsies. Results: 1,426 patients were screened and 1,345 patients were randomized with 11%, 49%, 34%, and 6% AJCC7 stage IIIA(N2), IIIB, IIIC and IV, respectively. This final analysis was performed per-protocol 3.5 years from the date the last patient was randomized, with 512 RFS and 199 OS events. The pembrolizumab group had a statistically significant improvement in RFS compared to the control group (pooled HDI and ipi10) with HR 0.740 (99.618% CI, 0.571 to 0.958). There was no statistically signifcant improvement in OS in the 1,303 eligible randomized overall patient population with HR 0.837 (96.3% CI, 0.622 to 1.297), or among the 1,070 (82%) patients with PD-L1 positive baseline biopsies with HR 0.883 (97.8% CI, 0.604 to 1.291). Gr 3/4/5 event rates were as follows: HDI 69/9/0%, ipi10 43/5/0.5% and pembrolizumab 17/2/0.3%. **Conclusions:** Pembrolizumab improves RFS but not OS compared to HDI or ipi10 in the adjuvant treatment of patients with high-risk resected melanoma. Pembrolizumab is a better tolerated adjuvant treatment regimen than HDI or Ipi10. Support: NIH/NCI NCTN grants CA180888, CA180819, CA180820, CA180863; and in part by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. Editorial Acknowledgement: With special thanks to Elad Sharon, MD, MPH, and Larissa Korde, MD, MPH. National Cancer Institute, Investigational Drug Branch, for their contributions to this trial, as well as Nageatte Ibrahim, MD, and Sama Ahsan, MD Merck. Clinical trial information: NCT02506153. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

9502 **Oral Abstract Session**

Neoadjuvant and adjuvant nivolumab (nivo) with anti-LAG3 antibody relatlimab (rela) for patients (pts) with resectable clinical stage III melanoma. *First Author: Rodabe Navroze Amaria, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Neoadjuvant therapy (NT) for pts with clinical stage III melanoma remains an active area of research interest. Recent NT trial data demonstrates that achieving a pathologic complete response (pCR) correlates with improved relapse-free (RFS) and overall survival (OS). Checkpoint inhibitor (CPI) NT with either high or low dose ipilimumab and nivolumab regimens produces a high pCR rate of 30-45% but with grade 3-4 toxicity rate of 20-90%. In metastatic melanoma (MM), the combination of nivo with rela (anti Lymphocyte Activation Gene-3 antibody) has demonstrated a favorable toxicity profile and responses in both CPI-naïve and refractory MM. We hypothesized that NT with nivo + rela will safely achieve high pCR rates and provide insights into mechanisms of response and resistance to this regimen. **Methods:** We conducted a multi-institutional, investigator-initiated single arm study (NCT02519322) enrolling pts with clinical stage III or oligometastatic stage IV melanoma with RECIST 1.1 measurable, surgically-resectable disease. Pts were enrolled at 2 sites and received nivo 480mg IV with rela 160mg IV on wks 1 and 5. Radiographic response (RECIST 1.1) was assessed after completion of NT; surgery was conducted at wk 9 and specimens were assessed for pathologic response per established criteria. Pts received up to 10 additional doses of nivo and rela after surgery, with scans every 3 mo to assess for recurrence. The primary study objective was determination of pCR rate. Secondary objectives included safety, radiographic response by RECIST 1.1, event-free survival (EFS), RFS, and OS analyses. Blood and tissue were collected at baseline, at day 15, day 28, and at surgery for correlative analyses. **Results:** A total of 30 pts (19 males, median age 60) were enrolled with clinical stage IIIB/IIIC/IIID/IV (M1a) in 18/8/2/2 pts, respectively. 29 pts underwent surgery; 1 pt developed distant metastatic disease while on NT. pCR rate was 59% and near pCR (< 10% viable tumor) was 7% for a major pathologic response (MPR, pCR + near pCR) of 66%. 7% of pts achieved a pPR (10-50% viable tumor) and 27% pNR (≥50% viable tumor). RECIST ORR was 57%. With a median follow up of 16.2 mos, the 1 -year EFS was 90%, RFS was 93%, and OS was 95%. 1-year RFS for MPR was 100% compared to 80% for non-MPR pts (p = 0.016). There were no treatment related gr 3/4 AEs that arose during NT; 26% of pts had a gr 3/4 AE that began during adjuvant treatment. **Conclusions:** Neoadjuvant and adjuvant treatment with nivo and rela achieved high pCR and MPR rates with a favorable toxicity profile in the neoadjuvant and adjuvant settings. Pts with MPR had improved outcomes compared to non-MPR pts. Translational studies to discern mechanisms of response and resistance to this combination are underway. Clinical trial information: NCT02519322. Research Sponsor: Bristol Myers Squibb, MD Anderson Melanoma Moonshot Program.

9503 **Oral Abstract Session**

Relatlimab (RELA) plus nivolumab (NIVO) versus NIVO in first-line advanced melanoma: Primary phase III results from RELATIVITY-047 (CA224-047). *First Author: Evan J. Lipson, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Immune checkpoint inhibitor therapy has revolutionized the treatment of patients with advanced melanoma. However, novel combinations are needed to optimize the benefit-risk profile. Lymphocyte-activation gene 3 (LAG-3) regulates an immune checkpoint pathway, which inhibits T-cell activity, and is upregulated in many tumor types including melanoma. Relatlimab (RELA), a human IgG4 LAG-3-blocking antibody, restores effector function of exhausted T cells. RELA in combination with nivolumab (NIVO; anti-programmed death [PD]-1) modulates potentially synergistic immune checkpoint pathways and can enhance antitumor immune responses. RELATIVITY-047 is a global, randomized, double-blind, phase II/III study evaluating a novel immune checkpoint inhibitor combination of RELA+NIVO as a fixed-dose combination (FDC) treatment in first-line advanced melanoma. **Methods:** Patients with previously untreated advanced melanoma were randomized 1:1 to receive RELA 160 mg + NIVO 480 mg FDC intravenously (IV) every 4 weeks (Q4W) or NIVO monotherapy 480 mg IV Q4W, stratified by LAG-3 expression, programmed death ligand 1 expression, *BRAF* mutation status, and AJCC (v8) M stage. The primary endpoint was progression-free survival (PFS) per RECIST v1.1 as assessed by blinded independent central review. Secondary endpoints were overall survival and objective response rate. PFS in prespecified subgroups and safety were additional objectives. **Results:** 714 patients were randomized to RELA+NIVO FDC (n = 355) or NIVO (n = 359). Patient characteristics were well balanced between treatment groups. Median follow-up was 13.2 months. Median PFS in the RELA+NIVO FDC group (10.1 months [95% CI, 6.4–15.7]) was significantly longer than in the NIVO group (4.6 months [95% CI, 3.4–5.6]; hazard ratio, 0.75 [95% CI, 0.6–0.9]; $P = 0.0055$). PFS rates at 12 months were 47.7% (95% CI, 41.8–53.2) and 36.0% (95% CI, 30.5–41.6) for RELA+NIVO FDC and NIVO, respectively. PFS favored RELA+NIVO FDC across key prespecified subgroups. The incidence of grade 3/4 treatment-related adverse events (TRAEs) was higher in the RELA+NIVO FDC group (18.9%) versus NIVO (9.7%). There were 3 treatment-related deaths with RELA+NIVO FDC and 2 with NIVO. TRAEs (any grade) led to treatment discontinuation in 14.6% and 6.7% of patients in the RELA+NIVO FDC and NIVO groups, respectively. **Conclusions:** First-line treatment with RELA+NIVO FDC demonstrated a statistically significant PFS benefit compared to NIVO monotherapy in patients with advanced melanoma. RELA+NIVO FDC was well tolerated with a manageable safety profile and without unexpected safety signals. This is the first phase III study of a novel FDC to demonstrate a clinically meaningful benefit by dual inhibition of the LAG-3 and PD-1 pathways. Clinical trial information: NCT03470922. Research Sponsor: Bristol-Myers Squibb.

9504 **Oral Abstract Session**

Lenvatinib (len) plus pembrolizumab (pembro) for patients (pts) with advanced melanoma and confirmed progression on a PD-1 or PD-L1 inhibitor: Updated findings of LEAP-004.

First Author: Ana Arance, Hospital Clinic Barcelona, Barcelona, Spain

Background: Initial results of the open-label, single-arm, phase 2 LEAP-004 study (NCT03776136) showed that len and pembro in combination had promising efficacy and manageable safety in pts with unresectable stage III-IV melanoma and confirmed PD on a PD-(L)1 inhibitor given alone or in combination. ORR was 21.4% with a 6.3-mo median DOR; ORR was 31.0% in patients with PD on prior anti–PD-1 + anti–CTLA-4. We present updated data from LEAP-004 and additional ORR subgroup analyses. **Methods:** Eligible pts with PD confirmed per iRECIST within 12 wk of the last dose of a PD-(L)1 inhibitor given alone or with anti–CTLA-4 or other therapies for ≥2 doses received len 20 mg/d once daily plus ≤35 doses of pembro 200 mg Q3W until PD or unacceptable toxicity. Primary end point is ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary end points are PFS and DOR per RECIST v1.1 by BICR, OS, and safety. ORR was calculated for pts with PD on prior anti–PD-1 + anti–CTLA-4, pts whose only prior anti–PD-(L)1 was in the adjuvant setting, pts with primary resistance (ie, best response of SD or PD to prior anti–PD-(L)1 in the advanced setting) and pts with secondary resistance (ie, PD following best response of CR or PR on prior anti–PD-(L)1 in the advanced setting). **Results:** 103 pts were enrolled. Median age was 63 y, 68.0% of pts had stage M1c/M1d disease, 55.3% had LDH > ULN (20.4% ≥2 × ULN), 58.3% received ≥2 prior treatments, 94.2% received therapy for advanced disease, and 32.0% received BRAF ± MEK inhibition. With median study follow-up of 15.3 mo (range 12.1-19.0), 17.5% of pts were still receiving study drug. ORR by BICR remained 21.4% (95% CI 13.9-30.5), although the number of CRs increased from 2 to 3. DCR was 66.0%. Median DOR increased to 8.2 mo, and the KM estimate of DOR ≥9 mo was 37.2%. ORR was 33.3% in pts with PD on prior anti–PD-1 + anti–CTLA-4 (n = 30), 18.2% in pts whose only prior anti–PD-1/L1 was in the adjuvant setting (n = 11), 22.6% in pts with primary resistance (n = 62), and 22.7% in pts with secondary resistance (n = 22). Median (95% CI) PFS and OS in the total population were 4.2 mo (3.8-7.1) and 14.0 mo (95% CI 10.8-NR); 12-mo PFS and OS estimates were 17.8% and 54.5%. Incidence of treatment-related AEs was as follows: 96.1% any grade, 45.6% grade 3-4, 1.0% grade 5 (decreased platelet count), 7.8% led to discontinuation of len and/or pembro, and 56.3% led to len dose reduction. **Conclusions:** The combination of len and pembro continues to show clinically meaningful, durable responses in pts with advanced MEL with confirmed progression on a prior PD-(L)1 inhibitor, including those with PD on anti–PD-1 + anti–CTLA-4 therapy, and regardless of primary or secondary resistance to prior anti–PD-(L)1 therapy. The safety profile was consistent with prior studies of len + pembro. These data support len + pembro as a potential regimen for this population of high unmet need. Clinical trial information: NCT03776136. Research Sponsor: Eisai Inc., Woodcliff Lake, NJ, USA, and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

9505 **Oral Abstract Session**

Lifileucel (LN-144), a cryopreserved autologous tumor infiltrating lymphocyte (TIL) therapy in patients with advanced melanoma: Evaluation of impact of prior anti-PD-1 therapy.

First Author: James Larkin, Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom

Background: Immune checkpoint inhibitors (ICI) have become standard of care for treatment of metastatic melanoma. Most patients with advanced melanoma progress on ICI and treatment options are limited for these patients. Progression may be through primary resistance (lack of response) or secondary resistance (initial response then progression). Lifileucel is an adoptive cell therapy using TIL, that has shown efficacy in patients with advanced melanoma who progress on/after an anti-PD-1 (Sarnaik, 2020). We present the 28-month (mos) follow-up data and highlight the impact of prior anti-PD-1 response and duration of exposure on outcome with lifileucel. **Methods:** C-144-01 is a Phase 2, open-label, multicenter study of efficacy and safety of lifileucel in patients with advanced melanoma who have progressed on anti-PD-1 therapy and BRAFi ± MEKi, if BRAF V600$^+$. We report long-term follow up on Cohort 2 (N = 66). Tumors were resected at local sites, processed in central GMP facilities for TIL production in a 22-day manufacturing process. Therapy consisted of nonmyeloablative lymphodepletion using 2 days of cyclophosphamide and 5 days of fludarabine, a single infusion of lifileucel, and up to six doses of IL-2. Objective response rate (ORR) was assessed by RECIST 1.1. Data cutoff was Dec. 14, 2020. **Results:** Baseline characteristics: 3.3 mean prior therapies (100% anti-PD-1; 80% anti-CTLA-4; 23% BRAFi/MEKi), high baseline tumor burden (106 mm mean target lesion SOD), 42% liver/brain lesions, 40.9% LDH > ULN. ORR by investigator was 36.4% (3 CR, one new CR developed at 24 mos; 21 PR). Median duration of response (mDOR) was not reached at median follow-up of 28 mos (DOR range: 2.2- 35.2 mos). In responders, the median cumulative duration and median prior lines of anti-PD-1 therapy was 4.4 mos (range: 1.4-22.5 mos), and 1.5 (range: 1-4). Data in Table demonstrates a meaningful increase in DOR to TIL with primary anti-PD-1 resistance and lower duration of time on prior anti-PD-1 therapy. No new safety risks have been identified for lifileucel during long-term follow-up. **Conclusions:** One-time lifileucel treatment results in a 36.4% ORR, and mDOR was not reached at 28 mos of median study follow up. One PR converted to a new CR at 24 months as responses continue to deepen. DOR is positively associated with primary resistance to prior anti-PD-1 therapy and with shorter cumulative prior duration of anti-PD-1 therapy. Lifileucel may offer a better clinical outcome when used earlier upon detection of progression on prior anti-PD-1 rather than retreatment with anti-PD-1 based regimens. Clinical trial information: NCT02360579. Research Sponsor: Iovance Biotherapeutics, Inc.

Univariate Cox-regression analyses on DOR.

	Cohort 2 Responders (N=24)	
	HR (95% CI)	nominal p value
Primary refractory to anti-PD-1/PD-L1 (Y vs N)	0.263 (0.075, 0.921)	0.0367
Duration of prior anti-PD-1/PD-L1 use (≤ median of 5.1 mos vs > median)	0.218 (0.056, 0.854)	0.0288

9506 **Oral Abstract Session**

CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma.

First Author: Jedd D. Wolchok, Medical Oncology, Memorial Sloan Kettering Cancer Center, and Weill Cornell Medical College, New York, NY

Background: In the phase 3 CheckMate 067 trial, a durable and sustained clinical benefit was achieved with nivolumab (NIVO) + ipilimumab (IPI) and NIVO alone vs IPI at 5-y of follow-up (overall survival [OS] and progression-free survival [PFS] rates: 52%, 44%, 26% and 36%, 29%, 8%, respectively). Here we report 6.5-y efficacy and safety outcomes. **Methods:** Eligible pts with previously untreated unresectable stage III or IV melanoma were randomly assigned in a 1:1:1 ratio and stratified by PD-L1 status, *BRAF* mutation status, and metastasis stage. Pts received NIVO 1 mg/kg + IPI 3 mg/kg for 4 doses Q3W followed by NIVO 3 mg/kg Q2W (n = 314), NIVO 3 mg/kg Q2W + placebo (n = 316), or IPI 3 mg/kg Q3W for 4 doses + placebo (n = 315) until progression or unacceptable toxicity. Co-primary endpoints were PFS and OS with NIVO + IPI or NIVO vs IPI. Secondary endpoints included objective response rate (ORR), descriptive efficacy assessments of NIVO + IPI vs NIVO alone, and safety. **Results:** With a minimum follow-up of 6.5 y, median OS was 72.1 mo with NIVO + IPI, 36.9 mo with NIVO, and 19.9 mo with IPI (table). Median time from randomization to subsequent systemic therapy was not reached (NR; 95% CI, 59.6–NR) with NIVO + IPI, 25.2 mo (95% CI, 16.0–43.2) with NIVO, and 8.0 mo (95% CI, 6.5–8.7) with IPI; 36%, 49%, and 66% of pts, respectively, received any subsequent systemic therapy. Median treatment-free interval (which excluded pts who discontinued follow-up prior to initiation of subsequent systemic therapy) was 27.6 mo (range, 0–83.0), 2.3 mo (range, 0.2–81.6), and 1.9 mo (range, 0.1–81.9) with NIVO + IPI, NIVO, and IPI, respectively. Of the pts alive and in follow-up, 112/138 (81%; NIVO + IPI), 84/114 (74%; NIVO), and 27/63 (43%; IPI) were off treatment and never received subsequent systemic therapy; 7, 8, and 0 pts, respectively, were still on treatment. Grade 3/4 treatment-related adverse events were reported in 59% of NIVO + IPI-treated pts, 24% of NIVO-treated pts, and 28% of IPI-treated pts. Since the 5-y analysis, no new safety signals were observed and no additional treatment-related deaths occurred. **Conclusions:** This 6.5-y analysis represents the longest follow-up from a phase 3 melanoma trial in the modern checkpoint inhibitor combination therapy and targeted therapy era. The results show durable improved outcomes with NIVO + IPI and NIVO vs IPI in pts with advanced melanoma. We observed improvement in OS, PFS, and ORR with NIVO + IPI over NIVO alone. Clinical trial information: NCT01844505. Research Sponsor: Bristol Myers Squibb.

	NIVO + IPI(N = 314)	NIVO (N = 316)	IPI (N = 315)
Median OS: all pts, mo (95% CI)	72.1(38.2–NR)	36.9(28.2–NR)	19.9(16.8–24.6)
6.5-y OS rate: all pts, % (95% CI)	49(44–55)	42(37–42)	23(19–28)
***BRAF* mutant**	57(47–66)	43(33–53)	25(17–34)
Median PFS: all pts, mo (95% CI)	11.5(8.7–19.3)	6.9(5.1–10.2)	2.9(2.8–3.2)
6.5-y PFS rate: all pts, % (95% CI)	34(29–40)	29(23–34)	7(4–11)
Investigator-assessed ORR, % (95% CI)	58.3(52.6–63.8)	44.9(39.4–50.6)	19.0(14.9–23.8)
Duration of response, mo (95% CI)	NR(61.9–NR)	NR(45.7–NR)	19.3(8.8–47.4)

9507 **Oral Abstract Session**

Five-year overall survival (OS) in COLUMBUS: A randomized phase 3 trial of encorafenib plus binimetinib versus vemurafenib or encorafenib in patients (pts) with *BRAF* V600-mutant melanoma.

First Author: Reinhard Dummer, University Hospital Zürich, Zurich, Switzerland

Background: Combined BRAF/MEK inhibitor therapy has demonstrated benefits on progression-free survival (PFS) and OS and is standard of care for the treatment of advanced *BRAF* V600-mutant melanoma. Here we report a 5-year update from the COLUMBUS trial. **Methods:** In Part 1 of COLUMBUS, 577 pts with advanced/metastatic *BRAF* V600-mutant melanoma, untreated or progressed after first-line immunotherapy, were randomized 1:1:1 to encorafenib 450 mg QD + binimetinib 45 mg BID (COMBO450), encorafenib 300 mg QD (ENCO300), or vemurafenib 960 mg BID (VEM). An updated analysis including PFS, OS, objective response rate (ORR; by blinded independent central review), and safety was conducted after minimum follow-up of 65.2 months (mo). Data are as is; study is ongoing. **Results:** At data cut-off (Sep 15, 2020), there were 131 (68%), 117 (60%), and 145 (76%) deaths in the COMBO450, ENCO300, and VEM treatment arms, respectively. The median OS (95% CI) and 5-year OS rate (95% CI) with COMBO450 were 33.6 (24.4–39.2) mo and 34.7% (28.0–41.5), respectively (median follow-up: 70.4 mo). The 5-year OS rate (95% CI) in COMBO450 pts who had normal lactate dehydrogenase (LDH) levels at baseline was 45.1% (36.5–53.2). Median OS and 5-year OS rates for ENCO300 and VEM, as well as for pts with normal and high LDH levels and > 3 organs involved at baseline, are shown in the table. For COMBO450, ENCO300, and VEM, the 5-year PFS rate was 22.9%, 19.3%, and 10.2%; ORR (95% CI) was 64.1% (56.8–70.8), 51.5% (44.3–58.8), and 40.8% (33.8–48.2); and the median duration of response (DOR) was 18.6, 15.5, and 12.3 mo, respectively. Safety results were consistent with the known tolerability profile of COMBO450. Additional efficacy and updated safety analyses will be presented. Following study drug discontinuation, the most common subsequent treatment in all arms was checkpoint inhibitors. **Conclusions:** Updated OS and DOR results with COMBO450 demonstrate continued long-term benefits in pts with *BRAF* V600-mutant melanoma. Clinical trial information: NCT01909453. Research Sponsor: Pfizer.

	COMBO450			ENCO300			VEM		
	Events/pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)	Events/pts (%)	Median OS (95% CI), mo*	5-year OS rate (95% CI)
All pts	131/192 (68.2)	33.6 (24.4–39.2)	34.7% (28.0–41.5)	117/194 (60.3)	23.5 (19.6–33.6)	34.9% (27.9–42.0)	145/191 (75.9)	16.9 (14.0–24.5)	21.4% (15.7–27.8)
LDH normal	81/137 (59.1)	51.7 (36.8–67.3)	45.1% (36.5–53.2)	79/147 (53.7)	35.3 (23.7–60.5)	41.8% (33.3–50.1)	95/139 (68.3)	24.5 (18.6–29.1)	28.4% (20.9–36.4)
LDH high	50/55 (90.9)	11.4 (9.0–17.4)	9.1% (3.3–18.4)	38/47 (80.9)	9.2 (7.0–16.2)	13.8% (5.6–25.6)	50/52 (96.2)	9.6 (8.5–11.5)	4.0% (0.7–12.1)
> 3 organs involved	35/42 (83.3)	11.6 (9.1–20.8)	–	32/44 (72.7)	15.7 (7.9–19.7)	–	39/45 (86.7)	10.9 (8.6–15.7)	–

*Unstratified Cox regression model.

9508 **Oral Abstract Session**

Five-year overall survival from the anti-PD1 brain collaboration (ABC Study): Randomized phase 2 study of nivolumab (nivo) or nivo+ipilimumab (ipi) in patients (pts) with melanoma brain metastases (mets). *First Author: Georgina V. Long, Melanoma Institute Australia, University of Sydney, and Royal North Shore and Mater Hospitals, Sydney, Australia*

Background: Preliminary data from the ABC (76 pts) and CheckMate 204 (94 pts) trials showed that nivo and nivo+ipi have activity in active melanoma brain metastases, with durable responses in a subset of pts. Here, we report updated 5-yr data from all pts enrolled on the ABC trial (NCT02374242). **Methods:** This open-label ph2 trial enrolled 3 cohorts of pts with active melanoma brain mets naïve to anti-PD1/PDL1/PDL2/CTLA4 from Nov 2014-Apr 2017. Pts with asymptomatic brain mets with no prior local brain therapy were randomised to cohort A (nivo 1mg/kg + ipi 3mg/kg, Q3Wx4, then nivo 3mg/kg Q2W) or cohort B (nivo 3mg/kg Q2W). Cohort C (nivo 3mg/kg Q2W) had brain mets i) that failed local therapy, ii) with neuro symptoms and/or iii) with leptomeningeal disease. Prior BRAF inhibitor (BRAFi) was allowed. The primary endpoint was best intracranial response (ICR) ≥wk12. Key secondary endpoints were IC PFS, overall PFS, OS, & safety. **Results:** A total of 76 pts (med f/u 54 mo) were enrolled; median age 59y, 78% male. For cohorts A, B and C: elevated LDH 51%, 58% and 19%; V600BRAF 54%, 56% and 81%; prior BRAFi 23%, 24%, 75%. Efficacy and toxicity are shown in the table. There were no treatment-related deaths. 1/17 deaths in cohort A & 4/16 in cohort B were due to IC progression only. **Conclusions:** Nivo monotherapy and ipi+nivo are active in melanoma brain mets, with durable responses in the majority of patients who received ipi+nivo upfront. A study of upfront ipi+nivo+/-SRS is underway (NCT03340129).Clinical trial information: NCT02374242. Research Sponsor: BMS, Other Foundation.

	A (ipi+nivo)	B (nivo)	C (nivo)
All patients	n=35	n=25	n=16
ICR	51%	20%	6%
5-yr IC PFS	46%	15%	6%
5-yr OS	51%	34%	13%
Rx naïve	n=27	n=19	n=4
ICR (Rx naïve)	59%	21%	25%
5-yr IC PFS (Rx naïve)	52%	14%	.
5-yr OS (Rx naïve)	55%	40%	25%
TRAE G3/4	63%	20%	13%

9509 **Clinical Science Symposium**

Overall survival benefit from tebentafusp in patients with best response of progressive disease. *First Author: Anthony M. Joshua, Kinghorn Cancer Centre, St Vincent's Hospital, Darlinghurst, NSW, Australia*

Background: Tebentafusp (tebe) is the first T cell receptor (TCR) therapeutic to demonstrate an overall survival (OS) benefit in a randomized Phase 3 (Ph3) study [NCT03070392]. In Ph2, 42% of pts with best overall response (BOR) of progressive disease (PD) survived > 1 year (yr), suggesting RECIST-based radiographic assessments underestimate OS benefit of tebe. Here we analyzed OS in the Ph3 study in a cohort of pts with BOR of PD by comparing tebe to the control arm of investigator's choice (IC). **Methods:** 378 pts were randomized in a 2:1 ratio to tebe vs. IC. BOR was assessed by investigators using RECIST v1.1. Treatment beyond first disease progression (TBP) was permitted for both arms. On the IC arm, only patients receiving pembrolizumab (pembro) continued with TBP and were included in the TBP-related analyses. No crossover to tebe was permitted; investigators were free to choose subsequent therapy. This analysis was conducted on the first interim analysis (data extracted Nov-2020). Kaplan-Meier estimates of OS were based on Day 100 landmark to eliminate immortal time bias and to capture majority of the PDs. **Results:** By Day 100, PD as BOR occurred in 52% (130/252) of tebe pts (PD-tebe) vs. 60% (76/126) of IC pts (PD-IC). Key baseline characteristics including lactate dehydrogenase, alkaline phosphatase, ECOG performance, age, and sex were similar between PD-tebe vs PD-IC. The proportion of pts with PD due to progression of target lesions (TL), non-TL, or new lesions were also similar between the two groups. More pts received TBP among PD-tebe 53% (69/130) vs PD-pembro 16% (10/61). Median duration of TBP was longer for PD-tebe (7 weeks) vs PD-Pembro (3 weeks). The safety profile of PD-tebe pts during TBP was similar to all tebe-treated pts. OS was superior for PD-tebe vs PD-IC, HR = 0.41 (95% CI 0.25-0.66), even when considering key baseline covariates. While some pts had regression of TL despite diagnosis of PD (< 10% of pts), the OS benefit remained even when limited to pts with best change of tumor growth of TL, HR 0.46 (0.29, 0.73). 58% (75/130) PD-tebe and 52% (40/76) PD-IC pts received subsequent therapies. In a landmark OS analysis of these pts beginning on 1st day of subsequent therapy, prior tebe was associated with better OS vs. prior IC, HR 0.59 (95%CI 0.36-0.96). **Conclusions:** Tebe is the first TCR therapeutic to demonstrate an OS benefit in a solid tumor. Surprisingly, a strong OS benefit from tebe is observed even in pts with BOR of PD, suggesting that RECIST-based radiographic assessments do not capture the complete benefit from tebe. The safety profile of tebe during TBP was consistent with that for long-term tebe treatment. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9510 **Clinical Science Symposium**

Percutaneous hepatic perfusion (PHP) with melphalan for patients with ocular melanoma liver metastases: Preliminary results of FOCUS (PHP-OCM-301/301A) phase III trial. *First Author: Jonathan S. Zager, H. Lee Moffitt Cancer Ctr, Tampa, FL*

Background: Ocular melanoma, the most common intraocular malignancy, frequently metastasizes to the liver but to date there is no established standard of care for hepatic-dominant ocular melanoma patients. The FOCUS trial began as a randomized, phase III trial (301) comparing PHP with best alternative care (BAC). The trial was subsequently amended (301A) to remove the BAC arm due to enrollment concerns. **Methods:** Eligible patients with hepatic-dominant ocular melanoma were randomized 1:1 to receive PHP or BAC (investigator's choice of TACE, pembrolizumab, ipilimumab, or dacarbazine) on the 301 trial. All eligible patients received PHP on the 301A trial. PHP patients could receive up to 6 PHP treatments, repeated every 6-8 weeks with melphalan dosed at 3.0mg/kg ideal body weight (IBW). Patients with progressive disease (PD) were discontinued from study treatment and all patients are followed until death. Patientswere imaged every 12 (±2) weeks until PD. The primary endpoint, ORR (per RECIST 1.1) as assessed by Independent Review Committee, will be characterized by the point estimate and 95% CI for each group (PHP and BAC). Categorical efficacy variables will be presented as frequency counts and percentages and 95% CI. Time-to-event variables will be summarized using Kaplan-Meier methods (median and 95% CI). **Results:** 144 patients were enrolled overall; 102 were assigned to PHP (301: n=43; 301A: n=59) and 42 were assigned to BAC. 91 PHP patients received treatment (301: n=40; 301A: n=51) and 32 BAC patients received treatment. At the time of this analysis, 4 PHP patients were still ongoing on study treatment with a minimum follow-up of 24 weeks. 79 PHP-treated patients and 29 BAC-treated patients were evaluable for response . ORR among PHP patients was 32.9% (26/79; 95% CI: 22.75-40.40%). ORR among BAC patients was 13.8% (4/29; 95% CI: 3.89-31.66%). The median PFS was 9.03 months (95% CI: 6.24-11.83) among PHP patients and was 3.06 months (95% CI: 2.69-5.65) among BAC patients; this difference was statistically significant (p=0.0004). Among the 94 patients assessed for safety after treatment with PHP, 40.4% of patients experienced a serious treatment-emergent adverse event, the majority of which were hematological and resolved without sequelae. There were no treatment related deaths in the trial. **Conclusions:** In this analysis of preliminary data from the FOCUS trial, PHP demonstrates a statistically superior ORR and significantly prolonged PFS in comparison with BAC in the treatment of hepatic metastases from ocular melanoma. The data is encouraging as efficacious treatments for hepatic metastases from ocular melanoma are desperately needed. These early data show an improvement over the previous phase III study in terms of both efficacy (ORR and PFS) as well as toxicity using second generation filters. Clinical trial information: NCT02678572. Research Sponsor: Delcath Systems, Inc.

9511 **Clinical Science Symposium**

Atezolizumab in combination with bevacizumab in patients with unresectable locally advanced or metastatic mucosal melanoma: Interim analysis of an open-label phase II trial. *First Author: Lu Si, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Mucosal melanoma is a rare malignant melanoma in Caucasians but ranks the second most common subtype in the Asian population. It is more often diagnosed at an advanced stage and responds poorly to current PD-1/PD-L1 inhibitors. Here we report the interim analysis results of ML41186, an open-label, multicenter, single-arm phase II study, aiming to evaluate the efficacy and safety of atezolizumab in combination with bevacizumab in patients (pts) with advanced mucosal melanoma. **Methods:** Eligible pts aged 18 to 75 years with histologically confirmed unresectable locally advanced or metastatic mucosal melanoma had at least one measurable lesion per RECIST version 1.1 at baseline, with an ECOG PS 0 or 1 and adequate hematologic and organ function. ML41186 is a Simon two-stage design study, if 22 pts completed ORR evaluation and more than 3 pts respond in stage I, the study then continue to Stage II. Atezolizumab and bevacizumab were administered at a fixed dose of 1200 mg and 7.5 mg/kg Q3W respectively (on day 1 of each 21-day cycle) until unacceptable toxicity or loss of clinical benefit. The primary endpoint is the objective response rate (ORR). The secondary endpoints include progression-free survival (PFS), duration of objective response (DoR), disease control rate (DCR), and safety. **Results:** By the cut-off date of 9th September 2020, 35 pts has been enrolled, among whom 22 pts in the stage I analysis set has completed two efficacy evaluation, while 28 pts (full analysis set) has completed at least one efficacy evaluation. In ITT populations (n=35), mean age was 58.9 years with 10 (28%) pts had ECOG PS of 1. LDH level elevated in 9 (25.7%) pts. More than half pts (19, 54.3%) had metastatic mucosal melanoma, of whom 3 (15.8%) pts had more than 3 metastasis sites and 4 (21.1%) pts had liver metastasis. In stage I analysis set (n=22), the best confirmed ORR was 36.4% (95% CI, 17.0%-59.3%). Median progression-free survival was 5.32 months (95% CI, 1.58-not reached), and the best confirmed DCR was 59.1% (95%CI, 36.4%-79.3%). The median confirmed DoR was not reached (95% CI, 2.76-NR). In the full analysis set (n=28), the unconfirmed ORR was 42.9% (95%CI, 24.5%-62.8%). In ITT populations (n=35), 28 pts (80%) experienced at least one adverse event (AE) and 5 pts (14.3%) experienced at least one grade 3-4 AEs. Only one patient experienced AE leading to treatment discontinuation. One patient died of autoimmune lung disease. **Conclusions:** The combination of atezolizumab plus bevacizumab showed promising benefit and was tolerable in pts with advanced mucosal melanoma. At the time of this interim analysis, the primary endpoint did not cross the futility boundary, thus the study will run into Stage II. Clinical trial information: NCT04091217. Research Sponsor: Shanghai Roche Pharmaceuticals Ltd., Shanghai, China.

9512 **Clinical Science Symposium**

A phase 2 clinical trial of neoadjuvant anti-PD-1 ab (Toripalimab) plus axitinib in resectable mucosal melanoma. *First Author: Chuanliang Cui, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: The outcome of patients (pts) with resectable mucosal melanoma (MM) is still poor. Toripalimab combined with axitinib has shown impressive results in metastatic MM with an ORR of 48.3% and a median PFS of 7.5 months in a phase 1b trial. It was hypothesized that this combination therapy might cause pathologic response in neoadjuvant setting for resectable MM, so we conducted this single arm phase 2 trial. **Methods:** Eligible pts were adults (aged 18 to 75) with histologically confirmed resectable (localized or regional lymph node metastasis) MM disease. Exclusion criteria included ocular or unknown primary melanoma, distant metastatic disease or previous use of anti PD-1 ab. Pts received toripalimab 3 mg/kg Q2W plus axitinib 5 mg BID for 8 weeks as neoadjuvant therapy, then surgery and the adjuvant toripalimab 3 mg/kg Q2W starting 2±1week after surgery for totally 52 weeks. The primary end point is pathologic response rate according to the International Neoadjuvant Melanoma Consortium (pCR+pPR, pCR is defined as the complete absence of residual viable tumor and pPR $\leq$ 50% of viable tumor cells). The secondary end point is RFS in the ITT population. Clinical trial information: NCT04180995. **Results:** From Aug 2019 to Dec 2020, 21 pts have been eligible and enrolled. Basic characteristics: median age 62 years; M: F 28.6% : 71.4%; primary sites 8 femal genital(1urethra, 7vagina), 5 esophagus, 4 ano-rectal, 4 head & neck(3 nasal,1 oral), in which 47.6% localized disease (T3/4 60%), 52.4% regional lymphatic disease; Gene mutation: 4 cKit (1 amplification), 2 Nras,1 Braf (N581), 1mTOR. This therapy was tolerable with grade 3-4 treatment related AEs of 23.8% (liver dysfunction 14.3%, hyperglycemia 9.5% and hypertension 4.8%). 13 pts had received surgeries (local excision 30.8%, wide excision ± CLND72.7%)and 5 pts still in neoadjuvant treatment. One patient was inoperable for bone metastasis, and 2 pts withdrew for covid 19 epidemic. At a median follow up time of 59 weeks, the pathologic response rate was 28.6% (4/14, 2 pCR, 2pPR). Of the post-surgical specimens, 61.5% (8/13) showed significant TIL infiltration, with 38.5% Brisk and 23.1% Nonbrisk according to the definition of AJCC 8th edition. Plenty of plasma cells, histiocyte and pigment with hyaline fibrosis were also found in responders. No recurrence or metastasis was observed in responders until now, with a RFS reaching more than 58weeks. 5 pts with pNR($>$ 50% viable tumor cells) got disease progression, with 1 local recurrence, 1 regional lymphatic metastasis, and 3 distant metastases. The median RFS has not been reached. **Conclusions:** Neoadjuvant toripalimab plus axitinib in resectable MM has shown promising pathologic responses with good tolerance, which supports further investigation of neoadjuvant therapies in MM. Survival is still in follow-up. Clinical trial information: NCT04180995. Research Sponsor: Shanghai Junshi biosciences Co.

9514 **Poster Discussion Session**

Phase II study of ceralasertib (AZD6738), in combination with durvalumab in patients with metastatic melanoma who have failed prior anti-PD-1 therapy. *First Author: Minsuk Kwon, Division of Hematology-Oncology, Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, South Korea*

Background: Alterations in DNA damage response (DDR) and repair are associated with genomic instability and increased somatic tumor mutational burden, and modulating DNA repair is a promising strategy to boost the efficacy of cancer immunotherapy. Ceralasertib is an oral inhibitor of the serine/threonine protein kinase Ataxia Telangiectasia and Rad3 Related (ATR), which is crucial to the cell's response to replication stress. **Methods:** This phase 2 trial was designed to evaluate the efficacy and safety of ceralasertib in combination with durvalumab in patients with metastatic melanoma (MM) who had failed to anti-PD-1 therapy. The study drug schedule was: ceralasertib at 240 mg BD on days 15 to 28 in combination with durvalumab at 1500 mg on day 1 in a 28-day cycle. The primary end point was overall response rate (ORR) by RECIST (v1.1). To investigate markers predictive of clinical outcome, fresh tumor biopsies were obtained from all enrolled patients before treatment. **Results:** From August 2019 to May 2020, 30 MM patients (median # of lines, 2; range, 2 - 5) were enrolled. All enrolled patients were exposed to prior anti-PD-1 treatment (immediate failure, n = 23). The ORR was 30.0% (9 PRs, 10 SDs, 10 PDs), DCR 63.3%, median PFS 7.1 months (95% confidence interval (CI), 3.6-10.6), and median OS was 14.2 months (95% CI, 9.3-19.1). Common adverse events of any grade were anemia (n = 23, 76.7%), anorexia (n = 20, 66.7%) and thrombocytopenia (n = 19, 63.3%). Common adverse events of grade 3 or more included anemia (n = 10, 33.3%). One death occurred due to febrile neutropenia in a patient with a pre-existing wound infection. **Conclusions:** Ceralasertib in combination with durvalumab demonstrated a promising anti-tumor activity, particularly in melanoma patients who failed to standard of care including anti-PD1 treatment. Clinical trial information: NCT03780608. Research Sponsor: None.

9515 **Poster Discussion Session**

Clinical activity of fianlimab (REGN3767), a human anti-LAG-3 monoclonal antibody, combined with cemiplimab (anti-PD-1) in patients (pts) with advanced melanoma. *First Author: Omid Hamid, The Angeles Clinic and Research Institute, a Cedars-Sinai Affiliate, Los Angeles, CA*

Background: Fianlimab and cemiplimab are two high-affinity, fully human, hinge-stabilized IgG4 monoclonal antibodies. In a Phase 1 dose escalation study, fianlimab combined with cemiplimab showed an acceptable safety profile and some clinical activity in pts with advanced malignancies. Here, we present safety and clinical activity data from two expansion cohorts of pts with advanced melanoma (anti–programmed cell death/ligand-1 [anti–PD-(L)1] naïve or experienced) who were treated with fianlimab + cemiplimab and had an opportunity for first on-treatment tumor assessment (cut-off date: Jan 4, 2021). **Methods:** Pts with advanced melanoma who had no prior anti–PD-(L)1 treatment (naïve) or prior anti–PD-(L)1 treatment within 3 months of screening (experienced) received fianlimab 1600 mg + cemiplimab 350 mg by IV infusion every 3 weeks. Tumor measurements were performed every 6 weeks for the first 24 weeks and subsequently every 9 weeks per RECIST v1.1. **Results:** 48 pts with advanced melanoma were treated with the combination therapy: 33 were anti–PD-(L)1 naïve and 15 were anti–PD-(L)1 experienced (median age: 69 years vs 59 years; male: 66.7% vs 46.7%; Caucasian: 87.9% vs 60%). The safety profile (including immune-related adverse events [AEs]) of fianlimab + cemiplimab combination therapy was similar to that of anti–PD-1 monotherapy with one exception. The rate of adrenal insufficiency, 8.3% (4/48) of pts, is similar to the rate previously observed with anti–PD-1 + anti–cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) combination therapy but higher than that observed with anti–PD-1 monotherapy. Grade $\geq$3 treatment-emergent AEs (TEAEs) occurred in 35.4% (17/48) of patients; Grade $\geq$3 serious TEAEs occurred in 22.9% (11/48) of patients; 8.3% (4/48) of patients discontinued treatment due to a TEAE. The most common TEAEs were fatigue (n = 15, 31.3%) and rash (n = 11, 22.9%). By investigator assessment, objective response rate (includes unconfirmed complete [CR] and partial responses [PR]) was 63.6% (3 CRs and 18 PRs) for anti–PD-(L)1 naïve pts and 13.3% (1 CR and 1 PR) for anti–PD-(L)1 experienced pts. Median progression-free survival and median duration of response for the anti–PD-(L)1 treatment naïve cohort have not been reached. Prognostic clinical markers and tumor biomarkers such as expression of LAG-3, PD-L1, and major histocompatibility complex II are being evaluated. Recruitment is ongoing. **Conclusions:** The safety profile of fianlimab + cemiplimab is similar to that observed with cemiplimab monotherapy and other anti–PD-1s, with the exception of higher rate of adrenal insufficiency. Fianlimab + cemiplimab combination has shown clinical activity for pts with advanced melanoma that is similar to anti–PD-1 + CTLA-4 combination therapy, but with lower demonstrated rates of TEAEs. Clinical trial information: NCT03005782. Research Sponsor: Regeneron Pharmaceuticals, Inc.

9516 **Poster Discussion Session**

Two dosing regimens of nivolumab (NIVO) plus ipilimumab (IPI) for advanced (adv) melanoma: Three-year results of CheckMate 511. *First Author: Celeste Lebbe, APHP Dermatology and CIC, U976, Université de Paris, Hôpital Saint-Louis, Paris, France*

Background: NIVO 1 mg/kg plus IPI 3 mg/kg (NIVO1 + IPI3) is approved for treatment (tx) of unresectable/adv melanoma, with demonstrated durable clinical benefit on long-term follow-up. Analysis of the phase 3b/4 CheckMate 511 study (NCT02714218) at 1 y showed that NIVO 3 mg/kg plus IPI 1 mg/kg (NIVO3 + IPI1) improves the safety profile of the combination; efficacy with the 2 regimens was similar in descriptive analyses. Here we present 3-y safety/efficacy results. **Methods:** Patients (pts) $\geq$ 18 y of age with previously untreated unresectable stage III/IV melanoma were randomized 1:1 to receive NIVO3 + IPI1 Q3W $\times$ 4 (N = 180) or NIVO1 + IPI3 Q3W $\times$ 4 (N = 178), both followed by NIVO 480 mg Q4W until progression/unacceptable toxicity. The primary endpoint was the incidence of grade (gr) 3–5 tx-related adverse events (TRAEs); secondary endpoints (descriptive analyses) included objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). The study was not powered to formally demonstrate noninferiority for efficacy endpoints. **Results:** At a median follow-up of 44.4 and 43.9 mo in the NIVO3 + IPI1 and NIVO1 + IPI3 groups, respectively, TRAEs led to tx discontinuation in 26% and 39% of pts; 57% and 42% of pts had received maintenance therapy. Gr 3–5 TRAE incidence remained significantly lower with NIVO3 + IPI1 than NIVO1 + IPI3 (33.9% vs 48.3%; odds ratio 0.55 [95% CI 0.36–0.84]). The most frequent TRAEs (any gr) were diarrhea (27%), fatigue (26%), and pruritus (26%) with NIVO3 + IPI1 and diarrhea (31%), pruritus (29%), and rash (27%) with NIVO1 + IPI3. In descriptive analyses, efficacy results were similar to those observed at 1 y. OS and tx-free–analysis outcomes were numerically similar in the 2 groups (table). **Conclusions:** At 3-y follow-up, NIVO3 + IPI1 continued to demonstrate an improved safety profile compared with NIVO1 + IPI3. In descriptive analyses, both groups demonstrated high 3-y OS rates that were numerically similar. This study provides important information regarding the benefit–risk profile of both dosing regimens of NIVO + IPI in pts with adv melanoma. Clinical trial information: NCT02714218. Research Sponsor: Bristol Myers Squibb.

Secondary endpoints	NIVO3 + IPI1 (N = 180)	NIVO1 + IPI3 (N = 178)	Stratified HR[a] (95% CI)
Investigator-assessed ORR, % (95% CI)	47 (40–55)	53 (45–60)	0.80[b] (0.53–1.21)
mPFS, mo (95% CI)	10.2 (6.2–21.9)	10.0 (6.3–40.9)	1.13 (0.85–1.50)
36-mo PFS rate, % (95% CI)	38 (30–46)	43 (35–50)	–
mOS, mo (95% CI)	NR (43.7–NR)	NR (40.8–NR)	1.03 (0.75–1.41)
36-mo OS rate, % (95% CI)	59 (51–66)	61 (53–67)	–
mTFI,[c,d] mo (range)	21.1 (0.2–48.9)[e]	22.6 (0.1–50.6)[f]	–
Pts alive and tx-free,[d,g] n (%)	72 (74)	72 (77)	–

[a]NIVO3 + IPI1 vs NIVO1 + IPI3. [b]Odds ratio. [c]Time from end of tx until subsequent cancer tx or last known date alive (if no subsequent cancer tx was received). [d]Post hoc analysis. [e]n = 132. [f]n = 127. [g]Pts free of study tx and subsequent systemic tx among those alive and in follow-up at database lock (n = 97 and 94). m, median; NR, not reached; TFI, tx-free interval.

9517 **Poster Discussion Session**

Avelumab in patients with previously treated Merkel cell carcinoma (JAVELIN Merkel 200): Updated overall survival data after more than five years of follow up. *First Author: Paul Nghiem, University of Washington Medical Center at South Lake Union, Seattle, WA*

Background: Merkel cell carcinoma (MCC) is a rare and aggressive skin cancer. Although MCC is considered chemosensitive, patients typically have limited survival benefit with chemotherapy. Before the approval of immune checkpoint inhibitors, patients with metastatic MCC (mMCC) had a poor prognosis, with a historical 5-year overall survival (OS) rate of approximately 14%. Avelumab (anti–PD-L1) became the first approved treatment for patients with mMCC, based on efficacy and safety data observed in the phase 2 JAVELIN Merkel 200 trial (NCT02155647), in which patients with mMCC received avelumab monotherapy. We report the long-term OS data from the cohort of patients with mMCC whose disease had progressed after ≥1 prior line of chemotherapy. **Methods:** Eligible patients had histologically confirmed, measurable (per RECIST 1.1) stage IV MCC. Patients received avelumab 10 mg/kg by intravenous infusion every 2 weeks until confirmed disease progression, unacceptable toxicity, or withdrawal. Long-term OS was analyzed; updated data for other efficacy endpoints, including response and progression-free survival, were not obtained. **Results:** A total of 88 patients were enrolled and received avelumab treatment. As of September 25, 2020 (data cutoff), median follow-up was 65.1 months (range, 60.8-74.1 months). Median OS was 12.6 months (95% CI, 7.5-17.1 months); the 48- and 60-month OS rates were 30% (95% CI, 20%-40%) and 26% (95% CI, 17%-36%), respectively. At data cutoff, treatment was ongoing in 1 patient (1.1%) and an additional patient (1.1%) had reinitiated avelumab after previously discontinuing treatment. Reasons for treatment discontinuation were disease progression (n = 45 [51.1%]), adverse event (AE; n = 11 [12.5%]), death (n = 10 [11.4%]), withdrawal of consent (n = 9 [10.2%]), loss to follow-up (n = 1 [1.1%]), protocol noncompliance (n = 1 [1.1%]), and other reason (n = 10 [11.4%]). At data cutoff, 19 patients (21.6%) had discontinued treatment but remained in follow-up, and 63 patients (71.6%) had died; causes of death were disease progression (n = 49 [55.7%]), unknown reason (n = 9 [10.2%]), AE not related to study treatment (n = 3 [3.4%]), and other reason (n = 2 [2.3%]). In total, 26 patients (29.5%) received subsequent anticancer therapy; the most common subsequent therapies after trial discontinuation were avelumab (n = 4 [4.5%]), carboplatin and etoposide (n = 4 [4.5%]), and pembrolizumab (n = 4 [4.5%]). **Conclusions:** Avelumab monotherapy led to meaningful long-term OS in a subset of patients with mMCC whose disease had progressed after chemotherapy. These results further support the role of avelumab as a standard-of-care treatment for patients with mMCC. Clinical trial information: NCT02155647. Research Sponsor: Funded by Merck KGaA, Darmstadt, Germany as part of an alliance between Merck KGaA and Pfizer.

9519 **Poster Discussion Session**

Intrathecal (IT) and intravenous (IV) nivolumab (N) for metastatic melanoma (MM) patients (pts) with leptomeningeal disease (LMD). *First Author: Ida John, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: MM pts with LMD have a dismal prognosis, with median overall survival (OS) < 3 months, no approved therapies and extremely limited clinical trial options. We previously reported initial safety findings from an open label, single arm, single center phase I/IB trial (NCT03025256), in which IT and IV N were well tolerated, without any CNS-specific or unexpected toxicity. Here we report an update on safety and maximum tolerated dose (MTD) for all patients enrolled, and efficacy for the completed dose cohorts. **Methods:** MM patients aged >18 with evidence of LMD by MRI and/or CSF cytology, ECOG PS ≤2 were treated with IT and IV N. Dexamethasone ≤4mg/daily and concurrent BRAF/MEK inhibitor(i) treatment was allowed. For cycle 1, IT N was administered via intraventricular reservoir on day (D)1. For subsequent cycles (every 14 days), pts received IT N on D1, followed by IV N 240 mg on D2. IT N doses evaluated were 5, 10, 20 mg and 50 mg. Blood and CSF were collected at multiple time points for translational research. The primary objectives of this first-in-human study were to determine the safety and MTD of IT N given with IV N in MM pts with LMD. Bayesian mTPI methodology was used to define the MTD. **Results:** To date, 23 pts have been treated: two at 5, three at 10, fourteen at 20 mg and four at 50 mg IT N. Median age at LMD diagnosis was 42 (28-73); 12 pts are male. All pts had radiographic evidence of LMD and neurological symptoms; 14 pts had positive CSF cytology at baseline. 21 pts received prior therapies for their metastatic melanoma: anti-PD1 (n = 19), BRAFi/MEKi (n = 14), chemo (n = 2), IT IL2 (n = 4) other (n = 2). 19 pts had prior XRT, including whole brain RT (n = 7). Two pts were treatment-naïve. The median number of IT N doses was five (1- 66). The combination regimen was well tolerated by all evaluable pts (n=23), with only five pts (22%) experiencing gr 3 AEs, and no reported gr 4 or 5 toxicities. Nausea (30%), diarrhea (26%), and rash (22%) were the most common AEs. Eight pts (23%) experienced AEs after IT N administration, all gr 1. Initial efficacy analysis included only pts (n=19) treated with first three dose levels (5-20mg). Median follow-up for these pts is 4.5 months (mos) (1.1, 31.5 mos) and median OS is 63 % at 3 mos, 42 % at 6 mos and 30% at 12 mos. **Conclusions:** The trial demonstrates the feasibility and safety of IT administration of modern immunotherapy for MM pts with LMD. No unexpected systemic or neurological toxicity was observed with 20mg IT N. 2 additional patients are required to complete the 50mg IT N cohort. OS rates at 6 and 12 mos are encouraging and support further evaluation of IT administration of immunotherapy agents for pts with MM and LMD. Final presentation will include results of LMD for all dose cohorts, composite response assessment and comparative analysis of longitudinal CSF samples to assess immunologic effects. Clinical trial information: NCT03025256. Research Sponsor: Bristol Myers Squibb .

9520 **Poster Discussion Session**

Phase II Study of TRIplet combination Nivolumab (N) with Dabrafenib (D) and Trametinib (T) (TRIDeNT) in patients (pts) with PD-1 naïve or refractory BRAF-mutated metastatic melanoma (MM) with or without active brain metastases. *First Author: Elizabeth M. Burton, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Targeted therapies (TT) & immunotherapies (IMT) have improved survival for pts with BRAF V600 mutated stage IV MM, however many pts still progress and ultimately die from their disease. Preclinical data support the rationale for combining TT and IMT, but trials evaluating triplet combinations in IMT-naïve pts have reported mixed results. Notably, pts with untreated brain metastases (BM) were excluded from prior triplet trials and have a median PFS of 5.6 months when treated with TT. Further, there remains an unmet need for effective therapies for pts after IMT failure, as retrospective studies have reported short median PFS (5 mos) for TT in this setting. We hypothesized that N in combination with DT is safe and will demonstrate clinical activity in BRAF-mutated pts naïve or refractory to PD1 therapy and in pts with BM. **Methods:** We conducted a single arm phase II study (NCT02910700) of NDT in pts with BRAF-mutated, unresectable stg III or stg IV MM. Prior IMT was allowed, but prior BRAF/MEKi was not. Pts with untreated BM and asymptomatic or mildly symptomatic/requiring steroids were also allowed. Pts received 3mg/kg IV Q2wks of N (later amended to 480 mg IV Q4wks), 150mg PO BID of D and 2mg PO QD of T, all starting on Day 1. The primary objective was to determine safety and efficacy (ORR by RECIST 1.1). Monitoring for safety and futility using Bayesian stopping rules was performed. Longitudinal tissue and blood samples were collected to perform correlative analyses. **Results:** Following a 6 pt safety run-in with no observed DLTs, 27 pts were treated w NDT. 17 pts were PD1 refractory, 10 were PD-1 naïve. 10 of these 27 pts had a history or presence of BM, including active BM. Median follow up was 18.4 months (range 3.2-45.9). ORR in 26 evaluable pts was 92% (3 CR, 21 PR). Among the PD1 refractory pts evaluable for response (n = 16), ORR was 88% (2 CRs, 12 PR). All 10 evaluable PD-1 naïve pts achieved a response. 4 of 7 evaluable pts w BM achieved an intracranial response (57%), including 2 CRs. The median PFS for all pts was 8.5mos (8.5mos in PD1 naïve pts, 8.2mos in PD1 refractory pts). Median PFS for pts without BM was 8.5mos, 8.0 mos for those with BM. Median OS for all pts was not reached, and no statistically significantly difference in OS by PD1 exposure or presence of BM. 78% of pts experienced treatment related grade 3/4 AEs and 6 pts (22%) discontinued all 3 drugs due to toxicities. **Conclusions:** NDT at full doses of all 3 agents has a toxicity profile consistent with previously reported triplet combinations and shows promising clinical activity in pts with IMT refractory disease and with BM. There were no significant differences in outcomes between pts with and without BM. Translational studies to delineate predictors and mechanisms of response and resistance are ongoing. Clinical trial information: NCT02910700. Research Sponsor: BMS.

9521 **Poster Discussion Session**

An immunogenomic analysis of melanoma brain metastases (MBM) compared to extracranial metastases (ECM). *First Author: Lucy Kennedy, Duke University Medical Center, Durham, NC*

Background: Previous work has shown that MBM have a unique molecular profile compared to ECM. Description of the biology of MBM will facilitate the design of rational therapies for patients (pts) with MBM. **Methods:** We analyzed a previously published dataset from MD Anderson Cancer Center, which includes RNA-seq on surgically resected FFPE MBM (88 tumors from 74 pts) and surgically resected ECM from the same pts (50 from 34 pts). WES on 18 matched pairs of MBM and ECM was available. The STAR pipeline was used to estimate mRNA abundance. The DESeq2 package was used to perform differential gene expression (DGE) analyses. Pathway analysis was performed using Gene Set Enrichment Analysis (GSEA). Paired DGE and GSEA analyses comparing MBM vs. lymph node metastases (LN mets, n = 16) and MBM vs. skin mets (n = 10) were performed. CIBERSORT estimated relative abundance of immune cell types in MBM and ECM. The GATK Mutect2 pipeline was used to call somatic mutations using paired normal tumor samples. Mutations were annotated using the Ensembl Variant Effect Predictor and visualized using the Maftools package in R. RNA-seq was available on 54 primary cutaneous melanoma (CM) pt samples, including 19 CM which did not recur, 19 CM which recurred as MBM, and 16 CM which recurred as ECM. Gene Ontology or KEGG Pathway analysis was performed using goana function of limma package in R. **Results:** Comparing MBM vs. LN and MBM vs. skin mets, paired DGE identified 136 and 89 up-regulated genes with a fold change > 2 and false-discovery rate (FDR) q-value < 0.05. Moreover, 308 and 659 down-regulated genes with a fold change < 0.5 were identified in MBM vs. LN and MBM vs. skin mets, respectively ($q < 0.05$). Paired GSEA found that autophagy signaling pathways may be up-regulated in MBM vs. LN and MBM vs. skin mets. On a single-gene level, comparing both MBM vs. LN and skin mets, the most strongly up-regulated genes in autophagy pathways were GFAP and HBB, whereas fold changes in the majority of other autophagy-related genes were low and did not reach significance. Comparison between CM which recurred in brain vs. CM which did not recur identified up-regulation of autophagy pathways. No difference in autophagy pathway expression was observed comparing between CM with any recurrence vs. without recurrence. CIBERSORT identified an increased proportion of immune suppressive M2 macrophages compared to tumor suppressive M1 macrophages in both MBMs and ECMs. **Conclusions:** Up-regulation of autophagy pathways was observed in pt-matched MBM vs. LN and skin mets. This finding seemed to be driven by up-regulation of GFAP and HBB, which could reflect changes in the tumor microenvironment (TME). Future studies using single-cell RNA-seq or spatial transcriptomic technology will dissect the TME. A higher M2:M1 ratio may contribute to an immune suppressive tumor microenvironment in MBM and ECM and is targetable. Validation of our findings in an independent Duke dataset is ongoing. Research Sponsor: None.

9522 **Poster Discussion Session**

Characterizing the tumor and immune landscape of melanoma patients treated with combined checkpoint blockade and MAPK targeted therapy.

First Author: Liron Zisman, Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel

Background: Melanoma therapy has been revolutionized by two novel therapeutic approaches: mitogen activated protein kinase (MAPK) targeted therapy (MTT) and immune checkpoint blockade therapy (ICB). Less than half of patients respond to ICB monotherapy, in part due to non-responsive tumor microenvironment (TME). It previously has been shown that MTT enhances anti-tumor immunity within the TME, thus providing a strong rationale for its combination with immunotherapy. Regimens combining MTT with ICB have had mixed results, and which patients should be treated with these combinations is unknown. **Methods:** The first arm (NCT03149029) of a planned two stage design was to enroll 14 patients (pts) harboring $BRAF^{V600}$ mutation treated with 2 weeks (wks) of MTT (dabrafenib plus trametinib) then 6 wks of concomitant MTT and pembrolizumab, followed by single-agent pembrolizumab thereafter. The primary endpoint is clinical benefit (CB) defined as partial/complete response or stable disease (per RECIST1.1) persisting at 24 wks. If 9 of 14 pts had CB, then 11 more pts would be enrolled for a total cohort of 25. Serial biopsies were performed prior to MTT, following the 2-week lead-in of MTT, and following six wks of combination immune therapy and MTT. Single-cell RNA-seq profiling of $CD45^+$ and $CD45^-$ cells was performed using both the smart-seq2 plate-based protocol and 10x genomics platform. **Results:** Sixteen pts were enrolled, with 14 receiving both MTT and ICB. Two pts did not receive ICB due to MTT toxicity. Only 5 had CB, and the second stage did not open. A 6th pt had CB extracranially with a new small brain met at wk 24 scans was considered CB for tumor analysis. A clustering analysis of 25 samples (n = 9 pts) showed that following MTT the abundance of CD8 T-cells as well as tumor IFNγ levels were significantly elevated in CB vs. no CB (NCB) patients. In addition, tumor associated macrophages (TAM) in NCB patients possessed mainly an M2 phenotype and expressed a significantly higher level of immune suppressor genes, such as HLA-G and CD52. Interestingly, NCB pts had a significantly higher expression of tumor TGFβ, which is a strong inducer of M2 macrophages. In contrast, most of the TAMs occupying the tumor of the CB pts had the M1 phenotype, and significantly expressed CD9, CD81 and CD82, important factors during antigen recognition and immunological synapse formation. **Conclusions:** Abbreviated MTT with ICB did not lead to increased clinical benefit at 24 wks in this small study. It is theorized that the tumor's ability to create a unique microenvironment by producing certain factors (e.g. TGFβ), modifies the immune system and may tilt its path into immune suppression thereby reducing the efficacy of this combinatorial therapy in melanoma pts with metastatic disease. These results may help identify pts most likely to benefit from combined MTT plus ICB and new targets to overcome resistance to these regimens. Clinical trial information: NCT03149029. Research Sponsor: Merck, U.S. National Institutes of Health.

9523 **Poster Discussion Session**

Effects of baseline lactate dehydrogenase (LDH), interferon gamma (IFN-g) expression, and tumor mutational burden (TMB) on treatment response to first-line atezolizumab (A) + vemurafenib (V) and cobimetinib (C) in $BRAF^{V600}$ mutation–positive advanced melanoma.

First Author: Caroline Robert, Gustave Roussy and Université Paris-Saclay, Villejuif-Paris, France

Background: The phase 3 IMspire150 study showed that first-line A+V+C improved investigator-assessed PFS vs placebo (P)+V+C in $BRAF^{V600E/K}$ mutation–positive advanced melanoma (hazard ratio 0.78; P= .0249). Prior biomarker analyses showed that IFN-g or TMB > 10 mut/Mb were associated with greater PFS benefits with A+V+C (Lewis et al. *J ImmunoTher Cancer* 2020;8:A188-A189). We further evaluated the association of these biomarkers with outcomes. **Methods:** Exploratory recursive partitioning analysis (RPA) was used to model associations between PFS and age (< 65 vs ≥65 y), Eastern Cooperative Oncology Group performance status (0 vs 1), liver metastases (yes vs no), metastatic sites (≤3 vs > 3), sum of longest tumor diameters (< 44 mm vs ≥44 mm), baseline LDH (normal [n] vs elevated [e]), TMB (< 10 vs ≥10 mut/Mb), PD-L1 (negative vs positive), and IFN-g (high [h; > Quartile 3; Q3] vs intermediate [> Q1 and ≤Q3] vs low [≤Q1]). Time-to-event analyses were summarized using Kaplan-Meier estimates. **Results:** The RPA analysis included 208/256 (81.3%) patients (pts) from the A+V+C arm of IMspire150 for whom LDH, TMB, IFN-g, and PD-L1 data were available. RPA showed that LDH was associated with PFS. In pts treated with A+V+C and n-LDH, h-IFN-g signature was associated with longer PFS and higher rates of objective response (OR) and complete response (CR) vs low/intermediate (l/i) IFN-g (2-y PFS: 59% vs 38%; ORR: 77% vs 69%; CR: 38% vs 15%, respectively); TMB ≥10 mut/Mb was associated with more favorable outcomes in pts with e-LDH (Table). In contrast, neither IFN-g nor TMB discriminated PFS outcomes in n-LDH or e-LDH pt subgroups receiving P+V+C. Pts with e-LDH and TMB < 10 mut/Mb had poor PFS outcomes, with 2-y PFS rates of 9% and 3% and lower rates of OR (51% and 62%) and CR (5% and 9%) in the A+V+C and P+V+C arms, respectively. Similar trends were observed for duration of response (DOR), and for the subset of pts with $BRAF^{V600E}$ mutation–positive melanoma. A+V+C improved PFS vs P+V+C across all subgroups with the exception of e-LDH and TMB < 10. **Conclusions:** IFN-g and TMB discriminated PFS benefit in pts receiving A+V+C but not for those receiving P+V+C. Durable responses were observed for pts treated with A+V+C in the n-LDH + h-IFNg subgroups. Research Sponsor: F. Hoffmann-La Roche.

	n-LDH + h-IFN-gamma	n-LDH + l/i-IFN-gamma	e-LDH + TMB ≥10	e-LDH + TMB < 10
A+V+C, n	26	110	35	37
Median PFS, mo (95% CI)	Not estimable (NE; 15.3-NE)	16.6 (11.1-23.0)	11.4 (6.2-NE)	5.6 (4.3-10.6)
Median DOR, mo (95% CI)	NE (16.8-NE)	20.4 (14.8-NE)	14.8 (10.4-NE)	9.0 (4.5-NE)
P+V+C, n	47	94	32	32
Median PFS, mo (95% CI)	12.9 (10.1-18.9)	12.5 (9.5-21.3)	7.3 (5.6-16.9)	7.6 (6.1-11.1)
Median DOR, mo (95% CI)	12.0 (9.4-NE)	18.7 (11.1-NE)	14.5 (7.7-NE)	7.7 (5.7-14.5)

9524 **Poster Discussion Session**

TMB and *BRAF* mutation status are independent predictive factors in stage IIIC/D/IV melanoma patients receiving adjuvant PD-1 antibodies.

First Author: Andrea Forschner, Department of Dermatology, University Hospital of Tuebingen, Tuebingen, Germany

Background: High tumor mutational burden (TMB) is associated with a favorable outcome in metastatic melanoma patients treated with immune checkpoint inhibitors. However, data are limited in the adjuvant setting. As BRAF mutated patients have an alternative with targeted adjuvant therapy, it is important to identify predictive factors for relapse and recurrence-free survival (RFS) in patients receiving adjuvant PD-1 antibodies. **Methods:** We systematically evaluated all melanoma patients who started adjuvant PD-1 antibody therapy at our center between March 2018 and September 2019 to identify predictive factors for outcome. The median follow-up time from start of adjuvant anti-PD-1 therapy was 22 months. Tumor and normal tissue of all stage IIIC/D/IV patients and of stage IIIA/B patients with relapse were sequenced using a 700 genes panel. Predictive factors for relapse and RFS were identified using univariate and multivariate logistic and Cox regression analysis. RFS was estimated by the Kaplan-Meier method. TMB high was defined as the top 20 % of the cohort, corresponding to TMB values ≥ 20 Var/Mb. **Results:** A total of 165 patients were included in this study. According to AJCC 8th the initial tumor stages at the beginning of adjuvant anti-PD-1 therapy were as follows: N = 80 stage IIIA/B (48 %), N = 85 stage IIIC/D/IV (52 %). 72/165 patients (44 %) suffered a relapse, 44/72 (61 %) with loco regional and 28/72 (39 %) with distant metastases. Sequencing results were available from 79 / 85 patients with stage IIIC/D/IV. Here we present the results of this cohort. TMB low (OR 17.46, 95%CI 4.03-75.55; p < 0.0001) or absence of BRAF V600E/K mutation (OR 4.13, 95%CI 1.36-12.53; p = 0.012) were statistically significant, independent predictive factors for relapse. Also, with regard to RFS, BRAF mutation status and TMB were statistically significant and independent predictive factors. In the table below we display results for the combined variables. Patients with BRAF V600E/K mutation and TMB high had the best outcome. **Conclusions:** We identified TMB high as positive predictive marker in stage IIIC/D/IVmelanoma patients with adjuvant PD-1 antibody therapy. In tumors with *BRAF* V600E/K mutation and concurrent low TMB, adjuvant targeted therapy with BRAF- and MEK-inhibitors may be an alternative. This is also supported by the data on adjuvant dabrafenib and trametinib, which showed a greater advantage in patients with low TMB, presumably due to less tumor heterogeneity. Research Sponsor: None.

Characteristic	No relapse N = 34	Relapse N = 45	*p*	1-year RFS (%; 95%CI)	2-year RFS (%; 95%CI)	*P*
BRAF V600E/K mutation + TMB high	4	0	*< 0.0001*	100	100	*< 0.0001*
No BRAF V600E/K mutation + TMB high	11	3		86 (67-100)	78 (56-100)	
BRAF V600E/K mutation + TMB low	12	13		56 (37-75)	42 (20-65)	
No BRAF V600E/K mutation + TMB low	7	29		33 (18-49)	19 (6-32)	

9525 **Poster Session**

Improved pyrexia-related outcomes associated with an adapted pyrexia adverse event (AE) management algorithm in patients (pts) treated with adjuvant dabrafenib + trametinib (dab + tram): Primary results of COMBI-APlus.

First Author: Victoria Atkinson, Princess Alexandra Hospital, University of Queensland, Greenslopes, Brisbane, QLD, Australia

Background: The long-term benefit of adjuvant dab + tram in pts with resected stage III *BRAF* V600E/K–mutant melanoma was demonstrated in COMBI-AD where AEs led to permanent discontinuation of dab + tram in 26% of pts, most often due to pyrexia (9%). The COMBI-APlus trial (NCT03551626) is designed to evaluate whether an adapted pyrexia management algorithm could reduce high-grade pyrexia and other pyrexia-related adverse outcomes, such as treatment cessation and hospitalization. **Methods:** COMBI-APlus is an open-label, Phase IIIb trial evaluating an adapted pyrexia management algorithm in pts with high-risk resected stage III BRAF V600E/K–mutant melanoma treated with 12 mo of adjuvant dab + tram. In the adapted algorithm, both dab and tram were interrupted promptly at the onset of pyrexia (temperature ≥ 38°C). In the event of suspected recurrent pyrexia, treatment may be interrupted in the presence of pyrexia syndrome (ie, chills, rigors, night sweats, or influenza-like symptoms without temperature ≥ 38°C) at investigator discretion. Treatment with dab + tram was restarted at the same dose level once pts were symptom free for ≥ 24 hours. The primary endpoint is the composite rate of grade 3/4 pyrexia, hospitalization due to pyrexia, or permanent discontinuation due to pyrexia vs a historical control from COMBI-AD (20%; 95% CI, 16.3%-24.1%). Secondary endpoints include relapse-free survival (RFS) and safety. **Results:** A total of 552 pts were enrolled. At the data cutoff (5 Oct 2020), all pts had completed 12 mo of treatment; median duration of follow-up was 18.4 mo. COMBI-APlus met its primary endpoint of significant improvement in composite rate of pyrexia. The composite rate was 8.0% (95% CI, 5.9%-10.6%), with rates of 3.8% for grade 3/4 pyrexia, 4.3% for hospitalization due to pyrexia, and 2.4% for discontinuation due to pyrexia. The estimated 12-mo RFS rate was 91.8% (95% CI, 89.0%-93.9%). The most common AEs (≥ 20%) were pyrexia (67.8%), headache (31.7%), blood creatine phosphokinase increase (27.9%), diarrhoea (27.0%), chills (26.4%), fatigue (25.7%), asthenia (23.6%), nausea (23.4%), rash (21.4%), and arthralgia (21.0%). AEs of any type led to permanent dab + tram discontinuation in 14.7% of pts. **Conclusions:** This primary analysis suggests the new adapted pyrexia management algorithm is effective in reducing grade 3/4 pyrexia, pyrexia-related hospitalization, and treatment discontinuation in pts receiving adjuvant dab + tram. The early efficacy appears consistent with that observed in COMBI-AD. The growing experience of oncologists in managing pyrexia with this simple algorithm may reduce the need for hospitalization or visits to a healthcare provider, which is highly desirable during the current COVID-19 pandemic. Thus, more pts can remain on treatment and derive benefit. Clinical trial information: NCT03551626. Research Sponsor: Novartis.

9526 **Poster Session**

Overall survival in patients who received checkpoint inhibitors after completing tebentafusp in a phase 3 randomized trial of first-line metastatic uveal melanoma. *First Author: Marlana Orloff, Sidney Kimmel Medical College of Thomas Jefferson University, Philadelphia, PA*

Background: Tebentafusp (tebe) is a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells. Tebe significantly improved OS compared to investigator's choice (IC) in first line (1L) mUM [NCT03070392]. In a phase (ph) 2 study of tebe in 2L+ mUM (NCT02570308), several checkpoint inhibitor (CPI) refractory pts who were retreated with CPI after tebe achieved durable clinical benefit [1]. We therefore evaluated clinical outcomes of post-tebe CPI in patients treated on the ph3 trial of tebe versus investigator's choice (IC) [NCT03070392]. **Methods:** In the ph3 trial, 378 HLA-A*02:01+ 1L mUM pts were randomized 2:1 to tebe (n=252) or IC (n=126) [pembrolizumab (82%), ipilimumab (12%) or dacarbazine (6%)]. No crossover to tebe was permitted, investigators were free to choose subsequent therapy, and there was no re-randomization at time of subsequent therapy. This analysis was conducted on the first interim analysis (data extracted Nov-2020). When pts received more than one subsequent therapy, the first was used in these analyses. Medians and 1-yr OS from the start of post-study therapy are obtained from standard Kaplan-Meier analyses; hazard ratios (HR) are from Cox regression models adjusted for age and gender. **Results:** 106/252 (42%) tebe pts received ≥ 1 subsequent therapy: 35% CPI, 9% chemo, 6% liver directed therapy (LDT), 6% other. 55/126 (44%) of IC pts received ≥ 1 subsequent therapy: 21% CPI, 10% chemo, 12% LDT, 10% other. Median time to first subsequent therapy was longer for tebe pts at 5.2 mo vs. IC pts at 3.8 mo. The median duration from start of first subsequent CPI to end date was longer in the prior tebe pts at 4 mo vs prior IC pts at 2.8 mo. From the start of any first subsequent therapy, prior tebe pts had longer OS compared to prior IC pts, HR 0.67 (95% CI 0.42, 1.07). Most of the subsequent therapy was CPI, and the OS benefit was also seen in this subset, HR 0.62 (95% CI 0.34, 1.14). For prior tebe pts, the median and 1-yr OS rates from start of any first subsequent therapy were 13 mo and 53% and from start of first subsequent CPI were 16 mo and 63%. Both were higher than the sequence of IC followed by any therapy (11 mo and 44%), IC followed by CPI (9 mo and 47%) and a recent meta-analysis of 2L+ mUM (7 mo and ~35% 1-yr OS rate). **Conclusions:** Pts who progressed on tebe and then received CPI had better OS compared to pts who progressed on IC and then received CPI. Further analysis will explore whether confounding factors are influencing this effect. These exploratory data suggest that tebe, relative to IC, may improve outcomes to subsequent CPI. (1)Yang J. et al. ASCO 2019, *J. Clin Oncol* 37:15_suppl, 9592. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9527 **Poster Session**

Co-primary endpoint of overall survival for tebentafusp (tebe)-induced rash in a phase 3 randomized trial comparing tebe versus investigator's choice (IC) in first-line metastatic uveal melanoma. *First Author: Jessica Cecile Hassel, Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany*

Background: Tebe is a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells. In this Phase (Ph) 3, randomized trial of first line (1L) metastatic uveal melanoma (mUM) [NCT03070392], tebe significantly improved overall survival (OS) vs. investigator's choice (IC) in the intention-to-treat population (ITT). In previous trials, tebe-related skin adverse events (AEs), hypothesized to be on-target, off-tumor activity against gp100-expressing melanocytes, were associated with improved OS. This association was tested prospectively as a co-primary endpoint in the Ph3 study. **Methods:** 378 1L HLA-A*02:01+ mUM pts were randomized 2:1 to tebe (n = 252) or IC (n = 126). Co-primary endpoints were 1) OS in all randomized pts (ITT) and 2) OS in tebe-randomized pts who develop any grade rash in week (wk) 1 vs. all receiving IC. Rash was defined as composite of preferred AE terms. Melanocyte-related AEs (MRAEs) were defined as pigment change AEs in the skin or hair. Overall study-wide alpha was controlled at 0.05, with 90% assigned to ITT and 10% to rash. This analysis was conducted on the first interim analysis (data extracted Nov-2020). **Results:** In the 245 tebe treated pts, the characteristic skin related AEs included most frequently rash (at any time) in 201 pts (82%), pruritis in 167 pts (68%), MRAEs in 109 pts (45%) and erythema in 69 pts (28%). While rash, erythema and pruritis mostly occurred in the first 4 weeks, MRAEs occurred after a median of 2.7 mo. Rash captures most pts, 201/227 (89%), who have any of these skin related AEs. Rash occurred in 146 pts (60%) by wk 1; 179 pts (73%) by wk 2; and 195 pts (80%) by wk 3. Tebe pts with wk 1 rash had significantly longer OS vs. the IC arm, HR 0.35 (95% CI 0.23, 0.53), $p < 0.0001$. The estimated 1-yr OS rates were 83% vs 58%, respectively. When expanded to include tebe pts with rash through wk 3, the 1-yr OS rate of 75% was still numerically higher than IC. The 50 (20%) tebe pts who did not experience rash by week 3 had 1-yr OS rate of 55%. **Conclusions:** In 1L mUM pts, tebe significantly improved OS compared to IC in the ITT analysis. Week 1 rash, presumed due to tebe redirection of T cells to gp100+ skin melanocytes, was associated with a very strong OS benefit. Therefore, rash may be a marker that the immune system can be mobilized by tebe to target gp100+ cells. The vast majority of tebe pts will develop a rash at some point, and tebe pts without rash may still derive benefit. Clinical trial information: NCT03070392. Research Sponsor: Immunocore.

9528 **Poster Session**

Results of phase II randomized study of intermittent versus continuous schedule of vemurafenib plus cobimetinib in BRAF-mutated advanced melanoma. *First Author: Maria Gonzalez-Cao, Instituto Oncológico Dr. Rosell, Barcelona, Spain*

Background: Combination of vemurafenib plus cobimetinib is approved for the treatment of BRAF-mutated advanced melanoma. Although patients initially respond to treatment, resistance emerges before 18 months in most cases. One of the key pre-clinical observations that supported an intermittent schedule was that resistant tumors suffer a fitness deficit in the absence of the drug, so modulation of the drug pressure through an intermittent dosing could delay the emergence of resistance. **Methods:** GEM1501 is a randomized phase 2 study comparing the activity of the combination of vemurafenib 960 mg every 12 h/d plus cobimetinib 60 mg/d in a standard (arm A) versus intermittent schedule (arm B). Arm A: four-week (w) cycles of daily vemurafenib for 4w plus cobimetinib for 3w-on and 1w-off-treatment. Arm B: first three cycles according to the standard schedule, followed by 6w-cycle with 2w-off vemurafenib & 3w-off cobimetinib. Primary endpoint was progression free survival (PFS) and secondary were objective response (OR) and treatment-related adverse events (TAEs). **Results:** 70 treatment-naïve patients were included. Results in arms A and B: median PFS 16.2 (95%CI 9.5, 24.1) vs 6.9 months (95%CI 5.2, 9.3) (p = 0.079)**;** OR in 25 (71.4%) (8 complete -23%-) vs 21 (60%) patients (5 complete -14%-); G3-4 TAEs 42.8% vs 40.0%, respectively. Analysis of $BRAF^{V600}$ mutation in tumoral cell free DNA (cfDNA) was performed in serial plasma samples in 41 patients. Twenty-one (51%) patients had detectable $BRAF^{V600}$ mutation in pretreatment cfDNA (preBRAF+). Significant differences in PFS were found according to preBRAF^{V600}: 8.2 months (95%CI 5.2, 13.6) in preBRAF+ vs non-reached (NR) (95%CI 2.8, NR) in preBRAF- (p = 0.017). In arm A, median PFS was 13.3 months (95% CI 4.6, NR) in preBRAF+ vs NR (95% CI 2.3, NR) in preBRAF-. In arm B, median PFS was 6.2 months (95% CI 0.3-8.3) in preBRAF+ vs NR (95%CI 2.8, NR) in preBRAF- (p = 0.003).$BRAF^{V600}$ mutation became undetectable in cfDNA after treatment initiation in all preBRAF+ patients. Different kinetic of $BRAF^{V600}$ mutation in cfDNA was found according to treatment arm. At progression, $BRAF^{V600}$ reappeared in cfDNA in all (5/5) cases treated in arm B, but only in 50% (3/6) of cases in arm A. NGS analysis of cfDNA at progression suggested different resistance mechanisms. **Conclusions:** The results of this study do not support the use of an intermittent schedule of vemurafenib plus cobimetinib in advanced melanoma. $BRAF^{V600}$ detection in pretreatment cfDNA is a prognostic factor of poor survival that it is independent of treatment schedule, although most striking differences favoring continuous arm vs intermittent arm were found in patients with detectable $BRAF^{V600}$ mutation on pretreatment cfDNA. Further research is required to determine the clinical value of the analysis of resistance mechanisms in cfDNA. Clinical trial information: 2014-005277-36. Research Sponsor: Spanish Melanoma Group, Pharmaceutical/Biotech Company.

9529 **Poster Session**

A phase 2 clinical trial on trametinib and low-dose dabrafenib in advanced pretreated $BRAF^{V600}/NRAS^{Q61R/K/L}$ wild-type melanoma (TraMel-WT): Interim efficacy and safety results. *First Author: Gil Awada, Department of Medical Oncology, Universitair Ziekenhuis Brussel, Brussels, Belgium*

Background: The mitogen-activated protein kinase (MAPK) pathway can be activated by alternative driver mutations in $BRAF^{V600}/NRAS^{Q61R/K/L}$ wild-type (wt) melanoma. MEK-inhibitor monotherapy has activity in $BRAF^{V600}/NRAS^{Q61R/K/L}$ wt melanoma, but is associated with considerate skin toxicity. Skin toxicity associated with the MEK-inhibitor trametinib (T) can be effectively mitigated by adding a low dose (50 mg BID) of the BRAF-inhibitor dabrafenib (LD-D) (Awada et al. Ann Oncol 2020). **Methods:** This two-stage, single-center phase 2 trial investigated T 2 mg QD in patients (pts) with advanced $BRAF^{V600}/NRAS^{Q61R/K/L}$ wt melanoma who previously progressed on treatment with checkpoint inhibitors. In case of dose-limiting T-related skin toxicity, LD-D (50 mg BID) was added to T (pre-amend). The trial was amended in June 2019 to administer T upfront with LD-D (post-amend). Objective response rate (ORR, by RECIST v1.1) served as the primary endpoint. A Simon's two-stage optimal design was used (p_0 0.10; p_1 0.30; alpha 0.05; power 0.80): in case of > 1 OR in the first 10 pts, 19 additional pts would be included in stage 2. The trial is considered positive if > 5 OR are observed. **Results:** As of February 9, 2021, 16 pts (3 pre-amend; 13 post-amend) were included (median age 56.5; male 56.3%; stage IIIB 6.3%, IV-M1a-c 68.8%, IV-M1d 25.0%; ECOG performance status 0-1 93.8%; normal lactate dehydrogenase 56.3%). Median duration of follow-up is 17.9 weeks (wks; range 1.9-90.1). The ORR in 14 evaluable pts is 42.9% (5 confirmed and 1 unconfirmed partial response), the disease control rate is 71.4%. Four OR are ongoing after a median follow-up of 8.0 wks (range 0.0-77.0), 2 responding pts progressed on therapy after respectively 16.6 and 24.0 wks. Four out of 6 OR are observed in pts with MAPK-pathway activating mutations (3 class II *BRAF* and 1 *GNAQ* mutation). Eight pts (50.0%) have progressed (median progression-free survival 16.4 wks [95% confidence interval [CI] 6.9-25.9]); 4 pts (25.0%) have died (median overall survival 54.7 wks [95% CI 37.6-71.8]). Adverse events (AE) are observed in all pts (grade [G] 3-4 9 [56.3%]). Two pre-amend pts added on LD-D due to dose-limiting T-related skin toxicity; no clinically relevant T-related skin toxicity was observed post-amend with the upfront addition of LD-D. The most frequent AE were creatine kinase increase (G1-2 11 [68.8%]; G3-4 1 [6.3%]), and anemia and acneiform rash (both G1-2 7 [43.8%]; G3-4 0). Therapy was temporarily interrupted due to AE in 11 pts (68.8%) and permanently interrupted in 1 pt (6.3%) due to recurrent pneumonitis. **Conclusions:** In this two-stage phase 2 trial, T plus LD-D was found to have promising antitumor activity and acceptable toxicity in pts with advanced pretreated $BRAF^{V600}/NRAS^{Q61R/K/L}$ wt melanoma, especially in the presence of identifiable somatic MAPK-pathway activating mutations. Clinical trial information: NCT04059224. Research Sponsor: Stichting tegen Kanker, Pharmaceutical/Biotech Company.

9530 **Poster Session**

Discrepancies in response and immune-related adverse events (irAE) of anti-PD-1 monotherapy between races and primary sites in patients (pts) with advanced nonacral cutaneous melanoma (NACM). *First Author: Xue Bai, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Ultraviolet (UV)-induced high tumor mutation burden (TMB) of NACM is associated with response to anti-PD-1 monotherapy (aPD-1). Anatomic location of the primary lesion (reflecting UV exposure) and race (reflecting eumelanin level) may serve as surrogates for TMB and be associated with varying response and irAE patterns. **Methods:** Pts with advanced NACM receiving aPD-1 between 2009-2019 were retrospectively analyzed from 5 institutions in the US, Australia and China. Best response, survival (PFS and OS), and organ/system-specific irAEs were compared by race (Caucasian [C] vs non-Caucasian [NC]) and primary anatomic site. **Results:** Among 697 patients, 616 were C, 81 were NC. Complete response rate (CRR) was 24.8% (95%CI, 21.4-28.4) and 2.6% (95%CI, 0.3-9.1) and ORR was 54.9% (95%CI, 50.9-58.9) and 15.6% (95%CI, 8.3-25.6) in C and NC, respectively (both P<.001). Median PFS was 16.5 (95%CI, 12.0-23.1) and 5.2 (95%CI, 3.6-7.6) months, median OS was 60.5 (95%CI, 49.9-not reached [NR]) and 29.2 (95%CI, 17.9-NR) months, in C and NC, respectively (P<.001 and =.04). In multivariate analyses, C had significantly higher CRR (OR 13.4, 95%CI 3.1-57.4), ORR (OR 10.6, 95%CI 4.6-24.5), and longer PFS (HR 0.5, 95%CI 0.4-0.7) than NC. Compared to a head primary site, NACM from less UV-exposed regions had significantly lower CRR (upper trunk, OR 0.6, 95%CI 0.4-0.96; lower limb, OR 0.5, 95%CI 0.2-0.9), ORR (lower limb, OR 0.6, 95%CI 0.3-0.9) and poorer PFS (perineum/buttock, HR 2.1, 95%CI 1.2-3.5; lower limb, HR 1.6, 95%CI 1.2-2.2) and OS (perineum/buttock, HR 3.8, 95%CI 2.2-6.8; lower limb, HR 1.7, 95%CI 1.2-2.4). Overall irAE incidence was similar between C and NC but irAE subtypes varied. C had significantly higher incidence of GI (12.2%, 95%CI 9.5-15.3% vs 1.2%, 95%CI, 0.03-6.7%, P=.001), respiratory (10.3%, 95%CI 7.8-13.2% vs 0, P<.001) and grade 3/4 (15.4%, 95%CI 12.4-18.8% vs 6.2%, 95%CI 2.0-13.8%, P=.03) irAEs; and lower incidence of endocrine (13.8%, 95%CI 10.9-17.0% vs 32.1%, 95%CI 22.2-43.4%, P<.001) and liver (4.8%, 95%CI 3.2-7.1% vs 13.6%, 95%CI, 7.0-23.0%, P=.005) irAEs. IrAEs did not vary by primary NACM site. **Conclusions:** Race and primary site are independently correlated with distinct response and survival outcomes in pts with advanced NACM receiving aPD-1. IrAE subtypes vary by race although overall irAE incidence does not. Research Sponsor: None.

9531 **Poster Session**

Characterization of cytokine release syndrome (CRS) following treatment with tebentafusp in patients (pts) with previously treated (2L+) metastatic uveal melanoma (mUM). *First Author: Richard D. Carvajal, Department of Medicine, Herbert Irving Comprehensive Cancer Center, Columbia University Medical Center, New York, NY*

Background: Cytokine-mediated adverse events (AEs) are commonly reported in pts treated with T cell engaging therapies. Tebentafusp (tebe), a bispecific consisting of an affinity-enhanced T cell receptor fused to an anti-CD3 effector that can redirect T cells to target gp100+ cells, has shown an overall survival benefit for pts with untreated mUM in a Ph3 trial (NCT03070392). Here we reviewed the incidence, kinetics, and outcome of CRS in tebe-treated pts on the IMCgp100-102 trial of 2L+ pts with mUM (NCT02570308). **Methods:** 127 HLA-A*02:01+ 2L+ mUM pts were treated with tebe at the RP2D of 68mcg following intra-patient dose escalation of 20 mcg dose 1 and 30 mcg dose 2. Pts were monitored overnight to allow management of hypotension and other cytokine-related AEs. Because the rate of severe CRS was low in Ph1, prophylactic corticosteroids, antihistamines or acetaminophen were not mandated. CRS was evaluated post-hoc according to ASTCT Consensus Grading criteria [1]. Circulating cytokines in serum were measured before and at 8hr and 12-24hr after dosing for the 1st, 3rd and 4th doses (n=105). This analysis was conducted on the primary analysis snapshot dated 04Jun20. **Results:** The most frequent treatment-related AEs that were likely cytokine-mediated included fever (80%), chills (64%), nausea (59%), hypotension (41%) and hypoxia (4%). In a post-hoc review using ASTCT criteria, 86% of pts (n=109) had any grade CRS. The majority of these 109 pts had either grade (G) 1 (n=42; 33%) or G2 (n=62; 49%), with few G3 (n=4; 3.1%), one G4 (0.8%), and no deaths. Onset of CRS began within 24 hours of administration and G≥2 hypotension or hypoxia typically resolved within 2 days of onset. Most CRS events occurred after the first 3 doses with a marked reduction in the frequency and severity of CRS thereafter; G3-4 CRS was limited to first two doses. Only 2 pts discontinued tebe due to CRS (1 G3 and 1 G4). Treatment of G≥2 CRS included iv fluids (n=45), iv steroids (n=18), oxygen (n=8), and vasopressor use (n=2). No pts received tocilizumab. Tebe induced a transient increase in peripheral cytokines, including IFNγ, IL-10, IL-6 and TNFα, within hours of tebe dosing, which were several fold higher in pts with CRS compared to pts without CRS. Higher levels of TNFα trended with severity of CRS. **Conclusions:** CRS, a common AE observed with all T cell engaging therapies, was frequently observed within 24 hours of initial tebe treatment. Most CRS events were mild or moderate in severity even without the use of prophylactic premedications, were reversible with standard management strategies, decreased in frequency and severity with subsequent doses, and rarely led to treatment discontinuation. Pts with CRS tended to have greater increases in serum cytokines, consistent with tebe's proposed mechanism of action. [1] Lee, DW et al. *Biol Blood Marrow Transplant* 2019. Clinical trial information: NCT02570308. Research Sponsor: Immunocore.

9532 **Poster Session**

Triplet therapy with pembrolizumab (PEM), encorafenib (ENC) and binimetinib (BIN) in advanced, BRAF V600 mutant melanoma: Final results from the dose-finding phase I part of the IMMU-Target trial. *First Author: Lisa Zimmer, Department of Dermatology, University Hospital, University Duisburg-Essen; German Cancer Consortium (DKTK), Partner Site Essen, Essen, Germany*

Background: Survival of BRAF-mutated melanoma profoundly improved since the introduction of immune checkpoint inhibitors (ICI) and MAPK pathway inhibitors (MAPKi). Response kinetics of ICI and MAPKi are complementary, mechanistic evidence indicates that MAPKi may affect the tumor immune microenvironment. Combined use of both drug classes may further enhance clinical benefit. IMMU-Target was set-up as a prospective, open-label, phase I/II trial, with a safety phase I part followed by a randomized phase II part, to study the tolerability and clinical activity of PEM, ENC and BIN triplet therapy. **Methods:** Treatment naïve adult patients (pts) with stage IIIB-IV (AJCC 2017), BRAF V600 mutant melanoma with measurable disease but no active brain metastasis were eligible. The dose finding part used a 3+3 design, starting with a dose level (DL) 0 applying the clinically recommended doses of PEM (200 mg Q3W), ENC (450 mg QD) and BIN (45 mg BID). In case of ≥2 dose-limiting toxicities (DLT), a reduction of the ENC and BIN doses (300 mg QD and 30 mg BID at DL-1, 200 mg QD and 30 mg BID at DL -2) was foreseen. Primary endpoints of the phase I part were safety and tolerability. **Results:** From April 2018 until May 2020, 14 pts with BRAF V600 mutations were enrolled. 2 of 3 pts at DL 0 developed DLT (creatine phosphokinase (CPK) elevations grade 3 plus cytokine release syndrome grade 4; gamma glutamyl transferase (GGT) elevations grade 3), and had to stop therapy early. Therefore, 3+3 further pts at DL -1 were included with no DLT observed in these 6 pts. One (isolated GGT elevations grade 3) of the 2 DLT observed in the 3 pts of DL 0 enrolled initially was questionable as DLT, as the patient had further episodes of isolated GGT elevations without therapy. As a result, further 5 pts were enrolled at DL 0: here no DLT-matching treatment-related adverse event (TRAE) occurred. In total, 12 out of 14 pts (86%) experienced a TRAE and 7 (50%) experienced a grade ≥3 TRAE; there were no fatal AE or TRAE-related deaths. Increases in alanine and in aspartate aminotransferases, GGT and CPK elevations (6 of 14 pts) were the most common grade 3-4 TRAE. In median, pts at DL 0 (n=8) received triplet therapy for 18 weeks (IQR 7.5-29), at DL-1 (n=6) for 46 weeks (IQR 27-102). The overall response rate was 64% (95% CI=35-87). At a median follow-up of 10.0 months at DL 0 and 27.0 months at DL-1, progression-free survival at 12 months was 37.5% (95% CI 9- 67) and 60% (95% CI 13-88), respectively. **Conclusions:** Triplet therapy was feasible and safe at both dose levels leading to clinically meaningful disease control. The phase II part was not initiated, since the clinical efficacy of PEM plus ENC and BIN is currently investigated in STARBOARD (NCT04657991), a prospective, randomized, placebo-controlled (PEM mono), double-blinded phase III trial. Clinical trial information: NCT02902042. Research Sponsor: Funding in part by Merck Sharp & Dohme and Array/Pfizer.

9533 **Poster Session**

Patterns and management of progression on first-line ipilimumab combined with anti-PD-1 (IPI+PD1) in metastatic melanoma (MM) patients. *First Author: Ines Pires Da Silva, Melanoma Institute Australia, Sydney, Australia*

Background: First line IPI+PD1 induces long-term response in 36% of MM patients (pts); however, the majority of pts will progress and may require further treatment, which is yet to be established. We studied the patterns of progressive disease (PD) on 1st line IPI+PD1, and the management and outcomes in MM pts. **Methods:** Demographics, disease characteristics, nature of PD, subsequent treatments and outcomes were examined in MM pts with PD on 1st line IPI+PD1. Multivariable analyses (MVA) identified factors associated with patterns of PD: innate resistance (IR) = PD as best response or stable disease (SD) < 6 mo; acquired resistance (AR) = PD after initial response or SD ≥ 6 mo. **Results:** 310 MM pts from 14 melanoma centres were included; 208 (67%) had PD during and 102 (33%) after ceasing IPI+PD1. Overall med. progression-free survival (mPFS) was 2.8 mo (CI 95% 2.7 – 3.0); 187 pts (60%) had IR (mPFS 2.2 [2.1 – 2.5]), 112 pts (36%) had AR (mPFS 8.5 [7.2 – 10.2]) and 11 pts (4%) had pseudoprogression, i.e. PD followed by response without changing treatment (mPFS 2.7 mo [1.4 – NA]). On MVA, pts with ECOG PS ≥ 1 were more likely to have IR vs AR; and within IR pts, those with head & neck primary melanomas and lung metastases were more likely to have PD < 1.5 mo. Most pts with IR (68%) had PD in multiple sites, while 61% AR pts had PD in a single site. Brain was most common site of single organ PD; 49% of IR and 41% of AR. Med. follow-up from PD was 32.7 mo (28.1 – 36.8). After PD, 61 pts (20%) had best supportive care (26% of IR and 11% of AR pts). 259 pts (80%) received further treatment: 39% IR pts had systemic treatment (ST) only and 27% had ST + local; 31% AR pts had ST only and 39% had ST + local. Of 200 pts (65%) who had ST(+/-local), 54% had 1 line of ST and 46% had ≥ 2; 1st line ST (ST1) was BRAF/MEKi in 36% of pts, PD1 in 32%, IPI+PD1 in 7%, investigational drugs in 11%, chemotherapy in 9% and others in 5%. ORR in IR pts was lower than in AR pts for every type of ST1 (see Table). Med. OS from PD was 11.4 mo (CI 95% 9.6 – 16.1); IR 6.4 mo (CI 95% 5.6 – 10.2) and AR 26.1 mo (CI 95% 17.1 – NA). **Conclusions:** These data suggest longer OS from PD for AR vs IR pts independent of ST type. BRAF/MEKi, rechallenge with PD1+/-IPI and investigational drugs showed activity after PD on IPI+PD1, while chemotherapy has no role in this context. Research Sponsor: None.

ST after PD on IPI+PD1	BRAF/MEKi	PD1	IPI+PD1	Investigational drugs	Chemotherapy
ORR 1st line, n/N (%)					
IR	30/51 (59)	7/27 (26)	1/5 (20)	1/15 (7)	0/15 (0)
AR	13/20 (65)	11/36 (31)	3/9 (33)	1/6 (17)	0/3 (0)
Total	43/71 (61)	18/63 (29)	4/14 (29)	2/21 (10)	0/18 (0)
ORR any line, n/N (%)	61/102 (60)	26/79 (33)	9/36 (25)	7/47 (15)	1/42 (2)
Disease control rate 1st line, n/N (%)	53/71 (75)	35/63 (56)	6/14 (43)	7/21 (33)	0/18 (0)
mPFS 1st line, mo (95% CI)	8.9 (6.0-15.4)	5.0 (3.6-12.6)	7.5 (2.7-NA)	2.9 (2.0-4.9)	1.7 (1.3-2.2)
12-mo PFS rate (%)	42	37	35	6	6
mOS 1st line, mo (95% CI)	18.9 (12.4-30.0)	32.6 (18.7-NA)	15.6 (10.5-NA)	17.7 (16.1-NA)	4.4 (3.2-13.5)

9534 **Poster Session**

Characteristics and probability of survival for patients with advanced melanoma who live five or more years after initial treatment with immune checkpoint blockade (ICB). *First Author: Kimberly Loo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: A subset of melanoma patients treated with ICB (ipilimumab [ipi], nivolumab [nivo], pembrolizumab [pembro] or nivo+ipi) will experience durable responses. While five-year survival rates have been reported for patients treated with ICB on clinical trials, little is known about the clinical characteristics, survival past five years, and patterns of late relapse of long-term survivors. **Methods:** We retrospectively reviewed all patients treated at Memorial Sloan Kettering for unresectable stage III/IV melanoma who survived at least five years following their first dose of ICB (N = 151). Demographics, disease characteristics, and nature of progression were examined. Overall survival (OS) was calculated from 5 years post-ICB. Time to Treatment failure (TTF) was calculated conditionally from 5 years out until next therapy, progression, or death. **Results:** Of the 151 long-term survivors, median age at first ICB treatment was 62 years (range 22-83), with 101 (66.9%) male and 50 (33.1%) female patients. Stage at first ICB treatment was unresectable stage III (26, 17.2%), M1a (21,13.9%), M1b (39, 25.8%), M1c (52, 34.4%), M1d (13, 8.6%). Melanoma subtype was cutaneous (122, 80.8%), unknown primary (24, 15.9%), mucosal (3, 2%), and acral (2, 1.3%). First ICB was ipi (108, 71.5%), PD-1 (nivo or pembro) (5, 3.3%), and nivo+ipi (37, 24.5%). The best overall response to first ICB was CR (76, 50.3%), PR (27, 17.9%), SD (16, 10.6%) and PD (32, 21.2%). Of the patients who progressed after initial ICB, 38 received subsequent systemic treatment as follows: PD-(L)1 in 20 (53%), BRAF ± MEK in 9 (23.7%), ipi in 7 (18.4%), and chemotherapy in 2 (5.3%). Median duration of follow-up among survivors (N = 138) was 93 months (range 60-192). From 5 years post-ICB, 85% (95% CI: 73-92%) survived an additional 5 years. In those who made it to 5 years without treatment failure (N = 72), the probability of remaining failure-free was 92% (95% CI: 86-99%) at 7 years. Of the 151 patients, only 4 patients (2.6%) experienced disease progression after 5 years. Three patients had radiographic or pathologic disease progression in the lymph nodes and one in the subcutaneous tissue. No patients progressed in the lungs, visceral organs, or CNS after 5 years. At time of analysis, 13 (8.6%) patients died after 5 years post ICB, none died of progressive melanoma. 6 patients died of unknown causes, 2 died of other causes, and 5 died of other non-melanoma cancer-related causes. **Conclusions:** Patients who survive five years after their initial immunotherapy have excellent overall survival and treatment failure-free survival. Given the anxiety surrounding survivorship and late progression, long-term survivors should be reassured of their excellent prognosis. These data suggest that aggressive follow-up schedules and imaging of melanoma patients after 5 years of survival may not be required. Research Sponsor: None.

9535 **Poster Session**

Clinical characteristics of SF3B1 mutant (mut) uveal melanoma (UM) and response to immune checkpoint inhibition (ICI). *First Author: Joe M Grimes, Columbia University Vagelos College of Physicians and Surgeons, New York, NY*

Background: Metastatic UM is associated with a median overall survival (OS) $<$ 1 year (yr) and overall response rate (RR) to ICI $<$ 18%. SF3B1 mut UM represent a clinically unique subset of UM, distinct from BAP1 mut disease, characterized by aberrant spliceosome machinery which may result in increased neoantigen presentation, increased immunogenicity, and sensitivity to ICI. To assess these hypotheses, we performed a multicenter retrospective analysis to assess the natural history and response to ICI in patients (pts) with SF3B1 mut UM. **Methods:** Patients were identified from institutional databases and the AACR Project GENIE Consortium. Data collected included: baseline and recurrent disease characteristics, molecular characteristics, treatments received, treatment response, and vital status. Efficacy endpoints included investigator assessed RECIST RR and OS. **Results:** 58 pts with deleterious SF3B1 mutations were identified: 56 R625; 1 D781G; 1 G742D. Median age at diagnosis (dx) was 52 (range, 14-87). 50% were female. 49 pts developed distant metastases. The median time from initial dx to metastasis was 6.1 years (yrs; range, 0.9 to 26.7). Initial metastatic sites (n = 48) were: liver-only (52%); non-liver-only (29%); mixed liver and non-liver disease (19%). The most common initial metastatic sites were: liver (71%), lung (29%), soft tissue (13%), lymph node (8%), and bone (4%). The median OS for all pts from time of metastasis was 3.9 years (95% confidence interval (CI), 2.3-6.2) with OS for pts with non-liver only disease at 6.2 yrs vs those with liver-only or mixed disease at 3.4 yrs (hazard ratio = 2.12, p = 0.14). 1-year OS rate from time of metastasis was 94% (95% CI, 0.86-0.99). 34 pts received ICI for metastatic disease at which time 27% had received a prior systemic therapy (median, 0; range, 0-3) and 35% had received a prior hepatic regional therapy (median, 0; range, 0-6). 15 pts received single-agent anti-PD1; 4 received ipilimumab alone; 15 received dual ICI. 10 pts received ICI with concurrent hepatic regional tx. Best response among 33 evaluable pts were: 9% partial response; 39% stable disease; 52% progressive disease. Median OS from ICI initiation was 20.2 months (95% CI, 13.1-27.4). 1-year OS from ICI initiation was 74% (95% CI, 0.59-0.90). **Conclusions:** SF3B1 mut UM is characterized by later development of metastases, more common involvement of extrahepatic sites, and longer OS when compared with historical datasets of molecularly unselected UM. Although a modest RR to ICI was observed, the median OS and 1-year survival rate post-ICI are numerically superior to historical controls. Given the more indolent course of SF3B1 mut UM, stratification by SF3B1 status should be included in future clinical trials. Research Sponsor: None.

9536 **Poster Session**

Pembrolizumab and all-trans retinoic acid combination treatment of advanced melanoma. *First Author: Martin McCarter, University of Colorado Comprehensive Cancer Center, Aurora, CO*

Background: Myeloid-derived suppressor cells (MDSCs) are potent suppressors of antitumor immunity and are commonly associated with poor outcomes in melanoma patients treated with immune checkpoint inhibitors. Inducing the differentiation of MDSCs using all-trans retinoic acid (ATRA) reduces MDSC frequency. This analysis seeks to assess the safety and efficacy of combining ATRA and pembrolizumab in advanced melanoma patients. **Methods:** This single arm, single institution, phase I/II study (NCT03200847) enrolled 24 patients diagnosed with stage IV melanoma. Eligible patients were over the age of 18 and had not been previously treated anti-PD-1 therapy. Treatment consisted of 200mg Q3W pembrolizumab plus the supplemental treatment of 150 mg/m2 ATRA orally for 3 days surrounding each of the first four infusions of pembrolizumab, with patients continuing pembrolizumab for up to two years until confirmed disease progression or unacceptable toxicity. The primary endpoints were safety and reduction in circulating MDSCs. Secondary endpoints were overall response rate (ORR), disease control rate (DCR), progression free survival (PFS) according to RECIST v1.1. **Results:** At data cut off (Feb, 2021) 22 patients were evaluable for tumor response. Median follow-up was 1.0 years (0.3-2 years). In general, the combination of pembrolizumab and ATRA was well tolerated. The most common treatment-related adverse events (AEs) were grade 1 or 2, including headache (22 pts, 92%), fatigue (18 pts, 75%), rash (16 pts, 66%), and nausea (8 pts, 33%), most of which corresponded with the 3-day course of ATRA treatment. Ten patients had grade 3 or higher AEs with most being common ICI-related AEs. The ORR was 60% and DCR was 83%. Six-month PFS rate was 62%. Excluding patients diagnosed with uveal melanoma (n = 2) the ORR was 72%, DCR was 86%, and the six-month PFS rate was 68%. Paired analysis showed sustained decreases in absolute numbers (p = 0.002) and percentage (p = 0.007) of circulating MDSCs ($CD3^-CD19^-CD56^-CD11b^+CD33^+HLA\text{-}DR^{-/low}$) 4-6 weeks after stopping ATRA. The study is ongoing and further data will be presented in the future. **Conclusions:** This study demonstrates that the combination of ATRA and pembrolizumab is well tolerated and suggests that reducing MDSCs with ATRA may enhance the efficacy of pembrolizumab. This strategy of targeting MDSCs in combination with pembrolizumab warrants further development. Research Funding: Merck. Clinical trial information: NCT03200847. Research Sponsor: Merck Sharp & Dohme Corp.

9537 **Poster Session**

Safety and efficacy of lifileucel (LN-144), an autologous, tumor infiltrating lymphocyte cell therapy in combination with pembrolizumab for immune checkpoint inhibitor naïve patients with advanced melanoma. *First Author: Sajeve Samuel Thomas, University of Florida Health Cancer Center at Orlando Health, Orlando, FL*

Background: Tumor infiltrating lymphocyte (TIL) cell therapy has demonstrated safety and efficacy in advanced melanoma, both in the pre-immune checkpoint inhibitor (ICI) setting (Goff, JCO 2016) and in patients who have failed anti-PD-1/PD-L1 therapy (Sarnaik, 2020). Combination of TIL and pembrolizumab (pembro) in ICI-naïve patients has demonstrated encouraging efficacy data with acceptable safety in head and neck squamous cell carcinoma (Jimeno, 2020). To improve treatment options in early lines, we explore a combination of LN-144 and pembro in patients with ICI-naïve advanced melanoma. **Methods:** IOV-COM-202 is a Phase 2 multicenter, multi-cohort, open-label study evaluating TIL cell therapy in multiple settings and indications. We report on Cohort 1A enrolling ICI-naïve advanced melanoma (unresectable or metastatic) patients for treatment with a combination of LN-144 and pembro. Key eligibility criteria include $\leq$ 3 lines of prior therapy, ECOG $<$ 2, one resectable lesion for lifileucel manufacturing, and $\geq$ 1 measurable lesion for response assessment. Primary endpoints are objective response rate (ORR) per RECIST 1.1 and safety as measured by incidence of Grade $\geq$3 treatment-emergent adverse events (TEAE). LN-144 is generated at centralized GMP facilities in a 22-day process. A nonmyeloablative lymphodepletion (NMA-LD) using cyclophosphamide and fludarabine is administered preceding a single LN-144 infusion, followed by $<$ 6 doses of IL-2 (600,000 IU/kg). Pembro is administered after tumor harvest but prior to NMA-LD and continues after lifileucel per label. **Results:** Seven patients have received lifileucel in combination with pembro as of data extraction date (Feb 14, 2021). Five of the 7 treated patients were treatment-naïve, 1 patient had prior BRAFi + MEKi and 1 had received prior chemotherapy; 71% had liver/brain lesions, 43% had LDH $>$ ULN. Mean SOD for the target lesions was 111 mm, with 86% of patients with $>$ 3 target lesions, representing advanced disease at baseline for this patient group. The TEAE profile was consistent with the underlying disease and known AE profiles of pembro, NMA-LD and IL-2. Six patients had a confirmed objective response with an ORR of 86% (1 CR, 5 PR) and 1 best response of SD. Three of the responding patients have remained off pembro due to pembro related AEs for 3, 4 and 13 months (mos), yet maintaining response. All responding patients remain in response with the longest duration of response being 16.8 mos. **Conclusions:** Lifileucel can be safely combined with pembro in patients with ICI-naïve advanced melanoma. The ORR of 86% is encouraging when compared to pembro alone in a similar patient population, especially considering the disease burden at baseline and persistence of responses in patients off therapy. Enrollment is ongoing and updated data to be presented. Clinical trial information: NCT03645928. Research Sponsor: Iovance Biotherapeutics, Inc.

9538 **Poster Session**

The use of cryoablation to overcome resistance to PD-1 blockade in unresectable melanoma. *First Author: Meghan Mooradian, Massachusetts General Hospital Cancer Center, Boston, MA*

Background: Percutaneous image-guided cryoablation (cryo) is an established minimally invasive oncologic treatment that modulates the immune microenvironment. We hypothesized that cryo can augment anti-tumor responses in melanoma patients progressing on immune checkpoint inhibitors (ICI). **Methods:** In this non-randomized phase II single-center study, subjects with unresectable melanoma progressing on ICI underwent cryo of an enlarging lesion and ICI continuation for a minimum of 2 additional cycles. Computed tomography was performed at 6-8 weeks following cryo to determine tumor response in non-ablated lesions per RECIST1.1, with confirmatory scans at 8-12 weeks. The primary endpoint was safety and feasibility. Secondary endpoints were overall response rate (ORR) and disease control rate (DCR) with DCR defined as the percentage of pts who achieve complete response (CR), partial response (PR), and stable disease (SD). Correlative analyses on pre- and post-cryo tumor biopsy and blood samples were performed. **Results:** From May 2018 through July 2020, 20 pts were screened, 18 enrolled and 17 treated per protocol. All pts received prior PD-1/PD-L1 monotherapy and 12 (67%) experienced primary resistance to ICI. Median follow-up was 8.5 months. Ablated lesions included lymph nodes (n = 4), lung/pleura (n = 4), soft tissue/bone (n = 3), adrenal (n = 3), chest wall (n = 1), and kidney (n = 1). Peri-procedural events occurred in 3 cases (pneumothorax, diaphragm puncture, osteomyelitis). One pt. with underlying ICI-induced hypophysitis experienced an adrenal crisis post-procedure, which rapidly corrected with stress-dose steroid administration; there were no de novo immune-related adverse events post-ablation and there were no grade 4/5 events. In evaluable pts (n = 17), ORR was 18% and DCR was 47% (3 PR, 5 SD). To investigate the inflammatory state of the tumor microenvironment prior to cryo, PD-1, CD8+ TIL IHC, was performed and will be presented at the meeting. Additional exploratory analyses (serial ctDNA analysis, single cell RNA sequencing, HLA-subtyping) are ongoing. **Conclusions:** Cryoablation in patients with unresectable melanoma following progression on ICI is feasible with an acceptable side effect profile. Efficacy data of this potentially synergistic approach in metastatic melanoma is encouraging. Correlative analyses are underway to identify biomarkers of response to this novel strategy. Clinical trial information: NCT03290677. Research Sponsor: Philanthropy - donations to the MGH melanoma group.

Characteristic	Patients (n = 18)
Median age (years)	63.5 (47-90)
ECOG Status, n (%)	
0-1	14 (78)
2	4 (22)
Line of therapy, n (%)	
1st	8 (45)
2nd	6 (33)
3rd	4 (22)
Median duration of ICI prior to cryo (days)	103 days (41 – 1250)
Best response (RECIST 1.1)*, n (%)	
CR	0
PR	3 (18)
SD	5 (29)
PD	9 (53)
Pts remaining on post-cryo ICI and/or who completed planned ICI course, n (%)	3 (18)

*Out of 17pts; 1pt did not have subsequent ICI and lacks confirmatory imaging.

9539 **Poster Session**

Apatinib in combination with camrelizumab, a humanized immunoglobulin G4 monoclonal antibody against programmed cell death-1, in patients with metastatic acral melanoma. *First Author: Xuan Wang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Patients(pts) with metastatic acral melanoma respond poorly to anti–PD-1 monotherapy. Apatinib, a vascular endothelial growth factor (VEGF) inhibitor, is a kind of anti-angiogenic drugs which have shown synergistic therapeutic effects in combination with PD-1 blockade. We conducted this single-center, open label phase trial to evaluate the safety and efficacy of camrelizumab in combination with apatinib in advanced treatment-naïve acral melanoma pts. **Methods:** Eligible participants were adult pts (aged 18 to 75) with histologically confirmed unresectable stage or distant metastatic acral melanoma. Exclusion criterion included unknown primary melanoma, brain metastatic disease or previous use of anti PD-1 ab. Pts received camrelizumab at 200mg intravenous infusion every 2 weeks, in combination with apatinib 250 mg orally once a day. The primary endpoint was ORR according to RECIST 1.1 criteria, and the secondary endpoints were safety and RFS. **Results:** Thirty pts were enrolled from April 2019 to January 2021. Basic characteristics: the mean age was 56.7 years, 22 pts were at stage, 33.3% had an elevated LDH level. Median tumor burden was 45mm (10-187). Gene mutation: Nras 4, cKit 3, Braf 2. Up to January 2021, 27 pts could be evaluated, in which 2 pts got CR, 4 pts achieved PR, and 63% experienced tumor shrinkage. The ORR and DCR were 22.2% and 77.8%, respectively. With a median follow up time of 8.3 months, the median PFS was 8.0 months (95% CI, 3.68, 10.19), the one-year durable response rate was 83.3% and the duration of response time was still not reached. Univariate analysis showed high LDH level was negatively associated with PFS. Whole exome data of baseline tumor biopsies revealed a positive correlation between high copy number variation (CNV) plus high mutational load (TMB) and efficacy，and all of the 4pts with MDC1 gene mutation got tumor shrink and 2 got PR. 96.7% pts experienced treatment-related AEs (TRAEs), including hand foot syndrome in 40%, proteinuria in 40%, liver dysfunction in 36.7%, and hypothyroidism in 30%. The grade 3-4 TRAEs were 33.3%. AE-related permanent discontinuation occurred in only 13.3% pts. 6 pts had delays of treatment due to the COVID-19 epidemic. No dose-limiting toxicities and suspected unexpected AEs were observed in the combination. **Conclusions:** The combination of apatinib plus camrelizumab was tolerable and showed promising antitumor activities and PFS improvement in pts with treatment-naïve metastatic acral melanoma. The survival is still in follow up. Clinical trial information: NCT03955354. Research Sponsor: Jiangsu Hengrui Pharmaceuticals Co.

9540 **Poster Session**

Predictors of overall survival (OS) in patients (pts) with melanoma brain metastasis (MBM) in the modern era. *First Author: Merve Hasanov, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The management and OS of pts with metastatic melanoma have improved due to new systemic therapies. However, relatively little is known about the use of these treatments (tx) and their association with OS in pts with MBMs. We reviewed a large cohort of MBM pts to assess how pt demographics, disease characteristics, and MBM tx impact OS in the current era. **Methods:** Under an institutional review board-approved protocol, retrospective data were curated and analyzed from pts diagnosed with, and received tx for, MBM from 2014 to 2018 at the MD Anderson Cancer Center (MDA). Pts diagnosed with uveal or mucosal melanoma or other cancers were excluded. Pt demographics; timing and features of initial melanoma dx; timing and features of initial MBM dx; prior, initial and subsequent tx; and OS were collected. OS was determined from MBM dx to last clinical follow-up (FU). Pts alive at last FU were censored. The Kaplan-Meier method and log-rank test were used to estimate OS and to assess univariate group differences, respectively. Multivariable (MV) associations of OS with variables of interest were investigated with Cox proportional hazards models. Initial treatment of MBM was assessed as a time-varying covariate. All statistical tests used a significance level of 5%. **Results:** A total of 401 MBM pts were identified. The median age at MBM dx was 61; 67% were male and 46% had a BRAF V600 mutation. At MBM diagnosis dx, most (70%) pts were asymptomatic; 70% had concurrent uncontrolled extracranial disease; 36% had elevated serum LDH. Prior tx included immunotherapy (IMT) for 39% and targeted therapy (TTX) for 17%. The median number of MBMs was 2; 31% had $>$ 3 MBMs. Median largest MBM diameter was 1.0 cm, 9% had MBM $>$ 3.0 cm, and 5% had concurrent leptomeningeal disease (LMD). Tx received after MBM dx included stereotactic radiosurgery (SRS; 53% as initial tx for MBM, 67% at any time after MBM dx), whole brain radiation therapy (WBRT; 16%, 35%), craniotomy (12%, 19%), IMT (37%, 74%), and/or TTX (22%, 40%). 31% received steroids during initial MBM tx. At a median FU of 13.4 (0.0 - 82.8) months (mos), the median OS was 15.1 mos, and 1- and 2-year OS rates were 56% and 40%. Notably, gender, time to MBM dx, and BRAF status were not associated with OS (univariate analysis). On MV analysis, clinical features associated with worse OS included increased age, increased primary tumor thickness, elevated LDH, $>$ 3 MBMs, +LMD, +symptoms, and prior tx with IMT. Among tx used at any time after MBM dx, WBRT (HR 1.9, 95% CI 1.5-2.5) was associated with worse OS; SRS (HR 0.7, 95% CI 0.5-0.8) and IMT (HR 0.6, 95% CI 0.5-0.8) were associated with improved OS. **Conclusions:** In one of the largest cohorts of MBM pts described to date, OS has improved in MBM pts in the current era. Prognostic factors for OS include pt age, primary tumor and MBM features, prior tx, and tx for MBM. Additional analyses to assess the interaction of tx, disease features, and OS will be presented. Research Sponsor: None.

9541 **Poster Session**

KEYNOTE-555 Cohort B: Efficacy, safety, and PK of pembrolizumab (pembro) 400 mg every 6 weeks (Q6W) as 1L therapy for advanced melanoma. *First Author: Conrad R. Jacobs, East Cape Onc, Cape Town, South Africa*

Background: In KEYNOTE-555, a model-based approach suggested expected drug exposure with pembro 400 mg Q6W is similar to that observed with approved doses of pembro 200 mg or 2 mg/kg Q3W. The pembro Q6W dose is now approved. We present interim efficacy, safety and PK of 1L pembro 400 mg Q6W for patients (pts) with advanced melanoma in KEYNOTE-555 Cohort B (NCT03665597). **Methods:** Eligible pts had unresectable stage III or IV melanoma, ECOG PS $\leq$1, and no prior systemic therapy for advanced disease.Pts received pembro 400 mg Q6W for up to 18 cycles ($\approx$2 years).The primary efficacy endpoint was ORR per RECIST v1.1 by blinded independent central review (BICR). Secondary endpoints included PFS by BICR per RECIST v1.1 and safety. PK profile and exposure were evaluated for cycle 1 and steady state (cycle 4). **Results:** Between May 2019 and Jan 2020, 101 pts were enrolled and received $\geq$1 dose of pembro. Baseline characteristics were generally similar to pt cohorts of historical pembro studies in advanced melanoma. As of the data cutoff date of August 6, 2020, all pts had $\geq$6 mo of follow-up and 40.6% of pts had discontinued study treatment. Median (range) duration of treatment and doses administered were 8.2 mo (1 day–13.9 mo) and 6 (1–11) doses, respectively. Observed exposure with pembro 400 mg Q6W had lower variability than model predictions and was within PK parameters from clinical experience with other pembro regimens (Table). ORR was 50.5% (95% CI 40.4–60.6). 12.9% of pts had CR and 37.6% had PR. Median PFS was 13.8 mo (95% CI 3.0–not reached). Estimated PFS rates were 56.5% at 6 mo and 54.3% at 12 mo. Treatment-related AEs of any grade occurred in 79.2% of pts (grade 3–4: 6.9% of pts; no deaths due to a treatment-related AE). The most common immune-mediated AEs were hyperthyroidism (6.9%) and hypothyroidism (6.9%). **Conclusions:** 1L treatment with pembro 400 mg Q6W yielded a clinically meaningful ORR in pts with advanced melanoma. PK, efficacy and safety results from KEYNOTE-555 Cohort B support prior findings from the model-based assessment and indicate that the benefit-risk profile for the more practical pembro 400 mg Q6W regimen is consistent with that of 200 mg or 2 mg/kg Q3W regimens. Clinical trial information: NCT03665597. Research Sponsor: Funding for this research was provided by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

PK metrics; data shown as geometric mean (μg/mL) and 95% CI.

	400 mg Q6W Cohort B[a]	400 mg Q6W model-predicted[b]	200 mg Q3W[c]	2 mg/kg Q3W[c]	10 mg/kg Q2W[c]
Cycle 1					
C_{min}	15.1	10.6	18.1	13.5	119.0
	13.5–16.9	10.4–10.8	17.8–18.3	13.3–13.6	117.1–120.6
C_{max}	127.0	123.0	59.1	44.1	220.3
	121.3–132.7	121.6–124.3	58.5–59.7	43.7–44.5	217.8–222.7
Steady state					
C_{min}	24.0	20.3	30.9	23.1	197.1
	20.6–27.9	19.8–20.9	30.5–31.4	22.7–23.4	193.4–200.2
C_{max}	150.0	147.5	92.8	69.2	428.2
	141.9–158.3	146.1–149.4	91.7–94.1	68.4–70.2	424.0–433.2

[a]Observed data. [b]Simulated using a reference population PK model not including KEYNOTE-555 Cohort B. [c]Simulated using a reference population PK model based on dataset of 2993 pts from KEYNOTE-001, 002, 006, 010, and 024.

9542 **Poster Session**

Comparing the clinical efficacies of anti-PD-1 antibody monotherapy and anti-PD-1 and anti-CTLA-4 combination therapy as first-line immunotherapy in Japanese advanced acral melanoma: A retrospective, multicenter study (JAMP-neo study).

First Author: Yasuhiro Nakamura, Saitama Medical University International Medical Center, Saitama, Japan

Background: Anti-PD-1 antibody monotherapy (PD1) has been commonly used for patients with advanced acral melanoma (AM). However, recent studies have demonstrated the limited clinical efficacy of PD1 in AM compared to non-acral cutaneous melanoma, particularly in nail apparatus melanoma. Although advanced AM patients are strong candidates for first-line anti-PD-1 and anti-CTLA-4 combination therapy (PD1+CTLA4), data on the clinical efficacy of PD1+CTLA4 in AM are lacking. Thus, we aimed to compare the clinical efficacies of PD1+CTLA4 and PD1 in Japanese advanced AM patients. **Methods:** We retrospectively reviewed the clinical records of advanced AM patients treated with PD1+CTLA4 or PD1 as first-line immunotherapy at 23 Japanese institutions. Clinical response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Survival was estimated using Kaplan-Meier analysis. Toxicity was assessed according to CTCAE 4.0. **Results:** A total of 192 patients (median age, 72 years) with advanced AM (palm and sole melanoma, 135; nail apparatus melanoma, 57) were included in the study. PD1+CTLA4 and PD1 were used as first-line immunotherapy in 39 and 153 patients, respectively. The baseline demographics and characteristics were similar between the PD1+CTLA4 and PD1 groups, except for age (median age 67.3 vs. 73.2; $P = 0.005$). The objective response rate (ORR) in PD1+CTLA4 was significantly higher than that of the PD1 group (38.5% vs. 16.3%; $P = 0.047$). The median progression-free survival (PFS) and overall survival (OS) in the PD1+CTLA4 group tended to be longer than those of the PD1 group, but the differences were not significant (median PFS 7.3 months vs. 4.5 months; $P = 0.19$, median OS 43.6 months vs. 18.2 months; $P = 0.19$). In the subgroup analysis of the palm and sole melanoma cohorts, no significant differences in ORR, PFS, and OS were observed between the PD1+CTLA4 and PD1 groups (ORR 31% vs. 20.8%; $P = 0.67$, median PFS 5.3 months vs. 5.9 months; $P = 0.87$, median OS not reached vs. 22.3 months; $P = 0.66$). Meanwhile, the nail apparatus melanoma cohort in the PD1+CTLA4 group exhibited significantly higher ORR, and longer PFS and OS than the PD1 group (ORR 60% vs 6.1%; $P < 0.001$; median PFS 19.6 months vs 3.8 months; $P = 0.008$, median OS 43.6 months vs 13.5 months; $P = 0.049$). Due to immune-related adverse events in all cohorts, the treatment cessation rate was higher in the PD1+CTLA4 group than the PD1 group (59% vs. 11.8%). **Conclusions:** PD1+CTLA4 was clinically more efficacious than PD 1 in advanced AM patients. Notably, advanced nail apparatus melanoma patients were strong candidates for first-line PD1+CTLA4. Research Sponsor: None.

9543 **Poster Session**

Durability of response to immune checkpoint inhibitors (ICI) in metastatic Merkel cell carcinoma (mMCC) after treatment cessation.

First Author: Alison Margaret Weppler, Peter MacCallum Cancer Centre, Melbourne, Australia

Background: mMCC is a rare, aggressive neuroendocrine cancer which often occurs in older patients (pts) with multiple comorbidities. While initial response rates to ICI are high, optimal treatment duration, durability of response after treatment cessation and response to retreatment with ICI is unknown. **Methods:** mMCC pts from 12 international centres who received at least one dose of ICI and subsequently stopped treatment without progression for a minimum of 12 weeks were studied. Demographics, disease characteristics and treatment course were examined. **Results:** 40 pts with mMCC were included. Pt characteristics are summarised in Table. Median time on treatment was 13.5 months (range 1 to 35). Median time to best response was 4.5 months (range 1 to 17) and median time receiving treatment after best response was 8 months (range 0 to 29). 25 pts (63%) stopped primarily due to being in a complete or partial response (CR or PR), 9 (23%) due to toxicity and 6 (15%) due to other reasons, primarily pt choice or comorbidities. At time of discontinuation, 30 pts (75%) were in a CR, 8 (20%) in a PR and 2 pts (5%) had stable disease (SD). After a median follow up of 12 months from discontinuation, 14 pts (35%) have progressed (PD); 5 (36%) at a previous site, 5 (36%) at a new site and 4 (29%) at both. PD occurred after a median of 5.5 months (range 4 to 29) off treatment. 4 pts (29%) had a CNS recurrence, none of whom previously had CNS involvement. Pts in CR at time of discontinuation were less likely to progress (CR: 26% PD *vs* non-CR: 67% PD, p=0.044), but still had a considerable rate of PD (CR: 26%, PR: 57%, SD: 100%). Those who progressed had numerically less cycles of ICI prior to treatment cessation (17 *vs* 32, p>0.05). Baseline disease factors, time to best response and duration of treatment after best response were not associated with PD. ICI was restarted in 8 of 14 pts (57%) with PD, with response rate to retreatment of 75% (4 CR, 2 PR, 1 SD, 1 PD – pt with leptomeningeal disease). Median time to best response at retreatment was 3 months (range 2 to 7), with all responses ongoing after a median of 10 months back on treatment. 3 pts had an isolated site of PD successfully treated with radiation therapy and remain in remission off ICI. **Conclusions:** ICI responses in mMCC do not appear as durable off treatment as in other cancers, including in patients who achieve a CR. Ongoing treatment should be considered, though initial data on response to retreatment is promising. Research Sponsor: None.

Patient characteristics.

	N (%)
Age (years)	
Median (range)	75 (52 to 92)
Gender	
Male	29 (73)
Female	11(28)
ECOG Performance Status	
0	13 (33)
1	23 (58)
2	2 (5)
Unknown	2 (5)
Stage	
Unresectable stage III	9 (23)
Stage IV	31 (78)
Number of metastatic sites	
1	21 (53)
2	11 (28)
3	5 (13)
4	3 (8)
Presence of visceral disease	17 (43)
Prior chemotherapy	17 (43)
Baseline immunosuppression	4 (10)
ICI	
Avelumab	36 (90)
Pembrolizumab	3 (8)
Other (Tislelizumab)	1 (3)

9544 **Poster Session**

Toxicity, response, and survival in older adults with metastatic melanoma treated with checkpoint inhibitors.

First Author: Nienke A De Glas, Leiden University Medical Center, Leiden, Netherlands

Background: Checkpoint inhibitors have strongly improved survival of patients with metastatic melanoma. Trials suggest no differences in outcomes between older and younger patients, but only relatively young patients with a good performance status were included in these trials. The aim of this study was to describe treatment patterns and outcomes of older adults with metastatic melanoma, and to identify predictors of outcome. **Methods:** We included all patients aged ≥65 years with metastatic melanoma between 2013 and 2020 from the Dutch Melanoma Treatment registry (DMTR), in which detailed information on patients, treatments and outcomes is available. We assessed predictors of grade ≥3 toxicity and 6-months response using logistic regression models, and melanoma-specific and overall survival using Cox regression models. Additionally, we described reasons for hospital admissions and treatment discontinuation. **Results:** A total of 2216 patients were included. Grade ≥3 toxicity did not increase with age, comorbidity or WHO performance status, in patients treated with monotherapy (anti-PD1 or ipilimumab) or combination treatment. However, patients aged ≥75 were admitted more frequently and discontinued treatment due to toxicity more often. Six months-response rates were similar to previous randomized trials (40.3% and 43.6% in patients aged 65-75 and ≥75 respectively for anti-PD1 treatment) and were not affected by age or comorbidity. Melanoma-specific survival was not affected by age or comorbidity, but age, comorbidity and WHO performance status were associated with overall survival in multivariate analyses. **Conclusions:** Toxicity, response and melanoma-specific survival were not associated with age or comorbidity status. Treatment with immunotherapy should therefore not be omitted solely based on age or comorbidity. However, the impact of grade I-II toxicity in older patients deserves further study as older patients discontinue treatment more frequently and receive less treatment cycles. Research Sponsor: Dutch Research Council (NWO).

	anti-PD(L)1				Ipilimumab				Ipilimumab + nivolumab				
	% of treated patients with toxicity	OR	95% C.I.	*p-value*	% of treated patients with toxicity	OR	95% C.I.	*p-value*	% of treated patients with toxicity	OR	95% C.I.	*p-value*
Age												
65-74	13.9	Ref		*0.255*	31.9	Ref		*0.859*	41.0	Ref		*0.543*
75+	16.6	1.23	(0.86-1.77)		31.0	0.96	(0.60-1.52)		47.4	1.02	(0.96-1.09)	
Number of comorbidities												
0	12.1	Ref		*0.781*	28.6	Ref		*0.922*	43.9	Ref		*0.410*
1-2	15.3	1.32	(0.71-2.45)		32.7	1.22	(0.67-2.20)		46.7	1.12	(0.53-2.35)	
3 or more	16.0	1.39	(0.75-2.60)		32.8	1.22	(0.65-2.28)		34.4	0.67	(0.30-1.51)	
Unknown	15.8	1.37	(0.35-5.29)		0.0	.			55.	1.60	(0.37-6.83)	
WHO classification												
0	15.2	Ref		*0.480*	34.3	Ref		*0.321*	47.8	Ref		*0.704*
1	15.1	0.99	(0.66-1.48)		25.9	0.67	(0.40-1.12)		40.5	0.75	(0.40-1.40)	
2	22.4	1.61	(0.89-2.93)		50.0	1.91	(0.65-5.68)		45.0	0.89	(0.34-2.37)	
3 or 4	0.0	.	(0.34-1.63)		0.0	.	(0.34-1.61)		.	.	(0.13-1.50)	
Unknown	11.8	0.75			27.8	0.74			28.6	0.44		

9545 **Poster Session**

Results from the phase Ib of the SENSITIZE trial combining domatinostat with pembrolizumab in advanced melanoma patients refractory to prior checkpoint inhibitor therapy.

First Author: Jessica Cecile Hassel, Department of Dermatology and National Center for Tumor Diseases (NCT), Heidelberg University Hospital, Heidelberg, Germany

Background: Anti-PD-1 +/- anti-CTLA4 antibodies are the current standard of care immunotherapy for advanced melanoma. However, a significant proportion of patients do not achieve disease control. Epigenetic modulation, particularly histone deacetylase (HDAC) inhibition, can overcome tumor escape mechanisms and thus might increase the susceptibility to immunotherapy. **Methods:** Advanced unresectable/metastatic cutaneous melanoma patients primary refractory or non-responding to prior checkpoint inhibitor (CI) therapy were treated with domatinostat at 5 different dose levels (DL) (100 mg (QD), 200 (QD), and 200 mg (BID) using two different schedules (D1-14 and D1-21 q3w) in combination with pembrolizumab (2 mg/kg) q3w to evaluate safety and tolerability. Tumor assessments were performed every 12 weeks and assessed using irRECIST. Sequential tumor biopsies were taken for gene expression analysis and peripheral blood for pharmacokinetic (PK) analysis. **Results:** We report on preliminary results from the phase Ib part of the ongoing study, data cut-off Feb 1st, 2021 a total of 40 patients have been enrolled. Patient characteristics show that the median number of pretreatments at stage IV was 3, 65 % of patients stage M1c (AJCC 7 or 8) and 35 % with elevated LDH at trial inclusion. Treatment emergent adverse events (AEs) related to domatinostat reported in ≥ 10% of patients were: diarrhea (23%), nausea (20%), fatigue (20%), rash (15%), pyrexia (13%), blood alkaline phosphatase increased (13%), vomiting (10%), dyspnea (10%), all grade 1 and 2 - except one maculo-papular rash grade 3. In total, 8 patients (20 %) developed ≥ grade 3 AEs, with no treatment-related deaths. Patterns of AEs resembled the known safety profiles of domatinostat and pembrolizumab with no increase of immune related AEs for the combination. Maximum tolerated dose was not reached. Four patients discontinued treatment per protocol due to AEs grade 3. We observed clinical activity with 1 complete response, 2 confirmed partial responses and 9 stable diseases (6 confirmed), resulting in a disease control rate of 30% in highly pretreated patients throughout all DLs. Notably, 3 out of 7 patients achieved disease control in DL 3 (domatinostat 200 mg BID D1-14, q3w) and were on treatment ≥ 1.5 years, indicating a trend of dose-dependent clinical activity. Domatinostat treatment resulted in a trend to higher intra-tumoral expression of MHC/APM genes and a more inflamed tumor microenvironment reflecting enhanced T cell infiltration. **Conclusions:** The combination of domatinostat and pembrolizumab was safe and well tolerated. The observed clinical activity in advanced melanoma patients refractory to previous checkpoint inhibition and the favorable translational findings warrant further development of domatinostat in combination with CI in melanoma and beyond. Clinical trial information: NCT03278665. Research Sponsor: 4SC AG.

9546 **Poster Session**

KEYNOTE-629: Health-related quality of life (HRQoL) with pembrolizumab (pembro) in patients (pts) with locally advanced (LA) or recurrent or metastatic (R/M) cutaneous squamous cell carcinoma (cSCC).

First Author: Åse Bratland, Oslo University Hospital, Oslo, Norway

Background: KEYNOTE-629 is a single-arm phase 2 study of pembro for cSCC. At second interim analysis (IA), pembro had robust and durable antitumor activity and manageable safety in LA and R/M cohorts. At first IA, pembro maintained HRQoL in the R/M cohort; LA was not analyzed because of ongoing accrual. HRQoL of pts with LA or R/M cSCC at second IA (database cutoff July 29, 2020; additional 15-mo follow-up since IA1 for the R/M cohort) is shown. **Methods:** Pts with LA or R/M cSCC received pembro 200 mg IV Q3W for ≤35 cycles. HRQoL was a prespecified exploratory end point assessed using EORTC QLQ-30 and EuroQol EQ-5D-5L instruments administered at baseline, wk 3, and wk 6; then Q6W through y 1; then Q9W until treatment end/discontinuation; and at the 30-day safety follow-up. HRQoL was analyzed in pts who received ≥1 pembro dose and completed baseline and ≥1 postbaseline HRQoL assessments. Mean change from baseline in EORTC QLQ-C30 global health status (GHS)/quality of life (QoL), physical functioning (PF), and EQ-5D-5L visual analog scale (VAS) scores were evaluated at wk 12 to ensure adequate completion rate and through last pt visit at wk 75 for EORTC QLQ-C30 GHS/QoL and PF scores. HRQoL was categorized as improved or deteriorated based on ≥10-point change in EORTC QLQ-C30 scores (considered clinically meaningful). **Results:** The HRQoL analysis population for LA had 47 pts for EORTC QLQ-C30 and EQ-5D-5L; the R/M cohort had 99 pts for EORTC QLQ-C30 and 100 for EQ-5D-5L. At wk 12, compliance rates were >75% for LA and >80% for R/M cohorts for EORTC QLQ-C30 and EQ-5D-5L. Mean change from baseline to wk 12 was minimal for EORTC QLQ-C30 GHS/QoL, PF, and EQ-5D-5L VAS scores for both cohorts (Table). Mean change from baseline in EORTC QLQ-C30 GHS/QoL and PF scores remained stable over 48 wk in the LA cohort (75-wk data unavailable) and over 75 wk in the R/M cohort. Most pts had improved or stable EORTC QLQ-C30 GHS/QoL and PF scores relative to baseline during follow-up. **Conclusions:** HRQoL was generally maintained with pembro in LA and R/M cSCC cohorts and was not negatively impacted by tumor progression or AEs. Clinical trial information: NCT03284424. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

		Change from baseline to wk 12, mean (95% CI)		Improved + stable,[a,b] % (95% CI)	Deteriorated,[a,c] % (95% CI)
LA cohort	**n**		**n**		
EORTC QLQ-C30 GHS/QoL	31	–0.27 (–10.93, 10.39)	47	76.6 (62.0, 87.7)	23.4 (12.3, 38.0)
EORTC QLQ-C30 PF	31	–1.29 (–8.77, 6.19)	47	74.5 (59.7, 86.1)	25.5 (13.9, 40.3)
EQ-5D-5L VAS	32	2.06 (–7.70, 11.82)	NA	—	—
R/M cohort	n		n		
EORTC QLQ-C30 GHS/QoL	69	4.95 (–1.00, 10.90)	99	71.7 (61.8, 80.3)	28.3 (19.7, 38.2)
EORTC QLQ-C30 PF	69	–3.38 (-8.80, 2.04)	99	64.6 (54.4, 74.0)	35.4 (26.0, 45.6)
EQ-5D-5L VAS	70	1.97 (–3.85, 7.79)	NA	—	—

[a]Change frombaseline to database cutoff. [b]≥10-point increase (improved) or <10-point change (stable) with confirmation at next visit. [c]≥10-point decrease (deteriorated).

9547 **Poster Session**

Checkpoint inhibition in immunosuppressed or immunocompromised patients with advanced cutaneous squamous cell carcinoma (CSCC): Data from prospective CemiplimAb-rwlc Survivorship and Epidemiology (C.A.S.E.) study.

First Author: Guilherme Rabinowits, Department of Hematology/Oncology, Miami Cancer Institute/Baptist Health South Florida, Miami, FL

Background: Immunosuppressed and/or immunocompromised patients are at increased risk for solid tumors and cutaneous malignancies. Limited data exist on the safety and effectiveness of immune checkpoint inhibitors (ICIs) in these patients because they are frequently excluded from clinical trials. Here, we describe the safety and effectiveness results from the initial cohort of immunosuppressed and/or immunocompromised patients with advanced CSCC enrolled in the C.A.S.E. study (NCT03836105). **Methods:** C.A.S.E. is a prospective, real-world, multi-center, longitudinal study evaluating the effectiveness, safety, quality of life, and survivorship in patients with advanced CSCC treated with cemiplimab. Patients received cemiplimab 350 mg intravenously every 3 weeks per routine standard of care. Patient demographics, disease characteristics, immunosuppression, and relevant medical history were collected. Immunosuppressive regimens varied amongst patients. Investigator assessment of objective response rate (ORR), safety, and tolerability was conducted. Data from 26 immunosuppressed and/or immunocompromised patients with advanced CSCC treated with cemiplimab are presented. Recruitment is ongoing. **Results:** As of November 17, 2020, 121 patients were enrolled in the C.A.S.E. study, of which 26 patients (median age: 74 years [IQR: 71-84]; 85% male; 89% Caucasian) were designated as immunocompromised or immunosuppressed due to a history of solid organ transplant (n = 6), autoimmune disorder (n = 11), or hematologic malignancy (n = 9). Median duration of cemiplimab exposure was 14 months (IQR: 9.1–42, range: 0, 67). Among 19 immunocompromised or immunosuppressed patients who enrolled in C.A.S.E. prior to their third dose of cemiplimab, ORR per investigator assessment was 47% (95% CI: 24–71); 1 (5%) patient had complete response; 8 (42%) had partial response. One patient had a treatment-related serious adverse reaction of organ transplant rejection. One (3.8%) patient discontinued treatment due to increased alanine aminotransferase (not treatment-related). Immune-related AEs (irAEs) occurred in 23% of patients. No treatment-related AEs led to death. **Conclusions:** The safety, tolerability, and effectiveness of cemiplimab in this initial cohort of immunosuppressed and/or immunocompromised patients with advanced CSCC appear to be consistent with those observed in clinical trials that excluded these patients. Further follow-up and additional data would add to our general understanding of safety and effectiveness of anti-PD1 therapy in immunocompromised and/or immunosuppressed patient populations overall. Clinical trial information: NCT03836105. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

9548 **Poster Session**

The influence of harvest method on dendritic cell function and clinical outcomes in a randomized trial of a dendritic cell vaccine to prevent recurrences in high-risk melanoma.

First Author: Alexandra Marion Adams, Brooke Army Medical Center, Fort Sam Houston, TX

Background: A randomized, double-blind, placebo-controlled phase IIb trial of the tumor lysate, particle loaded, dendritic cell (TLPLDC) vaccine was conducted to prevent recurrence in patients (pts) with resected stage III/IV melanoma. Two methods for dendritic cell (DC) harvest were used for vaccine production, including no pretreatment or pretreatment with granulocyte-colony stimulating factor (G-CSF) in an attempt to reduce blood draw volumes. This analysis investigates differences in clinical outcomes and RNA gene expression between these DC harvest methods for TLPLDC vaccine creation. **Methods:** The TLPLDC vaccine is created by loading autologous tumor lysate into yeast cell wall particles (YCWPs) and exposing them to phagocytosis by DCs. By investigator/pt choice, pts had 120mL of blood drawn for DC harvest, or pts received 300μg of G-CSF for pre-DC mobilization and a 50-70 mL blood draw 24-48 hours later. Total vaccine production time was 72 hrs. Pts were randomized 2:1 to receive TLPLDC or placebo (DCs exposed to empty YCWPs). 1-1.5 x10^6 cells/dose were injected intradermally at 0, 1, 2, 6, 12, and 18 months. Differences in disease free survival (DFS) and overall survival (OS) were evaluated by Kaplan Meier analysis between pts who did not receive pretreatment (TLPLDC), pts who did receive pretreatment with G-CSF (TLPLDC+G), and pts receiving placebo. RNA-seq analysis was performed on the total RNA of pts' prepared TLPLDC vaccines to assess gene expression. Relative RNA expression (RRE) was compared between TLPLDC and TLPLDC+G. **Results:** As previously reported, 144 pts were randomized: 103 received TLPLDC (46 TLPLDC, 57 TLPLDC+G) and 41 received placebo. There were no significant clinicopathologic or treatment differences between the three treatment arms. Survival was significantly improved in TLPLDC compared to TLPLDC+G or placebo, including 36-month OS (92.9% vs 62.8% vs 72.3% respectively, p = 0.022) and DFS (51.8% vs 23.4% vs 27.1%, p = 0.027). When compared to TLPLDC+G (n = 3) vaccine, RNA-seq from TLPLDC vaccine (n = 3) showed upregulation of genes associated with DC maturation, including HLA-DMB (RRE: 3.60), IFIT1 (3.38), CD27 (3.26), IFI44L (3.24), MX1 (2.96), HLA-DQA1 (2.67), HLA-DRA (2.40), CD49D (2.34) and CD74 (2.09), while downregulated genes were associated with DC suppression or immaturity including SERPINA1 (RRE:7.8), TLR2 (6.65), CCR1 (5.11), IL10 (4.19), CD93 (3.84) and CD14 (3.25). **Conclusions:** Pts receiving TLPLDC vaccine had significantly improved OS and DFS, while outcomes remained similar between those who received TLPLDC+G vs placebo. Pts who did not receive G-CSF had higher expression of genes linked to DC maturation and antigen processing and presentation, likely explaining the improvement in clinical efficacy. A phase III trial to further assess the TLPLDC vaccine to prevent recurrence is planned. Clinical trial information: NCT02301611. Research Sponsor: Elios Therapeutics.

9549 **Poster Session**

Survival outcomes associated with fewer combination ipilimumab/nivolumab doses in advanced-stage melanoma.

First Author: Vincent T Ma, University of Michigan, Ann Arbor, MI

Background: Standard combination ipilimumab/nivolumab (I/N) is given as 4 induction doses for advanced stage melanoma. While many patients receive less than 4 doses due to treatment-related toxicities, it is unclear if fewer doses of I/N may still provide long term clinical benefit. Our aim is to determine if response assessment after 1 or 2 doses of I/N can predict long-term survival and if fewer doses of I/N can achieve similar survival outcomes. **Methods:** We performed a single-center, retrospective analysis on a cohort of patients with metastatic or unresectable melanoma from 2012 to 2020 who were treated with standard I/N. Cox regression of progression free survival (PFS) and overall survival (OS) models were performed to assess the relationship between response assessment after 1 or 2 doses of I/N and risk of progression and/or death. Clinical benefit response (CBR) was assessed, defined as SD (stable disease) + PR (partial response) + CR (complete response) by imaging or physical examination. Among patients who achieved a CBR after 1 or 2 doses of I/N, a multivariable Cox regression of survival was used to compare 3 or 4 vs 1 or 2 doses of I/N adjusted by age, gender, pre-treatment LDH level, BRAF mutation status, primary melanoma site, time to initial assessment, brain metastasis, and liver metastasis. **Results:** 199 patients were identified and considered evaluable in our study. Median follow up was 28.8 months. Patients with CBR after 1 dose of I/N had improved PFS (HR: 0.23, 95% CI 0.14-0.39; p<0.001) and OS (HR: 0.19, 95% CI 0.10-0.38; p<0.001) compared to progressive disease (PD) [Table]. Patients with CBR (vs PD) after 2 doses of I/N also had improved PFS (HR: 0.17, 95% CI 0.11-0.26; p<0.001) and OS (HR: 0.13, 95% CI 0.07-0.23; p<0.001) [Table]. The survival risk comparing 3 or 4 vs 1 or 2 doses of I/N were HR 0.82 (95% CI 0.45-1.53; p=0.540) for PFS and HR 0.56 (95% CI 0.24-1.30; p=0.175) for OS. **Conclusions:** Clinical benefit response (CBR) after 1 or 2 doses of I/N may be predictive of long-term survival in advanced stage melanoma. Patients who have CBR after 1 or 2 doses of I/N may achieve a similar survival benefit with fewer doses of I/N. Longer follow up and prospective studies are warranted to validate our findings. Research Sponsor: None.

			Progression-Free Survival		Overall Survival	
Response assessment		**n**	**Hazard Ratio (95% CI)**	**p-value**	**Hazard Ratio (95% CI)**	**p-value**
After 1 dose of I/N	PD	46	1.00		1.00	
	CBR (SD+PR+CR)	82	0.23 (0.14 - 0.39)	<0.001	0.19 (0.10 - 0.38)	<0.001
After 2 doses of I/N	PD	49	1.00		1.00	
	CBR (SD+PR+CR)	122	0.17 (0.11 - 0.26)	<0.001	0.13 (0.07 - 0.23)	<0.001

9550 **Poster Session**

Complete responders to checkpoint inhibitors in advanced melanoma: Relapse risk factors, and patients' outcomes. *First Author: Amelie Dutheil, Dermatology Unit, Gustave Roussy Cancer Institute, Villejuif, France*

Background: Since the development of immune checkpoint inhibitors (ICI) for advanced melanoma, a small group of patients with an excellent and durable response has emerged. Complete response (CR) is achievable in about 10-20% of the patients and seem to have an excellent prognosis. However, 10 to 15% of them might relapse eventually. Our main objective was to determine factors associated with relapse after a CR to ICI in advanced melanoma. The second objective was to describe relapse modalities and tumor response to subsequent treatments. **Methods:** We performed a single-center, retrospective study, in 141 patients with a CR to ICI for advanced melanoma, treated at Gustave Roussy (France) from January 2010 to June 2020. CR was confirmed on two consecutive CT-scanner or PET-CT at least 3 months apart. Characteristics of the patients at diagnosis, during and after treatment were compared in both groups: CR with relapse and CR without relapse. The LASSO analysis, a statistical analysis using lambda penalization coefficient for prognostic studies, was performed regarding the many statistical variables analysed. **Results:** At data analysis, immunotherapy was interrupted in 94.3% of the patients and the median follow-up was 3.5 years since immunotherapy discontinuation. Eventually, 18 of 141 patients (12.8%) had relapsed and 126 (87.2%) had not. The statistical analysis identified three factors associated with melanoma recurrence: prior lines of therapy, the type of melanoma and the mutation status. Indeed, relapse risk was higher in patients with wild type melanoma (as opposed to BRAF or NRAS mutant melanoma), with a mucosal, acral or unknown primitive melanoma and who received prior lines of treatment. Other factors such as demographical characteristics, tumor burden, metastasis localization, type or grade of toxicity, pseudo progression, type of ICI, treatment duration, use of a complementary local treatment and pursuit/discontinuation of immunotherapy were not statistically associated with the duration of the complete response. In case of melanoma recurrence, reintroduction of immunotherapy provided tumor response in half of our patients: 13 of the 18 relapsing patients received immunotherapy after melanoma recurrence; allowing 3 CR, 2 partial responses and 1 stable disease. One third of the relapsing patients eventually died of disease progression. **Conclusions:** This study confirmed the excellent prognosis of CR to ICI in advanced melanoma, even after treatment discontinuation and identified 3 baseline factors associated with a risk of relapse: absence of BRAF or NRAS mutation, primary of acral, mucosal or unknown origin, and previous lines of therapy. Rechallenge with ICI was effective in 50% of the patients. Research Sponsor: None.

9551 **Poster Session**

The risk and tropism of central nervous system metastases (CNS) in patients with stage II cutaneous melanoma. *First Author: Paul Johannet, NYU Grossman School of Medicine, New York, NY*

Background: Recent data suggest that patients with stage III melanoma are at high enough risk for developing CNS metastases to consider routine surveillance neuroimaging (Journal of Clinical Oncology; PMID: 31990608). Given that a subset of stage II patients have a worse prognosis than stage III patients, we investigated the risk of developing brain metastases in stage II disease and compared it to the risk in stage III disease. **Methods:** We studied a cohort of prospectively enrolled melanoma patients who had protocol driven follow-up at New York University (NYU) Langone Health. We investigated both the incidence and time to development of CNS metastases, and explored whether the frequency of CNS metastases as a first isolated site of distant disease varies among the different stages. **Results:** The study cohort included a total of 1,102 patients (stage II: n = 619 with median follow-up 56.5 months; stage III: n = 483 with median follow-up 40.9 months). 85/619 (14%) stage II and 91/483 (19%) stage III patients developed CNS metastases (p = 0.03). The estimated 5-year cumulative incidence was 9% in stage IIA, 14% in stage IIB, and 29% in stage IIC patients (p = 0.0001). It was 10% in stage IIIA, 32% in stage IIIB, 23% in stage IIIC, and 49% in stage IIID (p = 0.0001). The CNS was the site of first metastasis for 32/154 (21%) stage II patients who developed distant disease compared to 28/214 (13%) stage III patients (p = 0.06). **Conclusions:** A subset of stage II patients are at an elevated risk for developing CNS metastases within 5 years of their initial diagnosis, which is comparable to that seen in stage III patients. The frequency of the CNS as a first site of metastasis in stage II melanoma suggests a propensity for brain tropism that cannot only be explained by a generalized pro-metastatic phenotype. Surveillance strategies that incorporate serial neuroimaging should be considered for these individuals. Research Sponsor: U.S. National Institutes of Health.

9552 **Poster Session**

Impact of systemic therapy sequencing on overall survival for patients with advanced BRAF-mutated melanoma. *First Author: B. Adi Kartolo, Division of Medical Oncology, Queen's University, Kingston, ON, Canada*

Background: Both immune checkpoint inhibitors (ICI) and BRAF targeted therapy (TT) are effective treatments for patients with advanced BRAF-mutated melanoma. However, the choice of first-line (1L) therapy is at the discretion of treating oncologists without clear guidance from current available data or established guidelines. Utilizing prospectively collected data from the Canadian Melanoma Research Network (CMRN) database, we provide real-world evidence to highlight the impact of sequencing these therapies. **Methods:** Prospective data from 9 cancer centres in Canada was retrieved from the CMRN database for patients with unresectable/metastatic melanoma, with BRAF targetable subtypes, who received at least one-cycle of 1L palliative-intent ICI or TT, and at least 1-year of follow-up. We categorized patients into 2 groups: 1L BRAF±MEK inhibitors with/without subsequent PD-1±CTLA-4 inhibitors (1L-TT), or vice versa (1L-ICI). The primary study outcome was overall survival (OS). Survival outcomes were analyzed through Kaplan-Meier methods, and multivariable Cox analysis was utilized to account for potential confounders. **Results:** Our study (N=235) included 152 and 83 patients in 1L-TT and 1L-ICI groups, respectively. Combined BRAF-MEK inhibitors accounted for 59% of the 1L-TT group, whereas single-agent IO accounted for 66% of the 1L-ICI group. There were 93 patients who received second-line (2L) therapy, with a non-significant trend of 1L-TT group receiving more 2L therapy compared to 1L-ICI group (65% vs. 43%, P=0.404). Neither treatment group showed significant differences in median time on 1L therapy (P=0.645) or 2L therapy (P=0.686). The 1L-ICI group was associated with a favourable median overall survival (OS) compared to 1L-TT group (19.3 vs. 10.0 months, P=0.031). Specifically, the ICI only group had the highest median OS, followed by TT-ICI sequence, ICI-TT sequence, and TT only groups respectively (not reached vs. 38.3 vs. 16.9 vs. 6.1 months, P<0.001). However, this OS benefit (HR 0.89, 95% 0.51-1.53, P=0.644) was non-significant upon controlling for confounders such as baseline metastatic sites >2 (HR 2.07, 95%CI 1.24-3.46, P=0.006) and ECOG ≥2 (HR 3.47, 95%CI 2.02-5.97, P<0.001) in multivariable Cox analysis. **Conclusions:** There was no significant difference in OS between 1L-TT and 1L-IO groups. Rather, OS is driven mostly by the patient's clinical status and tumour-associated features. Our study provides real-world evidence in an understudied area. Further studies are needed to validate our findings to inform guideline development. Research Sponsor: None.

Multivariable Cox analysis of study population (N=99).

	Overall Survival		
	HR	**95% CI**	**P-Value**
Number of Metastatic Sites >2	2.07	1.24-3.46	0.006
Presence of Brain Metastasis	1.66	0.951-2.90	0.074
ECOG ≥2	3.47	2.02-5.97	<0.001
Sequencing Group 1L-TT (Reference)	0.89	0.51-1.53	0.664

9553 **Poster Session**

IL-6 blockade for prophylaxis and management of immune-related adverse events (irAEs) with anti-PD-1 based immunotherapy. *First Author: Florentia Dimitriou, Melanoma Institute Australia, Sydney, Australia*

Background: Immune checkpoint inhibitors (ICIs) have activity across many tumor types, but activation of the immune system may also lead to significant, often steroid-refractory irAEs. We sought to determine the activity of tocilizumab, an anti-IL6R monoclonal antibody (mAb), in treatment or prevention of auto-immune irAE in ICI-treated patients (pts). **Methods:** Institutional databases from 2 melanoma centers were reviewed for pts treated with ICIs and tocilizumab. Treatment and melanoma outcomes were prospectively assessed. Longitudinal assessment of c-reactive protein (CRP) and assessment of clinical improvement (defined as irAE resolution to grade ≤1 CTCAEv5) or prophylaxis (absence of flare, defined as ≥ grade 2) were utilized to evaluate the benefit of tocilizumab. Paired Wilcoxon rank test was used to compare CRP levels prior to ICI administration, at the onset of irAEs and after tocilizumab administration. **Results:** 22 pts were identified. 2 pts were treated prophylactically (pre-existing dermatomyositis [n = 1] and giant cell arteritis [GCA, n = 1]) before the administration of PD1. 20 pts were treated for management of irAEs due to PD1 +/-CTLA4 (multiple concurrent irAEs [n = 3], steroid refractory irAES [hepatitis & pancreatitis, n = 2], steroid+anti-TNFα refractory colitis [n = 2], steroid+other immunosuppressive-refractory hepatitis [n = 1], cytokine release syndrome-related AEs [n = 6], musculoskeletal irAEs [n = 6]). 15 (68.2%) pts with irAEs required hospitalization and of those, 13 (86.7%) received tocilizumab whilst inpatient. Median time to irAE onset from ICI start was 48 days (range 8-786) and from irAE onset to tocilizumab administration 32 days (range 1-192). Median time to irAE resolution from tocilizumab administration was 7 days (range 1-799). Clinical improvement/benefit was demonstrated in 21/22 patients; one patient with ir-hepatitis did not respond. Median CRP prior to ICI administration was 32mg/L (range 0.3-99), at the onset of irAE 49.5mg/L (range 0.3-251, p = 0.055) and after the tocilizumab administration 18mg/L (range 0.3-18, p = 0.0015). Tocilizumab was well tolerated with self-limiting and transient toxicities in 17 (77.3%) patients. There were two grade 4 events; gastrointestinal tract perforation and Fournier gangrene, the latter unrelated to tocilizumab. Two (9%) patients died due to melanoma. From start of ICI, median progression-free survival (PFS) was 5.88 months and median overall survival (OS) was not reached. **Conclusions:** Tocilizumab was a well-tolerated and effective steroid-sparing treatment for both management of irAEs, as well as prevention of a flare of pre-existing auto-immune disorders during ICI administration. Prospective trials to evaluate its efficacy and impact on cancer outcomes compared with standard strategies are required. Research Sponsor: None.

9554 **Poster Session**

Safety and efficacy of HX008: A humanized immunoglobulin G4 monoclonal antibody in patients with locally advanced or metastatic melanoma—A single-arm, multicenter, phase II study. *First Author: Bin Lian, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: HX008 is a new recombinant humanized anti-PD-1 monoclonal antibody, belonging to human IgG4 / kappa subtype, which can selectively block the binding of PD-1 with its ligands PD-L1 and PD-L2. **Methods:** In this single arm phase 2 trial, eligible patients (pts) were aged from18 to 75, who previously failed with conventional treatment for locally advanced or metastatic melanoma, with an ECOG performance status of 0 or 1 and had measurable lesions according to the RECIST criteria (V1.1). Ocular melanoma, brain metastasis or previous use of anti PD-1 ab were excluded. Pts received HX008 3mg/kg every 3 weeks, until disease progression, intolerable toxicity or treatment discontinuation for any other reasons. The primary endpoint was ORR according to RECIST criteria, and the secondary endpoints were OS, PFS, DCR and the toxicity. The iRECIST criteria would also be used in the evaluation of response and treatment discontinuation. Clinical trial information: NCT04749485. **Results:** From Oct 2018 to Jan 2021, 119 pts have been eligible and enrolled. Basic characteristics: median age 59 years; 57 males (42.9%) ; stage 22%, stage 78%; primary: acral 52.1%, mucosal 19.3%, cutaneous 18.5% and unknown 10.1%; Gene mutation status: Braf 10.9%, Nras 9.2%, cKit 4.2%; condition of previous treatments: 67.26%, 25.21%,7.56% pts had received 1st, 2nd and 3rd line or above treatments respectively (chemotherapy 69.7%, targeted therapy 15.1%, immunotherapy 43.7%). The ORR according to RECIST V1.1 and iRECIST was 18.49% (1CR, 21 PR , 95% CI 11.96-26.64) and 20.17% (1 iCR, 23 iPR ,95% CI 13.37-28.50), respectively. For PD-L1 positive pts the ORR was 15.09% (95%CI 6.75-27.60) and 12% for negative (95%CI 10.98-32.83). For different subtypes, the ORR was 36.36% for cutaneous melanoma, 14.52% for acral primary, 8.7% for mucosal primary, and 25% for unknown primary. The DCR and iDCR was 44.54% and 47.06% , respectively. With a median follow up time of 13.2 months, the median PFS was 3.25 months (95% CI 2.0, 4.1) and the PFS rate at 1 year was 25.8% (95%CI 17.19,35.33). The median OS was 17.91 months (95% CI 13.08,NR) and the OS rates at 1 year was 63.9% (95% CI 53.02, 73.00). Median DOR has not reached and the DOR and iDOR rates at 1 year were 80.64% and 87.39%, respectively. TRAEs occurred in 89.9% of the pts, with grade 3/4 AEs 31.9%, the followings were those incidences ≥1%, hyperglycemia (2.5%), elevated aspartate aminotransferase (1.7%), elevated serum bilirubin (1.7%), elevated serum creatine phosphokinase (1.7%), elevated lipase (1.7%), hypoalbuminemia (1.7%), hypokalemia (1.7%) and diabetic ketoacidosis (1.7%). **Conclusions:** HX008 shows its efficacy and safety in locally advanced or metastatic melanoma pts in the treatments of 2nd line or above. Randomized controlled studies are now on pending. Clinical trial information: NCT04749485. Research Sponsor: Taizhou Hanzhong biomedical co. LTD.

9555 **Poster Session**

Encorafenib plus Binimetinib in patients with locally advanced, unresectable or metastatic BRAF^{V600}-mutant melanoma: First data of the multicenter, multinational, prospective, non-interventional longitudinal study BERING^{MELANOMA}. *First Author: Erika Richtig, Department of Dermatology, University of Graz, Graz, Austria*

Background: For the treatment of advanced BRAF^{V600}-mutated melanoma, targeted therapy (BRAF/MEK-inhibition) is a standard of care. Encorafenib + binimetinib (EB) were approved in the EU in Sep 2018 and in Switzerland in Nov 2019, based on positive results from COLUMBUS (NCT01909453), with a median progression-free survival (PFS) of 14.9 mo (4-year PFS: 26%) and overall survival (OS) of 33.6 mo (4-year OS: 39%). As data from controlled trials are based on selected populations, BERING^{MELANOMA} investigates the use of EB under real-world conditions in a broader population. **Methods:** BERING^{MELANOMA} is an ongoing, multi-national, multi-center, prospective, longitudinal, non-interventional study. It analyzes the effectiveness, quality of life and tolerability of EB-treatment under real-world conditions (primary endpoint: 1-year PFS-rate), focusing on the first- (1L) and second-line setting and including an evaluation of the impact of prognostic factors. The project aims to enroll up to 750 patients (pts) in a total of 80 German, Austrian and Swiss sites with a study duration of 8 yrs. So far, from Oct 2019 to Jan 2021, 153 pts have been included. Pts with prior BRAF-/MEK-inhibition (except adjuvant use completed > 6 mo) and > 1 prior treatment line were excluded. **Results:** Here we present the first planned interim analysis based on the initial 100 enrolled pts (91 treated / 89 evaluable; median follow-up: 8.1 mo). This analysis set shows a median age of 63.0 yrs (range 29.0-88.0), 52% of pts were female. 81% presented with distant metastases (brain: 31%), with an involvement of ≥3 organ systems in 51% and an elevated LDH in 42%. 54% of pts underwent prior systemic therapy (adjuvant: 28%; 1L: 24%, with ipilimumab + nivolumab as main 1L-treatment: 52%). EB was mainly administered in the 1L-setting (65%). Main reasons for EB-selection were: physician's preference (37%), efficacy (34%), quality of life (21%). Median estimated EB treatment duration was 12.7 mo (95%CI 8.3-NE), median relative dose intensity was 100% for both drugs. Treatment adaptations were required in 34% of pts. Adverse events (AE) were reported in 76% of pts (grade 3/4: 26%). Main AE (≥10%, all grades) were: nausea (18%), diarrhea (17%), CK increase (15%), fatigue (11%), gamma-GT increase (11%). No fatal toxicities were observed. **Conclusions:** This first interim analysis of BERING^{MELANOMA} shows an investigation of EB in a real-world population with advanced disease. Despite the poorer prognosis configuration as compared to the pivotal study, the observed treatment duration and tolerability profile are largely consistent with data derived from COLUMBUS without any new safety signals. The second interim analysis will be performed after enrollment of 200 pts and will include an initial analysis of effectiveness data. Clinical trial information: NCT04045691. Research Sponsor: Pierre Fabre Pharma GmbH (Germany), Pierre Fabre Pharma Austria (Austria), Pierre Fabre Pharma AG (Switzerland).

9556 **Poster Session**

Plasma thymidine kinase activity (TKa) as a novel prognostic biomarker in metastatic melanoma. *First Author: Hildur Helgadottir, Department of Oncology-Pathology, Stockholm, Sweden*

Background: In the recent decade, new effective immunotherapies and targeted therapies have emerged for the treatment of disseminated melanoma. However, a considerable fraction of patients does not respond or get lasting effects and the treatments also have significant side effects. Biomarkers can contribute with more knowledge on prognosis and the efficacy of these therapies in different patients. In other cancer types, the plasma activity of the enzyme thymidine kinase (TKa), has been demonstrated as a marker of tumor stage and prognosis. The TK enzyme is part of a reaction chain to introduce thymidine into the DNA strand. TK thereby has a key function in DNA-synthesis, -repair and cell division. Dividing cells release TK during mitotic exit and TK can thus be detected in the blood. This study is the first to investigate plasma TKa as a potential biomarker in melanoma patients. **Methods:** Plasma samples were collected within five days prior to treatment start in patients with unresectable metastatic cutaneous melanoma, treated with immunotherapy (anti-CTLA-4 and/or anti-PD-1) or targeted therapy (BRAF±MEK inhibitors). Plasma TKa levels were determined using the DiviTum TKa ELISA assay (Biovica, Sweden). TKa levels were correlated with the patients' baseline criteria, response rate (RR), progression free survival (PFS) and overall survival (OS). **Results:** Among the 124 study patients, the median TKa was 50 Du/L (range < 20-3491 Du/L). Significantly higher plasma TKa levels were found in patients with ECOG performance status ≥1 vs. 0-1 ($P<$ 0.001), M1c-d vs. M1a-b disease ($P<$ 0.001), ≥3 vs. 1-2 affected organs ($P=$ 0.002) or elevated vs. non-elevated LDH ($P<$ 0.001). In the patients treated with immunotherapy (n = 86) the RR was 63.2% vs. 37.9% in those with low (< 60 Du/L) vs. high TKa ($P=$ 0.024). The median PFS and OS was 19.9 and > 60 months in those with low TKa vs. 12.6 and 18.5 months in those with high TKa (HR for PFS: 1.73 (95% CI, 1.01-2.97), $P=$ 0.044 and HR for OS: 2.16 (95% CI, 1.17-3.98), $P=$ 0.011). In the patients treated with BRAF±MEK inhibitor (n = 38) a similar trend was observed, with shorter PFS and OS in those with high TKa, but the differences were not statistically significant. **Conclusions:** In this first study on plasma TKa in melanoma patients, high pretreatment TKa was significantly associated with poor baseline factors and poor response and survival in immunotherapy treated patients. Currently, plasma LDH is the only non-clinical factor that is routinely used as a prognostic marker in melanoma. Several other candidate markers have been described, such as PD-L1 tumor immunohistochemistry, tumor mutational burden, gut microbiome and circulating tumor DNA. Compared to these assays, TKa measured with DiviTum is a simpler, ELISA based test for a single plasma marker. TKa is hence a novel and interesting marker in melanoma and should be further studied to define its role as a prognostic and predictive marker in this disease. Research Sponsor: Swedish Cancer Society.

9557 **Poster Session**

Outcomes of non-treatment naive melanoma patients with central nervous system relapse. *First Author: Thiago Pimentel Muniz, Division of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, University of Toronto, Toronto, ON, Canada*

Background: Melanoma has a high probability of central nervous system (CNS) spread. Although first line nivolumab and ipilimumab resulted in 56% response rate and 29.2 months median overall survival (OS) in patients with melanoma brain metastases (MBM), there is paucity of data for patients who develop MBM after prior systemic therapy. As this subgroup is often underrepresented in clinical trials, we aimed to evaluate the OS of non-treatment naïve patients who develop MBM and identify factors related to survival. **Methods:** In this single-center, retrospective study, consecutive melanoma patients with > 90 days from exposure to either immune checkpoint inhibitor (ICI), targeted therapy (TT), or chemotherapy, to CNS relapse were included. OS was defined as the time between CNS relapse and death by any cause. The Log-Rank method was used to calculate OS. Cox regression analysis was used to identify differences between subgroups. Variables with a p value < 0.1 were included in a multivariate model. A p value < 0.05 was considered statistically significant. **Results:** Between 2012 and 2018, 135 patients were identified. Median age was 57 (29-92) years, 92 (68%) were male, and median number of prior systemic therapies was 2 (1-6). One-hundred and nine (81%) patients had cutaneous melanoma; acral lentiginous melanoma (ALM) comprised 11 (8%) patients. Molecular studies were available for 123 patients, of whom 61 (50%) were *BRAF* V600 mutant. Eighty-nine (66%) patients had prior ICI, of whom 33 (37%) had prior exposure to both anti-PD1 and anti-CTLA-4, either as monotherapy or combination. Amongst the *BRAF* V600 mutant population, 48 (79%) had prior TT. Radiotherapy was given to 112 patients, of whom 55 (49%) had SRS. Median follow-up was 41 (95% CI 30-51) months. Median OS was 6.4 (95% CI 5.3-7.5) months. Patients with ALM, > 3 MBM, ECOG 2-4 and active treatment at CNS relapse (< 30 days from last dose of treatment to MBM diagnosis) were at increased risk of death, whilst subsequent treatment with ICI was related to better survival (Table). On multivariate analyses, age (p = 0.007), subtype (p = 0.04), number of MBM (p = 0.01), active treatment at CNS relapse (p < 0.001) and subsequent ICI (p = 0.002) remained statistically significant. Exploratory analyses suggested subsequent treatment with anti-PD1 + anti-CTLA-4 (n = 42) compared favourably to subsequent anti-CTLA-4 only (n = 21) (13 x 7 months, p = 0.004), and was independent of prior ICI. **Conclusions:** Previously treated melanoma patients who develop MBM have a poor prognosis, but subsequent ICI therapy seems to be associated with better OS. Further clinical investigation to identify optimal anti-PD1-based therapies is warranted for non-treatment naïve patients who develop MBM. Research Sponsor: None.

Variable	HR (IC 95%)	p value
ALM subtype (vs. other cutaneous)	2.3 (1.02-5.1)	0.04
> 3 MBM	1.7 (1.07-2.8)	0.02
ECOG 2-4	2.7 (1.4-5.0)	0.001
Active Treatment	2.3 (1.4-4.0)	0.001
Subsequent ICI	0.3 (0.2-0.5)	< 0.001

9558 **Poster Session**

BRAF and _NRAS_ mutation status and response to checkpoint inhibition in advanced melanoma. *First Author: Olivier Jules van Not, University Medical Center Utrecht, Leiden, Netherlands*

Background: The ability to analyze tumor mutation profiles has altered the oncology treatment landscape over the past decades. However, little is known about the effect of specific gene mutations on the response to immune checkpoint inhibitors (ICIs) in patients with advanced melanoma. **Methods:** All unresectable stage IIIc and IV patients with *BRAF* V600, *NRAS* mutations and *BRAF* and *NRAS* wild-type patients treated with anti-PD-1 or ipilimumab-nivolumab between 2012 and 2020 were included from the Dutch Melanoma Treatment Registry, a nationwide population-based registry. Outcomes were objective response rate (ORR), progression-free survival (PFS), and overall survival (OS). A Cox model was used to analyze the association of possible prognostic factors with PFS and OS. **Results:** In total 1358 first-line patients treated with anti-PD-1 and 524 treated with ipilimumab-nivolumab were included. Median follow-up was 25.6 months for anti-PD-1 treated patients and 16.3 months for ipilimumab-nivolumab treated patients. The highest ORR, in first-line, to anti-PD-1 was in patients who were *BRAF* and *NRAS* wildtype (50.2%), compared to *BRAF* V600 (43.8%) and *NRAS* mutated patients (49.8%). ORR to ipilimumab-nivolumab was highest in *NRAS* mutated patients (44.9%), while ORR was 39.5% for *BRAF* mutated patients and 40.3% for wild-type patients. Median PFS in the anti-PD-1 treatment regimen was significantly higher ($p = 0.049$) for double wild-type patients (16.7 months) patients than for *BRAF* mutated patients (9.9 months) and *NRAS* mutated patients (11.3 months). PFS was not significantly different ($p = 0.11$) in the ipilimumab-nivolumab treatment cohort, with a median PFS of 6.5 months for the wild-type group, 10.8 months for the *BRAF* group, and 9.1 months for the *NRAS* group. In the anti-PD-1 treated patients, median OS was significantly higher ($p < 0.001$) for *BRAF* mutated patients (32.8 months) compared to *NRAS* (21.0 months) and wild-type patients (23.0 months). For ipilimumab-nivolumab treated patients, median OS was also significantly higher ($p < 0.001$) for *BRAF* mutated patients (36.5 months) than for *NRAS* mutated patients (11.8 months) and wild-type patients (16.1 months). After adjustment for potential confounders, the presence of a *BRAF* mutation remained associated with lower PFS in the anti-PD-1 treatment cohort and better OS in both treatment cohorts. Higher age, higher ECOG score, elevated LDH levels, liver metastases and brain metastases were associated with worse survival. **Conclusions:** PFS in first-line PD-1 was significantly higher for double wild-type patients than for *BRAF* mutant and *NRAS* mutant patients. PFS in ipilimumab-nivolumab treated patients did not significantly differ between *BRAF* mutant, *NRAS* mutant and double wild-type patients. OS was significantly higher for *BRAF* mutant patients in both treatment strata, which is probably the result of the subsequent BRAF/MEK-inhibition treatment option in this group. Research Sponsor: None.

9559 **Poster Session**

A phase 1b clinical trial of anti-PD-1 ab (Toripalimab) plus intralesional injection of OrienX010 in stage melanoma with liver metastases. *First Author: Jun Guo, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Liver metastasis was associated with reduced responses and PFS in melanoma patients (pts) treated with anti-PD-1 monotherapy, which is probably due to reduced marginal CD8+ T cell infiltration. Oncolytic virotherapy was found to increase CD8+ T cell infiltration in the injected lesions and improve the efficacy of anti-PD-1 ab in a phase 1b trial. We hypothesized that intratumoral oncolytic virus injection for liver metastasis in melanoma combined with systemic anti-PD-1 therapy might improve the efficacy, thus conducting this phase 1b trial with intratumoral OrienX010 - a HSV-1-derived oncolytic virotherapy with expression of GM-CSF combined toripalimab in liver metastatic melanoma pts. **Methods:** Eligible pts included those over 18 with injectable liver metastasis confirmed by biopsy with or without extra-hepatic metastasis; ocular melanoma and brain metastasis were excluded. Pts received intravenous toripalimab Q2W combined with ultrasound guided intratumoral injection of OrienX010 Q2W (8×10^7 pfu/ml, 10ml per injection) until intolerance or disease progression per iRECIST criteria. Liver biopsy would be performed at baseline and first tumor evaluation (8-12weeks). The primary endpoint was toxicity; secondary endpoints included ORR, DCR and PFS. Clinical trial information: NCT04206358. **Results:** From Jul 2019 to Dec 2020, 15 pts were eligible and enrolled. Baseline characteristics: median age 62 yrs; primary: mucosal 60%, cutaneous 20%, unknown primary 13.3%, acral 6.7%; gene mutation status: Braf 20%, Nras 6.7%; 73.3% got extra-hepatic metastasis: regional or distant lymph node 46.7%, lung 20.0%; LDH > ULN 20%; median size of injected lesions: 32mm(10-83mm); median number of liver metastasis: 4(1-10); median number of injection: 10 (3-36). AEs were all grade 1/2: pyrexia 86.7%, rigor 66.7%, elevated transaminase 53.3%, nausea/vomiting 40.0%, fatigue 26.7%. No grade 3-4 AEs. The ORR by investigator was 13.3% (2/15), DCR 46.7% (7/15); the response rate was 40%(6/15) for injected lesions, 28.5%(4/14) for non-injected lesions in liver, and 23% (3/13) for extra-hepatic metastasis. For biopsies of injected lesions at 8 to 12weeks, 30%(2 PR and 3 SD) showed no melanoma cells residual by immunohistochemistry, 46.7% got impressive TIL infiltration (Brisk n = 4 and Nonbrisk n = 3 according to the definition of AJCC 8th edition) compared with baseline in which all showed absence of TIL infiltration, also a large number of plasma cells, histiocyte and pigment were found with hyaline fibrosis. The PFS has reached 72 weeks for one PR pt. The median PFS was not reached. **Conclusions:** Systemic toripalimab combined with intrahepatic OrienX010 injection has shown remarkable pathological responses with good tolerance in melanoma liver metastases. Survival is still in follow-up. Clinical trial information: NCT04206358. Research Sponsor: Oriengene Biotechnology Ltd.

9560 **Poster Session**

Pyrexia-related outcomes upon application of an adapted pyrexia management algorithm in patients (pts) with _BRAF_ V600: Mutant unresectable or metastatic melanoma treated with dabrafenib plus trametinib (DabTram) in the COMBI-i trial. *First Author: Paolo Antonio Ascierto, Melanoma, Cancer Immunotherapy and Development Therapeutics Unit, Istituto Nazionale Tumori-IRCCS Fondazione "G. Pascale", Naples, Italy*

Background: First-line DabTram has shown long-term efficacy in pts with *BRAF* V600–mutant unresectable or metastatic melanoma in the Phase III COMBI-d and COMBI-v trials. Data from the Phase III COMBI-i trial comparing spartalizumab plus DabTram vs placebo plus DabTram (pbo-DabTram) demonstrated efficacy in the pbo-DabTram arm, consistent with historical data. Pyrexia (single preferred term [PT]) is the most common adverse event (AE) reported with DabTram (pooled COMBI-d [data cutoff: Jan 12, 2015] and COMBI-v [data cutoff: Apr 17, 2014]: any grade, 54.2%; grade ≥ 3, 5.4%; serious pyrexia AEs leading to hospitalization, 11.8%). A new pyrexia management algorithm was implemented in the COMBI-i trial to improve pyrexia-related outcomes. We report pyrexia-related outcomes in pts treated with pbo-DabTram in the control arm of COMBI-i part 3. **Methods:** COMBI-i (NCT02967692) part 3 is a double-blind, Phase III trial in which pts with previously untreated *BRAF* V600–mutant unresectable or metastatic melanoma were randomized 1:1 to receive spartalizumab (400 mg intravenously every 4 weeks) plus Dab (150 mg orally twice daily) and Tram (2 mg orally once daily) vs pbo-DabTram. In the adapted pyrexia management algorithm, both Dab and Tram are interrupted promptly at the first symptom of pyrexia or its associated prodrome (ie, chills, rigors, night sweats, or influenza-like symptoms). Treatment at the same dose level is restarted upon the improvement of symptoms if pts are symptom free for ≥ 24 hours. Pyrexia incidence rates presented are for the single PT of pyrexia. **Results:** At data cutoff (July 1, 2020), median follow-up was 27.2 mo for all pts enrolled in COMBI-i part 3 (N = 532). In the DabTram control arm, 52.7% (139/264) and 3.0% (8/264) of pts had any-grade and grade ≥ 3 pyrexia, respectively. Serious pyrexia AEs were reported in 6.1% (16/264), which led to hospitalization in 5.3% (14/264). Pyrexia led to dose interruption of both Dab and Tram in 39.0% (103/264), with 1.5% (4/264) permanently discontinuing both agents. Median relative dose intensity was 97.8% for Dab and 97.7% for Tram. **Conclusions:** Pyrexia-related outcomes, including grade ≥ 3 pyrexia (3.0% vs 5.4%) and serious pyrexia AEs leading to hospitalization (5.3% vs 11.8%), were improved in pts treated with DabTram in COMBI-i part 3 compared with historical data from COMBI-d/v. The adapted algorithm offers a simplified approach for managing pyrexia, thereby reducing the incidence of severe pyrexia while maintaining consistent efficacy with DabTram. Clinical trial information: NCT02967692. Research Sponsor: Novartis.

9561 **Poster Session**

Treatment outcomes in patients (pts) with melanoma brain metastases (MBM) treated with systemic therapy: A systematic literature review (SLR) and meta-analysis. *First Author: Hussein Abdul-Hassan Tawbi, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The introduction of immunotherapy and targeted therapy has revolutionized the treatment landscape for metastatic melanoma. However, clinical trial data in pts with MBM are scarce; here we summarize the available clinical evidence. **Methods:** An SLR was conducted by searching EMBASE, MEDLINE, and the Cochrane Central Register of Controlled Trials databases through November 13, 2020. When available, KaplanMeier (KM) curves for overall survival (OS) were digitized and converted to pseudo-individual pt data using the Guyot algorithm. A meta-analysis of the pooled KM curves was performed for selected interventions, including immunotherapies and targeted therapies. Median OS was calculated either through the meta-analysis of KM curves or as a weighted average of median OS (table). When interventions were reported in only 1 study, the value reported was used instead of the weighted average and compared qualitatively with the other results. Results for treatment modalities other than systemic agents will also be presented. **Results:** The SLR included 70 publications that evaluated systemic therapies in pts with MBM for qualitative evidence synthesis: 12 pertaining to 7 randomized controlled trials, 55 pertaining to 46 single-arm studies, and 3 involving nonrandomized comparative studies. The pt population was highly heterogeneous with respect to prior therapies, pt characteristics, and neurological symptoms. For the meta-analysis, a total of 25 KM curves from 12 studies representing 6 interventions and 1043 pts were digitized. Based on the pooled KM curves, median OS was numerically longer with nivolumab plus ipilimumab (NIVO + IPI; 28.3 mo; 95% CI, 19.731.9) than with the other interventions (range 5.711.8 mo; table). Similar OS benefit was also observed with NIVO + IPI when the weighted average of the median was used (in a long-term study, median OS was 29.2 mo) compared with the other interventions. **Conclusions:** Given the lack of comparative clinical trial data in pts with MBM, there remains an unmet need to determine the best approach to treat these pts. This analysis suggested a clinical advantage with NIVO + IPI compared with other systemic agents analyzed. The heterogeneity of the available data added uncertainty to our treatment assessments. Therefore, these findings warrant further research into the best approach to improve outcomes in pts with MBM. Research Sponsor: Bristol Myers Squibb.

	Pooled KM curves				Weighted samples			
Treatment	No. of studies	No. of KM curves	Pooled sample size, n	Median OS, mo (95% CI)	No. of studies	No. of cohorts	Pooled sample size, n	Median OS, mo
IPI	3	5	230	5.7 (4.66.8)	2	4	199	6.3
NIVO	1	3	41	9.8 (5.516.0)	1	2	41	13.3
NIVO + IPI	3	4	156	28.3 (19.731.9)	1	1	27	29.2[a]
Dabrafenib (DAB)	1	4	172	7.3 (not available)	1	4	172	6.9
Vemurafenib	4	5	319	11.8 (9.415.0)	4	6	382	12.5
DAB + trametinib	1	4	125	8.3 (6.99.7)	1	4	125	8.7
Pembrolizumab					1	1	23	17[a]

[a]As reported.

9562 **Poster Session**

Efficacy of cetuximab after immunotherapy (IO) in advanced cutaneous squamous cell carcinoma (CSCC). *First Author: Julian Andres Marin-Acevedo, Moffitt Cancer center, Tampa, FL*

Background: Anti-PD1 (aPD1) monotherapy with cemiplimab-rwlc or pembrolizumab is now considered standard of care for first-line management of advanced CSCC not amenable to surgery or curative radiotherapy. Previously chemotherapy or anti-EGFR agents were commonly used for these patients albeit with modest efficacy and limited duration of response. In prospective evaluation, the overall response rate (ORR) to cetuximab was 28% with disease control rate (DCR) of 69% at 6 weeks. The efficacy of second-line treatment following primary or acquired resistance to aPD1 therapy is not known. We investigated the activity of cetuximab in patients who progressed on previous IO therapy. **Methods:** We performed a single institution retrospective review from 9/28/18 (US approval date of cemiplimab-rwlc for CSCC) through 11/30/20 of patients with locally advanced or metastatic CSCC who received cetuximab after prior IO therapy. We identified patients who received cetuximab either immediately following IO therapy (cohort A) or as a subsequent line not immediately following IO therapy (cohort B). Primary endpoint was ORR with secondary endpoints of DCR, survival and toxicity. Median follow-up and survival times were calculated using the Kaplan-Meier method. **Results:** Thirteen patients, median age 72 years (62-82), all Caucasian, and 11 males (85%) were included in this study. Eleven pts received cetuximab immediately post-IO progression; two had additional intervening therapy post-IO before receiving cetuximab. Three patients received concurrent radiotherapy (palliative or definitive) with cetuximab. The ORR to cetuximab was 54% (7/13) including 1 complete and 6 partial responses. The cumulative 6-month DCR was 77%. All responses were observed in cohort A; both patients in cohort B had progressive disease as best response. Six of 7 initial responses are ongoing, including 3 in whom cetuximab was discontinued. At a median follow-up of 9.1 months, the median PFS has not been reached for the entire cohort. There were no unanticipated toxicities to cetuximab with rash (77%) and hypomagnesemia (54%) being the most common adverse events. **Conclusions:** In advanced CSCC, cetuximab used immediately after progression on aPD1 therapy yields notably higher and durable overall response than previously reported in the pre-IO therapy era. If validated in a larger dataset, this should be the preferred therapy for second-line treatment in advanced CSCC. Further exploration into the mechanism of this high efficacy of anti-EGFR therapy post aPD1 therapy is warranted. Research Sponsor: None.

9563 **Poster Session**

External validation of a Dutch predictive nomogram for complete response to T-VEC in an independent American patient cohort. *First Author: Emma H.A. Stahlie, Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Talimogene Laherparepvec (T-VEC) is a genetically modified herpes simplex type 1 virus and known as an effective oncolytic immunotherapy for injectable cutaneous, subcutaneous, and nodal melanoma lesions in stage IIIB-IVM1a patients. Recently, Stahlie et al. published (Cancer Immunol Immunother '21) a model for predicting a complete response (CR) to T-VEC based on 3 easily accessible tumor characteristics identified using univariable and multivariable logistic regression analysis. The aim of this study was to externally validate this model in an independent, American patient cohort. **Methods:** A total of 76 patients with stage IIIB-IVM1a melanoma treated with T-VEC at Moffitt Cancer Center were included. A second nomogram was built incorporating the same predictive factors: tumor size (diameter of largest metastasis in mm), type of metastases (cutaneous, subcutaneous and nodal) and number of metastases (cut-off: <20 and >20). Predictive accuracy was assessed through calculation of overall performance, discriminative ability, and calibration. Outcomes and previously published outcomes were compared. Statistical analyses were done using R software. **Results:** Overall performance of the validation dataset nomogram was calculated with the Brier score and found to be 0.195, demonstrating good overall performance and similar to the original model Brier score of 0.182. Discriminative power, assessed by calculating the area under the receiver operating characteristic (ROC) curve was similar for both models, 0.767 and 0.755 for the NKI and Moffitt, respectively, resulting in a fair discriminative ability. The calibration curve showed mostly slight underestimation for predicated probabilities >0.37 and slight overestimation <0.37. **Conclusions:** An independent dataset externally validated a recently published predictive nomogram for CR to T-VEC in stage IIIB-IVM1a melanoma, with both models resulting in overall performances that were comparable and good. The second model reinforces the conclusion that for the best response to T-VEC, it should be used early on in the course of the disease, when the patient's tumor burden is cutaneous with smaller diameter and fewer of metastases. Research Sponsor: None.

Clinicopathologic characteristics of both cohorts.

	Dutch (n=93)	American (n=76)
Median age (years, range)	69 (30–97)	77 (47 – 94)
Gender		
Male	40	42
Female	53	34
Location		
Head/neck	12	18
Upper extremity	2	13
Trunk	15	5
Lower extremity	64	40
Median Breslow depth (mm, range)	2.7 (0.5 – 8.2)	2.4 (0.4 – 15)
Ulceration		
Yes	28	24
No	48	43
Unknown	17	9
Stage at T-VEC		
3B	30	29
3C	56	40
3D	6	1
4 (M1a)	1	6
Median number of lesions (range)	7 (1 – 130)	4 (1 – 40)
Median diameter largest lesion (mm, range)	20 (0.5-100)	10 (4 – 86)
Metastasis subtype		
Cutaneous (dermal only)	32	25
Subcutaneous(subdermal +/- dermal)	53	46
Lymph nodes(nodal +/- subdermal +/- dermal)	8	5
Overall response rate	79%	71%
Complete response rate	62%	51%

9564 **Poster Session**

Outcomes of BRAF mutant metastatic melanoma (MM) patients (pts) after cessation of targeted therapy (TT) with BRAF or BRAF/MEK inhibitor(i). *First Author: Natalie Jackson, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Since their introduction into the clinic a decade ago, BRAF and BRAF/MEKi have dramatically changed the outcomes of pts with BRAF mutant MM. While typically, these agents are administered until progression (PD), other reasons for stopping TT include unacceptable toxicity, complete response to treatment, or pt/physician decision or preference. The outcomes for MM pts that stop TT for reasons other than PD are largely unknown. Here we report the clinical features and outcomes of the largest cohort of MM pts who stopped TT for reasons other than PD to date. **Methods:** Under an institutionally approved database, we identified MM pts treated at the MD Anderson Cancer Center with BRAF±MEK inhibitors, and their records were reviewed to identify pts that stopped TT for reasons other than PD. Pts demographics, treatment information and clinical outcomes were recorded. Overall survival (OS) time was computed from three start dates (initial diagnosis, initial unresectable stage III melanoma, 1st dose of TT) to last known vital sign. Pts alive at the last follow-up date were censored. Time to recurrence was computed from date of 1st dose of TT to recurrence. Pts who did not experience disease recurrence were censored The Kaplan-Meier method was used to estimate OS and time to recurrence. **Results:** A total of 58 pts were identified, 32 (55%) were male. Most pts had a BRAF V600E (n = 49) or V600K (n = 6) mutation. At TT initiation median age was 59.5 years (range 29- 95), LDH was within normal range in 46 (85%), median number of prior systemic therapies was 1 (range 0-5), with 50% of pts receiving prior systemic therapy. Most (n = 33; 57%) pts were treated with single agent BRAFi (12 with dabrafenib, 11 vemurafenib). Among pts treated with combination TT (n = 25), most received dabrafenib with trametinib (n = 21; 84%). Median TT treatment duration was 9.5 months (range 0.03-80.5 months). Reasons for TT discontinuation were unacceptable toxicity (n = 29; 50%) and pt or physician decision/preference in responding patients (n = 23; 40%). At time of TT discontinuation, 48% of pts had achieved a complete response (CR), 28% a partial response (PR), and 22% stable disease (SD), 1 patient had unknown disease status. With standard follow-up, after stopping TT, 40 pts (69%) have recurred or experienced PD, with a median time to recurrence of 14.9 months (95% CI:7.8-26.3 months). At PD, 32 (76%) of pts had new metastatic sites. After PD 26 pts (63%) pts received BRAF/MEKi, 11 (44%) achieved a CR and 6 (24%) a PR, and 5 (20%) for a response rate of 88%; while 3 (12%) pt had PD as best response and 1 was unknown. For the full cohort, the median OS from time of 1st dose of TT was 6.4 years. **Conclusions:** Among MM pts who stopped TT for reasons other than PD, the majority of pts recurred, but most responded to re-introduction of TT. This information can help to inform discussion with pts regarding cessation of, or re-challenge with, TT. Research Sponsor: Cancer Center Support Grant.

9565 **Poster Session**

Multicentre retrospective assessment of toxicity and response to immunotherapy in elderly patients with metastatic melanoma. *First Author: Shivanshan Pathmanathan, Department of Oncology, Gold Coast University Hospital, Gold Coast, QLD, Australia*

Background: The incidence of melanoma increases with age, however, elderly patients remain under-represented in landmark immunotherapy trials for metastatic melanoma. This study aims to investigate the impact of age on efficacy and toxicity of immunotherapy, and complications of immunosuppression to treat toxicity. **Methods:** A multicentre retrospective study involving centres in Australia [Gold Coast University Hospital, Cairns Base Hospital, Townsville University Hospital] was performed to compare the efficacy and toxicity of immunotherapy in metastatic melanoma in patients ≥70 years versus patients < 70 years treated between 2015 and 2019. Data collected included: baseline demographics, PFS, OS, Grade 3 or higher (Gr3+) adverse events as per CTCAEv5, adverse events leading to discontinuation, duration of steroids used to treat toxicity and complications secondary to steroids. Comparison of survival outcomes between the groups was calculated using Kaplan Meier, Log rank test and multivariate Cox regression analysis. Fisher exact test was used to determine differences in toxicity between the two groups. **Results:** A total of 229 patients were included with 106 patients ≥70years and 123 patients < 70 years. Baseline demographics were similar. Dual immunotherapy (ipilimumab + nivolumab) was less commonly used in patients ≥70years [13 v 38% p < 0.001]. Although the median PFS was numerically higher amongst ≥70years [10.8 v 6.9months p = 0.99], the landmark PFS was not [3yr PFS: 31 v 39%; 4yr PFS: 22 v 39%]. The median OS was similar in patients ≥70 years v < 70years [27.5 v 28.7 months p = 0.91], with similar landmark survival [3yr OS: 46 v 49%; 4yr OS: 42 v 49%]. Age was not associated with a difference in overall survival on multivariate analysis. There was no increase in Gr3+ adverse events in patients ≥70 years [22 v 21% p = 1.00] or discontinuation rates [26 v 20% p = 0.35]. There was one death in a patient < 70years secondary to colitis. There was a significantly higher rate Gr3+ adverse events in ≥70years patients receiving dual immunotherapy [71 v 35% p = 0.029] and a similar rate of Gr3+ adverse events with PDL1 inhibitors [13 v 11% p = 0.7]. Median duration of steroids was similar in both group [15 v 17wks], as was the median duration of high dose steroids defined as greater than 10mg of prednisone [5 v 6wks]. Complications of steroids was numerically higher in the elderly population [42 v 25% p = 0.15]. The most common adverse event to immunosuppression was infection. **Conclusions:** Patients ≥70years received similar benefit from immunotherapy in comparison to their younger counterparts. Toxicity related to PDL1 inhibitors was similar in both groups and was higher in patients ≥70years receiving dual immunotherapy. Patients ≥70 years had a clinically significant higher rate of complications secondary to steroids. Research Sponsor: None.

9566 **Poster Session**

Health-related quality of life (HRQoL) in patients (pts) with locally advanced basal cell carcinoma (laBCC) treated with cemiplimab: Analysis of a phase II, open-label clinical trial. *First Author: Alexander J. Stratigos, University of Athens, A. Sygros Hospital, Athens, Greece*

Background: Cemiplimab-rwlc is the first immunotherapy to receive approval in the US, fully for pts with laBCC and accelerated for metastatic BCC, post hedgehog inhibitors or for whom hedgehog inhibitors are not appropriate. Cemiplimab resulted in clinically meaningful anti-tumor activity in pts with laBCC who progressed on or were intolerant to hedgehog inhibitor therapy (NCT03132636). This analysis evaluated HRQoL in these pts. **Methods:** Adults with laBCC and ECOG performance status ≤1 (n=84) received IV cemiplimab 350 mg Q3W for up to 9 treatment cycles. At baseline (BL) and day 1 of each cycle (C), pts completed EORTC QLQ-C30 and SKINDEX-16 questionnaires that assess Global Health Status (GHS)/QoL, functioning, and BCC-related symptoms. Mixed-effects repeated measures (MMRM) models were used to estimate least squares (LS) mean (standard error [SE]) change from BL during treatment (i.e., across C2 to C9); changes ≥|10| points were considered clinically meaningful. Responder analyses were conducted in pts with non-missing data from BL to determine the proportions with clinically meaningful improvement or deterioration, or stability on QLQ-C30 and SKINDEX-16 at C2 and C9; a 10-point threshold was considered meaningful for both instruments. **Results:** BL scores showed moderate to high levels of functioning and low symptom burden. In MMRM models, overall changes from BL on QLQ-C30 indicated stability for GHS/QoL and all scales except for clinically meaningful worsening of fatigue (LS mean [SE] change 12.5 [3.9]; $P<.05$). In responder analysis, the majority of pts reported clinically meaningful improvement or stability at C2 and C9 on all QLQ-C30 functioning scales and the key symptom of pain but not fatigue (**Table**). On SKINDEX-16, MMRM models showed clinically meaningful improvement on the emotional subscale (LS mean [SE] change −13.2 [3.9]; $P<.05$) and stability on the symptom and functional subscales. Responder analysis showed clinically meaningful improvements or stability across the SKINDEX-16 subscales in approximately 80% of pts at C2, and 70–80% of pts at C9. **Conclusions:** In laBCC pts treated with cemiplimab, the majority reported clinically meaningful improvement or stability in GHS/QoL and functional status while maintaining a low symptom burden except for fatigue. Clinical trial information: NCT03132636. Research Sponsor: Regeneron Pharmaceuticals, Inc. and Sanofi.

Number (%) of pts with clinically meaningful improvement or stability/clinically meaningful deterioration.

	C2	C9
GHS/QoL	63 (87.5)/9 (12.5)	10 (58.8)/7 (41.2)
Physical functioning	58 (77.3)/17 (22.7)	14 (77.8)/4 (22.2)
Role functioning	52 (69.3)/23 (30.7)	11 (61.1)/7 (38.9)
Emotional functioning	60 (81.1)/14 (18.9)	12 (66.7)/6 (33.3)
Cognitive functioning	56 (75.7)/18 (24.3)	13 (72.2)/5 (27.8)
Social functioning	60 (81.1)/14 (18.9)	11 (61.1)/7 (38.9)
Pain	56 (74.7)/19(25.3)	14 (77.8)/4 (22.2)
Fatigue	46 (61.3)/29 (38.7)	8 (44.4)/10 (55.6)

9567 **Poster Session**

Pathology of durable stable disease in melanoma patients treated with ipilimumab, nivolumab, or ipilimumab, and nivolumab combination therapy. *First Author: Elizabeth Iannotti Buchbinder, Dana-Farber Cancer Institute, Boston, MA*

Background: As immunotherapy with checkpoint blockade becomes the backbone of melanoma treatment there is a need to better understand the biology associated with long term benefit. One particularly interesting set of patients are those with prolonged stable disease or response with residual findings on imaging. It is unknown if immunotherapy has led to scarring at the site of prior disease or if there are residual tumor cells being controlled by an ongoing immune response. Evaluating tissue from patients with prolonged responses provides a unique opportunity to determine the composition of residual lesions. Correlation with PET/CT helps determine if this is an accurate modality to reflect presence of residual viable tumor tissue. **Methods:** Metastatic melanoma patients that have attained long term stable disease after treatment with ipilimumab, nivolumab, or ipilimumab plus nivolumab were identified. Patients must have received ipilimumab, nivolumab or combination therapy 2+ years prior to enrollment and must have had stable disease for ≥ 6 months. Patients were consented and underwent PET/CT scans and biopsies of residual areas of stable disease. Pre- and post-treatment tissue samples underwent pathologic assessment to look at tumor cell content, fibrotic content, and inflammation. **Results:** Ten patients were consented for evaluation but only 7 met the screening criteria and underwent PET/CT and tissue biopsy. Six patients had FDG avid lesions on PET/CT which ranged in intensity from SUV 2.4-22. One patient had no FDG avidity in the areas of residual disease observed on CT. Biopsies from the residual stable lesions demonstrated predominantly necrosis and fibrosis with prominent pigment containing macrophages. One patient with an axillary nodal lesion with an SUV of 22 had active melanoma on pathology which was resected, and the patient has subsequently remained without progression of disease. **Conclusions:** Patients with durable stable disease after treatment with ipilimumab, nivolumab or ipilimumab and nivolumab combination therapy represent a unique population of melanoma patients treated with immune checkpoint inhibition. An examination of the residual lesions observed in these patients demonstrated predominantly necrosis and fibrosis consistent with resolving lesions. The presence of melanophages in these samples may suggest some ongoing immune surveillance. One patient did demonstrate residual melanoma suggesting the need for ongoing monitoring of this patient population. Research Sponsor: Bristol Myers. Squib.

9568 **Poster Session**

Tumor PD-L1 expression and gene panel mutational profile as outcome predictors of PD-1-based checkpoint inhibition therapy in metastatic melanoma: A prospective multicenter DeCOG study. *First Author: Selma Ugurel, Department of Dermatology, University Hospital Erlangen and Department of Dermatology, University of Würzburg, Essen, Germany*

Background: PD-1 checkpoint inhibition (CPI) has recently advanced to one of the most effective treatment strategies in melanoma. However, since a considerable proportion of patients shows upfront therapy resistance, baseline predictive biomarkers of therapy outcome are needed. **Methods:** This prospective multicenter study included metastatic melanoma patients whose formalin-fixed paraffin-embedded tumor tissue samples taken prior to the start of a systemic non-adjuvant therapy of any line were analyzed for PD-L1 expression on tumor cells by immunohistochemistry (clone 28-8, DAKO) and for COSMIC-annotated oncogenic mutations by 29-gene panel sequencing (MiSeq, Illumina). Clinical baseline and follow-up data were collected within the DeCOG multicenter skin cancer registry ADOREG. **Results:** From 09/2015 until 10/2020, 706 enrolled patients from 15 centers were evaluable for the endpoints best overall response (BOR), progression-free (PFS) and overall survival (OS). Thereof, 540 patients received PD-1-based CPI as first systemic treatment after tumor tissue analysis. 197/540 patients tested positive for PD-L1 (cut-off = 5%) in pre-treatment tumors, and revealed a favourable BOR (objective response 34.4% versus 19.1%; $p < 0.0001$), PFS (median 10.4 versus 4.2 months; $p < 0.0001$) and OS (median 45.1 versus 18.8 months; $p = 0.001$) compared to patients with PD-L1 negative tumors. 47/540 patients presented oncogenic mutations of three or more genes in pre-treatment tumors, and revealed a favourable BOR (objective response 46.8% versus 32.1%; $p = 0.041$), PFS (median 15.1 versus 6.1 months; $p = 0.008$) and OS (median not reached versus 25.2 months; $p = 0.027$) compared to patients whose tumors showed mutations in two or less genes. Multivariable Cox regression including sex, primary site, non-adjuvant systemic pre-treatment, serum LDH, and ECOG performance state demonstrated tumor PD-L1 expression and gene panel mutational profile as independent predictors of survival upon treatment with PD-1-based CPI. In contrast, in 106/706 patients treated with BRAF/MEK inhibitors as first systemic treatment after tumor tissue analysis, no association was found between tumor PD-L1 expression or gene panel mutational profile and therapy outcome. **Conclusions:** PD-L1 expression quantification and gene panel mutational profiling provide useful outcome predictors of PD-1-based CPI therapy in metastatic melanoma patients. Research Sponsor: Bristol Myers Squibb, Dermatologic Oncology Group (DeCOG) .

9569 **Poster Session**

Analysis of patients (pts) with in-transit metastases treated with nivolumab (NIVO) or ipilimumab (IPI) in CheckMate 238. *First Author: James Larkin, The Royal Marsden Hospital NHS Foundation Trust, London, United Kingdom*

Background: In the phase 3 CheckMate 238 study, NIVO has demonstrated improved recurrence-free survival (RFS) and distant metastasis-free survival (DMFS) vs IPI in pts with resected stage IIIB–C or IV melanoma, which was sustained at the 4-y analysis. Having in-transit metastases/satellites (ITM) is a poor prognostic factor, and pts with ITM are generally omitted from clinical trials. This study was the first and only adjuvant checkpoint inhibitor trial to include pts with ITM. Here, we present post hoc outcomes in this subgroup. **Methods:** Pts aged ≥15 y with completely resected stage IIIB–C or IV melanoma stratified by stage and tumor PD-L1 status were randomized 1:1 to NIVO (3 mg/kg Q2W; n = 453) or IPI (10 mg/kg Q3W for 4 doses, Q12W thereafter; n = 453) for a maximum of 1 y or until disease recurrence/unacceptable toxicity. Pts with ITM, with or without synchronous nodal involvement, were included. The primary study endpoint was RFS; overall survival (OS) was a secondary endpoint; and DMFS was exploratory. **Results:** Each of the 2 treatment groups had 164 pts with ITM. Baseline characteristics were generally similar between treatment groups in pts with or without ITM; in pts with ITM vs without ITM, tumor ulceration was less frequent in NIVO-treated pts, and fewer IPI-treated pts had PD-L1 expression ≥5%. RFS and DMFS favored NIVO vs IPI in all ITM subgroups (table). OS was similar to the intention-to-treat (ITT) population with no differences noted between treatment groups or between ITM subgroups. Among pts with or without ITM, dominant metastatic sites were lung and lymph nodes, followed by brain, liver, and soft tissue (in varying order). Similar metastasis patterns were observed in pts with ITM regardless of nodal involvement. Treatment-related adverse events (any grade and grade 3/4) in pts with ITM were similar to those of the ITT population. **Conclusions:** Results of this post hoc 4-y analysis of CheckMate 238 showed that safety and efficacy were similar in pts with or without ITM, supporting the use of adjuvant NIVO in pts with ITM, regardless of nodal involvement. Clinical trial information: NCT02388906. Research Sponsor: Bristol Myers Squibb, Pharmaceutical/Biotech Company.

	No ITM	No ITM	ITM	ITM	ITM with nodes	ITM with nodes	ITM, no nodes	ITM, no nodes
Treatment	**NIVO (n = 206)**	**IPI (n = 202)**	**NIVO (n = 164)**	**IPI (n = 164)**	**NIVO (n = 83)**	**IPI (n = 90)**	**NIVO (n = 81)**	**IPI (n = 74)**
4-y RFS, % (95% CI)	54 (47–61)	46 (38–52)	50 (42–58)	38 (30–45)	53 (41–63)	35 (24–45)	49 (37–59)	41 (29–52)
HR (95% CI)	0.77 (0.58–1.02)	—	0.63 (0.47–0.86)	—	0.57 (0.37–0.87)	—	0.72 (0.47–1.12)	—
4-y DMFS, % (95% CI)	60 (53–67)	53 (46–60)	58 (49–65)	53 (45–61)	59 (47–69)	51 (39–62)	56 (43–66)	56 (44–67)
HR (95% CI)	0.79 (0.58–1.07)	—	0.79 (0.56–1.11)	—	0.71 (0.44–1.14)	—	0.90 (0.55–1.49)	—
4-y OS, % (95% CI)	76 (69–81)	75 (68–81)	79 (72–85)	79 (72–85)	78 (67–86)	77 (67–85)	81 (70–88)	82 (70–89)
HR (95% CI)	0.93 (0.63–1.36)	—	0.89 (0.55–1.43)	—	0.81 (0.42–1.54)	—	1.03 (0.50–2.11)	—

9570 **Poster Session**

A phase Ib clinical trial of neoadjuvant OrienX010, an oncolytic virus, in combination with toripalimab in patients with resectable stage IIIb to stage IVM1a acral melanoma. *First Author: Xuan Wang, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/ Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Metastatic acral melanoma is very difficult to treat. Unlike cutaneous melanoma, acral melanoma responds poorly to checkpoint inhibitors in monotherapy. OrienX010 is a granulocyte-macrophage colony-stimulating factor expressing herpes simplex type-1 derived oncolytic virus. It has shown robust efficacy in metastatic acral melanoma, and may improve the response to checkpoint inhibitors. To evaluate the role of OrienX010 in combination with checkpoint inhibitors in acral melanoma, we conducted a Phase Ib neoadjuvant trial of OrienX010 in combination with the anti-PD-1 monoclonal antibody toripalimab in resectable stage IIIB-IVM1a acral melanoma (NCT04197882). **Methods:** Patients with resectable stage IIIB-IV M1a acral melanoma received neoadjuvant intratumoral OrienX010 up to 10 mL of 8 x 10^7 pfu/mL and intravenous toripalimab 3 mg/kg every 2 weeks for 4 – 6 doses prior to surgical resection. After resection, adjuvant toripalimab 3 mg/kg was administered every 3 weeks for up to 1 year. The primary endpoints were radiographic response rate per RECIST 1.1 and pathological response rate (pCR and pPR). The secondary endpoints were 1- and 2-year recurrence-free survival, and safety. **Results:** Between July 2019 and Jan 2021, 30 patients with regional metastatic acral melanoma were enrolled. Median age was 56.5 years, 14 (47%) were male, 19 (63%) had recurrent disease, and stage IIIB 12 (40%), IIIC 14 (47%), and IVM1a 4 (13%). Median tumor burden was 28mm (range, 10-80mm), and only 5 (17%) patients had melanoma mutations (2 cKIT, 1 NRAS, 2 BRAF). To date, of 24 patients who completed neoadjuvant treatment, 21 (88%) underwent surgery. Three (12%) patients did not undergo surgery due to disease progression prior to surgery and 6 patients are still receiving neoadjuvant treatment. Radiographic responses were seen in 10 (33%) patients. However, 17 of 21 (81%) patients showed pathologic responses in resected metastases, with 3 (14%) showing a pCR and 14 (67%) a pPR. Pathologic responses were associated with greater lymphoid infiltrate, hyaline fibrosis, and decrease in Ki-67 expression in the metastasis. At a median follow-up of 8.9 months, none of the patients who underwent resection have recurred. The neoadjuvant treatment was well tolerated, with all patients experiencing at least 1 treatment related adverse event (TRAE) and Grade 1 fever was most common . Three (10%) patients had a grade 3-4 TRAE, including 1 alanine aminotransferase increase and 2 wound infections. **Conclusions:** Neoadjuvant treatment with OrienX010 and toripalimab in resectable stage IIIB-IVM1a acral melanoma was well tolerated and produced a high pathologic response rate. To date, no patients have recurred, and recurrence-free survival evaluation is ongoing. This combination therapy warrants further evaluation in acral melanoma. Clinical trial information: NCT04197882. Research Sponsor: Oriengene Biotechnology Ltd.

9571 **Poster Session**

Management of resected stage III/IV melanoma with adjuvant immunotherapy. *First Author: Rebecca Johnson, Melanoma Institute Australia, Sydney, Australia*

Background: Adjuvant anti-PD1 therapy reduces the risk of recurrence in resected stage III/IV melanoma and is now standard care. Limited data exist beyond registration trials. We sought to explore the use of adjuvant immunotherapy in routine clinical practice. **Methods:** Patients (pts) from 11 Australian centres who received adjuvant nivolumab (nivo) for resected stage III/IV melanoma were included in this study. Efficacy, toxicity, surveillance, recurrence characteristics, management and further treatment outcomes were examined. **Results:** 471 pts received adjuvant nivo between 8/2018 to 3/2020. 318 (68%) were male, median age 64y (range 17-94), 28 (6%) were AJCC v8 IIIA, 194 (41%) IIIB, 175 (37%) IIIC, 11 (2%) IIID, and 63 (13%) IV. 65 (14%) pts had in-transit only disease, 152 (37%) pts were sentinel lymph node biopsy (SLNB+) and only 9 (6%) of these had CLND. 128 (27%) had BRAF mutant (BRAFmt) melanoma. Median time from resection to start of adjuvant nivo was 1.8 months (mo) (range 0.2-4.0). Median FU was 17.5 mo. 256 (54%) pts completed 12 months of nivo, 86 (18%) ceased early for toxicity, 76 (16%) for disease recurrence, 25 (5%) other reasons (COVID-19 8, co-morbidities 7, pt choice 10); 28 (6%) pts were still receiving nivo at data cut. Median duration of treatment was 10.4 mo (range 0-16.8). 117 (25%) pts recurred; 76 (65%) while ON nivo and 41 (35%) OFF nivo ($>$ 1 month after last dose, including 20 pts who stopped early for toxicity). 24 mo RFS was 69%. Median time to recurrence was 6.0 mo (95% CI 5.1, 7.5). 56 (48%) had first recurrence with locoregional (LR) disease only and 61 (52%) had distant +/- LR recurrence. Of those who recurred with LR disease only, 46/56 (82%) underwent surgery, 15/46 (33%) then had adjuvant radiotherapy, and 15/46 (33%) had 'second adjuvant' therapy with BRAF/MEK inhibitors (15/21, 71% BRAFmt pts). 10/56 (37%) pts who recurred with LR disease subsequently recurred distantly. 58/80 (73%) pts received systemic therapy at either 1st or subsequent unresectable recurrence. For recurrences ON nivo, 18 pts received combination ipilimumab (ipi) and nivo (ORR 44%), 4 pts had ipi monotherapy (ORR 0%), 7 pts had anti-PD1 + investigational agent (ORR 57%), 11 pts had BRAF/MEK inhibitors (ORR 82%). 1 pt had PD with ongoing PD1 monotherapy. For recurrences OFF nivo, no patients responded to PD1 alone (n = 1) or with an investigational agent (n = 1), ipi+nivo (n = 3), ipi monotherapy (n = 4) or chemotherapy (n = 2); 6 pts received BRAF/MEK inhibitors (ORR 50%). 2-year OS was 92%. **Conclusions:** Despite higher rates of discontinuation due to toxicity compared with clinical trial cohorts, the efficacy data appear similar. Most early recurrences are distant, and many with LR recurrence soon recur distantly thereafter. Second line adjuvant BRAF/MEK inhibitors are frequently used for resected LR recurrence. Both ipi+nivo and BRAF/MEK inhibitors appear to have activity after distant recurrence. Research Sponsor: None.

9572 **Poster Session**

Propensity weighted indirect treatment comparison of nivolumab (NIVO) versus placebo (PBO) as adjuvant therapy for resected melanoma: A number needed to treat and overall survival analysis. *First Author: Jeffrey S. Weber, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY*

Background: The CheckMate 238 trial demonstrated that NIVO improved recurrence free survival (RFS) vs. ipilimumab (IPI). The EORTC 18071 trial demonstrated that IPI improved RFS and overall survival (OS) vs. PBO. The current study pooled data from these two trials to indirectly assess the RFS and OS of NIVO vs. PBO and the numbers needed to treat (NNTs) for one additional recurrence-free survivor and survivor over 4 years. **Methods:** Patients with resected AJCC 7th edition stage IIIB/C cutaneous melanoma from CheckMate 238 (NIVO vs. IPI) and EORTC 18071 (IPI vs. PBO) were pooled together with inverse probability weighting to balance between-trial differences in baseline characteristics. NNTs were calculated for RFS and OS comparing NIVO vs. IPI and PBO over 4 years. To account for improved post-recurrence survival over time, a sensitivity analysis that adjusted for post-recurrence survival in the PBO arm of EORTC 18071 was performed. **Results:** A total of 278, 643, and 365 patients treated with NIVO, IPI, and PBO, respectively, were included. In the weighted samples, patients treated with NIVO had consistently higher RFS rates than those treated with IPI (HR [95% CI]: 0.69 [0.56, 0.85]) and PBO (HR: 0.49 [0.39, 0.61]). NIVO was associated with similar OS as IPI (HR: 0.80 [0.60, 1.08]) and superior OS compared to PBO (HR: 0.45 [0.33, 0.60]). At 4 years, the weighted RFS rate was 53.1% for NIVO, 41.8% for IPI, and 29.1% for PBO. The NNT to achieve one additional recurrence-free survivor was 4.2 for NIVO vs. PBO and 8.9 for NIVO vs. IPI. The NNT to obtain one additional survivor was 4.8 for NIVO vs. PBO and 22.2 for NIVO vs. IPI. The OS rate for PBO after adjusting for differences in post-recurrence treatments at 4 years was 64.1%, and the corresponding NNT of OS comparing NIVO vs. adjusted PBO was 8.5. **Conclusions:** In patients with resected AJCC 7th edition stage IIIB/C cutaneous melanoma, this indirect comparison showed that NIVO improved RFS and OS vs placebo, with OS improvement maintained after adjustment for post-recurrence therapy. Research Sponsor: Bristol Myers Squibb.

NNT in patients with resected stage IIIB/C cutaneous melanoma.

	RFS rate			RFS NNT (95% CI)		OS rate				OS NNT (95% CI)		OS NNT (95% CI) - sensitivity analysis
Follow-up time (years)	NIVO	IPI	PBO	NIVO vs. PBO	NIVO vs. IPI	NIVO	IPI	PBO	Adjusted PBO	NIVO vs. PBO	NIVO vs. IPI	NIVO vs. adjusted PBO
1	73.1%	61.1%	48.9%	4.1 (3.1, 6.1)	8.3 (5.3, 19.2)	97.6%	93.0%	84.9%	87.9%	7.9 (5.9, 11.9)	21.6 (13.5, 53.7)	10.4 (5.4, 104.1)
2	65.2%	50.8%	38.5%	3.7 (2.9, 5.3)	6.9 (4.6, 13.9)	88.4%	84.0%	70.5%	74.3%	5.6 (4.1, 8.8)	22.6 (-131.1 to 10.4)	7.1 (4.0, 22.9)
3	60.2%	44.7%	30.9%	3.4 (2.7, 4.7)	6.5 (4.4, 12.5)	81.8%	76.8%	59.8%	67.1%	4.6 (3.4, 6.8)	20.3 (-92.8 to 9.1)	6.8 (3.9, 29.0)
4	53.1%	41.8%	29.1%	4.2 (3.1, 6.3)	8.9 (5.3, 27.4)	75.8%	71.3%	55.0%	64.1%	4.8 (3.5, 7.7)	22.2 (-45.0 to 8.9)	8.5 (4.3, 771.8)

9573 **Poster Session**

Adjuvant anti-PD-1 ab (Toripalimab) versus high-dose IFN-a2b in resected mucosal melanoma: A phase randomized trial. *First Author: Chuanliang Cui, Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education/Beijing), Department of Renal Cancer and Melanoma, Peking University Cancer Hospital & Institute, Beijing, China*

Background: Immunotherapies including anti PD-1 ab and high-dose IFN-a2b (HDI) have been approved for adjuvant therapies in resected cutaneous melanoma, but their roles in mucosal melanoma are still unknown. To determine the efficacies of toripalimab versus HDI as adjuvant therapy in patients (pts) with resected mucosal melanoma, this open-label, phase randomized trial was conducted. **Methods:** Mucosal melanoma pts who have undergone complete resections of localized with or without regional lymphatic disease were randomly (1:1) assigned to receive HDI ($15x10^6$ IU/m^2/d1-5/w/ 4weeks IH, followed by $9x10^6$ IU tiw IH) or toripalimab (3mg/kg intravenously q2w) for 52 weeks unless disease recurrence, unacceptable toxicity or consent withdrawal. Head and neck primary would receive adjuvant radiotherapy within 6-8weeks after enrollment. The primary end point was RFS in the intention-to-treat population. Data cutoff was December 10, 2020. Clinical trial information: NCT03178123. **Results:** From Jul 2017 to May 2019, 187 pts were screened, and 145 were randomized into HDI group (n = 72) and toripalimab group (n = 73). The median age was 58years; M:F 37.2%: 62.8%; localized disease 80.7%, regional lymphatic disease 19.3%; local excision ± CLND 37.2%, wide excision ± CLND 62.8%; head and neck primary 39.3%(87.5% received adjuvant radiotherapy); PDL-1positive 51.0%(CPS≥1%, 22C3), PDL-1 negative 49.0%. There was no difference in baseline characteristics between two groups. At a median follow-up of 31.5 months, there were 93 RFS events (43 in HDI group vs. 50 in toripalimab group), 76 DMFS events (35 vs. 41respectively) and 65 OS events (30 vs. 35 respectively). The median RFS, DMFS and OS were shown in the table. In the HDI group, 32.6% of pts received anti PD-1 ab in the following treatment. Grade 3/4 AEs were reported in 83.3% of pts in HDI group (most decrease of leukocytes or neutrophils) and 15.1% of pts in toripalimab group (mainly increase of amylase or liver enzymes). Discontinuations of treatment due to any AE occurred in 20. 8% of HDI group and 15.1% of toripalimab group. **Conclusions:** Both adjuvant toripalimab and HDI therapy improve RFS of mucosal melanoma. Toripalimab shows longer RFS in PDL1 (+) subgroup and better tolerance than HDI. Clinical trial information: NCT03178123. Research Sponsor: Shanghai Junshi biosciences Co.

	Total		PDL1+		PDL1-	
	HD-IFN (N = 72)	PD-1 (N = 73)	HD-IFN (N = 36)	PD-1 (N = 38)	HD-IFN (N = 36)	PD-1 (N = 35)
Median RFS, mo.(95% CI)	13.9 (8.3-21.3)	13.6 (8.3-18.0)	11.1 (5.7-21.3)	17.3 (8.2-22.9)	14.6 (5.7-21.3)	11.3 (5.6-18.0)
HR (95% CI)	1.06 (0.69-1.63)		0.94 (0.53-1.65)		1.06 (0.59-1.90)	
Median DMFS, mo.(95% CI)	14.6 (8.3-21.3)	14.4 (9.7-21.4)	11.1 (6.6-21.3)	17.8 (9.3-24.3)	17.4 (8.3-21.8)	12.7 (8.3-18.0)
HR (95% CI)	0.98 (0.63-1.52)		0.81 (0.45-1.44)		1.03 (0.57-1.88)	
Median OS, mo.(95% CI)	NR (31.2-NR)	NR (28.1-NR)	NR (16.2-NR)	32, 9 (22.9-NR)	NR (26.2-NR)	NR (24.7-NR)
HR (95% CI)	1.08 (0.64-1.85)		0.99 (0.49-1.98)		1.18 (0.53-2.64)	

9574 **Poster Session**

Association of health-related quality of life (HRQoL) and treatment safety with nivolumab (NIVO) in patients (pts) with resected stage IIIB/C or IV melanoma: Analysis of CheckMate 238 four-year follow-up (FU) data.

First Author: Jeffrey S. Weber, Laura and Isaac Perlmutter Cancer Center, NYU Langone Health, New York, NY

Background: In CheckMate 238, NIVO 3 mg/kg vs ipilimumab 10 mg/kg showed significantly longer recurrence-free survival and a lower rate of grade 3–4 treatment-related adverse events (TRAEs) in pts with completely resected stage IIIB/C or IV melanoma. This analysis assessed the association of long-term HRQoL and TRAEs in NIVO-treated pts in this trial. **Methods:** HRQoL was assessed using EORTC QLQ-C30 (global health status [GHS] and physical/emotional functioning) and EQ-5D-3L visual analogue scale (VAS) questionnaires administered after randomization, during 1 y of treatment (wk 5, 7, 11, 17, 25, 37, and 49), at posttreatment FU visits 1 and 2 (FU1 and FU2; 30 and 114 days after last dose), and at survival FU visits up to 4 y after last dose (EQ-5D-3L only). NIVO-treated pts were grouped based on whether they had experienced a grade 3–4 TRAE, any-grade TRAE leading to NIVO discontinuation, or any-grade select (immune-related) TRAE on treatment or up to 100 days after last dose. Longitudinal change from baseline (BL) in scores was assessed for pts with and without TRAEs having patient-reported outcome data at BL and ≥1 post-BL assessment (HRQoL population) using descriptive statistics. QLQ-C30 subscale and VAS changes of 10 and 7, respectively, were considered clinically meaningful. **Results:** The HRQoL population comprised 446 of 453 pts randomized to NIVO. EQ-5D-3L assessments were completed by 81% of survivors (263/324) after 4 y post-randomization. Grade 3–4 TRAEs occurred in 17% of NIVO-treated pts (77/446). A slight trend toward deterioration of GHS from BL on treatment was noted, with clinically meaningful deterioration at posttreatment FU1 (mean [SD], −13.8 [25.0]) and FU2 (−10.3 [22.0]; last available time point). For the VAS, a similar trend on treatment was noted (−6.9 [28.3] at wk 11), with a clinically meaningful deterioration after NIVO discontinuation (−9.9 [27.0] at FU1) and a return to BL level by the start of survival FU. For pts without grade 3–4 TRAEs, mean change from BL scores remained stable (ie, no clinically meaningful deterioration on treatment or during FU). Any-grade TRAEs led to NIVO discontinuation in 9% of pts (42/446); HRQoL findings were similar to those for pts with grade 3–4 TRAEs. The most common any-grade TRAE was fatigue (35%). No clinically meaningful deterioration in VAS was noted for any select TRAE during FU except for hyperthyroidism (8%), with which deterioration occurred at FU1. EORTC QLQ-C30 physical and emotional functioning results will be presented. **Conclusions:** In CheckMate 238, pts with TRAEs showed early HRQoL deterioration after NIVO discontinuation, but HRQoL returned to BL levels with no sustained deterioration during survival FU. Overall, HRQoL was maintained on treatment and over a long-term FU period in pts with resected melanoma receiving adjuvant NIVO. Clinical trial information: NCT02388906. Research Sponsor: Bristol Myers Squibb.

9575 **Poster Session**

Postoperative radiotherapy in Merkel cell carcinoma (MCC).

First Author: Sonja Levy, Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: MCC is a rare and aggressive neuroendocrine malignancy of the skin. Postoperative radiotherapy (PORT) is recommended by current guidelines to reduce recurrences and improve survival in patients with locoregional MCC. However, evidence supporting these recommendations is conflicting and deviations from the protocol occur frequently, due to the generally elderly and frail patient population. We aim to evaluate the influence of PORT on survival in stage I-III MCC patients treated in the Netherlands. **Methods:** All patients with stage I-III MCC treated in three referral centers between 2013 and 2018 were included retrospectively. Recurrence free survival (RFS) and disease specific survival (DSS, including death from unknown causes) were compared between patients with and without PORT. Prognostic factors for DSS were analyzed using Kaplan-Meier curves, logrank test and cox regression. Since sentinel node biopsies (SN) are frequently omitted in this patient population, analyses were performed in patients with clinical (SN not performed) stage I/II (c-I/II-MCC), pathologic (SN negative) stage I/II (p-I/II-MCC) and stage III MCC (III-MCC), separately. Propensity score matching (PSM) was performed to assess possible confounding by indication. **Results:** In total 219 patients were included, of whom 54 had p-I/II-MCC, 82 had c-I/II-MCC and 83 had III-MCC. Median follow up time was 53.4 (IQR 32.8-62.4), 28 (11.8-43.3) and 30.8 (19.5-50.0) months, respectively. PSM identified no confounding by indication, analyses were therefore performed in the unmatched cohort. Majority of recurrences were regional in p-I/II-MCC (77.8%) and c-I/II-MCC (74.2%), and distant in III-MCC (61.7%). RFS was significantly different across all stages ($p<0.001$), DSS was similar for patients with c-I/II-MCC and III-MCC, which was significantly worse compared to patients with p-I/II-MCC (p=0.003). Survival times are shown in table. PORT did not improve RFS and DSS in patients with p-I/II-MCC and c-I/II-MCC. In patients with III-MCC, PORT was associated with improved RFS, but not with DSS. Multivariable analysis identified male gender (hazard ratio (HR) 1.94, p=0.030), performance status (PS) of 3 (HR 3.87, p=0.014) and an unknown PS (HR 5.45, p=0.004), primary tumor on the trunk (HR 2.67, p=0.008), c-I/II-MCC (HR 5.38, p=0.001) and III-MCC (HR 6.44, $p<0.001$) as predictors for DSS. Effect of PORT was not significant. **Conclusions:** In this retrospective cohort PORT did not show a DSS benefit in patients with stage I-III MCC. RFS was improved by PORT in III-MCC. PSM showed no confounding by indication. Research Sponsor: None.

		# patients	1 yr RFS	2 yr RFS	5 yr RFS	p	1 yr DSS	2 yr DSS	5 yr DSS	p
p-I/II-MCC	All	54				0.505				0.647
	No PORT	42	98%	87%	81%		100%	95%	82%	
	PORT	12	92%	92%	92%		100%	100%	100%	
c-I/II-MCC	All	82				0.343				0.132
	No PORT	50	70%	51%	51%		84%	68%	50%	
	PORT	32	80%	59%	59%		97%	83%	69%	
III-MCC	All	83				0.021				0.978
	No PORT	36	49%	30%	30%		97%	78%	63%	
	PORT	47	76%	48%	48%		98%	76%	62%	

RFS and DSS, logrank test for comparison.

9576 **Poster Session**

Isolated same-basin lymph node recurrence after precision lymph node excision for clinically evident melanoma metastasis.

First Author: Kevin Lynch, University of Virginia Health System, Charlottesville, VA

Background: While management of the nodal basin for melanoma has largely moved to observation for microscopic sentinel lymph node (SLN) metastasis, complete lymph node dissection (CLND) remains the current standard of care for melanoma patients with macroscopic, clinically detectable lymph node metastases (cLN). As CLND is associated with high surgical morbidity, we sought to study whether cLN may be safely managed by excision of only clinically abnormal nodes (precision lymph node dissection, PLND). Currently, a small subset of patients with cLN do not undergo CLND because of frailty or patient preference. We hypothesized that in these selected patients, PLND would provide acceptable regional control rates. **Methods:** Retrospective chart review was conducted at four academic tertiary care hospitals to identify melanoma patients who underwent PLND for cLN. cLN were defined as palpable or radiographically abnormal nodes. Recurrences were categorized as local/in-transit, same-basin lymph node, or distal lymph node/visceral. The primary outcome was isolated same-basin recurrence after PLND. **Results:** Twenty-one patients underwent PLND for cLN without synchronous distant metastases (characteristics of primary lesions summarized in Table). Reasons for forgoing CLND included patient preference (n=8), imaging indeterminate for distant metastases (n=2), comorbidities (n=4), loss to follow up (n=1), partial response to checkpoint blockade (n=1), or not reported (n=5). The inguinal node basin was the most common site (n=10), followed by the axillary (n=8) and cervical basins (n=3). A median of 2 nodes were resected at PLND, and 68% of resected nodes were positive for melanoma (median: 1, range: 1-3 nodes). Median follow-up was 23 months from PLND, and recurrence was observed in 28.6% of patients overall. Only 1 patient (4.8%) developed an isolated same-basin recurrence. The 3-year cumulative incidence of isolated same-basin recurrence was 5.3%, while risk of isolated local/in-transit recurrence or distant basin/visceral metastasis were 19.8% and 33.3%, respectively. Complications from PLND were reported in 1 patient (4.8%) and were limited to post-operative seroma and lymphedema. **Conclusions:** These pilot data suggest that PLND may offer acceptable regional disease control for cLN. Post-operative morbidity from PLND was also low, raising the possibility that PLND may provide adequate regional disease control without the morbidity associated with CLND. These data justify additional, prospective evaluation of PLND in selected patients. Research Sponsor: None.

Primary tumor characteristics.	
Tumor Location	
Upper Extremity	2
Trunk	5
Lower Extremity	4
Anal Canal	1
Unknown Primary	7
Not Reported	2
Tumor Histology	
Breslow Thickness*	3.0 (2.6-7.8)
Perineural/ Lymphovascular Invasion	31%
Ulceration	69%
BRAF Mutant	43%

*Median (IQR). Millimeters (mm).

9577 **Poster Session**

Evaluation of patients with surgically resected high-risk melanoma receiving adjuvant therapy in routine clinical practice in the United States.

First Author: Michael B. Atkins, Georgetown Lombardi Comprehensive Cancer Center, Washington, DC

Background: The management of patients with resected stage III melanoma has changed in recent years, and real-world data on recurrence patterns and adjuvant therapy responses are scarce. This study assessed adjuvant treatment patterns and outcomes in patients with advanced melanoma by *BRAF* status and relapse location. **Methods:** Patients diagnosed with stage III advanced melanoma between January 2011 and February 2020 in the nationwide Flatiron Health electronic health record–derived deidentified database were included if they were ≥18 years, received approved first-line (1L) adjuvant therapy after January 2018 with checkpoint inhibitors (CPIs; eg, nivolumab, pembrolizumab) or targeted therapies (TTs; eg, dabrafenib/trametinib), had 6 months' follow-up and had ≥1 visit after starting adjuvant therapy (Cohort 1). Patients from Cohort 1 were included in Cohort 2 if they had a recurrence following initiation of adjuvant therapy, and those from Cohort 2 were included in Cohort 3 if they had a distant recurrence and available documented *BRAF* status at any time. Time to next systemic treatment (TTNT), overall survival (OS) and relapse free survival (RFS) were estimated using Kaplan-Meier (KM) methods from adjuvant therapy start (Cohort 1), first recurrence date (Cohort 2) or first distant recurrence date (Cohort 3). **Results:** Cohort 1 included 447 patients receiving 1L adjuvant therapy; Cohort 2 included patients after first distant (n = 47) or local (n = 35) relapse; Cohort 3 included distant-recurrent patients with tumors that were *BRAF* wild type (WT) (n = 22) or *BRAF* mutant (n = 23). The majority of patients were aged < 65 years. Across cohorts, relative use of TTs vs CPIs was similar: Cohort 1 (4.5% vs 96%), Cohort 2 (2.4% vs 98%) and Cohort 3 (2.2% vs 98%). Nivolumab was the most frequent treatment used across cohorts (84%-88%). In Cohort 1, 1- and 2-year KM probabilities for OS, RFS and TTNT were 93.5%/83.8%, 83.2%/70.6% and 84.0%/62.4%, respectively. In Cohort 2, for patients with local recurrence, 6- and 12-month OS probabilities were 93.4% and 78.8%, respectively, which were substantially higher than those for patients with distant recurrence (64.5% and 46.9%). In Cohort 3, for patients with documented *BRAF* mutations, 6- and 12-month OS rates from disease recurrence were 79.1% and 49.4%, respectively, which were greater than for those with *BRAF*-WT tumors (54.1% and 46.3%). **Conclusions:** Early RFS and OS outcomes for patients with surgically resected Stage III melanoma appear comparable to those reported in randomized clinical studies. The majority of patients with advanced melanoma, including patients who experienced recurrence, initiated treatment with CPIs. OS rates were numerically greater for Cohort 3 patients with *BRAF*-mutant tumors. Outcomes for patients with distant recurrence after adjuvant therapy remain unfavorable and represent a continued unmet medical need. Research Sponsor: Genentech, Inc.

9578 **Poster Session**

Efficacy of adjuvant radiotherapy in recurrent melanoma after adjuvant immunotherapy.

First Author: Prachi Bhave, Westmead Hospital, Sydney, NSW, Australia

Background: Adjuvant (adj) radiotherapy (RT) halves the risk of locoregional (LR) recurrence in patients (pts) with high risk stage III melanoma after lymphadenectomy (CLND), however its role in the adj immunotherapy (IO) era without CLND is unknown. **Methods:** Pts with resected stage III melanoma who received adj IO and recurred with resectable LR only disease were studied. After resection of this 1st recurrence, adj RT may or may not have been administered. Disease characteristics, treatment at relapse and outcomes were examined. **Results:** 71 pts from 9 centres were included. Prior to adj IO, median age was 60y, 59% male, 56% BRAF mutant, 61% stage IIIC (AJCC V8), 52% underwent CLND and 17% had in-transit (IT) only disease. Adj IO included: 90% single agent anti-PD1, 8% ipilimumab-nivolumab (IN) and 1% nivolumab or IN (blinded on trial). Median duration of adj IO was 5 months. 21(30%) pts had high risk stage III disease at diagnosis, per previously established TROG criteria; 3 (4%) received upfront adj RT prior to recurrence. Median time to 1st recurrence was 7 months. 49 (69%) pts recurred during and 22 (31%) after cessation of adj IO. At 1st recurrence, 9 (13%) pts had stage IIIB disease, 55 (77%) IIIC, 7 (10%) IIID and 8 (11%) continued prior adj IO, 31 (44%) commenced therapy and 32 (45%) had no systemic therapy. 24 (34%) pts received adj RT after resection of 1st recurrence and 47 (66%) did not (Table). Adj RT was associated with a reduced risk of any 2nd recurrence (7/24, 29% vs 26/47, 55%, p=0.03) and LR 2nd recurrence (2/24, 8% vs 17/47, 36%, p=0.012). Whilst pts who received adj RT at 1st recurrence were more likely to have LN only disease, extra nodal extension and involved surgical margins, these factors did not significantly affect overall risk of 2nd recurrence on multivariate analysis. Of note, 70% of pts who did not receive adj RT at 1st recurrence had IT only disease, and though this did not significantly affect rate of 2nd recurrence (p=0.19), this likely reflects an inherent selection bias in this study. RT toxicity occurred in 16 (67%) pts, 10 with dermatitis only, and all grade 1 or 2. Median follow up was 22 months. Median recurrence free survival to 2nd recurrence was 23 months for all pts, not reached for those who had adj RT at 1st recurrence and 19 months for those who did not have adj RT (p=0.047). Median overall survival was not reached. **Conclusions:** Whilst adj RT appears to reduce 2nd recurrences, this may have been influenced by an unavoidable selection bias in the data, particularly an imbalance in the percentage of pts with IT disease. Prospective data with larger cohorts is needed to validate our results. Research Sponsor: None.

Patient Characteristics	Adjuvant RT at 1strecurrence N= 24	No adjuvant RT at 1strecurrence N= 47
1st Recurrence		
LR site	-	-
Nodal only	14 (58)	13 (28)
IT only	6 (25)	33 (70)
Nodal and IT	4 (17)	1 (2)
2nd Recurrence		
Total	7 (29)	26 (55)
LR	2 (29)	17 (65)
Within prior RT field	-	-
Yes	2	2
No	0	15
LR site	-	-
Nodal only	0	5
IT only	2	11
Nodal and IT	0	1
Distant	5 (71)	9 (35)

9579 **Poster Session**

The prognostic value of the interferon-gamma (IFNγ) signature in patients with macroscopic stage III melanoma treated with and without adjuvant systemic therapy.

First Author: Judith M. Versluis, Department of Medical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands

Background: Recently, trials have shown the benefit of adjuvant aPD-1 therapy in macroscopic stage III melanoma patients. This treatment has been incorporated in daily clinical practice, however, a substantial part of patients still does not benefit from this therapy, as they develop recurrences. The aim of this study is to evaluate the results of adjuvant aPD-1 therapy and the potency of the IFNγ signature as a prognostic or predictive marker, as it has proven to be predictive of response in neoadjuvant trials. **Methods:** Patients participating in an ongoing biobank study and naïve for systemic therapy were included, between 10-2017 and 06-2020, after complete resection of macroscopic stage III melanoma. Approval and reimbursement of adjuvant therapy in the Netherlands started in 12-2018, resulting in 2 cohorts of similar high risk patients: prior to availability of adjuvant aPD-1 (cohort A) and thereafter (cohort B). Data cut-off for clinical data was January 1st 2021. Transcriptome sequencing was performed on samples of stage III melanoma by CeGaT GmbH, IFNγ signature was determined on these data with the median as cut-off. Clinical data were compared between cohort A and B as intention-to-treat population, including patients with a recurrence before adjuvant therapy start (n=10). **Results:** In total, 99 patients were included: 50 in cohort A and 49 in cohort B. Majority of included patients had thick primary melanomas (Breslow >2mm in 59.6%) and stage IIIC/IIID disease (83.3%) according to AJCC 8th edition. At a median follow-up of 20.6 months (95% confidence interval [CI] 16.6-24.7), median recurrence-free survival (RFS) was 6.1 months (95%CI 3.9-8.4) versus 22.8 months (95%CI 8.7-36.9), significantly in favor of cohort B (p=0.011). Median overall survival (OS) was not reached in both patient groups, but was overall significantly different (p=0.040), favoring cohort B. RNA sequencing was performed in 25 patients who received adjuvant therapy and in 24 who did not, excluding patients with an early recurrence (<12 weeks). In both treatment groups median (p=0.003) and 12-months RFS (p<0.001) was significantly higher for IFNγ high patients, but both IFNγ low and high patients show higher RFS rates when receiving adjuvant aPD-1 therapy (Table). **Conclusions:** Our study confirms RFS and OS benefit of adjuvant aPD-1 for patients with macroscopic stage III melanoma. IFNγ has shown to be a prognostic marker in both patients who were and were not treated with adjuvant therapy, as both patients with IFNγ high and low signatures show benefit from adjuvant therapy. Research Sponsor: None.

		Median RFS (months)	12-months RFS
No adjuvant therapy	**IFN-γ low**	2.8 (95%CI 2.0-3.6)	6.9% (95%CI 0.0-20.3)
	IFN-γ high	13.0 (95%CI 3.1-23.0)	53.3% (95%CI 27.5-79.1)
Adjuvant therapy	**IFN-γ low**	5.1 (95%CI 0.0-12.1)	40.3%(95%CI 16.1-64.5)
	IFN-γ high	18.6 (95%CI 12.1-25.1)	70.1% (95%CI 47.7-92.5)

9580 **Poster Session**

Incidence, timing, and predictors of CNS metastasis in patients (Pts) with clinically localized cutaneous melanoma (CM).

First Author: Merve Hasanov, The University of Texas MD Anderson Cancer Center, Houston, TX

Background: Surveillance for CNS metastasis (mets) is not routinely performed in pts with clinically localized CM. Improved understanding of the incidence, timing and risk factors for the development of CNS metastasis in these pts may inform surveillance strategies. **Methods:** Under an IRB-approved protocol, demographics, tumor characteristics, and clinical events were collected for pts diagnosed from 1998 to 2019 with AJCC 8th edition stage I or II CM at MD Anderson Cancer Center. Dates of initial diagnosis, regional, distant non-CNS, and CNS mets were recorded. Symptoms and the extent of disease (brain, LMD, both) were recorded for pts with CNS mets. Cumulative incidence of distant mets (CNS and non-CNS) was determined using the competing risks method, including death; pts without CNS mets and alive at last follow-up were censored. Differences in cumulative incidence between groups were assessed using Gray's test. Associations between measures of interest and cumulative incidence were determined using proportional subdistribution hazards regression models. All statistical tests used a significance level of 5%. **Results:** 5,179 Stage I-II CM pts were identified. At a median follow up of 82 (0.0-268.8) months, 703 (13.6%) pts were diagnosed with distant mets, including 355 (6.9%) with CNS mets. Cumulative incidence of CNS mets was 0%, 2%, and 5% at 1, 2, and 5 years, respectively. Among pts with distant mets, the first site of distant mets was CNS only for 29 (4%), non-CNS only for 557 (79%), and both for 116 (17%) pts. At initial diagnosis of CNS mets, 195 (55%) pts were asymptomatic, and 46 (13%) had no active extracranial disease. Median time to any distant met was longer for pts who were diagnosed with CNS mets [40.0 (1.9-238.0) months] vs pts diagnosed with non-CNS mets only [31.4 (1.1-185.7) months, p < 0.001]. On multivariable analysis, risk of CNS mets was significantly associated with primary tumor location of scalp [Hazard Ratio (HR) 3.4, 95% Confidence interval (CI) 1.9-5.9], head/neck (HR 3.3, 95% CI 2.0-5.3), or trunk (HR 2.3, 95% CI 1.5-3.5) (vs upper extremity); acral lentiginous melanoma subtype (HR 2.0, 95% CI 1.2-3.6) (vs superficial spreading); increased T category (T2 HR 1.5, 95% CI 1.1-2.2; T3 HR 1.9, 95% CI 1.2-3.0; T4 HR 2.1, 95% CI 1.1-3.8; vs T1), Clark level (CL) (CL4 HR 2.1, 95% CI 1.2-3.7 vs CL2), and mitotic rate (MR) (MR 5-9/mm^2 HR 2.1, 95% CI 1.5-3.0; MR > 9/mm^2 HR 2.0, 95% CI 1.3-3.0; vs MR 0-4/mm^2). While high (> 9/mm^2) MR was associated with increased risk of CNS and non-CNS mets, intermediate (5-9/mm^2) was associated with CNS mets only. **Conclusions:** Primary tumor location, tumor thickness, and MR were strongly associated with risk of CNS mets. MR rate was more strongly associated with risk of CNS than non-CNS mets. Validation in independent cohorts may provide evidence to support CNS surveillance strategies in select pts with stage I-II CM who are deemed high risk for CNS mets. Research Sponsor: None.

9581 **Poster Session**

Genome-wide association study to reveal novel germline markers of melanoma survival.

First Author: Vylyny Chat, New York University Medical Center, Manhattan, NY

Background: Cutaneous melanoma (CM) is the most invasive form of skin cancer accounting for ~80% of all skin cancer related deaths. While tumor staging (based on recent AJCC classification) is routinely used in prognostic assessment, a large fraction of the outcomes is not explained by AJCC staging system. This urges for the discovery of a more personalized prognostic surrogates. Growing evidence highlights the role of germline genetics in CM progression; yet, to date no systematic prognostic germline study has been conducted in melanoma. We performed the first genome-wide association analysis (GWAS) to identify germline variants associated with melanoma survival. **Methods:** A cases/case GWAS was performed using the Infinium global screening array (GSA v3.0) to genotype 1,117 stage 0-III melanoma patients with no history of immunotherapy treatments ascertained at New York University Langone Health (NYULH). We randomly divided the study cohort into a discovery (N=630) and a validation (N=487) sets and tested the association of > 5 million imputed germline variants with melanoma overall survival (OS) by fitting Cox-proportional hazard ratio (HR) regression in an additive genetic model adjusting for sex, age at diagnosis, AJCC 8th staging, tumor anatomic sites, and top 3 principal components. **Results:** We found 151 independent variants associated with melanoma OS ($p< 5\times10^{-5}$) in the discovery cohort. Two of these associations validated in the independent replication set (*Bonferroni* threshold for 151 tests: p < 0.003) with enhanced clinical and statistical significance in the pooled meta-analysis: rs4128212 [HR =2.47(1.75-3.48); $p=2.2\times 10^{-7}$], and rs13212644 [HR =2.59 (1.72-3.88); $p=4.2\times 10^{-6}$]. We further tested the combined effect of these two variants and found the presence of at least one risk allele of the variants associated with a substantially increased risk of death, surpassing GWAS level of significance (HR=3.74 (2.43-5.74); $p=1.5\times10^{-9}$). **Conclusions:** We present the results of first GWAS testing an association of germline variation with melanoma OS. Stemming from a unique patient population with extensive clinical follow-up data, we identified two prognostic germline loci with large HR effect size >2.5 that were independently validated. The observed association is independent of established histopathologic markers. While rs4128212 was mapped to a putative cancer prognostic gene locus (PLPP4: phospholipid phosphatase 4), rs13212644 was an eQTL (expression quantitative trait loci) for GCLC (Glutamate-Cysteine Ligase Catalytic Subunit), a key regulator in glutathione synthesis previously linked with favorable melanoma survival. The significantly enhanced combined effect of these two loci (HR >3.5; $p<5\times10^{-9}$) indicates a great promise for their clinical utility as independent personalized predictive markers of melanoma progression. Research Sponsor: U.S. National Institutes of Health.

9582 **Poster Session**

Granulomatous and sarcoid-like immune related adverse events (irAEs) in melanoma patients following CTLA4 blockade adjuvant therapy: An analysis of 1670 high-risk patients. *First Author: Arish Noor, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Granulomatous and sarcoid-like lesions (GSL) affecting the skin, lungs, thoracic lymph nodes, eyes and other organs following treatment with immune checkpoint inhibitors (ICIs) have been described in sporadic reports in the literature but the true incidence is unknown. **Methods:** We sought to estimate the incidence of GSL in the context of prospectively conducted ECOG-ACRIN E1609 phase III adjuvant trial in high-risk resected melanoma (N=1670 patients) testing ipilimumab 3 mg/kg (ipi3) and 10 mg/kg (ipi10) versus high-dose interferon-α (HDI). Descriptive statistics were used to calculate the incidence. **Results:** Among 1670 total patients treated with ICIs or with HDI in E1609, 1034 were treated with ipilimumab and 636 with HDI. Six GSL cases were reported among 1670 total patients treated with ipilimumab or with HDI as summarized in the table along with the corresponding CTCAE grades. More cases were observed with ipi10, followed by ipi3 and HDI, respectively. Organs involved included skin and subcutaneous tissue (granuloma annulare, granulomatous dermatitis), eye (ocular sarcoidosis), lymph nodes (noncaseating granulomatous lymphadenitis), lung and mediastinal lymph nodes (sarcoidosis, granulomatous inflammation). **Conclusions:** The incidence of granulomatous and sarcoid-like lesions (GSL) with adjuvant ipilimumab therapy in high-risk melanoma is rare. Reported cases ranged in grade from 1-3 and appeared manageable. Since most cases are asymptomatic, it is possible that GSLs are under-recognized and therefore, under-reported. A larger analysis including patients treated with anti-PD1 antibodies is currently underway. Clinical trial information: NCT01274338. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

Organ(s)Involved	Ipi3 (N=523)	Ipi10 (N=511)	Total Ipi (N=1034)	HDI (N=636)
Ocular	-	1 (Gr 2)	1	-
Skin	-	1 (Gr 2)	1	-
Lung and Lymphatic	1 (Gr 3)	2 (Gr 3 x2)	3	1 (Gr 3)
Total (%)	1 (0.19%)	4 (0.78%)	5 (0.48%)	1 (0.16%)

9583 **Poster Session**

Adjuvant nivolumab in high-risk stage IIb/IIc melanoma patients: Results from investigator initiated clinical trial. *First Author: Melissa Wilson, Sidney Kidney Cancer Center, Thomas Jefferson University, Philadelphia, PA*

Background: Recent studies have shown 5-yr recurrence rates for Stage IIB and IIC melanoma of up to 46%. These high-risk patients currently have few options for adjuvant therapy to prevent this inevitable recurrence, with the only FDA approved therapy being high-dose interferon-alfa, which is quite toxic. However, there are now immunotherapies (anti-PD1) and targeted therapies (anti-BRAF and anti-MEK combinations) which are approved as adjuvants for Stage III patients, some of whom will have a lower baseline recurrence risk than those with Stage IIB/IIC melanoma. We sought to determine if adjuvant PD1 inhibition with nivolumab (N) would improve the recurrence free survival (RFS) compared to historical RFS rates. **Methods:** Our study (NCT03405155) is a single-arm, open label, multi-center, phase 2 clinical trial evaluating RFS at 24 months in patients with Stage IIB/IIC melanoma on treatment with N at 480 mg IV every 4 weeks for 12 cycles. Overall survival is a secondary endpoint. Associated translational research includes circulating tumor cell DNA and immune correlates. **Results:** Twenty three patients with Stage IIB and three patients with Stage IIC melanoma were enrolled onto the study and received at least one dose of N. At data cutoff, 22 patients remain in follow up, as four patients withdrew consent at different time points in the study – one patient after one dose who wished to discontinue, one due to concern for COVID and need for repeat visits, one due to insurance issues, and one due to recurrence and wish to discontinue (which was captured in study data and RFS calculations). Seventeen patients have been on the clinical trial for at least two years with nine patients having finished treatment but with less than two years follow-up; the median follow-up is currently 21.9 months. Two patients demonstrated melanoma recurrence, one after receiving cycle six of N and another one year after completing treatment, resulting in a 87.8% RFS (90% CI (64.2%-96.3%) at 2 years, compared to the historical RFS at 2 years of 70%. No N related serious adverse events (SAEs) were observed, with only 2% Grade 3 AEs observed (varied and unrelated to treatment) and all others were Grade 1-2, including 21% GI, 18% cutaneous, and 10% musculoskeletal, respiratory, and fatigue, each; overall, 2% of these Grade 1-2 AEs were treatment related. **Conclusions:** Our preliminary results show a trend towards improved RFS in patients with Stage IIB/IIC melanoma treated with nivolumab. The cohort has not reached a minimum follow up of at least 2 years for RFS; patients are continuing to be monitored. On study, we observed the expected adverse events, without evidence of new toxicities. Data maturation will reveal the full effect of adjuvant N on disease relapse and overall survival and distant metastasis-free survival in stage IIB/IIC melanoma patients. Clinical trial information: NCT03405155. Research Sponsor: BMS.

9584 **Poster Session**

Increased risk of immune-related hepatitis among adolescent and young adults (AYAs) with melanoma during immunotherapy with checkpoint inhibitors (ICIs). *First Author: Alicia Darwin, University of South Florida Morsani College of Medicine, Tampa, FL*

Background: Melanoma is the second most common malignancy affecting AYA patients after lymphoma. Nevertheless, AYA melanoma does constitute a minority of all melanoma cases. Additionally, the AYA population is not well represented in prospective clinical trials, including immunotherapy trials. While previous research has demonstrated the efficacy of ICIs across age groups, it remains unclear if toxicity profiles will be similar. In the general population, age-related changes in the immune milieu result in differential incidences of autoimmune diseases by age. This study aims to compare the toxicity profile between a cohort of AYA melanoma versus elderly melanoma patients receiving ICI therapy. **Methods:** In this single NCCN institutional study, electronic medical records of melanoma patients treated with ICIs between 01/2007-01/2019 were reviewed. Subjects receiving concurrent investigational agents or chemotherapy were excluded. The AYA cohort included those aged 15-40 years. The elderly cohort included those aged $\geq$65 years. Adverse events were coded according to CTC-AE version 5.0. Multivariable logistic regression analyses were performed. **Results:** Analyses included 184 treatment courses. In the AYA cohort (N = 57), median age at ICI initiation was 28.8 years (range: 17.9-39.3). In the Elderly cohort (N = 127), median age at ICI initiation was 72.3 years. More AYA patients (28.1% AYA vs. 7.9% Elderly) received ICI combination regimens. The most common adverse events amongst both cohorts were transaminitis (23.4%), rashes (49.5%), and diarrhea/colitis (20%). Incidences of pneumonitis, colitis, hypothyroidism, and hypophysitis did not differ significantly between cohorts. However, the AYA cohort experienced a higher incidence of transaminitis (38.6% AYA vs. 16.5% Elderly, p =0.001) and increased occurrence of treatment related hospitalization (26.3% AYA vs. 7.1% Elderly, p <0.001). Moreover, a higher proportion of severe grade $\geq$3 transaminitis occurred in the AYA group (27.3% AYA vs. 9.5% Elderly, p =0.004). While occurrence of transaminitis was significantly associated with combination ICIs, the association between AYA status and transaminitis remained significant after adjusting for ICI regimen (OR 2.75, 95% CI: 1.3-5.8). There was a trend toward shorter time to transaminitis onset among the AYA than Elderly cohort (median 53.0 vs. 74.5 days [nonparametric p= 0.28]). To date, median survival has not been reached in both groups (p= 0.09). **Conclusions:** In this large cohort of AYA melanoma patients treated with ICI, we found a significantly higher incidence of immune-related transaminitis than in the Elderly cohort. Other immune-related AEs were comparable between cohorts. This finding was independent of ICI regimen. Further investigation will be needed to understand these differences between the AYA and Elderly cohorts. Research Sponsor: None.

TPS9585 **Poster Session**

S1801: A randomized trial of adjuvant versus neoadjuvant pembrolizumab for melanoma. *First Author: Sapna Pradyuman Patel, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Although long term outcomes for most patients with early-stage melanoma is excellent following surgery, patients who have high-risk features such as lymph node involvement have poorer outcomes. Adjuvant therapy (AT) is currently considered for patients with stage III melanoma and selected patients with resected stage IV melanoma. Currently, AT for melanoma is anti-PD-1 or targeted therapy in the presence of a *BRAF* mutation. At this time, we are not able to predict which patients will derive benefit from AT and experience cure. While curative intent is the goal of treatment for primary melanoma, patients with bulky nodal involvement are at high risk of local or distant recurrence despite upfront surgery. Neoadjuvant treatment (NAT) offers the benefit of an early on-treatment pathological sample that can be profiled for biomarkers and correlated with response and survival. Treating with anti-PD1 while tumor remains visible in the body may generate a stronger immune response against *in vivo* tumor antigens compared to the traditional adjuvant setting where antigen is presented by microscopic residual tumor burden. Pilot studies of NAT with anti-PD-1 therapy have been initiated in melanoma. Multidisciplinary coordination in these cases is paramount. In these studies, an improvement in relapse-free survival and overall survival has been observed; additionally, pathologic response rates to NAT have been estimated in small studies. **Methods:** S1801 is a randomized phase II study of AT versus NAT with pembrolizumab (PEM, NCT03698019). Patients with measurable, clinically detectable and resectable cutaneous, acral, and mucosal melanomas without brain metastasis are eligible. Patients with Stage IIIB to oligometastatic, resectable Stage IV are randomized 1:1 to AT or NAT. Patients getting AT undergo surgery first followed by 18 doses of PEM 200 mg IV every 3 weeks. Patients getting NAT receive 3 doses of pre-operative PEM followed by surgery and then 15 doses of adjuvant PEM. Radiation may be given on either arm after surgery, at the investigator's discretion. Primary endpoint is event-free survival measured from the date of randomization to the date of first documented progression that renders the patient unable to receive planned protocol surgery, failure to begin adjuvant therapy within 84 days of surgery, relapse after surgery, or death due to any cause. Secondary endpoints include RECIST and iRECIST response rates, as well as a number of surgical outcomes. Safety monitoring is conducted with disease progression and toxicity thresholds. The key Translational Medicine objective of this trial is to determine the pathologic response rate to NAT after 3 doses of PEM. Surgical pathology grossing instructions to ensure readout for pathologic response are provided in the form of training slides. Enrollment is at 40% of a planned 500 patients. Clinical trial information: NCT03698019. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

TPS9586 **Poster Session**

Combination of radiomic and biomarker signatures as exploratory objective in a phase II trial with intratumoral BO-112 plus pembrolizumab for advanced melanoma. *First Author: Ivan Marquez-Rodas, Medical Oncology, General University Hospital Gregorio Marañón & CIBERONC, Madrid, Spain*

Background: Intratumoral immunotherapies are gaining interest in oncology, particularly in melanoma. These therapies, however, have faced some issues. For instance, standard response criteria do not accurately describe tumor burden, and responses may differ for injected/non injected lesions. Besides, target lesions may become non evaluable. Biomarkers provide interesting information for these therapies. In addition, some radiomic signatures have been associated with CD-8 infiltration. BO-112 is a double stranded synthetic RNA formulated with polyethyleneimine (PEI) that mimics a viral infection, mobilizing the immune system and changing tumor microenvironment. Clinical data are available from a first-in-human study, which showed ORR of 11% and DCR of 46% in patients who had developed progressive disease on immunotherapy. In patients with melanoma, this ORR was 20%. A phase 2 clinical study of BO-112 with pembrolizumab in patients with liver metastases from digestive tumors is ongoing. Both studies brought up data regarding how some biomarkers are increased after a single dose of BO-112 and correlated with responses. In this phase II study in patients with pretreated melanoma (NCT04570332), we will prospectively assess CD-8 and PD-L1 by immunohistochemistry, which will be compared with multi-parametric radiologic findings and correlated with clinical benefit. In addition, retrospective DNA sequencing will be performed. This kind of exploratory analysis in intratumoral immunotherapies might be key to identify predictive and prognostic factors. **Methods:** Phase 2, single arm, open label study of BO-112 with pembrolizumab in patients with advanced melanoma. BO-112 is administered once weekly (QW) in 1 to 8 tumor lesions, total dose 1-2 mg (depending on the number of injected lesions), for the first 7 weeks and then once every three weeks (Q3W); pembrolizumab 200 mg will be administered Q3W. Key eligibility criteria: advanced cutaneous or mucosal melanoma; patients must have progressed on or after treatment with an antiPD-1/L1 mAb; at least one measurable lesion amenable for weekly IT injection. Primary efficacy variable is ORR by RECIST 1.1, assessed by independent central radiologist (QUIBIM Precision platform). A 1-sided alpha of 4.19% and power of 81.8% are used. If less than 8 patients out of 40 have ORR, the study will not meet the statistical bar. Secondary endpoints include clinical activity by RECIST1.1 and iRECIST, overall survival, safety and PKs. Exploratory objectives include itRECIST and evaluation of CD-8 and PD-L1 expression by immunohistochemistry (Pangaea laboratory), which will be correlated with radiomic signatures (first order and second order) from standard-of-care computed tomography (CT) images. Enrollment is open and 1 of planned 40 patients has been enrolled. Nineteen sites are planned to participate. Clinical trial information: NCT04570332. Research Sponsor: Highlight Therapeutics, SL.

TPS9587 **Poster Session**

CAcTUS: A parallel arm, biomarker driven, phase II feasibility trial to determine the role of circulating tumor DNA in guiding a switch between targeted therapy and immune therapy in patients with advanced cutaneous melanoma. *First Author: Rebecca Lee, The Christie NHS Foundation Trust, Manchester, United Kingdom*

Background: Circulating tumor DNA (ctDNA; the tumour derived fraction of circulating free DNA in the blood) has been shown to be a biomarker of tumor burden/progression in many cancers. We recently accurately monitored treatment response and resistance in stage IV melanoma by ctDNA analysis in serial peripheral blood samples. Pre-clinical data has previously revealed that BRAF inhibition provokes a micro-environment with increased T cell infiltration, improved T cell recognition of melanoma associated antigens and reduced production of immunosuppressive cytokines that could enhance immune responses. We aimed to test the hypothesis that ctDNA could be implemented as a personalised, real-time liquid biopsy to identify when tumours are responding to targeted therapy in order optimise a switch to immunotherapy. **Methods:** We validated the ctDNA assays for BRAF mutation calling as a primary trial endpoint. We designed a phase II multicenter, parallel arm study across 6 UK sites, to assess primary objectives of i). Whether a ctDNA result can be turned around within 7 days and actioned in a clinically relevant timeframe ii). to assess whether a decrease in ctDNA levels of mutant *BRAF* by ≥80% from baseline on targeted therapy is an appropriate 'cut off' to instruct switching to immunotherapy. Secondary endpoints include Overall Response Rate (ORR) to immunotherapy, radiological/clinical and ctDNA determined progression free survival (PFS) on each treatment. Forty patients are planned based on inclusion criteria of stage IV or stage III unresectable cutaneous *BRAF* mutant melanoma, baseline ctDNA *BRAF* variant allele frequency (VAF) ≥1.5%, ECOG 0/1/2, no symptomatic brain metastases, no prior adjuvant nivolumab plus ipilimumab (N+I). Prior adjuvant dabrafinib + trametinib (D+T) is allowed as long as recurrence is >6 months from completion. Patients are randomised 1:1 to either standard Arm A; investigator choice of either D+T (150mg BD +2mg OD respectively) or N+I (1 mg/kg N +3 mg/kg I q3 wkly, then N 480mg q4 wkly) first line, then switch on progression to the other treatment. In the experimental Arm B; all patients start on D+T and have *BRAF* ctDNA monitored q2 wkly for 4 wks then q4 wkly. When ≥80% decrease vs. baseline in ctDNA *BRAF* VAF occurs, patients switch to N+I. If patients subsequently progress on N+I, they will resume D+T. The study is open with 9 patients enrolled at time of submission. Clinical trial information: NCT03808441. Research Sponsor: Bristol Myers Squibb, The Christie Charity and Cancer Research UK.

TPS9588 **Poster Session**

Clinical trial in progress: Phase II trial of defactinib (VS-6063) combined with VS-6766 (CH5126766) in patients with metastatic uveal melanoma. *First Author: Rino S. Seedor, Fox Chase Cancer Center, Philadelphia, PA*

Background: Despite successful treatment of primary uveal melanomas (UM), up to 50% of patients subsequently develop systemic metastasis, with the liver involved in up to 90% of patients. Currently there is no US FDA-approved treatment for metastatic uveal melanoma (MUM). Activating mutations in genes encoding alpha subunits of the heterotrimeric G proteins, GNAQ and GNA11, are found in 80-90% of UM. Recent information suggests that *GNAQ/GNA11*-oncogenic signaling involves a non-canonical pathway conferring the activation of YAP1, distinct from the activation of PLCβ and PKC-MEK-ERK, which may explain the failure of MEK inhibitors in MUM patients. Focal Adhesion Kinase (FAK) is a tyrosine kinase that provides a direct link between Gαq and tyrosine phosphorylation networks controlling YAP and UM growth. Interestingly, UM represents the human cancer harboring the highest level of FAK overexpression. Recent kinome-wide CRISPR-Cas9 screens revealed that FAK and RAF/MEK co-targeting may provide a new network-based precision therapeutic strategy for MUM treatment. **Methods:** This is an investigator-initiated, prospective, single arm, single-institution, phase II trial evaluating the combination of a FAK inhibitor (defactinib, VS-6063) with a RAF/MEK inhibitor (VS-6766, CH5126766) for the treatment of patients with metastatic uveal melanoma [NCT04720417]. The primary endpoint of the study is disease control rate (DCR) of 50% including complete response (CR), partial response (PR), and stable disease (SD) as determined by RECIST criteria version 1.1. Secondary endpoints include progression free survival, overall survival, and causality of adverse events. Exploratory endpoints include analysis of the pharmacodynamic profile, mechanism of resistance to the combination, and investigation of circulating free DNA as a biomarker. The efficacy of this combination treatment will be assessed using the Simon's two stage design. In stage I, a total number of 8 patients are accrued and if there are 2 or fewer overall responses among these 8 patients, further enrollment of patients may be stopped with the conclusion that DCR cannot be 50% or greater. Otherwise, an additional 10 patients will be accrued in stage II, resulting in a total sample size of 18 patients. Patients at 18 years or older with metastases from uveal melanoma will be eligible (any line of therapy). Defactinib (200 mg) will be administered orally twice a day in combination with VS-6766 (3.2 mg) administered orally twice a week for 3 weeks, in 28-day cycles. Dose modification will be considered based on toxicity. Treatment will be continued until maximum clinical benefit is obtained; disease progression or the development of intolerable side effects. Enrollment to stage 1 began in February 2021. Clinical trial information: NCT04720417. Research Sponsor: Verastem Oncology, Inc.

TPS9589 **Poster Session**

Ipilimumab, nivolumab and tocilizumab as first-line therapy for advanced melanoma. *First Author: Inderjit Mehmi, The Angeles Clinic & Research Institute, A Cedar-Sinai Affiliate, Los Angeles, CA*

Background: Interleukin 6 (IL-6) functions in the maintenance of hepatocytes, haemotopoietic progenitor cells, a variety of other tissues, and regulates the innate and adaptive immune system. IL-6 may play a role as a chronic inflammatory mediator in altering levels of acute phase proteins synthesized by the liver and circulating myeloid cells which have been shown to be associated with short survival with checkpoint inhibition and which are immune suppressive. The immunomodulatory properties of interleukin-6 may in part also be responsible for immune related adverse events, given the reversal of those toxicities observed with IL-6 receptor blockade in clinical practice. To assess if blockade of IL-6 binding is associated with a decrease in irAEs and/or an increase in efficacy defined as overall response rate (ORR) at week 24 in patients receiving ICB, we added tocilizumab to ipilimumab and nivolumab therapy. **Methods:** The current phase II trial is a two-stage design to assess the safety, tolerability, and grades 3-5 immune related toxicities of tocilizumab administered every 6 weeks up to week 24 in combination with ipilimumab at 1 mg/kg and nivolumab at 3 mg/kg every 3 weeks for 4 doses each during a 12 week induction period, then administered every 6 weeks with nivolumab at 240 mg flat dose every 2 weeks in maintenance for up to 24 weeks, and nivolumab alone will be given at 480 mg flat dose every 4 weeks thereafter for up to 2 years. Eligible patients include those age 18 or older with measurable and unresectable stages III/IV melanoma (cutaneous, acral, mucosal), without prior systemic treatment for metastatic disease. Adjuvant therapy (IFN-alpha, ipilimumab and/or nivolumab, or pembrolizumab) is allowed. Patients with metastatic melanoma of brain are allowed, if neurologically stable and off immunosuppressive steroids. A total of 18 patients will be treated in the first stage, and 49 additional patients in the second stage for a total of 67. The comparator data are from the N3I1 arm of Checkmate-511 trial, in which treatment-related grades 3-5 irAEs were 33.9% with a 45.6% response rate (1). Prespecified activity goal for the first stage of accrual has been met; second stage accrual began in January 2021. References: (1) Lebbé C, Meyer N, Mortier L, Marquez-Rodas I, et al. Evaluation of Two Dosing Regimens for Nivolumab in Combination With Ipilimumab in Patients With Advanced Melanoma: Results From the Phase IIIb/IV CheckMate 511 Trial. Journal of Clinical Oncology 2019 37:11, 867-875. Clinical trial information: NCT03999749. Research Sponsor: BMS and Genetech.

TPS9590 **Poster Session**

NCT04552223: A phase II study of nivolumab plus BMS-986016 (relatlimab) in patients with metastatic uveal melanoma (UM) (CA224-094). *First Author: Jose Lutzky, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Uveal melanoma (UM) is a rare disease but 50% of patients will eventually develop metastatic disease, for which not effective therapy is available. Liver-directed therapies, immunotherapy, targeted therapy and chemotherapy have limited activity [1]. Lymphocyte activation gene 3(LAG-3) is an immune checkpoint receptor associated with decreased T-cell effector function and tumor escape. Preclinical models have shown that dual inhibition of LAG-3 and PD-1 blockade generates synergistic anti-tumor activity [2]. Recent preclinical data indicates that uveal melanoma CD8+ T cells express the checkpoint receptor LAG3 to a greater extent than PD1 or CTLA4 [3,4]. Therefore, LAG3 is a potential candidate for checkpoint inhibitor immunotherapy in UM. Relatlimab is a human LAG-3-specific antibody isolated from immunized transgenic mice which binds to a defined epitope on LAG-3 with high affinity and specificity and potently blocks the interaction of LAG-3 with its ligand, MHC Class II. **Methods:** This is an open-label, single arm, single site investigator-initiated phase II study, NCT04552223. Based on Simon two-stage minimax design, 13 patients will be enrolled in Stage 1. If at least one response is noted, the study will proceed to Stage 2 and enroll an additional 14 patients. The null hypothesis will be rejected if 4 or more responses are observed among 27 patients. This design achieves 5% type I error and 80% power when the true ORR is 20%. The trial opened to accrual in December 2020. As of February 15, 2021 four patients had been enrolled the first stage of accrual. Main eligibility criteria include patients with biopsy proven metastatic uveal melanoma, previously untreated with PD-1, CTLA-4 and/or LAG-3 blocking antibodies and in good performance status. Enrolled patients are treated in the outpatient setting. Nivolumab 480 mg is mixed in the same bag with relatlimab 160 mg and administered intravenously over 60 minutes every 4 weeks until disease progression or intolerable toxicity for up to 24 months. The primary endpoint is best objective response rate (ORR). Secondary endpoints include disease control rate (DCR), progression-free survival (PFS), overall survival (OS), median duration of response (mDOR), and adverse events (AEs). Correlative studies will evaluate pre- and post-treatment characteristics of T cells in the tumor microenvironment and blood. Clinical trial information: NCT04552223. Research Sponsor: Bristol Myers Squibb, Sylvester Cancer Center trials grant.

TPS9591 **Poster Session**

Phase I/II trial of intratumoral administration of hu14.18-IL2, with local radiation, nivolumab, and ipilimumab in subjects with advanced melanoma. *First Author: Mark R. Albertini, University of Wisconsin, Madison, WI*

Background: We are studying an intratumoral (IT) in situ vaccine strategy using the GD2-reactive hu14.18-IL2 immunocytokine (hu-IC) to convert the injected tumor into a site of enhanced tumor antigen presentation, as has been shown in mice. Hu-IC is a humanized monoclonal antibody (mAb) covalently linked to two molecules of IL-2 at the Fc region. The hu14.18 mAb recognizes GD2, a disialoganglioside found in tumors of neuroectodermal origin. We previously studied intravenous (IV) hu-IC and reported immune activation and reversible toxicities (1). Surgery to resect recurrent stage III or stage IV melanoma combined with 3 courses of IV hu-IC resulted in prolonged tumor-free survival in some patients (2). Murine GD2+ tumor models showed enhanced antitumor activity and recruitment of T cells using hu-IC IT versus IV (3). In these models, the combination of radiation therapy (RT) followed by IT hu-IC dramatically potentiates the antitumor response and enhanced response to immune checkpoint blockade (4). Biological samples (blood and tumor) will be interrogated to identify biological mechanisms and develop biomarkers for future testing. **Methods:** This outpatient phase I/II trial uses a 3 + 3 design to determine maximum tolerated or maximum administered dose of IT hu-IC (planned dose level: 2 mg/m^2/day; de-escalation dose level: 1 mg/m^2/day) when given alone (Phase 1A: 3-12 patients), after RT (Phase 1B: 6-12 patients), after RT and in combination with nivolumab (Phase 1C: 6-12 patients), and after RT and in combination with nivolumab and ipilimumab (Phase 1D: 31-34 patients). The trial will evaluate safety, antitumor activity, and immunologic endpoints and includes an expanded Phase II cohort (Phase 1D). The IT injections (once daily x 3 days) are delivered every 21 days for 4 cycles and can then continue every 28 days for up to 13 cycles if there is response/stable disease and residual injectable tumor. Key inclusion criteria: 1) histologically proven, malignant melanoma that is advanced (Stage IV) or surgically incurable; 2) at least 1 (preferably 2) sites of disease amenable to safe repeated IT injections; and 3) must have received or declined at least one FDA approved therapy, either in the adjuvant setting or for metastatic disease, with an impact on survival. Two subjects have been accrued into Phase IA as of 2-4-2021. References: (1)King DM, et al. J Clin Oncol 22:4463-4473, 2004. (2)Albertini MR, et al. Can Imm Imm 67(10):1647-1658, 2018. (3)Yang RK, et al. J of Imm 189:2656-2664, 2012. (4)Morris ZS et al. Can Res 76:3929-3941, 2016. Clinical trial information: NCT03958383. Research Sponsor: U.S. National Institutes of Health, Other Foundation, U.S. National Institutes of Health, Philanthropic gifts to the UWCCC.

TPS9592 **Poster Session**

A phase II, open-label study to investigate the efficacy and safety of domatinostat in combination with avelumab in patients with advanced unresectable/metastatic Merkel cell carcinoma progressing on anti-PD-(L)1 antibody therapy: The MERKLIN 2 study. *First Author: Alexander Christopher Jonathan Van Akkooi, Department of Surgical Oncology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Merkel cell carcinoma (MCC) is a rare but highly aggressive human skin cancer often caused by the Merkel cell polyomavirus or extended exposure to sunlight. Since the approvals of avelumab globally and subsequently pembrolizumab (US only), anti–PD–(L)1 antibody therapies have become the standard of care for advanced/metastatic MCC patients in recent years. Still, a significant proportion of MCC patients do not respond to or relapse on anti–PD–(L)1 antibody monotherapy. Recent preclinical data suggest that the small molecule, selective class I histone deacetylase inhibitor (HDACi) domatinostat can overcome critical mechanisms of MCC resistance to checkpoint inhibitors. These escape mechanisms include the epigenetic downregulation of the antigen processing and presentation machinery, hence treatment with domatinostat is thought to favorably modulate the tumor environment allowing a reintroduction of anti–PD–(L)1 therapy for an improved and sustained clinical benefit. **Methods:** The study is a phase II, multicenter, single arm clinical trial of the orally administered HDACi domatinostat in combination with the anti–PD–(L)1 antibody avelumab for patients with advanced unresectable/metastatic MCC that are progressing on previous anti–PD–(L)1 therapy. ClinicalTrials.gov Identifier: NCT04393753. Key Inclusion Criteria are: histologically confirmed MCC, an ECOG performance status $\leq$ 1, MCC in an advanced, unresectable stage III or metastatic stage IV, and progressing on previous anti–PD–(L)1 antibody monotherapy within the last 12 weeks before planned first administration of study medication. Key Exclusion Criteria are: history of serious anti–PD–(L)1 therapy related adverse reactions prohibiting further avelumab treatment, more than one line of previous systemic anti neoplastic therapy other than anti–PD–(L)1 antibody monotherapy (excluded: palliative radiation therapy of single lesions within 2 weeks before planned administration of study medication), significant active or chronic disease (infections, immunodeficiencies, cardiovascular, psychiatric disorders). A total of 40 patients will be enrolled in up to 46 clinical study sites in Europe and USA. Anti-tumor activity will be primarily assessed by the objective response rate according to RECIST v1.1 as an exploratory analysis. Secondary objectives include additional efficacy assessments, safety, quality of life and pharmacokinetics of domatinostat in combination with avelumab. Correlative aims include evaluating biomarkers for association with clinical benefit. The first patient was enrolled on Oct. 16, 2020, 21 of 46 clinical sites are active and 4 out of 40 planned patients have been enrolled as of Feb. 15, 2021. Clinical trial information: NCT04393753. Research Sponsor: 4SC AG.

TPS9593 **Poster Session**

Winship 4851-19: A pilot study of neoadjuvant and adjuvant cemiplimab for high-risk cutaneous squamous cell carcinoma. *First Author: Michael C. Lowe, Department of Surgery, Emory University, Atlanta, GA*

Background: The PD-1 inhibitor cemiplimab was approved in 2018 for treatment of locally advanced or metastatic cutaneous squamous cell carcinoma (cSCC) that is not curable with surgery or radiation. This approval was based on the results of the phase 2 EMPOWER-CSCC-1 trial, which demonstrated an objective response rate of 47% with a significant number of these patients experiencing a durable response. However, patients with high risk cSCC that are able to undergo curative intent surgery are not candidates for checkpoint inhibitor therapy but still experience high rates of recurrence and/or systemic progression even when offered adjuvant radiotherapy. In light of data using checkpoint inhibitor therapy in the neoadjuvant setting in other cutaneous malignancies, we hypothesized that cemiplimab therapy would improve surgical outcomes and reduce long-term recurrence rates in patients with high-risk resectable cSCC if used in the perioperative setting. **Methods:** Winship 4851-19 is a single arm pilot study of cemiplimab in the neoadjuvant and adjuvant setting for high-risk resectable cSCC (NCT04428671). In the neoadjuvant phase, patients receive three doses of cemiplimab every three weeks followed by standard of care surgery. Radiation may be offered when clinically appropriate at the discretion of the investigator. In the adjuvant phase (following surgery +/- radiation), patients receive cemiplimab every three weeks to complete one year total of treatment. Eligible patients must have surgically resectable histologically proven high risk cSCC defined as: nodal disease with extracapsular extension or one node $\geq$20mm; in transit metastases $>$ 2cm from primary lesion; T4 head and neck primary tumor; perineural invasion; or recurrent cSCC with concurrent $\geq$N2b nodal disease, size $\geq$4cm or bony invasion, or poorly differentiated histology. Patients cannot have received prior immunotherapy and must have a ECOG performance status of 0 or 1. Primary objective is to establish pathologic response rate. Secondary objectives include assessments of local and distant recurrence and overall survival rates. We also plan to evaluate the immune profile of fresh tumor and blood to assess the impact of neoadjuvant cemiplimab on the tumor microenvironment and circulating immune responses. To date 5 of 20 patients have been enrolled; this sample size was selected based on feasibility and ability enroll within a timely fashion. Clinical trial information: NCT04428671. Research Sponsor: Regeron.

TPS9594 **Poster Session**

Phase II study of binimetinib with imatinib in patients with unresectable KIT-mutant melanoma. *First Author: Katy K. Tsai, University of California, San Francisco, San Francisco, CA*

Background: Immune checkpoint inhibitors (ICI) have transformed treatment for patients (pts) with advanced melanoma, as have BRAF/MEK inhibitors for pts with BRAF V600-mutant melanoma. However, pts with acral or mucosal melanomas are in particular need of more options given a lower objective response rate (ORR) to ICI, and lower incidence of BRAF V600 driver mutation. Such BRAF mutations are found in only 5-10% of acral/mucosal melanomas, while KIT mutations/amplifications are found in 10-20%. Even when present, a KIT alteration does not guarantee response to KIT inhibition, with only about one-third responding as previously shown in 3 phase II studies. A significant number of KIT-mutant melanomas have been shown to demonstrate NF1 or SPRED1 loss, with recent preclinical work showing that such alterations are associated with the loss of negative suppression of RAS, resulting in RAS activation and MEK dependence. We hypothesize that NF1 or SPRED1 loss cooperates with KIT mutations to drive melanomagenesis and resistance to KIT inhibition, and propose to target this vulnerability with a combination approach to targeted therapy. This phase II study will be the first to evaluate the efficacy and safety of binimetinib plus imatinib in pts with KIT-mutant melanoma. **Methods:** This is an investigator-initiated phase II study of binimetinib in combination with imatinib in pts with BRAF V600 WT, KIT-mutant unresectable melanoma who have progressed on or who are ineligible for ICI (NCT04598009). Pts will be ≥18 yo with performance status ECOG 0-2, and have unresectable Stage IIIB/C/D or Stage IV melanoma that is BRAF V600 WT and KIT-mutant by CLIA-certified testing platform. Pts will have progressed on prior ICI or other standard-of-care (SOC) therapies, or be ineligible for or unable to tolerate SOC therapies. Pts with brain metastasis will be eligible if clinically stable and determination made that no CNS-specific treatment is required prior to study start. Pts previously treated with a MEK inhibitor will be excluded. A Simon 2-stage Minimax design will be used; the null hypothesis that the true response rate is 0.1 will be tested against a one-sided alternative. 15 pts will be accrued in the first stage. If there are £1 responses, the study will be stopped. Otherwise, 10 additional pts will be accrued for a total of 25. The null hypothesis that the true response rate is 0.1 will be rejected if ≥6 responses are observed. This yields a type I error rate of 0.05 and power of 0.8017 when the true response rate is 0.3.Primary endpoint: ORR (RECIST). Secondary endpoints: duration of response, progression-free survival, overall survival, clinical benefit rate (CR, PR, or SD ≥16 weeks), safety profile (CTCAE). Exploratory objectives to include investigations of association between clinical response and baseline NF1 and SPRED1 status, and of pathologic correlates of acquired resistance. Study began enrolling pts in December 2020 and is ongoing. Clinical trial information: NCT04598009. Research Sponsor: Array/Pfizer.

TPS9595 **Poster Session**

Phase Ib/randomized phase II study combining hepatic percutaneous perfusion with ipilimumab plus nivolumab in advanced uveal melanoma: The CHOPIN trial. *First Author: Thaïs M.L. Tong, Leiden University Medical Center, Department of Medical Oncology/Radiology, Leiden, Netherlands*

Background: Uveal Melanoma (UM), although rare, is the most common intraocular malignant tumor in adults. Despite successful treatment of the primary tumor, approximately half of all patients will develop metastatic disease, mainly in the liver. Prognosis of metastatic UM is poor and overall survival (OS) has not improved over the last 30 years. Effective systemic therapies are lacking but recent literature suggests an improved effect of the combination of immunotherapy with ipilimumab/nivolumab (IPI/NIVO) as opposed to monotherapy. Percutaneous hepatic perfusion (PHP) is a liver-directed therapy that allows delivery of a high dose of melphalan to the liver with limited systemic toxicity. Efficacy of PHP has been demonstrated in phase II trials including patients with liver-dominant or liver-only metastases. In this study we combine PHP with IPI/NIVO with the goal of inducing a synergistic effect and improving disease control. The aim of the phase 1b is to establish the maximum tolerated dose (MTD) of IPI/NIVO when combined with PHP. The following randomized phase II trial aims to determine the efficacy of IPI/NIVO combined with PHP, compared to PHP alone. **Methods:** We initiated a prospective, single center, phase Ib and randomized phase II trial with a maximum of 88 patients in total. Patients with confirmed measurable hepatic UM metastases according to RECIST 1.1 and WHO performance score of 0-1 are included. Exclusion criteria are age > 75 years, treatment with systemic immunosuppressive medication and prior systemic treatment for metastasic UM. Phase Ib is a dose-escalation study consisting of two cohorts. The dose of IPI and NIVO is increased from 1mg/kg and 1mg/kg in cohort 1, to 1mg/kg and 3mg/kg, in cohort 2, respectively. The melphalan dose for the PHP is 3mg/kg (maximum dose of 220mg) in both cohorts. Treatment duration is 12 weeks consisting of 4 courses of IPI/NIVO with 2 PHP's in week 1 and 7. In phase II, the same treatment scheme as phase Ib is used in the treatment arm combining IPI/NIVO with PHP at the established MTD. The second treatment arm consists of 2 PHP's performed at a 6 week interval. Follow-up includes laboratory tests, CT-chest/abdomen and MRI-liver. Safety and toxicity are assessed according to the CTCAE V5.0. Radiological response is assessed according to RECIST 1.1 and irRECIST. Primary objective of phase Ib is to determine safety of the combination of IPI/NIVO with PHP defined by the MTD. In phase II the primary objective is the efficacy of combination treatment of IPI/NIVO with PHP defined by progression-free survival at one year. Secondary objectives include OS and overall response rate. Cohort 1 and 2 of phase Ib have been completed without dose limiting toxicities and the MTD is defined as IPI 1 mg/kg and NIVO 3 mg/kg. Accrual to phase II started in December 2020. An update will be presented at ASCO 2021. Clinical trial information: NCT04283890. Research Sponsor: Bristol Myers-Squibb and Delcath System Inc.

TPS9596 **Poster Session**

Multicenter phase I/II trial of encorafenib with and without binimetinib in combination with nivolumab and low-dose ipilimumab in metastatic BRAF-mutant melanoma. *First Author: Max Jameson-Lee, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Targeted therapy (BRAF + MEK inhibitors) and immunotherapy (anti-PD1 + anti-CTLA4) have improved overall survival for metastatic or unresectable *BRAF*$^{V600E/K}$mutant melanoma. Whereas targeted therapy has a high response rate, immunotherapy may deliver longer term disease control for a larger number of patients. Despite these treatments, patients with high risk metastatic melanoma such as those with brain or liver metastases, elevated lactate dehydrogenase (LDH) and bulky disease have inferior treatment outcomes with current therapies. A BRAF+MEK+PDL1 regimen has recently emerged however the role for this treatment remains unclear. Several recent trials combining MEK inhibition and immunotherapy have failed possibly because MEK inhibition can compromise T cell activation. Meanwhile the addition of CTLA4 blockade to PD1 inhibition appears to disproportionately benefit patients with non-T cell-inflamed tumors and potentially high-risk disease. For patients with high risk BRAF-mutant metastatic melanoma, further investigation of BRAF/MEK targeted and PD-1/CTLA-4 directed immunotherapy combination strategies remains a priority. **Methods:** This is an open label, multi-site, Phase 1/2 study of encorafenib (Enco) +/- binimetinib (Bini) + nivolumab (Nivo) + ipilimumab (Ipi) for the treatment of patients with unresectable or metastatic *BRAF*-mutated melanoma in high-risk cohorts (NCT04655157). An initial regimen confirming Phase I approach will be pursued on two schedules concurrently, with patients accruing equally to each group. Group 1 will receive 3mg/kg Nivo, and 1 mg/kg Ipi and 300mg Enco (12 participants, triple therapy) and Group 2 will receive 3mg/kg Nivo and 1mg/kg Ipi and 450mg Enco and 45mg Bini, (12 participants, quadruple therapy). Dose limiting toxicity (DLT) will be evaluated weeks 1-6. A recommended Phase II regimen (RP2R) [either triple or quadruple therapy] will be carried forward into two high risk metastatic disease cohort expansions of 30 participants each. Cohort 1 will include patients with symptomatic brain metastases, while cohort 2 will include patients with elevated LDH as well as either liver metastases OR bulky visceral disease (sum of longest diameters > 44mm). Patients meeting criteria for cohorts 1 and 2 will be placed in cohort 1. Patients with symptomatic brain metastases will be included with an ECOG up to 2 and on ≤ 4mg of dexamethasone or equivalent. Continuous Bayesian toxicity monitoring will be used throughout to monitor DLT. Pre and on-treatment tumor biopsies will assess changes in the tumor microenvironment while peripheral blood ctDNA and T cell Ki67% changes will assess early response and immune activation during triplet and quadruplet therapy. Clinical trial information: NCT04655157. Research Sponsor: Bristol Myers Squibb.

10000 **Oral Abstract Session**

The efficacy and safety of anti-CLL1 based CAR-T cells in children with relapsed or refractory acute myeloid leukemia: A multicenter interim analysis. *First Author: Hui Zhang, Guangzhou Women and Children's Medical Center, Guangzhou, China*

Background: Chimeric antigen receptor (CAR)-T cell therapy has demonstrated remarkable success in treating a variety of blood cancers, such as CD19 CAR-T for B-cell malignancies and BCMA CAR-T for myeloid myeloma (MM). However, similar achievement has yet to be replicated in patients with relapsed and refractory acute myeloid leukemia (R/R AML), primarily due to the AML heterogeneity, making it difficult to find an ideal CAR-T target. Previous efforts have targeted single CD33, CD123, LeY, NKG2D, or CD70 receptors, but the overall response rate is very disappointed. To address these challenges, we aim to find an effective target for AML without the need for the hematopoietic stem cells transplant (HSCT). In our study, CLL1 is chosen as a promising target as it is not expressed on normal HSCs, but highly expressed on AML blasts cells and leukemia stem cells (LSCs). Here we report the interim analysis from a Phase I clinical trial using anti-CLL1 based CAR-T cells to treat children with R/R AML. The primary and secondary objectives were to evaluate the safety and anti-AML responses, respectively, with long-term prognosis within those patients who did not receive allogeneic HSCT (allo-HSCT) as an additional objective. **Methods:** We have generated a 2nd generation of CLL1 CAR-T, the extracellular scFv was derived from a murine CLL1 monoclonal antibody, which was generated by hybridoma technology. Autologous CAR-T cells were manufactured in a cGMP facility. Between Oct 2019 and Jan 2021, 11 pediatric R/R AML patients were infused. CLL1 or CLL1-CD33 dual CAR-T cells were given by a dose at $0.3\text{-}1x10^6$/kg with a single dose after lymphodepleting conditioning with cyclophosphamide/fludarabine(Cy/Flu). **Results:** Of the 11 patients infused, Grade 3-4 hematologic adverse events were observed before and during CAR-T cell infusion, and no dose-limiting toxicities were observed. Meanwhile, grade 1-3 cytokine release syndrome was observed but without any lethal events. All the adverse effects were resolved after guideline-directed intervention. Anti-CLL1 CAR-T cells efficiently expanded *in vivo,* the median expansion peaking time was at Day 8. For these 11 R/R-AML patients, 10 patients completely responded to anti-CLL1 based CAR-T cell therapy, with CLL1 positive AML blast eliminated within one month. Among the responded 10 patients, 5 patients reached CR/MRD-, 3 patients reached CR/MRD+, 1 patient reached PR and 1 patient showed SD, with only CLL1 negative AML cells. **Conclusions:** Our study demonstrated that 10/11 patients responded to CLL1 CAR-T cell therapy within one month. For patients showing MRD+ with CLL1 negative AML blast, chemotherapy like Azacitidine, and combined with HSCT may help those patients to reach complete response. These initial results suggested that anti-CLL1 base CAR-T cells can be a well-tolerated and candidate option for treating children with R/R-AML. Clinical trial information: ChiCTR1900027684. Research Sponsor: Guangzhou Bio-gene, Other Foundation.

10001 **Oral Abstract Session**

Donor-derived CD7 CAR T cells for T-cell acute lymphoblastic leukemia. *First Author: Jing Pan, State Key Laboratory of Experimental Hematology, Department of Hematology, Beijing Boren Hospital, Beijing, China*

Background: Despite the success of chimeric antigen receptor T cell therapy in B cell malignances, there is currently no proved CAR T treatment for T cell neoplasms. We provide first evidence support the use of donor derived CAR T cells in T cell leukemia. **Methods:** In this phase 1 trial, CD7 CAR T cells were manufactured with T cells from prior SCT prior to a single infusion at doses of 5×10^5 or 1×10^6 (± 30%) cells per kilogram of body weight. donors, or from new donors who were HLA-matched or haploidentical, via leukopheresis and transduced with a lentiviral vector which carries a CD7 CAR construct. The primary endpoint was safety. Short-term efficacy was also assessed. **Results:** Results of 20 enrolled patients who received infusion are reported. Of 20 patients, 12 received previous HSCT-donor derived CAR T cells and 8 received fresh haplo-identical donor derived CAR T cells and plan to received transplantation as consolidation after remission.Adverse events included grade 3-4 hematologic toxicity in all (100%), grade 3-4 and grade 1-2 cytokine release syndrome in 2 (10%) and in 18 (90%), grade 1 neurotoxicity in 3 (15%), grade 1-2 graft-versus-host disease in 12 (60%), and grade 1 viral activation in 3 (15%) patients. Nineteen (95%) patients had a response, including 18 (90%) with complete remission and 1 (5%) with partial remission. Of 19 responders, 7 were bridged to SCT and remained minimal residual disease (MRD)-negative until last visit; 12 were followed up at a medium of 4.4 months, among whom 9 remained MRD-negative, 1 had a relapse, 1 discontinued for other treatment, and 1 died of pulmonary fungal infection at 5.5 months. CAR cells mostly persisted beyond 3 months. Patient CD7-positive healthy T cells were depleted, while CD7-negative T cells increased. **Conclusions:** We report the initial toxicity profile and anti-leukemia activity of a donor-derived CD7-targeted cellular immunotherapy for patients with relapsed or refractory T-ALL. (Funded by the National Key R&D program; ChiCTR.org number, ChiCTR2000034762). Clinical trial information: ChiCTR2000034762. Research Sponsor: the National Key R&D program.

Characteristics	Prior SCT donor (n=12)	New donor (n=8)	Total (n=20)
Median age (range) - years	14 (4-33)	10 (2-43)	11 (2-43)
Male sex - no. (%)	10 (83)	6 (67)	16 (80)
Previous therapy			
Median lines of therapy (range)	3 (2-4)	2 (2-3)	3 (2-4)
Radiotherapy - no. (%)	2 (22)	1 (13)	3 (20)
Allogeneic SCT - no. (%)	12 (100)	0 (0)	12 (60)
Donor lymphocyte infusion - no. (%)	10 (83)	0 (0)	10 (50)
Primary refractory disease - no. (%)	0 (0)	1 (13)	1 (5)
≥ grade 3 cytopenia before lymphodepletion- no. (%)	9 (75)	7 (88)	16 (80)
Baseline disease burden			
Bone marrow blasts - no. (%)			
>25%	2 (22)	4 (50)	6 (30)
5-25%	2 (22)	3 (38)	5 (20)
0.01-5%	6 (50)	1 (13)	7 (35)
<0.01%	2 (17)	0 (0)	2 (10)
Median bone marrow blasts (range) - %	1.60 (0.19-87.99)	11.22 (0.90-72.40)	6.17 (0.19-87.99)
Extramedullary disease - no. (%)			
CNSL	2 (22)	2 (25)	4 (20)
Diffused	3 (25)	2 (25)	5 (20)

10002 **Oral Abstract Session**

Targeted gene expression classifier identifies pediatric T-cell acute lymphoblastic leukemia (T-ALL) patients at high risk for end induction minimal residual disease positivity. *First Author: Lauren K. Meyer, University of California, San Francisco, San Francisco, CA*

Background: The heterogeneity of T-ALL has hindered biomarker identification and limited biology-based risk stratification. Historically, minimal residual disease (MRD) has been the strongest predictor of poor outcomes. However, stratification by MRD does not allow for risk-adapted therapy early in treatment, which may induce deeper remissions and decrease risk of relapse. We hypothesized that gene expression profiling at diagnosis may have prognostic value in identifying high risk patients. **Methods:** We analyzed RNA-seq data from 189 diagnostic samples from the Children's Oncology Group (COG) AALL0434 trial. Using leave-one-out cross-validation, we identified a set of genes that optimally differentiated MRD+ and MRD- samples. We then derived a risk score (RS) that indicates a probability of being MRD+ for a given gene expression pattern. Finally, we validated this model in an independent cohort of COG AALL1231 samples. **Results:** The AALL0434 early T-cell precursor (ETP) samples (n = 19), which have high rates of MRD+, had the highest RS, with an average of 81.3 (SD 18.7), versus 24.9 (SD 22.7) for non-ETPs (n = 146). Intriguingly, non-ETPs with RS $>$ 50 had a gene expression pattern that mirrored ETPs and was distinct from the remaining non-ETPs. In this RS $>$ 50 non-ETP cohort, 80% were MRD+, versus 20% of the $<$ 50 cohort ($p < 0.0001$). When applied to 31 diagnostic non-ETP samples from COG AALL1231, 57% of the RS $>$ 50 cohort were MRD+, versus 17% of the RS $<$ 50 cohort ($p = 0.05$). Importantly, AALL0434 used prednisone during induction, while AALL1231 used dexamethasone, indicating that the predictive value is independent of the induction steroid. Finally, we converted our model to the customizable Nanostring nCounter platform by analyzing 96 AALL0434 samples on the Nanostring assay. The Nanostring data closely recapitulated the RNA-seq data, with a tight correlation between the resulting RS (concordance correlation coefficient = 0.91). **Conclusions:** We have developed a gene expression classifier that differentiates a subset of non-ETP T-ALLs with an ETP-like gene expression pattern and a high risk of MRD+, and have adapted the classifier to a clinically tractable targeted platform. Identification of this high-risk subset at diagnosis has the potential to facilitate risk-adapted trials to evaluate the utility of novel or more intensive therapies aimed at improving clinical outcomes. Research Sponsor: Rally Foundation and Luke Tatsu Johnson Foundation, U.S. National Institutes of Health, UCSF Research Evaluation and Allocation Committee.

10003 **Oral Abstract Session**

Prognostic Impact of CNS-2 status in T-ALL: A report from the Children's Oncology Group. *First Author: Nathan Gossai, Children's Minnesota, Minneapolis, MN*

Background: In B-acute lymphoblastic leukemia (B-ALL), CNS2 was associated with inferior 5-year (yr) event-free and overall survival (EFS/OS) in recent trials. Here, we report the impact of CNS2 in T-ALL on AALL0434 and AALL1231, recently completed consecutive randomized phase 3 trials for children and young adults with T-ALL and T Lymphoblastic Lymphoma. This report is limited to T-ALL. Both trials used augmented Berlin Frankfurt Münster regimens. AALL0434 compared Capizzi escalating methotrexate+pegaspargase (C-MTX) vs High Dose MTX (HDMTX) +/- six nelarabine (Nel) courses; outcomes improved with CMTX and Nel. CNS1/CNS2 patients, except those defined as low risk (LR) received 12Gy cranial radiation (CRT); CNS3 patients received 18Gy CRT. AALL1231 randomized patients to +/- bortezomib (Bort). AALL1231 changed the AALL0434 backbone, using dexamethasone instead of prednisone throughout. CRT was given only to patients with CNS3 disease (18Gy) and those defined as very high risk (VHR) (12Gy). CNS2 patients could not be classified as LR on AALL0434 or standard risk (SR) on AALL1231. CNS1/CNS2 patients received the same intrathecal therapy frequency on both studies. **Methods:** CNS status was assigned at diagnosis. CNS2 defined as: presence of $<$ 5/ μL WBCs and cytospin positive for blasts or $\geq$ 5/μLWBCs with negative Steinherz Bleyer algorithm. Outcomes by CNS status were compared between AALL0434 and AALL1231. **Results:** From 2007-2014, AALL0434 enrolled 1562 evaluable T-ALL patients, including 1128 (72.8%) CNS1, 306 (19.7%) CNS2 and 116 (7.5%) CNS3. 90.8% received CRT, including 90.4% of CNS1 patients. 5yr EFS rates for CNS1, 2, and 3 were 85.2±1.3%, 83.1±2.6%, and 71.4±5.2% ($p = 0.0007$); OS rates were 90.4±1.1%, 89.2±2.1%, and 83.1±4.3% ($p = 0.0438$). There were no differences in 5yr disease free survival (DFS) between CNS1 and CNS2 treated with CMTX (89.7% vs. 92.9%, $p = 0.17$) or CMTX+Nel (91.8% vs. 89.9%; $p = 0.62$). AALL1231 accrued 614 evaluable T-ALL patients [CNS1 437 (71.1%), CNS2 134 (21.8%), CNS3 43 (7.0%)] from 2014 to early closure in 2017. Of these, only 12% were scheduled to receive CRT. 3yr EFS rates for CNS1, 2 and 3 were 84.1±2.1%, 84.6±3.8% and 78.6±7.9% ($p = 0.50$). 3yr OS was: CNS1 87.5±1.9%, CNS2 92.2±2.8%, CNS3 78.5±7.9% ($p = 0.017$). 3yr EFS was not statistically distinct without Bort in CNS1, 2 or 3 (85.3±2.9%, 81.4±5.6%, 71.9±13.4%) ($p = 0.10$) or with Bort (82.9±3.0%, 88.3±4.9%, 83.3±9,4%; $p = 0.43$). Intermediate risk (IR) CNS1 and CNS2 patients received identical therapy and had similar 3yr EFS (88.8±2.8% vs 88.8±3.5%, $p = 0.98$). **Conclusions:** Unlike in B-ALL, EFS/OS was similar for CNS1 and CNS2 on AALL0434 (with CRT) and AALL1231 (without CRT). Further, IR CNS1 and CNS2 on AALL1231 had similar outcomes with identical therapy. Thus, CNS2 status is non-prognostic in T-ALL on these contemporary COG regimens. CNS3 patients have poor outcomes in T-ALL despite CRT and intensive chemotherapy, novel approaches are needed. Clinical trial information: NCT00408005, NCT02112916. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

10004 **Oral Abstract Session**

Minimal residual disease at end of induction and consolidation remain important prognostic indicators for newly diagnosed children and young adults with very high-risk (VHR) B-lymphoblastic leukemia (B-ALL): Children's Oncology Group AALL1131. *First Author: Wanda L. Salzer, Uniformed Services University, Bethesda, MD*

Background: Children and young adults with very high risk (VHR) B-acute lymphoblastic leukemia (B-ALL) [13-30 years of age with any features or 1-30 years of age with adverse prognostic features including *KMT2A* rearrangements, iAMP21, hypodiploidy (<44 chromosomes/DNA index < 0.81), central nervous system disease, end of induction (EOI) minimal residual disease (MRD) >0.01%, or induction failure] collectively have a predicted 4-year disease free survival (DFS) of approximately 70%. Whether patients with VHR B-ALL who are MRD positive at EOI and become MRD negative at the end of consolidation (EOC) will have improved survival versus patients remaining MRD positive at EOC is unknown. **Methods:** Patients with newly diagnosed NCI high risk B-ALL enrolled on AALL1131 or NCI standard risk B-ALL enrolled on AALL0932 and classified as VHR at EOI were treated on the VHR stratum of AALL1131 which sought to improve DFS with intensive post-Induction therapy using fractionated cyclophosphamide (CPM), etoposide (ETOP) and clofarabine (CLOF).Patients were randomly assigned post-Induction to Control Arm (CA) with modified augmented BFM CPM + fractionated cytarabine + mercaptopurine, Experimental Arm 1 (Exp1) with CPM + ETOP, or Experimental Arm 2 (Exp2) with CLOF + CPM + ETOP during Part 2 of Consolidation and Delayed Intensification. Doses of vincristine and pegaspargase were identical on all arms. Exp2 was permanently closed September 2014 due to excessive toxicities, and these patients are excluded from this report. MRD was measured by 6-color flow cytometry at EOI and for those who consented at the EOC. **Results:** 4-yr DFS for all patients (n=823) with VHR B-ALL was 76.8 ± 2.0%. As we reported previously, 4-year DFS was not significantly different between CA and Exp 1 (85.5 ± 6.8% versus 72.3 ± 6.3%; p=0.76; Burke, Haematologica 2019). 4-yr DFS for patients who were EOI MRD <0.01%, (n=325) versus >0.01 (n=498) was 83.3% ± 2.6% vs 72.0% ± 2.8%, p=0.0013. 4-Year DFS of Patients EOI MRD > 0.01%. **Conclusions:** MRD is a powerful prognostic indicator in VHR B-ALL with inferior outcomes in patients who are EOI MRD positive. Among patients who were EOI MRD positive treated on Exp1, outcomes were similar for EOC MRD negative and EOC MRD positive, though numbers were small. In contrast, patients who were EOI MRD positive treated on CA that were EOC MRD negative had significantly improved DFS compared to those that were EOC MRD positive. The CA remains the standard of care for COG ALL trials. With this therapy, patients with VHR B-ALL that are EOI MRD positive and EOC MRD negative have significantly improved DFS compared to those that remain MRD positive at EOC. Clinical trial information: NCT02883049. Research Sponsor: U.S. National Institutes of Health.

	EOC MRD < 0.01	EOC MRD >0.01	P value
CA	77.6 ± 5.2% (n=141)	55.7 ± 21.4% (n=41)	p=0.0002
Exp1	74.8 ± 3.8% (n=192)	69.1 ± 9.3% (n=44)	p=0.305

10005 **Oral Abstract Session**

Clinical impact of molecular tumor profiling in pediatric, adolescent, and young adult patients with extra-cranial solid malignancies: An interim report from the GAIN/iCat2 study. *First Author: Alanna J. Church, Department of Pathology, Boston Children's Hospital and Harvard Medical School, Boston, MA*

Background: Next generation sequencing (NGS) assays are now a standard part of clinical care for many adult solid cancers. The significance of molecular tumor profiling for the care of children with cancer is not well understood.We aimed to determine the clinical impact of identifying genomic alterations by NGS for young patients with relapsed, refractory, or high-risk extracranial solid tumors. **Methods:** We report on the first 389 participants in a prospective cohort study enrolling patients at 12 institutions with extracranial solid tumors diagnosed at age 30 years or less. Targeted DNA NGS was performed on one or more tumor samples from each patient. Selected patients also had tumors subjected to RNA sequencing. Test results were returned to the treating oncologist and follow-up treatment and response data were collected.Identified genomic alterations were classified according to evidence of impact on diagnosis, prognosis or response to targeted therapy matched to an identified alteration (matched targeted therapy, MTT) using established guidelines. Response to MTT was determined and reported as a response if either there was radiographic response according to RECIST or the duration of therapy was > 4 months. **Results:** Molecular tumor profiling (MTP) was successful in 345 (89%) patients (mean age 11 years at diagnosis; 65% with sarcoma). Two hundred and ninety-nine patients with MTP results (87%) had one or more alterations of clinical significance. Genomic alterations with diagnostic, prognostic or therapeutic significance were present in 208 (60%), 51 (15%) and 240 (70%) patients, respectively. Of the 240 patients with tumors harboring genomic alterations designated as having therapeutic impact, 23 (11%) had Tier 1 molecular findings. 205 patients were eligible to receive MTT based on having a molecular alteration with therapeutic significance and sufficient follow-up; 31 of these patients (15%) received MTT. Seven patients (23%) receiving MTT responded, 6 of these were kinase fusions. All of the responders received targeted therapy matched to a fusion and 78% of diagnostically significant alterations were fusions. **Conclusions:** Molecular tumor profiling has a significant impact on diagnosis and treatment recommendations for young patients with extracranial solid tumors. These results emphasize the importance of fusion detection for patients with sarcomas and rare tumors. Clinical trial information: NCT02520713. Research Sponsor: Private donor.

10006 **Oral Abstract Session**

Integrated whole-exome and transcriptome analysis of 250 treatment-refractory or relapsed (R/R) childhood solid tumors. *First Author: Sara A. Byron, Translational Genomics Research Institute, Phoenix, AZ*

Background: The major genomic profiling studies that have helped define the molecular landscapes of pediatric cancers have typically focused on untreated pediatric cancers at diagnosis. Despite improvements in overall survival for childhood cancers, patients with treatment-refractory or relapsed (R/R) solid tumors face a poor prognosis. The genomic underpinnings of R/R disease are less well-characterized. Here, we describe the integrated genomic and transcriptomic analysis of 250 R/R solid tumors from 202 children profiled within precision medicine studies (NCT01355679, NCT01802567, NCT02162732) conducted by the Beat Childhood Cancer Consortium. **Methods:** Tumor-normal whole-exome and tumor mRNA sequencing was performed by Ashion Analytics (Phoenix, Arizona), a CAP-accredited, CLIA-certified laboratory, or within the research setting at TGen. Longitudinal tumor samples were sequenced for 20 patients. Variant calling included single nucleotide variants, indels, copy number alterations, and fusions. Integrated genomic and transcriptomic research analysis included microsatellite instability assessment, immunogenomic profiling, and functional gene set enrichment analysis. **Results:** Forty-six tumor types were represented, grouped into four general categories: sarcomas (36.1%; n = 73), neuroblastomas (29.2%; n = 59), CNS tumors (23.3%; n = 47), and other rare tumors (11.4%; n = 23). For patients with whole exome sequencing data, 78.3% (n = 144/184) of tumors bore a somatic alteration in at least one known cancer gene. Over one-third (39.1%; 72/184) of the cohort bore oncogenic fusions and/or oncogenic/likely-oncogenic hotspot mutations in a known cancer gene. Pathognomonic fusions were identified in 25% (46/184) of tumors, occurring most frequently in sarcomas. Pathogenic or likely pathogenic germline variants were identified in 8.7% (16/184) of patients. Microsatellite instability was detected in five different tumor types. Despite nearly all tumors (94%, 173/184) having at least one predicted strong binding neoantigen, over a quarter of tumors lacked transcript expression of these neoantigens or exhibited low MHC class I expression. Further, a subset of tumors showed elevated expression of the co-inhibitory immune checkpoint molecule *PDL1*. Transcriptional analysis and functional gene set enrichment analysis identified cross-pathology tumor clusters associated with immune signaling, development, and cellular signaling pathways. Longitudinal analysis revealed temporal heterogeneity pointing to the importance of re-biopsy at relapse for targeted treatment planning. **Conclusions:** Together, these data suggest R/R childhood solid tumors exhibit shared molecular features that are reflective of underlying biology, demonstrating the importance of comprehensive profiling to inform molecularly-guided treatment of R/R disease. Research Sponsor: Dell Inc. Powering the Possible Program, Other Foundation, U.S. National Institutes of Health.

10007 **Oral Abstract Session**

Factors impacting enrollment on NCI-COG Pediatric MATCH trial treatment protocols. *First Author: Donald Williams Parsons, Texas Children's Cancer Center Baylor College of Medicine, Houston, TX*

Background: The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial assigns patients age 1 to 21 years with relapsed or refractory solid tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms of molecularly-targeted therapies based on the genetic alterations detected in their tumor. Treatment arm assignments and enrollment decisions have now been made for 1000 study participants: we report here match and enrollment data and factors affecting treatment protocol enrollment. **Methods:** Patients enrolled in the Pediatric MATCH screening protocol were assigned to an open treatment protocol if an actionable mutation (aMOI) was detected by tumor DNA and RNA-based cancer gene panel sequencing. After a match, treatment protocol enrollment must occur within 8-12 weeks. Patient demographic data, reasons for not enrolling on treatment protocol (if applicable), and prior history of molecular testing were reported by study sites. The Fisher exact test was used to compare protocol enrollment rates between groups. **Results:** Results were analyzed for the first 1000 patients with testing completed (enrolled between July 2017 and October 2020). At least one tumor aMOI was detected in 310 (31%) patients and treatment protocol slots were available for 284 patients (28%). A total of 131 patients (46% of those matched) enrolled on a treatment arm. No difference in treatment protocol match or enrollment rate was observed for gender, race, or ethnicity. Both treatment protocol match rate (105/275, 38% vs 86/394, 22%) and enrollment rate (56/275, 20% vs 33/394, 8%) were significantly more frequent in patients with a reported history of prior molecular testing (p<0.0001). The most common reasons provided for not enrolling on a treatment protocol were: patient receiving other treatment (32% of responses), poor clinical status (16%), lack of measurable disease (11%), or ineligible diagnosis for that treatment arm (10%). Ineligibility due to history of excluded prior targeted therapy (6%) or inability to swallow capsules (4%) was less frequent. **Conclusions:** The rate of Pediatric MATCH treatment protocol enrollment has exceeded pre-study projections, due to more frequent actionable mutation detection and treatment assignment than anticipated (28% observed, 10% projected). This may in part reflect an increased number of targetable events in recurrent or refractory pediatric cancers. Correlative studies analyzing pre-treatment tumors from MATCH study patients are underway and will address this hypothesis. Prior history of molecular testing was associated with higher match and enrollment rate and poor clinical status was a common reason for not enrolling on a treatment protocol, suggesting that early molecular screening of children with solid malignancies may facilitate enrollment to biomarker-selected trials of targeted therapies. Clinical trial information: NCT03155620. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

10008 **Oral Abstract Session**

Selumetinib in patients with tumors with MAPK pathway alterations: Results from Arm E of the NCI-COG pediatric MATCH trial. *First Author: Carl E. Allen, Baylor College of Medicine Texas Children's Cancer Center, Houston, TX*

Background: The NCI-Children's Oncology Group (COG) Pediatric Molecular Analysis for Therapy Choice (MATCH) trial assigns patients age 1 to 21 years with relapsed or refractory solid tumors, lymphomas, and histiocytic disorders to phase 2 treatment arms of molecularly-targeted therapies based on genetic alterations detected in their tumor. Arm E evaluated the MEK inhibitor selumetinib (ARRY-142886) in patients whose tumors harbored activating alterations in the MAPK pathway (*ARAF*, *BRAF*, *HRAS*, *KRAS*, *NRAS*, *MAP2K1*, *GNA11*, *GNAQ* hotspot mutations; *NF1* inactivating mutations; *BRAF* fusions). **Methods:** Patients received selumetinib 25 mg/m2/dose (max 75 mg/dose) PO BID for 28-day cycles until disease progression or intolerable toxicity with response assessments obtained every 2-3 cycles. The primary endpoint was objective response rate (ORR); secondary endpoints included progression-free survival (PFS). Patients with low grade glioma were excluded. **Results:** A total of 21 patients (median age 14 years; range 5-21) were enrolled between 10/2017 and 8/2019, with 20 patients evaluable for response. Diagnoses were high grade glioma (HGG; n = 8), rhabdomyosarcoma (n = 7), adenocarcinoma (n = 2), and one each of MPNST, endodermal sinus/yolk sac tumor, plexiform neurofibroma (PN), and neuroblastoma. MAPK pathway alterations detected consisted of inactivating *NF1* mutations (n = 8), hotspot mutations in *KRAS* (n = 8), *NRAS* (n = 3), and *HRAS* (n = 1), and *BRAF* V600E (n = 2). No objective responses were observed. Three patients had a best response of stable disease (HGG with *NF1* mutation, 6 cycles; HGG with *KRAS* mutation, 12 cycles; PN with *NF1* mutation, 13 cycles prior to removal for dose-limiting toxicity). Six-month PFS was 15% (95% CI: 4%, 34%). Adverse events that were deemed possibly, probably, or definitely attributable to study drug included one case each of grade 3 uveitis, lymphopenia, and thromboembolic event; one grade 4 CPK elevation; and one grade 5 thromboembolic event. **Conclusions:** Selumetinib did not result in tumor regression in this cohort of children and young adults with treatment-refractory tumors with activating MAPK pathway alterations. Of note, two patients with HGG initially had stable disease, but ultimately progressed after 6 and 12 cycles, respectively. Selumetinib has previously demonstrated activity in low grade glioma and PN and is now FDA-approved for PN. The results of our study indicate that MAPK pathway mutation status alone is insufficient to predict response to selumetinib monotherapy. It is likely that selumetinib and other MEK inhibitors will require combination with targeted or cytotoxic agents for optimal efficacy in children with persistent or progressive cancers after front-line chemotherapy. Clinical trial information: NCT03213691. Clinical trial information: NCT03155620. Research Sponsor: U.S. National Institutes of Health.

10009 **Oral Abstract Session**

Oral selpercatinib in pediatric patients (pts) with advanced *RET*-altered solid or primary CNS tumors: Preliminary results from the phase 1/2 LIBRETTO-121 trial. *First Author: Daniel A. Morgenstern, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

Background: Activating *RET* alterations are oncogenic drivers of select pediatric and adult cancers. Selpercatinib is a first-in-class, highly selective and potent, CNS active *RET* kinase inhibitor. The manageable toxicity profile and durable anti-tumor activity in *RET*-altered cancers demonstrated in the LIBRETTO-001 phase 1/2 trial led to global approvals of selpercatinib in adults and adolescents with thyroid cancer and adults with NSCLC. **Methods:** LIBRETTO-121 (JZJJ) is a multicenter phase 1/2 trial in pts 0.5-21 years (yrs) of age with advanced, *RET*-altered solid or CNS tumors. Enrollment began in June 2019 and is ongoing. Selpercatinib is administered orally as capsule or liquid suspension BID continuously. Dosing started at the adult recommended phase 2 dose (RP2D) equivalent, 92mg/m^2 BID, to confirm RP2D in pts $\leq$2 yrs and $>$ 2 yrs. The phase 1 primary objective is to evaluate safety and dose limiting toxicities (DLTs). The phase 2 primary objective is to determine overall response rate by RECIST 1.1 or RANO by independent review. **Results:** As of 2-Oct-2020, 11 pts (6 male) aged 2–20 yrs (medullary thyroid cancer, n = 8; papillary thyroid cancer, n = 2; osteosarcoma, n = 1) had been treated (phase 1, n = 4; phase 2, n = 7). At baseline, 7 pts had measurable disease. *RET* alterations included fusions (n = 2), activating mutations (n = 8) and mutation with unknown clinical significance (n = 1). Prior therapies included surgery (n = 8), chemotherapy (n = 1), vandetanib (n = 1) and radiotherapy (n = 3), while 3 pts were previously untreated. Time on selpercatinib ranged from 0.9-13.4 months and 9 pts remain on treatment. One pt experienced a dose reduction and 2 pts experienced dose interruptions due to treatment-emergent adverse events (TEAEs) (elevated alanine aminotransferase [ALT] and bilirubin). There were no DLTs and no TEAEs that led to discontinuation of selpercatinib. TEAEs in $>$ 15% of pts included elevated alkaline phosphatase (ALP), constipation, headache, elevated aspartate aminotransferase (AST), diarrhea, hyperphosphatemia, hypoalbuminemia, hypothyroidism, nausea, pyrexia, urinary tract infection, vomiting and weight gain. Drug-related TEAEs in $>$ 15% of pts included elevated AST, elevated ALP, hyperphosphatemia and hypothyroidism. One pt reported TEAEs $\geq$ grade (G) 3 (elevated ALT, G3 and AST, G3) related to selpercatinib. Best response was unconfirmed partial responses in 4 pts, stable disease in 6 pts (two lasting $\geq$16 weeks) and progressive disease in 1 pt. **Conclusions:** These findings appear consistent with the adult trial results, showing preliminary evidence of safety and efficacy of selpercatinib in pediatric pts with *RET*-altered solid tumors. The phase 1 portion in pts $\leq$2 yrs and phase 2 portion at RP2D of 92mg/m^2 BID for pts $>$ 2 yrs are ongoing. Clinical trial information: NCT03899792. Research Sponsor: Eli Lilly and Company.

10010 **Oral Abstract Session**

Phase 2 trial of cabozantinib in children and young adults with refractory sarcomas, Wilms tumor, and rare tumors: Children's Oncology Group Study (ADVL1622). *First Author: Srivandana Akshintala, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute, Bethesda, MD*

Background: Cabozantinib is an inhibitor of multiple receptor tyrosine kinases (RTKs) including MET, VEGFR2, RET, and AXL. Preclinical and clinical data support these RTKs as potential therapeutic targets; Safety, tolerability, and responses were demonstrated in a COG phase 1 trial. We conducted a multi-center open label phase 2 trial to determine the activity of cabozantinib in select pediatric solid tumors (NCT02867592). **Methods:** Patients age 2-30 years old with selected relapsed or refractory cancer that was measurable (RECISTv.1.1) were eligible. Using a Simon minimax design, patients were enrolled to six strata: Osteosarcoma (OS), Ewing sarcoma (EWS), rhabdomyosarcoma (RMS), non-rhabdomyosarcoma soft tissue sarcoma (NRSTS), Wilms tumor (WT), and rare tumor (a non-statistical stratum including tumors of specific histologies or molecular features). Cabozantinib (40 mg/m^2/day) was administered on a continuous schedule (1 cycle = 28 days). For the OS stratum, activity was determined based on objective response rate (ORR, complete response (CR) + Partial response (PR)) or disease control success defined as at least stable disease (SD) for $\geq$ 4 months. For all other strata, the primary endpoint was ORR. Pharmacokinetics were performed in patients $<$ 19 years. **Results:** Between May 2017- Oct 2020, 109 patients enrolled (105 eligible, 104 evaluable for response and toxicity). Median age was 15.8 (range 5.6-27.1) years; 55 were male. In the OS stratum, 10/29 (34%) patients had central review confirmed disease control $\geq$ 4 months (2 PR, 8 SD), exceeding the protocol-defined criteria for activity of cabozantinib in OS. Median duration of therapy was 3 cycles (range 1-28+). In EWS, RMS, NRSTS, and WT strata (n = 13 evaluable patients each) no PR or CR were observed. In the rare tumor stratum (n = 23), 1/4 patients with renal cell carcinoma, 1/1 patients with RET fusion positive papillary thyroid cancer had a PR, and 1 patient with medullary thyroid cancer had a delayed PR. SD $\geq$ 6 cycles was seen in patients with EWS (n = 2), NRSTS (n = 5), WT (n = 3), and hepatocellular carcinoma (n = 1). At data cutoff (12/31/2020), 430 treatment cycles were administered; two patients remain on therapy. Cycle 1 and later cycle dose limiting toxicities (DLT) were seen in 20 (19%) and 39 (38%) patients, respectively. Common DLT were elevated liver enzymes, bilirubin, and lipase, hyponatremia, weight loss, anorexia, nausea, vomiting, wound dehiscence, palmar-plantar erythrodysesthesia, and pneumothorax. Day 1 pharmacokinetics (mean ± SD, n = 16) demonstrated a maximum plasma concentration of 556 ± 376 ng/ml, half-life 106 ± 102 hours, and area under the curve ($AUC_{0\text{-}24h}$) 8093 ± 4368 ng•h/mL. **Conclusions:** Cabozantinib is active in patients with relapsed refractory OS and deserves further study in this disease. PRs were also seen in select carcinomas. Activity is limited in other sarcomas and WT. Clinical trial information: NCT02867592. Research Sponsor: U.S. National Institutes of Health.

10011 **Oral Abstract Session**

Pilot study of nivolumab in pediatric patients with hypermutant cancers. *First Author: Daniel A. Morgenstern, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

Background: Responses to immune checkpoint inhibitors (ICI) in unselected pediatric solid tumors have been disappointing. We hypothesized that pediatric cancers with an increased tumor mutation burden (TMB) and/or replication repair deficiency (RRD) may be uniquely susceptible to ICI therapy. **Methods:** OZM-075 (NCT2992964) is a multicenter pilot study in patients (pts) aged 1-25 yrs with relapsed/refractory cancers (including CNS tumors). Pts were eligible only if tumor showed evidence of RRD (based on immunohistochemistry showing loss of expression of relevant RR protein) or elevated TMB $>$ 5mut/Mb determined by gene panel DNA sequencing. Pts with measurable or evaluable disease were eligible. Enrolment began in May 2017 and was completed in Nov 2020. Pts received programmed death-1 (PD-1) inhibitor nivolumab (NIVO) at a fixed dose of 3mg/kg every 2 weeks. Primary objective was objective response rate (ORR) by iRECIST or iRANO for those with measurable disease. Tumor tissue and serial blood samples were collected for analysis of biomarkers of response and survival. **Results:** As of 26Jan2021, 6 male and 5 female patients aged 9-18 yrs received treatment with NIVO (5 glioblastoma (GBM), 2 anaplastic astrocytoma (AA), 2 neuroblastoma, 1 colorectal adenocarcinoma (CRC), 1 adrenocortical carcinoma). 3pts had TMB 5-10mut/Mb, 5pts had TMB $>$ 10mut/Mb (range 14-837, median 64), 3 pts enrolled on basis of RRD. Time on treatment ranged from 0-21 months and 2 pts remain on therapy. Best OR was partial response (PR) in 2 pts (both GBM), with an additional patient with CRC achieving pathological CR. Remarkably one of the pts with PR showed early evidence of progression on imaging and elected to discontinue NIVO. Without further therapy, subsequent imaging 7 months later showed PR. Best response of stable disease was demonstrated in 5 further pts, lasting $\geq$5 months in 3 pts. Median overall survival (OS) not reached. Of 7 patients with relapsed GBM/AA, 5 were alive for $\geq$12 months following start of NIVO including 4 pts with confirmed TMB $>$ 10mut/Mb. **Conclusions:** This pilot study showed evidence of impressive clinical benefit particularly for relapsed GBM/AA patients for whom median survival is typically ~6 months (JCO 1995 13(1):112-). These data contrast previous pediatric data and suggest that in the context of RRD and hypermutation ICI therapy may provide profound long-term response and survival for these children. Analysis of other correlative biomarkers is ongoing. Clinical trial information: 2992964. Research Sponsor: BMS, Other Foundation.

10012 **Oral Abstract Session**

Changes in ctDNA levels after MIBG therapy in patients with relapsed or refractory neuroblastoma. *First Author: Kevin M. Campbell, Dana-Farber/ Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Circulating tumor DNA (ctDNA) is detectable in children with neuroblastoma. Less is known about how levels change during treatment and the implications of these changes. We evaluated ctDNA pre- and post- 131I-metaiodobenzylguanidine (MIBG) therapy. **Methods:** We utilized plasma samples from NANT11-01 (NCT02035137), a multi-center, open label, randomized phase II clinical trial evaluating MIBG with or without radiation sensitizers for patients with relapsed or refractory neuroblastoma. Plasma was collected at Baseline prior to MIBG, 72 hours (Hr72), 96 hours (Hr96), 15 days after MIBG (D15), and prior to a second course among patients without progression who received a second course (C2). Samples were analyzed for percent ctDNA levels using ultra-low passage whole genome sequencing. We evaluated associations between ctDNA findings with baseline disease measures of percent involvement in bone marrow, Curie score, and RECIST disease sum of diameters as well as overall response by NANT Response Criteria v1.2 (complete response or partial response coded as responders). **Results:** Eighty-four patients had a baseline sample and were included in this analysis. Of the 37 patients (44%) with detectable ctDNA at baseline, the median ctDNA level was 32% (range 3.9-91%). Baseline ctDNA levels showed a significant positive correlation with percent involvement in bone marrow (r=0.37; p= 0.0004) and Curie score (r=0.26; p = 0.018), but not RECIST sum of diameters for soft tissue sites (r=0.065; p=0.56).Following therapy, the proportions of patients with detectable ctDNA were: Hr72 47% (34/73; median level 28%); Hr96 50% (26/52; median 28%); D15 33% (7/21; median 4%); and C2 14% (3/21; median 50%). Rate of ctDNA detection was similar between responders and non-responders at baseline, Hr72, and Hr96, but lower among responders at D15 and C2 (Table). Among the 21 patients with C2 data, ctDNA levels were either undetectable (n=18) or lower than Cycle 1 Baseline (n=3). Among patients with detectable baseline ctDNA, the median relative ctDNA level at Hr72 (Hr72 ctDNA/baseline ctDNA) for non-responders was 0.87 (n= 24) vs. 1.16 for responders (n=7). In contrast, the median relative ctDNA level at C2 for non-responders was 0.56 (n=4) vs. 0 for responders (n=4). **Conclusions:** ctDNA is detectable in a substantial proportion of patients with relapsed / refractory neuroblastoma, with levels correlated with conventional measures of disease burden. Following MIBG therapy, early timepoints (Hr72 and Hr96) are less informative, whereas ctDNA becomes undetectable at D15 and C2 more commonly in patients with clinical response. Research Sponsor: None.

Proportion of patients with detectable ctDNA according to response to first course.

	Baseline	Hr72	Hr96	D15	C2
Responders	8/19 (42%)	9/17 (53%)	6/14 (43%)	0/2 (0%)	0/6 (0%)
Non-responders	29/65 (45%)	25/56 (45%)	20/38 (53%)	7/19 (37%)	3/15 (20%)

10013 **Oral Abstract Session**

Mortality among five-year survivors of childhood cancer: Results over five decades of follow-up in the Childhood Cancer Survivor Study. *First Author: Stephanie B Dixon, St Jude Children's Research Hospital, Memphis, TN*

Background: Adult survivors of childhood cancer are at greater risk for late mortality compared to the general population due to cancer and its treatment. Risk factors, patterns and specific causes of late mortality across the lifespan are not well established. **Methods:** All-cause, cause-specific, and health-related late mortality (HRM; excludes death from primary cancer and external causes) $>$ 5 years from diagnosis were evaluated in survivors diagnosed $<$ 21 years of age between 1970-1999. Cause of death was based on ICD codes from the National Death Index through December 2017. Cumulative mortality, mortality rates and standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) were estimated, overall and in 5- and 10-year survival periods. **Results:** Among 34,230 survivors (median time from diagnosis 29.1 years, range 5.0 - 48.0) the 40-year cumulative mortality was 23.3% (95% CI 22.7 - 24.0). Of 5,916 deaths, 3,061 (51.2%) were attributable to health-related causes including subsequent neoplasm (n = 1,458), cardiac (n = 504), and pulmonary causes (n = 238). All-cause mortality by time from diagnosis demonstrated a U-shaped distribution: 10.1 deaths/ 1000 person-years at 5-9 years, largely due to recurrence of the primary cancer, decreasing to 4.1 at 15-19 years before increasing to 18.5 at 40-48 years, attributable to an increasing mortality rate from HRM (2.3 at 5-9 years; 17.0 at 40-48 years). For the interval 5-9 years from diagnosis, survivors had an 18.1-fold (95% CI 17.3-18.9) higher risk of death from any cause, and a 13.1-fold (11.9-13.4) higher risk for HRM when compared to the general population. Although the SMRs declined with duration of follow-up, survivors had a 4-fold higher risk of death overall, attributable to a more than 4-fold increased risk of HRM. HRM 40-48 years from diagnosis was largely attributable to an increased risk of death due to subsequent neoplasm (SMR 6.0, 95% CI 4.9-7.2), cardiac (3.9, 2.9-5.0) and pulmonary (5.6, 3.6-8.4) causes. Cause-specific mortality remained markedly elevated at 40-48 years from diagnosis: CNS malignancy (SMR 11.7, 95% CI 5.4-22.3), benign meningioma (171.3, 34.4-500.5), valvular heart disease (39.8, 21.2-68.1), cardiomyopathy (10.4, 4.5-20.5), stroke (7.9, 4.6-12.6), and renal failure (5.6, 1.8-13.2). HRM was significantly higher among the youngest group of survivors (0-4 years at diagnosis), non-Hispanic blacks and those who received radiation to the brain, chest or total body, or who were exposed to anthracycline, alkylating or platinum chemotherapy. **Conclusions:** After five decades, aging survivors consistently remain at higher risk of all-cause mortality compared to the general, aging population, primarily due to a persistent 4-fold increased risk of HRM. Continued late-effects surveillance and reduction of therapies associated with long-term morbidity and increased mortality is essential. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

10014 **Oral Abstract Session**

Genetic and treatment risks for diabetes mellitus (DM) in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime (SJLIFE) cohorts. *First Author: Melissa A. Richard, Baylor College of Medicine, Houston, TX*

Background: Childhood cancer survivors face increased risk for DM, a polygenic trait also attributable to cancer treatment exposures, particularly abdominal radiation. We aimed to characterize the role of genetic and treatment risk factors for DM among two large cohorts of childhood cancer survivors. **Methods:** We performed a nested case-control genome-wide association study for DM managed with oral medications in the original CCSS cohort (diagnosed 1970-1986). Logistic regression was conducted in the total sample (N = 5083) and stratified by 1) European ancestry (EA) and 2) abdominal radiation. Replication of suggestive variants ($P < 1\times10^{-7}$) using Fisher's exact test was performed in independent cohorts: i) CCSS expansion diagnosed 1987-1999 (N = 2588) and ii) SJLIFE diagnosed 1962-2012 (N = 2182). To evaluate the effect of cancer treatment on the background genetic predisposition to DM, we estimated standardized effect sizes (Z') among EA survivors in each abdominal radiation group for 398 index variants from the largest population-based EA DM study. Radiation group Z' estimates were compared using linear regression. **Results:** In the original CCSS cohort we identified nine variants associated with DM and provide further support for four linked variants in the *ERCC6L2* locus. Among all survivors, the rs55849673-A allele was associated with increased odds for DM among survivors in the original CCSS cohort (minor allele frequency [MAF]-cases = 0.055; MAF-controls = 0.024; adjusted odds ratio [aOR] = 2.9, 95% CI: 2.0-4.2, $P = 3.7\times10^{-8}$). Allele frequencies were consistent in the CCSS expansion (MAF-cases = 0.075; MAF-controls = 0.028; P = 0.07) and SJLIFE (MAF-cases = 0.036; MAF-controls = 0.027; P = 0.5). Additionally, rs55849673-A estimates were consistent among EA survivors and stronger among survivors not treated with abdominal radiation (MAF-cases = 0.052; MAF-controls = 0.021; aOR = 3.6, $P = 1.6\times10^{-6}$). Notably, in the CCSS expansion all rs55849673-A EA carriers who developed DM did not receive abdominal radiation (MAF-cases = 0.1; MAF-controls = 0.026; P = 0.04). More broadly, the Z' of population-based DM index variants were 78% lower in survivors treated with abdominal radiation than survivors not treated with abdominal radiation (beta = 0.22; P = 0.01), indicating the background genetic risk for DM may be altered by treatment. **Conclusions:** We provide evidence for a novel locus of DM in childhood cancer survivors. This locus is a regulatory region associated with expression of *ERCC6L2*, a gene implicated in an East Asian population-based DM study. Taken together, our findings support the overwhelming effect of abdominal radiation on DM risk in childhood cancer survivors, relative to other risk factors, and provide insight on a genetic locus that may be useful for DM risk prediction in the context of cancer treatment. Research Sponsor: U.S. National Institutes of Health.

10015 **Oral Abstract Session**

Exercise and QUality diet After Leukemia (The EQUAL Study): An intervention trial in the Childhood Cancer Survivor Study (CCSS). *First Author: Emily S. Tonorezos, National Institutes of Health, National Cancer Institute, Rockville, MD*

Background: Survivors of childhood acute lymphoblastic leukemia (ALL) are at risk for obesity and cardiovascular (CV) disease. Exposure to cranial radiotherapy (CRT) increases risks. We tested whether a weight loss intervention that was successful in the general population could result in weight loss or improvements CV risk factors for ALL survivors. **Methods:** Obese and overweight 5-year ALL survivors diagnosed $<$ age 21 from CCSS were randomized to a 24-month remotely delivered diet/physical activity intervention or self-directed weight loss (control), stratified by CRT. The intervention emphasized a low calorie DASH diet and physical activity via an app, a website, and weekly coach calls. The primary endpoint was difference in weight loss after 24 months, using an intent-to-treat analysis. Secondary endpoints: differences in changes in blood pressure, cholesterol, and triglycerides. Analyses were performed using linear mixed effects; the study was designed to detect a difference of 2.75 kg. **Results:** Of 358 survivors (59% female, 91% White non-Hispanic, median age 37, IQR: 33-43), 181 were randomized to the intervention and 177 to control. Baseline mean (SD) weight was 98.6 kg (24.0) for intervention and 94.9 kg (20.3) for controls. 55 (30%) of intervention participants were adherent beyond one year. At 12 months, after controlling for CRT, sex, race/ethnicity, and age, the adjusted mean (SE) change in weight from baseline was -1.83kg (0.7) for intervention and -0.16kg (0.64) for control participants. At 24 months, the adjusted mean (SE) change in weight was -0.36kg (0.78) for intervention and +0.18kg (0.66) for control participants with the average difference of -0.54 kg (95%CI: -2.5,1.5, p=0.59) between the arms. A small proportion had at least 5% weight loss at 24 months (intervention 24%; control 17%). No significant differences in CV risk factors were observed. **Conclusions:** A 24-month phone and app/web-based diet and physical activity intervention that was successful for weight loss in the general population did not result in greater weight loss or improvement in CV risk factors among adult survivors of childhood ALL. Reduced adherence to the intervention beyond 12 months, or lack of ALL survivor-specific tailoring, may account for these findings. Clinical trial information: NCT02244411. Research Sponsor: U.S. National Institutes of Health.

All participants N = 358	No CRT	Difference (95%CI)	CRT
Weight (kg)	-0.54 (-2.5,1.5)	1.88 (-1.45,5.21)	-2.1 (-4.6,0.33)
Systolic Blood Pressure (mmHg)	-0.38 (-3.9,3.2)	-6.0 (-11.2,-0.57)	3.0 (-1.4,7.6)
Diastolic Blood Pressure (mmHg)	-1.3 (-4.1,1.5)	-4.2 (-9.0, 0.56)	0.74 (-2.7,4.2)
Insulin (mIU/L)	2.5 (-8.3,13.3)	8.5 (-15,32.2)	1.5 (-7.8,11.0)
LDL (mg/dL)	3.8 (-4.1,11.8)	3.5 (-9.8,16.9)	3.7 (-6.3,13.7)
HDL (mg/dL)	0.5 (-3.2,4.3)	2.0 (-2.9,7)	-0.24 (-5.2,4.7)
Triglyceride (mg/dL)	18 (-4.3,41.5)	16 (-19.751,9)	28 (0.3,57)
Total cholesterol (mg/dL)	6.6 (-3.3,16.4)	8.0 (-8.1,24.2)	5.8 (-6.7,18.5)

10016 **Oral Abstract Session**

Racial disparities in pediatric cancer care in the United States: An analysis of the Kids' Inpatient Database. *First Author: Sujith Baliga, Ohio State University-James Cancer Hospital Solove Research Institute, Columbus, OH*

Background: The impact of race and socioeconomic status (SES) on cancer mortality has been elucidated in adult patients, but is not well described in pediatric oncology. We hypothesize that racial and socioeconomic disparities exist in pediatric cancer patients, resulting in higher rates of hospitalization and mortality. **Methods:** We analyzed the Kids' Inpatient Database (KID) which shows national estimates of inpatient stays for pediatric patients. Inclusion criteria included patients who were ≤20 with a cancer diagnosis identified through the Clinical Classifications Software (CCS). Variables analyzed were discharge status, patient demographics, hospital characteristics, expected payment source, total visit charge, and length of stay. Initial comparisons between cancer and non-cancer related discharges were performed using a chi-square test. To estimate disparities by race, clinical comparisons were performed across five racial groups: White, Black, Hispanic, Asian/Pacific Islander, and Native American/Other. A multivariable logistic regression model was used to examine predictors of hospitalization and mortality. **Results:** From 2006-2012, there were 9,488,477 non-cancer related pediatric inpatient stays and 242,489 cancer related stays. Patients with cancer related visits were more likely to be white, male (54.9% vs 46.1%, $p < 0.0001$), older at admission, have private insurance (52.5% vs 41.7%), and were from a higher income quartile (76^{th}-100^{th} percentile, 25.2% vs 19.9%, $p < 0.001$). These patients also had a higher rate of death during admission (1.2% vs 0.5%, $p < 0.0001$), higher cost of visit charge ($25,097 vs $8,267, $p < 0.001$), longer length of stay (4 vs 2 days), and were less likely to be discharged (85.5% vs 92.0%, $p < 0.0001$).The four most frequent cancer diagnoses associated with hospital admission were leukemia (n = 75,807), Other and Unspecified Primary (n = 50,076), bone/connective tissue tumor (n = 42,477), and central nervous system tumor (n = 27,958). Patients who were non-white were more likely to die during their inpatient stay (1.5% Non-white versus 0.9% White, $p < 0.001$). On multivariate logistic regression, Black (OR: 1.61, 95% CI: 1.57-1.66, $p < 0.0001$) and Native American (OR: 1.39, 95% CI: 1.34-1.44, $p < 0.0001$) race, as well as lower income quartile (OR: 1.24, 95% CI: 1.19-1.28, $p < 0.001$) were associated with increased odds of death during admission. **Conclusions:** This is the largest observational study to date to identify the impact of race and SES on pediatric cancer hospitalization and mortality in the United States. Non-white race and lower SES was associated with significantly increased odds of death during admission. Given the significant difference in mortality by race, healthcare policy makers and insurance companies should investigate the specific drivers of increased admission and mortality and develop strategies to address inequity in cancer care. Research Sponsor: None.

10017 **Oral Abstract Session**

Disparities in cardiovascular risk factors by race/ethnicity among adult survivors of childhood cancer: A report from the Childhood Cancer Survivorship Study (CCSS). *First Author: David H Noyd, Duke University Health System, Durham, NC*

Background: Racial, ethnic, and socioeconomic disparities are documented in outcomes for childhood cancer survivors. Understanding whether childhood cancer modifies established disparities in cardiovascular risk factors (CVRFs) in the general population would inform strategies to reduce health inequities among survivors. **Methods:** The CCSS is a retrospectively constructed cohort with prospective follow-up consisting of 25,579 five year survivors of childhood cancer diagnosed between 1970 and 1999. We estimated the incidence of self-reported Common Terminology Criteria for Adverse Events (CTCAE) grade >2 CVRFs (hypertension, diabetes, dyslipidemia, and obesity) and multiple (>2) CVRFs among survivors. Multivariable Poisson regression estimated the rate ratios (RR) of CVRFs by race/ethnicity, adjusted for key treatment exposures and sociodemographics. **Results:** Within the CCSS cohort, there were 20,416 non-Hispanic White (NHW), 1625 non-Hispanic Black (NHB), and 2043 Hispanic survivors with the cumulative incidence estimates of each CVRF at age 40 displayed in Table. Survivors who self-reported "Other" or mixed race were excluded for this analysis (n=1495). NHB survivors were more likely to report hypertension (unadjusted RR 1.3; 95% Confidence Interval [CI] 1.0-1.6), diabetes (RR 1.6; 95% CI 1.0-2.4), obesity (RR 1.6; 95% CI 1.4-1.9), and multiple CVRF (RR 1.3; 95% CI 1.2-1.5), whereas Hispanic survivors were more likely to report diabetes (RR 1.7; 95% CI 1.2-2.4), obesity (RR 1.4; 95% CI 1.2-1.5), and multiple CVRFs (RR 1.1; 95% CI 1.0-1.3) compared with NHW survivors. These observed disparities in risks of CVRFs remained nearly unchanged even after adjustment for sociodemographic factors (age, sex, household income, education, marital status, employment, and insurance) and treatment exposures (Yes/No for anthracyclines, alkylators, and chest radiation). **Conclusions:** NHB and Hispanic adult survivors demonstrate a higher burden of CVRF compared with NHW survivors, particularly diabetes and obesity. The associated morbidity of these conditions and established increase they incur in risk of more severe cardiovascular disease emphasizes the need for interventions to mitigate CVRFs to promote health equity among these survivors. Research Sponsor: U.S. National Institutes of Health.

Cumulative incidence of CVRFs (Percentage, 95% CI) at age 40.

Race/Ethnicity	Hypertension	Diabetes	Dyslipidemia	Obesity	>2 CVRFs
NHW (n=20,416)	14.7 (14.0-15.3)	5.2 (4.8-5.6)	10.2 (9.6-10.7)	32.5 (31.6-33.3)	12.6 (12.0-13.2)
NHB (n=1625)	20.7 (17.7-23.7)	9.2 (7.2-11.2)	6.6 (4.6-8.6)	50.0 (46.4-53.3)	18.6 (15.5-21.6)
Hispanic (n=2043)	14.1 (11.8-16.4)	10.1 (8.2-11.9)	11.1 (8.9-13.2)	50.1 (47.0-53.1)	16.4 (13.9-18.9)

10018 **Poster Discussion Session**

Feasibility of pevonedistat combined with azacitidine, fludarabine, cytarabine in pediatric relapsed/refractory AML: Results from COG ADVL1712. *First Author: Katherine Tarlock, Seattle Children's Hospital, Seattle, WA*

Background: Outcomes for children with relapsed/refractory (R/R) AML and MDS are poor and new therapies are needed. Pevonedistat is an inhibitor of the NEDD-8 activating enzyme, a key regulator of the ubiquitin proteasome system that is responsible for protein turnover, cell growth and survival. In preclinical models, pevonedistat was synergistic with cytarabine (AraC) and azacitidine (aza). The combination of pevonedistat + aza in adults with AML demonstrated improved responses compared to either single agent. We evaluated the feasibility, toxicity and pharmacokinetics (PK) of pevonedistat in combination with aza, fludarabine, AraC (Aza-FLA) in children with R/R AML and MDS. **Methods:** Pevonedistat 20 mg/m^2, IV days 1, 3, 5, the recommended adult dose, was administered in combination with aza (75 mg/m^2, days 1-5), fludarabine (30 mg/m^2, days 6-10), and AraC (2000 mg/m^2, days 6-10). Intrathecal AraC was administered at the start of therapy and additional doses given to patients with CNS leukemia. If < 33% of the initial 6 enrolled patients experienced dose limiting toxicity (DLT) during cycle 1 the regimen would be considered tolerable and 6 additional patients could enroll to further assess tolerability and PK. Pevonedistat PK was determined during cycle 1 following doses 1 and 5. Response was evaluated after cycle 1. **Results:** A total of 12 patients were enrolled, median age was 13 years (range 1-21). All patients received prior chemotherapy, median number of prior regimens was 2 (range 1-5) and 3 (25%) patients had prior hematopoietic stem cell transplant. Diagnoses were AML NOS (n = 10, 83%), acute monocytic leukemia (n = 1), and therapy related AML (n = 1). One of the initial 6 patients had DLTs (hypertension, GGT elevation, and proteinuria); pevonedistat 20 mg/m^2 + Aza-FLA was considered tolerable. Six additional patients were enrolled, two had DLTs (weight loss, hypoxia). Overall, 3/12 (25%) of patients experienced DLTs. As expected, using the intensive Aza-FLA backbone, myelosuppression, electrolyte abnormalities, and hepatic transaminase elevation were common. Day 1 PK parameters (n = 12, mean±SD) were: C_{max}= 223±91 ng/mL, $AUC_{0\text{-}24h}$= 892±216 ng/hr/mL, $T_{1/2}$=4.3±1.2 hours, CL = 23.2±6.9 L/hr/m^2. PK parameters were similar following doses 1 and 5, for patients < 12 (n = 6) and ≥ 12 (n = 6) years, and to adult PK profiles. Ten patients were evaluable for response. The overall response rate was 30% (95% CI: 7,75) with 3 patients achieving a CR with incomplete hematologic recovery (CRi). **Conclusions:** Pevonedistat 20 mg/m^2 combinedwith Aza-FLA was tolerable in children with R/R AML. The toxicity of the regimen was similar to other intensive AML regimens. PK parameters were similar among the two age groups and were comparable to adults. Within the confines of a phase I study, there was limited anti-leukemic activity of the combination of pevonedistat +Aza-FLA in R/R AML. Clinical trial information: NCT03813147. Research Sponsor: U.S. National Institutes of Health, Other Foundation, Pharmaceutical/Biotech Company.

10019 **Poster Discussion Session**

Phase 1 study of pevonedistat (MLN4924) a NEDD8 activating enzyme inhibitor, in combination with temozolomide (TMZ) and irinotecan (IRN) in pediatric patients with recurrent or refractory solid tumors (ADVL1615). *First Author: Jennifer Foster, Texas Children's Hospital, Houston, TX*

Background: Pevonedistat (PEV), a first in class inhibitor of NEDD8 activating enzyme (NAE), prevents the activation of Cullin-RING ligases (CRL) necessary for proteasome mediated degradation of key regulatory proteins important in cell survival. In adults with solid tumors, the maximum tolerated dose (MTD) in combination with chemotherapy is 20-25 mg/m^2. Antitumor activity of PEV has been demonstrated in preclinical models of childhood cancer. *In vivo* additive activity has been demonstrated for PEV in combination with IRN and alkylating agents. The objectives of this study are to determine the MTD and recommended Phase 2 dose of PEV in combination with IRN and TMZ and describe the toxicities, pharmacokinetic (PK), and pharmacodynamics (PD) properties of this combination. **Methods:** We conducted a phase 1 trial of PEV in combination with IRN and TMZ in pediatric patients (pts) with recurrent or refractory solid tumors and brain tumors. During cycle 1, PEV was administered intravenously on days 1, 8, 10, and 12, with IRN (IV, 50mg/m^2) and TMZ (orally, 100mg/m^2), on days 8-12 of a 28 day cycle. In subsequent cycles, PEV was administered on days 1, 3, and 5, with IRN and TMZ on days 1-5 of a 21 day cycle. Dose escalation was determined using the Rolling 6 Design. **Results:** 30 pts enrolled. All pts were eligible and evaluable for cycle 1 dose limiting toxicity (DLT) assessment. Median (range) age was 13 (1-21) years; 19 (63%) were male. Eleven pts had brain tumors, and 19 pts had solid tumors. Six pts each enrolled on PEV dose levels (DL) 1 (15mg/m^2), 2 (20mg/m^2), 3 (25mg/m^2) and 4 (35mg/m^2) as well as an expanded PK cohort at DL4. Cycle 1 grade 3/4 toxicities include lymphopenia (n = 5), leukopenia (n = 4), neutropenia (n = 2), elevated ALT (n = 2), elevated AST (n = 1), diarrhea (n = 1), flu-like symptoms (n = 1). The most frequent non-dose limiting AEs in cycle 1 were anemia (87%), WBC decreased (77%), nausea (57%), diarrhea (53%), ALT increased (50%), AST increased (50%), and vomiting (50%). PK analyses showed the mean area under the curve at the 25 mg/m^2 dose level on day 8 (in combination with irinotecan and temozolomide) was 1300 hr•ng/mL, half-life (T $^1/_2$) was 5-6 hours, time to maximum concentration (Tmax) was 1 hour, and mean clearance was 20 L/hr/m^2. There were 3 DLTs, 2 of which were related to protocol therapy (diarrhea and thrombocytopenia), among 12 patients on DL4. Thus the MTD was not exceeded at any dose level. PK at the 25 mg/m^2 dose level are comparable to those in adult patients. PK from the 12 patients on DL4 (35mg/m^2) as well as responses of all patients are pending. **Conclusions:** PEV in combination with IRN and TMZ is well tolerated in children with solid or brain tumors. PEV PK was not altered by the addition of irinotecan and temozolomide. Further PK and PD analyses are ongoing to establish the recommended phase 2 dose. Clinical trial information: NCT03323034. Research Sponsor: U.S. National Institutes of Health.

10020 **Poster Discussion Session**

Low-dose metronomic topotecan and pazopanib in children with recurrent or refractory solid tumors: A C17 Canadian phase I trial (TOPAZ). *First Author: Arif Manji, The Hospital for Sick Children, University of Toronto, Toronto, ON, Canada*

Background: Low-dose metronomic topotecan (mTP) represents a novel approach to chemotherapy delivery which, in preclinical models, may work synergistically with pazopanib (PZ) in targeting angiogenesis. This study was designed to determine the recommended phase 2 dose (RP2D) of mTP/PZ in pediatric patients with solid tumors, while describing the safety and toxicity of this regimen. **Methods:** A phase I dose-escalation, pharmacokinetic (PK) and pharmacodynamic (PD) study of mTP/PZ was conducted at ten sites across Canada, enrolling pediatric patients aged 2-21 years with relapsed/refractory solid tumors. Patients were treated with oral mTP and PZ suspension daily without interruption in 28-day cycles, with dose escalation in accordance with the rolling-six design. Five dose levels (0.12/125, 0.16/125, 0.22/125, 0.22/160, and 0.3/160 mg/m^2/day of mTP/PZ) were evaluated. PK studies were performed on day 1 and at steady state, and PD studies included circulating angiogenic factors VEGFR1, VEGFR2, VEGF, endoglin and placental growth factor. **Results:** Thirty patients (pts) were enrolled, of whom 26 were evaluable for dose-limiting toxicity (DLT), with median age 12 years (3-20). The most common diagnoses included osteosarcoma (8), neuroblastoma (NB, 7), Ewing sarcoma/PNET (4), and rhabdomyosarcoma (4). The most common grade 3/4 adverse events (AEs) related to protocol therapy were neutropenia (18%), thrombocytopenia (11%), lymphocytopenia (11%), AST elevation (11%), and lipase elevation (11%). Only 2 cycle-1 DLTs were observed on study, both at the 0.3/160 mg/m^2 mTP/PZ dose level (2/5 pts) comprising persistent grade 3 thrombocytopenia and grade 3 ALT elevation. No AEs experienced beyond cycle-1 required treatment discontinuation. Best response was stable disease in 10/25 pts (40%) for a median duration of 6.4 months (1.7-45.1). One patient with refractory NB achieved stable disease for 45 months and continued on mTP/PZ via compassionate access after study closure. PK and PD results are pending at this time. **Conclusions:** The combination of oral mTP and PZ is safe and tolerable in pediatric patients with solid tumors, with a RP2D of mTP 0.22 mg/m^2/day and PZ suspension 160 mg/m^2/day. Ten patients achieved stable disease for a median of 6 months. The lack of objective responses suggests that this combination is likely of limited benefit for relapsed disease, but may play a role as maintenance therapy. Clinical trial information: NCT02303028. Research Sponsor: Novartis, C17 Research Grant.

10021 **Poster Discussion Session**

Naxitamab and GM-CSF for consolidation of high-risk neuroblastoma (HR-NB) patients in complete remission. *First Author: Jaume Mora, Pediatric Surgery Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain*

Background: Naxitamab was recently approved in the US in combination with GM-CSF for the treatment of patients (pts) with relapse/refractory HR-NB in the bone/bone marrow who have demonstrated a partial response (PR), minor response (MR), or stable disease (SD) to prior therapy. Here we describe the use of 5 cycles of naxitamab and GM-CSF through compassionate use for consolidation of HR-NB pts in first or subsequent complete remission (CR). **Methods:** HR-NB pts in CR (first or subsequent) after initial multimodal induction treatment were eligible. Disease status was assessed at study entry by histology of BM biopsies/aspirates obtained from bilateral posterior and bilateral anterior iliac crests, I-MIBG SPECT scan, and whole body MRI. FDG-PET was used for MIBG non-avid cases at diagnosis. Quantitative reverse transcription-polymerase chain reaction was used to assess MRD in pooled heparinized BM aspirates. Disease response was defined according to the revised INRC. Four BM aspirates and ^{123}I-MIBG SPECT scan or FDG-PET scans were performed after cycles 2 and 5 and every 3 months thereafter for one year in all pts to assess response. Naxitamab was administered over ≥30 min in the outpatient setting on Days 1, 3 and 5 at 3.0 mg/kg/infusion (9.0 mg/kg/cycle) in combination with GM-CSF at 250 ug/m^2/day on Days -4 to 0 and at 500 ug/m^2/day on days 1 to 5. Treatment cycles were repeated every 4 weeks. Survival curves were built from the time of naxitamab treatment initiation by Kaplan-Meier methods and compared using the log-rank test. **Results:** From June 2017 to November 30 2020, 73 pts were treated: 55 (75%) in first CR and 18 (25%) in second or more CR. Majority of pts were MYCN non-amplified (n=56, 77%), all stage 4, median age at treatment initiation 4.5 years. 61 (84%) pts had received >5 cycles of induction chemotherapy; 22 (30%) high-dose chemotherapy and autologous stem cell transplant (ASCT); and 36 (49%) radiotherapy before receiving naxitamab. 58 (79.5%) pts completed naxitamab therapy, 53 (73%) in continued CR. 10 (14%) pts relapsed during treatment and 5 (7%) had grade 4 toxicities: 2 apnea related to naxitamab; and 2 non-related: 1 opioid related chest rigidity syndrome and 1 stroke. 3-y event-free-survival (EFS) for all pts is 58% [95% CI, 43.5; 78.4], 74% for first CR and 19% for second or more CR (p=0.0029). 3-y OS for the whole group is 82% [95% CI, 66.8; 100.0], 92% for first CR and 66% for second or more CR pts (p=0.18). Univariate Cox models for CR group, MYCN status, number of chemotherapies, ASCT, radiotherapy, MRD, and age showed significant p value only for prior relapse as predictor of EFS (p=0.047). **Conclusions:** Naxitamab for HR-NB pts in CR provided excellent 3-y OS rates regardless of previous management. The only predictor for relapse is prior history of recurrence. Research Sponsor: Ymabs Therapeutics, Other Foundation.

10022 **Poster Discussion Session**

Efficacy of naxitamab in patients with refractory/relapse (R/R) high-risk neuroblastoma (HR-NB) by bone/bone marrow (BM) evaluation, potential sites of residual disease. *First Author: Brian H. Kushner, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: NB is the most common extracranial solid tumor in children and half of patients present with high-risk disease. Bone and BM are frequent sites of metastatic disease and can serve as a reservoir for residual disease driving relapse. Naxitamab, a GD2-binding monoclonal antibody, was recently approved in the United States in combination with GM-CSF for the treatment of pediatric patients ≥1 year of age and adult patients with R/R HR-NB in the bone/BM who have demonstrated a partial response (PR), minor response (MR), or stable disease (SD) to prior therapy. Here we describe outcomes from the registrational Trial 201 (NCT03363373) detailed by bone/BM involvement. **Methods:** HR-NB patients with primary refractory disease or incomplete response to salvage treatment following relapse or progressive disease (PD) (in both cases including SD, MR and PR) with disease limited to bone and/or BM were eligible. Naxitamab was administered over ≥30 min in the outpatient setting on Days 1, 3 and 5 at 3 mg/kg/infusion (9 mg/kg/cycle) in combination with GM-CSF at 250 μg/m2/day on Days -4 to 0 and at 500 μg/m2/day on days 1 to 5. Treatment cycles were repeated every 4 weeks. Response was assessed after Cycle 2 and then every 2-3 months by revised International Neuroblastoma Response Criteria (INRC) using BM biopsies/aspirates and 123I-MIBG scintigraphy or FDG-PET. Effectiveness was concluded if the lower limit of the Clopper-Pearson exact 95% confidence interval (CI) of overall response rate (ORR) was >20%. We report efficacy data on 22 patients and safety data on the first 25 patients enrolled. **Results:** 13 (59%) patients had NB in bone, 2 (9%) had NB in BM, and 7 (32%) had NB in both bone and BM. Summary of overall response and response by compartment. **Conclusions:** Naxitamab provided clinically meaningful activity in both bone and BM with ORR of 68% and had a manageable AE profile. Clinical trial information: NCT03363373. Research Sponsor: Y-mAbs Therapeutics.

Response compartment; n (%) patients	Response[a]		n (%)	95% CI (%)
Overall; n = 22	Best response	CR	13 (59%)	36%, 79%
	ORR	CR+PR	15 (68%)	45%, 86%
Bone compartment; n = 20/22 (91%)	Best response*	CR	14 (70%)	46%, 88%
	ORR	CR+PR	16 (80%)	56%, 94%
BM compartment; n = 9/22 (41%)	Best response**	CR	7 (78%)	40%, 97%
	ORR	CR+PR	7 (78%)	40%, 97%

*2/20 (10%) patients had PR, 2/20 (10%) had SD, and 2/20 (10%) had PD. **1/9 (11%) patient had minimal disease and 1/9 (11%) was not evaluable. [a] INRC denotes that osseous lesions without soft tissue mass are considered non-measurable by RECIST and do not require confirmatory assessment of response Median time to first CR was 5.6 weeks (range 5.3-29.3). 5/25 (20%) patients reported 6 naxitamab-related serious adverse events (SAEs): 4 anaphylactic reaction, 1 pyrexia, 1 respiratory depression. 3/25 (12%) patients discontinued treatment due to naxitamab-related Grade 4 AE: 2 anaphylactic reaction, 1 respiratory depression. No fatal events were reported.

10023 **Poster Discussion Session**

Updated outcomes for patients with completely resected pulmonary recurrent osteosarcoma: A report from the Children's Oncology Group. *First Author: Alexander J. Chou, Weill Cornell Medical College, New York, NY*

Background: Amongst patients with recurrent osteosarcoma (OS), those with resectable pulmonary-only relapse appear to have the best outcomes. Prior analysis of patients with completely resected recurrent OS enrolled on a Children's Oncology Group (COG) Phase 2 trial AOST0221, which studied the efficacy of inhaled GMCSF, showed a 12-month disease control rate (DCR12) of only 20% (95% CI, 10 – 34%). DCR12 based on this analysis was used as the historical benchmark for efficacy analysis in two recently completed trials, AOST1321 (completely resected cohort only) and AOST1421. We analyzed the stability of the DCR12 benchmark using data from these contemporary studies. **Methods:** Patients were eligible for AOST1321 if they had undergone resection of all sites of recurrent or refractory OS within 30 days of enrollment and for AOST1421 if they had lung only recurrent OS completely resected within 4 weeks of enrollment. AOST1321 evaluated denosumab while AOST1421 evaluated dinutuximab. Patients with refractory disease, extrapulmonary recurrence or without histological confirmation of relapse were excluded from this analysis. DCR12 was defined as having at least stable disease 12 months after the start of protocol therapy. We report the DCR12 observed on AOST1321, AOST1421 and AOST0221. **Results:** One hundred and twenty-eight evaluable patients with completely resected recurrent OS were enrolled on AOST0221 (N=49), AOST1321 (N=38) and AOST1421 (N=41). One hundred and one patients were included in this analysis (AOST0221: 37, AOST 1321: 25, AOST1421:39). DCR12 was 14 % (95% CI, 5% – 26%) for AOST0221, 24% (95%CI 10-42%) for AOST1321, and 31% (95% CI, 17% - 45%) for AOST1421. Risk for disease progression did not differ across the 3 included studies. DCR12 for all three studies combined was 23% (95% CI, 15% – 31%). **Conclusions:** Prognosis for recurrent OS remains dismal, even for those with resectable pulmonary-only disease. Although not statistically significant, dinutuximab may have activity in a select group of relapsed OS patients; combination studies using dinutuximab are planned. The previously described benchmark of disease control at 12 months remained relatively consistent in recent studies for those patients who have resectable pulmonary-only relapse. Therefore, DCR12 remains a useful outcome measure in fully resected OS with lung only metastases. Analyses are ongoing to better define the appropriate threshold to define investigational agent activity in this specific patient population. Research Sponsor: U.S. National Institutes of Health, United Therapeutics Corporation.

10024 **Poster Discussion Session**

Inflammatory myofibroblastic tumor: A multi-institutional study from the pediatric surgical oncology research collaborative. *First Author: Barrie S. Rich, Cohen Children's Medical Center, Queens, NY*

Background: Inflammatory myofibroblastic tumor (IMT) is a mesenchymal neoplasm of intermediate malignancy, predominantly seen in children and young adults. Given its rarity, data are limited. We describe the largest cohort of patients with IMT to date, with an aim to further characterize this poorly understood tumor. **Methods:** A multi-institutional review was performed at 18 North American hospitals participating in the Pediatric Surgical Oncology Research Collaborative to identify IMT patients ≤39 years, diagnosed from 2000-2018. Descriptive statistics are described as median and interquartile range. Multivariable analysis was used to identify predictors of event free survival (EFS). **Results:** 182 patients were identified with a median age of 11 years (5-17); 52% were female. 33% of tumors were thoracic, 26% abdominal/pelvic, 20% head/neck, and 14% genitourinary. Common presenting symptoms included pain (29%), respiratory symptoms (24%), weight loss (12%), and a palpable mass (10%). Median tumor size was 3.9 cm (1.9-6.5). Anaplastic lymphoma kinase (ALK) overexpression was identified via immunohistochemistry in 53% of patients tested. One third of patients had abnormal cytogenetics, with 12% of the entire cohort having an *ALK* mutation. 7% of patients had distant disease at diagnosis. 13% of patients received neoadjuvant therapy including chemotherapy (3%), ALK inhibitor (4%), radiation (0.5%), non-steroidal anti-inflammatories (NSAIDs) (7%), or steroids (2%). Of those who underwent resection with known margin status (n = 158), 66% had complete resection, 20% had microscopic positive margins, and 14% had gross residual disease. Just over 40% of patients had an en bloc resection of involved organs, most commonly lung (26%). 21% of patients received adjuvant therapy, including chemotherapy (3%), ALK inhibitor (9%), radiation (0.5%), NSAIDs (8%), or steroids (5%). 12% of all patients received an ALK inhibitor: 24% neoadjuvant, 62% adjuvant, and 14% without surgery. Median follow-up time was 36 months (14-69). Overall 5-year survival (OS) was 95% and 5-year EFS was 80%. Predictors of recurrence included respiratory symptoms, larger tumor size, or distant disease at diagnosis. Gender, race, age and primary site were not predictive of EFS. Likewise, there was no association of ALK overexpression or *ALK* mutation with EFS. The presence of gross or microscopic margins following resection was not associated with recurrence. **Conclusions:** IMT is a rare tumor with favorable OS. Five year recurrence rate was 20%. Presenting with respiratory symptoms, larger tumor size, or metastatic disease was associated with recurrence, while ALK positivity was not. Notably, a positive margin after resection was not associated with increased recurrence, indicating that aggressive attempts at surgical resection that would compromise form or function may not be warranted. Research Sponsor: None.

10025 **Poster Discussion Session**

Household material hardship and parental distress in a multicenter clinical trial for pediatric acute lymphoblastic leukemia. *First Author: Puja J. Umaretiya, Dana-Farber and Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Poverty is associated with inferior psychosocial function among parents of children with cancer. Severe parental distress during treatment predicts future poor mental health for both parents and children. It is also associated with impaired parental cognitive bandwidth and executive function, which may have implications for treatment adherence. Efforts to identify poverty-exposures amenable to intervention are essential to improving survivorship quality of life for the > 90% of children with acute lymphoblastic leukemia (ALL) who will be long-term survivors. Household material hardship (HMH) is a targetable poverty exposure defined as at least 1 of 3 unmet basic needs including food, housing, or utilities. Dana-Farber Cancer Institute (DFCI) ALL Consortium trial 16-001 is the first pediatric oncology clinical trial to systematically evaluate HMH. We investigated the hypothesis that HMH exposure independently predicts severe parent psychological distress during ALL therapy. **Methods:** Patients with newly diagnosed ALL ages 1-17 years were enrolled on the DFCI 16-001 embedded HMH cohort study at 8 U.S. and Canadian centers. Secondary interim analyses used baseline (within 32-days of trial enrollment) and 6-mos parent-reported sociodemographic data, the Kessler-6 (K6) Psychological Distress scale, and trial-collected child and disease data. Severe psychological distress was defined as a K6 > = 13. Multivariable cox regression evaluated baseline HMH-exposure and parent distress at baseline and 6-mos adjusting for child's initial ALL risk group (Very High Risk (VHR) vs other) and marital status (single vs dual parent). **Results:** Among 258 families with evaluable data, 34% reported baseline HMH. Families were predominantly English-speaking (54%) dual parent households (71%). Children were a median of 5.7 years (IQR 1.0-17.99) at diagnosis and predominantly non-Hispanic white (66%) with expected disease distribution by immunophenotype (84% B-cell). HMH (odds ratio (OR) 2.18, 95% confidence interval (CI) 1.0-4.31, p = 0.025) and VHR initial risk group (OR 2.32; 95% CI 1.06-5.06, p = 0.035) were independently associated with baseline severe psychological distress. Only HMH was independently associated with 6-mos severe psychological distress (OR 4.93, 95% CI 1.80-13.48, p = 0.002). Future analyses will investigate race and ethnicity associations with parental distress pending trial accrual for statistical power. **Conclusions:** HMH, a modifiable poverty exposure, is significantly associated with severe parent psychological distress at diagnosis that persists 6-months into pediatric ALL therapy. These findings identify a cohort at high risk of inferior mental health outcomes, and affirm the need for HMH-targeted interventions to support children and parents during cancer treatment to reduce poverty-associated outcome disparities in survivorship. Research Sponsor: U.S. National Institutes of Health.

10026 **Poster Discussion Session**

Financial hardship in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Paul C. Nathan, Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, ON, Canada*

Background: The impact of childhood and adolescent cancer on the long-term financial outcomes of survivors is poorly understood. We compared financial hardship between survivors and siblings enrolled in the CCSS and identified survivors at elevated risk. **Methods:** Survivors treated for cancer at age < 21 years in 1970-1999 and siblings responded to a survey (23 binary-response questions) at age ≥26 years administered in 2017-2019. Principal component analysis with promax rotation extracted 3 factors with eigenvalues > 1 and KR-20 reliability coefficients > 0.7, retaining items with factor loadings > 0.4. These factors were behavioral hardship (8 items, e.g., forgone needed medical care), material hardship/financial sacrifices (8 items, e.g., problems paying medical bills) and psychological hardship (3 items, e.g., worry about having enough money to pay rent/mortgage). Factor scores were calculated by adding the item responses and dividing by their standard deviation. Multiple linear regression examined the association of sociodemographic and cancer treatment variables with factor scores. **Results:** Among 3349 survivors (49% male; median age [range] 40.2 [26.0-67.4] years) and 976 siblings (42% male, median age 46.5 [26.1-69.2] years), survivors were more likely to report being sent to debt collection (29.5 vs 21.4%), problems paying medical bills (20.0 vs 11.9%), foregoing needed medical care (13.3 vs 7.7%) and worry/stress about paying their mortgage (32.8 vs 23.2%) or having enough money to buy nutritious meals (25.0 vs 16.2%), all P < 0.001. Survivors reported greater hardship than siblings on all 3 factors: behavioral hardship (standardized mean score 0.51 vs 0.36), material hardship/financial sacrifices (0.63 vs 0.44), psychological hardship (0.69 vs 0.44), all P < 0.001. Behavioral hardship was increased by female gender (regression coefficient [▫] 0.17, 95% CI 0.10-0.25), < high school (▫ 0.45, CI 0.12-0.79) or < college (▫ 0.18, CI 0.09-0.26) education, no (▫ 1.14, CI 0.93-1.35) or public (▫ 0.23, CI 0.10-0.35) health insurance, being divorced/separated (▫ 0.28, CI 0.10-0.46) and ≥250mg/m^2 anthracycline chemotherapy (▫ 0.09, CI 0.00-0.19). The same variables were significantly associated with the other two hardship factors, but total body irradiation and cranial radiation also contributed to the risk of material hardship/financial sacrifices, and ≥8g/m^2 cyclophosphamide equivalent dose and cranial radiation contributed to psychological hardship. **Conclusions:** Survivors of childhood and adolescent cancer are at elevated risk for financial hardship as compared to sibling controls. Those at highest risk can be defined using a combination of sociodemographic and treatment variables. This information can be used to inform targeted intervention strategies to reduce the risk of poor financial outcomes in this vulnerable population. Research Sponsor: U.S. National Institutes of Health.

10027 **Poster Discussion Session**

Low-dose radiation to cardiac substructures and late-onset cardiac disease: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: James Edward Bates, Emory University, Atlanta, GA*

Background: Thoracic radiotherapy (RT) is a risk factor for cardiac disease among survivors of childhood cancer based on studies considering RT doses to the entire heart. Dose to specific cardiac substructures may provide more precise dose-response associations to guide RT planning. We report associations between RT dose to cardiac substructures and risk of specific cardiac outcomes. **Methods:** We determined the cumulative incidences of CTCAE grade 3 – 5 coronary artery disease (CAD), heart failure (HF), and valvular disease (VD) among 25,481 5-year childhood cancer survivors diagnosed 1970 – 1999 in the CCSS. Median age at diagnosis was 6.1 years (0 – 20 years) and at last follow-up 29.8 years (5.6 – 65.9 years). For the 12,228 individuals receiving RT, fields were reconstructed on an age scaled computational phantom. Mean doses to the entire heart, cardiac chambers, valves, and left main, anterior descending (LAD), circumflex, and right coronary (RCA) arteries were estimated. Adjusted piecewise exponential models (including cumulative anthracycline dose) evaluated associations between mean RT dose to each structure and outcomes. **Results:** At 30 years from diagnosis, the cumulative incidences of grades 3 – 5 CAD, HF, and VD were 2.3% (95% CI 2.0 – 2.5), 2.6% (95% CI 2.4 – 2.9), and 0.6% (95% CI 0.5 – 0.8) respectively. Low dose RT (mean 5 – 9.9 Gy) to the RCA (relative rate [RR] = 2.6, 95% CI 1.6 – 4.1, p < 0.001), LAD (RR = 1.9, 95% CI 1.1 – 3.3, p = 0.019), and left ventricle (RR = 2.2, 95% CI 1.3 – 3.7, p = 0.002) was associated with increased risk of CAD relative to those not exposed; mean dose of 5 – 9.9 Gy to the entire heart was not (RR = 1.1, 95% CI = 0.8 – 1.6, p = 0.59). Table shows the associated cumulative incidences of CAD for these structures. Mean RT doses of 5 – 9.9 Gy to the aortic valve (RR = 4.6, 95% CI 1.5 – 14.0, p = 0.008) and tricuspid valve (RR = 5.5, 95% CI 2.0 – 15.1, p = 0.001) were associated with risk of VD compared to those with no RT; mean heart dose 5 – 9.9 Gy was not (RR = 0.6, 95% CI = 0.2 – 1.3, p = 0.16). No cardiac structure was significantly associated with an increased risk of HF at a mean dose of 5 – 9.9 Gy. Mean RT doses below 5 Gy were not associated with increased risks of CAD, HF, or VD; doses ≥10 Gy to nearly all substructures and the entire heart were. **Conclusions:** Low dose RT to the coronary arteries and cardiac valves (5 – 9.9 Gy) from RT is associated with increased risk of CAD and VD, respectively. Sensitivity to low dose RT may vary across the heart and doses to specific structures may be more predictive of late cardiac disease than whole heart dose. These data can guide RT planning to prioritize substructures for avoidance. Research Sponsor: U.S. National Institutes of Health, American Lebanese Syrian Associated Charities.

30-year cumulative incidence for CAD with low dose RT to selected cardiac substructures.

Structure	Mean RT Dose	CI (95% CI)
Entire Heart	None	0.9% (0.6 – 1.2%)
Entire Heart	5 – 9.9 Gy	1.0% (0.2 – 1.8%)
RCA	5 – 9.9 Gy	2.6% (1.4 – 3.7%)
LAD	5 – 9.9 Gy	1.7% (0.8 – 2.7%)
Left ventricle	5 – 9.9 Gy	2.3% (1.1 – 3.5%)

10028 **Poster Discussion Session**

Efficacy of clinical breast examination in chest-irradiated female survivors of childhood Hodgkin lymphoma (HL). *First Author: Florence Lennie Wong, City of Hope, Duarte, CA*

Background: Female survivors of childhood HL treated with ≥10 Gy of chest radiation are at high risk for breast cancer (BC). The Children's Oncology Group (COG) guidelines recommend CBE annually starting at puberty and then semiannually from age 25, plus lifetime annual mammography (MAM) and breast Magnetic Resonance Imaging (MRI) starting 8y after chest radiation or age 25, whichever is later. While imaging-based screening recommendations are largely consistent with US guidelines for women at high BC risk, only the COG guidelines recommend CBE. The benefits of lifetime CBE starting from puberty for life in chest-irradiated HL survivors is unknown. **Methods:** Life-years (LYs) and lifetime BC mortality risk were estimated from a simulated cohort of 5-million HL survivors using the data from 5y female survivors of HL in the Childhood Cancer Survivor Study (CCSS) treated with ≥10 Gy of chest radiation. The simulated cohort underwent annual MAM+MRI from age 25 for life, with and without annual CBE from age 11 (presumed age of puberty) to age 24 and with and without semiannual CBE from age 25 for life with 100% adherence. BC included in-situ and invasive BC. Treatment-related BC incidence and non-BC mortality risks were estimated from the CCSS data. Risks at age <25 were extrapolated from the CCSS estimates while risks beyond age 50 were extrapolated additionally using the US population rates. CBE sensitivity (17.8%, in-situ and invasive BC) and specificity (98%) and MAM+MRI sensitivity (84.2-86.0%, in-situ; 96.7-97.1%, invasive) and specificity (75.3%) were obtained from the medical literature. **Results:** The CCSS cohort included 1057 female HL survivors. BC (all invasive) developed in three patients at age <25 (ages: 23, 24, 24). In the simulated cohort receiving no screening, lifetime BC risk was 40.8% and BC mortality was 17.5%. HL survivors around age 50 were at a 7.4-fold higher risk of developing BC and a 5.2-fold higher risk of non-BC mortality when compared with the general population. Compared to no annual CBE for ages 11-24y, undergoing annual CBE did not increase gains in LYs or reduce lifetime BC mortality relative to no screening (Table). Among those who survived to age ≥25, undergoing semiannual CBE from age 25 for life compared to no semiannual CBE also resulted in little gain in LYs or reduction in lifetime BC mortality relative to no screening. **Conclusions:** Lifetime CBE starting at puberty in conjunction with MAM+MRI appears to add little survival benefits compared with no CBE, suggesting that COG guidelines may be revised without adverse effect on long-term outcomes for chest-irradiated female survivors of childhood HL. Research Sponsor: American Cancer Society, U.S. National Institutes of Health.

Strategy	Annual CBE 11-24y	Semiannual CBE 25y-life	LY gained	BC mortality reduced (%)
No screening	NA	NA	REF	REF
Entire HL cohort undergoing MAM+MRI from age 25 for life	No	Yes	0.47	10.6
	Yes	Yes	0.47	10.6
HL cohort age≥25y undergoing MAM+MRI from age 25 for life	NA	No	0.47	9.9
	NA	Yes	0.49	10.3

10029 **Poster Discussion Session**

Neurocognitive outcomes in survivors of early adolescent and young adult (eAYA) hematologic cancers from the Childhood Cancer Survivor Study (CCSS). *First Author: Amy Yuan Wang, University of Chicago Medicine, Chicago, IL*

Background: Neurocognitive impairment in eAYA hematologic cancer survivors has not been well described, despite intensive neurotoxic therapies. We examined prevalence and risk for such impairment in hematologic cancer survivors diagnosed during eAYA compared to a younger age. **Methods:** We identified 1,213 eAYA (diagnosed at 15-21 years; median [range] follow-up age 40 [30-54]) and 4,538 childhood (diagnosed at <15 years; median age 30 [17-48]) survivors of ALL (n= 301 vs 3274), AML (n= 77 vs 424), and Hodgkin lymphoma (HL; n= 835 vs 840) from the CCSS (diagnosed 1970-1999) who completed the Neurocognitive Questionnaire. Impairment was defined as a score >90% of normative data in task efficiency (TE), organization (Org), memory (Mem), and emotional regulation (ER) domains. 1,014 age-matched siblings were controls. Treatment by diagnosis group, chronic health conditions, health status and health behaviors were examined as risk factors for neurocognitive impairment using multivariable logistic regression. Adjusted odds ratios (ORs) and corresponding 95% CI are reported. **Results:** Prevalence of neurocognitive impairment (≥1 impaired domain) was similar for eAYAs and childhood survivors of HL (31.0% vs 29.6%, p=0.54) and AML (36.4% vs 40.3%, p=0.51), although eAYA AML survivors were more likely to have impaired Mem (OR=2.3, 95% CI 1.0-5.4). eAYA ALL survivors were less likely to have neurocognitive impairment than childhood ALL survivors (28.2% vs 38.5%, p<.001) due to lower risk for impaired TE (OR=0.7, 95% CI 0.4-1.0) and Org (OR=0.5, 95% CI 0.4-0.9). No factors, including cranial radiation (RT), explained the rate differences. Treatment by diagnosis group (including cranial RT in ALL, chest RT in HL, and salvage therapy use) was not consistently associated with neurocognitive impairment in eAYA survivors. However, anthracycline dose ≥120mg/m^2 was a risk factor for impaired ER (OR=6.0, 95% CI 2.0-17.9) only in eAYA ALL survivors. Presence of a neurologic health condition was associated with impairment in all 4 domains in eAYA (ORs ranged 1.7-2.9) and childhood cancer survivors (ORs ranged 1.9-5.3). eAYA survivors with a respiratory condition were more likely to have impaired TE (OR=2.1, 95% CI 1.2-3.8). Being in good general health was associated with less impairment across all 4 domains for eAYA (ORs ranged 0.2-0.4) and childhood survivors (ORs ranged 0.3-0.5). eAYA survivors who never smoked were less likely to have impaired ER (OR=0.4, 95% CI 0.2-0.6) than those who smoke. **Conclusions:** Survivors of hematologic cancers diagnosed during eAYA are susceptible to neurocognitive impairment at rates similar to those diagnosed at younger ages. Having comorbidities and being in fair/poor general health are risk factors for impairment. Higher anthracycline exposure in ALL survivors diagnosed during eAYA was the only therapy associated with impairment rates. Research Sponsor: None.

10030 **Poster Session**

Resolving driver events in MLL-r negative high-risk infant ALL. *First Author: Jennifer Seelisch, Children's Hospital London Health Sciences Centre, London, ON, Canada*

Background: Infant acute lymphoblastic leukemia (ALL) is the only subtype of childhood ALL whose outcome has not improved over the past two decades. The most important prognosticator is the presence of rearrangements in the *Mixed Lineage Leukemia* gene (MLL-r), however, many patients present with high-risk clinical features but without MLL-r. We recently identified two cases of infant ALL with high-risk clinical features resembling MLL-r, but were negative for MLL-r by conventional diagnostics. RNA sequencing revealed a partial tandem duplication in MLL (MLL-PTD). We thus aimed to determine if MLL-PTD, other MLL abnormalities, or other genetic or transcriptomic features were driving this subset of high-risk infant ALL without MLL-r. **Methods:** We obtained 19 banked patient samples from the Children's Oncology Group (COG) infant ALL trial (AALL0631) from MLL wildtype patients as determined by FISH and cytogenetics. Utilizing deep RNA-sequencing, we manually inspected the MLL gene for MLL-PTD, while also performing automated fusion detection and gene expression profiling in search of defining features of these tumors. **Results:** 3 additional MLL-PTDs were identified, all in patients with infant T-cell ALL, whereas both index cases were in patients with infant B-cell ALL. Gene expression profiling analysis revealed that all five MLL-PTD infants clustered together. Eight infants (7 with B-cell ALL) were found to have Ph-like expression. Five of these 8 infants were also found to have an IKZF1/JAK2 expression profile; one of these five had a PAX5-JAK2 fusion detected. Two infants (including the one noted above) had novel PAX5 fusions, known drivers of B-cell leukemia. Additional detected fusions included TCF3-PBX1 and TCF4-ZNF384. **Conclusions:** MLL-PTDs were found in both B- and T-cell infant ALL. Though Ph-like ALL has been described in adolescents and young adults, we found a substantial frequency of Ph-like expression among MLL-WT infants. Further characterization of these infants is ongoing. If replicated in other infant cohorts, these two findings may help explain the poor prognosis of MLL-WT ALL when compared to children with standard risk ALL, and offer the possibility of targeted therapy for select infants. Research Sponsor: C17: The 100% Fund - Phoebe Rose Rocks Foundation.

10031 **Poster Session**

Forecasting asparaginase quantity required to treat pediatric ALL in LMICs using ACCESS FORxECAST. *First Author: Terence M. Hughes, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Asparaginase (ASN) is a crucial component of pediatric acute lymphoblastic leukemia (ALL) protocols. ASN is available in three enzyme formulations: native from *Escherichia Coli* (*E. coli*), PEGylated from *E. coli* (PEG), and native erwinia from *Erwinia chrysanthemi* (Erwinase). PEG is typically preferred in high-income countries, while *E. coli* is more accessible in low and middle income countries (LMICs). Erwinase is reserved for patients who develop hypersensitivity. Short shelf lives, high prices, intermittent availability, and concern for substandard formulations in LMICs have created a need for proactive ASN demand estimates, particularly in LMICs. **Methods:** We modified FORxECAST, a publicly available tool that forecasts pediatric cancer drug quantity and cost, to estimate ASN quantity required to treat pediatric ALL in 2021 across all LMICs. Incidence data is based on the Global Childhood Cancer microsimulation model, which extrapolates country registries to estimate diagnosed pediatric ALL patients. We forecast ASN quantity for both a base regimen (BR), recommended by the International Pediatric Oncology Society (SIOP), and a more aggressive regimen (AR) used in some LMICs with more advanced supportive care capacity. For both BR and AR, we estimate ASN quantity across four scenarios, outlining how quantity would vary based on formulation and ability to switch in cases of hypersensitivity. **Results:** The estimated quantity of ASN required to treat all children diagnosed with ALL in LMICs in 2021, across scenarios and regimens, is provided (Table). If *E. coli* were used to treat all diagnosed pediatric ALL patients across LMICs, required quantity would range from 1,198 M IU (BR) to 1,661 M IU (AR) (Scenario 1). If PEG were used, required quantity would range 150 M IU (BR) to 473 M IU (AR) (Scenario 2). Accounting for hypersensitivity would require 77 M IU (BR) to 137 M IU (AR) Erwinase (Scenarios 3 and 4). **Conclusions:** We adapted FORxECAST to be ASN-specific and estimated demand in LMICs for a range of scenarios, including for second line Erwinase; accounting for hypersensitivity is particularly important because discontinuation typically results in lower cure rates. We also estimated how quantity of ASN required would increase with treatment intensity. These results provide the first quantification of ASN need for pediatric ALL in LMICs, creating a demand estimate that can inform private and public efforts to produce a reliable supply of high quality ASN for all children with ALL. Research Sponsor: Boston Children's Hospital, Dana Farber Cancer Institute, Dana Farber/Boston Children's Hospital Global Health Initiative, and the Division of Haematology/Oncology at The Hospital for Sick Children.

ASN Quantity for Diagnosed Pediatric ALL in LMICs (2021).

Scenario	BR	AR
1. *E. coli* [no hypersensitivity planning]	1,198	1,661
2. PEG [no hypersensitivity planning]	150	473
3. *E. coli* > Erwinase [hypersensitivity planning]	*E. coli*: 1,198 Erwinase: 77	*E. coli*: 1,661 Erwinase: 137
4. PEG > Erwinase [hypersensitivity planning]	PEG: 150 Erwinase: 77	PEG: 473 M Erwinase: 137

Quantities in millions of international units (M IU).

10032 **Poster Session**

Correlation of ex vivo drug sensitivity with clinical response in pediatric AML. *First Author: Ryosuke Kita, Notable Labs, Foster City, CA*

Background: Pediatric acute myeloid leukemia (AML) is a rare disease with roughly 500 cases diagnosed in the United States each year and has had minimal improvement in clinical outcomes over recent decades. Novel treatment development to improve outcomes may be enhanced with an accompanying test for predicting treatment response. We previously demonstrated that an *ex vivo* drug sensitivity assay (DSA) can predict clinical response in myelodysplastic syndrome. Here we investigated the use of the DSA in pediatric AML patients, including a subset participating in a clinical trial of atovaquone. Atovaquone is an FDA-approved anti-parasitic drug that was associated with lower relapse rates in adult AML patients. Adding atovaquone and other standard of care combination treatments into the DSA, we investigated whether the assay, performed on pre-induction samples, correlated with measures of clinical response. **Methods:** We assayed pre-induction blood or bone marrow samples from 22 de novo pediatric AML patients diagnosed at Texas Children's between 5/2015 and 10/2020 who consented to research (82% enrolled in clinical trial identifier NCT03568994). We subsetted this analysis to patients who received ADE (Cytarabine, Daunorubicin, Etoposide) (n = 20) induction, with the majority additionally receiving atovaquone (n = 16). For the DSA, samples were incubated with up to 25 compounds, including the treatment drug combinations and each of the compounds individually. After incubation, changes in tumor blast populations were assessed by flow cytometry. For each drug condition, drug sensitivity was calculated based on the number of blasts remaining after treatment. After quality control, downstream analyses were limited to 13 samples. Clinical response data, including minimal residual disease (MRD) percentage by flow cytometry and one year relapse-free survival, were correlated with the drug sensitivity results. **Results:** For the de novo subset analysis, we observed correlations between *ex vivo* drug sensitivity with both MRD percentage (r = 0.63) and one year relapse-free survival (RFS1, AUC = 0.92). The 3 patients with lowest *ex vivo* sensitivity had the highest MRD percentages (mean 21%). 2 of the 3 patients who did not achieve one year relapse-free survival had the lowest *ex vivo* sensitivity. Drug combination sensitivity correlated more with MRD and RFS1 than the single agents alone (single agent mean MRD r = 0.39). **Conclusions:** In our cohort, *ex vivo* DSA for ADE and atovaquone in pediatric AML cases correlated with both MRD and one year relapse-free survival. This suggests that clinical response in pediatric AML may be assessed prior to treatment using a DSA. This study also suggests that the DSA can be used to test drug combinations, and thus may be used for investigating novel treatment combinations. Further development of the DSA may benefit treatment decisions and prioritization of drug development. Research Sponsor: Notable Labs.

10033 **Poster Session**

Preclinical evaluation of the ETS inhibitor TK216 against relapsed and refractory childhood leukemia. *First Author: Ritul Sharma, University of Calgary, Calgary, AB, Canada*

Background: Although survival rates have improved in the recent past, relapse and refractory disease remain a significant cause of death in children with leukemia. This calls for an urgent need for the development of novel therapies that could effectively treat leukemias in children. The E26 transformation specific (ETS) family of transcription factors regulate various normal cellular functions but are abnormally expressed in various cancers, including leukemia. TK216 is an ETS inhibitor, that has shown pre-clinical activity and clinical efficacy in solid tumors. In this study, we explore the feasibility of using TK216 as a therapeutic agent for the treatment of high risk refractory pediatric leukemia. **Methods:** A panel of pediatric leukemia derived cell lines and primary blast cells representing a spectrum of molecular abnormalities seen in pediatric leukemia were treated *in vitro* with TK216 to determine cytotoxicity. Normal lymphocytes were used as controls and cell viability was determined 72 hours post-treatment by Alamar blue assay. The induction of tumor cell apoptosis and target modulation were detected by Western blotting. Alterations in the cell cycle were assessed by FACS analysis with PI staining. Drug combination studies were carried out with established anti-leukemic agents to identify synergy for greater therapeutic efficiency. **Results:** TK216 decreased cell viability in leukemia cells compared to normal lymphocyte controls in a dose-dependent manner with variations in sensitivity noted with inherent molecular abnormalities. The IC_{50} values observed ranged from 0.22 μM for the most sensitive cell line, MV4-11 to 0.95 μM for least sensitive cell line, SUP-B15. Apoptosis induction upon TK216 treatment was confirmed by PARP cleavage and caspase 3 activation. Cell cycle analysis demonstrated increased sub-G1 population of cells after TK216 treatment. A strong correlation between sub-G1 population and sensitivity of the cell line towards TK216 (47% in MV4-11 vs 3.72% in SUP-B15) was observed. Screening of a panel of 200 FDA approved anti-cancer agents in drug combination studies identified potential agents for drug synergy. Significant drug synergy was noted with TK216 in combination with the epigenetic modifier 5-azacytidine and the Bcl-2 inhibitor, Venetoclax. [Combination Index for Venetoclax and TK216, mean = 0.65 for MV4-11 and 0.33 for SUP-B15]. **Conclusions:** Data from our study demonstrate that the ETS inhibitor TK216 induces apoptosis and cell cycle arrest in pediatric leukemia cells at physiologically relevant concentrations. Our combination studies identified distinct anti-cancer agents that could be used for developing effective drug combination regimens with TK216. Overall, our findings provide essential preclinical data for the consideration of TK216 in early phase clinical trials for the treatment of selected high-risk and refractory childhood leukemia. Research Sponsor: Alberta Children's Hospital, Kids Cancer Care, Calgary .

10034 **Poster Session**

Novel methods to assess cell-free circulating tumor DNA in acute lymphoblastic leukemia. *First Author: Meghan G. Haney, University of Kentucky, Lexington, KY*

Background: Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, with a relatively high relapse rate, which is associated with poor prognosis. Currently, minimal residual disease (MRD) at the end of induction and consolidation therapy is the best predictor of patient relapse, however obtaining bone marrow aspirate is invasive and not always accurate. Another major concern in ALL is the presence of central nervous system (CNS) disease, which is often present long before clinical diagnosis can be made by flow cytometry. To circumvent these clinical challenges, we developed a new assay quantifying cell-free, circulating tumor (cfDNA) as a biomarker of disease progression, which can be correlated with MRD status as a predictor of relapse. cfDNA is frequently used to monitor progression of solid tumors, but pediatric leukemias lack common mutations that can be used to distinguish leukemic cfDNA from normal cfDNA. **Methods:** We examined two possible methods for using ctDNA as a biomarker: leukemia cell clonality and DNA methylation profiling. We developed a novel workflow for identifying VDJ rearrangements in leukemia cells and tracking their presence in cfDNA. We collected bone marrow, blood, and CSF samples from newly diagnosed patients, and cfDNA was isolated from blood and CSF samples throughout treatment. Invivoscribe Lymphotrack PCR assays combined with MinION (Oxford Nanopore Technologies) sequencing were used to identify the VDJ sequence of the immunoglobulin (B-ALL) or T-cell receptor (T-ALL) rearrangements of leukemic clones in genomic DNA. The MinION assay relies on patient-specific sequencing. We are also in the process of developing a universal assay that utilizes recurrent methylation changes in ALL to identify leukemic cfDNA in patient samples. **Results:** The MinION workflow was used to follow leukemic cfDNA throughout the course of treatment, and accurately identified MRD and CNS disease in patients. This workflow performed equivalent or better at detecting leukemic clones compared to MiSeq and droplet digital polymerase chain reaction (ddPCR), and is faster and less expensive than traditional Illumina sequencing. Methylation analysis of 865 ALL and 79 healthy samples yielded 55 regions and 19 specific methylation sites that were uniquely present in ALL samples. We are validating these sites by ddPCR to establish a panel of biomarkers to track ALL over time via cfDNA. **Conclusions:** The end goal of our study is provide a more sensitive and less invasive method for tracking MRD and CNS disease than current approaches. Results will ultimately be correlated with patient response to therapy, the presence of relapse or CNS disease, and overall outcomes determined by standard clinical diagnostic procedures. Research Sponsor: Kentucky Cabinet for Health and Family Services.

10035 **Poster Session**

Discovery and validation of a cross-platform 21-gene prognostic signature in neuroblastoma. *First Author: Mehul Gupta, Arnie Charbonneau Cancer Research Institute, University of Calgary, Calgary, AB, Canada*

Background: Neuroblastoma (NB) is the most common extracranial solid tumor in children. Despite the development of risk stratification tools to improve prognostication, prediction of patient survival outcomes in NB remains poor. In this study we used an unbiased machine-learning algorithm to develop and validate a transcriptomic signature capable of predicting 5-year overall (OS) and event-free survival (EFS) in these patients. **Methods:** The TARGET-Neuroblastoma dataset (n = 243) was used as the training set. Two independent NB cohorts, E-MTAB-179 (n = 478) and GSE85047 (n = 266) were used as validation sets. Elastic net regression was employed to identify transcripts associated with EFS. Association of the developed signature with EFS and OS was evaluated using univariate Cox proportional hazards (CoxPH), Kaplan-Meier, and 5-year receiver-operator characteristic curves in validation cohorts. Further, the independent prognostic value of the signature was assessed using multivariate CoxPH models with relevant clinicopathologic variables including age, INSS stage, and *N-Myc* amplification status in both validation sets. Finally, a nomogram was developed to integrate the signature with prognostic clinicopathologic variables to evaluate their combined efficacy for prediction of 5-year EFS and OS. **Results:** We identified a 21-gene signature that demonstrates significant association with EFS and OS in both E-MTAB-178 and GSE49710 validation cohorts. Moreover, the signature is independent of clinicopathological variables and can be effectively incorporated into a risk model, improving the prognostic performance. Several genes within the signature have been previously implicated in NB, including ECEL1, HOXC9 and ARAF1. **Conclusions:** To the best of our knowledge, we are the first to use an unbiased machine learning approach to generate a transcriptomic gene signature for neuroblastoma prognosis externally validated in multiple cohorts across platforms. This 21-gene transcriptomic signature significantly associated with EFS and OS in this disease. Combining this signature with current prognostic clinicopathologic variables will improve risk stratification of affected patients and may inform effective clinical decision-making. Research Sponsor: None.

	Signature alone		Signature with clinicopathologic variables	
	EFS	OS	EFS	OS
E-MTAB-179	HR: 5.869 (3.825-9.006), p < 0.0001 AUC: 0.827	HR 37.240 (11.760-117.900), p < 0.0001 AUC:0.904	HR 6.949 (4.320-11.180), p < 0.0001 AUC:0.837	No events in low-risk group, Log-Rank p < 0.0001 AUC:0.920
GSE85047	HR 3.736 (2.357-5.924) p < 0.0001 AUC:0.815	HR 4.941 (2.823-8.647) p < 0.0001 AUC:0.833	HR 5.460 (3.214-9.2274), p < 0.0001 AUC: 0.849	HR 11.891 (5.422-26.080), p < 0.0001 AUC:0.892

EFS = event-free survival; OS = overall survival, HR = hazard ratio, AUC = area under the curve.

10036 **Poster Session**

Racial and ethnic disparities in risk and survival in children with neuroblastoma: An updated analysis. *First Author: Caileigh Pudela, University of Chicago, Chicago, IL*

Background: Biologic and socioeconomic factors contribute to health disparities among patients with pediatric cancer. In an analysis of Children's Oncology Group (COG) neuroblastoma (NBL) patients (pts) diagnosed between 2001-2009, non-Hispanic Black (Black) pts were previously shown to have a higher prevalence of high-risk disease and worse event-free survival (EFS) compared to non-Hispanic White (White) pts. Here, we analyzed data in the International Neuroblastoma Risk Group Data Commons (INRGdc) to validate these findings. **Methods:** Three-year EFS and overall survival (OS) of COG pts diagnosed between 2001-2009 (Cohort 1; n = 4,358) and 2010-2016 (Cohort 2; n = 3,689) in the INRGdc with known race and ethnicity were estimated by the Kaplan-Meier method. Cox proportional hazards regression models were used to evaluate differences in EFS and OS between racial/ethnic groups. The association of clinical characteristics and tumor biomarkers with racial/ethnic groups were analyzed using Chi-square tests. **Results:** The distribution of race/ethnicity for pts in Cohort 1 and Cohort 2 was as follows, respectively: White: 72% (n = 3,136) and 70% (n = 2,575); Black: 11.4% (n = 495) and 10.7% (n = 397); Hispanic: 12.2% (n = 532) and 14.1% (n = 522); Asian and Hawaiian: 4% (n = 178) and 4.6% (n = 172); Native American: 0.4% (n = 17) and 0.6% (n = 23). In both cohorts, a higher proportion of Black pts had INSS stage 4 disease, age $\geq$ 18mo, and unfavorable histology tumors when compared to White pts (Cohort 1: p = 0.003; $p < 0.001$; $p < 0.001$, respectively vs Cohort 2: p = 0.014; $p < 0.001$; $p < 0.001$, respectively). No significant differences in the proportion of pts with *MYCN* amplified or diploid tumors were detected between Black and White pts in either cohort. Black pts had a higher prevalence of high-risk disease compared to White pts in both Cohorts 1 and 2 ($p < 0.001$ and $p < 0.001$, respectively). Among all pts in Cohort 1, EFS was 73% and OS was 83%. In Cohort 1, Black pts had worse EFS (68% vs 73%; HR = 1.31, 95%CI 1.11-1.55, p = 0.002) and OS (78% vs 84%; HR = 1.41, 95% CI 1.16-1.70, p = 0.001) compared to White pts. Among all pts in Cohort 2, EFS was 81% and OS was 88%. Black pts in Cohort 2 also had worse EFS compared to White pts (76% vs 82%; HR = 1.35, 95% CI = 1.03-1.76, p = 0.027), although no significant difference in OS was observed (p = 0.21). In analyses restricted to high-risk pts, no statistically significant difference in EFS and OS in Black vs White pts was detected in either cohort. **Conclusions:** In the modern treatment era, Black NBL pts continue to have a higher prevalence of high-risk disease and inferior 3-year EFS compared to White pts. The lack of significant difference in survival among high-risk NBL pts by race suggests that Black and White pts are receiving comparable treatments and responding similarly. The socioeconomic and/or genomic factors contributing to the higher proportion of Black pts with high-risk disease requires further investigation. Research Sponsor: None.

10037 **Poster Session**

Testing of B7-H3 targeting antibody-drug conjugate (ADC) MGC018 in models of pediatric solid tumors by the Pediatric Preclinical Testing Consortium (PPTC). *First Author: Raushan Kurmasheva, Univeristy of Texas Health Science Center San Antonio, San Antonio, TX*

Background: B7-H3 (encoded by the *CD276* gene) is an immunoregulatory molecule that is widely expressed in pediatric embryonal tumors and sarcomas, while expression is limited for normal tissues. Among PPTC models, osteosarcoma models showed highest CD276 transcript levels followed by Wilms tumor, neuroblastoma, rhabdomyosarcoma, and Ewing sarcoma. Protein expression by IHC generally followed expression at the RNA level, with high expression by IHC observed across a range of models. MGC018 is a duocarmycin-based humanized ADC targeting B7-H3 that shows selective cytotoxicity for B7-H3 expressing cancer cells, robust in vivo activity against a range of adult cancer preclinical models, a favorable pharmacokinetic and safety profile in cynomolgus monkeys, and has entered clinical testing for adults with cancer. Herein we report the in vivo antitumor activity of MGC018 against preclinical models of pediatric solid tumors. **Methods:** MGC018 was tested at 6 mg/kg administered intraperitoneally (IP) on Day 1. SYD988, an anti-CD20 ADC with the same linker and payload as MGC018, was used as a control arm at 6 mg/kg IP on Day 1. Osteosarcoma models, due to their slower growth kinetics and lower rates of tumor regression, were tested with n = 10 mice per arm, while the sarcoma and neuroblastoma models were tested with n of 1 or n of 2 designs, respectively. Activity was evaluated using response criteria mirroring clinical criteria (progressive disease (PD), stable disease (SD), partial response (PR), complete response (CR), and maintained CR (MCR)], by minimum relative tumor volume across all models, and by event-free survival (EFS) comparisons between treatment groups. **Results:** For neuroblastoma models (n = 9), 3 and 2 neuroblastoma models showed objective responses (PR/CR/MCR) or SD, respectively, to MGC018, while none showed an objective response or SD to SYD988. For osteosarcoma, results are mature for 1 of 5 models, with this model showing an MCR response to MGC018 and a PD response to SYD988. For Ewing sarcoma (n = 5), a PR and MCR were observed to MGC018 with the remaining models showing PD; for SYD988 a single CR was observed with the remaining 4 models showing PD. For rhabdomyosarcoma (n = 3) 2 MCR and 1 PD were noted for MGC018, while only PD was noted for SYD988. EFS duration exceeding 100 days to a single dose of MGC018 was observed for 2 rhabdomyosarcoma, 1 Ewing sarcoma, and 1 neuroblastoma model. Evaluation of the relationship between B7-H3 expression and response to MGC018 will be performed when results from all studies are completed. **Conclusions:** B7-H3 is an important target for immuno-oncology agents for childhood cancers. Our results provide proof-of-principle for the ability of MGC018 to produce profound antitumor activity in select pediatric solid tumor models in a B7-H3 specific manner. Research Sponsor: U.S. National Institutes of Health.

10038 **Poster Session**

Late health outcomes in survivors of Wilms tumor: A report from the St. Jude Lifetime (SJLIFE) cohort study. *First Author: Kayla L. Foster, St Jude Children's Research Hospital, Memphis, TN*

Background: We aimed to characterize late health, neurocognitive, and physical performance outcomes among survivors of Wilms tumor. **Methods:** Wilms tumor survivors (n = 280), $\geq$ 5 years from diagnosis, participating in SJLIFE were clinically assessed along with a community control sample (n = 625). Health outcomes were graded per a modified Common Terminology Criteria for Adverse Events (grade 1 [mild] to grade 4 [life threatening]). Standardized neurocognitive testing was graded using age-adjusted z-scores. Aerobic function (six-minute walk), mobility (timed up and go) and flexibility (sit and reach) were assessed. Associations between treatment exposures and prevalent conditions were examined by multivariable logistic regression, adjusted for current age, sex and race. **Results:** Survivors (59% female, 73% white), median age 3 years (range 0-15) at diagnosis and 31 years (9-58) at evaluation, were comprehensively evaluated on the St. Jude campus. Two-thirds (67%) were treated with doxorubicin (median dose 175 mg/m^2 range 52-490), 167 (60%) received abdominal radiation (median dose 12 Gy range 8.8-61.2) and 25% received chest radiation (12 Gy range 9-44). By age 40 years, survivors averaged 12.7 (95% confidence interval [CI] 11.7-13.8) grade 1-4 and 7.5 (CI 6.7-8.2) grade 2-4 conditions, compared to 4.2 (CI 3.9-4.6) and 2.3 (CI 2.1-2.5), respectively, among controls. The most prevalent medical conditions (grade $\geq$ 2) are reported in the table. Abnormal glucose metabolism was associated with abdominal radiation (relative risk [RR] 5.1 CI 1.4-19.0); restrictive pulmonary defects with chest radiation (RR 24.0 CI 3.2-180); and cardiomyopathy (RR 15.6 CI 1.9-128), pulmonary diffusion (RR 4.5 CI 1.3-15.1), and chronic kidney disease (RR 4.5 CI 1.3-16.1) with doxorubicin exposure. Survivors had a three-fold higher risk (standardized incidence ratio 3.5, CI 2.2-6.6) for subsequent neoplasms. Impairments (grade $\geq$ 2) in executive function (20% vs. 12%), attention (17% vs. 9%), memory (21% vs. 10%), and processing speed (20% vs. 8%) were more frequent in survivors than controls ($p < 0.05$). Impairments in aerobic function (13.6%), mobility (13.6%), and flexibility (11.1%) were higher than expected ($p < 0.01$). Significant associations were not identified between treatment exposures and neurocognitive or physical performance outcomes. **Conclusions:** Systematic clinical assessment identified a significant burden of chronic health conditions and previously unrecognized neurocognitive and physical performance limitations in survivors of Wilms tumor. Research Sponsor: U.S. National Institutes of Health.

	Survivors	Controls	p-value
Cardiomyopathy	6.5%	2.6%	**0.01**
Dyslipidemia	7.1%	2.9%	**< 0.01**
Hypertension	19.3%	11.2%	**< 0.01**
Abnormal Glucose Metabolism	8.0%	2.7%	**< 0.01**
Underweight	5.7%	2.2%	**0.03**
Peripheral Neuropathy	8.6%	2.6%	**< 0.01**
Abnormal Pulmonary Function	18.2%	3.2%	**< 0.01**
Chronic Kidney Disease	7.2%	0.6%	**< 0.01**

10039 **Poster Session**

Predicting response to chemotherapy in neuroblastoma using deep learning: A report from the International Neuroblastoma Risk Group. *First Author: Siddhi Ramesh, University of Chicago Pritzker School of Medicine (Chicago, IL), Chicago, IL*

Background: Metaiodobenzylguanidine (MIBG) scans are a radionucleotide imaging modality used to evaluate neuroblastoma stage at diagnosis and also determine disease response following therapy. Curie scoring is used to semi-quantitatively assess disease burden from an MIBG scan on a scale from none (0) to widespread throughout the body (30). While a Curie score $\leq$2 after six cycles of induction chemotherapy has been shown to be prognostic of outcome, there is no established correlation between diagnostic Curie score and outcome. Deep learning models, such as convolutional neural networks (CNN), have been shown to learn generalizable patterns within images for successful classification of metastases and detection of multiple adult cancers. We hypothesized a CNN could be developed to predict response to induction chemotherapy, a proxy for outcome, using diagnostic MIBG scans. **Methods:** DICOM MIBG scans and associated clinical data from a Children's Oncology Group (COG) pilot study for children diagnosed with high-risk neuroblastoma (ANBL12P1; NCT1798004) were deidentified and linked to clinical data by the Pediatric Cancer Data Commons and obtained from the International Neuroblastoma Risk Group Data Commons. Patients were defined as having a poor response to induction chemotherapy if their Curie score after four cycles of induction chemotherapy was $\geq$2. An independent external validation cohort was comprised of 29 images from 26 high-risk patients treated at the University of Chicago with clinically-annotated diagnostic and post-cycle six induction DICOM MIBG scans. The CNN was trained using 2D whole body MIBG scans obtained at diagnosis. We developed the CNN using a transfer learning approach using the Xception architecture as the base layer. Hyperparameter optimization was performed using an 80%-20% train-validation strategy. Model performance was evaluated using area under the receiver operating characteristic curve (AUROC). **Results:** Among 146 patients with high-risk neuroblastoma enrolled on ANBL12P1, 104 had available diagnostic and end-induction MIBG scans. There were no differences in clinical or biological characteristics between included and excluded patients. The base model CNN was able to predict which patients had a poor response to induction chemotherapy with an AUROC of 0.72 in the validation set from the ANBL12P1 cohort. Additionally, the CNN was able to predict patient response to therapy with an AUROC of 0.64 in an independent external dataset from University of Chicago. **Conclusions:** Our study suggests it is feasible to apply machine learning of diagnostic MIBG scans to predict response to chemotherapy for high-risk neuroblastoma patients. Given these promising results, further work to improve AUROC and performance within larger datasets is ongoing. Research Sponsor: U.S. National Institutes of Health.

10040 **Poster Session**

Preclinical evaluation of an engineered oncolytic herpes simplex virus for pediatric osteosarcoma. *First Author: Sara Hutchins, University of Alabama at Birmingham, Birmingham, AL*

Background: Osteosarcoma is the most common primary bone tumor in children. For those with relapsed or metastatic disease, the five-year survival rate is approximately 20%, and survivors often suffer from long-term disability from current therapies. The high morbidity and mortality for these patients highlight a great need for improved therapies. One such novel therapeutic approach is oncolytic herpes simplex virus (oHSV) immunovirotherapy. We previously demonstrated that M002, an engineered oHSV that contains deletions of the neurovirulence gene preventing infection of normal cells, effectively infects and kills neuroblastoma and rhabdomyosarcoma. Currently, similar oHSVs are being evaluated in early phase clinical trials for children and adults with relapsed or refractory brain tumors. To date, there has been limited investigation of oncolytic virotherapy in osteosarcoma. Thus, we sought to examine the ability of oHSV, M002, to infect and kill osteosarcoma cells *in vitro*. **Methods:** We evaluated two long-term passaged human osteosarcoma cell lines, U2-OS and MG-63. Flow cytometry was used to assess baseline expression of oHSV viral entry-mediated receptors (CD111, CD112, syndecan, HVEM). Single and multi-step viral recovery experiments measured virus infectivity and replication. Cells were infected with increasing multiplicity of infection (MOI) of M002, and cell viability was measured 72 hours post-infection via alamarBlue assay. **Results:** Both MG-63 and U2-OS cells expressed HSV entry molecules (Table) including high levels of the primary HSV entry molecule CD111. Single step virus recovery experiments in MG-63 cells infected at a MOI of 10 plaque-forming units (PFU)/cell demonstrated a 3 log-fold increase in virus titer from 12 to 24 hours post-infection. For multi-step experiments, MG-63 cells were infected with a MOI of 0.1 PFU/cell; viral replication significantly increased from $1.1x10^3$ PFU at 6 hours post-infection to $3.8x10^{10}$ PFU at 72 hours post-infection. M002 successfully decreased osteosarcoma viability with a lethal dose in 50% of cells (LD_{50})of 2.82 and0.67 PFU/cell for MG-63 and U2-OS cells, respectively. Notably, at a virus MOI of 5 PFU/cell, viability was decreased by 64% ± 0.1% ($p<0.001$ vs control) in MG-63 cells and 96% ± 0.1% ($p<0.001$ vs control) in U2-OS cells. **Conclusions:** MG-63 and U2-OS osteosarcoma cells express high levels of HSV entry receptors. Virus recovery experiments demonstrated the ability of M002 to infect cells and replicate over time. The viability of osteosarcoma cells significantly decreased following infection with M002. These data suggest M002 may be a promising novel therapeutic option for patients with osteosarcoma and warrant further investigation for translation to the clinical setting. Research Sponsor: Vince Lombardi Cancer Foundation - Bart Starr Award.

	CD111	CD112	Syndecan	HVEM
MG-63	97% (± 0.32%)	89.3% (± 0.54%)	88% (± 0.27%)	84.1% (± 0.24%)
U2-OS	93% (± 0.04%)	44% (± 0.33%)	5.5% (± 0.06%)	12.7% (± 0.1%)

10041 **Poster Session**

Nonhematologic neoplasia in biallelic BRCA2 mutated Fanconi anemia. *First Author: Vasant Chinnabhandar, University of Minnesota, Minneapolis, MN*

Background: Fanconi anemia (FA) is a cancer predisposition disorder. Affected individuals do not tolerate conventional doses of chemotherapy or radiation well. Biallelic BRCA2 mutations cause a rare (~3%) form of FA. Most patients with this subtype have a family history of breast cancer and die in early childhood. Optimal management remains uncertain. Herein, we report the world's largest single center cohort of biallelic BRCA2 patients, with a focus on non-hematologic malignancies. **Methods:** The University of Minnesota's prospectively maintained FA database was analyzed for data on biallelic BRCA2 mutated FA patients. IRB-approved consent was obtained for all subjects. **Results:** Twenty patients with biallelic BRCA2 were identified. Median age of FA diagnosis was 1.5 years (range: 0-16.2 years). All patients had a significant history of cancer in the family with breast cancer being particularly frequent (65%). Eight (40%) patients developed non-hematologic neoplasia before 18 years of age. These included 10 malignant tumors and 4 benign neoplastic lesions; 3 patients had more than one solid tumor (see Table). Surgical resection was attempted in all malignant tumors, dose reduced adjuvant chemotherapy was utilized in 5 cases and radiation in one case. Thirteen (65%) patients developed hematologic malignancies (AML=6, ALL=3, MDS=4), all without preceding marrow failure. Fourteen patients underwent allogeneic HCT. Eleven patients have died, 3 from solid tumors and 5 from leukemias. Nine patients are currently alive, of whom 3 are post-HCT. Only 4 (age range: 6.5-16.3 years) patients in the cohort remain free of any oncologic diagnoses. **Conclusions:** Patients with FA due to biallelic BRCA2 mutations have a unique phenotype with an extraordinarily high risk of early-onset de-novo acute leukemia and solid tumors, often both diagnosed in the same patient. They require extensive, lifelong cancer surveillance from an early age to optimize outcomes. Therapy for malignant diagnoses should aim to minimise exposure to genotoxic / crosslinking agents and radiation. BRCA2 mutation testing in family members and appropriate genetic counselling is essential. Additionally, a family history of BRCA2 mutated cancers should prompt FA testing in offspring with any relevant FA-related clinical findings. Nonhematologic neoplasia and therapy. Research Sponsor: None.

Patient	Non-hematologic neoplasia (Age at diagnosis in years)	Therapy
1.	Wilms tumor (WT) (0.6)	Surgery
2.	WT (6.5)	Surgery
	Rectal adenocarcinoma (16.1)	Surgery + chemotherapy
	Ovarian germ cell tumor (16.8)	Surgery + chemotherapy
3.	Focal hepatic hyperplasia (1.7)	Nil
4.	Medulloblastoma (MB) (1.8)	Surgery + chemotherapy
5.	Neuroblastoma (0.5)	Surgery
	Bilateral retinoblastoma (0.4)	Surgery + radiation
	MB (3.3)	Nil
6.	Hyperplastic nephrogenic rests (0.3)	Surgery
	Low grade brain tumor (1.3)	Nil
	MB (2.7)	Surgery + chemotherapy
7.	Low grade glial neural lesion (0)	Surgery
8.	WT (2.2)	Surgery + chemotherapy

10042 **Poster Session**

Health-related quality of life (HRQoL) among pediatric patients with neurofibromatosis type 1 (NF1) and plexiform neurofibroma (PN) in the United States (U.S.). *First Author: Xiaoqin Yang, Merck & Co., Inc., Kenilworth, NJ*

Background: PNs occur in 30-50% of pediatric patients with NF1, often resulting in debilitating pain and dysfunction. Children with NF1 PN report significantly worse HRQoL than the general population, though real-world evidence is limited. Research is needed to better characterize HRQoL among this patient population in the US. **Methods:** Patients ages 8-18 years with NF1 PN in the US who were treatment naïve or new users of selumetinib (≤1 month of use) were recruited through the Children's Tumor Foundation to participate with their caregivers in an online cross-sectional survey in December 2020 and January 2021. Caregivers of similar patients ages 2-7 years also participated. Measures included the Pediatric Quality of Life Inventory (PedsQL; Acute version), EQ-5D-Y, Pain Interference Index (PII), Numeric Rating Scale (NRS-11), and the Patient-Reported Outcomes Measurement Information System (PROMIS) mobility and upper extremity functioning subscales. Patients provided self-reported responses; caregivers provided proxy responses and patient demographic and clinical characteristics. **Results:** 61 patients and 82 caregivers responded to the survey. Median (range) age of patients was 12.0 (8-14) years, and 53.7% were female. Most were treatment naïve (97.6%), white/Caucasian (85.4%), and had an NF1 and PN diagnosis for > 5 years (80.5% and 68.3%, respectively). On the PedsQL (range: 0-100; higher = better; mean scores typically > 80 among healthy patients), mean patient scores were 50.3 (school functioning), 56.1 (emotional functioning), 60.7 (social functioning), and 63.7 (physical functioning); the mean total score was 58.5.Caregiver-proxy mean scores were similar, ranging from 54.0 for school functioning to 65.0 for physical functioning, with a mean total score of 59.1. On the EQ-5D-Y, more than half of patients reported experiencing "some" or "a lot" of problems with pain or discomfort (65.6%) and with feeling worried, sad or unhappy (62.3%). Among patients with pain in the last 7 days, mean scores on the PII (range: 0-6; higher = more interference) were 3.0 for patients and 2.7 for caregiver proxies. Almost 75% of them reported moderate or severe pain on the NRS-11. Among patients with movement difficulty in the past 7 days, mean t-scores from the PROMIS scales (distribution mean = 50; higher = better) were 40.2 for mobility and 39.5 for upper extremity functioning among patients and 36.0 and 29.1, respectively, among caregivers. Within dyads, patients generally reported better functioning, on average, than their caregiver proxies. **Conclusions:** The humanistic burden of NF1 PN among this pediatric patient population is substantial, especially regarding pain, emotional functioning, and physical functioning. Results highlight an unmet need to be addressed for improving HRQoL in pediatric patients with NF1 and PN. Research Sponsor: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

10043 **Poster Session**

Predicting decreased health-related quality of life (HRQL) in adult survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Fiona Schulte, University of Calgary, Calgary, AB, Canada*

Background: This study examines temporal patterns in HRQL among adult survivors of childhood cancer, and socio-demographic, lifestyle and health status predictors of decline in HRQL. **Methods:** Adult survivors of childhood cancer (4755, 55.2% female, 86.9% non-Hispanic white) completed baseline (T0) and follow-up (T1 in 2003, T2 in 2014) surveys (median[SD] age 32.4[7.5] at T1, time since diagnosis to T1 23.0[4.5], T1-T2 interval 11.7[0.6] years). Socio-demographic (e.g., age, sex, educational attainment, annual family income), lifestyle (physical inactivity, smoking) and health status predictors were collected at T0 and T1. Chronic conditions graded ≥2 by CTCAE defined as presence, and mental and cognitive status with ≥1SD from norms defined as poor. SF-36 Physical and Mental Component Summary (PCS/MCS; mean 50/SD 10) at T1 and T2 classified HRQL as optimal (≥40) or suboptimal (< 40). Multivariable logistic regression identified risk factors (T0, T1 or status change T0-T1) of decreased HRQL (i.e., optimal to suboptimal) using a backward selection method ($p < 0.1$), adjusting for sex, race, age at T1 and years between T1-T2. The sample was randomly split into training (80%) and test (20%) datasets to develop and validate prediction models; Area Under the ROC Curve (AUC) evaluated model performance. **Results:** From T1-T2, 8.1% and 8.3% of survivors reported decreased PCS and MCS. AUCs of training/test models were 0.75/0.74 for decreased PCS and 0.72/0.68 for decreased MCS. Risk factors at T0 or T1 predicting decreased PCS included female sex (OR 1.67, 95%CI 1.25-2.24), younger age (OR 1.04, 95%CI 1.02-1.06), < college/vocational education (OR 1.59, 95%CI 1.02-2.46), family income < $20,000 (OR 2.00, 95%CI 1.21-3.30), obesity (OR 1.97, 95%CI 1.32-2.92), chronic health conditions (neurologic OR 2.47, 95%CI 1.69-3.60; musculoskeletal OR 2.27, 95%CI 1.42-3.64; endocrinological OR 2.25, 95%CI 1.44-3.52; gastrointestinal OR 1.89, 95%CI 1.32-2.69; pulmonary OR 1.66, 95%CI 1.06-2.59; cardiovascular OR 1.53, 95%CI 1.14-2.06) and depression (OR 1.79, 95%CI 1.20-2.67). Risk factors at T0 or T1 predicting decreased MCS included unemployment (OR 1.68, 95%CI 1.19-2.38), smoking (OR 2.03, 95%CI 1.37-3.00), physical inactivity (OR 1.48, 95%CI 1.05-2.09), poor mental health (depression OR 4.29, 95%CI 2.44-7.55; somatization OR 1.63, 95%CI 1.05-2.53) and poor cognitive status (task efficiency OR 1.90, 95%CI 1.34-2.68; organization OR 1.67, 95%CI 1.12-2.48). **Conclusions:** Nearly 10% of childhood cancer survivors have significant late-onset decline in HRQL. Chronic health conditions predict decreased physical HRQL, whereas smoking, physical inactivity and poor mental health predict decreased mental HRQL. Interventions targeting modifiable lifestyle and health conditions should be considered to prevent decreased HRQL for childhood cancer survivors. Research Sponsor: U.S. National Institutes of Health, American Lebanese Syrian Associated Charities (ALSAC).

10044 **Poster Session**

Late morbidity and mortality among survivors of neuroblastoma treated with contemporary therapy: A report from the Childhood Cancer Survivor Study. *First Author: Danielle Novetsky Friedman, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Survival rates for neuroblastoma vary widely based on risk group. Therapies have evolved over the past four decades to de-intensify treatment for individuals with low/intermediate risk disease and intensify therapy for those with high risk disease. Risk stratification is predicted to result in differential outcomes in late morbidity and mortality; the magnitude of these differences has not been well studied. **Methods:** We evaluated late mortality, subsequent malignant neoplasms (SMN) and chronic health conditions (CHC) graded according to CTCAE v4.03 among 491 5-year CCSS survivors of neuroblastoma diagnosed 1987-1999 at ≥1 year of age. Using age, stage at diagnosis, and treatment, survivors were classified into risk groups (low [n=182]; intermediate [n=70]; high [n=239]). Standardized mortality ratios (SMR) and standardized incidence ratios (SIR) of SMN were calculated using rates from NCHS and SEER, respectively. Cox regression models estimated hazard ratios (HR) and 95% confidence intervals (CI) for CHC compared to 1,029 CCSS siblings. **Results:** Among survivors (48% male; median age 22 years, range 7-42; median follow-up 19 years, range 5-29), 80.4% with low risk disease were treated with surgery alone, while 77.8% with high risk disease received surgery, radiation, chemotherapy ± transplant. The 15-year cumulative incidence of all-cause mortality was 9.2% (CI: 7.1-11.4), with a recurrence-related mortality of 7.3% (CI: 5.3-9.3) and SMN-related mortality of 0.3% (CI: 0-0.7). All-cause mortality was significantly higher in all risk groups: (low, SMR=5.8 [CI: 2.6-13.0]; intermediate, SMR=5.7 [CI: 1.4-23.5]; high, SMR=38.6 [CI: 27.9-53.5]). The risk of SMN was elevated among high risk survivors (SIR=25.1, CI: 16.7-37.6), but did not differ from the US population for survivors of low or intermediate risk disease. Table describes the HR of CHCs (grades 1-5 and 3-5) in survivors, by risk group, as compared with siblings, as well as categories of CHCs for which survivors were at increased risk. **Conclusions:** Long-term survivors of neuroblastoma have a high risk of late morbidity and mortality; risk is particularly pronounced among survivors of high risk disease. Vigilant lifelong medical surveillance will be required for this relatively young population as they age. Research Sponsor: U.S. National Institutes of Health.

CHCs in neuroblastoma survivors, by risk group, compared to siblings.

Low	Intermediate	*High*	HR (95% CI)
Any grade 1-5 CHC	2.0 (1.5-2.6)	2.9 (2.0-4.3)	6.9 (5.7-8.2)
Endocrine	3.9 (2.1-7.2)	5.9 (2.9-12.1)	27.7 (17.6-43.5)
Hearing	4.0 (1.7-9.0)	11.3 (4.8-26.3)	17.9 (9.7-32.9)
Gastrointestinal	-	-	21.3 (8.0-56.8)
Cardiac	2.5 (1.3-4.6)	4.7 (1.9-11.7)	10.9 (6.7-17.7)
Renal	-	4.1 (1.8-9.4)	10.8 (6.2-19.0)
Neurologic	2.4 (1.4-4.1)	4.5 (2.3-8.8)	6.1 (4.0-9.2)
Any grade 3-5 CHC	3.0 (1.5-6.3)	10.5 (3.6-30.9)	21.3 (13.5-33.6)
Cardiac	4.1 (1.2-13.5)	12.6 (3.3-47.9)	12.7 (4.6-35.0)

10045 **Poster Session**

Accelerated aging and mortality in long-term survivors of childhood cancer: A report from the St. Jude Lifetime Cohort (SJLIFE). *First Author: AnnaLynn M. Williams, St. Jude Children's Research Hospital, Memphis, TN*

Background: Survivors of childhood cancer have functional limitations and health-related morbidity consistent with an accelerated aging phenotype. We characterized aging using a Deficit Accumulation Index (DAI) which examines the accumulation of multiple aging-related deficits readily available from medical records and self-report. DAI's are used as surrogates of biologic aging and are validated to predict mortality in adult cancer patients. **Methods:** We included childhood cancer survivors (N = 3,758, mean age 30 [SD 8], 22 [9] years post diagnosis, 52% male) and community controls (N = 575, mean age 34 [10] 44% male) who completed clinical assessments and questionnaires and who were followed for mortality through December 31st, 2018 (mean follow-up 6.1 [3.1] years). Using the initial SJLIFE clinical assessment, a DAI score was generated as the proportion of deficits out of 44 items related to aging, including chronic conditions (e.g. hearing loss, hypertension), psychosocial and physical function, and activities of daily living. The total score ranged 0 to 1; scores $>$ 0.20 are robust, while moderate and large clinically meaningful differences are 0.02 and 0.06, respectively. Linear regression compared the DAI in survivors and controls with an age*survivor/control interaction and examined treatment associations in survivors. Cox-proportional hazards models estimated risk of death associated with DAI. All models were adjusted for age, sex, and race. **Results:** Mean [SD] of DAI was 0.17 [0.11] for survivors and 0.10 [0.08] for controls. 32% of survivors had a DAI above the 90th percentile of the control distribution ($p < 0.001$). After adjustment for covariates, survivors had a statistically and clinically meaningfully higher DAI score than controls (β = 0.072 95%CI 0.062, 0.081; $p < 0.001$). When plotted against age, the adjusted DAI at the average age of survivors (30 years) was 0.166 (95% CI 0.160,0.171), which corresponded to 60 years of age in controls, suggesting premature aging of 30 years. The mean difference in DAI between survivors and controls increased with age from 0.06 (95% CI 0.04, 0.07) at age 20 to 0.11 (95% CI 0.08, 0.13) at age 60, consistent with an accelerated aging phenotype ($p = 0.014$). Cranial radiation, abdominal radiation, cyclophosphamide, platinum agents, neurosurgery, and amputation were each associated with a higher DAI (all $p \leq 0.001$). Among survivors, a 0.06 increase in DAI was associated with a 41% increased risk of all-cause mortality (HR 1.41 95%CI 1.32, 1.50; $p < 0.001$). **Conclusions:** Survivors of childhood cancer experience significant age acceleration that is associated with an increased risk of mortality; longitudinal analyses are underway to validate these findings. Given the ease of estimating a DAI, this may be a feasible method to quickly identify survivors for novel and tailored interventions that can improve health and prevent premature mortality. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

10046 **Poster Session**

Determinants of symptom clusters and associations with health outcomes in childhood cancer survivors: A report from the St. Jude Lifetime Cohort (SJLIFE). *First Author: Hyewon Shin, Clemson University, Clemson, SC*

Background: Childhood cancer survivors experience concurrent symptoms, but associations with health outcomes are unknown. We characterize symptom clusters among adult survivors of childhood cancer in SJLIFE and tests associations with health-related quality of life (HRQL) and clinically assessed physical and neurocognitive performance. **Methods:** This cross-sectional study includes survivors diagnosed when $<$18 years of age, ≥10 years off-therapy, and ≥18 years of age at evaluation. Survivors rated 37 symptoms over 10 domains (cardiac, pulmonary, sensory, motor, nausea, pain, fatigue, memory, anxiety, depression), representing 3 broader symptom groups (physical, somatic, psychological). They also underwent a rating of HRQL (SF-36 PCS/MCS) and testing of physical performance (quantitative sensory, motor, endurance, mobility) and neurocognition (processing speed, executive function, attention, memory problems). Latent class analysis determined survivors with distinct symptom burden. Polytomous logistic regression identified risk factors of symptom clusters; multivariable regression tested associations of symptom clusters with health outcomes. **Results:** Among 3,085 survivors, mean [SD] age at evaluation was 31.9 [8.3] years, time from diagnosis was 28.1 [9.1] years, 49.7% were female, 37.1% were treated for leukemia and 33.0% for solid tumors. Four groups of survivors with distinct symptom burden were found: Cluster 1 (52%, low prevalence in all 3 symptom groups); Cluster 2 (16%, low in physical, moderate in somatic, high in psychological); Cluster 3 (18%; high in physical, moderate in somatic, low in physiological); and Cluster 4 (14%, high in all 3 symptom groups). Compared to the lowest symptom burden (Cluster 1), survivors with highest burden (Cluster 4) were significantly more likely to be female (OR 2.5; 95%CI 1.9, 3.4), have below a high school education (OR 7.7; 95%CI 4.5, 13.3), no insurance (OR 1.5; 95%CI 1.1, 2.3) and previous exposure to corticosteroids (OR 1.8; 95%CI 1.0, 3.0). High physical, moderate somatic and low psychological symptom burden (Cluster 3) was associated with below high school education (OR 2.7; 95%CI 1.4, 5.0), exposure to platinum agents (OR 2.2; 95%CI 1.4, 3.7) and brain radiation ≥30Gy (OR 4.0; 95%CI 2.3, 6.9) in contrast to Cluster 1. Survivors in Cluster 4 had the poorest PCS, MCS, physical and neurocognitive outcomes vs in Clusters 2 or 3, whereas those in Cluster 1 had the best outcomes (F-values for 4 clusters: 291.4 [PCS], 269.2 [MCS], 61.5 [physical], 36.9 [neurocognitive], p-values $<$0.001; effect sizes for Clusters 4 vs 1: 0.4-2.0 [4 outcomes]). **Conclusions:** Nearly 50% of survivors belong to symptom clusters with ≥1 moderate/high burden groups, associated with the socio-demographic and treatment exposures. Survivors in the highest symptom burden cluster had the poorest HRQL and functional outcomes. Research Sponsor: U.S. National Institutes of Health.

10047 **Poster Session**

Development and validation of a prediction model for kidney failure in long-term survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Natalie Lucy Wu, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: Kidney failure (need for dialysis or kidney transplantation, or death due to kidney disease) is a rare but serious late effect for survivors of childhood cancer. We aimed to develop a model using demographic and treatment characteristics to predict individual risk of kidney failure among five-year survivors of childhood cancer. **Methods:** CCSS survivors without kidney failure at five years after cancer diagnosis (n = 25,483) were assessed for subsequent kidney failure by age 40. Outcomes were self-reported and corroborated by the Organ Procurement and Transplantation Network and the National Death Index. A sibling cohort (n = 5045) served as a comparator. Piecewise exponential models with backward selection estimated the relationships between potential predictors and kidney failure and were converted to integer risk scores. Additional results from the St. Jude Lifetime Cohort Study (SJLIFE, n = 2490) and the National Wilms Tumor Study (NWTS, n = 6760) validated the models. **Results:** Among CCSS survivors, 204 developed late kidney failure. We developed a model with sex, race/ethnicity, age at cancer diagnosis, nephrectomy, exposure to specific chemotherapy, any abdominal radiation, presence of genitourinary anomalies, and early-onset hypertension (Table). Risk scores achieved an area under the curve (AUC) and concordance (C) statistic of 0.65 and 0.68 for kidney failure by age 40. Validation cohort AUC and C statistics were 0.83/0.86 for SJLIFE (8 cases) and 0.61/0.63 for NWTS (91 cases). An alternative model with specific chemotherapy doses and kidney-specific radiation dosimetry had similar AUC and C statistic (0.67/0.70). Integer risk scores were collapsed to form statistically distinct low (score $<$3; 87 cases of 17,326), moderate (score 3-5; 63 cases of 4667), and high (score 6+; 18 cases of 401) risk groups. These groups corresponded to cumulative incidences in CCSS of kidney failure by age 40 of 0.6% (95% CI 0.4-0.7%), 2.3% (95% CI 1.6-3.2%), and 9.4% (95% CI 4.4-16.7%), compared with 0.2% (95% CI 0.1-0.5%) among siblings. **Conclusions:** Using readily available information, we were able to identify low, moderate, and high risk groups for developing kidney failure following treatment for childhood cancer. These prediction models may help guide screening and interventional strategies for higher risk survivors. Research Sponsor: Childhood Cancer Survivor Study.

Risk scores by variable for kidney failure prediction model*.

Male sex (vs Female)	1
Black, non-Hispanic race/ethnicity (vs Other)	1
Age <10y at cancer diagnosis (vs 10+y)	1
Nephrectomy (vs None)	2
Ifosfamide (vs None)	2
Platinum (vs None)	1
Anthracycline (vs None)	1
Abdominal radiation (vs None)	1
Kidney/bladder/genital anomalies (vs None)	2
Hypertension within 5y of cancer diagnosis (vs None)	4

*Risk scores 0, 1, 2, 3, and 4 correspond to relative risks $<$1.3, 1.3-1.9, 2.0-2.9, 3.0-4.9, and ≥5.0, respectively.

10048 **Poster Session**

Health-related unemployment trends among survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Neel S. Bhatt, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: The impact of treatment era and chronic health conditions on health-related unemployment among childhood cancer survivors has not been studied. **Methods:** Childhood cancer survivors (age ≥25 years) enrolled in the CCSS (3,420 diagnosed in the 1970s, 3,564 in the 1980s, and 2,853 in the 1990s) were matched 1:5 on sex, race/ethnicity, census bureau division, age, and year of survey to the Behavioral Risk Factor Surveillance System (BRFSS), a nationally representative population. Among survivors, health-related unemployment was defined as self-reported unemployment due to illness/disability and for BRFSS participants as self-reported inability to work. To standardize follow-up, health-related unemployment was assessed either in 2002-05 or 2014-16 for both cohorts. Sex stratified standardized prevalence ratio (SPR) and relative SPR (rSPR) with 95% confidence intervals (CI) for health-related unemployment were estimated using multivariable generalized linear models, with BRFSS background rates to assess the impact of treatment era and moderate to severe health conditions (per the Common Terminology Criteria for Adverse Events). **Results:** Prevalence of health-related unemployment in survivors (median age 9 years [range 0-20] at diagnosis and 33 years [25-54] at follow-up) was significantly higher compared to BRFSS participants (females: 11.3% vs 3.7%; SPR 3.0, 95% CI 2.7-3.3; males: 10.5% vs 3.0%; SPR 3.5, 95% CI 3.1-3.9). Health-related unemployment risks declined among survivors in more recent decades ($p_{trend} < 0.001$) for females: 1970s SPR 3.8, 95% CI 3.2-4.5, 1980s SPR 2.9, 95% CI 2.5-3.5, 1990s SPR 2.5, 95% CI 2.1-3.0; and males: 1970s SPR 3.6, 95% CI 2.9-4.4, 1980s SPR 3.8, 95% CI 3.1-4.7, 1990s SPR 3.0, 95% CI 2.5-3.7. Among survivors, multivariable models identified associations between presence of specific health conditions and elevated health-related unemployment (Table) adjusting for all statistically significant health conditions, race/ethnicity, treatment era, age at survey, and diagnosis. Among females, rSPR for endocrine conditions differed between 1970s and 1990s (interaction p = 0.04); fewer significant health conditions remained in the final model for males. **Conclusions:** While prevalence for health-related unemployment has declined over time, childhood cancer survivors remain at higher risk compared to the general population. These elevated risks are associated with chronic health conditions and affect female survivors more than male survivors. Research Sponsor: U.S. National Institutes of Health.

	Female:		Male:	
Health Conditions	rSPR of health-related unemployment	95% CI	rSPR of health-related unemployment	95% CI
Hearing	1.8	1.5, 2.3	1.6	1.3, 2.0
Vision	1.9	1.5, 2.4	1.9	1.4, 2.5
Endocrine, 1970s	1.0	0.7, 1.4	-	-
1980s	1.2	0.9, 1.6	-	-
1990s	1.7	1.2, 2.5	-	-
Respiratory	1.6	1.1, 2.5	-	-
Cardiac	2.2	1.8, 2.7	1.7	1.3, 2.2
Musculoskeletal	2.3	1.7, 3.0	1.8	1.3, 2.5
Neurologic	3.9	3.2, 4.8	4.6	3.6, 5.9

10049 **Poster Session**

Accelerated cognitive decline in adult survivors of pediatric central nervous system (CNS) tumors: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Nicholas Steve Phillips, St. Jude Children's Research Hospital, Memphis, TN*

Background: Survivors of pediatric CNS tumors may be at elevated risk for accelerated cognitive decline as they age through adulthood relative to the general population, which may be an early risk factor for dementia. **Methods:** Longitudinal analysis of 512 CNS tumor survivors (52.3% female, mean [SD] 30.6 [7.1] years at T1) and 232 siblings (57.8% female, mean [SD] 34.2 [8.4] years at T1) from the CCSS was conducted using the Neurocognitive Questionnaire (NCQ) to assess task efficiency, emotional regulation, organization and memory at two timepoints separated by a mean of 11.6 [0.7] years. Impairment in each NCQ domain was defined as a score ≥ 90th percentile of the CCSS sibling distribution at each survey, with decline defined as moving from unimpaired at T1 to impaired at T2. Treatment exposures were abstracted from medical records. Chronic health conditions were self-reported at T1 and graded according to CTCAE v4.3. Relative risk of decline for group, treatment and chronic condition predictors was estimated using generalized linear models with robust variance estimates. Mediation analysis examined direct effects of treatments and mediating effects of chronic conditions. All models were adjusted for age, sex, and race. **Results:** At T1, survivors demonstrated higher frequency of impaired memory (24.5% vs. 6.5%, $p < 0.001$), emotional regulation (14.3 % vs. 5.6%, $p < 0.001$), task efficiency (43.3% vs. 13.8%, $p < 0.001$) and organization (17.7% vs. 10.8%, p = 0.015) than siblings. Among those unimpaired at T1, more survivors vs. siblings declined in memory (34.7% vs. 7.8; RR 4.2, 95% CI 2.6-6.9), emotional regulation (15.5% vs. 5.0%; RR 2.8, 95% CI 1.5-5.3), task efficiency (22.7% vs. 7.0%; RR 2.9, 95% CI 1.7-5.2), and organization (14.5% vs. 2.9%; RR 4.9, 95% CI 2.1-11.0) by T2. Decline in survivor memory was associated with exposure to craniospinal irradiation (RR 1.9, 95% CI 1.3-2.8) and focal irradiation (RR 1.6, 95% CI 1.1-2.3) compared with no radiation, and exposure to Ara-C (RR 1.7, 95% CI 1.0-2.8) and cyclophosphamide (RR 1.7, 95% CI 1.01-2.8). Independent of therapy, serious/disabling or life-threatening cardiopulmonary conditions at T1 predicted future decline in memory (RR 1.5, 95% CI 1.02-2.2) and organization (RR 2.0, 95% CI 1.1-3.6), with the presence of 2 or more cardiopulmonary conditions associated with even higher risk (memory RR 2.6, 95% CI 2.0-3.1; organization RR 3.4, 95% CI 1.1-10.5). Chronic conditions did not mediate associations between treatment exposures and cognitive decline. **Conclusions:** CNS tumor survivors are at elevated risk for impairment and accelerated cognitive decline compared to siblings. Cranial radiation, Ara-C, cyclophosphamide, and cardiopulmonary morbidity are risk factors for decline. Survivors with these exposures/conditions may benefit from interventions to prevent additional future cognitive decline. Research Sponsor: U.S. National Institutes of Health.

10050 **Poster Session**

Psychosocial impacts of the COVID-19 pandemic on young adult cancer survivors and parents of children with cancer. *First Author: Stephanie M Smith, Division of Hematology/Oncology, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA*

Background: The COVID-19 pandemic has affected oncology practice in a variety of ways. We sought to evaluate the impact on pediatric oncology parent and young adult (YA) patient experiences, concerns, and perceived stress. **Methods:** We conducted a cross-sectional Internet-based survey of parents and YA patients in the pediatric oncology and survivorship clinics at Stanford between June-December 2020. Patients were recruited in person by clinic staff or through the electronic patient health portal. Surveys (available in English and Spanish) included the NIH Perceived Stress Scale (PSS-10) and investigator-developed questions evaluating clinical practice changes, concerns about health and cancer care, and pandemic-related challenges. Bivariate analyses evaluated associations between demographic, clinical, and pandemic-related factors and (a) concern about the pandemic affecting health and cancer care, and (b) perceived stress. **Results:** Among 81 participants (66 parents, mean age 41.6 ± SD 9.6; 15 YAs, mean age 21.9 ± 8.4 years), 37% self-identified as Hispanic/Latino, 36% non-Hispanic white, and 21% Asian. Twenty-eight percent were on treatment and 47% had completed treatment (79% < 5 years prior). Thirty percent reported cancer-related appointment changes, largely rescheduling (75%) and/or switching to telehealth (42%). Nearly half (45%) of parents and 27% of YAs reported feeling 'very' or 'extremely' concerned about the pandemic affecting their child's/their health or cancer care. Race/ethnicity emerged as the only demographic feature that was significantly associated with high concern (p = 0.018), with 57% of Hispanic/Latino and only 21% of non-Hispanic white respondents reporting high levels of concern. Specific concerns included fear of severe infection, immunosuppression, and whether infection would change treatment and compromise effectiveness. Parents and YAs reported 'a lot' or 'a great deal' of challenges in their personal/family life (61%) and work/professional life (48%). Among these were having less support from friends/family (35%), reduced wages/work hours (31%), and job loss (20%) with 20% reporting ≥ 3 challenges. On the PSS-10, stress in the past month was high for parents (mean 30 ± 4) and YAs (mean 31 ± 5.1) on a scale of 0-40. Risk factors for higher stress included: male gender (p = 0.028), less support from family/friends (p = 0.002), and experiencing ≥ 3 pandemic-related challenges (p = 0.013). **Conclusions:** Our findings confirm the prevalent worry and stress that pediatric oncology patients and families are experiencing during the COVID-19 pandemic. Better communication about cancer care service changes may help to alleviate some concerns. Supportive care resources may also help patients and families cope with psychosocial stressors, particularly among at-risk groups. Research Sponsor: None.

10051 **Poster Session**

Standardization of fertility preservation discussion amongst pediatric oncology and bone marrow transplant patients. *First Author: Chandni Dargan, Children's Mercy Hospital, Kansas City, MO*

Background: As treatment for pediatric malignancies improves long term survival, physicians are shifting focus to late effects of therapy such as infertility. Currently, options for fertility preservation include cryopreservation of mature oocytes, sperm, and gonadal tissue, although barriers remain present. Within our division, we lacked a standard approach to discussing fertility preservation options. **Methods:** Records from 474 pediatric patients with new oncologic diagnoses at CMH from 2014-2020 were retrospectively reviewed. We evaluated the frequency that reproductive health discussions were documented in pubertal males and females requiring chemotherapy or radiation treatment. We implemented a standard fertility preservation note and patient handouts, then surveyed our department to identify diagnoses that place patients at risk for infertility and barriers to formalized fertility consultations. We then provided educational sessions to address these barriers with pre- and post-evaluation to measure efficacy. Our longitudinal assessment, encompassing multiple points of intervention, was compared to results from previous chart review (2010-2013). **Results:** Of 474 patients diagnosed between 2014-2020, 175 (90 females, 85 males) warranted a fertility discussion per inclusion criteria. 61 (67.8%) females received a fertility discussion and of those 8 (8.9%) completed oocyte or gonadal tissue preservation, all between 2017-2020. 52 (61.2%) males received a fertility discussion and 20 (23.5%) completed sperm cryopreservation, with even distribution pattern between 2014-2020. Following implementation of an electronic fertility consult process and standardized fertility preservation documentation, there was an increase in documented fertility discussions from 30% in 2014 to 63.6% in 2020. Internal department survey responses identified a lack of comfort with knowing fertility preservation options available and diagnoses that should prompt this conversation. Education sessions with pre- and post-provider assessment demonstrated more comfort discussing fertility preservation (average score increase from 3.44 to 4.33) and knowledge regarding diagnoses at higher risk of infertility (average score increase from 3.67 to 4.33). **Conclusions:** Integration of a standardized fertility preservation process and addressing barriers identified within our division have led to a 33.6% increase in fertility discussions over the last 6 years. While the data shows a promising increase in oocyte and ovarian tissue preservation, sperm banking completion rates remained unchanged. Further steps include incorporation of an automated fertility consultation order into electronic chemotherapy orders, hospital-wide identification of other high-risk patient populations, and continued education of patient, families, and the health care team. Research Sponsor: None.

10052 **Poster Session**

Integration and feasibility of symptom burden assessment and early palliative care into an adolescent and young adult leukemia clinic. *First Author: Amy Yuan Wang, University of Chicago Medicine, Chicago, IL*

Background: Patients (pts) diagnosed with hematologic malignancies during adolescence & young adulthood (AYA) are a uniquely challenging population who are understood to have robust supportive care needs. Here, we describe their symptom burdens and the feasibility of integrating palliative care into an outpatient, multi-disciplinary AYA leukemia clinic at an academic medical center. **Methods:** Palliative care was introduced into the AYA clinic in 8/2020 to provide symptom-focused care. Pre-existing clinic services included psychologists, pharmacists, and social workers. All established pts receiving routine follow up were referred by the oncology team to the Supportive Care team, which provided same-day palliative care consultation in the same clinic space with a telehealth option and as needed follow-up. To describe baseline symptom burdens, a random cross-sectional sample of pts completed a multi-domain symptom assessment (SA) using validated self-report instruments including physical (Edmonton Symptom Assessment Scale [ESAS]); emotional (Brief Symptom Inventory-18 [BSI-18]); financial (FACIT-COST); cognitive (Childhood Cancer Survivor Study – Neurocognitive Questionnaire); spiritual (FACIT -Spiritual Well-being Scale); and quality of life (QOL) (FACT-General) measures. All pts have a diagnosis of acute or chronic leukemia and were on active treatment or in survivorship. **Results:** Over 6 months, 30 pts (median age 29 years at assessment, range 18-45 years) received symptom-focused palliative care over 16 combined clinics with 81 total encounters averaging 5 pts (range 1-8) per clinic. 47% were female. No pts declined palliative care. Pts received on average 2.7 follow up visits (range 1-6), with 50% of encounters resulting in adjustments to medical management. Common issues addressed included pain, muscle cramps, neuropathy, anxiety, insomnia, depression, nausea, and non-pharmacological symptom control remedies. Of 46 pts, 31 (67%) completed the SA (median age 30 years at assessment, range 18-43 years); 48% were female; 84% were on treatment. 100% of pts reported fatigue, and 48% reported $> = 1$ severe symptom (range 0-7) based on the ESAS with "poor feeling of well-being" as the most common (23%). 45% met criteria for BSI-18 emotional distress, and 45% reported some neurocognitive impairment. Emotional distress ($p < 0.01$), financial toxicity ($p = 0.03$), low spiritual well-being ($p < 0.01$), and presence of pain, nausea, or depression ($p < 0.05$) were all associated with lower QOL. **Conclusions:** AYA pts with leukemia undergoing treatment and in survivorship experience high symptom burden with poor QOL. It is feasible to both assess symptom burden and provide early palliative care focused on symptom management in an outpatient, multi-disciplinary clinic setting. Research Sponsor: None.

10053 **Poster Session**

Assessment of physician perceptions of pediatric palliative care for children with cancer in Latin America. *First Author: Michael McNeil, St. Jude Children's Research Hospital, Memphis, TN*

Background: While great strides have transpired in pediatric cancer management in high-income countries (HICs), more than 80% of all children with cancer live in low- and middle-income countries (LMICs),where fewer than 20% will be cured. The World Health Organization (WHO) has stated that early integration of palliative care is an ethical responsibility in the management of children with life-limiting illness. While structural barriers impact the ability to deliver pediatric palliative care (PPC), underlying stigma also prevents early integration of PPC. **Methods:** The Assessing Doctor's Attitudes on Palliative Treatment (ADAPT) survey was created for physicians of all specialties who care for children with cancer, initially used in Eurasia. Survey questions evaluated provider perceptions on timing of palliative care integration, scope of palliative treatment, physician responsibility, and ethical issues. This survey was adapted for use in Latin America, including translation to Spanish and reviewed by regional palliative care specialists for syntax, comprehension, and cultural relevance. The survey was then distributed to physicians treating children with cancer in the region. To assess provider's perspectives on palliative care, we used fifteen statements from the WHO 2018 guidelines, describing general palliative care principles. Results are reported as percent of alignment with guidelines. **Results:** A total of 1,039 participants from 16 countries in Latin America completed the survey, with a median country response rate of 66% (range 26%-100%). Thirty-six specialties were represented with 34% general pediatricians and 23% pediatric hematologist/oncologists. The majority (59%) had received no PPC training and 37% had no access to PPC experts for consultation in their practice setting. On average, provider's perspectives on PPC were aligned with the WHO guidelines (81% alignment, range 53%-96%). However, almost half (42%) felt that the integration of pediatric palliative occurred too late in the course of treatment. Additionally, less than half (47%) of respondents felt comfortable addressing the physical symptoms of their patients, 33% felt comfortable addressing emotional symptoms, and only 26% felt comfortable addressing grief and bereavement for the patient's family. The most common barriers identified were a lack of home-based services (87%), a lack of physician knowledge on the role of PPC (84%), and physician discomfort in discussing palliative care with families (81%). Nearly all (95%) wanted more training in PPC. **Conclusions:** Most physicians who completed the survey were not confident in providing symptomatic and supportive care for their patients and families. This study will guide targeted interventions for education in PPC for physicians in Latin America as well as interventions to address barriers which impede earlier palliative care integration in the region. Research Sponsor: None.

10054 **Poster Session**

Lessons from COVID-19, challenges of remote learning for childhood cancer survivors. *First Author: Kathy Ruble, Johns Hopkins University, Baltimore, MD*

Background: More than half of childhood cancer survivors (survivors) will have neurocognitive deficits that impact schooling, most commonly reflecting attention and executive dysfunction. Schools are legally bound (IDEA, 2004) to support eligible students with Individualized Education Program (IEP) informed instruction and related services (e.g. assistive technology, speech-language, physical, or occupational therapy) to foster academic success. However, these service provision were not designed under the constraints of remote learning. The COVID19 shift to remote learning is likely to extend beyond the pandemic especially for medically fragile students. This quality improvement project describes challenges for survivors during remote learning and recently developed related patient education materials. **Methods:** Interviews with families were used to identify themes around challenges during remote learning, which informed development of a 29-question survey disseminated via flyer in local oncology clinics and social media posts by local childhood cancer organizations in Fall 2020. **Results:** The survey was completed by 67 parents describing their affected child (mean age= 8.6 years; 60% male; 78% White, 12% Black, 95% non-Hispanic). Most children (74%) had completed therapy (43% for leukemia, 18% for brain tumor; 39% other). The majority (86%) attended public school and 37% received special education or related services: speech-language (26%), occupational (23%), and physical (14%) therapies, and vision services (3%). Fully remote learning was reported for 73%, in-person 4%, and hybrid learning for 14%. The majority (57%) reported observing greater difficulty with attention and focus during RL, indicating difficulty occurred about half of the time during related services therapies, class and/or small group video instruction. Technology-related challenges included difficulty navigating online instruction/equipment (28%), reading difficulty (16%), and difficulty seeing materials/lack of vision supports (18%). Findings did not differ based on treatment or IEP status ($p>0.50$). Few (14%) reported their school team discussed assistive technology options for online learning. Parents indicated the most helpful supports for addressing challenges included speech-to-text tools, screen readers, and audio books. Parents reported their oncology team was helpful in making referrals to neuropsychology and therapies and completing documentation necessary to secure supports. **Conclusions:** Childhood cancer survivors, irrespective of diagnosis or IEP status, report challenges with remote learning. Families find a lack of information or special accommodations as roadblocks to success. Oncology providers were identified as valued resources, so educational materials (https://tinyurl.com/nxbhj5or) were developed for oncology teams to share with families. Research Sponsor: Patient Centered Outcomes Research Institute (PCORI).

TPS10055 **Poster Session**

Phase II study of nivolumab and ipilimumab in children and young adults with INI1-negative cancers. *First Author: Suzanne J. Forrest, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Several aggressive pediatric and young adult cancers are characterized by *SMARCB1* inactivation resulting in loss of INI1 expression, including rhabdoid tumors, epithelioid sarcoma and undifferentiated chordoma. These malignancies are associated with a poor prognosis and few effective treatment options for relapsed or refractory disease. Prior studies and emerging data suggest INI1-negative cancers may be uniquely susceptible to treatment with immune checkpoint inhibitors: Many INI1-negative pediatric tumors express PD-L1 and are infiltrated by immune cells, and there are reports of patients with advanced INI1-negative cancers with clinical responses to immune checkpoint blockade (Forrest et al. Clinical Cancer Research, 2020). We hypothesize that INI1 loss predicts tumor response to immune checkpoint inhibition (ICI). **Methods:** This is an ongoing multicenter, phase II, open-label clinical trial to evaluate the activity of nivolumab and ipilimumab in patients aged 6 months to 30 years with relapsed or refractory INI1-negative cancers (NCT04416568). The study enrolls patients in 2 strata: extracranial solid tumors in Stratum 1 and intracranial solid tumors in Stratum 2. Patients treated with prior ICI are excluded. Patients are treated with intravenous (IV) nivolumab 3mg/kg plus ipilimumab 1mg/kg IV every 3 weeks for 4 cycles followed by nivolumab 3mg/kg (max dose 240mg) IV every 2 weeks for up to 1-year. The primary objective is to evaluate the objective response rate (ORR) by Response Evaluation Criteria in Solid Tumors (RECIST) for Stratum 1 and by Response Assessment in Neuro-Oncology (RANO) criteria for Stratum 2. The trial has a 2-stage design targeting a 25% or greater response rate, with each stratum assessed independently. The analysis for Stage 1 in a given Stratum will be performed after 10 patients are enrolled. If a sufficient number of responders are observed, an additional 10 patients will be enrolled at Stage 2. Secondary endpoints include progression-free survival, overall survival, and disease control rate at 12 months. Correlative aims include assessing tissue and blood biomarkers associated with treatment response. Enrollment began 14 Aug 2020 and is ongoing. Clinical trial information: NCT04416568. Research Sponsor: Gateway for Cancer Research, Philanthropic funding.

TPS10056 **Poster Session**

FIREFLY-1: A phase 2 study of the pan-RAF inhibitor DAY101 in pediatric patients with low-grade glioma. *First Author: Lindsay Baker Kilburn, Children's National Hospital, Washington, DC*

Background: The mitogen-activated protein kinase (MAPK) signaling pathway is an essential pathway that regulates key cell functions such as growth, survival, and differentiation. Genomic alterations and dysregulation of the MAPK pathway including BRAF fusions, point mutations (e.g. BRAF V600) and in-frame deletions have been described in many different types of malignancies, including pediatric low-grade glioma (pLGG) and other pediatric cancers. The identification of the KIAA1549:BRAF fusion in 2008 led to deeper understanding of the genomic events driving growth of pLGG (Jones, Cancer Res 2008). Despite the low-grade histology and excellent long-term survival, pLGGs are often associated with tumor- and treatment-associated morbidity and significant late-effects that persist throughout the lifespan of the patient. DAY101 is an oral, highly selective, CNS-penetrant small-molecule, Type II pan-RAF kinase inhibitor that is being developed for patients with pLGG harboring an activating BRAF-alteration. DAY101 has demonstrated tumor inhibition in preclinical models and has achieved clinically meaningful and durable responses in 7/8 patients with RAF-altered LGG in a pediatric phase 1 trial, including 2 complete responses, 3 partial responses, 2 stable disease and 1 progressive disease with a median time to response of 10.5 weeks. Patients have been treated for up to two years with no discontinuations due to toxicity or disease progression (Wright, SNO 2020). **Methods:** FIREFLY-1 is an open-label, multi-center, international Phase 2 study with DAY101 in pediatric and young adult patients between the ages of 6 months and 25 years with LGG harboring a documented BRAF-alteration as determined by local laboratory testing. DAY101 is administered orally once a week on a continuous 28-day schedule. Patients who respond will be treated for a minimum of two years after which they may at any point, opt to enter a "drug holiday" discontinuation period. Dosing is based on body surface area. DAY101 is available in a pediatric-friendly oral liquid formulation and tablets. The primary endpoint is objective response rate based on Response Assessment for Neuro-Oncology (RANO) as determined by an independent review committee. Secondary endpoints include objective response rate based on Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group criteria, duration of response and safety. Exploratory endpoints include quality-of-life measurements as well as functional outcomes. Molecular abnormalities will be characterized through the analysis of archival tissue. Enrollment began in February 2021 and is ongoing. Clinical trial information: NCT03429804. Research Sponsor: DOT-Therapeutics 1.

10500 **Oral Abstract Session**

Breast cancer screening for carriers of ATM, CHEK2, and PALB2 pathogenic variants: A comparative modeling analysis. *First Author: Kathryn P. Lowry, University of Washington, Seattle Cancer Care Alliance, Seattle, WA*

Background: Inherited pathogenic variants in ATM, CHEK2, and PALB2 confer moderate to high risks of breast cancer. The optimal approach to screening in these women has not been established. **Methods:** We used two simulation models from the Cancer Intervention and Surveillance Modeling Network (CISNET) and data from the Cancer Risk Estimates Related to Susceptibility consortium (CARRIERS) to project lifetime breast cancer incidence and mortality in ATM, CHEK2, and PALB2 carriers. We simulated screening with annual mammography from ages 40-74 alone and with annual magnetic resonance imaging (MRI) starting at ages 40, 35, 30, and 25. Joint and separate mammography and MRI screening performance was based on published literature. Lifetime outcomes per 1,000 women were reported as means and ranges across both models. **Results:** Estimated risk of breast cancer by age 80 was 22% (21-23%) for ATM, 28% (26-30%) for CHEK2, and 40% (38-42%) for PALB2. Screening with MRI and mammography reduced breast cancer mortality by 52-60% across variants (Table). Compared to no screening, starting MRI at age 30 increased life years (LY)/1000 women by 501 (478-523) in ATM, 620 (587-652) in CHEK2, and 1,025 (998-1,051) in PALB2. Starting MRI at age 25 versus 30 gained 9-12 LY/1000 women with 517-518 additional false positive screens and 197-198 benign biopsies. **Conclusions:** For women with ATM, CHEK2, and PALB2 pathogenic variants, breast cancer screening with MRI and mammography halves breast cancer mortality. These mortality benefits are similar to those for MRI screening for BRCA1/2 mutation carriers and should inform practice guidelines. Research Sponsor: Breast Cancer Research Foundation, U.S. National Institutes of Health.

	Mortality Reduction Mean (Range)			Life Years Gained per 1000 Women Mean (Range)			False Positive Screens per 1000 Women Mean (Range)		
Strategy	ATM	CHEK2	PALB2	ATM	CHEK2	PALB2	ATM	CHEK2	PALB2
Mammography at 40	38% (38-39%)	38% (38-39%)	36% (35-38%)	291 (263-319)	370 (330-409)	621 (559-684)	2,224 (2,222-2,227)	2,174 (2,172-2,175)	2,092 (2,085-2,099)
+MRI at 40	54% (53-54%)	54% (53-54%)	52% (51-53%)	420 (388-452)	533 (489-577)	921 (876-967)	4,569 (4,555-4,583)	4,441 (4,438-4,443)	4,233 (4,213-4,252)
+MRI at 35	58% (57-58%)	57% (56-58%)	54% (54-55%)	473 (447-498)	591 (555-627)	992 (959-1,025)	5,001 (4,979-5,023)	4,871 (4,861-4,880)	4,661 (4,635-4,688)
+MRI at 30	59% (58-60%)	58% (57-60%)	55% (55-55%)	501 (478-523)	620 (587-652)	1,025 (998-1,051)	5,415 (5,393-5,437)	5,284 (5,249-5,319)	5,075 (5,057-5,093)
+MRI at 25	60% (59-61%)	59% (58-60%)	56% (55-56%)	510 (489-531)	630 (599-661)	1,037 (1,013-1,061)	5,932 (5,907-5,957)	5,802 (5,789-5,815)	5,592 (5,563-5,621)

10501 **Oral Abstract Session**

Nearly half of *TP53* variants are misattributed to Li-Fraumeni syndrome: A clinical evaluation of individuals with *TP53* variants detected by hereditary cancer panel assays on blood or saliva. *First Author: Alison Schwartz, Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Boston, MA*

Background: Multigene panel testing (MGPT) has identified *TP53* pathogenic or likely pathogenic (P/LP) variants in patients with diverse phenotypes from no cancer to classic Li-Fraumeni syndrome (LFS). There is increasing recognition of variants at low allelic fraction (VAF) for *TP53* in particular, which can be suggestive of post-zygotic mosaicism or aberrant clonal expansion (ACE), comprising clonal hematopoiesis of indeterminate potential (CHIP) or occult hematologic neoplasia. Distinguishing among these categories is essential because of widely different cancer risk and management implications for patients and their relatives. We report an evaluation of *TP53* positive probands to determine germline versus somatic status from a cancer genetics clinic. **Methods:** We reviewed probands with *TP53* P/LP variants by MGPT on blood (N = 83) or saliva (N = 1) samples from 2012-2019. Available VAFs were collected from commercial testing laboratories. Probands positive for a known familial variant, who met LFS testing criteria without indication of low VAF, or who carried the Brazil founder p.R337H variant were considered germline. For those with uncertain germline status, data was obtained from ancillary testing of family members, cultured skin fibroblasts, and other somatic benign or tumor tissues. *TP53* variants were further categorized based on all available data. **Results:** Of the 84 probands, 28 (33%) had germline *TP53* P/LP variants determined by above initial criteria; 18 (21%) were confirmed germline through ancillary testing. Seven (8%) individuals were classified as having constitutional mosaicism. In eleven (13%) individuals, the *TP53* variants were consistent with ACE, in 9 (11%) with CHIP and in 2 (2%) with a hematologic malignancy (1 CLL, 1 NHL). Five (6%) cases could not be categorized despite ancillary testing. Fifteen (18%) probands declined any further workup. **Conclusions:** A *TP53* P/LP variant found on peripheral blood or saliva MGPT does not always originate in the germline. In a clinical cancer genetics cohort, only 54% of patients had *TP53* P/LP germline variants; these patients plus those with constitutional mosaicism (8%) require intensified surveillance. Assessment of VAF, family member testing, and analysis of *TP53* in cultured fibroblasts or other tissue samples may distinguish germline and constitutional mosaicvariantsfrom the ACE spectrum. Expanding use of MGPT will increase this clinical challenge, which may motivate the modification of lab reports to include VAF and possible non-germline explanations. The findings of this study support a framework of multiple strategies to discern true constitutional status of a *TP53* P/LP variant. Research Sponsor: None.

10502 **Oral Abstract Session**

Ancestrally unbiased polygenic breast cancer (BC) risk assessment. *First Author: Elisha Hughes, Myriad Genetics, Inc., Salt Lake City, UT*

Background: BC risk is influenced by single-nucleotide polymorphisms (SNPs) with small effects that can be aggregated into polygenic risk scores (PRSs). PRSs have primarily been developed and validated for populations of European descent. To make a PRS available for all women, we developed and validated a novel global PRS (gPRS) that utilizes individual ancestral genetic composition. **Methods:** Ancestry-specific PRSs corresponding to 3 continental ancestries were developed from 149 SNPs (93 BC and 56 ancestry-informative): an African PRS was developed using a cohort of 31,126 self-reported African American patients referred for hereditary cancer testing; an East Asian PRS was developed based on published data from the Asia Breast Cancer Consortium; and a European PRS was developed using data from the Breast Cancer Association Consortium and 24,259 European hereditary cancer testing patients. For each patient, ancestry-informative SNPs were used to calculate the fractional ancestry attributable to each of the 3 continents. The gPRS was the sum of ancestry specific PRSs weighted according to genetic ancestral composition. In an independent validation cohort (N = 62,707), we evaluated discrimination and calibration of gPRS, and compared performance against a previously described 86-SNP PRS for women of European ancestry. Associations of SNPs and PRSs with BC were analyzed using logistic regression adjusted for personal and family cancer history, age, and ancestry. Odds ratios (ORs) are reported per standard deviation within the corresponding patient population. P-values are reported as two-sided. **Results:** The gPRS was strongly associated with BC in the full validation cohort and in sub-cohorts defined by self-reported ancestry (Table). 95% (88/93) of BC SNPs had $\geq$1% frequency of risk alleles within each of the self-reported populations. Compared to the aforementioned 86-SNP PRS, the gPRS showed improved discrimination overall, and within each sub-cohort, with the exception of the Asian population where the sample size was too small to show superiority of either score. The 86-SNP PRS was calibrated for white non-Hispanic women but mis-calibrated for non-European ancestries. The gPRS was properly calibrated for all women. **Conclusions:** The 149-SNP gPRS is validated and calibrated for women of all ancestries. Combined with clinical and biological risk factors, this approach may offer improved risk stratification for all women, regardless of ancestry. Research Sponsor: Myriad Genetics, Inc.

Validation Cohort	Total N	N w/ BC	OR (95% CI)	P-value
All	62,707	15,137	1.41 (1.38 – 1.44)	2.5×10^{-212}
Asian	1,325	396	1.25 (1.07 - 1.45)	3.7×10^{-03}
Black/African	6,743	1,754	1.23 (1.16 - 1.31)	8.5×10^{-11}
Hispanic	5,847	1,066	1.35 (1.24 - 1.46)	1.6×10^{-13}
Mixed Ancestry	2,681	400	1.59 (1.39 -1.82)	2.4×10^{-12}
Non-European	14,959	3,435	1.29 (1.23 –1.36)	2.5×10^{-25}
White and/or Ashkenazi	42,897	10,288	1.44 (1.40 – 1.48)	6.3×10^{-172}

10503 **Oral Abstract Session**

Adrenal-permissive *HSD3B1* genetic inheritance and risk of estrogen-driven postmenopausal breast cancer. *First Author: Nima Sharifi, Cleveland Clinic, Cleveland, OH*

Background: Genetic factors that contribute to endogenous estrogen synthesis and postmenopausal breast cancer risk are unknown. We set out to test the hypothesis that homozygous inheritance of the common 1245A→C missense-encoding polymorphism in *HSD3B1*, which is common (8-10%) in White populations, functionally adrenal permissive and increases synthesis of the aromatase substrate, androstenedione, is associated with postmenopausal estrogen receptor-positive breast cancer. **Methods:** A prospective single institution study of postmenopausal estrogen receptor-driven breast cancer for determination of *HSD3B1* genotype, circulating steroid concentrations, and adrenal-permissive genotype frequency compared with the genotype frequency in the general population and in estrogen receptor-negative breast cancer. Validation was performed in 2 breast cancer genomic studies with estrogen receptor documentation. The primary outcome is the adrenal-permissive genotype frequency in postmenopausal estrogen receptor-positive breast cancer and the general population. Genotype comparisons were also done with postmenopausal estrogen receptor-negative breast cancer and the association with circulating adrenal androgen concentrations determined. **Results:** The prospective and validation studies had 199 and 1628 women, respectively. The adrenal-permissive genotype frequency in postmenopausal White women with estrogen-driven breast cancer in the prospective cohort was 17.5% (21/120) compared with 9.6% (429/4451) in the general population [p = 0.0077]. The adrenal-permissive genotype frequency for estrogen-driven postmenopausal breast cancer was validated using the Cambridge and TCGA genomic datasets together: 14.4% (56/389) compared with 6.0% (9/149) for estrogen receptor-negative breast cancer (p = 0.007) and the general population (p = 0.005). Circulating androstenedione concentration was significantly higher for women with the adrenal-permissive genotype compared with the other genotypes (p = 0.03). **Conclusions:** The adrenal-permissive genotype is associated with estrogen-driven postmenopausal breast cancer. These findings link genetic inheritance of endogenous estrogen exposure to estrogen-driven breast cancer and have broad implications for risk stratification, prevention, potential biomarkers for hormonal therapy response and possibly other clinical outcomes related to estrogen physiology in postmenopausal women. Research Sponsor: U.S. National Institutes of Health.

10504 **Oral Abstract Session**

Underdiagnosis of germline genetic prostate cancer: Are genetic testing guidelines an aid or an impediment? *First Author: Edward D. Esplin, Invitae, San Francisco, CA*

Background: Pathogenic/likely pathogenic (P/LP) germline genetic variants are estimated to occur in 10-15% of all prostate cancer (PCa) patients. However, genetic testing for PCa patients is underutilized, partially due to complicated and restrictive testing guidelines developed at a time when the cost of testing was high. We conducted a study based in community urology clinics to determine the incidence of P/LP variants in PCa patients who met and did not meet the NCCN 2019 PCa germline genetic testing criteria. **Methods:** An IRB-approved, multicenter, prospective registry was initiated with 15 community and academic urologists nationwide. Eligibility criteria included patients with a PCa diagnosis unselected for personal or family history, stage or histology who had not been previously tested. Consecutive patients ages 18-90 were consented and underwent an 84-gene germline panel test. HIPAA-compliant electronic case report forms distributed to clinician collected information on patient diagnoses, NCCN testing criteria, and results-based recommendations. **Results**: To date, 640 enrolled patients have genetic testing results available. Overall, 69 (10.8%) patients had 72 P/LP variants detected, 15% of which were in *BRCA1/2*. Of the 532 patients for whom we have clinician-reported data, 293 (55%) met NCCN criteria and 239 (45%) did not. Median age was 70 (range 44-90). Overall, 11.1% (59/532) of patients with clinician-reported data had a P/LP variant. 36 (12.3%) of patients who met NCCN criteria and 23 (9.6%) of patients who did not meet criteria had a P/LP variant. The difference in P/LP rate between the two groups was not statistically significant (p=0.33). If only a conservative 12-gene PCa panel was considered, P/LP yield was 5.5% (29/532), with 8 (28%) of these patients missed by guidelines. Stratification by self-reported ethnicity was: 76% White/Caucasian (52 patients w/ P/LP), 18% Black/African American (2 patients w/ P/LP), and <5% each of Hispanic or Asian. **Conclusions**: There was no statistically significant difference in the yield of P/LP variants between patients who met and those who did not meet NCCN PCa guidelines, reinforcing that a significant number of P/LP variants are missed if NCCN guidelines are required for genetic testing. Expanded panel testing yields more medically actionable P/LP variants than testing *BRCA1/2* alone or PCa panels with 12 genes. While 18% of the cohort was Black/African American, there was a lower P/LP rate (2%) relative to other groups, indicating that more research is needed to understand genetic variation in underrepresented populations with PCa. Research Sponsor: Invitae.

10505 **Oral Abstract Session**

Germline mutations in DNA damage repair genes and *HOXB13* among African American men diagnosed with early-onset prostate cancer. *First Author: Jennifer Lynn Beebe-Dimmer, Barbara Ann Karmanos Cancer Institute/Wayne State University, Detroit, MI*

Background: Inherited defects in DNA damage repair (DDR) genes (e.g. *ATM, BRCA1/2*) and the tumor suppresser gene *HOXB13* are rare in the general population, but have been observed at a higher rate among men with early-onset and advanced prostate cancer. However, most studies include few, if any, African American men, highlighting the need to understand the contribution of mutations in these genes in this high-risk population. **Methods:** A population-based cohort of 757 African American men diagnosed with prostate cancer at age 62 years or younger were identified and enrolled through the Metropolitan Detroit Cancer Surveillance System (MDCSS), one of NCI's founding members of the SEER program. Participants completed a short survey to collect information on family history, medical history (including cancer-related treatment), surveillance, and health behaviors. Each participant submitted a saliva or blood sample for genetic analyses and consent for tumor tissue if available. All clinical data were collected through linkage with the MDCSS registry. Full exome sequencing was performed and herein, we report the mutation patterns observed in a panel of DNA repair genes and *HOXB13*. All variants were ranked according to frequency (MAF < 1%); REVEL, SIFT and PolyPhen scores for pathogenic potential; evidence from existing literature; and prevalence in the cohort. **Results:** Among the 744 African American prostate cancer cases with adequate DNA for sequencing and thus included in this analysis, the mean age at diagnosis was 55.6 years, 29% reported a family history of prostate cancer in a first degree family member, and 40% were initially diagnosed with intermediate- to high-risk disease (stage T3/T4 and/or Gleason 4+3 and higher at diagnosis). We identified 20 variants that were either known or predicted to be pathogenic in 11 candidate genes (*ATM, ATR, BRCA1/2, BRIP1, CHEK2, FANCA, HOXB13, MSH2, PALB2, and PMS2*). These particular variants were more common among men diagnosed before age 55 and in men with high grade cancer in this cohort. **Conclusions:** Our results suggest that mutations in DDR genes and *HOXB13* may be important cancer risk factors for African American men diagnosed with early-onset and intermediate- to high-risk disease. Further study is necessary to describe the spectrum and prevalence of genetic mutations in this population including the characterization of variants of unknown significance. Research Sponsor: Department of Defense.

10506 **Oral Abstract Session**

Completion of lung cancer screening after a baseline order for LDCT at five diverse health systems. *First Author: Christine Neslund-Dudas, Henry Ford Health System, Detroit, MI*

Background: In 2014 and 2015, the Affordable Care Act required coverage of, and CMS began reimbursing for lung cancer screening (LCS). Previous studies have shown that when new screening tests or treatments become available, disparities in disease outcomes often increase due to those with fewer resources having less access and greater barriers to care. African American men have historically had higher incidence of and death due to lung cancer than white males in the U.S., raising concerns regarding access to LCS and the potential for increases in disparities in lung cancer. We aimed to determine whether individual or neighborhood level factors were associated with completion of a baseline screening after an order for LCS low dose CT (LDCT) was placed. **Methods:** In a retrospective study conducted within the five health systems of the Lung Population-based Research to Optimize the Screening Process (PROSPR) Consortium, we determined adherence to baseline LDCT after a health care provider placed an order for LCS (January 2014 through June 2019). Follow-up was available through September 2019. Patients of interest for this analysis were current or former smokers, age 55 to 80 with a 30+ pack-year smoking history. Smoking history and other individual level variables were determined through electronic medical records. Neighborhood factors were derived from the 2010 Census and multivariable logistic regression was used. **Results:** Of the 13,920 patients that had at least one order for a baseline LCS exam, 14.1% were non-Hispanic Black, 70.3% were non-Hispanic White, and 15.7% were of other or unknown race. Overall, 61.2% of patients completed a LDCT within 90 days and 71.9% completed a scan by the end of follow-up. Completion of a baseline scan differed by health system (LDCT at 90-days, range 51% - 84%, p<0.0001) and increased in general across scan year (range 49.1%-66.0%, p <0.001). In multivariate logistic regression models, males (aOR=1.15, 95% CI 1.07-1.23, p=<0.0001), former smokers (aOR=1.31, 95% CI 1.21-1.40, p <0.0001), and those with a prior history of any cancer (aOR=1.16, 95% CI 1.02-1.32, p=0.03) were more likely to complete LDCT. Blacks were marginally less likely to have completed a baseline LDCT (aOR=0.90, 95% CI 0.81-1.00, p=0.06) within 90 days of an order. Sex modified the associations of race on completion of orders (p=0.08) (Black men aOR=0.81, 95% CI 0.70-0.94, p=0.006 ; Black women aOR=0.99, 95% CI 0.86-1.14, p=0.89). **Conclusions:** This multisite study indicates Black men in particular may have a lower likelihood of completing a baseline LCS after an order for screening is placed. As lung cancer screening programs move forward, attention should be given to factors associated with reduced uptake and adherence of screening to ensure disparities in lung cancer outcomes do not persist and increase. Provider and health system factors that may impact LCS uptake should be explored in future studies. Research Sponsor: U.S. National Institutes of Health.

10507 **Oral Abstract Session**

Second primary malignancies (SPM) in African American (AA) and white patients with multiple myeloma in the National Veterans Affairs (VA) healthcare system. *First Author: Sarah Premji, Baylor College of Medicine, Houston, TX*

Background: In the recent decade, novel therapies have led to significant improvements in overall survival (OS) in symptomatic multiple myeloma (MM). With this increase in OS, there is an increase in the incidence of second primary malignancies (SPM) in patients with MM. This is related to multiple factors; we hypothesize that racial disparities also play a role. There is a paucity of studies with large, high quality datasets evaluating racial disparities in SPMs in MM. Our goal is to explore patterns of incidence of SPMs in US Veterans with MM, focusing on racial disparities. **Methods:** We conducted a retrospective cohort study based on electronic health record (EHR) and cancer registry data recorded in the VA's Corporate Data Warehouse (CDW) between January 1, 1999 and January 1, 2018. We compared incidence of SPMs (defined as malignancies occurring after the diagnosis and treatment initiation of MM) using the standardized incidence rate ratio (IRR). Univariate and multivariable analyses were performed, using a Cox model adjusting for age, race, gender, treatment era, smoking status, and stage at MM diagnosis. **Results:** There were 8467 Veterans (97.4% male) with MM identified with self-reported race: White, 5029 (59.4%); AA, 2178 (25.7%); and other or unknown, 1260 (14.9%). At 7.5 years of follow up, 430 (5.1%) MM patients developed SPM while 8037 did not. 982 had received HSCT (Hematopoietic Stem cell transplant) of whom 65 (6.62%), a significantly higher proportion developed SPM versus those without HSCT (n = 7485) of whom 365 (4.87%) developed SPM (p = 0.024). Among those Veterans who had SPM 380 (88.3%) had solid tumors, 50 (11.6 %) had hematological malignancies. Of 88.3% with solid SPM the distribution was: prostate cancer, 113 (29.7%); digestive tract cancers, 63 (16.6%); lung cancer, 55 (14.4%); and GU (bladder/renal/testicular), 48(12.6%). The cumulative incidence of developing SPM increased steadily over time for the duration of this study period of 7.5 years from diagnosis. The median age of diagnosis for Whites was 68.2 years and for AA was 64.3 years, (p < 0.001) demonstrating that MM occurred earlier in AA. The hazard ratio for AA versus whites to develop SPMs was 1.21 (0.975-1.505) (p = 0.0823). However, the risk of prostate cancer was significantly higher in AA with an adjusted hazard ratio of 1.81 (1.196-2.739) (p = 0.005). No racial disparities were observed in the incidence of other types of SPMs. **Conclusions:** Our study suggests that the risk of SPMs does not plateau over a patient's lifetime. HSCT was found to be an independent predictor of SPM, while smoking and agent orange were not. Our cohort is one of the largest groups of AA with MM in published literature. AA did not have a higher incidence of SPMs overall; but had a significantly higher incidence of prostate cancer than whites. We hope to develop an individualized predictive model for SPM in patients with MM. Research Sponsor: Veterans Affairs.

10508 **Oral Abstract Session**

Disparities in pan-cancer patients undergoing germline cancer risk assessment by self-reported race/ethnicity and ancestry. *First Author: Ying L Liu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Disparities in access to germline testing for cancer patients (pts) have been demonstrated; however, disparities in post-testing care are unknown. We sought to evaluate germline findings and subsequent genetic counseling/care in cancer pts undergoing tumor-germline sequencing to explore differences by self-reported ancestry. **Methods:** Pan-cancer pts were prospectively consented to tumor-normal sequencing via a custom NGS panel (MSK-IMPACT) from 1/2015-12/2019 inclusive of germline analysis up to 88 genes. Germline analysis was performed as a research non-billable test in 97.5% of cases. Referral to clinical genetics service (CGS) was recommended for all pts with a new positive (likely pathogenic/pathogenic) germline variant (PV). Ancestry was defined using self-reported Federal definitions of race/ethnicity and designations of Ashkenazi Jewish (AJ) ancestry. Pts were categorized into mutually exclusive groups: AJ, White, Non-White (Asian, Black/African American, Hispanic, Other), and unknown. All pts self-identifying as Hispanic were classified as such, regardless of race. Abstracted data on germline findings and downstream CGS follow-up were compared across groups using non-parametric statistical tests. **Results:** Among the 15,775 pts in this cohort (59.6% White, 15.7% AJ, 20.5% Non-White [6.9% Asian, 6.8% Black, 6.7% Hispanic, 0.1% Other], and 4.2% unknown), 2663 (17%) had a PV. AJ pts had the highest rates of PV (n = 683, 27.6%), and Non-White pts had a lower proportion of PV (n = 433, 13.6%) compared to Whites (n = 1451, 15.5%), $p < 0.01$, with differences mostly due to increased prevalence of moderate/low penetrance variants in White and AJ pts. These findings were consistent across multiple tumor types. Prior knowledge of the PV (424/2663, 16%) was more common in Non-White (19.9%) and AJ (19.2%) than White pts (13.4%), $p < 0.01$. Among 2239 pts with new PV, all were referred to CGS, and 1652 (73.8%) pts were seen. Non-White pts had lower rates of completing visits (67.7%) than White (73.7%) and AJ pts (78.8%), $p < 0.01$, with the lowest rates occurring in Black (63%) and Hispanic (68.1%) pts. All pts without a visit (n = 587) received a close out letter including 139 pts (6.2% of pts with new PV) who had no documentation of receipt of results in the medical record. Higher rates of non-disclosure were observed in Non-White (6.7%) compared to White (5.4%) and AJ (3.4%) pts with new PV, p = 0.032; non-disclosure did not vary by gene penetrance. There was a non-significant trend towards lower rates of cascade testing at CGS in Asian and Black pts with ongoing analysis. **Conclusions:** Even when traditional barriers to genetic testing were minimized, Non-White pts were less likely to receive recommended cancer genetics follow-up for subsequent cancer risk counseling, with potential implications for oncological care, cancer risk reduction, and at-risk family members. Research Sponsor: U.S. National Institutes of Health, This work was supported by the Robert and Kate Niehaus Center for Inherited Cancer Genomics. MSKCC is supported by the NCI Core grant P30 CA008748.

10510 **Poster Discussion Session**

Clinically sufficient vitamin D levels at breast cancer diagnosis and survival outcomes in a prospective cohort of 3,995 patients after a median follow-up of 10 years. *First Author: Song Yao, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: There have been suggestive findings for better cancer survival with vitamin D supplementation in the recent VITAL trial. The findings are consistent with meta-analyses based on earlier randomized trials testing daily supplement vitamin D intake. As there is no ongoing or planned randomized trial of vitamin D supplementation in sight for women after breast cancer diagnosis, we evaluated relationships between serum levels of vitamin D and breast cancer outcomes in a large prospective cohort of breast cancer survivors. **Methods:** We measured 25-hydroxyvitamin D (25OHD) levels in serum samples collected at the time of diagnosis from 3,995 women with incident breast cancer enrolled in the Pathways Study, a large prospective cohort established in 2006 at Kaiser Permanente Northern California with active follow-up (FU). Potential determinants of 25OHD levels, including a polygenic score, were examined. Vitamin D levels were categorized based on clinical cutoffs as deficient (< 20 ng/ml), insufficient (20 to < 30 ng/ml), or sufficient ($\geq$30 ng/ml). These levels were then evaluated in relation to overall survival (OS), breast cancer-specific survival (BCSS), recurrence-free survival (RFS), and invasive disease-free survival (IDFS). Cox proportional hazards models were adjusted for non-clinical, clinical, and treatment factors and were further stratified by stage, estrogen receptor (ER) status, and body mass index (BMI). **Results:** Vitamin D supplement use, lower BMI, and self-reported white race were the strongest determinants of higher 25OHD levels. The polygenic score was significantly associated with 25OHD levels but explained only 0.3% of the variance. The median FU was 9.6 years (range: 0.3-13). Compared to those with deficient vitamin D levels, patients with sufficient levels had significantly better survival outcomes, which remained after controlling for various covariates (OS: HR [95% CI] = 0.73 [0.58-0.91]; BCSS: HR = 0.78 [0.56-1.09]; RFS: HR = 0.79 [0.65-0.97]; IDFS: HR = 0.82 [0.68-0.99]). Associations were similar by ER status, but stronger among patients with more advanced stage disease and those with underweight or normal BMI. Black patients had the lowest 25OHD levels, which contributed to their poorer survival compared to white patients. Adding 25OHD levels to the Cox model of OS lowered the HR associated with Black vs. white race from 2.03 (1.57-2.62) to 1.79 (1.37-2.32). **Conclusions:** Sufficient vitamin D levels at the time of diagnosis were associated with improved breast cancer prognosis. Consistent with results from randomized trials, our findings from a large observational cohort of breast cancer survivors with long FU provide the strongest evidence to date for maintaining sufficient vitamin D levels in breast cancer patients, including among Black women and those with more advanced stage disease. Research Sponsor: U.S. National Institutes of Health.

10511 **Poster Discussion Session**

Dietary intervention influence on physical activity in the Women's Health Initiative randomized Dietary Modification trial. *First Author: Kathy Pan, Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center, Torrance, CA*

Background: In the Women's Health Initiative (WHI) Dietary Modification (DM) randomized trial, after 8.5 years dietary intervention and 19.5 years cumulative (median) follow-up, dietary intervention participation was associated with a statistically significantly 22% lower breast cancer mortality (P = 0.02). In observational studies, physical activity has been associated with lower breast cancer risk with emerging results now indicating, compared to inactivity, any increase in physical activity has health benefits. Currently, longitudinal data on whether an intervention targeting dietary change influences other health-related behaviors as a gateway effect is limited. To evaluate whether randomization to a dietary intervention was associated with self-directed change in physical activity. **Methods:** In the WHI DM trial, 48,835 postmenopausal women, ages 50-79 years, with no prior breast cancer and baseline normal mammogram were randomized at 40 US clinical centers to a dietary intervention (19,541) or a comparison group. Dietary goals were to reduce fat intake to 20% of energy and increase intake of vegetable, fruit, and grains addressed in 18 group sessions in year 1 then quarterly. Neither randomization group received specific or ongoing instructions to increase physical activity, but physical activity was referenced in written materials given to the intervention groups in 7 of the 56 sessions. Episodes per week of moderate or vigorous recreational physical activity (MVPA) were collected at baseline and serially through 15.9 years follow-up by self-report questionnaire. Marginal longitudinal logistic regression models were used to assess physically inactive (MVPA = 0) or physically active (MVPA $>$ 0) participants by randomization group. Marginal Poisson regression models estimated mean weekly MVPA by randomization group. **Results:** 45.6% of participants reported 0 MVPA at baseline which largely persisted throughout follow-up. During cumulative follow-up, relative to the comparison group, dietary intervention group participation was associated with 7% lower physical inactivity rate (odds ratio [OR] 0.93 95% confidence interval [CI] 0.91, 0.95, $P < 0.001$) and a 4% higher mean MVPA (ratio of means [RM] 1.04 95% CI 1.02, 1.06, $P < 0.001$). The association between dietary intervention participation with higher physical activity level was stronger with increasing BMI (P-interaction 0.01) and for women with waist circumference $\geq$ 88 cm (P-interaction 0.02). **Conclusions:** In conclusion, in a randomized trial setting, a low-fat dietary pattern intervention was associated with a significantly lower physical inactivity rate and significantly higher moderate and vigorous physical activity level which could be associated with health benefits. Clinical trial information: NCT00000611. Research Sponsor: U.S. National Institutes of Health.

10512 **Poster Discussion Session**

Analysis of real-world (RW) data for metastatic breast cancer (mBC) patients (pts) with somatic *BRCA1/2* (s*BRCA*) or other homologous recombination (HR)-pathway gene mutations (muts) treated with PARP inhibitors (PARPi). *First Author: Felipe Batalini, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA*

Background: PARPi are approved for treatment of pts w/ HER2-negative mBC and germline *BRCA1/2* (g*BRCA*) pathogenic or likely pathogenic variants (muts); however, clinical benefit has also been demonstrated in mBC pts w/ *sBRCA* or other HR-pathway gene muts. Using a RW Clinico-Genomic Database (CGDB), we assessed outcomes for pts w/ *gBRCA* muts compared to pts w/ either s*BRCA* or other HR-pathway muts treated w/ PARPi. **Methods:** 6,329 mBC pts from ~280 US cancer clinics were included in the Flatiron Health (FH) -Foundation Medicine (FM) CGDB, which includes comprehensive genomic profiling (CGP) linked to de-identified, electronic health record (EHR)-derived clinical data. Eligible pts had mBC, received care in the FH network from 1/1/2011-9/1/2020, and had tissue CGP by FM. Pts classified as *gBRCA*: positive germline result in EHR and *BRCA* mut predicted germline per FM's somatic, germline, zygosity algorithm (SGZ) (Sun et al PMID 29415044). Non-g*BRCA*: negative germline results in EHR and a somatic BRCA (s*BRCA*) mut per SGZ or *BRCA* wild-type w/ another HR mut per CGP result. Pts w/o a documented *gBRCA* result in EHR, unknown FM *BRCA* SGZ result, or conflicting results were excluded. RW overall survival (rwOS) and RW progression-free survival (rwPFS) from start of PARPi for pts w/ *gBRCA* and non-*gBRCA* mBC were compared using Kaplan-Meier analysis and Cox regression adjusted for mBC line number, prior platinum, age at PARPi initiation, race, and receptor status. **Results:** Among pts who received PARPi in the mBC setting, 44 had *gBRCA* and 18 had non-*gBRCA*: 9 s*BRCA* (5 *BRCA1*, 4 *BRCA2*), 4 *PALB2*, 2 *ATM*, and 1 each of *ATM+CDK12*, *BARD1+FANCF+RAD54L*, and *CHEK2*. Of HR muts 76% were confirmed biallelic: 33/44 *gBRCA* (11 unknown), 8/9 *sBRCA*, 3/4 *PALB2*, and 3/5 other (1 unknown). Neither median rwPFS nor rwOS from start of PARPi were significantly different between the non-g*BRCA* and g*BRCA* cohorts (rwPFS: 7.0 [4.6-11.3] vs 5.5 [4.3-7.2] months (mos), aHR: 1.19 [0.57 – 2.43]; rwOS: 15.0 [7.95-16.3] vs 11.5 [9.46-NA] mos, aHR: 0.85 [0.36-1.98]). For 9 pts w/ *sBRCA* mut, median rwPFS was 7.1 mos (range 1.4-12.4) and all pts had progressed by data cut off. **Conclusions:** Despite small pt numbers and limitations from RW data, our results suggest that pts w/ biallelic non-g*BRCA* mBC may derive similar benefit from PARPi when tumor CGP detects a s*BRCA* mut or germline or somatic mut in other HR-pathway genes. These findings are consistent w/ the results from TBCRC-048 (Tung et al PMID 33119476) and support further randomized trials exploring the efficacy of PARPi in this population. Research Sponsor: Foundation Medicine.

	gBRCA (n = 44)	*Non-gBRCA* (n = 18)
Median age at PARPi, yrs	55.5	64.5
Community practice, n (%)	41 (93)	18 (100)
Line Number, n (%)		
1	2 (5)	4 (22)
2	11 (25)	3 (17)
3	7 (16)	4 (22)
4+	24 (55)	7 (39)
Prior platinum, n (%)	18 (41)	5 (28)
Caucasian white, n (%)	33 (75)	12 (67)
Combo therapy, n (%)	7 (16)	5 (28)

10513 **Poster Discussion Session**

The marginal diagnostic benefit of pancreatic cancer molecular profiling after germline testing. *First Author: Evan Justin Walker, University of California San Francisco, San Francisco, CA*

Background: Germline genetic testing is now universally recommended for patients (pts) with pancreatic ductal adenocarcinoma (PDAC) for purposes of both familial screening and therapeutic guidance. Treatment selection can be further informed by tumor molecular profiling (TMP) to identify targetable somatic alterations in pts with advanced disease, but this is inconsistently applied. Determination of the rate of actionable findings identified with TMP after germline testing, which we term marginal diagnostic benefit, may inform practice patterns and workflow in this patient population. **Methods:** This retrospective analysis included all pts with PDAC who underwent germline testing and TMP at UCSF over a 4-yr period. Medical records were reviewed for demographics, disease-specific data, and germline testing/TMP clinical reports. Alterations classified as 'pathogenic' or 'likely pathogenic' were included, and were deemed 'actionable' if there was clinical or preclinical evidence of benefit from targeted therapy in any cancer, as previously described. **Results:** From 1/2016-1/2020, 144/738 (20%) UCSF pts with PDAC completed both germline testing and TMP. Germline testing identified actionable pathogenic alterations in 10 (7%). TMP confirmed 8/10 of these alterations and identified 3 additional therapeutic targets. Among the 134 pts without actionable germline findings, TMP identified 45 new therapeutic targets in 41 (31%) pts, increasing the overall rate of actionable findings from 7% to 35%. Most (35/58, 60%) actionable alterations involved genes associated with the Homologous Recombination DNA Damage Repair (HR-DDR) pathway (Table). 80% of pts with HR-DDR pathway alterations (9/10 germline, 19/25 somatic) received platinum-based chemotherapy. Four pts were treated with targeted therapy based on test results: PARP-inhibitor (n = 2, germline *BRCA1* and *PALB2* mutations), PARP-inhibitor + ATR inhibitor (n = 1, somatic *ARID1A* mutation) and mTOR inhibitor (n = 1, somatic *STK11* deletion). **Conclusions:** In this analysis, PDAC TMP after germline testing increased the detection of actionable alterations (the marginal diagnostic benefit) by five-fold. As more somatic tumor alterations become actionable with the development of targeted therapeutics, TMP is a necessary complement to germline testing to fully inform personalized treatment decisions for all pts with PDAC. Research Sponsor: None.

Targetable Molecular Findings	Detected by Germline Testing (n = 10)	Additional Alterations Detected by TMP (n = 48)
HR-DDR Pathway Alterations*	10 (100%)	25 (52%)
***PI3K/AKT/mTOR* Pathway Alterations**	–	8 (17%)
***CDK4/6* Amplifications**	–	4 (8%)
***KRAS* G12C Mutation**	–	4 (8%)
***HER2* Amplification**	–	3 (6%)
***BRAF* Activating Mutation**	–	1 (2%)
***RET* Activating Mutation**	–	1 (2%)
***EGFR* Activating Mutation**	–	1 (2%)
***NOTCH2* Amplification**	–	1 (2%)

**ARID1A* (15), *ATM* (6), *BRCA1* (5), *CHEK2* (3), *BRCA2* (1), *BRIP1* (1), *FANCA* (1), *MRE11A* (1), *PALB2* (1), *RAD51C* (1).

10514 **Poster Discussion Session**

Clinical impact of medical policy supporting universal germline testing for patients with colorectal cancer. *First Author: Sarah M. Nielsen, Invitae, San Francisco, CA*

Background: Colorectal cancer (CRC) affects approximately 104,000 patients (pts) annually in the United States, up to 45% of which are estimated to be genetic and/or familial. Aligned with clinical guidelines, in 2020, a large U.S. insurer established Medical Policy allowing for and reimbursing germline genetic testing (GGT) for all CRC pts. This study reports overall uptake of GGT in CRC pts under this inclusive policy, actionable findings and treatment implications for pts tested, stratified by self-reported ancestry/ethnicity. **Methods:** Two independent de-identified datasets were reviewed, including administrative claims data of commercially insured and Medicare Advantage enrollees, aged 18+ with CRC (≥1 claim with ICD10 C18, C19 or C20 in the first position) who were continuously enrolled (CE) in the health plan from 1/2019-10/2020. Evidence of genetic testing based on CPT codes, was examined during 2020. A second de-identified dataset of CRC pts whose GGT was billed to the insurer under the Medical Policy, was also reviewed. Patient demographics, clinical information and GGT results were descriptively analyzed. **Results:** Of the >18,000,000 CE enrollees, 55,595 were identified as CRC pts, of whom 1,675 (3%) received GGT. From the GGT dataset, 788 pts had test results available for review. 143 (18%) pts had pathogenic/likely pathogenic (P/LP) variants in genes including *MSH2,MLH1, PMS2, MSH6, CHEK2, APC, BRCA2, ATM, MUTYH* (biallelic). Of pts with P/LP variants, 96 (67%) were potentially eligible for precision therapy and/or clinical treatment trials. Overall, 133 (93%) had P/LP variants in genes with precision therapy, clinical trial and/or published management implications. In a subset of pts (n=674) with ethnicity data; Asian, Black/African-American and Hispanic pts showed lower relative uptake of germline testing than Caucasians (Table). **Conclusions:** Despite Medical Policy allowing for GGT for all pts with CRC, only 3% of eligible pts received testing. If all CRC pts had been tested, these data suggest up to 6,705 pts with P/LP variants conferring potential eligibility for precision therapy (PD-1/PD-L1 inhibitors) or clinical treatment trials (PARP inhibitors), and an additional 2,602 pts with mutations in genes with published management recommendations, could have been identified, but were missed. Additional research is needed to identify obstacles to systematic implementation of this Medical Policy, the best timing of GGT to prevent CRC and improve access to underrepresented populations. CRC patients with germline genetic testing. Research Sponsor: None.

Self-reported ancestry/ethnicity	Patients N, %	P/LP N, %	Negative N, %	VUS N, %
Asian	28, 4%	6, 21%	11, 39%	11, 39%
African-American	65, 9%	15, 23%	26, 40%	24, 36%
Hispanic	60, 8%	6, 10%	28, 46%	26, 43%
Caucasian	521, 77%	99, 19%	241, 46%	181, 34%
Total	674	126,18%	306, 45%	242, 35%

VUS - variant of uncertain significance.

10515 **Poster Discussion Session**

Limitations of direct-to-consumer (DTC) genetic testing for hereditary breast and ovarian cancer. *First Author: Neelam Vijay Desai, Beth Israel Deaconess Medical Center, Boston, MA*

Background: With the advent of DTC genetic testing, individuals have access to genetic testing without input from a healthcare professional. DTC testing now exists for the 3 Ashkenazi Jewish (AJ) *BRCA1/2* founder variants. DTC testing may provide false reassurance to individuals that they do not carry a pathogenic or likely pathogenic variant (PLPV) in *BRCA1/2* or other cancer-risk genes. **Methods:** Multi-panel genetic testing was performed in 348,692 individuals for a clinical indication of hereditary breast/ovarian cancer (Clinical cohort) and 7,636 self-referred ostensibly healthy individuals (Healthy cohort) by a clinical testing laboratory. The primary analysis evaluated PLPVs for Group 1 genes: *BRCA1/2* AJ founder variants and Group 2: full sequence *BRCA1/2*. Secondary analyses assessed PLPVs in Group 3: high-risk breast cancer genes (*BRCA1/2, CDH1, PALB2, PTEN, STK11, TP53*), Group 4: all breast or ovarian cancer-risk genes (Group 3 genes plus *ATM, BARD1, BRIP1*, truncating *CHEK2, EPCAM, MLH1, MSH2/6, NF1, PMS2, RAD51C/D*) and Group 5: 41 cancer-risk genes; these analyses were limited to participants who tested for all 41 genes. Potentially mosaic variants were excluded. **Results:** Table illustrates PLPVs found in both cohorts. The *BRCA1/2* AJ founder variants account for only ~11% (1513/13,987) and ~30% (19/64) of the *BRCA* PLPVs in the Clinical and Healthy cohorts, respectively. Even among AJ individuals, testing only for the 3 founder variants will miss ~10% (52/513) of all *BRCA1/2* PLPVs. Evaluating only the *BRCA*AJ founder variants missed a higher percentage of PLPVs in other cancer-risk genes. **Conclusions:** The 3 *BRCA1/2* AJ founder variants analyzed by DTC testing account for a small fraction of PLPVs in cancer-risk genes in the general population, and miss 10% of *BRCA* PLPVs even among AJ individuals. Greater public education is needed to dispel the misconception that DTC tests are equivalent to clinical assessment and comprehensive genetic testing. PLPVs identified in Clinical and Healthy Cohorts. Research Sponsor: None.

	Primary Analysis (N=356,328)			Secondary Analyses (N=83,101)						
Cohort	Group 1 AJ Founder [N,%]	Group 2 Full *BRCA1/2* [N,%]	% Founder / all *BRCA1/2* PLPV	Cohort	Group 1 AJ Founder [N, (%)]	Group 2 Full *BRCA1/2* [N, (%)]	Group 3 Hi-risk breast [N, (%)]	Group 4 Breast/ ovarian [N, (%)]	Group 5 41 genes [N, (%)]
Healthy N=7636 (5% AJ)	19 (0.2%)	64 (0.8%)	29.7%	Healthy N=5792	12 (0.2%)	46 (0.8%)	60 (1.0%)	137 (2.4%)	195 (3.4%)
Clinical N=348,692	1,513 (0.4%) 461 (4.4%)	13,987 (4.0%) 513 (4.9%)	10.8% 89.9%	Clinical N=77,309	367 (0.5%)	2,721 (3.5%)	3,489 (4.5%)	6,069 (7.8%)	6,749 (8.7%)
AJ (alone)	218 (3.3%)	313 (4.7%)	69.6%						
AJ (mixed)	10 (0.06%)	992 (6.3%)	1.0%						
Asian	6 (0.02%)	1,118 (4.4%)	0.5%						
Black	74 (0.3%)	1,542 (6.4%)	4.8%						
Hispanic	558 (0.3%)	7,028 (3.3%)	7.9%						
White	186 (0.4%)	2,481 (4.9%)	7.5%						
Other									

10516 **Poster Discussion Session**

Early age of onset and broad cancer spectrum persist in *MSH6* and *PMS2*-associated Lynch syndrome. *First Author: Ying L Liu, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Recently updated NCCN guidelines for management of germline *MSH6* and *PMS2* pathogenic/likely pathogenic (P/LP) variant carriers suggest a more modest phenotype with later onset colorectal cancer (CRC) and limited extra-colonic cancers compared to other Lynch Syndrome (LS) genes. However, data are limited, and a comprehensive understanding of the risk spectrum and age of cancer onset is critical for cancer screening and risk-reduction. We sought to characterize *MSH6* and *PMS2*-associated cancers and age of diagnosis in those with mismatch repair deficient (MMRD)/ microsatellite instability-high (MSI-H) tumors, a hallmark of LS pan-cancer. **Methods:** Pts consented to IRB-approved protocols of tumor/germline sequencing or to a prospective registry of LS pts at a single institution from 2/2005-01/2021 were reviewed to identify those with germline heterozygous *MSH6*/*PMS2* P/LP variants; pts with constitutional MMRD (CMMRD) were excluded. In cancer-affected pts, tumors were evaluated for MSI and/or MMR protein expression via immunohistochemistry. Tumor types were tabulated, and clinical variables were correlated with MMR/MSI status using non-parametric tests. **Results:** We identified 243 pts (159 female, 94 male) with P/LP germline *MSH6/PMS2* variants, and 186 (77%) pts had a confirmed cancer [*MSH6* 111/148 (75%); *PMS2* 75/95 (79%)]. Overall, 51 (21%) pts had multiple primary cancers, 35 (24%) in *MSH6* and 16 (17%) in *PMS2* (p = 0.20), resulting in 261 total tumors, 160 in *MSH6* and 101 in *PMS2*. Of the 191 tumors with molecular assessment, 118 (62%) were MMRD/MSI-H, including CRC (n = 54), endometrial (EC, n = 34), small bowel (SBA, n = 6), ovarian (OC, n = 5), urothelial (n = 5), pancreato-biliary (n = 4), gastroesophageal (n = 3), non-melanoma skin (n = 3), prostate (n = 2), breast (n = 1), and brain (n = 1). While CRC and EC were more likely to be MMRD/MSI-H (79% each) compared to other cancers (37%) ($p < 0.001$ overall, $p = 0.001$ for *MSH6*, and $p < 0.001$ for *PMS2*), 25% of all MMRD/MSI-H tumors in both genes were comprised of non-CRC/EC cancers. Notably, there were 6 SBAs (5 in *PMS2*, 1 in *MSH6*), and all were MMRD/MSI-H. There were 17 OCs (12 in *PMS2*, 5 in *MSH6*), and of the 12 that underwent molecular assessment, 5 (41.7%) were MMRD/MSI-H (3 *PMS2*, 2 *MSH6*). Among MMRD/MSI-H CRC and EC, median age of diagnosis was 51.5 (range 27-80) and 55 (range 39-74) respectively, with 9/54 (17%) of CRC (4 in *MSH6*, 5 in *PMS2*) diagnosed < age 35, the suggested upper threshold for initiation of colonoscopy per NCCN. **Conclusions:** Despite being lower penetrance LS-associated genes, pts with *MSH6/PMS2* P/LP variants remain at risk for a broad-spectrum of cancers and very early-onset CRC, with 17% of MMRD/MSI-H CRC presenting prior to upper threshold of initiation of colonoscopic screening per NCCN. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

10517 **Poster Discussion Session**

Cancer-specific mortality associated with germline genetic testing results among women with breast cancer or ovarian cancer treated with chemotherapy. *First Author: Allison W. Kurian, Stanford Cancer Institute, Stanford University School of Medicine, Stanford, CA*

Background: Breast and ovarian cancer patients increasingly undergo germline genetic testing. While studies suggest a greater chemotherapy benefit for carriers of *BRCA1/2* pathogenic variants, little is known about whether pathogenic variants in other genes are associated with cancer mortality. **Methods:** Georgia and California Surveillance, Epidemiology and End Results (SEER) registry records of women diagnosed with breast cancer or ovarian cancer from 2013-2017 were linked to results of clinical germline genetic testing from four participating laboratories. Patients were included if they linked to a genetic result, had stages I-III breast cancer or I-IV epithelial ovarian cancer and received chemotherapy. Multivariable Cox proportional hazard models were used to examine the association of genetic results, demographic and clinical factors with cancer-specific mortality. **Results:** 21,348 breast and 4,320 ovarian cancer patients were analyzed with median follow-up of 41 months. Pathogenic variants were present in 12% of patients with estrogen and progesterone receptor-positive, HER2-negative breast cancer, 9% with HER2-positive breast cancer, 17% with triple-negative breast cancer and 18% with ovarian cancer. Pathogenic variants were most common in *BRCA1/2, CHEK2, PALB2, ATM* and *BRIP1*. Among triple-negative breast cancer patients, mortality was lower with pathogenic variants in *BRCA1* (hazard ratio (HR) 0.27, 95% confidence interval (CI) 0.17-0.45) and genes other than *BRCA1/2* (HR 0.33, CI 0.13-0.81) versus no pathogenic variant. Genetic results were not associated with mortality in other breast cancer subtypes. Among ovarian cancer patients, mortality was lower with pathogenic variants in *BRCA2* (HR 0.36, CI 0.26-0.49) and in genes other than *BRCA1/2* (HR 0.48, CI 0.33-0.70). **Conclusions:** Among breast and ovarian cancer patients treated with chemotherapy, those with germline pathogenic variants in several cancer-associated genes had equivalent or lower short-term mortality than those testing negative. These results may guide patient counseling and clinical trial design. Research Sponsor: U.S. National Institutes of Health.

10518 **Poster Discussion Session**

Chemoprotective effect of metformin against HR+/HER2- breast cancer among women with type-2 diabetes. *First Author: Soumya Chikermane, University of Houston, College of Pharmacy, Houston, TX*

Background: Type-2 diabetes mellitus (T2DM) increases the risk of breast cancer among postmenopausal women. Metformin has demonstrated a chemoprotective effect in breast cancer, however its role in HR+/HER2- breast cancer (HR+/HER2- BC), the most common subtype, has not been studied among older women with T2DM in the United States. This study evaluated if increased exposure to metformin is associated with a reduced risk of HR+/HER2- BC among postmenopausal women with T2DM. **Methods:** A case-control study was performed using the Surveillance, Epidemiology, and End Results (SEER)-Medicare data (2008-2015). Those diagnosed with HR+/HER2- BC as their first/only cancer after incident T2DM diagnosis were cases. The event date was the date of HR+/HER2- BC diagnosis in cases, and randomly assigned to non-cancer T2DM controls based on the distribution in cases. Cases were matched to up to 4 controls each using incidence density sampling with replacement. Metformin exposures were defined as cumulative dose, average intensity and adherence, measured during the 1-year lookback period prior to the event date. Dose (mg) was categorized as: 0, 0-30,000, 30,001-136,000, 136,001-293,000, and $>$ 293,000. Average intensity per day (mg/day) was categorized as: 0, 1-500, and $>$ 500. To evaluate adherence, those without metformin claims during the lookback period were excluded. Adherence measures were: binary proportion of days covered (PDC) ($\geq$0.80, $<$ 0.80) and adherence trajectories. Group based trajectory modeling was used to identify trajectories (adherent, slow decline, rapid decline, and early discontinuation). The Anderson Behavioral Model was used to guide selection of covariables: demographic and clinical variables (diabetes severity, metabolic syndrome, comedications, and health status). Conditional logistic regression was used to evaluate the association between exposure to metformin and the risk of HR+/HER2- BC. **Results:** The main cohort included 690 cases and 2747 controls. A decremental reduction in odds of HR+/HER2- BC in the highest cumulative dose (OR = 0.72, 95% CI: 0.55-0.95; OR = 0.60, 95% CI: 0.42-0.85) and intensity (OR = 0.61, 95% CI:0.46-0.82) categories of metformin was observed compared to the no-metformin group. Those non-adherent to metformin had 45% (OR = 1.45, 95% CI: 1.08-1.94) increased odds of HR+/HER2- BC compared to those adherent. The risk of HR+/HER2- BC in the adherent (OR = 0.67, 95% CI: 0.39-1.14), slow decline (OR = 0.75, 95% CI: 0.43-1.32) and rapid decline (OR = 0.73, 95% CI: 0.41-1.31) trajectories was not statistically significant compared to the early discontinuation trajectory. **Conclusions:** This retrospective study based on SEER-Medicare found an association between high dose and intensity of metformin use with reduced odds of incidence of HR+/HER2- BC among postmenopausal women with T2DM. Adherence to metformin also showed protective effect against HR+/HER2- BC. Research Sponsor: None.

10519 **Poster Discussion Session**

Development of AI-powered imaging biomarker for breast cancer risk assessment on the basis of mammography alone. *First Author: Ki Hwan Kim, Lunit Inc., Seoul, South Korea*

Background: There is increasing interest in early detection of breast cancer by utilizing MRI in high-risk populations. However, it is still challenging to define and enrich the high-risk population. In this study, we developed an artificial intelligence (AI)-powered Imaging Biomarker in Mammography (IBM) to discover unique mammographic patterns, beyond simple density evaluations, that are related to breast cancer. **Methods:** A total of 49,577 mammography exams were collected to develop the AI-powered IBM, in which 6,218 were cancers. First, we evaluated the hypothesis that the unaffected breast of cancer patients would have a different pattern than that of non-cancer patients, by training AI (IBM-A) with unaffected breast in cancer patients and breasts of non-cancer patients. We then utilized further images of the cancer patients to train AI (IBM-B). This time we used both affected and unaffected breasts of cancer patients and breasts of non-cancer patients, allowing IBM-B to additionally learn patterns related to breast cancer. The IBMs were evaluated using the internal data (n = 2,058) that included 719 cancers. To demonstrate the feasibility of early detection by using IBM-B, it was tested with external data (n = 4,158) from an independent institution. This included pre-index exams (n = 292) taken prior to index exams acquired at the time of cancer diagnosis. **Results:** With the internal data, IBM-A showed AUC of 0.842, suggesting that AI could learn the difference between the normal breast of cancer patients and non-cancer patients. With IBM-B, which used additional cancer images to train, AUC was improved to 0.852. Based on the internal validation, IBM-B was chosen for the external validation, in which pre-index examinations were used only. IBM-B showed AUC of 0.777 in discriminating the pre-index exams of cancer patients and those of non-cancer patients. The radiologists excluded the apparent missed cancers (n = 87) by reviewing the pre-index exams retrospectively. After, the recalculated AUC of IBM-B was 0.770, suggesting that IBM-B can distinguish between mammograms of patients who will develop breast cancer in the future and those who will not. The mean IBM-B scores in pre-index exams of cancer group (0.580) were significantly higher than those in the normal (0.258, $P < 0.001$) and benign (0.258, $P < 0.001$) groups. **Conclusions:** AI-powered IBM could detect the unique parenchymal pattern associated with high breast cancer risks, and we show the potential of the AI-powered IBM to be used as an independent biomarker to select high-risk populations based on mammography alone. Research Sponsor: Lunit Inc.

	Total (n = 292)		Invasive cancer (n = 235)	
Mean score of IBM-B	**Index exams**	**Pre-index exams**	**Index exams**	**Pre-index exams**
Normal (n = 1693)	0.258	-	-	-
Benign (n = 2173)	0.261	-	-	-
Cancer Visible in pre-index (= missed cancer, n = 87)	0.687	0.587	0.721	0.580
Invisible in pre-index (n = 205)	0.627	0.572	0.638	0.580

10520 **Poster Discussion Session**

Gene methylation and cytological atypia in random fine needle aspirates for assessment of breast cancer risk: 10-year follow up in average risk women. *First Author: Erica Wrubel, Northwestern University, Chicago, IL*

Background: Alterations in DNA methylation occur early in tumorigenesis, and are a potential breast cancer risk biomarker. We previously reported a study where healthy volunteers underwent random fine needle aspiration (rFNA) of the breasts; cumulative methylation index of eight preselected tumor suppressor genes (CMI) was associated with the presence of cytological atypia in rFNA samples. We now report 10-year follow-up of this population, to evaluate whether increased CMI is associated with subsequent breast cancer development. **Methods:** 380 women, unselected by breast cancer risk, were enrolled. Demographics, breast cancer risk factors, lifetime Gail model risk estimates (Gail-LR), and %breast density were obtained at baseline. rFNA samples were assessed for cytopathology (Masood Score, MS) and CMI. Patients were contacted annually for 10 years to ascertain development of invasive or non-invasive breast cancer. In univariate analysis, log-rank test was used to compare breast cancer incidence rates between individuals with high and low baseline measures (separated by median). Area under the ROC curve was used to evaluate the cancer prediction accuracy. In multivariate analysis, the effect of CMI (after log-transformation to reduce skewness) was further studied using Cox regression model adjusting for confounding baseline variables. **Results:** 362 women participated in follow up. At a median follow up time of 9.5 years after rFNA sampling, 16 women developed invasive or non-invasive breast cancer. There were no significant differences between women who developed cancer and those that did not in regard to demographic factors, %breast density, MS, or Gail-LR. On univariate analysis, Gail-LR was higher in women who developed cancer (13.0 vs. 16.5, p=0.08). The largest hazard ratios were observed from high breast density (2.30, 95% CI 0.8, 6.6) and high CMI (2.26, 95% CI 0.8, 6.6, p=0.07). In breast cancer prediction, the AUC for CMI was 0.64 (95% CI 0.51, 0.77). In separate bivariable models that adjusted for age, Gail-LR, MS, and %breast density, the HR for log CMI was consistently above unity, with a p value consistently below 0.1, except for the model that included MS (see Table). **Conclusions:** Elevated CMI has potential as a robust predictor of future breast cancer occurrence in average risk women, even when adjusted for breast density or cytologic atypia. Our prior analysis established that CMI is not susceptible to variation with menstrual cycle phase and menopausal status. These features support its further evaluation in larger trials. Clinical trial information: NCT00896636. Research Sponsor: Avon Foundation #02-2011-109 awarded to S. A. Khan, V. Stearns, and S. Sukumar, Other Foundation.

Models adjusting log CMI for covariates.

	Log CMI HR	log CMI p value	Covariate HR	Covariate p value
Log CMI + age	1.56	0.0990	0.93	0.0624
Log CMI + % breast density	1.61	0.0739	1.01	0.6473
Log CMI + Gail-LR	1.62	0.0742	0.02	0.4898
Log CMI + MS	1.54	0.1470	1.54	0.8350

10521 **Poster Session**

Mismatch repair gene alteration subtypes impact age of onset of mismatch repair-deficient cancers. *First Author: Aifen Wang, Zhangjiagang TCM Hospital Affiliated to Nanjing University of Chinese Medicine, Suzhou, China*

Background: This study investigated whether mismatch repair (MMR) gene alterations and alteration subtypes impacted age at onset of MMR-deficient cancers. **Methods:** A retrospective study of association of MMR-deficient alterations and age of onset of MMR-deficient lung, breast, prostate, bladder, colorectal, endometrial, and/or ovarian cancers was conducted by using cBIPORTAL dataset. **Results:** A total of 815 participants with MMR-deficient alterations were enrolled, 346 males and 469 females (median age 63 years; age range, 20-90 years). Males were diagnosed as colorectal and bladder cancer at later ages than females. When stratified by alteration type, individuals with *MSH6* or *PMS2* missense alterations had later ages of onset of colorectal cancer than those with no missense alterations. Participants with *MSH2* AMP alterations were older at the diagnosis of endometrial cancer than those without *MSH2* AMP alterations. Females with *MLH1* missense alterations had later ages of onset of ovarian cancer than those with no missense alterations. Individuals with *PMS2* AMP alterations were confirmed with lung cancer at later ages than those with no *PMS2* AMP alterations. Carriers with *MSH6*or *PMS2* missense alterations were older at the time of diagnosis of prostate cancer than those with no missense alterations. **Conclusions:** Gene alterations and subtype of alterations could stratify carriers with MMR-deficiency in bespoke surveillance. The mechanism of the association of MMR-deficient alterations and alteration subtypes and age at the diagnosis of MMR-deficient cancers needs to be further study. Research Sponsor: ZhongNan Hospital of Wuhan University Science Technology and Innovation Cultivating Fund.

Distribution of MMR deficient alterations, presenting age at onset of MMR-deficient cancers.

	MLH1		*MSH2*		*MSH6*		*PMS2*	
MMR deficient cancers	Number (% of total)	Median age (range)	Number (% of total)	Median age (range)	Number (% of total)	Median age (range)	Number (% of total)	Median age (range)
Colorectal cancer	71 (30)	67 (20-86)	72 (30)	60 (24-90)	107 (45)	64 (27-90)	58 (24)	66 (24-86)
Endometrial cancer	34 (24)	56 (43-87)	48 (31)	57 (33-83)	61 (38)	57 (33-87)	39 (36)	63 (33-87)
Ovarian cancer	13 (24)	62 (48-77)	24 (45)	64 (41-83)	21 (40)	67 (41-83)	16 (30)	53 (37-73)
Prostate cancer	28 (25)	59 (51-85)	44 (39)	62 (49-85)	45 (40)	62 (49-85)	39 (35)	62 (50-83)
Bladder cancer	19 (24)	65 (49-90)	26 (31)	64 (31-87)	27 (38)	64 (31-87)	31 (39)	70 (36-85)
Lung cancer	26 (20)	65 (35-81)	56 (44)	65 (33-87)	51 (40)	64.5 (33-76)	58 (46)	65 (38-84)
Breast cancer	25 (25)	63 (31-83)	31 (31)	52 (32-90)	38 (38)	51 (29-90)	24 (24)	53 (29-78)

10522 **Poster Session**

The landscape of germline mutations and the relationship with tumor mutation burden in Chinese patients with lung cancer. *First Author: Jian Shi, Department of Medical Oncology, Fourth Hospital of Hebei Medical University, Shijiazhuang, China*

Background: Lung cancer is one of the most common types of cancer, ranking the first in the incidence and mortality of malignant tumors in the world and China. Although studies have been reported that genetic susceptibility to lung cancer is associated with certain germline mutations, the relationship between lung cancer risk and inherited genetic factors remains relatively elusive. However, the effect of germline mutation on TMB in lung cancer has not been explored. Herein, DNA genomic profiling was performed through NGS with a 539-gene panel to explore the germline mutations and the relationship with TMB in Chinese patients with lung cancer. **Methods:** We retrospectively analyzed the germline mutations through a comprehensive 539-gene profiling of 3541 Chinese patients with lung cancer. 539-gene panel contained germline mutations in 90 hereditary tumor-associated genes. We screened out the pathogenic and likely pathogenic germline mutations according to the standards and guidelines for the interpretation of sequence variants of The American College of Medical Genetics and Genomics (ACMG), and picked out there is no records in Clinvar database and no literature report. TMB of tissue or blood ctDNA in 3541 patients were further analyzed in with pathogenic mutations (P group), with likely pathogenic mutations (LP group), and no germline mutations group (Non-P group). The difference in TMB was analyzed via the Wilcoxon sign test. **Results:** In 3541 patients with lung cancer, 177 (4.999%) patients were identified harboring pathogenic or likely pathogenic germline mutations, in which 78 P group and 99 LP group, the rest 3364 were Non-P group. The highest prevalence of germline mutation was found in *BRCA2* (0.565%), *ATM* (0.339%), *MUTYH* (0.282%), and *BRCA1* (0.254%). In 177 patients with pathogenic or likely pathogenic germline mutations, 67 mutations were recorded as UNK (unknow) in Clinvar database and no literature report. The media TMB of tissue in P group, LP group and Non-P group were 5.149, 5.535 and 5.547 respectively. The media TMB of blood ctDNA in P group, LP group and Non-P group were 4.257, 3.945 and 4.483 respectively. There was no statistical difference in TMB between P and Non-P groups (tissue $p = 0.98$; ctDNA $p = 0.5$). **Conclusions:** In our study, we firstly identified 67 novel germline mutations and studied on the relationship between germline mutations and TMB in lung cancer, which expanded the understanding of germline mutations. Research Sponsor: None.

10523 **Poster Session**

Management impact of preoperative germline genetic testing in patients with breast cancer at the Lifespan Cancer Institute. *First Author: Kaitlyn P. Lew, Brown University, Providence, RI*

Background: Breast cancer is a heterogenous disease and management is complex. Advances in next generation sequencing has allowed genetic testing to be more accessible. However, conveying results to patients and care team can be challenging due to various variant classifications. Diagnostic results have the potential to guide management. Nondiagnostic results can be misinterpreted. The extent to which preoperative genetic testing affects management of newly diagnosed breast cancer is unknown. **Methods**: Newly diagnosed breast cancer patients were identified via review of breast tumor board between May 2019 and March 2019 followed by chart review to collect detailed information. **Results:** 408 newly diagnosed breast cancer cases were queried. Genetic evaluation was recommended and completed in 68%, not recommended (did not meet NCCN criteria) in 30% and declined in 2.7%. The genetic evaluation recommended cohort was associated with a higher mastectomy rate in comparison with when not recommended (31% vs. 9%, p=0.0001). Of those who completed genetic testing: 12% harbored a pathogenic/likely pathogenic variant (PV/LPV), 26% had a nondiagnostic variant of uncertain significance (VUS) and 61% had negative testing. Comparison between nondiagnostic test results (negative and VUS) and diagnostic test results revealed significantly increased number of women in the diagnostic group who chose mastectomy over breast conservation therapy (BCT, nondiagnostic 20% vs diagnostic 39%, p=0.018). When negative, VUS, and PV/LPV were each independently analyzed, diagnostic test results again revealed a significantly increased number of mastectomies over BCT ($p<0.05$). Comparison of surgical choices in nondiagnostic VUS vs. negative results was not significantly different (Table). Comparing the surgical timelines, completing a genetic evaluation did not affect surgery timing (mean 2.3 vs. 2.2 months, $p>0.5$). **Conclusions:** Germline genetic testing in patients with newly diagnosed breast cancer impacts clinical management. Those harboring a diagnostic result were more likely to choose mastectomy over BCT. Not surprisingly, mastectomy rate was higher among those where genetic evaluation was recommended, possibly due to concerning personal or family history. The mastectomy rate was higher among those with a diagnostic result, indicating an understanding of the genetic testing significance by patients and the care team. More importantly, those who harbored nondiagnostic VUS did not make significantly different surgical choices compared with negative genetic testing, highlighting the critical role of proper genetic counseling and being part of the care team. We conclude consideration of genetic evaluation is clinically useful and feasible without affecting the surgical timeline. Research Sponsor: None.

	BCT*	MRM*
Normal	121 (77)	36 (23)
PV/LPV	19 (61)	12 (39)
VUS	49 (89)	6 (11)

*Number of patients (%).

10524 **Poster Session**

Uptake of genetic counseling and testing in a clinic based population of women with breast cancer. *First Author: Alexandra Wehbe, Wayne State University, Detroit, MI*

Background: Carriers of pathogenic variants in cancer susceptibility genes have an elevated risk of developing breast, ovarian, and other cancers.We conducted a medical record review to determine the uptake of genetic counseling and testing in a clinic-based population of women with breast cancer. **Methods:** Medical records of 150 women with breast cancer seen at the Karmanos Cancer Institute between January-December 2018 were reviewed to determine the proportion eligible for genetic testing according to National Comprehensive Cancer Network guidelines. We also assessed genetics referral rates, appointment completion and results of genetic testing. Using chi-square and ANOVA tests, we analyzed the association of demographic and clinical factors with eligibility and referral to genetic counseling. **Results:** The average age of diagnosis was 57.1 years old, with 68.7% of women diagnosed with stage I-III disease, and 31.3% diagnosed with stage IV disease. There were 91 (60.7%) women who met NCCN criteria for genetic testing, of which 46.2% ultimately underwent genetic testing. Eligible women were more likely to be younger (52.6 vs. 64.0 years old), White (75.0% vs. 54.5%), and have Medicaid (75.0%) or private insurance (72.9%) vs. Medicare (44.8%). Women who met NCCN criteria were 3.5 times more likely to be referred for genetic counseling than those that did not meet eligibility criteria. Women were also more likely to be referred if they had early-stage disease compared to stage IV (67.8% vs. 48.3%), and Medicaid or private insurance compared to Medicare (71.4%, 72.0% and 40.0%, respectively). Of eligible women, 59.3% had a genetic counseling appointment scheduled, and of those, 78.0% attended their appointment. There were no apparent differences in appointment completion based on race with similar percentages of Black and White women completing their appointments (74.0% and 77.0% respectively). Women with stage IV disease were more likely to complete their appointments (83.0%) compared to women with stages I-III (74.0%) and fewer women with Medicare completed their genetic counseling appointment (56.0%) compared to women with Medicaid (83.0%) and women with private insurance (83.0%). Among women who attended their appointment, 95.9% underwent genetic testing. Of women who had genetic testing, 8.5% had a pathogenic variant and 30.4% had a variant of unknown significance. **Conclusions:** The results of this study indicate that lack of genetic counseling referrals contribute to a gap between the need for and completion of genetic testing. By understanding barriers to genetic counseling and testing, future clinical initiatives could effectively improve accessibility to genetic counseling services. Research Sponsor: None.

10525 **Poster Session**

Closing the gap: Trends in inconclusive rates on hereditary cancer testing across racial/ethnic groups. *First Author: Foluso Olabisi Ademuyiwa, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: Several groups have described disparities in genetic test results for inherited breast cancer predisposition, with a disproportionate number of variants of unknown significance (VUS) reported in non-Caucasian individuals. These disparities are due in part to the underrepresentation of non-Caucasians in reference databases and clinical genetic testing cohorts. Over the past few years, diversification efforts have been made however, little data exists on how ethnicity- and gene-specific VUS rates have changed over time and whether such disparities have improved or worsened. **Methods:** We retrospectively reviewed demographic information and test results for individuals who underwent hereditary cancer multigene panel testing between March 2012 and September 2020 at a single laboratory. Individuals who self-reported as African American, Asian, Caucasian, or Hispanic on the test requisition form and whose testing included *ATM, BRCA1, BRCA2, CHEK2* and *PALB2* (five commonly tested breast cancer predisposition genes with management guidelines) were included in the study (n = 284,130). The frequency of germline variants of unknown significance (VUS) in the five geneswas assessed in September 2015 and September 2020. **Results:** Amongst patients tested between March 2012 and September 2015, 82.8% of the study cohort self-reported as Caucasian and 17.2% were not Caucasian (6.5% African American, 6.0% Hispanic, and 4.6% Asian). The proportion of non-Caucasian individuals in the study cohort increased slightly by September 2020 to 22.8% (77.2% Caucasian, 9.2% African American, 8.4% Hispanic, and 5.3% Asian). Consistent with previous reports, Caucasians had the lowest VUS rate overall in both 2015 and 2020. This was also true at the individual gene level, with the exception of *CHEK2*. Over time, we observed a relative decrease in VUS rates across all ethnicities. Between 2015 and 2020, the overall VUS rate for the five included genes in non-Caucasian individuals was reduced by 32.0% in non-Caucasians compared to 23.6% in Caucasians. The absolute difference in VUS rate between non-Caucasians and Caucasians decreased from 7.9% in 2015 to 4.5% in 2020. **Conclusions:** While VUS rates for commonly tested breast cancer predisposition genes remain higher in non-Caucasians relative to Caucasians, our results demonstrate that this gap has been reduced over a five-year time period. These findings may be indicative of efforts by clinicians and laboratories to reduce these disparities. Further studies are necessary to improve the clinical utility of genetic testing in under-represented populations. Research Sponsor: Ambry Genetics.

	ATM		*BRCA1*		*BRCA2*		*CHEK2*		*PALB2*	
	2015	2020	2015	2020	2015	2020	2015	2020	2015	2020
African American	10.2%	5.2%	1.5%	1.6%	4.2%	2.8%	1.1%	0.8%	2.0%	1.3%
Asian	6.3%	5.1%	3.2%	2.3%	5.0%	4.2%	2.5%	2.5%	5.8%	2.2%
Caucasian	4.1%	3.2%	0.9%	0.8%	2.0%	1.5%	1.9%	1.5%	1.5%	1.1%
Hispanic	6.1%	4.2%	1.3%	1.0%	2.6%	2.5%	2.8%	2.1%	1.6%	1.2%

10526 **Poster Session**

Breast cancer ER, PR, and HER2 expression variance by germline cancer predisposition genes. *First Author: Grace Wei, USF Health Morsani College of Medicine, Tampa, FL*

Background: The association between breast cancer characteristics and survival with estrogen receptor (ER) and progesterone receptor (PR) expression has been primarily studied via binomial categories, ER-positive and ER-negative. In order to better characterize germline genetic influences on these markers, we investigated their IHC expression semi-quantitatively in cancer predisposition germline pathogenic variant (PV) carriers of the following genes: *BRCA1,BRCA2, PALB2, TP53, PTEN, CDH1, ATM, CHEK2*, and Lynch syndrome genes. The HER2 expression was also analyzed. **Methods:** We conducted a retrospective chart review of patients with germline panel genetic testing for cancer predisposition genes at Moffitt Cancer Center's GeneHome clinic. Inclusion criteria included 1) women ≥18 years old, 2) breast cancer diagnosis, 3) cancer predisposition germline panel genetic test results, 4) available ER and PR expression levels, and 5) available HER expression and/or amplification status. ER, PR, and HER2 status were compared between PV carriers and non-PV carriers via Mann-Whitney U at $p>0.05$. **Results:** A total of 847 cases were reviewed for the study. Among 658 patients with a breast cancer diagnosis and complete ER PR data, 365 cases (55.5%) were non-PV carriers and 293 cases (44.5%) carried a PV in at least one of the genes listed above. Among 635 cases with available HER2 expression/amplification status, 355 (55.9%) cases were non-PV carriers and 288 (45.4%) cases were PV-carriers. When compared with non-PV carrier controls, *BRCA1* PV carriers' breast tumors had significantly lower ER and/or PR expression. Further, *BRCA2* and *TP53* PV tumors also displayed moderately lower ER expression. Contrarily, *CHEK2* tumors displayed higher ER and PR expression compared to controls. Further, *BRCA1* and *BRCA2* PV carriers were more likely to have HER2- breast cancers. **Conclusions:** Differences in ER, PR, HER2 expression levels were observed in germline PV carrier breast cancers, signaling differential impacts by germline PVs on the tumor evolution process. It is likely that tumor differences in PV carriers influence responses to therapies, including hormone therapy, anti-HER2 therapy, and subsequent survival. Research Sponsor: None.

ER, PR and HER2 expressions based on germline pathogenic variants.

	ER% mean (SD)	P-Value	PR% mean (SD)	P-Value	HER2- Case No. %	HER2+ Case No. %	P-Value
BRCA1	14.3 (32.7)	0	6.41 (20.2)	0	58 (98.3%)	1 (1.7%)	0
BRCA2	69.0 (38.0)	0.001	45.3 (37.7)	0.19	63 (95.5%)	3 (4.5%)	0
TP53	52.1 (46.7)	0.011	38.6 (44.7)	0.306	13 (61.9%)	8 (38.1%)	0.084
PALB2	68.2 (39.5)	0.114	39.5 (34.4)	0.163	20 (90.9%)	2 (9.1%)	0.112
ATM	80.1 (34.0)	0.609	51.0 (40.0)	0.631	21 (80.8%)	5 (19.2%)	0.471
CHEK2	93.3 (17.4)	0.003	72.0 (34.6)	0.001	32 (80.0%)	8 (20.0%)	0.462
MMRs	60.9 (47.8)	0.285	40.4 (42.5)	0.454	11 (61.1%)	7 (38.9%)	0.093
PTEN	96.8 (3.82)	0.305	83.8 (17.9)	0.066	4 (100%)	0 (0.0%)	0.368
Control/ Reference	*78.0 (34.5)*	-	*48.8 (41.1)*	-	*276 (77.7%)*	*79 (22.3%)*	-

10527 **Poster Session**

Use of comprehensive next-generation sequencing to identify pathogenic germline variants with therapeutic relevance in metastatic breast cancer. *First Author: Nicole Margo Grogan, University of Michigan Rogel Cancer Center, Ann Arbor, MI*

Background: Among patients with early-stage breast cancer, approximately 6-10% have a pathogenic germline variant (PGV) conferring inherited cancer predisposition. In contrast, few studies have explored the frequency and types of PGVs identified in patients with metastatic breast cancer (MBC); therefore, additional data is needed. **Methods:** From 2011-2020, 278 patients with MBC underwent fresh tumor biopsy and blood sample collection for paired tumor/normal DNA (targeted exome capture with analysis of 1700 genes) and RNA (tumor transcriptome) sequencing through the Michigan Oncology Sequencing (Mi-ONCOSEQ) program. Somatic and germline alterations were annotated and classified according to degree of clinical actionability with results returned to treating oncologists. Retrospective chart review was performed to determine if: 1) a PGV was identified prior to Mi-ONCOSEQ testing, 2) patients met National Comprehensive Cancer Network (NCCN) guideline criteria for genetic testing on the basis of personal or family cancer history and 3) patients received subsequent therapy informed by a PGV. **Results:** Forty-eight of the 278 patients (17.3%) had at least one PGV identified, with a total of 50 PGVs identified in this cohort. Only twelve of these PGVs (24%) had been identified prior to Mi-ONCOSEQ testing. The most frequent PGVs identified were in CHEK 2 (n = 9, 18%), MUTYH (n = 6, 12%), BRCA 1 (n = 5, 10%), BRCA2 (n = 5, 10%), ATM (n = 4, 8%) and PALB2 (n = 4, 8%). Somatic loss of heterozygosity events (LOH) occurred in 30 of the 50 cases with PGVs identified (60%). LOH events were observed in 83.3% of BRCA1, BRCA2, ATM and PALB2 PGVs, but were less frequently observed with CHEK2 (33.3%) and MUTYH (66.7%). Two hundred sixteen out of 278 patients (77.7%) in this cohort met NCCN criteria for genetic testing, although six patients with a PGV identified (CHEK2: n = 5; MUTYH: n = 1) did not meet NCCN criteria. Twenty-nine PGVs identified (58%) had potential therapeutic relevance and 11 patients (22.9%) received targeted therapy based on the PGV. **Conclusions:** The frequency of PGVs identified in this cohort is nearly double the frequency reported for patients with early-stage disease, suggesting that certain PGVs may confer worse prognosis. CHEK2, the most frequently identified PGV, was less likely to have an identifiable LOH event. The direct role of CHEK2 PGVs in tumor pathogenesis is uncertain, but other mechanisms of silencing the wild type allele must be considered. Despite the majority of patients meeting NCCN criteria for genetic testing, those with PGVs in CHEK2 were less reliably identified by this mechanism. The majority of PGVs identified were of potential therapeutic relevance, supporting the recommendation for genetic testing in all patients with MBC. Research Sponsor: U.S. National Institutes of Health.

10528 **Poster Session**

Identification and management of pathogenic mutations in *BRCA1, BRCA2,* and *PALB2* in a tumor-only genomic testing program. *First Author: Brittany L. Bychkovsky, Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Tumor-genomic testing is increasingly used to guide treatment decisions in cancer patients. Although tumor-only testing cannot definitively distinguish between germline versus somatic alterations, the identification of pathogenic or likely pathogenic (P/LP) variants in certain genes should prompt consideration of germline testing. Germline P/LPs in *BRCA1*, *BRCA2* and *PALB2* (*B1B2PAL*) are associated with hereditary cancer syndromes. **Methods:** We reviewed tumor-only genomic data (Dana-Farber Oncopanel) between 10/2016 and 6/2018 to examine the prevalence of P/LPs in *BRCA1, BRCA2,PALB2* among adult cancer patients at Dana-Farber Cancer Institute/Brigham and Women's Hospital. We characterized the frequency of P/LPs by primary tumor type, confirmation by germline testing before or within 12 months after Oncopanel testing or not, and factors associated with germline testing. **Results:** Among 7,575 patients, the median age was 62 (range 18-99); 53.9% were female. A total of 272 (3.6%) had P/LPs in *BRCA1* (n = 90), *BRCA2* (n = 162) and/or *PALB2* (n = 29). P/LPs in *B1B2PAL* were detected in 5.3% (38/712) of breast, 11.9% (34/285) of ovarian, 6.6% (18/272) of pancreatic, and 5.1% (12/234) of prostate cancers. P/LPs in *B1B2PAL* were also detected in other neoplasms (12.9% (8/62) of non-melanoma skin, 5.0% (43/855) of colorectal, 7.6% (20/264) of endometrial, and 4.6% (10/216) of head and neck cancers). Of 169 patients who had not had prior germline testing, 29/169 (17.2%) completed germline testing within 12 months after Oncopanel; 13 (7.7%) referred for testing declined or did not complete testing within 12 months, 14 (8.3%) died before or within 3 months of the Oncopanel results, and 113 (66.9%) had no documented germline testing within 12 months. Among 132 patients who had germline testing, 117 (88.6%) had a clinical indication based on personal or family history compared to 66/140 (47.1%) who did not undergo germline testing. Among 132/272 (48.5%) germline-tested patients, 70.5% were positive for a germline mutation in *B1B2PAL*; the remainder had somatic *B1B2PAL* mutations only. Germline testing was more often performed in patients with *B1B2PAL*-associated tumors (breast, ovarian, pancreatic and prostate cancers) or other clinical indications for germline testing. **Conclusions:** A low but clinically meaningful rate of P/LPs in *BRCA1, BRCA2* and *PALB2* was detected by tumor-only genomic testing in diverse malignancies. Given the implications of *B1B2PAL* alterations on treatment and familial cancer risk, our data support current NCCN guidelines recommending germline testing among patients with cancer and P/LPs in *B1B2PAL* detected on tumor-genomic testing and highlights the need for systems to ensure germline testing when indicated. Research Sponsor: None.

10529 **Poster Session**

Genetic counseling and testing rates among community cancer programs for patients with breast cancer following site-directed quality improvement. *First Author: Leigh Boehmer, Association of Community Cancer Centers, Rockville, MD*

Background: National Comprehensive Cancer Network (NCCN) guidelines recommend testing for highly penetrant breast/ovarian cancer genes in several scenarios, including women with early-onset (≤ 45 years) or metastatic HER-2 negative breast cancer regardless of family history. A 2018 Association of Community Cancer Centers (ACCC) survey (N = 95) showed that > 80% of respondents reported ≤ 50% testing rate of patients with breast cancer who met guidelines. To improve rates of genetic counseling(GC)/testing, ACCC partnered with 15 community cancer programs to support site-directed quality improvement (QI) interventions. **Methods:** Pre- and post-intervention data from 9/15 partner programs for genetically at-risk women with early-onset or HER-2 negative metastatic breast cancer (MBC) were analyzed. Pre-intervention data were collected between 01/01/2017 and 06/30/2019 while post-intervention data were collected as early as 07/01/2019 and as late as 10/01/2020. QI project scope ranged from creation of testing eligibility education to implementation of a virtual GC clinic. De-identified data collected included: family history documentation; GC appointment; test results; and timing of results relative to surgical date. **Results:** The pre-intervention cohort included 2691 women and the post- cohort included 3104 women who were eligible for GC. Early-onset patients in the post-intervention group attended a GC appointment 83% (331/401) of the time and 74% (296/401) had genetic test results, with 92% (271/296) receiving results before surgery. Sixty-one percent (1387/2267) of women with HER-2 negative MBC in the post-intervention group received GC, compared to 36% (658/1845) in the pre-intervention group. There was an overall increase in the number of MBC patients with documented test results following GC in the post-intervention cohort (55% (1243/2267) versus 15% (273/1845); $p < 0.0001$). Rates of GC appointments improved overall, regardless of family history documentation. Rates among those with a documented high-risk family history improved from 57% (729/1284) to 85% (1485/1741) following QI interventions ($p < 0.0001$). There was also a significantly higher rate of GC provided in the post-intervention group among women with negative family histories (40% (462/1155) versus 23% (181/778); $p < 0.0001$). GC also increased from 6% (35/629) to 45% (94/208) of women in the post-intervention cohort with no documentation of family history ($p < 0.0001$). **Conclusions:** Genetic testing is underutilized in women with breast cancer. Significant improvement was achieved with QI initiatives specifically designed to target easily identified populations meeting guidelines for GC/testing. This project demonstrates the importance of attention to practice-directed strategies aimed at improving identification of risk as well as follow through to GC/testing. Research Sponsor: Pfizer, Inc.

10530 **Poster Session**

Cancer surveillance in adults with germline *TP53* pathogenic variants: A single-center observational study. *First Author: Thomas Meyskens, Department of General Medical Oncology, Leuven Cancer Institute, University Hospitals Leuven, Leuven, Belgium*

Background: Germline pathogenic variants (PV) in the tumor suppressor gene *TP53* are associated with a high risk of developing diverse malignancies, often at young age, and predispose to Li-Fraumeni syndrome (LFS). Surveillance programs for presymptomatic PV carriers have shown survival benefit in a non-randomized trial. Here we describe the surveillance findings and clinical outcomes of adults with *TP53* PV undergoing a standardized screening protocol. **Methods:** We identified adults with germline PV in *TP53* who underwent surveillance at the University Hospitals Leuven, Belgium, between 04/2013 and 08/2020. Patients with prior cancer were allowed, while patients with an active malignancy requiring treatment at diagnosis of the *TP53* PV were excluded. Surveillance was performed per modified Toronto protocol, including annual whole body diffusion-weighted MRI (WB-DWI/MRI), brain MRI, abdominal ultrasound (US), endoscopic surveillance, laboratory tests, dermatological examination and breast MRI/US in females. The primary aim was to evaluate the number and type of malignancies and premalignant lesions diagnosed during screening and to assess the proportion of malignancies detected by surveillance. Secondary outcomes were the cancer detection rate during the first year of screening, the proportion of carriers with false-positive findings, and overall survival. **Results:** We included 42 adults from 20 apparently unrelated families. Median age was 38y (range, 17-70y) and 23 had a history of prior cancer. After a median follow-up of 41.5mo, we diagnosed 18 cancers in 12/42 participants (29%). Overall survival was 95% in all participants, including 2 carriers who opted to discontinue surveillance. Surveillance detected 10/18 cancers (56%), the majority of whom through WB-DWI/MRI (6/10; 60%). No malignancies were identified with brain MRI. In 5/42 individuals (12%), surveillance detected a malignancy during the first year of screening. Only 2/10 cancers discovered with surveillance (1 soft tissue and 1 bone sarcoma) belong to the LFS core tumors. Cancers not detected with surveillance (8/18) were 6 non-melanoma skin cancers and 2 interval cancers (sarcoma post radiation, secondary acute leukemia). Additionally, we detected 27 premalignant lesions in 11/42 patients (26%), of whom 78% were diagnosed by colonoscopy. False-positive findings occurred in 7/42 patients (17%) and were mostly seen with WB-DWI/MRI. **Conclusions:** Adults with germline PV in *TP53* that undergo surveillance have high cancer detection rates. The majority of malignancies were asymptomatic at diagnosis and detected with WB-DWI/MRI. Despite the high cancer incidence, few LFS core cancers were diagnosed and survival was encouraging. Increased genetic testing changes the clinical picture of germline *TP53* carrier populations, justifying the transition from LFS to a wider concept of heritable *TP53*-related cancer syndrome. Research Sponsor: None.

10531 **Poster Session**

Twenty-one-gene recurrence score (RS) in germline (g)*CHEK2* mutation-associated versus sporadic breast cancers (BC): A multi-site case-control study. *First Author: Anosheh Afghahi, University of Colorado, Aurora, CO*

Background: Genomic assays, such as RS, are used to determine chemotherapy benefit in early-stage, estrogen receptor (ER)- and/or progesterone receptor (PR)-positive, HER2 negative BC patients (pts). Currently, guidelines to use pts' germline genetic testing results to guide adjuvant therapy are lacking. Several reports have indicated worse outcomes for BC pts with g*CHEK2* pathogenic variants (PV). We investigated whether PV in *CHEK2* were associated with increased RS. **Methods:** Patient-level clinical data and RS were derived from electronic medical records of seven medical centers between years 2013-17. Confirmation of RS using the Genomic Health provider portal was performed. 38 pts with germline PV in *CHEK2* (15 pts/39.5% with c.1100delC mutation) and RS score (cases) were matched with BC pts whose genetic testing did not identify PV (controls) using a 1:2 matching schema. Pts were matched based on age at diagnosis and lymph node (LN) status. LN negative pts were further matched based on T-stage. A multivariate random intercept linear mixed model of *CHEK2* mutation status on RS was performed, adjusting for PR. A secondary ordinal univariate analysis was conducted that categorized RS into low, intermediate and high risk (< 18, 18-30, and > 30, respectively). P-values were reported based on a null hypothesis of no effect against a two-sided alternative. **Results:** The median RS for cases was 19.5 (interquartile range [IQR]: 15 to 25) and the median RS for controls was 18 (IQR: 12 to 22). A greater proportion of cases were categorized as high risk (10.5%) compared to controls (5.6%), and a smaller proportion of cases were categorized as low risk (36.8%) compared to controls (49.3%). Cases had higher grade and increased proportion of PR-negative BC as compared with controls (grade 1: 12.1% of cases versus 32.4% of controls; PR-negative: 7.9% of cases versus 5.6% of controls). The variables used to match cases and controls (age, lymph node status, and T-stage) had similar summary statistics. The RS was 1.97-point higher in pts with g*CHEK2* PV compared to controls, after adjusting for PR (95% confidence interval [CI]: 1.02-point lower to 4.96-point higher; $p = 0.194$). The secondary analysis of *CHEK2* mutation status on an ordinal RS risk group yielded comparable results; on average, the odds of being high risk compared to the combined intermediate/low risk groups was 1.72 times higher in cases compared to controls (95% CI: 0.77 to 3.80; $p = 0.181$), but these differences were not significant. **Conclusions:** Our case-control study did not show a statistically higher RS for BC that develops in pts with g*CHEK2* PV. Further studies are warranted to evaluate the association between type of *CHEK2* PV (frameshift versus missense) and other modifying genetic variables and RS. Research Sponsor: None.

10532 **Poster Session**

Identifying individuals with primary central nervous system tumors at risk for hereditary cancer syndromes using the Utah Population Database. *First Author: Nicholas Shawn Whipple, Division of Pediatric Oncology, Department of Pediatrics, University of Utah, Salt Lake City, UT*

Background: CNS tumors are the most common solid tumors and the deadliest cancers in children. Approximately 10% of children with a CNS tumor harbor a hereditary cancer syndrome (HCS), but many will not be tested for a HCS. The Utah Population Database (UPDB) contains comprehensive cancer registry data for Utah families and can determine multigenerational cancer pedigrees across an archive of 5.8 million individuals. Early identification of HCSs results in improved cancer surveillance and outcomes, reducing the impact of CNS tumors in children. We hypothesize that the UPDB can identify children and families with HCSs not previously identified. **Methods:** We queried the UPDB for individuals ages 0-39 diagnosed with a primary CNS tumor (malignant and benign) between 1966-2017 and generated cancer pedigrees of 3 generations or more for probands, extending to at least third-degree relatives. Specialized software calculated a familial standardized incidence ratio (FSIR) to determine families with excess clustering of CNS tumors. Clinical cancer genetics experts reviewed pedigrees to confirm patterns of HCS. **Results:** We identified 4,634 CNS tumors in 4,550 individuals, of whom 2,233 (49%) reside in high-quality pedigrees containing ≥2 grandparents, at least 1 from both maternal and paternal sides. To identify families with excess clustering of CNS tumors, we selected pedigrees with an FSIR $P < 0.05$ and ≥2 affected patients, resulting in 161 high-risk families with a mean of 170 (median 96) relatives per pedigree of 3-6 generations. Among these 161 families, there were 2,017 unique relatives (first-third degree) of CNS probands with 2,355 tumors (any site), for a per pedigree average of 14.7 tumors in 12.5 relatives. Review of the 10 highest risk pedigrees indicated that 4 meet HCS criteria, including Li-Fraumeni (n = 2), von Hippel-Lindau (n = 1), and rhabdoid tumor predisposition (n = 1). **Conclusions:** The UPDB can produce multigenerational cancer pedigrees that identify individuals and families at risk of harboring a HCS who warrant germline testing. These findings should encourage clinicians to perform thorough family history screening and to always consider workup for associated HCSs. Research Sponsor: Intermountain Foundation at Primary Children's Hospital.

10533 **Poster Session**

Rare *BAP1* variant of unknown significance (VUS) and analysis of *BAP1* codon 146 genomics: Potential germline and therapeutic implications. *First Author: Jo-Ellen Murphy, Foundation Medicine, Cambridge, MA*

Background: The *BAP1* gene (*BRCA1*-Associated Protein) encodes a protein ubiquitin carboxyl-terminal hydrolase (BAP1), which removes ubiquitin moieties and regulates various cellular functions including DNA repair. This association has driven interest in defining if *BAP1* variants confer susceptibility to PARP inhibitors (PARPi). Germline and somatic *BAP1* alterations are both rare, mostly unique, often classified as VUS's, and associated with a broad range of overlapping tumor types. Based on the identification of a *BAP1* R146K VUS variant in tumor, also previously identified as germline, an analysis of *BAP1* codon 146 alterations was initiated to explore potential genetic and therapeutic implications. **Methods:** 394,756 tumor specimens were tested using hybrid capture-based genomic profiling (Foundation Medicine) for all variant types and Tumor Mutational Burden (TMB). *BAP1* codon 146 cases were analyzed for clinicogenomic features and germline results when available. **Results:** *BAP1* codon 146 variants were identified in 23 unique patients across the following tumor types: cholangiocarcinoma (CCA) (4), mesothelioma (4), NSCLC (3), RCC (2), ocular melanoma (2), and carcinoma of unknown primary (CUP) (3); many of which overlap with known and suspected germline associated *BAP1* syndromic tumor types. *BAP1* R146 mutations were classified as VUS in 16 patients and 7 were likely or known pathogenic. In 20 of the 23 cases where zygosity could be determined 16 (80%) were homozygous and 4 (20%) were heterozygous. In 2 of the 3 NSCLC cases, the *BAP1* variant appeared likely somatic and/or associated with a high TMB. A previously reported germline *BAP1* variant in a RCC patient, R146K, occurred 5 times in our tumor database. One case which was homozygous in tumor and confirmed in germline occurred in a patient who had both breast and CCA. She also had a sibling with RCC who shared the germline *BAP1* R146K variant along with multiple 1st and 2nd degree relatives with RCC, mesothelioma, melanoma, liver cancer, colon cancer, and a cancer of unknown primary. **Conclusions:** Codon 146 of *BAP1* localizes to the UCH (ubiquitin carboxyl hydrolase) domain, which includes the BARD1 interaction region. Loss of BAP1 activity as a consequence of germline or somatic mutation likely impacts ubiquitination status and activity of downstream proteins, such as those involved in DNA repair. For patients with suspected *BAP1* inactivating alterations, often seen in non-homologous recombination deficiency related tumor types, PARPi therapy may be relevant. As demonstrated here, variants identified through tumor testing may also aid in re-classification of germline VUS's. These results support the further investigation and validation of *BAP1* alterations for germline risk stratification and therapeutic strategies with either PARPi and/or other therapies specific to tumors with impaired chromatin remodeling. Research Sponsor: None.

10534 **Poster Session**

Germline alterations among Hispanic men with prostate cancer. *First Author: Justin Shaya, University of California San Diego, Moores Cancer Center, La Jolla, CA*

Background: With the growing indications for germline testing in prostate cancer (PCa), there is accumulating evidence that African American and Hispanic men with PCa are significantly under-tested compared to non-Hispanic white (NHW) men. Given this, little is known about the pathogenic germline variant landscape in Hispanic men with PCa. **Methods:** This was a retrospective cohort analysis of 17,256 men with PCa who underwent diagnostic germline testing through a commercial laboratory (Invitae) from 2015-2020. Self-identified Hispanic and NHW men were selected for comparative analysis. The primary endpoint was the rate of pathogenic/likely pathogenic (PLP) germline alterations in Hispanic men among 25 genes associated with PCa. Secondary endpoints included comparison of PLP rates in Hispanic vs NHW men, the rate of specific PLP alterations, and the rate of variants of uncertain significance (VUS). Fisher's exact test was used to compare germline alteration rates for significance. **Results:** We identified 508 Hispanic and 12,542 NHW men with PCa who underwent testing during the study period. Median age at the time of testing was 69 vs 67 years in Hispanic vs NHW cohorts. A family history of PCa was reported in 21.1% (N=108) vs 27.3% (N=3428) in the Hispanic vs NHW cohorts, respectively (p=0.002). The PLP alteration rate was 7.1% in the Hispanic cohort and this rate was numerically lower but not significantly different when compared to the NHW cohort (9.7%) (p=0.058). A significantly higher rate of VUS was seen in the Hispanic cohort (Table). The four most frequently detected genes with PLP alterations in both cohorts were *ATM, BRCA1, BRCA2,* and *CHEK2*. Only the rate of *CHEK2* alterations was significantly different between cohorts among all 25 genes analyzed (Table). **Conclusions**: In this analysis, the PLP alteration rate among Hispanic men was 7.1%, a much higher rate than has been previously reported, and the germline genomic landscape was similar to that of NHW men. The VUS rate was significantly higher among Hispanic men, a known consequence of under-testing among minority populations.These data support germline testing in Hispanic men with prostate cancer and emphasize the importance of improving testing rates. Research Sponsor: None.

Germline characteristics.

Germline Characteristic	Hispanic	Non-Hispanic White	p-value
PLP alteration rate*	7.1%	9.7%	0.058
ATM	1.2%	1.6%	0.71
BRCA1	0.6%	0.6%	1.00
BRCA2	2.8%	2.5%	0.67
CHEK2	0.8%	2.6%	0.006**
MSH2, MSH6, MLH1, or PMS2	1.2%	1.2%	0.82
VUS alteration rate	21.5%	16.6%	0.005**
VUS detected *without* a co-occurring PLP alteration	19.3%	15.0%	0.010**
VUS detected *with* a co-occurring PLP alteration	2.2%	1.6%	0.27

*Shown are the most commonly detected PLP alterations among the 25 genes analyzed. **Significance concluded if p<0.05.

10535 **Poster Session**

Pan-cancer evaluation of homologous repair deficiency somatic mutations and response to first-line anti-neoplastic therapy. *First Author: Jessica A. Lavery, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Homologous recombination is a major mechanism of defective DNA repair, but it remains uncertain whether homologous repair deficient (HRD) tumors have favorable prognosis or are more/less likely to respond to treatment than tumors lacking such mutations. **Objective:** To determine whether lung (NSCLC) and colorectal (CRC) HRD+ tumors have better survival or response to chemotherapy than HRD- tumors. **Methods:** Patients with de novo stage IV NSCLC or CRC who had next generation sequencing (NGS) between 2015-2018 from one of four cancer centers were identified. Records were curated using the PRISSMM framework to ascertain treatment, overall survival (OS) and progression free survival based on imaging (PFS-I) and oncologists' notes (PFS-M). Each NSCLC or CRC tumor was categorized as HRD+ if NGS revealed an oncogenic/likely oncogenic mutation in: *ATM, BAP1, BARD1, BLM, BRCA1, BRCA2, BRIP1, CHEK2, FAM175A, FANCA, FANCC, NBN, PALB2, RAD50, RAD51, RAD51C, RTEL1,* or *MRE11A* based on the OncoKB database. The tumor was categorized as HRD- if no oncogenic mutation in any of these genes was evident and HRD indeterminate (HRD?) if no mutation was identified but the panel did not include all genes. OS, PFS-I and PFS-M from start of first line therapy were reported by HRD status. The percentage with a good response to first line therapy (≥2x the median) and exceptional response (≥3x the median) was estimated for each endpoint. **Results:** For NSCLC 4% were HRD+, 59% HRD- and 37% HRD?. For CRC there were 5% HRD+, 60% HRD- and 35% HRD?. There were no significant differences for any survival endpoint between patients who were HRD+ vs HRD- in univariable analyses. The proportion of good and exceptional responders to first line systemic chemotherapy also did not vary by HRD status, though patients with HRD+ CRC were potentially more likely to be exceptional responders. Similarly, no differences between HRD+ and HRD- tumors were apparent for the subgroup receiving platinum containing therapy. **Conclusions:** NSCLC and CRC patients with somatic mutations in HRD oncogenic genes did not differ from patients lacking such a mutation with respect to OS or PFS. CRC patients with HRD+ tumors may be more likely to be exceptional responders, but sample sizes are limited. By May, the analysis will include breast and pancreatic cancer cases. Research Sponsor: American Association for Cancer Research GENIE BPC.

	NSCLC HRD- = 411; HRD+ = 29; HRD? = 257			CRC HRD- = 406; HRD+ = 32; HRD? = 235		
Endpoint HRD + - or ?	**Median (95% CI), y**	**Good response**	**Exceptional Response**	**Median (95% CI), y**	**Good Response**	**Exceptional Response**
OS						
-	1.6 (1.4, 2.0)	28%	9%	2.5 (2.0, 2.7)	18%	5%
+	1.5 (.71, 2.8)	24%	7%	2.0 (1.2, —)	31%	22%
?	1.2 (1.1, 1.6)	31%	13%	1.9 (1.7, 2.2)	24%	5%
PFS-I						
-	.47 (.42, .56)	31%	16%	0.79 (.71, 0.84)	18%	10%
+	.43 (.21, .61)	14%	3%	0.85 (.69, 1.2)	19%	12%
?	.42 (.34, .51)	27%	18%	0.73 (.63, 0.84)	21%	14%
PFS-M						
-	.59 (.54, .69)	28%	16%	1.0 (.90, 1.1)	28%	16%
+	.61 (.41, 1.0)	21%	10%	1.0 (.82, 2.1)	21%	10%
?	.58 (.49, .67)	27%	17%	1.0 (.85, 1.1)	27%	17%

10536 **Poster Session**

Genetic ancestry and clinical outcomes to immune checkpoint inhibitors among seven common cancers. *First Author: Amin Nassar, Brigham and Women's Hospital, Boston, MA*

Background: Prior studies and clinical trials report associations between self-reported race and clinical outcomes to Immune Checkpoint Inhibitors (ICIs). However, comprehensive studies of ancestry-associated differences in clinical outcomes have not been performed. We derived genetic ancestry scores and assessed clinical outcomes in 1341 patients with cancer treated with ICIs. **Methods:** Patients at the Dana-Farber Cancer Institute treated with ICIs only and with relevant cancer types and targeted exome sequencing data (Oncopanel) were included. Relevant cancer types included colorectal adenocarcinoma (CRC), esophagogastric adenocarcinoma (EGC), head and neck squamous cell carcinoma (HNSCC), melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and urothelial carcinoma (UC). We developed a bioinformatics pipeline to infer fine-scale genetic ancestry for each patient (n=1341) directly from tumor sequencing data by leveraging off and on-target sequenced reads and external ancestry reference panels. Three ancestry scores were determined (African, East Asian, European). Overall survival (OS) and time-to-treatment failure (TTF) were compared by Cox logistic regression between ancestral populations. Hazard ratio (HR) was derived using multivariable analysis, adjusted for single versus combination therapy, prior lines of therapy, and tumor mutational burden (TMB, as percentiles). **Results:** Median follow-up was 37.8 months (m; interquartile range: 35.7-39.5m). Common cancer types included CRC (n=52), EGC (n=114), HNSCC (n=88), melanoma (n=274), NSCLC (n=571), RCC (n=99), and UC (n=143). A higher East Asian ancestry (EAS) was significantly associated with worse OS (p=0.03) and TTF (p=0.002) in patients with RCC, independent of the histologic subtype (Table). There was no significant association between any of the three ancestral populations and clinical outcomes in the other 6 cancer types. **Conclusions:** We described clinical outcomes to ICIs across three global populations in 7 cancers. As the medical field re-evaluates the use of self-reported race in clinical decision-making, we utilize a novel ancestry pipeline that can be readily applied to tumor-only sequencing panels and better characterize non-white populations. We find no ancestry differences in clinical outcomes except in patients with RCC treated with ICIs which will require future validation. We plan to analyze genomic correlates of response by ancestry in each of the cancer types to better understand these diverge clinical behaviors. Research Sponsor: None.

RCC cohort.

	HR (95%CI)					
	EAS	**African American**	**Prior lines of therapy**	**Single versus combination**	**Percentile TMB**	**Non-clear cell versus clear cell histology**
OS (58/99 events)	226 (2-32271)	2 (0.4-9.9)	1.3(1-1.7)	1.8 (0.9-3.6)	0.9 (0.3-2.7)	2.5 (1.2-5.2)
TTF (83/99 events)	1000 (14-73792)	0.4 (0.1-1.7)	1.1 (0.8-1.3)	2.0 (1.2-3.5)	0.7 (0.3-1.7)	2.7 (1.4-5.1)

10537 **Poster Session**

The protean phenotype of MSH6 pathogenic variants (PV) in Lynch syndrome (LS) patients (pts). *First Author: Michelle J McSweeny, Fox Chase Cancer Center, Philadelphia, PA*

Background: LS is among the most common hereditary cancer (CA) syndromes. PVs in MSH6 are 2-4 fold more common in the population (1/758) than those in MLH1 (1/1946) or MSH2 (1/2841), and are increasingly regarded as lower penetrance for CRC due to published data supporting later mean age of CRC onset and lower CRC risk. Unlike for MLH1/MSH2, NCCN 2020 CA risk estimates recognize only endometrial CA (EC) and CRC risks in MSH6+ carriers as clearly above SEER population estimates. Further, risks of other LS manifestations such as skin disease/Muir-Torre, ovarian CA (OC), and possible rare tumors in LS like sarcoma, have been minimally characterized in MSH6+ carriers. **Methods:** Pedigree data for 44 MSH6+ index (first-evaluated family member by our program) pts consecutively ascertained since 2009 at Fox Chase (FCCC) were reviewed. 1 pt w/a rare MSH6 uncertain variant w/personal history (PHx) of MSH6-expression deficient EC (age 50) and MSH6-deficient sebaceous skin CA (age 50) and a strong family history (FHx) c/w LS is also included here. 34% (15/44) index pts were referred to FCCC for cascade testing due to a known MSH6 PV in the family. Of the remaining 29 index pts, ascertainment included: 14% w/positive universal LS tumor screening, 21% w/early-onset or synchronous LS CA, 14% w/multi-gene panel for PHx of OC, 10% w/incidental MSH6+ result (2 had testing for PHx breast CA, 1 tumor genomic profiling), and 28% w/PHx and/or FHx of LS CA warranting genetic testing. Age of CA onset and path data were verified in $>$ 90% index pts. **Results:** Index pts had a mean age of 55.5 yrs, and 77% were female. Overall, 11% (5/44) of MSH6+ index pts were found to have LS at diagnosis of synchronous primary CAs (3 EC/OC, 1 CRC/CRC, 1 CRC/EC), and 4/5 of these occurred $<$50 yrs. An additional 20% (9/44) index pts reported PHx of $>$2 metachronous LS CAs. OC was the presenting CA in 14% (6/44) female index pts; 2 additional index pts had rarer OC variants (Mullerian duct @ 41, primary peritoneal CA @ 50). Skin manifestations of LS were documented in 9.1% (4/44) index pts (3 sebaceous, 1 SCC in-situ/Bowen's disease); 1 other family had documented sebaceous CAs in an FDR (father) but the 2 daughters seen @FCCC (both 30s) had yet to develop skin lesions. 2 index pts were found to have LS after developing early-onset breast CA (age 39) and contralateral breast CA (ages 50 and 54). Finally, 7% (3/44) index pts had a PHx of sarcoma: 2 were liposarcomas (ages 57 and 67), and 1 was a dermatofibrosarcoma. 2 other index pts had siblings w/childhood sarcomas. **Conclusions:** Our data, encompassing 44 MSH6+ pts evaluated in our clinic and consecutively ascertained, suggest MSH6 PV carriers develop synchronous primaries (11%), common and rare OC histologic types (18%), sarcomas (7%) and skin disease/Muir-Torre (9%). While common in the population and lower penetrance for CRC, MSH6 PV can behave in uncommon ways and may have significant extra-colonic CA risks such as OC, sarcoma and skin manifestations. Research Sponsor: U.S. National Institutes of Health.

10538 **Poster Session**

Identification and characterization of de novo TP53 mutation carriers in Li-Fraumeni syndrome families: A single institution experience. *First Author: Carlos Christian Vera Recio, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Li-Fraumeni syndrome (LFS) is an inherited cancer syndrome mainly caused by a deleterious mutation in TP53. An estimated 48% of LFS patients present due to a deleterious de novo mutation (DNM) in TP53. The knowledge of DNM status, DNM or familial mutation (FM), of an LFS patient requires genetic testing of both parents which is often inaccessible, making de novo LFS patients an understudied population. Famdenovo.TP53 is a Mendelian Risk prediction model used to predict DNM status of TP53 mutation carriers based on the cancer-family history and several input genetic parameters, including disease-gene penetrance. The good predictive performance of Famdenovo.TP53 was demonstrated using data collected from four historical US cohorts. We hypothesize that by incorporating penetrance estimates that are specific for different types of cancers diagnosed in family members, we can develop a model with further improved calibration, accuracy and prediction. **Methods:** We present Famdenovo.CS, which uses cancer-specific penetrance estimates that were derived previously using a Bayesian semi-parametric competing risk model, to calculate the DNM probability. We use our model to analyze 101 families recently collected from the Clinical Cancer Genetic program at MD Anderson Cancer Center (CCG-TP53) that includes 20 families with known DNM status and 81 families with unknown DNM status. We used the concordance index (AUC), observed:expected ratios (OE) and Brier score (BS) to measure our model's discrimination, calibration and accuracy, respectively. We estimate the proportion of probands that present a DNM and compare DNM to FM carriers in several areas including: cancer types diagnosed, age at diagnosis, number of primary cancers diagnosed, sex, amino acid change caused by mutation in TP53. **Results:** Famdenovo.CS showed equally good discrimination and calibration performance to Famdenovo.TP53, while improving the overall accuracy, demonstrated by a decrease in the Brier score of -0.09 (95% CI: [-0.02, -0.19]). Of the 101 probands in the CCG-TP53 cohort, we predict 39 to be DNMs and 62 to be FMs. The cancer types and ages of diagnosis observed in FMs and DNMs are similarly distributed. **Conclusions:** Famdenovo.CS shows improved model accuracy in the CCG cohort. DNMs in TP53 are a prevalent cause of LFS and we did not find differences in the clinical characteristics of DNM and FM carriers. Our model allows for a systematic identification and characterization of TP53 DNM carriers. Research Sponsor: U.S. National Institutes of Health, Cancer Prevention and Research Institute of Texas.

10539 **Poster Session**

Differential effects of the 2015 American Cancer Society guidelines on screening mammography exams based on socioeconomic status. *First Author: Kathleen M. Capaccione, Department of Radiology, Columbia University Irving Medical Center, New York, NY*

Background: Guidelines for screening mammography have changed several times since initiation of regular screening mammography in the 1970's. Most recently, in 2015, the American Cancer Society (ACS) revised their screening guidelines, recommending that a patient discuss screening mammography with her primary care doctor (PCP) between the ages of 40-44 and should begin yearly screening at age 45; after age 54, ACS recommended screening every other year. Prior to this, from 2003-2015, ACS had recommended screening mammography every year beginning at the age of 40. We hypothesized that these guidelines were adopted to varying degrees in different patient populations and may have disproportionately reduced screening mammography utilization in socioeconomically disadvantaged populations. **Methods:** Here, we analyzed monthly screening mammography rates over time in two large New York City hospitals, one in a socioeconomically advantaged area and the other in a socioeconomically disadvantaged area. Using our radiology records query system, we searched for monthly screening mammography numbers for women by decade from 2012 to 2018. We performed statistical analysis to evaluate changes in number of exams over time. Student's t-tests were used to evaluate for significant differences. **Results:** In both groups of 40-49 year old patients, monthly mammograms increased from 2012-2016. In the socioeconomically advantaged group, this increase continued until 2018 resulting in an overall 400% increase in screening mammograms over time. The change in ACS screening guidelines had no effect on the rate of screening mammography in this group. Conversely, after the revision of the ACS guidelines in 2015, there was a marked decline in screening mammography in the 40-49 year old group in the socioeconomically disadvantaged population. By 2018, there was a statistically significant difference in women screened in all age groups (40-49, $p<.0001$; 50-59, $p<.0001$; 60-69, $p<.01$; 70-79, $p<.0001$; 80+, $p<.0001$) between these two patient populations. **Conclusions:** These data suggest that implementation of the 2015 ACS screening guidelines had a disproportionate effect on patients from socioeconomically disadvantaged areas and that these effects have led to significant disparities in screening mammography trends over time. We postulate that lower levels of health literacy may have contributed to misunderstanding of the screening guidelines. More research is needed to elucidate the underlying etiology of these disparities and ensure that women from all socioeconomic backgrounds receive appropriate screening mammography. Over time, this may result in disproportionate breast cancer morbidity and mortality in populations not receiving appropriate screening. Research Sponsor: None.

10540 **Poster Session**

Community-based lung cancer screening adherence to Lung-RADS recommendations. *First Author: Roger Y. Kim, University of Pennsylvania, Philadelphia, PA*

Background: In the NLST and NELSON trials, most low-dose CT (LDCT) screen-detected lung cancers were not diagnosed during the first round of screening, suggesting that longitudinal adherence to lung cancer screening (LCS) recommendations is key. Adherence was as high as 95% in clinical trials, but limited data exist regarding LCS adherence in clinical practice. We aimed to determine adherence to Lung-RADS recommendations among community-based patients undergoing LCS. **Methods:** We performed a multicenter retrospective cohort study of patients screened for lung cancer at healthcare systems within the Lung Population-based Research to Optimize the Screening Process (PROSPR) Consortium. We included 55-80 year-old current or former smokers who received a baseline (T0) LDCT with a Lung-RADS score between January 1, 2015 and September 30, 2017 and excluded patients who were diagnosed with lung cancer prior to the T0 scan. Over a 24-month period, we calculated the proportion of patients adherent to Lung-RADS recommendations and evaluated associations with patient-level (age, sex, race, ethnicity, smoking status, body mass index, Elixhauser comorbidities, year of T0 scan, and Lung-RADS score) and census tract (median family income, level of education) data, using multivariable logistic regression with mixed effects to account for site variability. **Results:** Of the 6,723 patients in our cohort (median age 65 years [IQR 60-69]; 45.1% female; 73.0% white; 59.0% current smokers), 5,583 (83.0%) had Lung-RADS 1 or 2 T0 scans, 733 (10.9%) Lung-RADS 3, 274 (4.1%) Lung-RADS 4A, and 133 (2.0%) Lung-RADS 4B or 4X. Overall, 55.2% (3,709/6,723) of patients were adherent (Table). In the final multivariable model, Black patients had reduced adherence compared to white patients (adjusted odds ratio [aOR] 0.79, 95% CI 0.66-0.94), while greater adherence was observed in former smokers compared to current smokers (aOR 1.33, 95% 1.19-1.49). Compared to individuals with a negative T0 scan (Lung-RADS 1 or 2), those with Lung-RADS 3 (aOR 1.56, 95% CI 1.31-1.86), 4A (aOR 1.63, 95% CI 1.24-2.15), or 4B/4X (aOR 3.59, 95% CI 2.30-5.60) T0 scans had greater odds of adherence. **Conclusions:** In the largest study of real-world patients receiving LCS to date, adherence to Lung-RADS recommendations is lower than previously observed in clinical trials. Our results highlight the need for further study of system-level mechanisms to improve longitudinal LCS adherence rates. Research Sponsor: U.S. National Institutes of Health.

Lung-RADS Score	Lung-RADS Recommendation	Definition of Adherence	Adherence, %
1	12 month LDCT	9-15 month LDCT or CT chest	52.5% (2,931/5,583)
2			
3	6 month LDCT	3-9 month LDCT or CT chest	67.1% (492/733)
4A	3 month LDCT or PET/CT	2-6 month LDCT, CT chest, or PET/CT	66.4% (182/274)
4B	Chest CT, PET/CT, and/or	<3 month LDCT, CT chest, PET/CT, or procedure (bronchoscopy,	78.2% (104/133)
4X	tissue sampling	mediastinoscopy, percutaneous procedure, thoracic surgery)	

10541 **Poster Session**

Global tissue stiffness on breast MR elastography: High-risk dense breast patients have higher stiffness compared to average-risk dense breast patients. *First Author: Bhavika K. Patel, Mayo Clinic, Phoenix, AZ*

Background: Biomechanical tissue properties may vary in the breasts of patients at elevated risk for breast cancer. We aim to quantify *in vivo* biomechanical tissue properties in various breast densities and in both normal risk and high risk women using Magnetic Resonance Imaging (MRI)/MRE and examine the association of biomechanical properties of the breast with cancer risk. **Methods:** In this IRB–approved prospective single-institution study, we recruited two groups of women differing by breast cancer risk to undergo a 3.0 T dynamic contrast enhanced MRI/MRE of the breast. Low-average risk women were defined as having no personal or significant family history of breast cancer, no prior high risk breast biopsies and a negative mammography within 12 months. High-risk breast cancer patients were recruited from those patients who underwent standard of care breast MR. Within each breast density group (non-dense versus dense), two-sample *t*-tests were used to compare breast stiffness, elasticity, and viscosity across risk groups (low-average vs high). **Results:** There were 50 low-average risk and 86 high-risk patients recruited to the study. The risk groups were similar on age (mean age = 55.6 and 53.6 years), density (68% vs. 64% dense breasts) and menopausal status (66.0% vs. 69.8%). Among patients with dense breasts, mean stiffness, elasticity, and viscosity were significantly higher in high risk patients ($N = 55$) compared to low-average risk patients ($N = 34$; all $p < 0.001$). In the multivariate logistic regression model, breast stiffness remained a significant predictor of risk status (OR=4.26, 95% CI [1.96, 9.25]) even after controlling for breast density, MRI BPE, age, and menopausal status. Similar results were seen for breast elasticity (OR=4.88, 95% CI [2.08, 11.43]) and viscosity (OR=11.49, 95% CI [1.15, 114.89]). **Conclusions:** Structurally-based, quantitative biomarker of tissue stiffness obtained from global 3D breast MRE is associated with differences in breast cancer risk in dense breasts. As such, tissue stiffness could provide a novel prognostic marker to help identify the subset of high-risk women with dense breasts who would benefit from increased surveillance. Research Sponsor: Mayo Clinic MEGA grant.

MRE parameters MRI background parenchymal enhancement (BPE) by breast density and risk status.

Characteristic	Non-Dense, Normal Risk (*N* = 16)	Non-Dense, High Risk (*N* = 31)	Non-Dense *p*-Value	Dense, Normal Risk (*N* = 34)	Dense, High Risk (*N* = 55)	Dense *p*-Value
Breast Stiffness Mean (*SD*)	1.07 (0.18)	1.69 (1.19)	0.008	1.16 (0.21)	2.14 (1.12)	<0.001
Breast Stiffness Median (Range)	1.05 (0.65–1.44)	1.09 (0.54–4.36)	—	1.15 (0.76–1.67)	1.37 (0.92–4.09)	—
BPE (#, % Minimal or Mild)	14 (87.5%)	28 (90.3%)	>0.99	20 (58.8%)	35 (63.6%)	0.66

10542 **Poster Session**

Risk factors for early-onset colorectal cancer in China. *First Author: Zhe Pan, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China*

Background: The incidence of colorectal cancer among persons aged < 50 years (early-onset colorectal cancer, EOCRC) has increased since the early 1990s. However, the risk factors contributing to this trend remain largely unknown. **Methods:** We conducted a retrospective study of participants who were aged < 50 years and without a previous cancer history, using the China Kadoorie Biobank cohort study. We analyzed data related to demographics, lifestyle habits, family history, and comorbidities of EOCRC cases with participants without colorectal cancer in this age group (controls). Univariate and multivariate-adjusted cox regression models were used to estimate the associations with risk factors. **Results:** We identified 225 EOCRC cases and 88842 controls that include the final analyses. Of the 225 EOCRC patients, 105 (46.7%) were colon cancers and 120 (53.3%) were rectum cancers. EOCRC cases were older, have more intake of fish and eggs, have higher BMIs, diabetes, and family history of cancer compared with controls ($P < 0.05$). After adjustment for potential confounding factors, increasing age (HR 2.18, 95%CI 2.05-2.31), BMI (HR 1.06, 95%CI 1.01-1.11), family history of cancer (HR 1.41, 95%CI 1.00-1.98), and more intake of fish (HR 1.54, 95%CI 1.09-2.19) were significantly associated with a higher risk of EOCRC. In sensitivity analyses stratified by cancer site (colon and rectum), the results remained consistent. **Conclusions:** Based on the large Chinese cohort study, we found increasing age, higher BMI or obesity, family history of cancer, and more intake of fish were independent risk factors for EOCRC. Further studies are needed to identify factors that cause the increasing incidence of EOCRC in China and other countries, and explore the potential mechanism behind. Research Sponsor: This work was supported by grants (2016YFC0900500, 2016YFC0900501, 2016YFC0900504,) from the National Key Research and Development Program of China, grants from the Kadoorie Charitable Foundation in Hong Kong and grants (088158/Z/09/Z, 104085/Z/14/Z, 1040, Grants from the National Natural Science Foundation of China (number 82072620) and Guangdong Basic and Applied Basic Research Foundation (number 2020A1515110056).

	Unadjusted Models			Adjusted Models		
Variables	HR	95%CI	P Value	HR	95%CI	P Value
Age	2.15	2.03-2.28	< 0.001	2.17	2.04-2.30	< 0.001
BMI	1.06	1.02-1.10	0.006	1.05	1.00-1.10	0.0305
Female	0.99	0.76-1.30	0.96	0.91	0.54-1.53	0.7144
Alcohol user	0.95	0.73-1.23	0.66	0.98	0.72-1.32	0.8724
Intake of Eggs	1.93	1.03-3.65	0.04	1.70	0.90-3.21	0.1052
Intake of Fish	1.66	1.23-2.24	< 0.001	1.39	1.02-1.90	0.0398
Family history of cancer	1.60	1.14-2.25	0.006	1.41	1.00-1.98	0.0477
Diabetes	2.66	1.31-5.38	0.007	1.21	0.59-2.47	0.6036

10543 **Poster Session**

Analysis of breast cancer screening results in urban areas of Henan Province. *First Author: Guo Lan-Wei, The Affiliated Cancer Hospital of Zhengzhou University, Zhengzhou, China*

Background: Breast cancer is the most common female cancer in China. Reasonable and effective screening is an important means to reduce the mortality of breast cancer. This study was to evaluate the compliance and efficacy of breast cancer screening in urban areas of Henan province from 2013 to 2019. **Methods:** A cluster sampling method was used to select the residents of 40-74 years old in Henan province to investigate the risk factors and breast cancer risk assessment. For subjects with high risk of breast cancer, those aged 40-44 conduct breast ultrasound examination; those aged over 45 conduct breast ultrasound combined with mammography examination. BI-RADs classification was used as the evaluation standard in both examinations. BI-RADS 3 class was defined as suspicious and BI-RADS≥4 class was defined as positive. Chi-square test was used to analyze the compliance rate and breast cancer detection rate among different groups. **Results:** A total of 29 111 residents at high risk for breast cancer were recruited in this study. They were 55.03 ± 7.91 years old, of which 13 760 took the following breast ultrasound or mammography examination, yielding a participation rate of 47.27% (13 760/29 111). The detection rates of suspected positive patients, positive patients and breast cancer patients were 23.40% (3 220/13 760), 2.55% (351/13 760) and 0.30% (41/13 760), respectively. Among the screening population, the highest detection rate of suspected positive patients was found in the 45-49 age group [27.79% (935/3 365)], the highest detection rate of positive patients was found in the 50-54 age group [2.98% (97/3 257)], and the highest detection rate of breast cancer was found in the 65-69 age group [0.49% (5/1 012)]. The detection rate of breast cancer positive patients by breast ultrasound combined with mammography examination was 2.95% (316/10 728), which was significantly higher than that of breast ultrasound alone [1.99% (213/10 728)] or mammography examination alone [1.25% (134/10 728)]. **Conclusions:** Breast ultrasound combined with mammography examination as a means of screening for breast cancer can significantly increase the detection rate of breast cancer positive patients. The next step should be to improve the compliance of the population, as well as the organization's implementation and service capabilities of the screening provider, to improve screening effectiveness. Research Sponsor: Key Science and Technology Program of Henan Province, China (192102310353).

10544 **Poster Session**

An ultrasensitive method for noninvasive pan-cancer early detection based on targeted methylation sequencing of cell-free DNA. *First Author: Tiancheng Han, Genecast Precision Medicine Technology Institute, Beijing, China*

Background: Screening the biomarkers from the cell-free DNA (cfDNA) of peripheral blood is a non-invasive and promising method for cancer diagnosis. Among diverse types of biomarkers, epigenetic biomarkers have been reported to be one of the most promising ones. Epigenetic modifications are widespread on the human genome and generally have strong signals due to the similar methylation patterns shared by adjacent CpG sites. Although some epigenetic diagnostic methods have been developed based on cfDNAs, few of them could be applied to pan-cancer and their sensitivities are barely satisfactory for early cancer detection. **Methods:** Targeted methylation sequencing was performed using our in-house-designed panel targeting regions with abundant cancer-specific methylation CpGs. The cfDNA samples from 80 healthy individuals and 549 cancer patients of 14 cancer types were separately sequenced. The dataset was randomly split into one discovery dataset and one validation dataset. Moreover, cfDNA samples from four cancer patients were diluted with the healthy cfDNAs to generate 12 *in vitro* simulated samples with low circulating tumor DNA (ctDNA) fraction. Additionally, DNAs extracted from 130 unmatched tumor formalin fixation and paraffin embedding (FFPE) samples of 10 cancer types were sequenced to screen the diagnostic biomarkers. Adjacent CpG sites were first merged into methylation-correlated blocks (MCB) according to their correlations of methylation levels in tumor DNAs. The MCBs with higher methylation levels in tumor DNAs than that of healthy cfDNAs (from the discovery dataset) were defined as our hypermethylation biomarkers. For each cfDNA sample, a hypermethylation score (HM-score) was computed to measure the overall methylation level difference of selected biomarkers. The performance of our method was evaluated with the real-world dataset, while the limit of detection was estimated using the simulated low-ctDNA samples. **Results:** Our model based on 37 hypermethylation MCB biomarkers achieved an area under the curve (AUC) of 0.89 and 0.86 in the real-world pan-cancer discovery and validation cfDNA datasets, respectively. Furthermore, the overall specificity and sensitivity are 100% and 76.19% in the discovery dataset, and 96.67% and 72.86% in the validation dataset. In the validation dataset, 28/40 (70%) of early-stage colorectal cancer patients and 10/20 (50%) of non-small-cell lung cancer patients were successfully diagnosed. Additionally, all the simulated samples with theoretical ctDNA factions over 0.5% were predicted as diseased, demonstrating the ability of our method to detect tumor signals at early stages. **Conclusions:** Our cfDNA-based epigenetic method outperforms currently available methods in various cancer types, and is promising to be applied to early-stage cancer detection and samples with low ctDNA fractions. Research Sponsor: None.

10545 **Poster Session**

Impact of the sessile serrated polyp pathway on predicted colorectal cancer outcomes in the CRC-AIM model. *First Author: John B. Kisiel, Mayo Clinic, Rochester, MN*

Background: Approximately 20–30% of colorectal cancers (CRC) arise from the serrated polyp pathway. The multitarget stool DNA (mt-sDNA) test has greater sensitivity to detect sessile serrated polyps (SSPs) than a leading fecal immunochemical test (FIT). However, most modeling analyses do not account for the contribution of the SSP pathway to risk of CRC. We used the CRC-AIM model to assess the impact of the SSP pathway on predicted CRC outcomes with mt-sDNA or FIT screening. **Methods:** A simulated cohort of average-risk US patients underwent triennial mt-sDNA or annual FIT screening from ages 50–75. The percentage of CRCs arising from the SSP pathway were modeled at 0% (base case), 20%, and 30%, with stool screening adherence based on theoretical (100%) or previously reported (mt-sDNA 71%; FIT 43%) rates. Published SSP sensitivities for mt-sDNA and FIT were used. All other model inputs were identical to CISNET models. Sensitivity analyses used screening adherence rates of 40–70%. Key outcomes were life-years gained (LYG), CRC incidence and CRC mortality per 1000 patients. **Results:** Including SSPs in the model demonstrated a greater loss of LYG with FIT than mt-sDNA (Table). At 100% adherence, compared with base case, modeling 20% or 30% SSP pathway CRCs resulted in a decrease of 9–15 LYG with FIT and 2–4 LYG with mt-sDNA, a decrease in CRC incidence reduction of 3.9–6.1% with FIT and 0.7–1.1% with mt-sDNA, and a decrease in CRC mortality reduction of 2.6–4.0% with FIT and 0.4–0.8% with mt-sDNA. Using previously reported adherence, compared with base case, modeling 20% or 30% SSP pathway CRCs resulted in a decrease of 13–20 LYG with FIT and 2–5 LYG with mt-sDNA, a decrease in CRC incidence reduction of 4.4–6.9% with FIT and 0.6–1.1% with mt-sDNA, and a decrease in CRC mortality reduction of 3.5–5.4% with FIT and 0.4–0.9% with mt-sDNA. Assuming reported adherence and 30% SSP pathway CRCs, mt-sDNA had 48 more LYG, 14.6% greater CRC incidence reduction, and 12.4% greater CRC mortality reduction than FIT. Assuming 30% SSP pathway CRCs, outcomes favored mt-sDNA vs FIT even after modeling equivalent adherence rates ranging from 40–70%. **Conclusions:** After incorporating the SSP pathway into the model, outcomes with mt-sDNA neared those of FIT at 100% screening adherence rates and surpassed FIT at more realistic reported screening adherence rates. Research Sponsor: Exact Sciences Corporation.

CRC outcomes for triennial mt-sDNA and annual FIT after assuming 0%, 20%, or 30% SSP pathway CRCs and assuming either 100% or reported screening adherence rates.

	Triennial mt-sDNA			Annual FIT		
Screening Adherence Rates	% CRCs from SSPs	LYG	CRC Incidence Reduction, %	CRC Mortality Reduction, %	LYG	CRC Incidence Reduction, %	CRC Mortality Reduction, %
100%	0%	300	64.2	72.0	321	69.4	76.9
	20%	298	63.5	71.6	312	65.5	74.3
	30%	296	63.1	71.2	306	63.3	72.9
mt-sDNA, 71%; FIT, 43%	0%	286	61.0	68.7	253	52.2	60.8
	20%	284	60.4	68.3	240	47.8	57.3
	30%	281	59.9	67.8	233	45.3	55.4

Data are per 1000 individuals.

10546 **Poster Session**

Contribution of family history of melanoma to associated risk factors: Analysis of an Internet-based risk assessment tool. *First Author: Ryan M O'Keefe, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA*

Background: Risk factors for melanoma (ML) include UV exposure, sunburns, multiple nevi, and fair skin. Smoking and alcohol use may also play a role. Demographics associated with increased UV exposure include male gender, white race, age 18-29, and high-income. Those with family history (FH) of ML have increased risk of developing ML themselves yet are often unaware or do not engage in preventive behaviors. We sought to understand the association between FH of ML and other personal risk factors for cancer. **Methods:** Since 2009, voluntary participants could receive personalized information regarding their cancer risk via the OncoLink.org *Reduce My Risk* tool. Survey data was collected on demographics, FH, risk-factors, and risk-associated behaviors. Use of data was IRB approved. Differences between respondents with v. without FH of ML were analyzed using chi-square test and adjusted via logistic regression. **Results:** 25255 responses were analyzed; 1928 (7.6%) had FH of ML. Of these, median age was 26 (range 18-75), 73.1% were female, 88.6% from North America, 91.4% White, 78.2% had at least some college, and 62.0% household income > $45,000. Comparing those with FH of ML to those without, no significant differences were observed in education, income, or home setting. Those with a FH of ML were less likely to be "light" smokers (< 1 pack per day) but were more likely to be both "light" drinkers and "heavy" drinkers (Table). There were no significant differences in BMI or exercise habits. Those with FH of ML were more likely to sunbathe, to have had "blistering" sunburns, have 50+ moles, show signs of sun damage on their skin, and have dysplastic nevi (Table). There were no differences in use of indoor tanning beds (Table). **Conclusions:** Those with a FH of ML were more likely to sunbathe and to report skin damage and history of blistering sunburns; they were more likely to use tanning beds, though not statistically significant. These behaviors are modifiable and may suggest parental influence on sun-protective behaviors. Those with FH also reported increased non-modifiable risks. Future work should continue to explore targeted intervention for those with a FH of ML to educate on risk and promote sun-protective behaviors. Research Sponsor: OncoLink - Hospital of the University of Pennsylvania.

	Pos FH	Neg FH	OR	95% CI	p-value
< 1 Pack / Day	129 (6.7%)	2043 (8.8%)	0.74	0.61–0.89	0.002
1+ Packs / Day	56 (2.9%)	644 (2.8%)	1.02	0.76–1.35	0.885
1-7 Drinks / Week	886 (46.0%)	9486 (40.7%)	1.22	1.10–1.36	< 0.001
8+ Drinks / Week	232 (12.0%)	2565 (11.0%)	1.29	1.09–1.51	0.002
"Love to Sunbathe"	286 (14.8%)	2510 (10.8%)	1.15	1.00–1.33	0.05
Tanning Bed Use	524 (27.2%)	4732 (20.3%)	0.94	0.84–1.06	0.316
Sunburns As Child or Teen	857 (44.5%)	5945 (25.5%)	1.71	1.54–1.90	< 0.001
50+ Moles on Skin	466 (24.2%)	3305 (14.2%)	1.46	1.29–1.63	< 0.001
Dysplastic Nevi	47 (2.4%)	203 (0.9%)	1.66	1.18–2.31	0.003

10547 **Poster Session**

Red blood cell folate, high-risk human papillomavirus risk and cervical intraepithelial neoplasia development: A large Chinese community-based cohort study of cervical screening. *First Author: Wei Wang, The Second Hospital of Shanxi Medical University, Taiyuan, China*

Background: Although low folate status has been implicated in cervical carcinogenesis, large-scale population-based prospective cohort studies controlling for high-risk types of human papillomavirus (hrHPV) infection are lacking. The aim of this study is to evaluate the associations of red blood cell (RBC) folate, hrHPV infection risk and cervical intraepithelial neoplasia (CIN) development. **Methods:** In this prospective, population-based cohort study, we analyzed the cross-sectional data of 2304 women from a large cervical cancer screening program of 40,000 women aged 19-65 years in the Chinese rural area from 2014-2015. We conducted a nested case-control study including 35 CIN1 progression cases and 105 CIN1 regression controls. A logistic regression model was used to evaluate the associations of RBC folate and hrHPV infection risk and CIN1 development. **Results:** The median RBC folate concentration decreased gradually with cervical lesion severity. The risks of CIN 1 and CIN2 or worse (CIN 2+) in the 1st quartile of RBC folate concentration were significantly higher than those in the 4th quartile (Odds Ratio [OR], 2.27; 95% confidence interval [CI], 1.71-3.01 and OR, 2.33; 95% CI,1.52-3.56; respectively). We did not observe a significant relationship between hrHPV infection and CIN1 risk in the unadjusted and adjusted models, however, a statistically significant association was observed for CIN2+. Interestingly, RBC folate concentration was not associated with hrHPV infection among women with CIN1 or CIN2+. After full adjustment for potential confounders, a highly significant inverse linear relation between RBC folate concentration and CIN2+ was observed (P-overall < 0.001, P-nonlinearity $= 0.969$). We further observed a positive additive interaction between RBC folate concentration and hrHPV infection on the risk of CIN2+ (P-interaction < 0.01). Moreover, during the 21-month follow-up, CIN1 progression risk was significantly higher in the lowest RBC folate quartile (1st quartile compared with 4th quartile: OR, 3.86; 95% CI,1.01-14.76). **Conclusions:** Our findings indicates that RBC folate is inversely associated with the risk of higher-grade CIN and CIN1 progression in the Chinese rural population, either with or without hrHPV infection. Therefore, improving folate status has the potential to prevent higher-grade CIN and cervical cancer among women in the areas without mandatory folic acid food fortification. Clinical trial information: ChiCTR-ROC-15006479. Research Sponsor: This project was supported by the Special Public Welfare Industry Research of National Health and Family Planning Commission of China (grant number: 201402010).

10548 **Poster Session**

Risk-reducing salpingo-oophorectomy and breast cancer incidence among BRCA-mutation carriers. *First Author: Tamar Perri, Gynecologic Oncology Department, Sheba Medical Center, Ramat Gan, Israel*

Background: Uncertainty exists with regard to the role of bilateral salpingo-oophorectomy in altering the risk of breast cancer in BRCA-mutation carriers. **Methods:** Included were 1645 healthy Jewish Israeli BRCA1/2 -mutation carriers from a single center without prophylactic mastectomy. Carriers with and without risk-reducing bilateral salpingo-oophorectomy (RRBSO) were matched according to BRCA-mutation type (BRCA1 vs. BRCA2) and year of birth (±1 year). Hormonal and reproductive variables were compared and incidence of breast cancer recorded. Association between RRBSO and breast cancer was studied. **Results:** Seventy-seven and 50 matched-pairs had BRCA1 and BRCA2 mutation respectively. Fifty-two carriers had breast cancer, 21 in RRBSO-group and 31 in no- RRBSO group, with no statistically significant difference. When analysing each mutation group separately, stratified by age at surgery, no association between RRBSO and breast cancer incidence was found among BRCA1-mutation carriers. However, in BRCA2 mutation carriers, RRBSO was associated with a statistically significant decreased overall incidence of breast cancer, HR = 0.2 (confidence interval 0.44-0.913, p = 0.038). Breast cancer incidence was lower after 5, 10,15 and 20 years in BRCA2-mutation carriers with RRBSO compared to no-RRBSO. Age at menarche, age at surgery, parity and oral contraceptive use were not significant risk factors for breast cancer. Hormone replacement therapy was used by 62 mutation carriers, 52 in the RRBSO group and 10 in the no-RRBSO group, and its use did not alter breast cancer risk (p = 0.463). **Conclusions:** According to our findings, RRBSO is associated with a reduced risk of breast cancer only in BRCA2 mutation carriers, regardless of HRT use. Research Sponsor: None.

10549 **Poster Session**

Attention to diet, exercise, and weight in the oncology clinic: Results of a national patient survey. *First Author: Jennifer A. Ligibel, Dana-Farber Cancer Institute, Boston, MA*

Background: Obesity and related factors are increasingly associated with increased risk of developing and dying from cancer. The American Society of Clinical Oncology (ASCO) conducted a survey of cancer patients to assess their experience in receiving recommendations and referrals related to weight, diet and exercise as a part of their cancer care. **Methods:** An online survey was distributed to potential participants between March and June 2020 via ASCO channels and patient advocacy organizations, with an estimated reach of over 25,000 individuals. Eligibility criteria included being 18 years, living in the US, and having been diagnosed with cancer. Logistic regression was used to determine factors associated with recommendation and referral patterns. **Results:** In total, 2419 individuals responded to the survey. Most respondents were female (75.5%), 61.8% had an early-stage malignancy, 38.2% had advanced disease, and 49.0% were currently receiving treatment. Breast cancer was the most common cancer type (36.0%). Average BMI was 25.8 kg/m^2. The majority of respondents consumed £2 servings of fruits and vegetables per day (50.9%) and exercised £2 times per week (50.4%). Exercise was addressed at most or some oncology visits in 57.5% of respondents, diet in 50.7%, and weight in 28.4%. Referrals were less common: 14.9% of respondents were referred to an exercise program, 25.6% to a dietitian and 4.5% to a weight management program. In multiple regression analyses, racial and ethnicity minority respondents were more likely to receive advice about diet (Odds Ratio [OR] 1.92, 95% CI 1.56-2.38) and weight (OR 1.64, 95% CI 1.23-2.17) compared to non-Hispanic whites, individuals diagnosed with cancer in the past 5 yrs (vs $>$ 5 yrs) were more likely to receive advice about exercise (OR 1.48, 95% CI 1.23-1.79), and breast cancer patients were more likely to receive advice about exercise (OR 1.37, 95% CI 1.11-1.68) and weight (OR 1.46, 95% CI 1.03-2.07) than other cancer patients. Overall, 74% of survey respondents had changed their diet or exercise after cancer diagnosis. Respondents reporting that their oncologist spoke to them about increasing exercise or eating healthier foods were more likely to report a change in behavior than those whose oncologists did not (exercise: 79.6% vs 69.0%, $P < 0.001$; diet 81.1% vs 71.4%, $P < 0.001$). Respondents whose oncologist had spoken to them about exercise were more likely to exercise $>$ 2 times per week compared to respondents whose oncologists did not address exercise (53.5% vs 44.1%, $P < 0.001$). **Conclusions:** In a national survey of oncology patients, slightly more than half of respondents reported attention to diet and exercise during oncology visits. Provider recommendations for diet and exercise were associated with positive changes in these behaviors. Additional attention to diet and exercise as part of oncology visits is needed to help support healthy lifestyle change in cancer patients. Research Sponsor: None.

10550 **Poster Session**

Reductions in cancer screening: The consequence of changes in routine care during the COVID-19 pandemic. *First Author: Ashley Kim, GRAIL, Inc., Menlo Park, CA*

Background: The COVID-19 pandemic imposes significant impact on daily activities with regard to public health orders and individual responses to the pandemic. Much of the direct or indirect impact is potentially in reductions in healthcare encounters for services such as preventive care. Here, we quantified changes in cancer screening rates to better understand the impact of the evolving COVID-19 implications and shifts in health-seeking behaviors. **Methods:** We conducted a retrospective analysis of cancer screening rates during March-June 2019 (pre-COVID-19) and March-June 2020 (post-COVID-19 restrictions), using Optum's de-identified Clinformatics Data Mart Database which includes Medicare and commercially insured members. Members meeting age and/or sex criteria as detailed in the United States Preventive Services Task Force recommendations for breast, colorectal, lung, prostate, and cervical cancer screening represented the eligible membership for screening. Procedure and laboratory services were used to identify those who received cancer screening. Analyses were conducted cross-sectionally by cancer screening type. **Results:** Eligible cohorts were identified from insured members within March-June 2019 and 2020 (2019: 17,931,318; 2020: 17,521,411). The percent of eligible members screened in March-June 2019 was 19.3%, 9.4%, 16.7%, 0.4%, and 7.8% for breast, cervical, prostate, lung, and colorectal cancer, respectively. Changes in screening rates from 2019 to 2020 are summarized in Table, with the sharpest decline in April. The percent change from 2019 to 2020 during the combined March-June period for each cancer screening type was statistically significant ($p<0.0001$). **Conclusions:** Routine cancer screening rates from March-June 2020 showed meaningful reductions when compared to the same period in 2019, with substantial declines during the initial peak of the pandemic in April. These declines may be impacted by variations in regional restrictions with tighter restrictions leading to larger screening declines and loosening restrictions reflecting catch-up screening. Efforts to promote cancer screening in a safe and timely manner are crucial given individual risk factors, to reduce later stage cancer diagnoses and improve clinical outcomes. Research Sponsor: GRAIL, Inc.

Percent change in eligible members screened for cancer (March-June 2019/2020).

	Breast	Cervical	Prostate	Lung	Colorectal
Population Included	Females aged 50-74 years, no history of breast cancer	Females aged 21-65 years, no history of cervical cancer	Males aged 55-69 years, no history of prostate cancer	Males and Females aged 55-80 years, no history of lung cancer	Males and Females aged 50-75 years, no history of colorectal cancer
March-June	-42.8%	-42.8%	-28.7%	-31.5%	-42.3%
March	-34.5%	-35.3%	-24.8%	-14.6%	-29.2%
April	-85.0%	-78.9%	-61.8%	-84.7%	-73.4%
May	-50.7%	-49.8%	-32.6%	-40.6%	-52.9%
June	-4.0%	-2.2%	8.5%	19.0%	-18.3%

10551 **Poster Session**

Trends in cancer screening volumes at an urban health center during the COVID-19 pandemic. *First Author: Mahir Khan, University of Illinois at Chicago, Chicago, IL*

Background: The Coronavirus-19 (COVID-19) pandemic has disrupted cancer screening for reasons including healthcare resource preservation, infection control efforts, and patient factors. There is limited literature quantifying this interruption of care, particularly in vulnerable and racial/ethnic minorities. **Methods:** We compared the volume of cancer screening at the University of Illinois Hospital & Health Sciences System before and during the COVID-19 pandemic using data obtained from the electronic medical record. Modalities included mammogram, ultrasound, and MRI for breast; Pap test for cervical; colonoscopy, CT colonography, and flexible sigmoidoscopy for colorectal; low-dose CT for lung; and prostate-specific antigen test for prostate. Of note, screening and diagnostic tests could not be distinguished for colorectal cancer. We examined percent changes in cancer screening counts for each month from February 2020-August 2020, using January 2020 as a reference. Results were stratified by gender, race, and ethnicity. **Results:** Screening volume declined rapidly after January 2020, with the nadir for each cancer site occurring in April 2020: breast (n = 0, -100%), cervical (n = 169, -84%), colorectal (n = 35, -89%), lung (n = 0, -100%), and prostate (n = 108, -72%). Values recovered by August 2020 for most cancer sites except cervical cancer, which remained decreased (-23%). There were no differences in screening trends by gender. With respect to race, breast screening volume in Black patients decreased earlier and exhibited slower recovery compared to White patients. White patients had poorer cervical screening recovery than Black patients by August 2020 (-60% vs. -23%). Hispanics had poorer recovery of breast screening compared to non-Hispanics by August 2020 (-23% vs. 6%). **Conclusions:** We observed widely decreased cancer screening attributable to COVID-19. Breast cancer screening data specifically showed persistent disparities affecting Black and Hispanic patients. Despite the reassuring recovery of multiple screening methods by August 2020, an increase above baseline is needed to compensate for initial declines. Further studies will likely reveal long-term consequences of this unprecedented situation. Research Sponsor: None.

	Breast Count (% change)	Cervical Count (% change)	Colorectal Count (% change)	Lung Count (% change)	Prostate Count (% change)
Jan 2020	555 (Reference)	1041 (Reference)	333 (Reference)	14 (Reference)	390 (Reference)
Feb 2020	528 (-5%)	921 (-12%)	298 (-11%)	33 (136%)	428 (10%)
March 2020	280 (-50%)	744 (-29%)	173 (-48%)	23 (64%)	303 (-22%)
April 2020	0 (-100%)	169 (-84%)	35 (-89%)	0 (-100%)	108 (-72%)
May 2020	0 (-100%)	224 (-78%)	67 (-80%)	3 (-79%)	209 (-46%)
June 2020	222 (-60%)	580 (-44%)	168 (-50%)	6 (-57%)	266 (-32%)
July 2020	523 (-6%)	690 (-34%)	266 (-20%)	9 (-36%)	373 (-4%)
August 2020	545 (-2%)	797 (-23%)	319 (-4%)	20 (43%)	353 (-9%)

Cancer screening before and during the COVID-19 pandemic.

10552 **Poster Session**

Efficacy of HPV vaccination among seropositive, DNA negative cohorts. *First Author: Colm Mac Eochagain, St James' Hospital, Dublin, Ireland*

Background: Prophylactic HPV vaccination of naïve cohorts is known to be highly effective in the prevention of incident HPV infection and HPV-associated cervical premalignancy. Conversely, vaccination of women with active (DNA+) HPV infections has been demonstrated to be ineffective. Vaccine efficacy among previously exposed, but currently uninfected women, i.e. those who have serological evidence of a prior HPV infection without corresponding detectable HPV DNA, remains incompletely defined. This meta-analysis assessed the serotype-specific efficacy of prophylactic HPV vaccination against HPV16/18 persistent infection (PI) and cervical intraepithelial neoplasia (CIN) among seropositive, DNA negative (SPDN) women enrolled to RCTs of HPV L1-based vaccines. **Methods:** The study protocol was prospectively registered on PROSPERO (CRD42020206888). Searches were conducted on 08/16/20 on MEDLINE, EMBASE, SCOPUS and CENTRAL. RCTs of L1-based prophylactic bivalent or quadrivalent HPV vaccines, reporting serotype-specific clinical efficacy endpoints in the HPV16/18 seropositive, DNA-negative populations were included. Two authors independently screened studies, extracted data and assessed for bias. Data for SPDN women were extracted from subgroup analyses within primary and secondary publications, publication supplements, and manufacturers' clinical study reports. Relative risks (RR) of 6-month persistent infection (6mPI), 12-month persistent infection (12mPI), CIN1+ and CIN2+ were pooled using a random-effects model. **Results:** A total of 1727 citations were reviewed. 8 studies, with a total of 9569 SPDN participants, met all eligibility criteria. The relative risk of 6mPI (RR: 0.22, 95% CI 0.08-0.61, p = 0.018), 12mPI (RR: 0.20, 95% CI 0.05-0.80, p = 0.035), CIN1+ (RR:0.13, 95% CI 0.05-0.30, p = 0.003) and CIN2+ (RR: 0.15, 95% CI 0.04-0.59, p = 0.022) was significantly reduced in the vaccinated compared to the unvaccinated group. The number needed to vaccinate (NNV) to prevent one case of CIN1+ and CIN2+ was 152 and 208 respectively. **Conclusions:** Our findings suggest high serotype-specific efficacy for HPV vaccination among cohorts of women with evidence of prior HPV 16/18 infections. Women without DNA evidence of active infection may be seronegative, implying naïve status and $>$ 99% efficacy; or seropositive, implying SPDN status and 87% efficacy against CIN1+ for HPV 16/18. Women without DNA evidence of HPV 16/18 infection should be offered prophylactic HPV vaccination regardless of prior exposure history. Research Sponsor: None.

10553 **Poster Session**

Sociodemographics, lifestyle determinants, and viral infections in patients with head and neck cancer undergoing radiotherapy in Taiwan: A prospective cohort study. *First Author: Kevin Sheng-Kai Ma, Department of Life Science, National Taiwan University, Taipei City, Taiwan*

Background: Human papillomavirus (HPV) screening has been implemented to monitor both cervical cancer and head and neck cancer. In this prospective cohort study, we determined sociodemographic, behavioral, and infectious etiology for head and neck squamous cell carcinoma (HNSCC) in Taiwan using data collected from an anonymous sexually transmitted infections screening program. **Methods:** An anonymous sexually transmitted infections screening program was conducted at a medical center during 2016, in which sociodemographic characteristics including gender, age, marital status, education level, and occupation; medical history regarding underlying comorbidities and history of receiving HPV and other vaccines; lifestyle determinants including betel quid chewing, drug using, and sexual behaviors, were inquired. Blood, anal swab, and penile swab samples were collected to determine viral infections using polymerase chain reaction (PCR). With PCR, 37 HPV genotypes were detected. Regular follow-ups were made for patients enrolled in the screening program until end of 2020, during which all suspected malignancies were recorded upon referrals to oncologists. From this prospective cohort, odds ratios (ORs) of HNSCC for sociodemographic, lifestyle, and infectious variables were derived with logistic regression (R version 4.0.1). $P < 0.05$ was considered statistically significant. **Results:** A total of 376 patients were enrolled. Most patients were men (n = 372), with a median age of 27 years. There were 124 (32.98%) HPV-positive patients and 78 (20.74%) HIV-positive patients. Among HPV-positive patients, 20 (25.64%) were of high-risk genotypes. During the follow-up, 44 patients developed HNSCC and all received radiotherapy. Multivariate analysis revealed that patients who were single (OR = 1.43, 95% CI = 1.12-1.83, P = 0.01) or widowed (OR = 2.47, 95% CI = 1.88-3.25, $P < 0.001$) had higher risk of HNSCC than patients who were married. Patients aged 51-60 (OR = 2.93, 95% CI = 2.10-4.09, $P < 0.001$) and over 60 (OR = 1.89, 95% CI = 1.45-2.47, $P < 0.001$) presented higher risks of HNSCC, compared with those aged below 20. Patients addicted to betel quid chewing had high HNSCC risk (OR = 1.29, 95% CI = 1.11 – 1.50, $P < 0.001$). However, patients with HPV infections did not present with higher HNSCC risks (OR = 0.925, 95% CI = 0.852 – 1.003, P = 0.058). **Conclusions:** In this prospective cohort study, the elderly, unmarried patients, and patients addicted to betel quid chewing, presented with high HNSCC incidence. On the contrary, the association between HPV infection and HNSCC was insignificant. As both betel nut-chewing and HPV infection could be prevented, we advocate for comprehensive screening and patient education for HNSCC prevention. Research Sponsor: None.

10554 **Poster Session**

One-stop-shop for cancer screening: A model for the future. *First Author: Ezra Bernstein, Integrated Cancer Prevention Center, Tel-Aviv Medical Center, Tel-Aviv, Israel*

Background: Cancer is the second leading cause of death globally. Early detection will often greatly reduce mortality for many cancers, increase treatment effectiveness, and improve the quality of life for cancer patients, and, by implementing evidence-based prevention strategies, 30–50% of cancers can be prevented. Screening for different cancer types separately is inefficient. A solution is the Integrated Cancer Prevention Center (ICPC), a program with specialists in each discipline who test for multiple cancers during one visit. **Methods:** This is a prospective cohort study of 17,104 self-referred, asymptomatic patients who visited the Integrative Cancer Prevention Center (ICPC) between January 1, 2006, and December 31, 2019. Clinical, laboratory, and epidemiological data were recorded by multiple specialists. Patients were given follow-up recommendations and diagnoses when appropriate. The primary measure was the detection and staging of new malignant lesions. Secondary measures included cost-benefit and mortality benefit. **Results:** We screened 8618 men and 8486 women with an average age of 47.11 ± 11.71 years. Of 259 cancers detected through the ICPC, 49 (18.9%) were stage 0, 115 (44.4%) were stage I, 31 (12%) were stage II, 25 (9.7%) were stage III, and 32 (12.4%) were stage IV. Seventeen cancers were missed, only six of which were within the scope of the ICPC, and 189 cancers developed > one year after the last visit to the ICPC. Compared to the stage of detection for cancers in the US, all cancers except for colon were detected at an earlier stage at the ICPC. Lung was the most significant with 86.7% of cancers detected at stage 0, I, or II at the ICPC compared to only 49.3% caught at those stages in the US. **Conclusions:** This is a proof of concept for a one-stop-shop approach to asymptomatic cancer screening in a multidisciplinary outpatient clinic. It offers evidence that this screening framework can and should be replicated in other healthcare settings and on a national policy level as it saves lives and money. The encouraging results presented here should further the conversation about the utility of screening and add momentum to the movement for increased screening. Research Sponsor: None.

Stages of detection for cancers detected by the ICPC.

	Stage 0	Stage I	Stage II	Stage III	Stage IV
Bladder	1	0	0	0	0
Brain	0	0	0	0	0
Breast	10	12	7	11	0
Cervical	9	1	0	0	0
Colon	1	7	3	5	4
Hematological	0	0	0	1	12
Hepatobiliary	0	0	0	0	2
Laryngeal	0	1	1	0	0
Lung	0	11	2	1	1
Neuroendocrine	0	1	0	0	1
Oral	0	2	0	0	0
Other	1	0	0	0	2
Ovarian	0	2	0	1	2
Pancreatic	0	1	0	0	3
Prostate	0	23	10	1	2
Renal	0	8	4	0	1
Skin (BCC)	14	2	0	0	0
Skin (SCC)	4	3	0	0	0
Skin (Melanoma)	8	10	0	0	0
Soft Tissue	0	0	1	0	0
Testicular	0	5	0	0	0
Thyroid	0	22	0	5	0
Upper GI	0	0	1	0	1
Uterine	1	2	1	0	0
Total	**49 (18.9%)**	**115 (44.4%)**	**31 (12%)**	**25 (9.7%)**	**32 (12.3%)**

10555 **Poster Session**

Adverse consequences of the COVID-19 pandemic on breast cancer stage distribution and breast cancer disparities. *First Author: Genevieve A. Fasano, Weill Cornell Medicine/New York Presbyterian, New York, NY*

Background: The COVID-19 surge in March 2020 resulted in a hiatus placed on screening mammography programs in support of shelter-in-place mandates and diversion of medical resources to pandemic management. The COVID-related economic recession and ongoing social distancing policies continued to influence screening practices after the hiatus was lifted. We evaluated the effect of the hiatus on breast cancer stage distribution on the diverse patient population of a health care system in New York City, the first pandemic epicenter in the United States. **Methods:** Breast cancer patients diagnosed January 1, 2019 to December 31, 2020 were analyzed, with comparisons of stage distribution and mammography screen-detection for three intervals: Pre-Hiatus, During Hiatus (March 15, 2020 to June 15, 2020), and Post-Hiatus. Results were stratified by African American (AA), White American (WA), Asian (As) and Hispanic/Latina (Hisp) self-reported racial/ethnic identity. **Results:** A total of 894 patients were identified; of these, 549 WA, 100 AA, 104 As, and 93 Hisp comprised the final race/ethnicity-stratified study population. Overall, 588 patients were diagnosed Pre-Hiatus, 61 During-Hiatus, and 245 Post-Hiatus. Nearly two-thirds (65.5%) of the Pre-Hiatus cases were screen-detected versus 49.2% During-Hiatus and 54.7% Post-Hiatus (p = 0.002). Frequency of tumors diagnosed < 1 cm declined from 41.9% Pre-Hiatus to 31.7% Post-Hiatus (p = 0.035). WA patients were more likely to have screen-detected disease compared to AA in the Pre-Hiatus period (69.1% vs. 56.1%; p = 0.05) but non-significantly more likely to have screen-detected disease compared to As and Hisp patients (66.2% vs. 56.9%; p = 0.08). In the Post-Hiatus period, the frequency of screen-detected disease was highest among WA patients (63.0%) compared to all other racial/ethnic groups (AA; 48.1%, As-33.3%, and Hisp-40%; p = 0.007). Similar patterns were observed for frequency of tumors diagnosed ≤1cm Pre-Hiatus (WA-44.3% vs AA-26%, p = 0.02; and vs. As-41.3%, Hisp-48%; p = 0.09), and Post-Hiatus (WA-37.7% vs. AA-18.2%, As-30.8%, Hisp-23.5%; p = 0.25). **Conclusions:** The 3-month pandemic-related mammography screening hiatus resulted in a more advanced stage distribution for New York City breast cancer patients, and worsened pre-existing race/ethnicity-associated disparities, especially for AA pts. Research Sponsor: None.

10556 **Poster Session**

Impact of a sustainable breast and cervical cancer screening program in spite of COVID-19 pandemic: The AMPATH experience in Kenya. *First Author: Stephen Kiptoo, AMPATH Oncology, Eldoret, Kenya*

Background: Cancer is the third leading cause of death with about 48,000 new yearly diagnoses in Kenya. Breast and cervical cancers are the major leading cancers in females, both of which are curable with access to timely and effective care. To meet population health goals, early abnormalities of the cervix and breast must be treated promptly to maximize the chance for cure. The AMPATH Breast and Cervical Cancer Control Program (ABCCCP) was initiated to improve access to screening and diagnostic services for breast and cervical cancer in Kenya by addressing the barriers of cancer care through a population health approach, working with communities and the Ministry of Health in Kenya with a potential for scaling these efforts to other parts of the region. **Methods:** We performed an interim analysis 3 years into a 5-year program, to assess the impact of COVID-19 on our screening program. Statistical descriptive summaries were used to show the trend of screening using visual inspection with acetic acid and breast clinical examination. The screening was conducted facility-based along with community screening upon requests across nine counties. Also, we conducted capacity building through mentoring of health care providers and initiating a telemedicine program to improve patient care and management plans. **Results:** From 2018-2021, we conducted training, connected 12 centers with telemedicine capacity and screened a total of 100,973 persons were for breast and cervical cancer. The yearly trends demonstrate that the facility routine screenings were maintained: 23,421 (2018); 27,997 (2019); and 28,045 (2020). The total women seen through organized mass screenings however declined (10,304 (2018); 10,107 (2019); and 1,099 (2020), respectively) as this type of screening was stopped after the onset of COVID-19 pandemic. Of all women screened, 3,019 (2.98%) had clinical abnormalities requiring follow-up per standard of care including 1,781(1.8%) who were eventually histologically confirmed to have cancer. During our first and second year of the program, 83 physicians were trained on cancer management and treatment, 341 nurses were trained on breast and cervical cancer screening procedures, and 247 community health workers (CHW) were trained on the importance of screening to enlighten the community on awareness. However, this training was suspended in our year three due to COVID-19. **Conclusions:** An integrated training program utilizing CHW, nurses and physicians are an effective means for breast and cervical cancer screening in LMC, such as Kenya. This capacity building allows flexibility and sustainability even in the midst of the global COVID-19 pandemic. We also demonstrated successful integration with the county government for program sustainability. The use of telemedicine has greatly enhanced our screening and patient care across several facilities in western Kenya. Research Sponsor: Lily Foundation.

10557 **Poster Session**

Cancer screening utilization in patients diagnosed with cancer types with and without recommended screening modalities. *First Author: Ariella Cohain, Thrive, An Exact Sciences Company, Cambridge, MA*

Background: Several studies have shown screening methods can detect cancer at earlier stages and improve cancer prognosis; however, only four cancer types (breast, colorectal, cervical, and lung) currently have screening methods recommended by the United States Preventive Services Taskforce (USPSTF). In 2021, these four cancers are expected to make up roughly 40% of new cases and cancer deaths, meaning that the majority of cancer deaths will be associated with cancer types lacking recommended screening. We sought to characterize patients who were diagnosed with cancer types with and without recommended screening modalities to demonstrate the gaps in screening faced by the majority of cancers today. **Methods:** The Geisinger Health System (GHS) Phenomics Initiative Database (PIDB) provides deidentified data from electronic health, billing, and imaging records, and a tumor registry. PIDB was used to identify patients aged 50 to 76 who had cancers diagnosed between 2008 and 2020 and a record of USPSTF-recommended cancer screenings within GHS prior to diagnosis. Analysis focused on patients who received care at GHS during their screening-eligible intervals. **Results:** Between 2008 and 2020, 13,347 incident invasive cancers were identified in the GHS tumor registry. Of these, 40% (N = 5,331) were cancer types with a recommended screening modality. 57% of these cases (N = 3,039; 23% of all incident cancers) occurred in patients who underwent screening in the interval preceding diagnosis. Screening adherence was significantly associated with stage at diagnosis; patients who were not screened for their diagnosed cancer were more than twice as likely to have a late-stage diagnosis as compared with patients who received screening (multivariate ordinal logistic regression, OR = 2.16, $p < 0.001$). Patterns of screening adherence in this population are complex; however, 57% of these patients had received screening for a different cancer type. The majority of incident cancers were of those types with no recommended screening modality (N = 8,016; 60% of all incident cancers). Of these, most (N = 6,252; 78%) had been screened for at least one of breast, lung, colon, or cervical cancer and nearly half (N = 3,607; 45%) were current for all guideline-recommended screenings. Not surprisingly, stage at diagnosis was not associated with adherence to any or all screening modalities (multivariate ordinal logistic regression, p = 0.11 and p = 0.45). **Conclusions:** The majority (79%) of individuals diagnosed with cancer had a history of adherence to at least one screening recommendation. Out of all cancer patients, only 23% were screened specifically for the cancer with which they were subsequently diagnosed, a group that is associated with a lower odds of a late-stage diagnosis. This suggests that the majority of cancer patients who underwent any cancer screening did not benefit from earlier stage diagnosis. Research Sponsor: None.

10558 **Poster Session**

TNF-alpha immunosuppressive use and future malignancy risk. *First Author: Conor Driscoll, Northwestern Medicine, Chicago, IL*

Background: Tumor Necrosis Factor Alpha (TNF-a) inhibitors suppress the immune system in patients with systemic inflammatory conditions. Long term data assessing future cancer risk for these patients is not known. We assessed long term risk of malignancy in patients with Rheumatoid Arthritis [RA], Inflammatory Bowel Disease [IBD], Psoriasis [PS], and Ankylosing Spondylitis [AS], who were or were not exposed to a TNF-a inhibitor. **Methods:** This was a retrospective, cohort study conducted using electronic medical record data for patients with complete demographic and treatment data at Northwestern Medicine from years 1998 to 2020 (RA: n = 10763; IBD: n = 12106; PS: n = 1920; AS: n = 5103). Inverse Probability of Treatment Weighting (IPTW) was used to balance the distributions of age, race, gender, smoking status, and follow-up time across exposure groups within each inflammatory condition type. Relative risk (RR) of malignancy based on TNF-a exposure was assessed using logistic regression. **Results:** 2583 (24.0%) of RA, 2185 (18.0%) of IBD, 1811 (94.3%) of PS, 572 (11.2%) of AS patients had TNF-a exposure. Median follow-up for patients was 43 months. The RR for any cancer was higher for patients exposed to a TNF-a agent with rheumatoid arthritis (RR 1.121 (95% CI 1.02-1.23, p = 0.015) and psoriasis (RR 1.763 (95% CI 1.32-2.37, $p < 0.001$). The relative risk of any cancer was lower in patients exposed to a TNF-a agent with IBD (RR 0.858 (95% CI 0.78-0.94, p = 0.001). No significant difference in relative risk associated with TNF-a exposure was detected with ankylosing spondylitis (RR 0.929 (95% CI 0.8-1.08, p = 0.344). **Conclusions:** Patients with RA or PS and TNF-a exposure had higher RR of overall malignancy. Patients with IBD and TNF-a exposure had lower risk of overall malignancy. TNF-a immunosuppression may alter cancer risk differently based on the disease states for which it is being used. This information is critical when counseling patients on long term risk and screening strategies when considering TNF-a inhibition. Research Sponsor: None.

10559 **Poster Session**

Understanding factors associated with uptake of lung cancer screening among individuals at higher risk. *First Author: Abdi Gudina, University of Rochester Medical Center, Rochester, NY*

Background: Lung cancer is the leading cause of cancer death in the U.S, accounting for about 25% of all cancer mortality. The U.S Preventive Services Task Force has recommended annual screening for lung cancer using low-dose computed tomography (LDCT) scanning for individuals at higher risk (aged 55-80 years with a >30 pack-year smoking history). Early detection using LDCT scanning reduces lung cancer specific mortality by 20%. Despite its efficacy, the uptake of annual lung cancer screening among high-risk individuals remains low (< 18%). The purpose of this study was to identify factors associated with the uptake of lung cancer screening in high-risk individuals in the U.S population. **Methods**: Data for this study were obtained from the 2017-2019 Behavioral Risk Factor Surveillance System (BRFSS), a population-based survey conducted annually by the Centers for Disease Control and Prevention (CDC) in collaboration with health departments in all 50 states, Washington, DC, and the U.S territories. We restricted our sample to high-risk individuals aged 55-80 years with a >30 pack-year smoking history. Only subjects with complete data on all predictor variables (age, gender, race/ethnicity, marital status, education, income, insurance, COPD, current smoking status, primary care provider) and the outcome variable (uptake of lung cancer screening) (n = 11, 714) were included in the final analysis. Chi-square tests were used to compare the uptake of lung cancer screening by demographic and socioeconomic factors. Multivariable logistic regression models were used to model the association between the predictors and the outcome variable. **Results**: Individuals with no health insurance (OR: 0.64; 95%CI: 0.46-0.90), no primary healthcare provider (OR: 0.40; 95%CI: 0.31-0.52), no chronic obstructive pulmonary disease (COPD) (OR: 0.35; 95%CI: 0.31-0.0.40) and who were females (OR: 0.86; 95%CI: 0.76-0.96) were less likely to participate in annual lung cancer screening. Individuals aged 65–69 years (OR: 1.65; 95%CI: 1.38-1.97), 70–74 years (OR: 1.77; 95%CI: 1.46-2.14) or 75–80 years (OR: 1.42; 95%CI: 1.16-1.76) were more likely to receive annual lung cancer screening compared with those aged 55-59 years. Race/ethnicity, level of education, level of income, marital status, and current smoking status had no significant association with the uptake of annual lung cancer screening. **Conclusions**: Our study identifies factors associated with lower uptake of annual lung cancer screening (no health insurance coverage, no primary healthcare provider, no COPD, and female gender). The findings from this study have important implications for the design of more effective interventions to target specific subgroups for the uptake of annual lung cancer screening. Research Sponsor: University of Rochester Medical Center.

10560 **Poster Session**

Young patients with cancer related to modifiable behaviors in the United States: What can we learn from them? *First Author: John Chan, Palo Alto Medical Foundation, Palo Alto, CA*

Background: We proposed to examine trends in modifiable behaviorally related cancers among younger men and women in the United States. **Methods:** Alcohol-associated cancers, HPV-associated, obesity-associated, physical inactivity-associated, and tobacco-associated were defined using ICD-O-3 site codes. From 2001 and 2017, registry data were obtained from the United States Cancer Statistics database. SEER*Stat 8.3.8 and Joinpoint regression program 4.8.0.1 were used to calculate the trends of associated cancers expressed per 100,000. **Results:** Of the young women (ages 20-49 years) the incidence of cancers in 2017 associated with alcohol, smoking and obesity were 89/100,000, 43/100,000 and 64/100,000 respectively. Based on analysis of trends of women from 2001 to 2017, obesity, physical inactivity and alcohol related cancers increased with an annual percent change (APC 2.31%, 1.67%, 0.46%, $p < 0.001$). Using a projection model, in Hispanic women, obesity related cancers will become the highest incidence cancers by 2035, surpassing alcohol and physical inactivity. Of the young men (ages 20-49 years) the incidence of cancers in 2017 associated with alcohol, obesity, and tobacco were 23/100,000, 36/100,000 and 44/100,000 respectively. On trends analysis, obesity, physical inactivity, and alcohol related cancers have increased (APC 2.0%, 1.65%, 0.17%, $p < 0.001$, $p < 0.001$, p = 0.044), whereas tobacco-related cancers are decreasing with an APC of -0.44% ($p < 0.001$). When examining different regions, the highest APC for obesity and physical inactivity related cancers was 2.43% in the Midwest ($p < 0.001$). Using a prediction model, obesity is predicted to surpass alcohol and physical inactivity related cancers for men 20-49 years old by 2035. **Conclusions:** In women, most modifiable factors associated with cancer are increasing except in HPV related cancers. In men, these rates of cancer are increasing except in tobacco related cancers. However, rates of obesity related cancers are on the rise in Hispanic women and younger men in southern U.S. regions. Obesity is projected to become the major modifiable factor for many associated cancers. Research Sponsor: Fisher Foundation and Denise Cobb Hale.

10561 **Poster Session**

Validation of a high performing blood test for multiple major cancer screenings. *First Author: Linhao Xu, AnchorDx Medical Co., Ltd, Guangzhou, China*

Background: Early detection at the localized stage is pivotal for the successful treatment of various cancer types. Although several cancers already have routine screening approaches, the comprehensive utilities are impeded for various reasons, e.g., low accuracy, high cost, limited availability of required facilities, especially in the developing countries. Therefore, an accurate, cost-effective, and non-invasive test for multiple major cancer screening is in high demand. We previously reported a cfDNA methylation test, which can detect five major cancer types with high specificity and sensitivity, especially at the early stage (stage I). These five major cancers, including lung cancer (LC), breast cancer (BC), colorectal cancer (CRC), gastric cancer (GC), and esophageal cancer (EC), account for 56% of new cancer cases and 60% of cancer-related deaths yearly in China. Here, we report the result in an independent cohort as a further validation of this multi-cancer screening test. **Methods:** The high-throughput targeted methylation profiling platform, Aurora, was used to analyze the plasma samples from an independent retrospective cohort containing 505 healthy controls and ~200 cases for each cancer type. A locked model based on our previous pilot study (reported in AACR 2020 and 2021) was applied to this data set to assess the overall performance. **Results:** The Area Under Curves (AUC) of the classifier for LC, BC, CRC, GC and EC are 97.3%, 96.2%, 92.0%, 94.0% and 93.5%, respectively. At a fixed specificity of 99%, the sensitivities for LC, BC, CRC, GC and EC are 84%, 75%, 82%, 85% and 78%, respectively. **Conclusions:** A methylation blood test for five major cancer screening has been validated in a large retrospective cohort. Its high sensitivity for each cancer type, especially at the early stage (stage I), and easy to use suggests it can be implemented in real clinical world. A large prospective clinical trial is undergoing to further validate this test in asymptomatic populations. Research Sponsor: AnchorDx Medical Co., Ltd.

10562 **Poster Session**

Factors associated with breast self-examination in Mexican young women with breast cancer. *First Author: Andrea Becerril Gaitan, Centro de Cancer de Mama, Hospital Zambrano Hellion TecSalud, Tecnologico de Monterrey, San Pedro Garza Garcia, NL, Mexico*

Background: Breast cancer (BC) is the most common cause of cancer-related death and morbidity among young women in Latin America. This group has a higher prevalence of advanced disease stages at diagnosis compared to their older counterparts. Thus, strategies aimed at detecting BC at early stages are imperative. Breast self-examination (BSE) remains a useful strategy for BC detection, especially in women who do not routinely undergo screening with imaging studies. This study aims to evaluate factors related with BSE practice in Mexican young women with BC and assess its association with earlier disease stages. **Methods:** Women aged ≤40 newly diagnosed with BC from 2014 to 2020 at three cancer referral centers in Mexico accrued in the Joven & Fuerte cohort were included and asked to complete a socio-demographic survey. Fisher's exact and Mann-Whitney U tests were used to evaluate associations between BSE and socio-demographic characteristics, as well as disease stages. **Results:** A total of 554 patients with a median age at diagnosis of 36 years (range: 19-40) were analyzed. Most patients (65%) were married or in a domestic partnership, and the majority were housewives (63%). Regarding educational background, 64% had completed at least high school, and up to 84% had a monthly income < 11,600 Mexican pesos (US$ 581). Overall, 85% of patients had public insurance, 6% had private insurance, and 9% were uninsured. The distribution of clinical stages at diagnosis was: 0 (2%), I (11%), II (45%), III (32%), and IV (10%). BC detection methods were: 85% by self/partner exam, 11% by an imaging study, and 4% by a healthcare professional. A total of 443 (80%) patients practiced BSE, of which 50% did it on a monthly basis, 18% every 2-3 months, and the remaining 12% every 4-12 months. Notably, a higher educational level (≥ high school *v* ≤ middle school) was positively associated with BSE practice (RR: 1.28; 95%CI 1.06-1.54; $p = 0.005$). No significant association was found between BSE and age (≤35 *v* > 35), marital status (in a relationship *v* no), occupation (housewive *v* other), monthly income (< 11,600 *v* ≥11,600) or medical coverage (public/uninsured *v* private). Patients that performed BSE were more likely to be diagnosed with early BC (stages 0-II) compared to those that did not (61% *v* 45%; $p = 0.003$). No association was found between BSE frequency and stage at diagnosis. Noteworthy, patients with private insurance were more likely to be diagnosed with stages 0-II compared to those with public or no insurance (80% *v* 56%; $p = 0.007$). **Conclusions:** The significant association between BSE and earlier stages at diagnosis found in this study highlights the need to raise awareness and promote this practice among young women with the objective of downstaging BC diagnoses. Public health interventions such as educational and social media campaigns that aim to improve the correct practice of BSE might be particularly useful in settings with inadequate screening programs. Research Sponsor: None.

10563 **Poster Session**

Young-onset colorectal cancer: A call for action. *First Author: Iosune Baraibar, Vall d'Hebron Institute of Oncology (VHIO), Medical Oncology, Vall d'Hebron University Hospital (HUVH), Barcelona, Spain*

Background: Young-onset colorectal cancer (YOCR) is defined as diagnosis below the age of 50. Over the past decades, the incidence of YOCRC has increased at an alarming rate, but causes and pathogenesis still remain unknown. Early detection of colorectal cancer (CRC) has demonstrated to improve survival. Despite these facts, adults < 50 years old are not yet included in screening programs and YOCRC is not well characterized. We aimed to characterize the clinical and molecular characteristics of YOCRC in patients (pts) diagnosed at our institution. **Methods:** Consecutive pts with a diagnosis of CRC below the age of 50 visited for the first time at Vall d'Hebron University Hospital in Spain between January 2017 and October 2020 were included in the analysis. Data of clinicopathologic features and treatment were collected retrospectively from medical records. **Results:** 205 pts met the inclusion criteria, 111 (54%) were females, 8 (4%) presented a personal history of cancer at diagnosis and 109 (53%) a family history of cancer. Age at diagnosis was: < 30: 10 (5%), {30 – 40): 52 (25%), {40-45): 51 (25%), {45-50): 92 (45%). Site of primary tumor was: right colon: 50 (24%), left colon: 107 (52%): rectum: 48 (24%). Stage at diagnosis was I: 3 (1%), II: 14 (7%), III: 60 (29%), IV: 128 (63%). 6 of 14 (43%) and 44 of 60 patients (73%) with stage II and III CRC presented disease progression after initial treatment, respectively. Molecular status was: *KRAS* mutation: 74 (36%), *NRAS* mutation: 7 (3%), *BRAF* mutation: 12 (6%), MSI-H: 12 (6%). 43 pts (21%) had documentation of genetic counseling. Median (range) number of lines of treatment for metastatic disease was 3 (1-7), 53 pts (30%) received at least 4 lines of treatment. Median (range) number of metastatic sites was: 2 (1-6). 114 patients (55.6%) had died at the cut-off timepoint. **Conclusions:** YOCR is usually diagnosed with a more advanced stage than standard-onset CRC, with a poorer course of the disease. Further studies in young adults with CRC should address this phenomenon to understand the underlying causes, and prioritize genetic counseling. Our results support the unmet need of initiating screening programs in adults younger than 50 years, the urgency for a global consensus and a call for action. Research Sponsor: None.

10564 **Poster Session**

Interactive online skin cancer training game "Whack-a-Mole" assesses training strategies and real-time feedback on melanoma identification among U.S. adults. *First Author: Margaret I Sanchez, Sylvester Comprehensice Cancer Center-University of Miami Miller School of Medicine, Miami, FL*

Background: Cutaneous melanoma is a deadly form of skin cancer. Several studies have shown that early melanoma detection is associated with decreased mortality through self-examination and dermatology full-body skin exams. ABCD rule and the ugly duckling sign (UDS) are used to identify melanomas, but little research has explored the comparative efficacy of these approaches. This investigation compares the effectiveness of different mole identification training strategies and explores the effect of real-time feedback on decision-making. **Methods:** We developed an online melanoma identification game that tests differences between training types and expert feedback on mole identification. This online RCT tests a 4 (training: ABCD, UDS, both, control) X 3 (feedback: standard, motivational, control) factorial design on melanoma identification, skin cancer beliefs (perceived susceptibility and self-efficacy), and skin cancer prevention intentions. Standard feedback included expert evaluations of moles, whereas motivational feedback added statements grounded in fear appeals theory to encourage skin self-examination. An online research panel service was used to recruit 1025 US adults. Participants were randomly assigned to condition, completed a pretest, participated in the game intervention, and completed a posttest. Gameplay incorporates the same mechanics as *Tinder* (swipe left on benign moles and swipe right on malignant moles). **Results:** In total, participants reviewed 48 moles, 12 of which were melanomas. We used two-way ANCOVA for the analysis. ABCD training resulted in significantly higher melanoma identification than the control ($p = .011$). Every training type resulted in significantly higher self-efficacy than the control ($p = .007$). Additionally, there was a significant main effect of feedback on self-efficacy ($p = .001$), where both standard and motivational feedback elicited significantly higher levels of self-efficacy than the control condition. Around 88% of participants intend to conduct skin self-exams and wear sunscreen. **Conclusions:** Our data suggests that "Whack a Mole" is an efficacious tool for melanoma training. ABCD and UDS training with interactive feedback are important to improve accuracy and ability for melanoma identification. Research Sponsor: None.

10565 **Poster Session**

The impact of socioeconomic status on stage at presentation, receipt of diagnostic imaging, receipt of treatment, and overall survival in colorectal cancer patients. *First Author: Rajan Shah, University of Toronto, Faculty of Medicine, Mississauga, ON, Canada*

Background: Socioeconomic factors have been identified to influence patterns of care in colorectal cancer yet current literature findings are sparse, conflicting, and often incomplete. As such, this study investigates the impact of socioeconomic status (SES) on stage at presentation, receipt of diagnostic imaging, receipt of treatment, and overall survival (OS) in a universal healthcare system. **Methods:** The Ontario Cancer Registry was accessed to identify a cohort of patients diagnosed with colorectal adenocarcinoma from 2007-2016 in Ontario, Canada. Linkage to administrative datasets allowed study of the impact of SES, measured by mean neighbourhood household income divided into quintiles (Q1-Q5; Q1 = lowest income), on stage, imaging, treatments, and OS. Multivariable regression analyses of all endpoints were adjusted for age, sex, comorbidity, and rurality with OS models also adjusting for imaging and treatment. **Results:** 39,802 colon and 13,164 rectal patients were identified. Lower SES patients were more likely to present at a higher stage in both cohorts. Lower SES colon patients were less likely to receive magnetic resonance imaging (MRI) of the abdomen, liver resection, adjuvant oxaliplatin, and all palliative systemic therapies studied. In rectal patients, lower SES was associated with decreased receipt of MRI pelvis, rectal cancer resection in early stages, adjuvant oxaliplatin, and most palliative chemotherapies studied. All OS models found that lower SES was associated with poorer OS. **Conclusions:** These findings suggest disparities across the continuum of cancer care persist even within a universal healthcare system. Further efforts should be directed towards temporal research, identifying barriers, and subsequently applying this information to actionable policies. Research Sponsor: None.

10566 **Poster Session**

Impact of COVID-19 pandemic in 2020 on the diagnosis and management of breast cancer in Korea: A multi-institutional study. *First Author: Young-Joon Kang, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, South Korea*

Background: Since the COVID-19 pandemic began in early 2020, there have been many reports that it has had a significant impact on screening, case identification and referral in cancer diagnosis. We investigated the diagnostic and therapeutic status of breast malignancy before and after the COVID-19 pandemic at the multi-institution level. **Methods:** We have reviewed the records of patients with breast cancer from February 2019 to July 2020 in six university hospitals in Korea. The patients were divided into two groups according to the initial date of cancer diagnosis: Period A, from February to April and Period B, from May to July in 2020. The two groups were compared for the same periods in 2019. The goals were to determine whether breast cancer screening and diagnosis have been delayed and thus resulted in stage migration. We also examined the difference in the number of surgeries in patients diagnosed with breast cancer during those periods. **Results:** The total of 1,669 breast malignancy diagnosis was made in the grouped periods of 2019, and 1,369 diagnoses in 2020. All patients were screened by PCR test for COVID-19 prior to hospitalization, and none of them tested positive. Overall, there was a 9.9% reduction in the number of diagnoses than in 2019 and the decrease was more significant in Period A (11.1% vs. 8.7%). According to the age, there was no difference until the 30s but decreased from those in their 40s and above. The decline was more pronounced in the elderly. The COVID-19 pandemic has affected breast cancer screening (decreased by 27.4%) and more diminished in Period A (41.0% vs. 19.0%). Invasive breast cancer stage was not statistically different in Period A compare with 2019 ($p = 0.170$). But the stage in Period B was different ($p = 0.032$), and more patients were observed in advanced stages in 2020. The decrease in surgery was noticeably observed in Period A (4.6%, from 480 to 438 surgeries) and not in Period B. The analysis of reconstruction surgery was similar. **Conclusions:** Patients with COVID-19 increased exponentially from late February in Korea. However, the number of patients per day decreased to less than 100 on March 15 and then flattened. The health care system for cancer was not overloaded and restrictions on visiting hospital were minimal. Analysis in the pandemic period of the 6-month showed that the number of breast cancer screening, diagnosis and surgeries decreased compared with the previous year. Those decreases were prominent in Period A when the COVID-19 patient surged. The upstage migration of breast cancer was generally insignificant but slightly occurred in Period B. The outbreak of infectious disease makes patients reluctant to come to the hospital, especially in the elderly. We need to discuss the potential long-lasting deleterious effect of the COVID-19 pandemic on cancer diagnosis and management. And we should prepare for how to deal with the backlog caused by the COVID-19 pandemic. Research Sponsor: None.

10567 **Poster Session**

Outcomes for cancer patients on systemic anti-cancer therapies during the COVID-19 pandemic from the CAPITOL (COVID-19 Cancer PatIenT Outcomes in North London) cohort study. *First Author: Valerie Crolley, Barts Cancer Institute, London, United Kingdom*

Background: One of the major challenges with COVID-19 has been the changes to cancer services, including changes to the type of systemic anti-cancer treatment being delivered to patients. There needs to be a better understanding of which cancer patients are at the greatest amount of risk to make informed decisions on how cancer treatment can be altered to protect patients from COVID-19 infection. The CAPITOL (COVID-19 CAncer PatIenT Outcomes in North London) study investigated the outcomes of patients receiving systemic anti-cancer therapies (SACT) with regards to COVID-19 infection, as patients with cancer are hypothesised to be at higher risk. **Methods:** CAPITOL collected data from all patients receiving SACT at two cancer centres. The effect of clinical characteristics on the incidence and severity of COVID-19 infection in patients on SACT was the primary outcome, and we used univariable and multivariable models in our analysis, adjusting for age, gender and comorbidities. **Results:** 2871 patients were analysed from 2nd March to 31st May 2020, all of whom received SACT; during this time period 68 (2.4%) were diagnosed with COVID-19. Receiving SACT increased the risk of death when contracting COVID-19 (adjusted (adj.) OR 9.84; 95% CI 5.73 – 16.9). The risk of contracting COVID-19 was increased by receiving chemotherapy (adj. OR 2.99; 95% CI = 1.72 - 5.21), with the risk significantly increased by high dose chemotherapy (adj. OR 2.36, 95% CI 1.35 – 6.48). Patients with comorbidities (adjusted OR 2.29; 95% CI 1.19 - 4.38), or with a respiratory or intrathoracic neoplasm (adj. OR 2.12; 95% CI 1.04 - 4.36) were also at increased risk of contracting COVID-19. Cancer patients who received targeted treatment had a reduced risk of contracting COVID-19 (adj. OR 0.53; 95% CI 0.30 – 0.95), while there was no significant change in risk caused by treatment intent (curative versus palliative), hormonal- or immunotherapy and solid versus haematological cancers. **Conclusions:** To the best of our knowledge, this is one of the first investigations into the risk of contracting COVID-19 in a cohort of all cancer patients on SACT. We found that patients on SACT are more likely to die if they contract COVID-19. The type of SACT received by cancer patients can affect their likelihood of contacting COVID-19, with chemotherapy increasing risk, targeted therapy decreasing risk and a potential protective effect for hormonal and immunotherapy. Research Sponsor: None.

10568 **Poster Session**

Prior tonsillectomy and subsequent risk of breast cancer in females: Systematic review and meta-analysis. *First Author: Salah Eddine Oussama Kacimi, Faculty of Medicine, University of Tlemcen, Tlemcen, Algeria*

Background: Exposure to recurrent infections in childhood was linked to an increased risk of cancer in adulthood. There is also evidence that a history of tonsillectomy, a procedure often performed in children with recurrent infections, is linked to an increased risk of leukemia, and Hodgkin lymphoma. Tonsillectomy could be directly associated with cancer risk or it could be a proxy for another risk factor such as recurrent infections and chronic inflammation. Nevertheless, the role of recurrent childhood infections and tonsillectomy on the one hand, and the risk of breast cancer (BC) in adulthood remain understudied. Our study aims to verify whether a history of tonsillectomy increases the risk of BC in women. **Methods:** A systematic review was conducted using PubMed, Google Scholar, Scopus, Embase and Web of Science databases from inception through November 2020 to identify the studies which explored the association between history of tonsillectomy and BC in females. The Newcastle Ottawa Scale was used to assess the quality of included studies. Odds ratio (OR) was used to measure effect size. The Random/Fixed effects model was applied to synthesize the associations between tonsillectomy and BC risk based on heterogeneity. Heterogeneity was assessed using the I-squared statistic. A forest plot was generated, and publication bias was assessed. The leave-one-out sensitivity analysis was performed to check if results were driven by a single study. **Results:** Seven studies with a total of 7259 patients were included in our analysis; out of them, 2200 patients were diagnosed with BC. Patients with a history of tonsillectomy ($n = 2843$) showed higher subsequent risk of developing BC (OR = 1.252; 95% CI = 1.115 - 1.406; $P < 0.001$; $I^2 = 9\%$) as compared to patients without a history of tonsillectomy ($n = 4416$). Using the leave-one-out sensitivity analysis to iteratively remove one study at a time, we confirmed that no single study had a substantial influence on the overall effect size. **Conclusions:** Our study supports and confirms the evidence that a history of tonsillectomy is associated with an increased risk of breast cancer. These findings are also an argument in support of the hypothesis that recurrent childhood infections are linked with adulthood breast cancer. Research Sponsor: None.

10569 **Poster Session**

Trends in incidence and mortality of squamous cell carcinoma of the skin: An observational analysis of the Global Burden of Disease database from 1990 to 2017. *First Author: Dorothy Yang, St George's University Hospitals NHS Foundation Trust, London, United Kingdom*

Background: Epidemiological data relating to non-melanoma skin cancer (NMSC), including squamous cell carcinoma (SCC), is highly under-reported and under-studied due to its lower metastatic potential. In recent years, incidence and prevalence of SCC has increased in many countries due to earlier detection, increased ultraviolet light exposure, as well as increasing life expectancy. This investigation compared trends in SCC incidence, mortality and disability-adjusted life years (DALYs) in 33 countries. **Methods:** We utilized the Global Burden of Disease (GBD) database for 33 countries, including the European Union nations as well as other selected high-income countries including the UK and USA. We extracted data including age-standardized incidence rates (ASIRs), age-standardized mortality rates (ASMRs) and DALYs for SCC of the skin from 1990 to 2017. Joinpoint regression analysis was used to describe the trends. **Results:** For both sexes, the highest ASIRs were seen in the USA and Australia: ASIRs were 362.8/100,000 and 283.7/100,000 respectively for males, and 171.2/100,000 and 152.4/100,000 respectively for females. Males had higher ASIRs than females at the end of the observation period in all countries. In contrast, the highest ASMRs for males were observed in Australia (2.77/100,000) and Latvia (2.44/100,000), while the highest ASMRs for females were observed in Romania (0.95/100,000) and Croatia (0.90/100,000). The highest DALYs for both sexes were seen in Australia and Romania: DALYs were 58.4/100,000 and 43.8/100,000 respectively for males, and 16.9/100,000 and 14.9/100,000 respectively for females. Over the observation period, there were more countries demonstrating decreasing trends in mortality than in incidence. There was also a disparity between which countries had comparatively high mortality rates and which had high incidence rates – for instance, the USA, which had by far the highest SCC incidence rates, had among the lower mortality rates. Overall reductions in DALYs were observed in 24 of 33 countries for males, and 25 countries for females. **Conclusions:** Over the past 27 years, although trends in SCC incidence have risen in most countries, there is evidence that mortality rates have been decreasing, especially towards the end of the observation period. Overall, burden of disease as assessed using DALYs has decreased in the majority of countries. Future work will explore potential explanatory factors for the observed disparity in trends in SCC incidence and mortality. Research Sponsor: None.

10570 **Poster Session**

Demographical differentials of lung cancer survival in Bangladeshi patients. *First Author: Muhammad Rafiqul Islam, National Institute of Cancer Research and Hospital, Dhaka, Bangladesh*

Background: Lung Cancer is the leading cause of cancer-related mortality and most common cancer in worldwide with more than a million deaths annually. 20.8% cancer related death caused by lung cancer and more than half of lung cancer occurred in Asia. Differences In the epidemiology of lung cancer among the developing country may shed light on possible genetic and demographical influences on lung cancer survival. Demographic stratification of lung cancer patients of Bangladesh is remain unclear due of lack of data We tried to figure out the demographic pattern and its impact on survival in Bangladeshi lung cancer patient. **Methods:** Previously diagnosed primary lung cancer patients attending Medical Oncology department of National Institute of cancer research and Hospital, a tertiary care center of Bangladesh, between 2018 and 2019 were included. Demographic and clinical data were collected retrospectively from the medical records. **Results:** A total of 1868 consecutive patient (1580 males, 288females) diagnosed to have lung cancer; Mean age was 60 years which quite early compare to other countries. Older than 70-year age groups had worse survival outcome (hazard ratio 1.04: 95% confidence interval: 1.17–1.68). Below 50-year group had better outcome with standard adjuvant or palliative chemotherapy whereas older groups had better survival with sequential radiotherapy and chemotherapy or concurrent chemo radiation (Hazard Ratio 0.45; 95% confidence interval: 0.30–0.67). Sex was not a predicting factor for overall survival (Hazard ratios 1.04 95% confidence interval 0.89- 1.22, P = 0.621). But, Male had better treatment response than the female (Hazard ratio and 95% confidence interval: 0.51 and 0.42-0.61, P = < 0.001). Education level had significant impact on survival outcome (Hazard ratio 0.58 and 95% confidence interval: 0.47-0.71, P = < 0.001). Underweight group had worse survival than the normal BMI group (Hazard ratio1.18 and 95% confidence interval 1.05-1.31, P = 0.005). Having the Comorbid condition at the time of diagnosis had shorter survival (Hazard ratio 1.16 and 95% confidence interval 1.04-1.30 P = 0.007). Histological variation had no survival benefit among the squamous, small cell or other histological types (p = 0.214, 0.494, 0.658 respectively). But adenocarcinoma or small cell carcinoma had better treatment response outcome. Eastern Cooperative Oncology Group performance status (ECOG-PS) 4 had worse outcome (Hazard ratio 1.95, 95% confidence interval 1.37–2.79; P = < 0.001). **Conclusions:** The socio-demographic related survival in lung cancer needs to be fully elucidated because of its implication in the design of experimental protocols for targeted chemoprevention, early disease screening, molecular marker based staging, and individualized treatment. Due to its extraordinary disease burden and the international variability in demographic variables, the lung cancer requires continual monitoring. Research Sponsor: None.

10571 **Poster Session**

Prognostic value of *pre-infection* routine laboratory parameters for COVID-19 mortality in tumor patients: Results of the ADHOK Coronavirus Tumor Registry. *First Author: Romina Roesch, Technische Universität Dresden, Dresden, Germany*

Background: Tumor patients (pts.) are considered susceptible to severe COVID-19 after SARS-CoV-2 infection. However, they represent a heterogeneous group of individuals with variable risk. Identification of vulnerable subgroups is important for prioritization of vaccination strategies and possible early therapeutic intervention after infection. **Methods**: Tumor pts. with PCR-confirmed SARS-CoV-2 infection were included in the multicentric ADHOK registry by 22 institutions. Detailed information about tumor disease and treatment, as well as routine laboratory parameters determined at least 10 days prior to SARS-CoV-2 infection, was collected retrospectively. The primary endpoint was defined as the outcome of the SARS-CoV-2 infection, graded according to the WHO: asymptomatic, mild, moderate, severe, critical, and COVID-19-related death. **Results**: Until Feb. 5, 2021, 215 pts. (67% with solid tumors, 33% with hematological neoplasms) were included in the registry. 74% of the pts. had an active malignancy. The course of SARS-CoV-2 infection was rather variable: 66% of the pts. remained asymptomatic or showed a mild-to-moderate course, while the rest developed severe or critical disease. The COVID-19-related mortality rate was 24%. *Pre-infection* routine laboratory values were available for 104 pts., obtained at a median of 21 days before SARS-CoV-2 infection. Compared to COVID-19 survivors, COVID-19 non-survivors showed significantly higher median levels of absolute neutrophil count (ANC: 3.6 vs. 6.4 /nL; p = 0.006, n = 91), neutrophil-to-lymphocyte ratio (NLR: 2.2 vs. 7.2; p = 0.005, n = 75), C-reactive protein (CRP: 9.9 vs. 42.0 mg/L; p = 0.001, n = 104), and lactate dehydrogenase (LDH: 213.0 vs. 267.0 U/L; p = 0.016, n = 78). When categorized by a median split, COVID-19 mortality was significantly higher in pts. with ANC > 4.4 /nL (4% vs. 55%, p < 0.001), NLR > 4.1 (5% vs. 58%, p < 0.001), CRP > 15.4 mg/L (18% vs. 46%, p = 0.003), LDH > 236 U/L (15% vs. 49%, p = 0.003) and lymphocytes < 1.3 /nL (41% vs. 11% p = 0.002). In multivariable analysis, ANC and CRP showed a strong and significant association with COVID-19-related death (OR 23.0 and 7.7, p = 0.007 and 0.029, respectively). To develop an easy-to-apply *pre-infection* score, we combined ANC and CRP and were able to separate three groups of pts. with significantly different COVID-19 outcomes (p < 0.001) (Table). **Conclusions**: Our results unveil subgroups of tumor pts. who may be at increased risk of severe COVID-19 and point to *pre-infection* routine laboratory parameters with potential prognostic power: ANC and CRP may help identify pts. at risk for severe COVID-19 before SARS-CoV-2 infection. Research Sponsor: Arbeitsgemeinschaft der Haematologen und Onkologen im Krankenhaus e.V, Research funds of the Klinikum Bayreuth GmbH, Germany.

Pre-infection parameters	Score = risk for severe COVID-19	COVID-19-related mortality (%) (n = 83)
Absolute neutrophil count (ANC) < 4 /nL	0 = low	0%
ANC > 4 /nL and CRP < 20mg/L	1 = increased	30%
ANC > 4 /nL and CRP > 20mg/L	2 = high	68%

10572 **Poster Session**

Outcomes for hospitalized cancer patients with COVID-19 during the height of pandemic in New York City. *First Author: Amelia Sawyers, NYU Grossman School of Medicine, New York, NY*

Background: Several reports have suggested that cancer patients are at increased risk for contracting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and suffering worse coronavirus disease 2019 (COVID-19) outcomes. However, little is known about the impact of cancer status on presentation and outcome. Here, we report on the association between cancer status and survival in hospitalized patients who tested positive for SARS-CoV-2 during the height of pandemic in New York City. **Methods:** Of the 6,724 patients who were hospitalized at NYU Langone Health (3/16/20 - 7/31/20) and tested positive for SARS-CoV-2, 580 had either active cancer (n = 221) or a history of cancer (n = 359). Patients were classified as having active malignancy if they either received treatment within six months of their COVID-19 diagnosis or they had measurable disease documented at the time of their hospitalization. Patients were categorized as having a history of cancer if there was no evidence of measurable disease or there were no treatments administered within six months of their COVID-19 diagnosis. We compared the baseline clinicodemographic characteristics and hospital courses of the two groups, and the relationship between cancer status and the rate of admission to the intensive care unit (ICU), use of invasive mechanical ventilation (IMV), and all-cause mortality. **Results:** There was no differences between the two groups in their baseline laboratory results associated with COVID-19 infection, incidence of venous thromboembolism, or incidence of severe COVID-19. Active cancer status was not associated with the rate of ICU admission ($P = 0.307$) or use of IMV ($P = 0.236$), but was significantly associated with worse all-cause mortality in both univariate and multivariate analysis with ORs of 1.48 (95% CI: 1.04-2.09; $P = 0.028$) and 1.71 (95% CI: 1.12-2.63; $P = 0.014$), respectively. **Conclusions:** Active cancer patients had worse survival outcomes compared to patients with a history of cancer despite similar COVID-19 disease characteristics in the two groups. Our data suggest that cancer care should continue with minimal interruptions during the pandemic to bring about response and remission as soon as possible. Additionally, these findings support the growing body of evidence that malignancy portends worse COVID-19 prognosis, and demonstrate that the risk may even apply to those without active disease. Research Sponsor: U.S. National Institutes of Health.

10573 **Poster Session**

Trends in breast cancer incidence among young women aged 20 to 49 years in the United States. *First Author: Shuai Xu, Washington University School of Medicine, St. Louis, MO*

Background: Breast cancer in young women is diagnosed at more advanced stages and has a less favorable prognosis. We investigated trends in breast cancer incidence by race/ethnicity, hormone receptor status, and tumor stage in women aged 20-49 years over the past 25 years, as well as the impact of period and cohort effects on these trends. **Methods:** We used data from Surveillance, Epidemiology, and End Results (SEER) 13 registries for 1993-2002 and SEER 18 registries for 2003-2017. We calculated age-standardized incidence rates and annual percent change (APC), and stratified by race/ethnicity, hormone receptor status (estrogen receptor [ER] and progesterone receptor [PR]), and tumor stage (I-IV) for 222,424 women aged 20-49 years with a primary invasive breast cancer. We performed age-period-cohort analysis (presented as incidence rate ratios [IRR]) to investigate the effects of age, period, and cohort on incidence trends using the 1948 cohort and 1993-1997 period as the reference groups, respectively. **Results:** Between 2010-2017, invasive breast cancer incidence increased (APC = 0.67%, 95%CI: 0.32 to 1.03) among women aged 20-49 years, after being stable from 1993-2010. There were differences by race over the 25-year period (1993-2017). We observed significant increases in incidence among non-Hispanic White (NHW) (APC = 0.25%, 95%CI: 0.16 to 0.34), non-Hispanic Asia/Pacific Islander (NHAPI) (APC = 0.58%, 95%CI: 0.34 to 0.82), and Hispanic women (APC = 0.59%, 95%CI: 0.34 to 0.83), but not among non-Hispanic black (NHB) women (APC = 0.14%, 95%CI: -0.06 to 0.34). Incidence increased for ER+ tumors but decreased for ER- tumors: ER+/PR+ (APC = 2.39%, 95%CI: 2.20 to 2.58), ER+/PR- (APC = 1.46%, 95%CI: 1.05 to 1.87), ER-/PR+ (APC = -6.33%, 95%CI: -7.31 to -5.33), and ER-/PR- (APC = -0.70%, 95%CI: -1.09 to -0.32). The decrease in ER-/PR- tumors appeared largely driven by decreases among HNW women. Incidence for stages I (APC = 0.31, 95%CI: 0.07 to 0.55), II (APC = 0.99, 95%CI: 0.82 to 1.16), and IV (APC = 2.88, 95%CI: 2.37 to 3.39) tumors increased while that for stage III tumors decreased (APC = 0.81%, 95%CI: -1.04 to -0.59). Both the cohort and period effects impacted incidence, with the cohort effect almost 10 times larger than the period effect. Age-specific relative risk by birth cohort initially decreased between 1948 and 1958 but steadily increased from 1958 to 1993. Breast cancer incidence was higher among women born in the 1988 (IRR = 1.17, 95%CI: 1.07 to 1.28) and 1993 (IRR = 1.22, 95%CI: 0.99 to 1.51) cohorts than for those born in 1948 cohort. **Conclusions:** Breast cancer incidence is increasing among young women, mainly driven by increases in ER+ tumors. Prevention efforts need to focus on how we can address factors driving the increase in ER+ tumors and also learn from what has worked for decreasing ER- tumors. Research Sponsor: U.S. National Institutes of Health.

10574 **Poster Session**

Socioeconomic background in relation to stage at diagnosis in women with breast cancer. *First Author: Juan Manuel Ariza, Cancer Registry (Loire-Atlantique, Vendee), Nantes, France*

Background: Breast cancer (BC) has been associated with socioeconomic deprivation and rural residence. However, it's still unclear how these factors interplay to affect the frequency and incidence of early and advanced BC. **Methods:** Taking advantage of the Loire-Atlantique/Vendée cancer registry (France), we investigated the association between early (TNM stage < 2) and advanced (TNM stage ≥ 2) BC and the socio-economic background (SB) of women diagnosed in the study region from 2008 to 2015. Socioeconomic status was studied using the residence information of every patient linked to the European Deprivation Index (EDI), an ecological index constructed to reflect individual deprivation experienced at the smallest geographical unit of France (IRIS = 2000 inhabitants). To investigate SB, we created a composite variable using the EDI and the urban/rural context information, to define 4 categories: affluent-urban, affluent-rural, deprived-urban, and deprived-rural. Two statistical approaches were implemented: i) mixed-effects logistic regression models to examine the likelihood (relative risk, RR) of being diagnosed with advanced BC, and ii) Poisson regression for modeling incidence rates of early and advanced stages. Analyses were stratified by age (< 45, 45 to 74, $>$ 75 years) with a random intercept at the IRIS level. For the strata 45 to 74, the models were adjusted for organized screening. **Results:** During the study period, 14,542 BC cases were recorded. Compared to the women diagnosed in the most affluent-urban areas, a higher proportion of cancer diagnosed at an advanced stage was observed in the women living in more deprived-rural areas (aged < 45 years, RR = 1.48 95% CI 1.17 - 1.73; aged 45 to 74 years, RR = 1.22, 95% CI 1.02-1.42; aged > 74 years, RR = 1.08, 95% CI 0.85-1.27). Furthermore, while in the population under 74 years, incidence rates of early BC in deprived-rural women were reduced by 25-85 % in comparison to affluent-urban women (IRR: 0.33 to 0.97 95% CI 0.16 -0.98), the rates of advanced BC were unaffected by deprivation-rurality (Deprived rural vs Affluent urban, IRR: 1.06 to 1.13 95% CI 0.79 -1.72). For the population over 74 years, we were unable to detect any associations between SB and BC incidence by stage at diagnosis. **Conclusions:** Advanced stage at diagnosis was more frequent among deprived–rural women aged under 74 years and coincided with the low incidence rates of early stages in this population. No disparities in the incidence rates of advanced BC were detected according to their SB in any age classes, suggesting other factors may be stronger contributors to the advanced stage at diagnosis. Future research should investigate whether screening practices may influence the disparities in the early stage at diagnosis for women under 74. Research Sponsor: SIRIC-ILIAD Nantes, France.

10575 **Poster Session**

Incidence and trend of Epstein-Barr virus-related cancer: A surveillance, epidemiology, and end results program based study. *First Author: Jiayi Shen, Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Epstein-Barr virus (EBV) infection was highly prevalent, as was found in more than 90% of the adults globally. EBV infection has been found to be related with several types of cancer and classified as group 1 carcinogen by the International Agency for Research on Cancer. The association between EBV infection and malignancy was observed in Burkitt lymphoma (BL), Hodgkin lymphoma (HL), extranodal natural killer (NK)/T-cell lymphoma (NNKTL), gastric cancer (GC) and nasopharyngeal cancer (NPC). In this study, we aimed to analyze the incidence and the trend of incidence of these virus-related cancer and to identify whether the trend was similar between them. **Methods:** This was a retrospective analysis based on the data from Surveillance, Epidemiology, and End Results (18 registries, 2000-2017), which totally included 71,415 patients. EBV-related cancers were defined as BL, HL, NNKTL, GC and NPC. Age-adjusted incidence rates were displayed as per 100,000 persons. In terms of incidence trend, we calculated the average annual percent change (AAPC). AAPC was considered significantly different from 0 when the *P*-value was smaller than 0.05. The impact of the epidemiological and clinical characteristics on the incidence trend was estimated, with cancer type, histology, age, sex and race considered. **Results:** Incidence rates of EBV-related cancers were 6.68 per 100,000 persons in 2000 and 5.80 in 2017, of which the AAPC was -0.8 (95%CI, -1.1 - -0.5, *P*-value < 0.001). (Table) Similar with EBV-related cancer as a whole, the APCCs of BL, HL and GC were statistically significantly smaller than 0, except that the APCCs of NNKTL and NPC were statistically significantly larger than 0 and not statistically significantly different from 0 respectively. The incidence of EBV-related cancer also decreased in mixed cellularity classical HL, nodular sclerosis classical HL, adenocarcinoma of GC, signet ring cell carcinoma in GC, undifferentiated carcinoma of NPC, squamous cell carcinoma of NPC, patients diagnosed at the age of 20-39 years old and 60-79 years old, male patients and race as white, black or Asian, but increased in classical HL, NOS, nodular lymphocyte predominant HL and non-keratinizing carcinoma of NPC. **Conclusions:** Incidence of EBV-related cancer decreased during 2000 and 2017, which was consistent in BL, HL and GC. Research Sponsor: None.

Rate and APCC of EBV-related cancers.

EBV-related cancers	Rate in 2000	Rate in 2017	APCC	*P*-value
EBV-related cancers	6.68 (6.46 - 6.90)	5.80 (5.62 - 5.99)	-0.80 (-1.10 - -0.50)	< 0.001
BL	0.37 (0.32 - 0.43)	0.32 (0.28 - 0.37)	-1.60 (-3.00 - -0.10)	< 0.001
HL	2.93 (2.79 - 3.07)	2.53 (2.41 - 2.65)	-0.80 (-1.30 - -0.40)	< 0.001
NNKTL	0.02 (0.01 - 0.03)	0.09 (0.07 - 0.11)	1.90 (0.20 - 3.60)	< 0.001
GC	2.77 (2.63 - 2.92)	2.35 (2.24 - 2.46)	-0.70 (-1.10 - -0.40)	< 0.001
NPC	0.59 (0.53 - 0.66)	0.52 (0.47 - 0.58)	-0.60 (-1.30 - 0.10)	0.10

10576 **Poster Session**

Leukemia in hospitalized patients with inflammatory bowel disease: An analysis of the National Inpatient Sample (NIS) database. *First Author: Colin Wikholm, MedStar Georgetown University Hospital, Washinton, DC*

Background: Inflammatory bowel disease (IBD) and use of immunosuppressive therapy in IBD is linked with increased risk of leukemia. We studied the NIS database from 2003-2017 to analyze trends in any type of leukemia in IBD hospitalizations over time and examined the role of age, sex, and race. **Methods:** We analyzed NIS data of all adult hospitalizations for ulcerative colitis (UC) or Crohn's disease (CD) with any type of leukemia as a primary or secondary diagnosis using validated ICD 9/10 codes. Age, sex, and racial demographics were collected. Trend analysis of leukemia was performed with Cochran-Armitage and Jonckheere-Terpstra tests. **Results:** Overall Trends: From 2003-2017, a total of 11,385 of 2,235,413 (0.51%) CD hospitalizations and 8,105 of 1,324,746 (0.61%) UC hospitalizations contained diagnosis of leukemia. An increase in leukemia was seen in both CD and UC group from 0.24% to 0.79% (pTrend < 0.0001) and 0.28% to 0.81% (pTrend < 0.0001) respectively. Sex: In both UC and CD patients, leukemia diagnoses were predominantly male in 2003 but approximated a near 1:1 ratio by 2017 (Table). In CD, the proportion of female (FEM) leukemia diagnoses grew from 31.33% to 45.05% from 2003 to 2017 (pTrend = 0.1898). In UC, the proportion of female leukemia diagnoses grew from 27.49% to 45.79% from 2003 to 2017 (pTrend = 0.0030). Age: Leukemia was more common with increasing age, with no significant changes in proportion of cases between age groups over time (pTrend $> .05$). Ethnicity: White patients composed 87.80% and 84.24% of leukemia diagnoses in CD and UC, respectively. In CD, an increasing proportion of leukemia diagnoses occurred in black (BK) patients, and a decreasing proportion occurred in white patients (pTrends $<.0001$; Table 1) during the study time. No trends in race were observed in the UC group (pTrend = 0.4229). **Conclusions:** Our study showed an increased prevalence of leukemia in CD and UC hospitalizations from 2003-2017 which may be related to increasing use of immunosuppressants such as anti-TNF medications. In both CD and UC, leukemia was male-predominant, but increasingly female by 2017. Rate of leukemia diagnosis increased with age. In the CD group but not the UC group, leukemia was increasingly prevalent in black patients. Research Sponsor: None.

	Leukemia (%) Prevalence		Sex and Leukemia		Race and Leukemia	
Year	CD*	UC*	CD (% FEM)	UC (% FEM)*	CD (% BK)*	UC (% BK)
2003	0.24	0.28	31.33	27.49	0	0
2004	0.34	0.27	43.15	46.71	2.86	11.53
2005	0.46	0.41	47.24	46.39	2.08	15.4
2006	0.41	0.4	52.58	43.62	0.92	2.17
2007	0.47	0.47	40.9	43.54	6.86	7.47
2008	0.39	0.51	50.57	43.07	1.72	4.57
2009	0.43	0.63	54.18	44.87	2.24	5.4
2010	0.49	0.62	52.44	42.74	8.76	6.72
2011	0.42	0.69	51	49.05	9.57	5.46
2012	0.52	0.6	50.27	46.22	5.62	6.19
2013	0.52	0.62	48.11	42.64	8.89	5.65
2014	0.55	0.66	56.65	53.85	11	4.96
2015	0.57	0.73	47.42	46.34	9.62	4.43
2016	0.67	0.85	48.99	46.43	5.44	6.91
2017	0.79	0.81	45.05	45.79	8.39	9.34

pTrend $< .05$ is designated by '*'.

10577 **Poster Session**

The global burden of 29 cancer groups from 2010 to 2019: A systematic analysis for the Global Burden of Disease study 2019. *First Author: Jonathan M Kocarnik, Institute for Health Metrics and Evaluation, Seattle, WA*

Background: Cancer is a major cause of morbidity and mortality worldwide, and global efforts to reduce health loss from cancer require systematic estimates that can measure progress from national to global levels. As part of the Global Burden of Diseases, Injuries, and Risk Factors Study 2019 (GBD 2019), we examined global cancer burden in order to highlight areas where cancer burden is inequitably distributed and to inform cancer control efforts around the world. **Methods:** Using estimation methods from GBD 2019, we analyzed the incidence, mortality, years lived with disability, years of life lost (YLLs), and disability-adjusted life years (DALYs) for 29 cancer groups and 204 countries and territories from 2010 to 2019. Cancer burden was compared to health burden from other categories of diseases and injuries in the GBD. Results were assessed globally and by socio-demographic index (SDI), a summary measure of income per capita, average educational attainment, and total fertility rate. Point estimates and 95% Uncertainty Intervals (UIs) are reported. **Results:** There were 23.6 million (95% UI 22.2-24.9 million) incident cancer cases globally in 2019 (17.2 [15.9-18.5] million excluding non-melanoma skin cancer), and 10.0 (9.36-10.6) million cancer deaths. There were 250 (235-264) million DALYs globally due to cancer, 97% of which came from years of life lost. The leading five cancers by DALYs in 2019 were: tracheal, bronchus, and lung cancer (45.9 [42.3-49.3] million); colon and rectum cancer (24.3 [22.6-25.7] million); stomach cancer (22.2 [20.3-24.1] million); breast cancer (20.6 [19.0-22.2] million; and liver cancer (12.5 [11.4-13.7] million). Compared to other diseases and injuries in the GBD, cancer was responsible for the second-highest number of deaths, YLLs, and DALYs globally in 2019. These rankings of cancer burden differed by SDI quintile: cancer was the leading cause of absolute DALYs in high SDI countries but was ranked 10th in low SDI countries. From 2010-2019, the number of global cancer cases increased by 26.3% (20.3-32.3%), deaths by 20.9% (14.2-27.6%), and DALYs by 16.0% (9.29-22.8%). The largest annualized rate of change in absolute cases and deaths over this period occurred in the low and low-middle SDI quintiles. **Conclusions:** Cancer cases and deaths are growing globally, with the largest relative growth over the last decade occurring in low to middle SDI countries. Improvements in cancer prevention efforts and ensuring access to timely diagnosis and care will be necessary to make equitable progress in reducing the global burden of cancer. Research Sponsor: Bill and Melinda Gates Foundation, Other Foundation.

10578 **Poster Session**

The lung cancer obesity paradox: An analysis of 432,924 patients. *First Author: Brittany Miles, UTMB Health, League City, TX*

Background: The lung cancer obesity paradox is the unexpected inverse relationship between body mass index (BMI) and lung cancer mortality. While there is a growing body of evidence to support the existence of the obesity paradox in lung cancer, little is known about its magnitude and relationship to cancer incidence and its impact on outcomes from surgery, chemotherapy, immunotherapy, and radiation treatment. **Methods:** To evaluate the impact of obesity on lung cancer incidence, we used TriNetX, a global federated health research network providing access to electronic medical records (diagnoses, procedures, medications, laboratory values, genomic information) from approximately 69 Million patients in 49 large Healthcare Organizations. We evaluated 2 patient cohorts of 216,462 adult smokers aged 18 to 75 that were matched for age, race, gender, and ethnicity. One cohort of patients carried a diagnosis of overweight and obesity (ICD-10 code E66), while the other cohort required exclusion of those diagnoses. **Results:** We found a statistically significant decrease in lung cancer incidence for patients with obesity (1.407% vs 2.039%, $p < 0.0001$), in addition to superior overall survival (95.344% vs 92.039%, $p < 0.0001$). A subset analysis of patients who contracted lung cancer showed a statistically significant benefit in median survival in favor of patients with overweight and obesity (851 vs 602 days, p value 0.0009). **Conclusions:** These findings support the existence of the obesity paradox in lung cancer, and its positive impact on both lung cancer incidence and outcome. Research Sponsor: None.

10579 **Poster Session**

Hereditary cancer testing in an ethnically diverse U.S. population. *First Author: Michele Basiliere, Progenity, Inc., Ann Arbor, MI*

Background: The clinical utility of hereditary cancer multigene testing is well-established. Most testing has been performed in the White European population, with a relative shortage of data in other ethnic groups. Evaluation of hereditary cancer variants within diverse ethnic populations is important to drive accurate variant interpretation. This study aims to review the outcomes of hereditary cancer testing in an ethnically diverse U.S. population. **Methods:** We conducted a retrospective analysis of 8,888 test results from a 31-gene hereditary cancer test using next-generation sequencing with copy number variant analysis. Results were separated into seven categories based on the ethnicity selected on the test requisition: African American (AA), Asian (A), Ashkenazi Jewish (AJ), Hispanic (H), White (W), Other (O), and Unknown (U). O was used for any handwritten ethnicity or if multiple ethnicities were selected and U if no ethnicity was chosen. We quantified the number of negative, positive (pathogenic or likely pathogenic (P/LP) variant) and variant of uncertain significant (VUS) results for each ethnic group. We tallied the gene and variant for each result with a positive, negative or VUS. We used a Fisher's Exact test and Bonferroni-adjusted p-values to account for multiple hypothesis testing. **Results:** Of the 8,888 orders reviewed, 45% were non-White ethnic groups. The P/LP variant rate was lower for AA (4%, p=2e-04) compared to W (9%). The VUS rate was higher for O, AA and A (48%, 56%, and 57%; p=0.0045, 3.1e-17 and 4.8e-06, respectively), compared to 38% in W. Lower negative rates were found in A and AA (37% and 40%; p=0.00024 and 9.4e-10, respectively), and trending lower in O (46%, p=0.0097), compared to 58% for W. The VUS rate for H is 41% (p value = 0.095). **Conclusions:** Our results suggest that non-Whites may be at a disadvantage when it comes to hereditary cancer multigene testing due to the higher rate of VUS results. The inverse correlation between the overall rates of VUS and negative results when comparing these populations suggests there may be limited variant information for the non-White population in medical literature and available databases. This underrepresentation may make it more difficult to accurately characterize a variant. Despite the small sample size, these findings are consistent with previous publications; however, gene specific outcomes could not be evaluated. This finding suggests that providers could give these patients uninformative results more often, which has potential to impact screening protocols for these families. More research is needed to understand the impact of variant classification across ethnicities to decrease health disparities. Research Sponsor: None.

10580 **Poster Session**

Point of care genetic testing in a breast cancer survivorship clinic. *First Author: Lori Ranallo, University of Kansas Cancer Center, Westwood, KS*

Background: : Breast cancer survivorship care (BCSC) includes the ongoing assessment of personal and family cancer history and offering genetic education, counseling and testing to survivors who meet NCCN, ASBrS and Medicare guidelines for germline genetic testing. It is reported that approximately 8% of patients with breast cancer (BC) will have a clinically actionable germline mutation. However, lower than expected rates of testing are seen in both the acute and extended phases of BCSC. We sought to identify the number of patients seen in a long-term survivorship clinic who had previously undergone or currently qualified for germline testing, and the prevalence of germline variants in BC survivors. **Methods:** In a Nurse Practitioner (NP) led clinic, 2,184 non-selected BC survivors were screened to determine if: germline testing was previously completed or if update germline testing or initial germline testing is needed (with a 3-generation review of family history). BC survivors eligible for initial or update germline testing (411 patients) were provided with genetic education, counseling, and offered multigene panel testing. Seven (7) BC survivors declined testing. **Results:** From May 2019 – January 2021, 2,184 BC survivors were seen in the clinic. The average age of survivors = 60.2 yrs; average time since diagnosis = 10.7 yrs; and average age at diagnosis = 50.1 yrs, gPV were identified in 10.4%. Out of pocket cost on average was $50.00 for 2.0% of those tested. **Conclusions:** Within a comprehensive Breast Cancer program where genetic testing is common practice, there is an ongoing need to screen breast cancer (BC) survivors for genetic testing eligibility. A significant number of BC survivors will test positive for a pathogenic mutation (10.4%) a decade after an initial diagnosis. Genetic testing is a necessary step to stratify a BC survivors' risk of developing secondary cancers, appropriate screening and prevention strategies, cascade testing, and for some, treatment planning. This individualized approach to BCSC is often described, but difficult to put into action. Time/access and drop rates with a referral model are barriers. Incorporating a point of care genetic testing model requires additional support (genetic extender), professional development, education, and a commitment to provide patient centric care. Research Sponsor: None.

Germline Testing	Total Tested (n = 404)	
Positive Family History Results	75% (n = 300)	**Most common gPV identified**
Pathogenic Variant	10.4% (n = 42)	CHEK2 (9), MUTYH (7), ATM (6) and APC (3), BRCA2 (3)
VUS	30% (n = 121)	
No Pathogenic Variant	59.6% (n = 241)	
Positive Family History Results	75% (n = 300)	
Pathogenic Variant	11.2% (n = 45)	
VUS	29% (n = 116)	
No Pathogenic Variant	59.8% (n = 240)	

10581 **Poster Session**

Germline pathogenic variants in cancer predisposition genes among women with invasive lobular cancer of breast. *First Author: Siddhartha Yadav, Mayo Clinic, Rochester, MN*

Background: The prevalence of germline pathogenic variants (PVs) in cancer predisposition genes among women with invasive lobular breast cancer (ILC) and the risk of ILC in PV carriers is not well-defined. **Methods:** The study included 2,999 women with ILC and 32,544 unaffected controls from a population-based cohort; 3,796 women with ILC and 20,323 women with invasive ductal carcinoma (IDC) undergoing clinical multigene panel testing (clinical cohort); and 125,748 exome sequences from unrelated women without a cancer diagnosis in the gnomAD 3.0 dataset. Frequencies of germline PVs in breast cancer predisposition genes (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, PALB2, PTEN, RAD51C, RAD51D*, and *TP53*) were compared between women with ILC and unaffected controls in both cohorts and between women with ILC and IDC in the clinical cohort. **Results:** The frequency of PVs in breast cancer predisposition genes among women with ILC was 6.5% in the clinical cohort and 5.2% in the population-based cohort. In case-control analyses, *CDH1* and *BRCA2* PVs were associated with high risks of ILC (Odds ratio (OR) $>$ 4), and *CHEK2*, *ATM* and *PALB2* PVs were associated with moderate (OR = 2-4) risks. *BRCA1* PVs and *CHEK2* p.Ile157Thr were not associated with clinically relevant risks (OR $<$ 2) of ILC. PV frequencies in these genes in ILC and IDC were similar except for PV frequencies in *BRCA1* and *CDH1*. **Conclusions:** The study establishes that PVs in *ATM*, *BRCA2*, *CDH1*, *CHEK2* and *PALB2* are associated with an increased risk of ILC, whereas *BRCA1* PVs are not. The similar overall PV frequencies for ILC and IDC suggest that cancer histology should not influence the decision to proceed with genetic testing. While, multigene panel testing may be appropriate for women with ILC, *CDH1* should be specifically discussed in the context of low prevalence and attendant gastric cancer risk. Research Sponsor: U.S. National Institutes of Health.

10582 **Poster Session**

Rate of incidental germline findings detected by tumor-normal matched sequencing in cancer types lacking hereditary cancer testing guidelines. *First Author: Timothy A. Yap, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Up to 10% of all cancers are associated with hereditary cancer syndromes; however, guidelines for germline testing are currently limited to patients and families with specific cancer types (ovarian, breast, prostate, pancreatic, etc.). Although germline alterations have been shown in genes associated with cancers such as bile-duct, head & neck, brain, bladder, esophageal, and lung cancers, genetic testing is not routinely offered (PMID: 28873162). In such cancers, a guidelines-based approach may fail to detect cancer risk variants found by tumor-normal (T/N) matched sequencing. Here, we report the prevalence of incidental germline findings in patients with the aforementioned 6 cancer types and highlight frequently mutated genes by cancer type. **Methods:** We retrospectively analyzed next-generation sequencing data from de-identified records of 19,630 patients tested using TempuslxT T/N matched assay. Incidental germline findings (i.e., single nucleotide variants and small insertions/deletions) detected in 50 hereditary cancer genes were determined for: bile duct (n = 466), head & neck (n = 673), esophageal (n = 395), brain (n = 1,391), bladder (n = 810), and lung (n = 5,544), where n = total patients. For comparison, we also included 4 cancer types that frequently undergo germline testing: ovarian (n = 2,042), breast (n = 3,542), prostate (n = 2,146), and pancreatic (n = 2,621). **Results:** We detected incidental pathogenic/likely pathogenic germline variants (P/LPV) in 6.5% (601/9,279) of patients diagnosed with the 6 selected cancer types lacking hereditary cancer testing guidelines. The highest prevalence of P/LPV was identified in patients with bladder (8%), brain (6.9%), and lung (6.5%) cancers. Frequently mutated genes (Table) include *ATM* (n = 62), *BRCA2* (n = 60), *BRCA1* (n = 33), *APC* (n = 27), and *CHEK2* (n = 21). Of note, the Ashkenazi Jewish variant (p.I1307K) was the most frequent mutation in APC. For cancer types where patients frequently undergo germline testing, the rates of incidental germline findings in descending order were ovarian (15%), breast (12%), prostate (9.4%), and pancreatic (8.5%) cancers. **Conclusions:** In addition to enhanced variant calling, T/N matched sequencing may identify germline variants missed by a guidelines-based approach to testing. The identification of such germline findings may have clinical implications for the patient, as well as at-risk family members, thereby resulting in the opportunity for genetic counseling and risk-stratified intervention. Research Sponsor: None.

				Top altered genes/cancer type (n)										
Cancer type	Total # Patients	# Patients with P/LPV	P/LPV incidence (%)	*ATM*	*APC*	*BRCA1*	*BRCA2*	*CHEK2*	*MSH2*	*MSH6*	*NF1*	*PALB2*	*RAD51D*	*TP53*
Bladder	810	65	8	6	3	3	8			4				3
Brain	1391	96	6.9			7		5			6	7		11
Lung	5,544	362	6.5	47	22	17	44	16						
Esophagus	395	22	5.6	4		3	2							2
Bile duct	466	26	5.6	3		3	3		2				2	
Head & Neck	673	30	4.5	2	2		3		2					3

10583 **Poster Session**

Variant reclassification and its impact on clinical care in an Asian cancer center. *First Author: Jianbang Chiang, National Cancer Centre Singapore, Singapore, Singapore*

Background: Genetic testing has demonstrated clinical utility in the identification and subsequent surveillance of patients with cancer predisposition syndromes. However, the increased likelihood of encountering a variant of uncertain significance (VUS) in individuals of non-European descent such as Asians may be challenging to both clinicians and patients in interpretation and management. VUS can be reclassified as more data becomes available. VUS reclassification is important, as it may have implications for surveillance and treatment. This study aims to evaluate the prevalence and patterns of variant reclassification in an Asian country and its impact on patient management. **Methods:** A prospective cohort of patients seen at the Cancer Genetics Service at the National Cancer Center Singapore between February 2014 to March 2020 was evaluated. The frequency, direction and time to variant reclassification was assessed by comparing the reclassified report against the original report. **Results:** A total of 1412 VUS were reported in 49.9% (845/1695) of patients. Over six-years, 6.7% (94/1412) of variants were reclassified. Most VUS (94.1%; 80/85) were downgraded to benign/likely benign variant, with a smaller proportion of VUS (5.9%; 5/85) upgraded to pathogenic/likely pathogenic variant. Actionable VUS upgrades and pathogenic/likely pathogenic variant downgrades, that resulted in management changes, happened in 31.0% (39/126) of patients. The median and mean time taken for reclassification were 1 and 1.62 year(s) respectively. **Conclusions:** Clinicians need to put in place a system for review of variants, as variant reclassification can lead to changes in management in nearly 1/3 of patients. Management should be based on the patient's personal history, family history and variant interpretation. We propose a clinical guideline to standardize management of patients with VUS. For clinically relevant or suspicious VUS, follow-up is recommended every two years, as actionable reclassifications may happen during this period. Research Sponsor: Singapore Ministry of Health National Medical Research Council.

10584 **Poster Session**

An evaluation of gender discrepancies in genetic referrals for BRCA testing for indicated malignancies. *First Author: Wesley Smith, Prisma Health-Upstate, Greenville, SC*

Background: Tumor suppressing genes BRCA1 and BRCA2 were discovered in 1990 and 1994, respectively, with mutations linked to hereditary breast-ovarian cancer syndromes (HBOCs). The discovery of these mutations has led to screening of at-risk patient populations and their family members. Women with BRCA1 or BRCA2 mutations are generally recommended to have prophylactic bilateral mastectomies and oophorectomies to decrease their future risk of cancer. While the initial discovery mostly focused on cancers in women, research has shown that BRCA mutations increase the risk of other cancers such as prostate cancer and pancreatic cancer, that also affect men. Previous research suggests that men are three times less likely to receive genetic testing in cancer driven by a 10:1 disparity in HBOC genetic testing. This was thought to be due to the lack of information on the importance of HBOC testing along with social roles in health. We wanted to evaluate the magnitude of the potential gender gap in BRCA testing in men compared to women. **Methods:** This was an IRB-approved, single center retrospective study to evaluate the rate of referrals to genetics for BRCA testing. Eligible patients had a personal history of cancer meeting criteria for BRCA testing per NCCN recommendations. Chart review was performed for patients with ovarian cancer, female breast cancer 45 years and younger, female triple negative breast cancer 60 years and younger, metastatic prostate cancer, all male breast cancer that have made an office visit since 2017, and pancreatic cancer since 2019. Rates of referral for genetic testing was the primary outcome and the groups were compared via the Chi-Square test. **Results:** 1,320 patients were included in the study, of which 664 were men and 656 were women. 128/664 (19.3%) of men were referred to genetics for screening compared to 527/656 (80.3%) for women ($p < .001$). Additionally, 42/128 (32.8%) men who were referred for screening did not complete genetic screening compared to 72/527 (13.7%) women ($p < .001$). A total of 62/541 (11.5%) patients who completed screening had either a BRCA1 or BRCA2 mutation. **Conclusions:** In our study, men were referred for BRCA testing significantly less than women for primary cancers, despite recommendation from the NCCN. In addition, men were also more than twice as likely not to complete genetic screening even if referred. The integration of genetics and oncology will continue to grow as personalized medicine continues to drive more treatment options. Closing this gender gap is important not only for familial screening purposes but also for treatment implications as patients with germline BRCA mutations are eligible for poly ADP ribose polymerase (PARP) inhibitors (e.g. olaparib) in both metastatic prostate cancer and pancreatic cancer. Further quality improvement initiatives are needed in order to close this gap by increasing education of the importance of BRCA testing in men. Research Sponsor: None.

10585 **Poster Session**

Germline testing and somatic tumor testing for *BRCA1/2* pathogenic variants in ovarian cancer: What is the optimal sequence of testing? *First Author: Janice S. Kwon, University of British Columbia, Vancouver, BC, Canada*

Background: In 2020 ASCO recommended that all women with epithelial ovarian cancer have germline testing (GT) for *BRCA1/2* mutations, and those without a germline pathogenic variant (PV) should have somatic tumor testing (TT), to determine eligibility for PARP inhibitor (PARPi) therapy (GT-TT strategy). An alternate strategy is to start with tumor testing first, and to conduct germline testing only in those with a PV in the tumor, or a significant family history (TT-GT strategy). The objective was to conduct a cost-effectiveness analysis comparing the 2 testing strategies. **Methods:** A Markov Monte Carlo simulation model compared the costs (USD) and benefits of the 2 testing strategies. According to local empiric data, a sufficient tissue sample for TT was available in 99% of cases, otherwise the patient would only have GT. Sensitivity of TT was 99% for detecting germline PV. Only those with *BRCA1/2* PV were eligible for PARPi. Primary outcomes included the number of women eligible for PARPi, with progression-free years of life (PFLY) gained based on SOLO1 data, and the incremental cost-effectiveness ratio (ICER). Monte Carlo simulation estimated the number of women who would have GT and TT, and the total with germline or somatic *BRCA1/2* PV eligible for PARPi. Sensitivity analyses accounted for uncertainty around various parameters. **Results:** The GT-TT strategy was more effective but more costly than TT-GT in identifying patients eligible for PARPi. Table summarizes the average lifetime costs, benefits, and Monte Carlo simulation estimates for 10,000 women diagnosed with advanced epithelial ovarian cancer annually in the USA. The incremental benefit from the GT-TT strategy would be achieved at substantial cost to the health care system, with an ICER of $119,340 per PFLY gained relative to the TT-GT strategy. The results were highly sensitive to the sensitivity of TT to detect germline PV, and the costs of GT and TT. Assuming that GT was less than 50% of the cost of TT, the sensitivity of TT had to exceed 98% for the TT-GT strategy to be cost-effective. **Conclusions:** Although the ASCO recommended strategy of *BRCA* germline testing followed by tumor testing for those without a pathogenic variant may be more effective in identifying ovarian cancer patients for PARP inhibitor therapy, it is more costly. The ASCO strategy is justified if the sensitivity of tumor testing is not sufficiently high. However, assuming high tumor testing performance rates, tumor testing first followed by germline testing if there is a PV in the tumor and/or family history is a cost-effective strategy. Research Sponsor: Michael Smith Foundation for Health Research, Pharmaceutical/Biotech Company.

		TT-GT	GT-TT
Average lifetime outcomes	Cost	$109,730	$111,115
	Incremental cost	-	$1,384
	Effectiveness (PFLY)	2.684	2.6956
	Incremental benefit	-	0.0116
	ICER	-	$119,340
Monte Carlo simulation (n=10,000)	Tumor testing	9902	8021
	Germline testing	2748	10,000
	Eligible for PARPi	2178	2197
	Germline *BRCA* PV identified	1884	1898

10586 **Poster Session**

Clonal hematopoiesis association with cardiac function and mortality in patients with solid tumors. *First Author: Jessica A. Regan, Duke University Medical Center, Department of Medicine, Durham, NC*

Background: Clonal hematopoiesis (CH) is the presence of expanded somatic clones in hematopoietic cells and is associated with higher overall mortality (OM). Studies suggest atherosclerotic cardiovascular disease may drive mortality, but the detailed mechanisms remain unclear. CH mutations can be detected in solid tumor sequencing, often confounding genomic tumor analysis. We evaluated the association of CH in solid tumor next-generation sequencing (NGS) with echocardiographic findings and OM. **Methods:** Sequential adult patients treated at the Duke Cancer Institute with solid tumor NGS analysis by FoundationOne were captured retrospectively. CH mutations present at a variant allele fraction ≥2% across 57 genes previously associated with hematologic malignancies were included. Patients with echocardiograms between 2 years before NGS testing and up to 5 years afterward were analyzed. Association between CH mutations with cardiomyopathy (CM, left ventricular ejection fraction $< 45\%$) and global longitudinal strain (GLS) was determined using logistic and linear regression, respectively. In a subset of patients with detailed cancer diagnosis date and clinical follow-up, Cox proportional hazard models were used to associate CH mutations with OM, with or without *TP53*/*KRAS* (included in most CH analyses but highly prevalent in solid tumors). Analyses were adjusted for age, gender and race. **Results:** Of 3029 patients with NGS testing, 2212 (73.0%) carried at least one CH related mutation, the majority of which were in *TP53*/*KRAS*. When excluding *TP53*/*KRAS,* CH mutations were observed in 806 of 3029 (26.6%) patients. CH mutations were associated with age (est 2.1, 95% CI 1.1-3.2, $p < 0.001$). Excluding *TP53*/*KRAS* strengthened the association between CH and age (est 2.8, 95% CI 1.8-3.9, $p < 0.001$). Echocardiogram data were available in 828 patients, of whom 48 (5.8%) had CM. CH mutations were not associated with CM (OR 1.3, 95% CI 0.6-2.6, $p = 0.5$), however when excluding *TP53* and *KRAS*, CH mutations were associated with lower odds of (OR 0.4, 95% CI 0.1-0.9, $p = 0.03$). GLS was available in 423 patients and was not associated with CH mutations ($p = 0.8$ with *TP53*/*KRAS*; $p = 0.4$ without *TP53*/*KRAS* as CH). In 222 patients with clinical information, OM did not differ between the CH vs no CH cohorts (HR 0.8, 95% CI 0.6 = 1.2, $p = 0.3$ inclusive of *TP53*/*KRAS*). When excluding *TP53*/*KRAS* mutations, in this population of patients with cancer, non-*TP53*/*KRAS* CH was associated with less OM (HR 0.6, 95% CI 0.4-0.9, $p = 0.01$). **Conclusions:** In this patient population with cancer, CH mutations did not associate with higher CM. In contrast to prior studies, CH detected in solid tumor does not associate with OM in this population. CH mutations confound tumor sequencing and these findings support the value of paired tumor-blood sequencing to determine true CH. Consensus around CH variants should be undertaken in future studies. Research Sponsor: Duke University.

10587 **Poster Session**

Genetic assessment of hereditary breast and ovarian cancer in the Harris Health System: A five-year, single-center experience. *First Author: Nicole Higashiyama, Lester and Sue Smith Breast Center, Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, TX*

Background: Identifying patients with hereditary breast cancer is critical since lifetime breast cancer risk is as high as 85% for those with germline BRCA1/2 mutations and preventive interventions can reduce that risk. However, genetic assessments and counseling are often underutilized among racial/ethnic minority populations. Reducing this genetic testing gap is important since hereditary breast/ovarian cancer syndromes occur among racial/ethnic minorities at least as frequently as non-Ashkenazi Jewish, non-Hispanic White populations. More information on variants in these populations is also needed to better define their genetic susceptibility. **Methods:** We conducted a retrospective study of adult patients evaluated for genetic testing for hereditary breast/ovarian cancer by a genetic counselor between October 1, 2009 and September 30, 2014 in Harris Health System which is a large, county health system composed mostly of underserved and minority patients. Data from 2015-2019 is currently being extracted and we are reporting the first 5 years of data. Descriptive statistics were used to summarize patient data. **Results:** 659 patients underwent genetic counseling (10.5% non-Hispanic White, 24.4% Black, 56.9% Hispanic, 5.9% Asian, and 2.3% other). Five patients had Ashkenazi Jewish ancestry. The majority of patients completed testing (87.4%) with 72.7% receiving financial assistance. Among those who did not complete testing, only 12.0% declined, while 66.3% did not meet guideline-based criteria or were recommended to have an affected relative tested. Multigene panel testing was not available until April 2014, so most underwent BRCA sequencing (75.0%) and/or a BRCA large rearrangement test (61.0%). 36.1% received multigene panel testing, 4.6% single site analysis, and 4.4% p53 sequencing. Deleterious mutations occurred in 98 (14.9%) patients: BRCA1 (n = 60), BRCA2 (n = 25), PALB2 (n = 7), ATM (n = 3), and other (n = 3). The distribution of races/ethnicities among those with deleterious mutations was similar to the overall population (7.1% non-Hispanic White, 18.4% Black, 69.4% Hispanic, 3.1% Asian, and 2.0% other). 80.6% of those with deleterious mutations had breast cancer. High rates of bilateral mastectomies were performed in patients with deleterious mutations: BRCA1 60%, BRCA2 55%, PALB2 57.1%, and ATM 33%. Risk-reducing salpingectomy or salpingo-oophorectomy was performed in 56.7% BRCA1, 60% BRCA2, 28.5% PALB2, and 33.3% other mutation carriers. **Conclusions:** We demonstrate that with the support of financial assistance programs, most patients who receive genetic counseling will accept genetic testing in a socioeconomically underserved, racially/ethnically diverse population. Identification of high-risk patients in these groups is critical since pathogenic variants in this population were common and more than half underwent risk-reducing procedures. Research Sponsor: None.

10588 **Poster Session**

Testing for mutations in *BRCA1* and *BRCA2* among ovarian cancer patients at a diverse academic medical center. *First Author: Caitlin Taylor, Emory University Hematology Medical Oncology-Fellowship Program, Atlanta, GA*

Background: Testing for mutations in *BRCA1* and *BRCA2* is recommended for all women with ovarian cancer (OC), given important implications for treatment and prognosis. Despite this recommendation, studies show that only a small percentage of OC patients (pts) undergo genetic testing (GT). In this study, we evaluated rates of genetics referral, counseling and testing among OC pts at an academic medical center. Our goal was to identify factors associated with lower rates of GT. Given the large Black population at our center, we specifically wanted to evaluate the association between race and GT given limited existing data on this issue. **Methods:** Retrospective chart review was performed evaluating rates of referral and uptake for GT, and percentages of *BRCA* mutation carriers among pts with OC diagnosed and treated at Emory's Winship Cancer Institute between 2008 and 2018. Associations between age, race, histology, family history (FH), performance status, provider characteristics and genetics referral and testing were evaluated using logistic regression models. **Results:** Of the 171 pts who met inclusion criteria, the majority were age 55 or older (62%) with high grade serous carcinoma (60.8%). Pts were predominantly Caucasian (59.4%), followed by Black (29.1%), Asian (10.3%) and Hispanic (1.2%). Overall, GT rates were low with 44.7% of pts referred for genetic counseling and 39.8% receiving testing. Among pts who did receive GT, the percentage of deleterious *BRCA1* and *BRCA2* mutations identified was 11% and 8.8% respectively. Variables correlating with higher likelihood of genetics discussion, referral and testing included serous histology (50% vs 23.9% non-serous, $p < 0.001$), Caucasian or Asian race (87.5% Asian, 58.8% Caucasian vs 42.2% Black, $p = 0.003$) and seeing a medical oncologist (67.5% vs 44.7% seeing gynecologic oncologist alone, $p = 0.004$). Notably, while fewer Black women were referred for GT (25.9% vs 74.1% Caucasian), those that did undergo GT were found to have higher rates of *BRCA1* and *BRCA2* mutations when compared to Caucasian pts (22.2% vs 8.2% *BRCA1*; 11.1% vs 6.0% *BRCA2*). Pts with a FH of OC were more likely to undergo GT (69.2% vs 37.9%, $p = 0.027$), and pts with a FH of breast cancer were more likely be referred for testing (57.1% vs 39.6%, $p = 0.042$), suggesting that FH impacted referral patterns. **Conclusions:** The rates of GT among OC pts at our institution were lower than expected despite the broad recommendation for GT in this population. It is imperative to improve access to GT for all OC pts regardless of FH, and in particular among Black pts given the higher rates of *BRCA* mutations in this population. Pts and providers must work together to overcome barriers to genetics referral and testing in order to improve GT rates and clinical outcomes. Further research is needed to design interventions that may help improve adherence to this important recommendation in the future. Research Sponsor: None.

10589 **Poster Session**

A comprehensive literature review and meta-analysis on prevalence of BRCAm, HRRm and HRD+ across tumor types. *First Author: Changxia Shao, Merck & Co., Inc., Kenilworth, NJ*

Background: Poly (ADP-ribose) polymerase inhibitor (PARPi) may have broad application in the treatment of cancer patients with mutations in BRCA (BRCAm) or other homologous recombination repair genes (HRRm) or with homologous recombination deficiency positive (HRD+). A literature review and meta-analysis were conducted to evaluate the prevalence of BRCAm, HRRm, and HRD+ across tumor types. **Methods:** Comprehensive searches for eligible studies in Ovid MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Cochrane reviews were performed in May 2020 to capture studies published in English, within 10 years for manuscripts and 3 years for abstracts across geographic regions. A weighted summary estimate was calculated for BRCAm. A summary estimate with corresponding 95% CI was calculated using random-effects models for HRD+ and HRRm. **Results:** A total of 342 eligible studies with at least 100 samples were included in the review of BRCA1/2m prevalence, containing a total of over 469,000 samples across 24 tumor types. The most frequent indications examined in the included studies were breast (study number n = 144), ovarian (53), prostate (17) and pancreatic (11) cancers. The prevalence of germline BRCA1m (gBRCA1m) and gBRCA2m was 5% and 4% for breast, 12% and 5% for ovarian, 1% and 3% for prostate, and 1% and 4% for pancreatic cancer, respectively. The prevalence of somatic BRCA1m (sBRCA1m) and somatic BRCA2m (sBRCA2m) was 3% and 3% for breast, 7% and 5% for ovarian, 3% and 5% for prostate, and 1% and 3% for pancreatic cancer, respectively. Few studies evaluated endometrial, lung and colon cancers, the prevalence of gBRCA1m or gBRCA2m was generally less than 1%, and the prevalence of sBRCA1m and sBRCA2 ranged 1 to 3%. Seven publications were identified where HRD+ was defined by either BRCAm or genomic instability score (GIS) $\geq$ 42 across breast, ovarian and pancreatic cancers. The overall HRD+ prevalence was 56% (95%CI: 48, 64), with similar prevalence observed across the 3 tumor types and was 50% (34, 66) for the 3 studies only counting GIS$\geq$ 42. 194 studies across 26 tumor types were identified that examined HRRm as mutations in one or more HRR genes other than BRCA1/2m. The definitions of HRRm varied substantially across the studies, and ATM (2.8%), CHEK2 (1.6%), and PALB2 (1.6%) accounted for most of the observed mutations among HRR genes. **Conclusions:** Prevalence of BRCAm, HRRm and HRD+ varied by cancer type. This comprehensive meta-analysis enriches the knowledge in this field and demonstrates the need to standardize the measurement of HRRm and HRD.Understanding the prevalence of these biomarkers could have important clinical implications. Research Sponsor: Merck & Co.

10590 **Poster Session**

Distribution of BRCA1/2 germline and somatic alterations across cancer type. *First Author: Jingde Chen, Shanghai East Hospital, Tongji University School of Medicine, Shanghai, China*

Background: PARP inhibitors (e.g. Olaparib or niraparib) have been approved by FDA as a targeted therapy for many tumors harboring germline or somatic BRCA1/2 (g or sBRCA1/2), including ovarian cancer, prostate cancer, breast cancer and pancreases cancer. It is imperative to study the distribution of BRCA1/2 across cancer type. In this study, we aim to assess the landscape of BRCA1/2 alterations in solid tumors and evaluate the feasibility of circulating tumor DNA (ctDNA) tested by next-generation sequence (NGS) as a tool to detect BRCA1/2 alterations. **Methods:** For tissue specimen, genomic DNA from formalin fixed paraffin-embedded (FFPE) tumor specimens or fresh tumor tissues was used for sequence analysis. Genomic DNA (gDNA) from white blood cells was extracted using the QIAamp DNA Mini Kit (Qiagen). For ctDNA, cell-free DNA libraries were prepared using the KAPA Hyper Prep Kit following the manufacturer's protocol. The captured libraries were loaded onto a NovaSeq 6000 platform (Illumina) for 100bp paired-end sequencing. The testing was performed in the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA) -certified 3D Medicines Library. **Results:** A total of 27, 835 patients were tested using tumor tissue during Jan. 1th 2017 to June 1th 2020, including 43% (N = 12089) of non-small cell lung cancer, 19% (N = 5357) of colorectal cancer, 8% (N = 2181) of liver cancer, 6% (N = 1621) of gastric cancer, 5% (N = 1479) of biliary tract cancer, 4% (N = 1084) of kidney cancer, 4% (N = 1045) of pancreas cancer, 3% (N = 689) of breast cancer and 2% (N = 599) of ovarian cancer. Across all tumor types, the known or likely deleterious BRCA1/2 alterations were identified in 2147 (7.7%) patients. Ovarian cancer had the highest frequency of BRCA1/2 alteration (23.4%), followed by endometrial cancer (12.7%) and breast cancer (10.6%). BRCA1/2 alteration was found in 8.8% prostate cancer and 4.2% pancreas cancer respectively. Across all tumor types, the known or likely deleterious gBRCA1/2 alterations were identified in 369 (1.3%) patients. Notably, ovarian cancer had the highest frequency of gBRCA1/2 alteration (13.9%), followed by breast cancer (7%), prostate cancer (4.4%) and endometrial cancer (4.1%). No clear hotspot mutations and mutated codons were spread throughout g or sBRCA1/2 mutations. Additionally, among 15699 patients who suffered ctDNA sequencing, any known or likely deleterious sBRCA1/2 alterations were identified in 358 (2%) patients. Similar to the results of tissue sequencing, ovarian cancer had the highest frequency of sBRCA1/2 alteration (16.67%), followed by endometrial cancer (9.68%), prostate cancer (7.18%) and breast cancer (5.58%) in the blood cohort. **Conclusions:** BRCA1/2 alterations existed across tumor types and the landscape of g or sBRCA1/2 alterations varied according to cancer type. Furthermore, ctDNA can be used as a potential tool to detect BRCA1/2 alterations. Research Sponsor: None.

10591 **Poster Session**

Racial disparities in genetic testing of breast cancer patients. *First Author: Solange Bayard, Weill Cornell Medicine, New York, NY*

Background: TNBC is disproportionately prevalent in African American (AA) populations and in women with BRCA-1 germline mutations. BRCA mutation carriers are candidates for targeted therapy with PARP-inhibitors, and testing results may influence risk-reducing surgery choice. **Methods:** We evaluated genetic testing patterns and outcomes for TNBC patients treated in the prospectively maintained databases of academic cancer programs in two metropolitan cities in the Northeast (New York City, NYC) and Midwest (Detroit, Det), 1998-2018. Median follow up was 3.73 years. Testing patterns were also analyzed by time, comparing pts diagnosed before versus after the mid-2013 Supreme Court ruling that expanded testing availability by banning gene patenting. **Results:** Of 810 pts, 600 were from NYC and 200 from Det; 202 were AA and 488 WA. Pts undergoing genetic testing were younger (median age 50 vs 62; $p < 0.0001$). Compared to WA, AA pts were less likely to undergo genetic testing overall (23.8% vs 42.0%; $p < 0.0001$) and within site (NYC: 25.6% vs 42.8%, $p = 0.008$; Det: 22.3% vs 38.6%, $p = 0.025$). No significant differences were seen in frequency of pathogenic BRCA mutations (AA-14.6%; WA-29.3%) or VUSs (AA-6.3%; WA- 4.9%); $p = 0.20$. Genetic testing disparities were reduced among pts diagnosed after mid-2013 (AA-31.4% vs WA-44.0%; $p = 0.01$) compared to pre-mid-2013 (AA-18.3% vs WA-40.7%; $p < 0.0001$). No differences were seen in local or distant recurrence free survival between patients with BRCA, BRCA variants of uncertain significance, non-BRCA mutations, and patients without genetic mutations (local recurrence $p = 0.827$; distant recurrence $p = 0.574$). This outcome equivalence was consistent when stratified by WA vs AA identity. **Conclusions:** Genetic testing has increased for TNBC pts following the mid-2013 Supreme Court ban on gene patenting, but race-associated disparities persist. Pts undergoing genetic testing are more likely to undergo risk-reducing mastectomy, but testing results do not affect survival outcomes, regardless of race. Addressing genetic testing disparities will become increasingly important as mutation-associated targeted therapies are identified through advances in precision medicine. Research Sponsor: None.

10592 **Poster Session**

Oncologists' (ONCs) perceptions of tumor genomic profiling (TGP) and barriers to communicating secondary hereditary risk to African American (AA) patients. *First Author: Michael J. Hall, Fox Chase Cancer Center, Philadelphia, PA*

Background: TGP identifies targets for precision cancer treatments. TGP may also identify secondary hereditary cancer risks, necessitating complex decision support during informed consent. ONCs are poorly trained in the communication of genetic information, particularly for patients with low health literacy, poor knowledge of genetics, and high medical mistrust. AA patients are especially vulnerable in this setting. **Methods:** We conducted semi-structured interviews with 10 ONCs to assess perceived barriers related to communication of secondary hereditary risks of TGP, probing barriers unique to AA patients. Informed by results, an Internet-based survey was developed/distributed to a convenience sample of 50 ONCs nationwide to assess TGP knowledge, genomics confidence, and perceptions related to communication of secondary hereditary risk. **Results:** Six themes emerged from interviews: risk/benefits of TGP, knowledge of genetics, discussing hereditary risk, value/harm of TGP, unique risks in AA, and training needs. Most ONCs felt uncomfortable discussing hereditary risks of TGP w/patients. Seven out of 10 identified socio-economic status, medical mistrust, discrimination, genetic counseling non-compliance, low health literacy and family relationships as factors important to consider with AA patients. Online survey participants were 52% White, 66% male, with median age of 42 years. Education in the interpretation/communication of TGP was largely informal (56% reported only informal training) and 46% reported perceived gaps in their education. Genomic confidence was associated w/higher use of TGP ($p = 0.05$), but was not associated w/knowledge or years in practice; however, low knowledge was associated w/more perceived barriers to TGP and w/negative attitudes toward the value of TGP and the challenge of communication of possible hereditary risks ($p = 0.05$). Early-career ONCs were more likely to endorse perceived barriers to communication of genetic risk information from TGP to AA patients. Overall 86% ONCs felt additional online training in communication of secondary hereditary risks of TGP would be useful. **Conclusions:** ONCs recognize unique needs and barriers for AAs related to communication of secondary hereditary genetic information from TGP. Many feel uncertain about how/whether to address barriers and recognize the need to improve their skillset to do so. Training is critical to ensure informed decision making in vulnerable populations. Research Sponsor: American Cancer Society.

10593 **Poster Session**

Evaluation of proband adherence and satisfaction with a prospective cascade testing protocol. *First Author: Maria Smith, NYU Grossman School of Medicine, Brooklyn, NY*

Background: We sought to evaluate the feasibility of a Cascade Testing (CT) protocol for family members of probands with actionable germline mutations associated with endometrial or ovarian cancer. Here, we characterize proband compliance with contacting family members for CT and proband satisfaction/regret. **Methods:** In this prospective study, consenting patients with pathogenic germline mutations associated ovarian or endometrial cancer completed a demographic survey and were asked to contact first- and second-degree relatives with genetic testing results. After a 1–3-month period, probands completed a survey indicating how many relatives had been contacted. At 3 months following consent, probands were asked to complete the validated Impact of Event Scale (IES) and Decision Regret Scales (DRS). Characteristics of probands who contacted relatives and those who did not were compared. **Results:** The study has accrued 57 probands since opening in March 2019. Germline mutations identified in the 57 probands include 27 *BRCA1* (47.4%); 21 *BRCA2* (36.8%); 3 *BRIP1* (5.3%); 2 *MLH1* (3.5%); 2 *MSH2* (3.5%); 3 *MSH6* (5.3%); 3 *PMS2* (5.3%); 1 *EPCAM* (1.8%); 1 *RAD50* (1.8%). Twenty-four (42.1%) probands had a history of cancer (breast 12; ovarian 8; uterine 2; other 5). Of the probands, 32 (56.1%) completed follow-up questionnaires and 29 (50.9%) had contacted relatives about participating in CT. In total, 67 relatives were contacted. Probands contacted an average of 1 relative, ranging from 1-20. Of the 29 probands who contacted relatives, 13 (44.8%) completed IES and DRS questionnaires. The median IES score was 0 out of 75 (IQR 0.0-4.5) and the median DRS score was 0 out of 100 (IQR 0.0-11.3). When comparing characteristics of probands who contacted relatives with those who did not, those with annual household incomes <$75,000 were more likely to contact relatives vs those with incomes ≥$75,000 (77.8% vs 39.5%; p=0.01). There was no association between contacting relatives and personal cancer history, race/ethnicity, education status, or age (Table). **Conclusions:** Half of probands enrolled in this study contacted relatives about CT, and those with household incomes <$75,000 were more likely to contact relatives than those with higher incomes. Overall, probands reported little/no regret or distress after contacting relatives about genetic testing results. Research Sponsor: None.

	Contacted (N=29)	Did not contact (N=28)	P-Value
Personal Cancer History—N (%)	14 (58.3)	10 (41.7)	0.42
Race/Ethnicity—N (%)			1.00
Non-Hispanic White	20 (50.0)	20 (50.0)	
All Other	9 (52.9)	8 (47.1)	
Education—N (%)			1.00
College degree or higher	26 (50.0)	26 (50.0)	
No college degree	3 (60.0)	2 (40.0)	
Household income—N (%)			0.01
<$75,000/year	14 (77.8)	4 (22.2)	
≥$75,000/year	15 (39.5)	23 (60.5)	
Age —median (IQR)	44.0 (34.0-52.0)	40.0 (27.5-49.0)	0.65

10594 **Poster Session**

Multicancer hereditary syndrome testing: Genetic counselors' perspectives. *First Author: Christine B. Weldon, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: The accessibility of cancer hereditary syndrome testing has increased, and the cost has declined significantly in the past few years. We conducted a national, quantitative survey of genetic counselors (GCs) to assess their perspectives on what influences hereditary cancer genetic testing decisions and practices, with a focus on cost. This survey was funded by NIH, conducted by UCSF TRANSPERS, and supported by the National Society of Genetic Counselors (NSGC). **Methods:** The survey was developed through literature review, expert interviews, and a pilot. Sent to the NSGC Cancer Special Interest Group via email. Chi-square tests were used to examine variability. **Results:** The survey response rate was 56% (202/363). Multiple hereditary cancer syndrome tests are discussed often/always by 86% of genetic counselors (GCs). The existence of an institutional protocol on multiple hereditary cancer syndrome testing was reported by 35.4% of GCs. When asked about GC counseling encounters, GCs report insurance rarely/never pays for: 25.2% pre-test in-person, 39.7% for pre-test tele-genetics, 35.4% post-test in-person, and 52.9% post-test tele-genetics. GCs rated clinical factors higher than cost as influencing decision for multiple hereditary syndrome cancer testing (table); the total cost of the test was least important. These patterns were similar across the GCs institution types and years in practice. **Conclusions:** We found consistent use of multiple hereditary cancer syndrome tests, with less focus on cost, out-of-pocket, and insurance coverage and more of a focus on clinical indicators. GCs reported challenges with reimbursement for GC counseling encounters. The shift toward more genetic counseling encounters via tele-genetics necessitates evaluation of insurance reimbursement. Research Sponsor: U.S. National Institutes of Health.

How important are the following factors in your decision to discuss and possibly order multiple hereditary cancer syndrome testing?	Moderately / Very Important n = 202 %
Limited family structure, unknown family history, and/or patient adopted without biological relative history knowledge	81
Patient's request and or question about multi-gene syndrome testing	81
Personal and family history reveal only one major cancer type	56
Single syndrome test is more clinically appropriate for patient	53
Concern about increased likelihood of variants of uncertain/unknown significance	51
Concern about unexpected pathogenic/likely pathogenic variant in a gene not associated with phenotype	49
Expectation that patient may be willing to pay for test if insurance doesn't cover it	47
Standards or protocol of your clinic, organization, institution	44
Concern that patient share of payment / out of pocket is too much	43
Concern that patient's insurance may not cover multiple-syndrome testing	41
Patient with no phenotype based on personal or known family history	38
Concern that total cost of test (cost to insurance/payer plus co-pay) is high	32

10595 **Poster Session**

Prevalence and spectrum of pathogenic variants among patients with multiple primary cancers. *First Author: Brittany L. Bychkovsky, Cancer Genetics and Prevention, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA*

Background: Multiple primary cancers (MPCs) are a hallmark of cancer predisposition syndromes. We aim to characterize the frequency of germline pathogenic/likely pathogenic variants (PVs) among patients with MPCs. Herein we report the frequency of PVs by sex, number of cancers and age at diagnosis among a laboratory-based cohort of patients with MPCs. **Methods:** Patients with MPCs who underwent germline genetic testing with Ambry Genetics from 3/2012 to 12/2016 were included in our cohort. Eligible individuals had multigene panel testing, which included 21 genes, at minimum**:** *ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2,PTEN, RAD51C, RAD51D, STK11,* and *TP53*. Clinical factors including age at diagnosis, age at testing and cancer type were obtained from test requisition forms and clinical notes. Patients with > 1 PVs were excluded from the analysis. Using Rv.3.3.3., the frequencies of PVs by sex, number of cancers and age at diagnosis were compared using two-sided $\chi 2$ tests or Fisher's exact test when the number was < 10. **Results:** Of the 9820 patients with MPCs tested for the 21 genes above, 104 (1.1%) had multiple PVs and were excluded. Among the remaining 9716 patients in the analytic cohort, most were female (91.1%) and white (71.0%). The median age at testing was 63 years (IQR: 16) and the median ages of first and second cancer diagnosis were 49 (IQR: 18) and 58 (IQR: 17) years, respectively. Overall, 1406 (14.5%) were found to have PVs: 14.3% of females and 16.2% of males. The prevalence of PVs increased with the number of primary cancers (PCs) as follows, 2 PCs: 13.1% (95% CI:12.4-13.8%), 3 PCs: 15.9% (95% CI:14.0-18.0%), >4 PCs: 18.0% (95% CI:13.7-23.3%), (p < 0.01). Among patients with 2 PCs (n = 8145), differences in the prevalence of PVs by age at diagnosis were significant: 2 PCs diagnosed at an age < 50 (13.5%, 95% CI:12.0-15.1%), 1 PC diagnosed at an age < 50 (14.8%, 95% CI:13.4-16.5%), 2 PCs diagnosed at age >50 years (12.1%, 95% CI: 11.1-13.2%), (p = 0.01). PVs were most frequently identified in: *BRCA2* (2.2%) *BRCA1* (2.0%), *CHEK2* (1.9%) and *ATM* (1.5%). There were also significant differences in the frequencies of PVs in *BRCA1*, *BRCA2* and *MLH1* by sex (p < 0.05). **Conclusions:** These data demonstrate a high frequency of germline PVs among both males and females with MPC. The frequency of PVs was higher among patients with a higher number of PCs. Differences in the prevalence of PVs by age at cancer diagnosis while significant, were not meaningful as 12.1% of individuals with 2 PCs diagnosed at age >50 years had germline PVs. Limitations include the homogenous testing population (predominately female and white) and small numbers in some patient categories. These data may aid in counseling patients with MPCs and their families as well as encourage less restrictive genetic testing of this population. Further analysis of PV frequencies by specific cancer combinations was conducted and will follow. Research Sponsor: None.

10596 **Poster Session**

Identification of potential germline (GL) variants by routine clinical comprehensive genomic profiling (CGP) and confirmatory GL testing in 24 tumor types. *First Author: Kristen Hanson, Advocate Aurora Health, Milwaukee, WI*

Background: Tumor CGP may identify both somatic and GL variants, though confirmatory testing is required to verify which variants originate from the GL. Studies have shown CGP can identify patients who both do and do not meet criteria for genetic counseling (GC). Ideally, improved annotation from tumor CGP could more appropriately direct GC referrals. We explore how a computational algorithm might be used to influence GC and confirmatory GL testing for variants in inherited cancer predisposition genes. **Methods:** 849 patients from the Aurora Oncology Precision Medicine Program who had routine hybrid-capture based CGP by Foundation Medicine from 8/2018-8/2020 were eligible. A previously published algorithm, SGZ (Sun et al PMID 29415044) which incorporates allele frequency, aneuploidy, and admixed copy number modeling was used to predict whether each single nucleotide variant (SNV) was GL or somatic. SGZ predictions for SNVs in 24 actionable inherited cancer predisposition genes were available to Aurora for review as part of standard screening to identify appropriate GC referrals. For patients who had GL testing, variants in genes on both assays were compared. **Results:** 76 pathogenic (P) or likely pathogenic (LP) variants predicted to be GL by SGZ were detected in 73/849 (9%) patients: *ATM* (7), *BAP1* (2), *BRCA1* (13), *BRCA2* (8), *BRIP1* (1), *CHEK2* (18), *FH* (0), *FLCN* (2), *MLH1* (1), *MSH2* (0), *MSH6* (3), *MUTYH* (12), *PALB2* (3), *PMS2* (1), *POLE* (0), *RAD51C* (1), *RAD51D* (0), *RET* (1), *SDHA/B/C/D* (0,0,0,0), *TSC2* (0), and *VHL* (3). 27/73 (37%) patients had GL testing. 25/26 (96%) variants were confirmed to be GL in origin and 1 additional variant was detected by CGP in a region not interrogated by the GL assay: *ATM* (2/2), *BRCA1* (6/6), *BRCA2* (2/2), *BRIP1* (1/1), *CHEK2* (9/9), *FLCN* (0*/1), *MSH6* (1/1), *MUTYH* (2/2), *PALB2* (1/1), *RAD51C* (1/1), and *VHL* (0/1). Variants were confirmed in bladder, breast, CRC, glioma, NSCLC, ovary, pancreas, prostate, sarcoma, and gastric cancer. The *VHL* variant was discordant in a leiomyosarcoma. **Conclusions:** We identified the potential real-world clinical impact of computationally screening solid tumor patients undergoing routine CGP for potential P/LP GL variants. Predicting GL results with SGZ for 24 inherited cancer predisposition genes was highly concordant with confirmatory GL testing independent of tumor type. CGP annotations can facilitate GC referral and GL testing for at-risk patients, particularly in tumor types which may not typically meet guidelines for GL testing. Research Sponsor: None.

N=73 patients harboring P/LP variants predicted to be GL by SGZ.

	GL SGZ prediction	GL testing	Confirmed GL
ATM	7	2	2
BAP1	2	0	0
BRCA1	13	6	6
BRCA2	8	2	2
BRIP1	1	1	1
CHEK2	18	9	9
FH	0	0	0
FLCN	2	1	0*
MLH1	1	0	0
MSH2	0	0	0
MSH6	3	1	1
MUTYH	12	2	2
PALB2	3	1	1
PMS2	1	0	0
POLE	0	0	0
RAD51C/D	1/0	1/0	1/0
RET	1	0	0
SDHA/B/C/D	0/0/0/0	0/0/0/0	0/0/0/0
TSC2	0	0	0
VHL	3	1	0

*Gene was not interrogated by GL assay.

10597 **Poster Session**

Prevalence of germline testing criteria in breast cancer patients in the Brazilian public health system: A retrospective study. *First Author: Robson dos Santos dos Santos Borges, Grupo Oncoclinicas, Hospital Felicio Rocho, Hospital Alberto Cavalcanti, Belo Horizonte, Brazil*

Background: Identification of a germline mutation in a breast cancer predisposition gene has implications for the patients and their families. The National Comprehensive Cancer Network (NCCN) has published guidelines for genetic testing. In Brazil, this assessment is covered by health insurance in accordance with criteria defined by the National Supplementary Health Agency (ANS). For the majority of the population, served by the public health system (SUS), the assessment is not routinely available. **Methods**: In order to determine the prevalence rates of NCCN and ANS criteria for germline testing in breast cancer (primary outcome) we retrospectively analyzed data from patients treated at two SUS oncology centers in Belo Horizonte, Minas Gerais, Brazil, between 01/01/18 and 12/31/19. The secondary outcomes were comparisons between the groups with and without germline testing criteria (NCCN and ANS) regarding overall survival, clinical and epidemiological characteristics. The association between qualitative variables was calculated using the Chi-square and Fisher tests. The Kaplan-Meier method was used to analyse the survival data and the differences between the groups were tested using the log-rank test. The level of significance was 5%. **Results**: A total of 357 patients were included in the final analysis. The presence of germline testing criteria were found in 126 patients (35%) according to NCCN guidelines and in 82 patients (23%) according to ANS guidelines. None of them were tested for germline mutations. The most common criteria were women up to 60 years old with triple negative tumors (n = 43, 12% of all patients) and diagnosis of cancer up to 45 years old (n = 75, 21% of all patients) according to ANS and NCCN criteria, respectively. When the group of patients who met at least one criterion for germline testing were compared with the group who did not met any criteria, we found in the first group: more ductal carcinomas and less lobular tumors ($p = 0.009$), more grade 3 tumors ($p = 0.002$), more triple negative tumors ($p < 0.001$), more neoadjuvant treatments ($p = 0.008$) and less hormonal therapies ($p = 0.011$). After a median follow up of 13.5 months there were 22 deaths in the cohort, 7 in the group with testing criteria (5.7%) and 15 in the group without testing criteria (6.4%). There was no statistical significant difference between the groups in terms of overall survival ($p = 0.77$). **Conclusions**: To our knowledge this is the first study to evaluate the prevalence of NCCN and ANS criteria for germline testing in patients with breast cancer treated in the Brazilian public health system. Our results show that more than a third of those patients are candidates for germline testing. Moreover, the data highlight a serious shortcoming in the management of breast cancer and must be considered in the development of public health policies for routine germline testing in that population. Research Sponsor: None.

10598 **Poster Session**

Impact of race on biomarker testing among HER2- advanced breast cancer (ABC) patients (pts) in the United States: Results from a real-world study. *First Author: Reshma L. Mahtani, Sylvester Cancer Center, University of Miami, Deerfield Beach, FL*

Background: African Americans (AA) have the highest breast cancer (BC) mortality rate. Access to treatment is a known contributing factor. In the past 4 years, several targeted therapies for HER2- BC have become available which require testing for specific biomarkers. This study assessed the impact of race on biomarker testing rates in HER2- ABC pts receiving treatment in the US. **Methods:** Oncologists were recruited to abstract data from medical charts for the next 8-10 pts receiving treatment with HER2- ABC during Sept 2019-Apr 2020. Pts records were stratified by race and categorized into 3 mutually exclusive cohorts [White/Caucasian (White), AA, Other]. The other race cohort was excluded from this analysis due to small sample size. Differences in pt demographics/clinical characteristics were analyzed via Fisher's exact tests. Testing rates for actionable biomarkers (i.e. *BRCA1/2*, PIK3CA, PD-L1) were compared between White and AA pts utilizing logistic regressions controlling for age, known family history of a *BRCA*-related cancer, hormone receptor (HR) status and practice setting (academic vs. community). Further analyses by age will be presented. **Results:** This analysis included 378 pts records, provided by 40 oncologists. Mean age was 64 years; 77% had HR+/HER2- ABC; 20% had advanced triple negative breast cancer (TNBC), 3% had ABC with an unknown HR status. Compared to White pts, AA pts were significantly more likely to have advanced TNBC (27% vs. 18%, $p<0.05$). Compared to White pts, AA pts had significantly lower *BRCA1/2* mutation (mut) testing rates (Table). Numerically lower rates of PIK3CAmut and PD-L1 testing were observed among AA pts (Table). *BRCA1/2*mut positivity rate (germline [g] and/or somatic [s]) was higher among AA vs. White pts (30% vs. 22%). Positivity rate for PIK3CAmut was lower for AA vs. White pts (8% vs. 11%). **Conclusions:** A higher than expected *BRCA1/2*mut positivity rate was observed than previously reported in the literature. This is likely because this analysis included s*BRCA1/2*mut and represented a high risk pt population. Across all biomarkers assessed, AA pts had lower testing rates than White pts. This suggests racial disparities in testing rates of actionable biomarkers. Consistent with guidelines, and with the increased availability of targeted therapies, focused efforts should be developed to increase biomarker testing in AA pts. Funding: Pfizer Biomarker Testing Rates by Race. Research Sponsor: Pfizer.

	White[a] n=231	AA n=88	OR[b] (95% CI)	P-value
All *BRCA1/2*mut tested, %	79	66	0.44 (0.24-0.81)	**<0.01**
***s*BRCA1/2mut tested only**	*21*	*23*	*1.10 (0.60-2.01)*	*0.77*
***g +/- s* BRCA1/2mut tested**	*51*	*37*	*0.56 (0.33-0.94)*	***0.03***
***Unknown* BRCA1/2mut tested**	*8*	*6*	*0.71 (0.25-2.03)*	*0.52*
PIK3CAmut tested, %	50	44	0.76 (0.44-1.29)	0.31
PD-L1 tested, %	59	54	0.80 (0.46-1.39)	0.43

[a]Reference value (ref) [b]Compared to ref, <1 is lower testing rates, 1 = the same testing rates, >1 is higher testing rates.

10599 **Poster Session**

Compliance with germline testing in pancreatic cancer in a rural tertiary care hospital. *First Author: Catherine Travaline, Geisinger Medical Center, Danville, PA*

Background: Pancreatic cancer is the 7th most common cause of cancer death worldwide and is projected to be the second leading cause of cancer death in the next decade. Personalized care is becoming more of a reality with pharmacological regimens targeting specific genetic mutations. In March 2019, the National Comprehensive Cancer Network (NCCN) guidelines were updated to recommend germline testing (GT) in all patients with pancreatic adenocarcinoma (PDAC) considering 1 in 10 may have a germline mutation (GM). The goal of this study was to quantify compliance with these recently updated guidelines. **Methods**: The electronic medical records and survivorship data of all patients diagnosed with PDAC between January 1, 2017 and October 1, 2020 were reviewed. April 1, 2019 was used as the transition point (TP) for guideline updates. Descriptive statistics for all variables were determined. The rate of ordered referrals to genetic counseling (GC), as well as completion rate, was calculated. **Results:** A total of 304 patients were diagnosed with PDAC during the study period (223 prior to the TP). A total of 54 patients were referred for GC and 41 had GT ordered. The rate of GC referrals ordered after the TP was significantly higher than before the TP (22/81, 26.6% vs. 32/223, 14.4%; p-value 0.010). Almost 60% of patients who had genetic evaluation had private insurance. The patients who completed GT were significantly more likely to have a documented family history of cancer (61.0% vs 4.2%; p-value <.0001Patients who completed GT had more problems on their problem list (median 10 vs 7, $p = 0.001$). The median overall survival (OS) for all patients in the study was 7.8 months (95% CI: 6.3-9.8). **Conclusions:** Overall compliance with the updated NCCN guidelines significantly improved; however, it was below 25%. This study showed that there may be some lingering bias toward GT in PDAC solely for those who have a family history of cancer. Although patients with stage IV PDAC have poor outcomes, GT may still improve surveillance for family members. The approval of olaparib in patients with BRCA1/2 mutations based on the POLO trial is likely to increase provider compliance as it provides a viable maintenance strategy in these patients. Patient complexity was unlikely to affect GT rate. Assessment of provider awareness was outside the scope of this study. There is need for continued advocacy for awareness and implementation of guidelines that highlight the importance of germline evaluation on prevention, surveillance, and treatment in pancreatic adenocarcinoma. Research Sponsor: None.

10600 **Poster Session**

Evaluation of cohort diversity in development and validation studies of hereditary cancer genetic risk assessment models. *First Author: Amanda Gammon, Huntsman Cancer Institute, Salt Lake City, UT*

Background: Multiple models estimate a person's chance of harboring a pathogenic variant increasing cancer risk. Some pathogenic variants are more common in individuals from specific ancestries, such as the *BRCA1* and *BRCA2* founder variants in Ashkenazi Jews. Yet data remains limited on the larger variant spectrum seen among people of different ancestral backgrounds and whether or not the pathogenic variant frequency differs in many populations. Due to this, it is important that genetic risk assessment models be validated in a diverse cohort including Black, Indigenous, People of Color (BIPOC). **Methods:** A literature search was conducted to identify published development and validation studies for the following genetic risk assessment models: BRCAPRO, MMRPRO, CanRisk/BOADICEA, Tyrer-Cuzick, and PREMM. Validation studies that only evaluated the cancer risk prediction capabilities of the models (and not the genetic variant risk prediction) were excluded. The following participant information was abstracted from each study: total number of participants, gender, race, and ethnicity. Authors were contacted to obtain missing information (if available). **Results:** 12 development and 12 validation studies of the genetic risk assessment models BRCAPRO, MMRPRO, CanRisk/BOADICEA, Tyrer-Cuzick, and PREMM were abstracted. Of the validation studies, five were internal validation studies conducted by the model developers, and seven were external validation studies. Four external validation studies compared multiple models. 75% (18/24) of papers did not include reporting of participant race or ethnicity information in their published reports. External validation studies (4/7, 57%) more often reported participant race/ethnicity than development (0/12, 0%) or internal validation (2/5, 40%) studies. The external validation studies for BRCAPRO reporting race/ethnicity information involved cohorts that ranged from 50-51% non-Ashkenazi Jewish white, 28% African American, 1% Asian, 2-49% Hispanic, and 19-42% Ashkenazi Jewish. The external validation studies for MMRPRO and PREMM reporting race/ethnicity information involved cohort that ranged from 0-82% white, 4-100% Asian, 7% Black, and 7% Hispanic. **Conclusions:** Increased reporting of participant ancestry and ethnicity is needed in the development and validation studies of genetic risk assessment models. BRCAPRO's validation cohorts have included a higher percentage of Hispanic and Black/African American participants, while MMRPRO and PREMM have been validated in a higher percentage of Asian participants. As debate continues about the utility of currently used racial categories in genetics research, it will be important to determine how best to report on participant diversity. These findings highlight the continued need for genetics researchers to engage BIPOC and identify ways to diversify their participant cohorts. Research Sponsor: None.

10601 **Poster Session**

Assessing somatic and germline variants in cancer patients. *First Author: Charité Ricker, Division of Oncology, USC Keck School of Medicine, Norris Comprehensive Cancer Center, Los Angeles, CA*

Background: The increasing integration of somatic and germline testing into oncology practice allows physicians to target oncologic therapy and identify those with cancer predisposition. We explored the impact of a somatic assay (liquid biopsy, LB) on the identification of patients appropriate for germline genetic testing. **Methods:** We identified a cohort of diverse cancer patients with LB to assess for targetable somatic gene variants at LAC+USC Medical Center between 2016 and 2020 (n= 467). To enrich the cohort for variants that may reflect germline findings, we focused on the 46 patients (9.9%) who had at least one variant identified with a cell-free DNA (cfDNA) fraction of 25.00% or greater. Retrospective chart review extracted demographics and medical history with variables related to cancer history and treatment. LB variants were classified based on whether germline confirmation was indicated and the results of germline tests, when done, were reviewed. **Results:** Table summarizes the characteristics of the 46 patients identified to have at least one variant on LB in ≤ 25% of the cfDNA. The most frequently mutated genes on LB were *TP53* (n=18, 39%), *KRAS* (n=11, 24%), *APC* (n=8, 17%), *BRCA2* (n=7, 15%), *PIK3CA* (n=6, 13.0%), and *BRCA1* (n=4, 9%). Seventeen patients (40%) were referred for genetic counseling and 13 (30%) underwent germline testing of whom 10 (77%) carried pathogenic variants (PV). All germline PV were concordant with LB variants identified. Four patients with PV *BRCA2* on LB and confirmed to be germline, had lung or biliary tract diagnoses, which are not part of the typical *BRCA*-tumor spectrum. Thirty-three patients were not referred for genetic counseling, though 24 (72%) had LB-identified variants in cancer predisposition genes and 18 (54%) merited a genetics referral. Among patients with germline mutations, three (23%) had targeted therapy and two (15%) had preventive surgery to address second primary cancer risk. Among the 467 patients with LB results, there were an additional 13 patients (not included in the enriched group) known to have a cancer predisposition gene PV. Only two (15%) had findings on LB reports that suggested germline testing would be indicated. **Conclusions:** While the purpose of somatic testing is to identify targeted therapy, it can provide germline insight, especially for patients not typically referred for genetic assessment. Further education and guidance is needed to assure that this aspect of somatic testing is appreciated by oncology providers and acted upon. Research Sponsor: None.

Age **Median (range)**	55 (21-80)
Sex - no. (%)	
Male	19 (41.3%)
Female	27 (58.7%)
Race/Ethnicity **- no. (%)**	
Hispanic/Latino	29 (63.0%)
Asian	9 (19.6%)
White	6 (13.0%)
Black	2 (4.3%)
Cancer Diagnoses: **Lung/Thoracic**	
Gastrointestinal	14 (30.4%)
Gynecological	14 (30.4%)
Breast	6 (13.0%)
Skin/Soft Tissue	4 (8.7%)
Other	4 (8.7%)
Highest Cancer Stage:	
Limited	12 (26.1%)
Advanced	34 (73.9%)

10602 **Poster Session**

Circulating tumor DNA (ctDNA) as a tool to help guide germline testing in patients with solid malignancies. *First Author: Nikita P. Patel, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL*

Background: As the use of circulating tumor DNA (ctDNA) is more widely implemented, incidental identification of pathogenic variants reflecting germline alterations in cancer predisposition genes will occur more frequently. Such mutations are expected to have a high mutant allele frequency (MAF) or occur in genes typically associated with inherited syndromes. When a similar analysis was conducted by our group, we found that MAF of about 30% or greater in *BRCA1/2* was associated with confirmed putative germline mutations in patients with breast cancer (Jacob et al & Davis et al, SABCS 2020). In this study, we extended this analysis to non-breast malignancies. **Methods:** Patients with non-breast solid malignancies and ctDNA testing between 2015-2020 were retrospectively identified from Northwestern Medicine. All ctDNA was analyzed using Guardant 360 (Guardant Health, Inc. Redwood City, Ca). Patients with ctDNA samples with mutations at high MAF (>30%) and those with *BRCA1/2* mutations at any MAF were identified. We reviewed these charts for referral to genetic counselors and/or CLIA-approved germline testing. Descriptive analysis was reported for these findings. Genetic alterations were classified as pathogenic or of unknown significance based on OncoKB (Chakravarty et al, JCO PO 2017). **Results:** We identified ctDNA samples of 548 patients with non-breast solid malignancies, of whom 56 had gene mutations occurring at high MAF (>30%). Predominant cancer subtypes were lung (48%), colorectal (21%), pancreatic (7%), ovarian (3.5%), prostate (3.5%), and gastroesophageal (3.5%). The most common gene mutations identified were *TP53* (46%), *BRCA1/2* (18%), *EGFR* (18%), *APC* (13%), and *KRAS* (9%). 87.5% were pathogenic and 12.5% were of unknown significance. 11 patients (19.6%) had germline testing of whom 6 tested positive. These germline mutations were in *BRCA2* (n = 3), *EGFR*, *APC*, and *TP53*. In addition to the 10 patients with *BRCA1/2* mutations at high MAF (>30%), we identified 70 patients with *BRCA1/2* mutations at low MAF (< 30%). 54% were pathogenic and 46% were of unknown significance. 11 patients (14%) had germline testing of whom 3 tested positive for *BRCA2*, all at high MAF. 1 patient with a *BRCA2* mutation at low MAF of 1.4% tested positive for a different germline *BRCA2* variant. **Conclusions:** In patients with advanced cancers, ctDNA analysis can reveal variants with MAF >30% that are reflective of a germline mutation. Unfortunately the rate of genetic testing in these patients was low (20%). Future studies with germline testing in patients with high MAF variants would help understand the prevalence of germline variants. This can facilitate developing a more standardized approach for genetic counselor referral to identify families that may benefit from interventions for early detection or prevention of future cancers. Research Sponsor: None.

10603 **Poster Session**

Prospective genomic testing of unselected cancer patients yields insights about cancer susceptibility and noncancer disease with therapeutic implications. *First Author: Stacy W. Gray, City of Hope, Duarte, CA*

Background: Clinicians have used strict criteria to determine eligibility for cancer susceptibility (CS) testing and have limited genetic assessment to cancer-related genes. However, half of all CS mutation carriers are missed by criteria-based testing and there may be an unrecognized opportunity to modify care for patients who have rare but actionable genetic disorders as defined by the American College of Medical Genetics (ACMG). With the aim of improving patient outcomes through precision genomics, we initiated an enterprise-wide program to offer somatic and germline sequencing to all patients. **Methods:** We offer consented patients clinical grade paired somatic & germline WES/ RNA seq and panel germline testing for cancer (156 genes) and ACMG disorders (59 genes). Results are reviewed by a Precision Oncology Tumor Board. Somatic results are returned by the treating team. Germline results are returned by phone (genetic counselor, GC) followed by a clinic visit (GC+MD) for those with pathogenic/likely pathogenic (P/LP) mutations and selected variants of uncertain significant. We evaluated the proportions of patients with somatic findings suggestive of germline conditions and those carrying P/LP mutations in CS and ACMG genes. **Results:** 1,804 patients enrolled and received somatic sequencing: 52% female; 51% non-Hispanic White/ 20% Hispanic White/ 18% Asian/ 4% Black/ 7% other; median age 64. Review of somatic data suggest that 14% have findings suggestive of germline conditions based on factors such as TMB, MSI, and young age. Of the patients offered germline testing, >95% opted to receive CS/ACMG results. To date, we have sequenced 684 patients for CS and 647 for ACMG. 18% of patients had P/LP mutations in CS genes and 4% had P/LP mutations in ACMG non-cancer genes (Table). **Conclusions:** Prospective somatic/germline sequencing of unselected cancer patients reveals tumor findings suggestive of germline disorders and identifies patients with CS and non-cancer genetic conditions. These findings highlight the promise of a comprehensive sequencing approach to help guide cancer treatment, management of unrecognized cancer risk and the need for concomitant management of rare disorders such as arrhythmogenic cardiomyopathy and susceptibility to adverse reactions with anesthesia. Research Sponsor: Internal COH.

Result	**n (%)**
Cancer: all P/LP	182 (26.6)
Cancer: all P/LP minus CFTR	125 (18.3)
Highly penetrant cancer genes	
BRCA2	11 (1.6)
APC, ATM, BLM, FH, MSH6	4 (0.6) each gene
BRCA1, H0XB13, NF1, TP53,	3 (0.4) each gene
MSH2, PALB2	2 (0.3) each gene
CDH1, MEN1, PMS2, RB1, SDHA, SDHB, SDHD	1 (0.15) each gene
Moderately-penetrant/autosomal recessive genes	
CFTR	75 (11.6)
MUTYH	18 (2.6)
CHEK2	13 (1.9)
>23 genes with	<1% each gene
ACMG: all P/LP	72 (11.1)
ACMG: P/LP non-cancer	26 (4)
ACMG non-cancer gene frequency	
ATP7B	13 (2.0)
RYR1	4 (0.6)
PKP2	3 (0.5)
LDLR, MYBPC3	2 (0.3)
APOB, KCNQ1	1 (0.2)

10604 **Poster Session**

Subsequent primary cancers among survivors of adolescent and young adult onset cancers in the United States. *First Author: Hyuna Sung, American Cancer Society, Atlanta, GA*

Background: Adolescent and young adult (AYA) cancer survivors are at increased risk of subsequent primary cancer (SPC); however, a comprehensive examination of risk patterns across cancer types is lacking in the U.S. **Methods:** SPC incidence and mortality was calculated among >1-year cancer survivors aged 15 to 39 years at first primary cancer (FPC) diagnosis during 1992-2016 in 12 Surveillance, Epidemiology, and End Results registries. Rates were expressed as number of cases/deaths per 10,000 person-years and compared with those expected in the general population using standardized incidence (SIR) and standardized mortality ratios (SMR). **Results:** Among 202,440 survivors of AYA-onset cancers (mean age at FPC diagnosis, 31.8 years; 60.7% women), 6,675 SPC cases (34.3 per 10,000) and 3,786 SPC deaths (19.4 per 10,000) occurred during 1,955,119 person-years of follow-up (mean, 9.7 years), corresponding to an SIR of 1.58 (95%CI = 1.54-1.62) and SMR of 4.19 (95%CI = 4.06-4.33. In men, overall incidence and mortality SPC rates were statistically significantly higher for each of 21 FPC types compared with risks in the general population, except for thyroid cancer mortality. In women, risk was statistically significantly higher for 14/23 FPC types for incidence and 19/23 FPC types for mortality. SIRs were highest in survivors of pancreatic cancer (SIR = 5.68, 95% CI = 2.94-9.93; 84 per 10,000), Kaposi sarcoma (SIR = 5.15, 95%CI = 4.62-5.73; 116 per 10,000) and liver cancer (SIR = 4.97, 95%CI = 2.57-8.68; 68.4 per 10,000) in men, and acute lymphoid leukemia (SIR, 3.27, 95% CI = 2.22-4.64; 49.5 per 10,000), Hodgkin lymphoma (SIR = 2.47, 95% CI = 2.22-2.73; 51.6 per 10,000), and bone sarcoma (SIR = 2.41, 95%CI = 1.80-3.16; 47.6 per 10,000) in women. SMRs were highest in survivors of pancreatic cancer, acute lymphoid leukemia, and stomach cancer in men, and liver cancer, acute lymphoid leukemia, and soft tissue sarcoma in women. **Conclusions:** Overall and type-specific risk patterns of SPCs among AYA cancer survivors differ considerably across FPC type, highlighting the need for targeted approaches for cancer prevention and surveillance in survivorship care planning. Research Sponsor: None.

10605 **Poster Session**

Mutant *PPM1D* and *TP53* populate the hematopoietic compartment after peptide receptor radionuclide therapy (PRRT) exposure. *First Author: Abhay Singh, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Mutations in *TP53* and *PPM1D* are putative drivers associated with therapy related-myeloid neoplasm (T-MN) and have been identified in pre-treatment blood samples obtained at the time of primary malignancy, predating clinically evident T-MN. Genomic analysis of patients(pts) who undergo leukemogenic therapies will help understand T-MN biology and devise risk mitigation strategies. PRRT (Lu 177) for neuroendocrine tumors is associated with enhanced risk of T-MNs. The mechanism for T-MN induced by PRRT is largely elusive due to the novelty of this drug. **Methods:** We analyzed initial (n=13) and serial blood samples (n=4) prior to and following PRRT for clonal mutations in order to elucidate the role of PRRT in exerting selective pressures on HSCs. Genomic DNA was analyzed using a targeted myeloid 100-gene panel and a variant allele frequency (VAF) cutoff 1% was used to call clonal hematopoiesis (CH). **Results:** Fifty-four percent pts had CH, despite relatively young age of cohort (median age 58 years, range 41-75) and minimal chemo-radiotherapy exposure; baseline characteristics and molecular profile of cohort is published [Singh et al. *Blood* 2020; 136 (Supplement 1): 35–36]. Serial sample analysis in 4 pts (Table 1) demonstrates that PRRT exposure is associated with clonal evolution and accompanying cytopenias in 75% (3/4) pts. Pt-1 (age 67) with normal baseline hemogram developed persistent cytopenias after PRRT, accompanied by emergence and expansion of mutant-*PPM1D* (m*PPM1D;* VAF 20%). These data suggest that cytopenias result from repopulation of the HSC compartment by m*PPM1D* cells. In Pts 2 and 3 (age 74 and 75), we note expansion of m*TP53* and m*PPM1D* clones respectively, also associated with the development of cytopenias. Pt-4 was younger (age 59) and developed no cytopenias. Exposure to PRRT was associated with loss of m*TET2* and m*DDX41*, possibly due to lack of clonal fitness of m*TET2/DDX41* clones and the relatively young HSC microenvironment. **Conclusions:** We conclude that mutations in *PPM1D* and *TP53* are clinically relevant, contribute to clonal cytopenias and may increase risk of future T-MN. The temporal association of m*TP53* and m*PPM1D* expansion with PRRT exposure in our analysis suggests selection of these clones in response to PRRT-induced stress, outcompeting wild type and less therapy-resistant HSCs. Our study along with others will inform future efforts to strategize methods of surveillance and early detection for clonality assessment and chemoprevention, to reduce adverse effects of leukemogenic therapies. Research Sponsor: KL2/BTC award from University of Buffalo's CTSI (S.T.).

ID	Gene	Mutation Type	VAF (%)	Nucleotide Change	Post PRRT (VAF%)
Pt-1	No mutation				20% (*PPM1D*)
Pt-2	***TP53***	**SNV**	**1.67**	**c.586C>G**	**5%**
	ASXL1	**SNV**	**1.04**	**c.1954G>A**	**0%**
Pt-3	*TP53*	**SNV**	**1.78**	**c.842A>T**	**5%**
	PPM1D	**Truncating**	**1.65**	**c.1508C>A**	**3%**
Pt-4	*PPM1D*	**Truncating**	**1.24**	**c.1709C>G**	**2.7%**
	TET2	Frameshift	2.60	c.3732_3733del	0%
	DDX41	SNV	2.65	c.878G>A	0%

*SNV = Single nucleotide variants.

TPS10606 **Poster Session**

A phase II open label, single arm study to evaluate the efficacy of pembrolizumab for leukoplakia. *First Author: Ashleigh Porter, UCLA, Los Angeles, CA*

Background: The presence of pre-cancerous oral lesions such as leukoplakia or erythroleukoplakia are known risk factors for the development of squamous cell carcinoma of the head and neck (SCCHN), however preventative agents have not yet shown clinical benefit. The risk of malignant transformation varies but has been quoted as high as 36% in some studies. While the primary mode of treatment of these lesions is largely surgical, recurrence rates are high. Pembrolizumab is a potent and selective humanized monoclonal antibody that is designed to directly block the interaction between PD-1 and PD-L1 (as well as PD-L2) that is currently FDA-approved for treatment of SCCHN. We have hypothesized that the treatment of oral premalignant lesions with pembrolizumab would be an effective and well-tolerated strategy to prevent transformation to invasive cancer. **Methods:** This study is an open-label, phase II study that will accrue 26 patients with leukoplakia, erythroleukoplakia, or proliferative verrucous leukoplakia with documented moderate to severe dysplasia or carcinoma in situ to be treated with pembrolizumab 200mg every 3 weeks for a total of 6 months. Patients must have visible and measurable lesions that will be both photographed and measured in two dimensions at each visit from the start of treatment until 12 months post-enrollment. Biopsies will be required at diagnosis and following the final treatment, with an optional biopsy following cycle 2 and at progression of disease. Major exclusion criteria include patients with mild dysplasia or hyperplasia, prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks of Day 1 of study, or patients with a known additional malignancy that is active. Patients will also be excluded if they have received anti-PD-1, anti-PD-L1 or anti-PD-L2 treatments in the past. The primary objective is clinical response rate at 6 months, and will be quantified as the percentage of patients with a complete response (CR) and partial response (PR) at 6 months. A CR is defined as complete resolution by visual inspection for 4 weeks of more and a PR is defined as 50% or greater reduction of the product of the 2 dimensions of a single lesions or the sum of all lesions. Progressive disease (PD) is defined as unequivocal increase (greater than or equal to 5mm in one dimension and greater than 20% increase) or the development of new lesions. Secondary objectives will include histologic response rate at 6 months, change in clinical impression based on photographs, clinical response rate at 9 and 12 months, and toxicity. Additional exploratory objectives will include PD-L1 expression in leukoplakia lesions as well as p16 expression, presence of tumor infiltrating lymphocytes, and immunohistochemical as well as RNA sequencing gene expression profiling which may allow for the identification of novel biomarkers. Enrollment began in June 2019 and is ongoing. Clinical trial information: NCT03603223. Research Sponsor: Merck.

TPS10607 **Poster Session**

A PAncreatic cancer screening study in individuals with New-onset or DeteriOrating diabetes MEllitus (PANDOME study). *First Author: Richard C. Frank, Nuvance Health, Norwalk, CT*

Background: Pancreatic adenocarcinoma (PC) has a persistently high mortality as it presents in the advanced stages and has largely not benefited from the genomic and immunotherapeutic revolutions in oncology. Improvements in screening to detect early stage cancers are therefore urgently needed. Screening studies such as those from the International CAPS Consortium have demonstrated improved survivals in hereditary high risk individuals. In the sporadic population, individuals with new-onset diabetes (NOD) or long-standing deteriorating diabetes (DD) are at substantially increased risk of PC in the 12 months following these diagnoses and have been proposed as target populations for screening efforts. This trial will study the benefits of PC screening in the latter populations in a community setting. **Methods:** Individuals $\geq$ 50 years of age with either NOD or DD will be eligible. Criteria for NOD (within the past 12 months) include: fasting blood glucose $\geq$ 126 mg/dL, random blood glucose $\geq$ 200 mg/dL, or HbA1c $\geq$ 6.5%, with confirmed prior normal values. For those without prior glycemic values, a HbA1c $\geq$ 7.0% is required. Transition from pre-diabetes requires an increase in HgA1c of $\geq$ 0.5%. DD is defined by an increase in HbA1c of $\geq$ 2% within the past six months that is not associated with medication noncompliance or weight gain. Study participants will undergo every 6 months: evaluation by an APRN, testing for anxiety and depression and blood donation for biobanking purposes. High resolution MRI/MRCP with gadolinium will be performed at study entry and annually for 2 years. Images will be reviewed at a multi-disciplinary tumor board consisting of body-image certified radiologists, interventional gastroenterologists, hepatobiliary surgeons and medical oncologists. MRI results will be classified according to a novel PANC-RADS system. High-risk pancreatic findings will be further interrogated by endoscopic ultrasound (EUS). Study endpoints include detection rate of high-risk lesions, referrals for EUS and surgery and detection of incidental findings leading to unnecessary procedures. Adverse psychological impacts will be assessed through HADS testing. Target accrual: 500 patients within 3 years. Clinical trial information: NCT03937453. Research Sponsor: The Naughton Family Fund.

TPS10608 **Poster Session**

Comparing the clinical impact of pancreatic cyst surveillance programs: A trial of the ECOG-ACRIN cancer research group (EA2185). *First Author: David Weinberg, Fox Chase Cancer Center, Philadelphia, PA*

Background: The optimal surveillance strategy for pancreatic cysts, which occur in up to 20% of the adult population, is ill defined. Although risk of malignant degeneration of these cysts is low, pancreatic cancer mortality remains high. Two cyst surveillance guidelines, one proposed by an international consensus group (Fukuoka) and the other by the American Gastroenterological Association (AGA), are accepted standards. Both rely on radiographic and endoscopic ultrasonographic imaging. They differ in indications for, and intervals between, imaging tests, with the Fukuoka guideline advocating more intensive imaging. Clinical guidelines that provide discordant recommendations may undercut the quality and/or value of care, and have implications for societal health care costs. The primary objective of this prospective trial is to compare the clinical effectiveness and associated resource utilization of the Fukuoka and AGA guidelines for pancreatic cyst surveillance. Secondary objectives include a comparison of resource utilization and patient reported outcomes. We are also collecting and banking radiomics data and biospecimens to identify novel methods that might improve cancer risk stratification. **Methods:** 4606 asymptomatic patients with newly identified pancreatic cysts $\geq$1cm in diameter are being randomized 1:1 to high intensity (Fukuoka) or low intensity (AGA) surveillance. The primary endpoint is a composite of any pancreatic cancer without surgery, unresectable pancreatic cancer or cancer $>$ T1a, N0 at surgery, and benign disease at surgery. This sample size will provide 90% power to identify a 30% relative difference in the primary outcome at 5 years between the two study arms. Study duration is 8 years in total, allowing for 2 years of cohort enrollment, 5 years of prospective follow-up, and six months reserved for study initiation and close out. Study participants must be $\geq$ 50 years and $\leq$ 75 years with an ECOG Performance Status 0-1 at baseline. Participants must have received a CT or MRI within 6 months of registration that identifies a new $\geq$1 cm pancreatic cyst. Patients with a prior diagnosis of a pancreatic cyst, pancreatic malignancy or a history of pancreatic resection are not eligible. Additional exclusion criteria include a history of acute or chronic pancreatitis, a family history of pancreatic adenocarcinoma in 1 or more first degree relatives, imaging findings or clinical signs that would prompt immediate surgical consideration (enhancing mural nodule, solid component in cyst, pancreatic duct $>$ 10mm, cyst causing obstructive jaundice), a comorbid illness that precludes pancreatic cyst resection, pregnancy or current participation in an established surveillance program. As of February 4, 2021, thirty three (33) participants have been enrolled from two hundred (200) potential sites. Clinical trial information: NCT04239573. Research Sponsor: U.S. National Institutes of Health.

TPS10609 **Poster Session**

Engaging the radiology community in the National Clinical Trials Network: The ECOG-ACRIN TMIST experience. *First Author: Etta Pisano, Beth Israel Deaconess Medical Center, Boston, MA*

Background: ECOG-ACRIN launched the Tomosynthesis Mammographic Imaging Screening Trial (TMIST) through the National Cancer Institute's National Clinical Trials Network (NCTN)— a network of academic medical centers, community hospitals, and private clinical practices that are committed to participating in NCI-funded clinical trials. The NCI NCTN was developed to support rapid trial start-up of NCI-funded cancer control/prevention, cancer treatment, and non-therapeutic clinical trials that occur within the institution through centralized institutional administration and shared clinical resource allocation (personnel, lab services). TMIST is a randomized clinical trial assessing two breast cancer screening imaging modalities, tomosynthesis and digital mammography, in the population of women presenting for screening mammography and therefore requires active involvement of radiology. **Methods:** TMIST seeks to enroll 164,946 women, ages 45 to 74 years who present for screening mammography. Because the population under evaluation are women already scheduled for screening mammography, the mammography clinic is critical to successful recruitment as well as adherence to imaging randomization assignments over a 5-year period and therefore must be actively engaged in this trial with a breast imaging radiologist championing the trial within this service. To get active engagement of breast imaging radiologists, we needed to first make them aware of TMIST. Breast imaging radiologists that were already actively involved in the NCTN received notification of the trial through the NCTN email lists. So our goal was to come up with a strategy to reach out to breast imaging radiologists that were not active members in the NCTN. This was achieved through in-person informational sessions to introduce the trial at national and international breast imaging meetings, introduction of the trial and the workings of the NCTN network to the radiology community through articles placed in American College of Radiology (ACR) newsletters, ads promoting TMIST on ACR social media platforms, and direct email by the TMIST study chair to key radiology stakeholders. As of February 15, 2021, there are 115 sites open: 106 in the U.S. and 9 internationally with an additional 54 sites planning to open. A total of 39,366 women are enrolled in the trial with two-thirds also consenting to optional blood and/or buccal cell collection. Minority populations' participation in the trial is over 20%. A significant drop in enrollment occurred in Spring 2020 coinciding with the suspension of mammography services globally due to COVID-19 beginning mid-March 2020. Enrollment and follow-up screening visits for TMIST restarted in May 2020 and gradually ramped back up to pre-COVID totals in September 2020. Our highest monthly accrual so far occurred in November 2020 with 2,148 subjects enrolled. Clinical trial information: NCT03233191. Research Sponsor: U.S. National Institutes of Health.

11000 **Clinical Science Symposium**

Novel approach to improve the diagnosis of pediatric cancer in Kenya via telehealth education. *First Author: Tyler Severance, Riley Hospital for Children, Division of Pediatric Hematology Oncology, Indianapolis, IN*

Background: Childhood cancer has an annual incidence of 150-160 cases per million children worldwide but remains vastly under-diagnosed in low to middle income countries (LMIC) such as in Sub-Saharan Africa. Moi Teaching and Referral Hospital (MTRH) is the only tertiary referral hospital in western Kenya and serves a population of 25 million people, including 10 million children. The average number of pediatric cancer diagnoses was 216 cases annually in 2017-2019, well below the anticipated 1500 cases based on cancer epidemiology data. We recently completed a comprehensive Needs Assessment suggesting that due to inadequate pediatric oncology education, many clinical diagnoses are missed and correct diagnostic tests are not obtained at county hospitals. Local medical staff expressed interest in educational programs to help augment their understanding and diagnostic evaluation of pediatric oncology. **Methods:** To address these disparities in medical knowledge, we implemented Project ECHO – a validated virtual guided practice and telementoring model – to connect multidisciplinary specialists at MTRH with staff in medically underserved communities in western Kenya for ongoing training, technical assistance, and mentorship. The ECHO program follows a Hub-and-Spoke design where the specialists at MTRH and pediatric oncologists at Riley Hospital functioned as the "hub" team and the health care workers at county hospitals were the "spokes". Sessions were freely available on Zoom twice monthly and featured both a didactic topic presented by experts and a spoke-led case-based discussion. The discussion utilized dialogue education to promote learning and engagement among the spokes with mentorship from the hub team. **Results:** The ECHO program launched successfully in January 2020 with a curriculum focused on pediatric oncology for general health care workers. A total of 22 sessions occurred with an average of 23 learners (primarily staff at community hospitals within the referral region) per session. Despite the COVID-19 pandemic, the year-end analysis in January 2021 demonstrated 286 new pediatric patients were diagnosed with cancer at MTRH representing a 33% increase over the 3-year average. **Conclusions:** The implementation of a telehealth education platform – Project ECHO – focused on diagnosing pediatric cancer in medically underserved communities in Kenya, is a useful model to increase the recognition and earlier referral of childhood cancer in LMICs. Research Sponsor: Takeda Pharmaceutical Company, Indiana Clinical and Translational Sciences Institute.

11001 **Clinical Science Symposium**

Sexual harassment of oncologists. *First Author: Ishwaria Mohan Subbiah, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Few studies have used comprehensive validated measures to investigate the incidence and impact of workplace sexual harassment experienced by physicians (and none, to our knowledge, by oncologists). **Methods:** We conducted a cross-sectional survey of ASCO's Research Survey Pool with targeted social media outreach to examine the prevalence and types of sexual harassment (SH) experienced by oncologists. Using the Sexual Experiences Questionnaire (SEQ), we measured their work experience of three SH forms (gender harassment [GH], unwanted sexual attention [USA], sexual coercion [SC]) in the past year by institutional insiders (peers/superiors) and patients/families separately. Controlling for race, career stage & specialty, multivariable (MV) regression models assess the impact of SH (independent variable) on 4 dependent variables of mental health (MHI5), perceptions of workplace safety (single item), job satisfaction (MOAQ) & 3-item measure of turnover intentions (in non-trainees). **Results:** Of 271 respondents, 250 were physicians in practice and 21 were residents/fellows; 153 (56%) were women, 168 (62%) practiced in academic settings & 227 (84%) were medical oncologists. SH by peers/superiors was reported by 189 (70%) overall, including 80% of women and 56% of men ($p<0.0001$). GH was reported by 79% of women and 55% of men ($p<0.0001$), USA by 22% of women and 9% of men ($p=0.005$), and SC by 3% of women and 2% of men ($p=0.42$). SH by patients and/or families was reported by 67% of women and 35% of men ($p<0.0001$), GH by 66% of women and 34% of men ($p<0.0001$), USA by 5% women and 6% men ($p=0.80$), and SC by 1% women and 1% men ($p=0.72$). MV analysis showed past-year SH from peers/superiors was significantly associated with decreased mental health (β -0.45, p 0.004), workplace safety (β -0.98, $p<0.001$) and increased turnover intentions (β 0.93, $P<0.0001$). SH from patients/families was similarly significantly associated with mental health (β -0.41, p 0.002), workplace safety (β -0.42, p 0.014) and turnover intentions (β 0.58, p 0.0004). SH from insiders (β -0.64, p 0.001) but not patients (p 0.55) was significantly associated with job satisfaction. Furthermore, there were no significant interactions between the respondents' gender and the SH scores in any of the models of impact. **Conclusions:** This is the first study in oncology to systematically characterize the incidence of sexual harassment experienced by oncologists. Our findings demonstrate the impact of sexual harassment on men and women oncologists on multiple domains of workplace experience. This study provides critical data to inform the need for and design of effective protective and preventive workplace policies in oncology. Research Sponsor: None.

11002 **Clinical Science Symposium**

A post-COVID survey of current and future parents among faculty, trainees, and research staff at an NCI-designated cancer center. *First Author: Annie P. Im, UPMC Hillman Cancer Center, Pittsburgh, PA*

Background: Challenges for women in science and academic medicine have been well documented, which include gender disparities related to parental and domestic responsibilities that interfere with work or career opportunities. We aimed to evaluate the experiences and working environment at an NCI-designated Cancer Center for current and future parents in the post-COVID era. We hypothesized there would be differences in the experiences of parents between men and women, and between trainees, faculty, and staff. **Methods:** A 61-question online survey for current and future parents was developed by the Women's Task Force of the Hillman Cancer Center (HCC) in Pittsburgh, Pennsylvania. Questions focused on perceived attitudes towards parents, the supportive nature of the working environment for parents, experiences with breastfeeding as a working parent, and childcare responsibilities pre- and post-COVID. The survey was sent to 562 scientific faculty, physicians, trainees, and research staff at HCC. Comparisons between groups of interest were performed using a chi-square test. **Results:** There were 214 respondents (38% response rate) with even representation: 38% were faculty, 27% were trainees, and 35% were research staff; 59% were female. 6% of respondents reported being "discouraged or excluded from participating in specific activities due to having or planning children", and 24% felt "moderately supported" as a parent at work. Regarding breastfeeding, 58% reported that the decision to breastfeed was moderately impacted by returning to work, and of the women who were currently or recently breastfeeding, 42% reported that there were not enough lactation rooms in their building. Other questions in the survey aimed to evaluate what further support would be helpful for parents. 40% reported that on-site childcare would help better support them as a parent, especially because 47% documented that finding childcare was difficult and 53% documented that they looked at ≥4 daycares or nannies. Further, 49% reported that they did not know where to look for resources in finding childcare. Pre-COVID, 32% reported spending 2-3 hours a day on childcare and/or home responsibilities; post-COVID, 55% reported spending ≥4 hours a day. These effects were more pronounced in women compared to men ($p < 0.05$). Pre-COVID, 40% reported that they were unable to participate in work events due to childcare responsibilities, which increased to 54% post-COVID, and was most pronounced in faculty and trainees compared to staff ($p < 0.05$). **Conclusions:** Our survey describes some of the universal challenges of working parents in Oncology, which have been exacerbated by COVID. The impact of COVID was more pronounced in women. Further studies are needed for systematic interventions or policies that improve support for working parents, including unified resources and working groups for current and expecting parents. Research Sponsor: Cancer Center funds.

11003 **Poster Discussion Session**

Digital footprint of hematology-oncology fellowship programs: Identifying gaps after the first virtual recruitment season. *First Author: Ana I. Velazquez Manana, University of California, San Francisco, San Francisco, CA*

Background: The COVID-19 pandemic has led to unprecedented restrictions to travel and in-person activities that limit hematology/oncology (HO) fellowship programs' (FP) recruitment activities. Prospective applicants rely on websites and social media (SOME) to guide their decisions of applying or ranking a FP. We aim to evaluate HO FP's digital footprint in order to identify informational gaps. **Methods:** The AMA Fellowship and Residency Electronic Interactive Database (FREIDA) was queried for all HO programs. We searched Google, Twitter, Instagram, Facebook, and YouTube for HO FP pages. Content was evaluated using published criteria. Qualitative content analysis of SOME posts is planned. **Results:** Our analysis includes 176 FP that actively recruited during the 2020 match season. Over half (57%, n = 100) were university-based and the median number of fellow positions per year was 4 per FP (range 0-16). Most FP had websites (95%, n = 167) with varying information (Table) for prospective applicants. Twenty percent (n = 33) included a diversity statement. While 63% (n = 106) of FP provided application information, only 51% discussed visa requirements. Few FP websites included key information such as why fellows chose a particular FP (7%, n = 12), accolades of fellows (3%, n = 5), or employment location of alumni (25%, n = 44). Only 42% (n = 69) provided city , and 5% (n = 8) showed fellows socializing. Thirty-four FP (19%) have informational videos (range 1-10) in YouTube (length range: 1:37-18:15min). Most (82%; n = 28) were published since May 2020 in alignment with the FP recruitment season. Twitter was the second most common SOME platform, used by 19% (n = 32) of FP. 56% (n = 18) joined Twitter since May 2020 correlating with the current recruitment season. The number of Twitter followers (median 119, range: 0-1408) and posts (median 47, range: 0-687) varied across FP. Only 4% used Facebook and 6% Instagram. **Conclusions:** Our analysis of FP's digital footprint revealed that applicants participating in the 1st virtual HO recruitment season were provided limited online information. Programs can use online content to provide information on resources, research opportunities, and achievements of faculty and fellows that can guide applicant decision making. In the era of COVID-19, highlighting the diversity and breath of each FP, hospital, and city are vital to attract a diverse and talented pool of trainees. Research Sponsor: None.

	N (%)
Educational activities	104 (62)
- Wellness curriculum	25 (15)
Description of clinical training sites	120 (72)
- Bone marrow transplant service	120 (72)
Sample schedule	108 (65)
Research experiences/requirements	130 (78)
- Formal training (T32 or Masters)	37 (23)
- Research from current fellows	32 (19)
List of current fellows	111 (67)
List of faculty	101 (60)
Benefits/resources for daily living*	59 (35)
Parental policies	30 (18)

*Housing, meals, parking, transport, etc.

11004 **Poster Discussion Session**

Analysis of hematology and oncology fellowship website content and diversity representation. *First Author: Arun Muthiah, Rhode Island Hospital-The Warren Alpert Medical School of Brown University, Providence, RI*

Background: Fellowship in hematology and oncology (HO) is widely sought after but lags behind all other internal medicine subspecialties in attracting applicants underrepresented in medicine (URM). An approach to appealing to URMs involves preexisting in-person strategies but also adapting virtual tools to promote inclusion. Specifically, program websites serve as the first impressions of a program, as well as influence the perception of diversity and inclusion. We evaluated the content and diversity representation of HO program websites to facilitate a generally more informed and URM-considerate recruitment. **Methods:** The websites of 2019-2020 ACGME accredited HO programs were assessed between June 1st to July 1st, 2020. Data focused on 30 informational categories, derived from published methodology, along with three additional categories concerning diversity, based on suggestions for inclusive graduate medical education recruitment strategies, were compared using two-tailed *t* tests. We defined websites with 70% or more of the 30 informational categories as "comprehensive websites." Affiliation with a National Cancer Institute (NCI) Designated Cancer Center, NCI Designated Cancer Center + National Cancer Center Network (NCCN) member institution, and a top 50 ranked cancer hospital by U.S. News was also considered in the analysis. **Results:** A total of 156 program websites were analyzed: 37.2% NCI; 19.9% NCCN; 29.5% U.S. News ranked. Only 31 (19.9%) were "comprehensive websites," and 34 (21.8%) had information pertaining to at least one of the diversity categories. There was a significant association between inclusion of diversity content and being a "comprehensive website" ($p = 0.001$). Compared to those that were neither designated nor ranked, programs designated by NCI, NCCN, or ranked by U.S. News were more likely to have more complete information available ($p < 0.001$, $= 0.008$, and < 0.001, respectively). However, only programs ranked by U.S. News were more likely to include information about diversity on their websites ($p = 0.006$). **Conclusions:** The vast majority of HO fellowship program websites were not comprehensive, including a lack of diversity and inclusivity content. NCI designation, NCCN participation, and US News ranking were significantly associated with more complete fellowship websites. Given the context of the COVID-19 pandemic in which institution visitation is restricted, program websites may have elevated importance in recruitment. HO programs should direct resources to offering more complete and inclusive websites to better inform applicants, including URM residents. Research Sponsor: None.

11005 **Poster Discussion Session**

COVID-19 and medical education: Rethinking student assessment—The Virtual Observational Standard Clinical Examination. *First Author: Mariana Abal, Instituto Oncologico Henry Moore, Capital Federal, Buenos Aires, Argentina*

Background: The COVID-19 pandemic introduced new challenges for medical education. In particular, student assessment posed some of the most urging questions. How do we evaluate practical skills when our universities are on lockdown and our hospitals are working on a shortage of personnel? Is it possible to evaluate these skills via online means, mitigating the effects in students' career development? This paper presents an online evaluation experience implemented at Instituto Oncológico Henry Moore-Universidad del Salvador, Buenos Aires in the postgraduate program of Clinical Oncology. The Virtual Observational Standard Clinical Examination (V-OSCE) is a technology-based adaptation of the Observational Standard Clinical Examination (OSCE) (JCO 34 (15), Abstract e18150, 2017) implemented in previous years. **Methods:** The V-OSCE took place in November 14, 2020 and consisted on a half-day evaluation during which students rotated through 8 stations (Table). The exam ran on three platforms: Blackboard Collaborate for the interactive elements of all stations; University online campus (Moodle platform) for student questionnaires, and Google Forms for the evaluators' assessment of each student. Students and evaluators participated in various training sessions, and were given a month to practice before the exam. All interactions were recorded and an anonymous survey on students' experience and opinions was conducted after the exam. **Results:** A total of 25 postgraduate Oncology students participated in the V-OSCE. 24 students (96%) completed all stations on time with minimum or no network connection issues. Student opinions: 24 students completed the exam experience anonymous survey; 23 found the exam tech-friendly and valued the practice time provided. When asked to score the exam in a scale of 1 to 10: 80% of the students ranked the exam with 9 or 10; and 20%, with 7 or 8. **Conclusions:** A) It is feasible to design new ways to assess medical students via online means. B) The experience of an OSCE can be translated to an online environment with minimum technological requirements. C) The COVID-19 pandemic effects are extensive, with serious implications in medical education. However, it has proved to be an opportunity to rethink our educational practices, design innovative formative experiences, and assess new skills that will remain significant even long after the pandemic has ended. Research Sponsor: None.

V-OSCE stations.

Station		Skills assessed	Duration
I	Interaction with a curable patient	Doctor-patient online interaction	30 min
II	Interaction with an incurable patient		30 min
III	Ethics Committee	Online collaborative work and peer interaction	60 min
IV	Tumor Board		60 min
V	Scientific paper reading comprehension	Individual knowledge and skills	15 min
VI	Differential diagnosis with patient images		15 min
VII	Genetic report interpretation		15 min
VIII	Scans interpretation		15 min

11006 **Poster Discussion Session**

Trends in female representation in clinical practice guidelines (CPGs) among major cancer organizations. *First Author: Madhuri Chengappa, Nazareth Hospital, Philadelphia, PA*

Background: While women representation and sex disparities in National Comprehensive Cancer Network (NCCN) and European Society of Medical Oncology (ESMO) has been studied in a limited set of CPGs, the sex representation and disparity trend over time among all NCCN and ESMO CPG panelists has not been studied. Our study evaluates the current sex disparities and female representation for all NCCN and ESMO CPGs as of 2020 and compared it to the 2010 CPGs of both organizations. **Methods:** The 2010 and 2020 version of NCCN and ESMO CPGs were examined from their respective websites and archives. We catalogued the number of female versus male panelist for each CPG. We discerned the sex of the panelists based on google search and the panelists' affiliated institutional websites. **Results:** 60 NCCN (2020), 51 NCCN (2010), 78 ESMO (2020) and 55 ESMO (2010) CPGs inclusive of all cancers by site, detection prevention and risk reduction, supportive care, and guidelines for specific population were reviewed. NCCN 2020 CPGs had 55.5% female representation. 35 (58%) NCCN CPGs had predominant female representation (>50% of the members being female) whereas 24 CPG (40%) were male predominant (>50% of the members being male). Solid tumors had 24 CPGs with male predominance and hematological malignancies had 14 CPGs with female predominance. Cancers specific to women had higher proportion of female panelist. NCCN 2010 CPGs had 27.1% female representation. Both solid tumors and hematological malignancies had male predominance (82% and 75% respectively). Breast cancer screening, palliative care and older adult oncology CPGs were female predominant. ESMO 2020 had 27.8% female representation. Both solid tumors (37 CPGs) and hematological malignancies (17 CPGs) had predominant male representation (72% and 85% respectively). Breast and ovarian cancer CPGs were female predominant. ESMO 2010 had 23.2% female representation. Male representation was predominant in both solid tumors (35 CPGs) and hematological malignancies (9 CPGs). Breast, cervical and ovarian cancer CPGs were female predominant. **Conclusions:** Over the last decade, proportion of female panelists in NCCN CPGs has doubled with more than 50% representation among its 60 CPGs, indicating adequate representation of women. In ESMO, although there has been a significant improvement in female representation in hematological malignancies over time, it continues to have overall female underrepresentation (<30%). Research Sponsor: None.

	Total CPGs	Total Panelist	Total Female	Total Male	Solid tumor panelist		Hematological Malignancies panelist	
					Female	Male	Female	Male
NCCN 2010	51	1267	343 (27.1%)	924 (72.9%)	136 (18.1%)	617 (81.9%)	43 (25.4%)	126 (74.6%)
NCCN 2020	60	2522	1400 (55.5%)	1122 (44.5%)	532 (49.2%)	550 (50.8%)	336 (56.6%)	258 (43.4%)
ESMO 2010	55	228	53 (23.2%)	175 (76.8%)	36 (23.7%)	116 (76.3%)	1 (5.3%)	18 (94.7%)
ESMO 2020	78	802	223 (27.8%)	579 (72.2%)	124 (27.8%)	322 (72.2%)	22 (15.3%)	122 (84.7%)

11007 **Poster Discussion Session**

Where are the women and underrepresented minorities in medicine? Race/ethnicity and gender representation in oncology journals' editorial boards. *First Author: Shruti Rajesh Patel, Mayo Clinic, Rochester, MN*

Background: The proportion of women & underrepresented groups in medicine (URM) in the field of hematology and oncology remains low, particularly in academic leadership positions. Editorial board appointments allow physicians to have a substantial impact on the nature of the published scholarly work and serve as a platform for academic opportunities. We aimed to assess gender and race/ethnicity representation in editorial board positions in hematology and oncology journals. **Methods:** Editorial leadership board members from 60 journals from oncology, hematology, radiation oncology, and surgical oncology were reviewed, 54 journals were included in the analysis. Gender and race/ethnicity were determined based on publicly available data for editor-in-chief (EiC) and second-in-command (SiC) (including deputy, senior, or associate editors). Descriptive statistics and chi-squared were estimated. **Results:** A total of 793 editorial board members are included in the analysis. 72.6 % were men and 27.4 % were women. 71.3% of editorial leadership were non-Hispanic white with Asian editorial board members representing the second largest majority at 23.3%. The editorial position was significantly different among men and women ($p = 0.038$) with women filling only 15.9% (10/63) of the EiC positions. Of these 10 women, the racial breakdown was 90% white and 10% Asian. In the prevalence odds ratio (pOR), women were about half as likely to be in the EiC position compared with men [pOR: 0.47, 95%CI (0.23, 0.95, $p = 0.03$)]. Women represented 28.4% (207/730) of SiC editorial positions. White editors had the highest representation at 71.0% in the SiC editorial positions, followed by Asian editors at 16.0%. Notable differences were seen in gender proportions between journal specialties ($p = 0.001$); with surgical oncology and hematology having the lowest female representation at 11.9% and 22.7%, respectively. **Conclusions:** Women and UIM are markedly underrepresented in leadership roles on Editorial Boards in hematology and oncology journals. Importantly, the representation of minority women physicians in EiC positions is at an inexorable zero which is a sign of unconscious attitudes that may exclude women and minorities from certain positions. It is imperative that we work to move towards a more diverse and inclusive editorial board to ensure critical perspectives are heard and scientific discovery is fostered. Research Sponsor: None.

Editor's Race/Ethnicity (%)	Editor-In-Chief Female n (%)	Editor-In-Chief Male n (%)	Second-In-Command Female n (%)	Second-In-Command Male n (%)
White	9 (19.6)	37 (80.4)	155 (29.9)	363 (70.1)
Black	0 (0.0)	2 (100.0)	1 (16.7)	5 (83.3)
East Asian	0 (0.0)	5 (100.0)	34 (29.1)	83 (70.9)
South Asian	1 (10.0)	4 (80.0)	9 (17.6)	42 (82.4)
Middle Eastern & North African	0 (0.0)	3 (100.0)	3 (23.1)	10 (76.9)
Hispanic	0 (0.0)	2 (100.0)	5 (23.8)	16 (76.2)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	4 (100.0)

11008 **Poster Discussion Session**

Authorship gender equity in global oncology publications. *First Author: Paula Hornstein, Northeastern University, Boston, MA*

Background: There is increasing recognition of authorship inequity in academic medicine specialty publications. Analyses in other specialties note that female authors consistently comprise a minority of the first authors and an even smaller percentage of last authors. While this trend may be improving, we hypothesize that significant authorship gender disparities still exist in global oncology journals. **Methods:** This study comprehensively analyzes the gender distribution of authors for articles published in the Journal of Clinical Oncology Global Oncology (JCO GO), a premier journal in the field, from its inauguration in 2016 to March 2020. A total of 608 articles were identified as matching one of the following six article types: original report, editorial, commentary, case report, special article, and review article. We collected data such as the author's position, gender, institutional affiliation, and country affiliation. Author gender was categorized as male, female, or indeterminate based on first name probabilities assessed by genderize.io, with a threshold probability of 0.8 based on prior studies. Authorship distribution was analyzed by region and country income level according to the World Bank classification. **Results:** Of the 608 article first authors, 47.5% were identified as male, while 41.4% were female. Male authors made up a comparatively higher proportion of the 592 last authors; 57.1% were identified as male compared to 32.1% who were female. A similar trend was seen among the 4102 middle authors; 51.4% were identified as male and 38.1% were female. The percentage of authors deemed indeterminate in the cohort was less than 11%. Female authors were more underrepresented among authors from low-income countries; they made up 21.6% of first authors and 9.1% of last authors. Authorship gender by world regions is summarized in Table below. **Conclusions:** Our analysis shows that authorship inequities persist in global oncology publications. Female authors from lower-income countries, and regions in Sub-Saharan Africa and South Asia, were markedly underrepresented. The underlying reasons for underrepresentation of female authors are multifactorial; further studies are needed to elucidate these factors and to develop and evaluate mitigating strategies. Research Sponsor: None.

Summary of author gender percentages by world regions.

	Overall	East Asia & Pacific	Europe & Central Asia	Latin America & Caribbean	Middle East & North Africa	North America	South Asia	Sub-Saharan Africa
First Author, n	608	52	36	89	48	226	79	78
Male, %	47.5	34.6	44.4	48.3	47.9	40.3	60.8	64.1
Female, %	41.4	36.5	52.8	49.4	29.2	47.3	31.6	30.8
Indeterminate, %	11.0	28.8	2.8	2.2	22.9	12.4	7.6	5.1
Last Author, n	592	49	53	79	37	241	69	64
Male, %	57.1	51	64.2	69.6	59.5	48.5	63.8	64.1
Female, %	32.1	22.4	32.1	30.4	37.8	42.3	14.5	18.8
Indeterminate, %	10.8	26.5	3.8	0	2.7	9.1	21.7	17.2

11009 **Poster Discussion Session**

Gender and racial/ethnic disparities in academic oncology leadership. *First Author: Gavin Jones, University of Kentucky, Lexington, KY*

Background: Gender & racial/ethnic leadership disparities have been independently identified in academic hematology/oncology (HO) and radiation oncology (RO). Here, we evaluate gender and racial/ethnic intersectionality from the trainee to the leadership level. **Methods:** All ACGME accredited HO and RO training program websites were queried to identify constituent trainees, academic faculty, program directors (PD) and department chairs (DC), with a leadership position defined as PD or DC. Individual gender & race/ethnicity was determined using externally validated software tools (Gender-API, NamSor, & Onolytics), publicly available descriptors, and image review. We grouped individuals into 6 categories: White Male (WM), White Female (WF), Asian Male (AM), Asian Female (AF), Underrepresented Groups in Medicine (as defined by AAMC) Male (URMM) and Female (URMF). The chi-squared goodness-of-fit test was applied to examine if deviations exist between the observed vs. expected proportions of gender/race dyads in trainees, PD, and DC compared to academic faculty. **Results:** We identified 7,722 individuals from 2019-2020: 1,759 trainees (HO=1525; RO=234), 5,726 faculty (HO=4834; RO=892), 242 PD (HO=149; RO=93) and 237 DC (HO=144; RO=93). Leadership positions were most often comprised by WM (52.6%), and least often comprised by URMF (2.9%). Combined HO/RO analysis revealed significant differences in the observed representation of trainees & DC vs expected levels based on total faculty, respectively: WM (33.7% & 60.3% vs. 42.3%), WF (19.2% & 13.9% vs. 22.3%), AM (20.75% & 16.9% vs. 16.4%), AF (17.9% & 2.5% vs. 12.7%), URMM (4.09% & 5.5% vs. 3.5%) and URMF (4.3% & 0.8% vs. 2.8%), $p<0.01$. No differences were seen between PD vs total faculty. On subset analysis, there were significant differences observed in HO programs at the trainee, PD and DC levels compared to total faculty, whereas significant differences in RO programs were seen only at the DC level [Table]. **Conclusions:** Gender & racial/ethnic disparity is present in academic oncology. Specifically, women of all races/ethnicities are proportionally underrepresented in DC positions in HO and RO programs. These data can serve as a benchmark to raise awareness and monitor progress towards a more balanced workforce in oncology. Research Sponsor: None.

Program	Role	WM (%)	WF (%)	AM (%)	AF (%)	URMM (%)	URMF (%)	p-value
HO	**Faculty (n=4834)**	42.16	23.09	15.60	13.01	3.45	2.72	-
	DC (n=144)	57.64	19.44	14.58	1.39	5.56	1.39	p<0.01
	PD (n=149)	41.61	24.16	10.74	13.42	2.68	7.38	p>0.01
	Fellows (n=1525)	32.52	19.67	20.66	18.62	3.87	4.66	p<0.01
RO	**Faculty (n=892)**	42.71	17.94	20.96	11.21	3.92	3.25	
	DC (n=93)	64.52	5.38	20.43	4.30	5.38	0	p<0.01
	PD (n=93)	50.54	16.12	22.58	8.60	1.07	1.07	p>0.01
	Residents (n=234)	41.45	16.67	21.37	13.25	5.56	1.71	p>0.01

11010 **Poster Discussion Session**

U.S. radiation oncology and medical oncology department faculty diversity trends by sex and underrepresented in medicine status over five decades. *First Author: Sophia C. Kamran, Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA*

Background: Academic faculty are critical in training future generations of oncologists to care for our increasingly diverse cancer patient population. It is unclear if the growing imperative to address disparities in racial/ethnic and gender representation in the medical field has resulted in corresponding progress in the composition of academic radiation and medical oncology (RO, MO) departments. Herein we report trends in faculty diversity, overall and by academic rank, among US radiation and medical oncologists over the past 5 decades. **Methods:** Data were acquired from the Association of American Medical Colleges (AAMC) Faculty Roster between 1970-2019 for academic RO and MO departments to determine sex and race/ethnicity trends over five decades. Underrepresented in Medicine (URM) was defined as individuals identifying as Black, Hispanic, and Native American. Linear regression models were used to estimate slopes and associated p-values. **Results:** Total faculty complements grew over time in both RO and MO departments. The number of URM female faculty increased by 0.85/year in RO and 0.79/year in MO (P-trend<0.001), compared to non-URM female faculty, which increased by 11.3/year in RO and 7.9 in MO (P-trend<0.001). URM male faculty increased by 1.4/year in RO and 1.1/year in MO (P-trend<0.001), compared to non-URM male faculty, which increased by 25.5/year for RO and 12.2/year for MO (P-trend<0.001). Males represented the majority of URM and non-URM faculty for both RO and MO. The proportion of females grew more than the proportion of URM faculty over the study period for both RO and MO. There were also significant differences in diversity by faculty rank. Although MO outperformed RO in terms of the proportion of female faculty members with more advanced rank, female faculty members had a lower academic rank than their male counterparts in both specialties. At every rank, there was a low number of URM faculty represented among both MO and RO (Table). **Conclusions:** Gender and racial/ethnic diversity of academic RO and MO faculty has increased over time but has not kept pace with the diversity of the US population served, particularly with respect to URM status. The proportion of female faculty in both specialties demonstrates more promising growth, and may inform measures to achieve similar progress in recruiting and retaining URM faculty in both MO and RO. Research Sponsor: None.

2019 rank among RO and MO faculty.

	Instructor	Assistant Professor	Associate Professor	Full Professor
RO Females	42.2%	30.2%	27.5%	20.8%
MO Females	41.0%	42.7%	41.8%	28.0%
RO URM	6.1%	6.2%	3.9%	4.0%
MO URM	4.5%	6.6%	7.3%	4.7%

11011 **Poster Discussion Session**

Minding the gap: Gynecologic oncology practices differ by gender. *First Author: Sarah Madhu Temkin, Washington, DC*

Background: Although most gynecologic oncologists (GOs) are now women, gender differences in clinical practice and compensation persist. Practice characteristics and infrastructural support that may influence gender-based differences were explored. **Methods:** Every 5 years, the Society of Gynecologic Oncology (SGO) conducts a member survey that provides details on member demographics, practice characteristics, activities, and revenue. Between 8/15-9/30/19 SGO members received a direct link to the survey. Gender was self-identified. Differences in responses were evaluated by gender. **Results:** Of 1425 surveys delivered, 690 were completed (48% response rate). 312 (45%) identified as male; 367 (53%) as female; 1 nonbinary; 1 other; 7 no response. Male GOs were more likely white (75 vs 68%, p=0.048), married (91 vs 81%, p<0.001), heterosexual (94 vs 90%, p=0.045), and hold an academic rank of professor (23 vs 12%, p<0.001). Practice setting and number of partners were similar. Chemotherapy prescribing was more common for females (82 vs 73%, p=0.004), but other clinical activities were similar (Table). Female GOs had lower clinical volumes than males for cervical, ovarian, vaginal/vulvar cancer and benign gynecologic procedures. Females reported fewer medical assistants and transcriptionists supporting their clinical activities. Overall and practice support was higher for male GOs although hospital support was similar for both genders. Female GOs reported more time spent on research (26 vs 19%, p=0.005), but the same research support. **Conclusions:** Clinical activities, specifically chemotherapy prescribing, and support differ for male and female GOs and may explain gender inequities. Clinical support should be equalized to maximize workplace productivity regardless of gender. Coordination of support between the practice and hospital and standard compensation for chemotherapy prescribing could decrease the large gender wage gap in this specialty. Research Sponsor: None.

	Male (n=312)	Female (n=367)	P-value
Clinical Activities			
Chemo Prescribing	73%	82%	**0.004**
2+ hospitals	37%	39%	0.639
Intraop consults	75%	77%	0.363
Medical admissions	75%	77%	0.568
OB coverage	61%	64%	0.450
ED coverage	67%	74%	0.075
Calls/month	9.0	10.2	0.356
% FTE time			
Clinical	63	63	1.000
Research	19	26	**0.005**
Admin	15	13	0.981
Teaching	10	9	0.183
Case Volumes/year			
Cervix	20.8	13.4	**0.005**
Corpus	74	65	0.075
GTD	3.1	2.7	0.575
Ovary	34.6	26	**0.008**
VaginaVulva	11.5	8	**0.001**
Benign Cases/month	26.1	13.5	**0.034**
FTE support			
APP	1.9	1.9	0.897
Surgical Assist	0.8	0.5	0.145
Nurse	4.2	3.3	0.069
Medical Assistant	2.9	1.9	**0.005**
Receptionist	4.2	3.4	0.145
Transcriptionist	0.4	0.2	**0.016**
Billing	1.2	1	0.300
Pharmacist	1.6	1.0	0.096
Social Work	1.4	1.2	0.160
Genetic Counselor	1.4	1.4	0.788
Research Staff	3.6	2.7	0.210
Administrator	1.2	1.0	0.280
Staff (Practice)	8.6	5.8	**0.038**
Staff (Hospital)	11.9	10.1	0.144
Total Staff	**19.3**	**14.8**	**0.010**

11012 **Poster Discussion Session**

The positive impact of mentoring on burnout: Organizational research and best practice interventions for cancer hospital employees. *First Author: Katelyn Cavanaugh, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: While burnout is not a new concept, combating it is becoming an increasingly important focus for organizations across all industries. Recently, the World Health Organization recognized burnout as an "occupational phenomenon" (WHO, 2019), and it was included in the 11th Revision of the International Classification of Diseases, where it is defined as "a syndrome conceptualized as resulting from chronic workplace stress that has not been successfully managed." The University of Texas MD Anderson Cancer Center addresses burnout at the institutional level in support of all 22,000 workforce members. One avenue of this work focuses on mentoring. Mentorship, both formal and informal, has demonstrated positive effects to include empirical investigations that demonstrate its benefit in reducing risk of burnout in multiple settings for a variety of audiences (Qian et al., 2014; Thomas & Lankau, 2009; van Emmerik, 2004; Varghese at al., 2020). Although mentoring is not as flashy as other interventions, what the last year has shown is that people need human connection now more than ever. **Methods:** In order to investigate the relationship between burnout and mentoring in our organization, we analyzed responses to our biennial voluntary employee survey, in which all employees were asked whether they are involved in a mentoring relationship and completed a single-item burnout scale. **Results:** We analyzed the survey data using a chi-square test and found that employees participating in mentoring relationships were less likely to report burnout than employees who are not participating in a mentoring relationship, $\chi 2$ (1, 14,486) = 17.431, $p < 0.005$. The same pattern held for all types of employees; faculty, classified staff, leaders, clinical employees, and non-clinical employees, indicating that the experience of mentorship may be universal regardless of role, rank, and type of work. We suspect that the benefits of mentoring are bi-directional for mentors and mentees, though this should be investigated directly. **Conclusions:** Both formal and informal types of mentoring programs exist within MD Anderson to support retention, professional fulfillment, and reduce burnout. All employees have access to a centralized online mentoring platform to find a mentor. Formal mentoring support is also provided through various programs developed for specific professional cohorts, including physicians, advanced practice providers, and registered nurses. In addition, informal mentoring support is offered in the form of employee volunteer wellness champions. Together, these formal and informal mentoring programs have positively influenced burnout across the organization. Research Sponsor: None.

Frequencies and percentages for burnout and mentoring.

	No Burnout	Burnout
Mentoring n	3,783	1,237
Mentoring %	75.40%	24.60%
No Mentoring n	6,828	2,638
No mentoring %	72.10%	27.90%
Total n	10,611	3,875
Total %	73.30%	26.70%

11013 **Poster Discussion Session**

Perpetrators of workplace bullying and gender discriminations experienced by women gynecologic oncologists. *First Author: Linda Hong, Loma Linda University School of Medicine, Loma Linda, CA*

Background: A high prevalence of gender discrimination and harassment has been described among gynecologic oncologists (GOs). This study examined the work environment for women GOs and delineated the perpetrators of negative behaviors. **Methods:** An internet-based, IRB exempt survey of members of a 472-member Facebook group "Women of Gynecologic Oncology (WGO)" was conducted. Using REDcap survey platform, members provided demographics, practice infrastructure, personal experience with workplace bullying, gender discrimination, microaggressions, and outcomes. Demographic, practice and work environments and perpetrators of negative behaviors were summarized using descriptive statistics. **Results:** Between 7/20 and 8/19/2020, 250 (53%) of active WGO members participated in this survey. Most respondents were younger than 50 years old (93.6%); white (82.2%) and non-Hispanic (94.3%). A majority were married (84.7%) with children (75.2%). Practice environments included academic (152, 61.0%), private practice (31, 12.4%), and hospital employed (57, 22.9%). 89.9% supervised trainees. 130 (52.0%) respondents reported bullying, 140 (56.0%) gender discrimination, and 83% having experienced gender-based microaggressions. Age, race, ethnicity, practice setting, division director or chair gender or department reporting structure were not significantly associated with these experiences. Perpetrators of bullying, gender discrimination, and microaggressions were widely distributed (Table). Of those reporting bullying, 61 (46.6%) reported a male perpetrator, 25 (19.1%) female and 45 (34.4%) an equal gender distribution; of those reporting discrimination 105 (74.5%) reported a male perpetrator, 9 (6.4%) female and 27 (19.1%) an equal gender distribution. 32.9% of survey respondents acknowledged having been written up for speaking up in a way that would have been tolerated from a male colleague. 18.3% of respondents have changed jobs because of bullying; 13.5% because of discrimination. **Conclusions:** Women GOs report high rates of workplace bullying, gender discrimination, and microaggressions regardless of practice setting that often impact their careers. Perpetrators of these behaviors are multiple and varied. Proactive and deliberate interventions to improve the work environments for women GOs are urgently needed. Research Sponsor: None.

Total n = 250	Colleague with authority	Colleague at same level	Hospital administrator	Hospital staff	Patient	Trainee
Bullying (n = 130)	109 (83.8)	33 (25.4)	23 (17.7)	52 (40.0)	32 (24.6)	21 (16.2)
Gender discrimination (n = 140)	108 (77.1)	49 (35.0)	23 (16.4)	58 (41.4)	61 (43.6)	13 (9.3)
Microaggressions						
Told to smile more (n = 77)	46 (59.7)	12 (15.6)	14 (18.2)	14 (18.2)	36 (46.8)	3 (3.9)
Given clothing suggestions (n = 49)	35 (72.9)	4 (8.3)	13 (27.1)	6 (12.5)	5 (10.4)	5 (10.4)
Told to act more female (n = 40)	29 (72.5)	6 (15)	6 (15)	9 (22.5)	6 (15)	4 (10)
All data reported in n (%)						

11014 **Poster Discussion Session**

Impact of COVID-19 on work-related fatigue and satisfaction among oncology providers in Latin America: An analysis of the HOLA COVID-19 study. *First Author: Ana I. Velazquez Manana, University of California, San Francisco Medical Center, San Francisco, CA*

Background: The well-being of oncology providers (OP) is in jeopardy with increasing workload, limited resources, and personal challenges that result from the COVID-19 pandemic. We aim to evaluate the impact of COVID-19 on work-related (WR) satisfaction and fatigue among OP in Latin America. **Methods:** We conducted an international cross-sectional online survey of OP practicing in Latin America. The survey was administered in English, Spanish, and Portuguese. Data was analyzed using descriptive statistics and Chi-square tests. **Results:** In August 2020, 704 OP from 20 Latin American countries completed the survey (77% of 913 who started the survey). Table outlines baseline characteristics. Higher frequency of WR fatigue (67% vs. 58%, p=0.010) and exhaustion (81% vs. 70%, p=0.001) were reported by OP who cared for patients with COVID-19, compared to OP who cared for patients without COVID-19. Providers that observed delays in referrals to radiation (p=0.002) and surgery (p=0.04) reported WR fatigue at higher rates than their counterparts. Higher exhaustion (p=0.016) and dissatisfaction (p=0.046) were reported by OP who lacked access to supportive services, as social work. A significantly higher proportion of women reported WR fatigue (72% vs. 56%, p=0.003) and exhaustion (86% vs. 68%, p=0.001), when compared to men. Women were more likely than men to endorse higher current levels of fatigue when compared to pre-COVID-19 (61% vs. 46%, p=0.0001). To reduce stress, women were more likely than men to cut the time spent watching the news (p=0.002). Both genders declined research collaborations and speaking opportunities. **Conclusions:** Fatigue and dissatisfaction with work-life were prevalent among OP in Latin America. Higher rates of WR fatigue were seen in women, OP caring for patients with COVID-19, and OP with patients who experienced cancer care delays. Our data imply that OP may be a prime target for psychosocial support, particularly as current challenges will continue for the foreseen future. Baseline characteristics (N=704). Research Sponsor: None.

	N (%)
Gender	
Women	297 (42)
Specialty	
Medical Oncology/Hematology-Oncology	321 (46)
Hematology	101 (14)
Surgical Oncology	175 (25)
Radiation Oncology	81 (12)
Gynecologic Oncology	23 (3)
Practice setting	
University/Academic Hospital	278 (39)
Private Practice	404 (57)
Providers caring for patients with COVID-19	396 (57)
Provider satisfaction during COVID-19	
Unsatisfied with work-life	159 (23)
Unsatisfied with family life	148 (21)
Work-related fatigue	
"I've felt exhausted by my work"	535 (76)
"I feel fatigued when I wake up in the morning and have to start another day at work"	442 (63)
"I feel more fatigued and exhausted than pre-COVID-19"	369 (53)
Measures to reduce stress and fatigue	
Watched less news	359 (51)
Decreased clinical load	177 (25)
Declined research collaborations	69 (10)
Declined speaking opportunities	115 (16)

11015 **Poster Session**

A pilot study to prevent burnout in junior oncology doctors during the COVID-19 pandemic in a tertiary U.K. center. *First Author: Alfred Chung Pui So, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom*

Background: Burnout is a syndrome defined by emotional exhaustion, depersonalisation and loss of personal accomplishment. It is a growing concern amongst doctors, particularly in oncology, who face the added stress of delivering life changing results to patients and managing end of life care. This has potential for negatively impacting mental health, job satisfaction and ultimately patient care. This has been compounded by the COVID-19 pandemic and the uncertainty around complex oncological treatment decisions, longer working hours, redeployment, and constant changes to working patterns to meet the evolving clinical need. In response to this, a novel wellbeing intervention was designed by the educational lead consultant and psychologists to prevent burnout during the pandemic. **Methods:** Junior doctors working at a single UK cancer centre during the COVID-19 pandemic were invited to attend weekly 30 minute wellbeing sessions facilitated by a clinical psychologist throughout their oncology placement (average 4-6 months). Sessions had an average attendance of 3-6 doctors and began with a 5 minute breathing and relaxation exercise followed by a mixture of clinical debriefing, reflective practice, and mindfulness strategies. Trainees were invited to have individual sessions if required. Surveys based on the 14 point Warwick Edinburgh Well Being Scale (WEMWBS) were conducted at the start and end of placement. Additional qualitative feedback was collated. **Results:** Throughout a 6 month period, 10 doctors participated in this study. Baseline WEMWBS scores revealed average mental wellbeing (n = 8), high mental wellbeing (n = 1) and probable depression (n = 1). Median baseline WEMWBS score was 52(41-62). Median number of sessions attended was 11(3-14). Post intervention, there was no significant deterioration in baseline WEMWBS score (mean change +2.2; p= 0.34). When doctors were asked about their optimism for the future, there was a significant increase by +0.4 points (p= 0.037). With respect to participant feedback, 100% were either 'satisfied' (n = 1) or 'very satisfied' (n = 9) with the group facilitation and 100% found the group sessions either 'helpful' (n = 7) or 'very helpful' (n = 3). Trainee feedback described the benefits of reflecting in a structured and safe environment, breathing exercises, and learning mindfulness strategies. **Conclusions:** Burnout is a serious concern amongst junior oncologists and is rising as a result of COVID-19. We present a novel intervention that promoted psychological flexibility and importantly maintained mental wellbeing throughout the pandemic. Further studies are planned to develop evidence based interventions to tackle this important issue. Research Sponsor: None.

11016 **Poster Session**

Prevalence and risk factors of burnout among female oncology professionals from the Middle East and North Africa (MENA). *First Author: Atlal Abusanad, Faculty of Medicine, Department of Medical Oncology, King Abdulaziz University, Jeddah, Saudi Arabia*

Background: Burnout (BO) is a recognized challenge among oncology workforce. It affects both genders with a higher frequency among women. This study examined the factors contributing to the development of burnout among women in oncology from the Middle East and North Africa (MENA). **Methods:** An online cross-sectional survey was distributed to oncology professionals from different countries in the MENA region. The validated Maslach Burnout Inventory (MBI) of emotional exhaustion (EE), Depersonalization (DE), and Personal Achievement (PA) plus questions about demography/work-related factors and attitudes toward oncology were included. Data were analyzed to measure BO prevalence and related factors. **Results:** Between February 10 and March 15, 2020, 545 responses were submitted by female professionals. The responses pre-dated the COVID-19 pandemic emergence in the region. BO prevalence was 71% among female professionals. Women aged $<$ 44 years represented 85% of the cohort. Sixty-two percent were married, 52% with children and one-third practiced a hobby. Two-thirds worked in medical oncology, worked for $<$ 10 years and 35% worked in academia. The majority (73%) spent $>$ 25% on administrative work daily. Nearly half of the respondents (49%) expressed a recurring thought of quitting oncology and 70% had no burnout support or education. Inability to deliver optimal care was reported as distressing for career development in 82%. Factors significantly influencing the BO risk are listed in Table. Marital status, having children, academia and years in practice did not impact the risk of BO among female oncologists form MENA. **Conclusions:** High BO prevalence was reported among female oncology professionals from MENA. The majority of women oncology workforce were young and early- to mid-career in this cohort. Younger age, practicing in North African countries, high administrative load and the recurring thought of quitting were associated with increased risk of burnout. Whereas, practicing a hobby and enjoying oncology communication decreased the BO risk. Burnout support and education specifically for women in oncology is needed. Research Sponsor: None.

Multivariate logistic regression analysis for factors affecting the risk of developing burnout in female oncology professionals.

Factors	Ad-OR (CI 95%)	P Value
Age < 44 years	2.26 (1.22 - 4.19)	0.010
North Africa	2.43 (1.35 - 4.38)	0.003
Admin work > 50%	1.75 (1.07 - 2.86)	0.026
Always thinking about quitting	11.91 (3.37 - 42.05)	<0.001
Sometimes thinking about quitting	5.61 (3.28 - 9.62)	<0.001
Practicing hobby	0.60 (0.02 - 1.52)	0.042
Enjoying inter-personal and professional communication of oncology	0.42 (0.26 - 0.68)	<0.001

11017 **Poster Session**

Self-reported gender bias encountered by hematology and oncology fellows. *First Author: Nino Balanchivadze, Henry Ford Hospital, Detroit, MI*

Background: Gender-related bias and discrimination have been well documented, particularly in male-dominated fields such as surgery, and have been associated with increased risk for physician burnout. In hematology/medical oncology, women make up between 41% and 49% of first-year fellows, but represent less than 40% of the academic hematology/oncology workforce. We aimed to study current hematology/oncology fellow perceptions about gender-related bias and challenges to inform interventions that promote gender equity. **Methods:** An anonymous 18-question survey was sent online to 165 adult and 75 pediatric hematology/oncology fellowship programs. Two group comparisons to analyze survey responses between genders were performed using chi-square, or Fisher's test (if cell counts $<$ 5), and Wilcoxon Rank Sum tests. **Results:** A total of 133 fellows completed the survey, where 88 self-identified as female (66%) and 45 (33.83%) self-identified as male. Most participants were White (52%), followed by Asian (29%), Hispanic (9%), Middle Eastern (5%), and Black (3%). Most respondents (n = 100; 75%) were age 31-40 years. More than half (54%) were enrolled in adult hematology/oncology fellowships, 24% were enrolled in pediatric hematology/oncology fellowship programs, and 88% practiced in University-based programs. Compared to male respondents, female fellows were more likely to report experiencing gender bias ($p < 0.001$), felt more insecure in their job ($p = 0.043$), felt second-guessed by colleagues ($p < 0.001$), and were more likely to believe that they had been unfairly denied a promotion ($p = 0.003$). In addition, female respondents were more likely to report having been mistaken as a non-physician ($p < 0.001$) and were more concerned about perceived gender bias. Female respondents reporting gender bias used techniques such as wearing a white coat ($p < 0.0001$), emphasizing a professional look ($p < 0.0001$), and ensuring "Doctor" ($p < 0.0001$) was clearly written on their badge more often than male fellows. When asked about how to combat gender-related challenges, female fellows more often recommended formal lectures and instruction about gender bias for attending physicians and non-physician staff. Suggestions about mitigating gender-related bias included encouraging same-sex mentors and open discussions about existing bias. **Conclusions:** Female hematology/oncology fellows reported facing gender-related bias and challenges in daily practice and often used specific techniques to face these challenges. Transparency and directed education about gender bias may help mitigate these challenges to create better working environments for fellows. Research Sponsor: None.

11018 **Poster Session**

Moral distress, organizational climate, and the risk of burnout among oncology physician assistants. *First Author: Eric Daniel Tetzlaff, Fox Chase Cancer Center, Philadelphia, PA*

Background: Moral Distress (MD) is the result of barriers or constraints that prevent providers from carrying out what they believe to be ethically appropriate care and has been associated with burnout. Advances have been made in our understanding of burnout in the oncology (Onc) workforce but our understanding of MD remains limited. This study was initiated to explore associations between moral distress, burnout, and the organizational climate (OC) for Onc Physician Assistants (PAs). **Methods:** A national survey of onc PAs was conducted in 2020. MD and Burnout were assessed with the Maslach Burnout Inventory and the Measure of MD – Healthcare Professionals (MMD-HP). To assess OC, the Nurse Practitioner Primary Care OC Questionnaire (NP-PCOCQ) was revised for Onc PAs and assessed professional visibility (PV), administrative relations (AR), physician relations (PR), and professional autonomy and support (PAS). A robust Poisson regression model was used to estimate risk ratios (RR) for burnout associated with MD and OC variables. **Results:** Respondents who completed the survey included 146 Onc PAs that were mostly female (90%), White/Caucasian (84%), married/partnered (78%), and in medical Onc (73%). Mean MMD-HP score was 71.5 and burnout was reported by 39.7% of PAs. MMD-HP scores did not differ based on specialty, practice setting or practice type. PCOCQ subscale scores were lower for PAs with burnout vs. without burnout ($p=0.003$ to $p < 0.001$). Increasing levels of MD were associated with increased levels of emotional exhaustion ($p<0.001$), depersonalization ($p<0.001$) and a higher overall rate of burnout. For Low, Medium and High MMD, burnout rates were 10%, 44% and 66% respectively ($p<0.001$). Risk of burnout was associated with increasing levels of MD, which remained when adjusted for the PCOCQ subscales. An interaction model with the PCOCQ subscales and the association between burnout and MD was not significant. **Conclusions:** Higher levels of MD and unfavorable organizational climate are associated with Onc PA burnout. The relationship between MD and burnout does not appear to be moderated by organizational climate. Additional research is needed to identify potential moderators of the MD/Burnout relationship. Risk Ratio estimate for Burnout. Research Sponsor: Association of Physician Assistants in Oncology, Other Government Agency.

Covariate adjustment for Organizational Climate Subscales*	Medium vs Low Moral Distress		High vs Low Moral Distress		
	RR estimate	95% CI	RR estimate	95% CI	p-value**
Moral Distress (MD) only	4.34	1.78-10.63	6.60	2.81-15.52	<0.001
MD + Professional Visibility	4.18	1.76-9.92	5.98	2.57-13.93	<0.001
MD + Administrative Relations	3.73	1.52-9.17	5.38	2.24-12.95	<0.001
MD + Physician Relations	4.42	1.87-10.45	6.28	2.72-14.54	<0.001
MD + Professional autonomy and support	4.03	1.69-9.59	5.91	2.54-13.72	<0.001

* Each subscale was included in a separate model ** p-value for MMD-HP variable (tertiles) from each model.

11019 **Poster Session**

Impact of COVID-19 pandemic on well-being and work-related burnout among healthcare workers at an academic center. *First Author: Richa Dawar, Jackson Memor Hosp, Miami, FL*

11019**Background:** COVID-19 pandemic has not only caused an unprecedented distress in the community, but also significant physical and psychological exhaustion amongst healthcare workers (HCWs), that could lead to serious effects on our healthcare system. This study was conducted to assess burnout among oncologists and other healthcare professionals at a large academic center. **Methods:** An electronic 10-minute questionnaire was sent to actively employed physicians, APRNs and PAs at the University of Miami. Survey items evaluated various personal and professional characteristics including COVID related stress. Burnout was examined with Maslach Burnout Inventory (MBI), which evaluated severity across two domains: emotional exhaustion and depersonalization. The logistic regression model was used to estimate association between study variables and high burnout levels. Odds ratio (ORs) and corresponding 95% confidence interval (CI) were obtained. Continuous variables were tested using two-sample t-test by high burnout status. **Results:** The survey was sent to 739 HCWs, out of which 182 (24.6%) completed the entire survey; 63.7% were physicians, 8.6% fellows, and 27.4% APRN or PA. The pandemic led to rescheduling of professional activities (22.2%), increased workload (59.5%), job insecurity (28.6%), and decreased leadership opportunities (32.2%). 62.3% of respondents reported decreased exercise; 44.8% reported new sleep disorder; 56.1% reported increased home responsibilities; childcare arrangements were affected in 60.6%; 61.4% struggled to maintain work-life balance. 70 of 182 respondents were broadly from the fields of Oncology and Palliative Care. 9 out of these 70 respondents reported high depersonalization, 27 reported high emotional exhaustion, and 33 reported overall high burnout symptoms on either emotional exhaustion or depersonalization scales. Amongst physicians holding positions from PGY4 through licensed attendings with less than 5 years' experience, 62.5% (95%CI=35.4-84.8) showed high burnout rate (10 of 16), which was not statistically different from older physicians (11 of 27=40.7% (95%CI=22.4-61.2)). No difference in burnout was seen for other study variables including gender, marital status, and race/ethnicity. **Conclusions:** COVID-19 pandemic has incited not only an unmatched level of practice changes, but also extraordinary psycho-social uncertainty, leading to a considerable impact on HCWs' well-being. Long working hours, lack of sleep, fear of losing job, transition to tele-medicine, risk of getting infection and putting their family at risk, lack of childcare, pressure of home schooling-all seem to have caused an increased physical and psychological pressure among HCWs and warrants an examination of potential coping mechanisms. This study sets the stage for more elaborate research to illustrate and guide the development of wellness programs imperative to the well-being of HCWs. Research Sponsor: None.

11020 **Poster Session**

Gender disparities in National Institute of Health funding for hematologic malignancies, hematopoietic stem cell transplantation, and cellular therapeutics. *First Author: Raheel Sufian Siddiqui, Division of Hematologic Malignancies and Cellular Therapeutics, University of Kansas Medical Center, Kansas City, KS*

Background: Gender inequality in research funding has been studied extensively; however, the literature lacks evidence in Hematology. We investigated trends in National Institutes of Health (NIH) funding for hematologic malignancies (HM), hematopoietic stem cell transplantation (HSCT), and cellular therapeutics (CT). **Methods:** The data on Hematology funding was retrieved from NIH Research Portfolio Online Reporting Tools (RePORT) Categorical Spending for fiscal years 2018 and 2019. A total of 6351 entries were reported. Only grants (n=1834) that were related to HM, HSCT, and CT were included. After excluding non-relevant, 975 principal investigators (PIs) were included in the analysis. Additional data regarding PIs was ascertained from the Scopus database, LinkedIn, Doximity, and departmental websites, including the number of publications, number of years of active research, H-index, highest degree, gender, and institution. Data were analyzed using SPSS version 21. Bivariate analyses, using chi-square and t-test, and linear regression analyses were performed. **Results:** In 2018 and 2019, 1834 grants totaling $799.4 million were awarded by the NIH for malignant hematology research (men 1301, 71% vs women 533, 29%). Of 975 PIs, 680 (70%) were men and 295 (30%) were women. Table highlights gender disparities in NIH funding and associated factors. Most of the grant recipients were Ph.D. or M.D./Ph.D. About 70% of total funding was awarded to male PIs. There were no gender differences in the mean number of grants and mean grant amount. Women had significantly lower years of active research and academic productivity. **Conclusions:** Although the gender gap in academic hematology has decreased in recent years, the latest trend suggests significant gender inequality in NIH funding for malignant hematology, transplantation, and cellular therapy. Research Sponsor: None.

Demographic characteristics of all NIH Grant Recipients in Malignant Hematology (HM, HSCT, CT), 2018-2019.

PIs	Total (n=975)	Men (n=680)	Women (n=295)	P value
Total grants awarded, n (%)	1834 (100)	1301 (71)	533 (29)	
Total amount, sum (range)	$799,386,695 (3,184-31,000,002)	$554,274,945 (3,184-10,427,034)	$245,111,750 (4,344-31,000,002)	
Number of grants per PI, mean (SD)	1.9 (1.4)	1.9 (1.5)	1.8 (1.1)	0.265
Total grant amount, mean (SD)	$819,884 (1,420,226)	$815,110 (1,073,553)	$830,887 (2,005,088)	0.873
Publications, mean (SD)	139.7 (175.9)	159.5 (195.7)	94.0 (105.4)	<0.001
Years of active research, mean (SD)	24.5 (12.1)	26.0 (12.4)	21.1 (10.8)	<0.001
H-index, mean (SD)	40.0 (32.7)	44.0 (34.6)	30.9 (25.4)	<0.001
Degree, n (%)				
MD	296 (30)	213 (31)	83 (28)	0.005
MD/PhD	221 (23)	167 (25)	54 (18)	
PhD	440 (45)	284 (42)	156 (53)	
Graduate student/others	18 (2)	16 (2)	2 (1)	

11021 **Poster Session**

Corresponding about death: Analyzing letters from patients with cancer to medical students. *First Author: Tianyi Zhang, University of California, San Francisco, San Francisco, CA*

Background: Clinicians frequently discuss death and dying with patients who have cancer. However, the doctor-patient hierarchy and the unfamiliar clinical environment may prevent these patients from discussing death and dying authentically. Patients may feel more comfortable expressing themselves when given the time and space to write at home. Firefly, an award-winning program at UCSF, facilitates written correspondence between patients with cancer and medical students over the course of one year. Firefly's archive contains thousands of patient letters and constitutes a unique resource for analyzing authentic patient expression outside of the clinical context. The aim of the current study is to improve curricula pertaining to severe illness and end-of-life by providing educators with an analysis of authentic patient perspectives about death and dying expressed in these letters. **Methods:** We (two medical students, an expressive artist, and an oncologist) read all Firefly letters written by patients between 2014 and 2019 and identified 12 patients whose letters meaningfully discussed death or dying. We performed a thematic analysis of these letters using the Buckman three-stage model of dying as a reference. **Results:** Four themes emerged: turmoil; grief; making peace; and past, present and future. The first three themes aligned with the Buckman stages. The fourth theme—past, present and future—spanned the three stages and also elaborated the Buckman model by describing multiple paths that patients may take after passing through these stages. **Conclusions:** The authentic ways in which patients with cancer discussed death and dying in their letters provided deep insight into their coping process. The Buckman model appears useful for framing death and dying from the patient perspective but may not fully reflect modern oncologic care in which many patients live for years beyond a severe or terminal diagnosis. Educators can use the identified themes to shape medical school curricula pertaining to severe illness and end-of-life care. Research Sponsor: None.

11022 **Poster Session**

The clinician educator career in oncology. *First Author: Meredith Elana Giuliani, Department of Radiation Oncology, University of Toronto; Radiation Medicine Program, Princess Margaret Cancer Center, Toronto, ON, Canada*

Background: There has been progress in both the definition of the work of a clinician educator (CE) and the skillset required. The CE career pathway has not been studied in oncology. Our aim is to study the current state of oncologists' identification as a CE and their perceptions of the barriers and enablers for a CE career. **Methods:** A 27-item cross-sectional survey was completed by ASCO program directors (PDs) and associate/assistant PDs (APDs). The survey asked about their current career and perceptions about CE careers including barriers/enablers. Prior to distribution, the survey was reviewed by experts in oncology education and approved by the ASCO Education Council. Frequency statistics are presented. **Results:** Eighty-eight of 297 PDs/APDs responded (30%). 70 (80%) perceived CE as a viable career track, 48 (55%) had a CE track available to faculty at their institution and 72 (82%) considered themselves as a CE. Most PDs/APDs (59; 67%) reported no formal medical education training for their trainees and the majority (67; 76%) did not have a CE track for their fellows. While medical education responsibilities are perceived to be common amongst graduates (39% reporting >50% of graduates), 59 (67%) of PDs/APDs reported <10% of their trainees pursue medical education as a research focus. Compared to clinical, laboratory or discovery research, 71 (81%) of PDs/APDs felt their fellows were less or significantly less prepared for a career in education research. Table highlights the perceived barriers/enablers to a CE career. **Conclusions:** Many PDs/APDs perceive themselves as clinician educators. However, little to no formal education training currently exists to identify and nurture trainees into careers in education. Identification of training milestones in education and establishing guidelines for academic promotion for CEs in oncology are needed. Research Sponsor: None.

Top Perceived Barriers/Enablers to a Clinician Educator Career in Oncology.

Barriers

1. **Unclear career path and/ or lack of opportunity for future academic promotions**
2. **Lack of jobs or career options focused on education**
3. **Competing expectations to pursue academic career in clinical, translational, or lab-based research**
4. **Perceived difficulty in obtaining funding for medical education research**
5. **Lower perceived importance relative to clinical or basic science research**
6. **Perceived decreased prestige of an education focused career**
7. **Insufficient mentorship by senior faculty**

Enablers

1. **Develop a toolkit for training program directors**
2. **Provide guidance on a clinician educator academic career pathway**
3. **Provide more educational sessions at ASCO on medical education topics**
4. **Develop a network of clinician educators to promote collaboration and community of practice**
5. **Sponsor mentored postdoctoral fellowships in medical education**
6. **Provide mentorship opportunities (virtually or in-person) to existing clinician educators**
7. **Provide special sessions for fellows on careers in medical education**

11023 **Poster Session**

Faculty development: What do we know about barriers, enablers, and satisfaction levels among African oncology faculty? *First Author: Miriam Claire Mutebi, Department of Surgery, Aga Khan University Hospital, Nairobi, Kenya*

Background: Faculty development (FD) programs and initiatives have been shown to improve teaching, learning, and overall satisfaction levels of academic faculty. However, these benefits are not fully realized in resource constrained settings like those found in some Sub-Saharan African academic institutions, that often face many FD challenges. Improving FD activities in the region may enhance the capacity of oncology faculty to address these challenges. We sought to examine African oncology faculty's satisfaction and the perceived enablers and barriers with current FD opportunities. **Methods:** We randomly surveyed oncology faculty ($n = 21$) through the African Organization for Research and Training in Cancer (AORTIC) listserv and conducted semi-structured interviews with nine ($n = 9$) faculty involved in African oncology training programs to ascertain their perspectives on faculty development activities including curriculum development, teaching, and learning. All survey respondents and interview participants are current members of the AORTIC. Descriptive and inferential statistical techniques, and thematic analysis were used to analyze the survey and interview data respectively. **Results:** Interim survey results revealed that 64% of academic oncology faculty believe that there are barriers to their FD at their current academic institutions. Barriers cited for FD from the interviews include the competitive nature of FD courses and programs, limited online learning opportunities, poor internet access, time constraints, language barriers, and high costs associated with FD activities. A significant minority of the survey respondents (43%) were dissatisfied with their overall FD. Access to curriculum development opportunities ($\chi^2 = 10.97$, $p = 0.001$) and longer duration of practice ($\chi^2 = 7.9$, $p = 0.019$) were significantly associated with an increased overall satisfaction with FD of oncology faculty. Themes emerging from the interviews also revealed that participants believe that addressing issues relating to access to local institutional support and opportunities including funding, reduced fees for individuals from low- and middle-income countries, getting time off work from local institution, and availability of online FD education will enable them to increase their participation in FD activities. **Conclusions:** A considerable number of African oncologists face many FD challenges and are therefore dissatisfied with the current state of their FD. Incorporating the recommendations offered by participants into faculty development planning activities may improve faculty satisfaction levels, remove barriers, and improve outcomes for learners. Also, the finding that access to curriculum development opportunities leads to increased levels of satisfaction with FD could guide FD for faculty in African oncology training programs. Research Sponsor: Royal College of Physicians and Surgeons of Canada(RCPSC).

11024 **Poster Session**

Design, implementation, and assessment of an online-based oncology education program for medical students: An ASCO Oncology Student Interest Group initiative. *First Author: Duaa Kanan, Bahçeşehir University School of Medicine, Istanbul, Turkey*

Background: Undergraduate medical education in oncology is often fragmented and non-standardized among medical schools (BMC Med Educ 17:100, 2017). Oncology education initiatives are thus critically needed to increase cancer awareness and improve medical students' understanding of the principles and multidisciplinary approach of oncology. We designed and implemented an online education program with the aim of providing medical students with an early exposure to the field of oncology. Our program was adapted from the *Australian Ideal Oncology Curriculum for Medical Schools* and included six sessions covering the basics of cancer biology, prevention and screening, diagnosis and patient management, principles of treatment modalities, principles of surgical oncology, as well as counselling and communications skills. **Methods:** Medical students at our institution were invited to participate. We also invited medical students from other faculties via the support of student groups namely the nation's medical student union and our ASCO Oncology Student Interest Group (OSIG). Invitations were sent by email and/or via social media along with a brochure outlining the conference's program and instructions to use the Zoom platform. Students were asked to voluntarily fill online pre- and post-conference anonymous surveys. Students self-assessed their competency, personal attributes, future career aspirations, and provided an evaluation of the program. A five-point Likert scale was used for most questions, in which 1 indicated strong disagreement and 5 indicated strong agreement with the statement. **Results:** Nearly 300 students from over 50 medical schools in Turkey attended the live program. Only students (n = 228) who completed both the pre- and post-conference surveys were included in our study. ASCO OSIG members made up 24.1% (n = 55) of the students. Among the participants, 73.7% (n = 168) were preclinical students (years 1-3) and 26.3% (n = 60) were clinical students (years 4-6). Students' overall self-reported rating of their knowledge significantly improved in each of the six sessions, with the greatest pre-post difference observed for diagnosis and patient management (2.51 ± 1 vs 3.87 ± 0.81) followed by principles of treatment modalities (2.54 ± 0.96 vs 3.79 ± 0.88), $P < 0.001$. Most students believed the program was beneficial in improving their current understanding of oncology with a mean of 4.43 ± 0.76. Most students (92.5%) were "likely" or "very likely" to recommend the program to their colleagues. **Conclusions:** Students' evaluation of the online oncology program demonstrated significant benefit and knowledge improvement. Our successfully piloted teaching model of oncology for medical students can be adapted and implemented at medical schools globally. Further development and continuation of our educational initiative is undergoing. Research Sponsor: None.

11025 **Poster Session**

Improving feedback for hematologists and oncologists in training. *First Author: Ilana Schlam, Medstar Washington Cancer Institute, Washington, DC*

Background: Feedback is an integral part of the learning process, allowing learners to remain on course in reaching competence in clinical, research, and interpersonal skills. However, the impact of teaching feedback during hematology-oncology training has not been studied. We aimed to identify barriers in delivering and receiving high-quality feedback in our fellowship program and to create a curriculum aimed at teaching fellows and faculty how to engage in more effective feedback conversations. **Methods:** This pilot study aimed at determining and addressing perceived barriers to high-quality feedback in the hematology-oncology fellowship program. A pre-intervention questionnaire, consisting of Likert scale and open-ended questions, was administered to identify barriers to giving feedback and to assess satisfaction with the quality of feedback received in our fellowship program. The results of the baseline questionnaire were utilized to build a virtual interactive three-session workshop provided by the ASCO Quality Training Program in which the importance of feedback and methods of providing effective feedback were taught. Topics included feedback set-up, low-inference observation, and a structured approach to reinforcing and modifying feedback. One month after the intervention the participants completed a follow up questionnaire. This project was developed through the ASH Medical Educators Institute. **Results:** Each questionnaire was completed by 11 participants. The two main barriers to high-quality feedback identified were the discomfort with both giving and receiving feedback, and the lack of protected time. At baseline only 54% of the participants reported they were comfortable giving feedback, increasing to 81% post- intervention. Pre-intervention, 81% of participants reported they did not have protected time for feedback, decreasing to 64% after the intervention and institution of weekly protected time for feedback. Half of the participants reported that the feedback was not actionable in the initial questionnaire, decreasing to 10% post-intervention. Overall, fellows reported that their feedback was mostly focused on notes, followed by presentations and interpersonal skills. Faculty reported that most of the feedback they received was about time management and patient care. **Conclusions:** This pilot study helped address a major barrier to improvement and growth within our training program and confirmed that feedback skills must be taught and practiced. A 6-hour virtual workshop showed tangible results in the satisfaction with and quality of feedback given to both fellows and faculty. Our findings are salient as we completed the intervention during the COVID pandemic. Limitations of the study include its single-institutional design and sample size. A major challenge anticipated is sustainability, which will be addressed by maintaining periodic lectures and assigning protected time for feedback. Research Sponsor: None.

11026 **Poster Session**

Impact of advanced clinical and translational research educational programs on oncology specialties and career development. *First Author: Aron Simkins, Division of Hematology & Oncology, George Washington University School of Medicine & Health Sciences, Washington, DC*

Background: The Clinical and Translational Science Award (CTSA) Program currently supports more than 50 leading medical research institutions in the U.S. with the aims of training, promoting and developing future translational science researchers, with particular emphasis on advanced Clinical and Translational Research (CTR) education. No prior studies have evaluated career development in oncologists who have completed CTR training. The objective of this study is to examine the impact of advanced CTR training on career development, return-on-investment and research productivity in Oncology specialties. **Methods:** With IRB approval, we conducted a survey study of U.S.-based Hematology/Oncology (H/O), Radiation Oncology (RO), and Surgical Oncology (SO) members of the American Society of Clinical Oncology who completed CTR training. Data was anonymized and collected through Research Electronic Data Capture (REDCap). Outcomes were compared using Chi-square test for frequency data. **Results:** We received 225 survey responses (62.1% H/O, 23.3% RO, 13.2% SO, 1.4% others). About 28.4% (n = 64) of the respondents had a PhD or Master's degree in CTR (Group A) compared to 71.6% (n = 161) with graduate certificates or non-degree granting courses in CTR (Group B). Specialty ratio was equally distributed between both groups. Overall, 79.7% vs 57.5%; $P < 0.001$ of respondents worked in academia, of which 55.2% had tenure track positions. Over 49 different CTSA Programs throughout the U.S. were represented. In terms of impact with new research projects, the ability to secure funding and opportunities for multidisciplinary collaboration, satisfaction with CTR training was higher among Group A compared with Group B ($P < 0.001$; $P < 0.01$; $P < 0.01$ respectively). In terms of research output, higher satisfaction was seen in Group A (67.2% vs 47.4%; $P < 0.01$), however total publications per year were not statistically significant ($P = 0.135$). Usefulness of a CTR degree on career advancement, a difference of 50.0% vs 19.1%; $P < 0.001$ was noted. Similarly, usefulness regarding new job opportunities and return-on-investment also favored Group A ($P < 0.001$). Overall satisfaction with training was significantly higher in Group A (73.4% vs 48.7%; $P = 0.004$). **Conclusions:** This study is the first to report satisfaction ratings for CTR training among oncology specialties. Although no significant difference was observed in terms of publication output, those with higher levels of advanced degrees were more satisfied with their CTR training, and viewed it as more impactful to career advancement and research productivity. The evidence presented is useful for informing career development for oncology residents and fellows offered CTR degrees during their training. Research Sponsor: None.

11027 **Poster Session**

The cognitive load of inpatient consults: A convergent parallel mixed methods study using the consult cognitive load instrument. *First Author: Sam Brondfield, University of California, San Francisco, CA*

Background: Consultation is crucial for inpatient care and a primary responsibility of fellows. Understanding the cognitive load associated with the complex skill of consultation would enhance fellow learning. The authors aimed to determine themes describing the fellow experience during consults, align these themes with Consult Cognitive Load (CCL) scores, and identify strategies to manage cognitive load. **Methods:** The authors studied 16 fellows using mixed methods. Fellows who accepted an invitation completed a consult followed by the CCL, a measure of cognitive load during consults, and an interview. Three authors conducted a thematic analysis. Member checks and triangulation with fellows supported theme trustworthiness. Subsequently, three authors rated the extent and cognitive demand of each theme expressed in each transcript. The authors measured interrater reliability and used Spearman correlation to describe the association of these ratings with CCL scores. The authors examined themes to identify strategies that educators might use. **Results:** Analysis revealed four themes: "nature and scope," which conceptually aligned with intrinsic cognitive load (IL); "leveraging resources," which had elements of both IL and extraneous cognitive load (EL); "extraneous factors," which aligned with EL; and "drivers," which aligned with germane cognitive load (GL). Interrater reliability for extent and demand ratings ranged from 0.57 to 0.79. The correlation between "nature and scope" and IL was 0.37, "extraneous factors" and EL 0.71, and "drivers" and GL 0.32. "Leveraging resources" did not correlate with IL (0.06) or EL (-0.09). Potential strategies based on themes included offering level-appropriate assistance to match IL, focusing the fellow's attention to reduce EL, and providing succinct teaching to promote GL. **Conclusions:** This study provided deep insight into the fellow consult experience and suggested trustworthy strategies that educators can use to design and guide consult learning. The theme "leveraging resources" merits further exploration. Research Sponsor: UCSF Education Innovations Grant.

11028 **Poster Session**

Oncology trainees' perceptions and knowledge of therapeutic cannabis use. *First Author: Poorva Bindal, Beth Israel Deaconess Medical Center, Boston, MA*

Background: Evidence shows that cancer patients are interested in learning about medicinal cannabis and frequently ask their oncologists for recommendations. To determine whether oncology training is adequately preparing physicians to address this topic, we conducted a national survey of oncology trainees to determine attitudes, practices, and knowledge about medical cannabis in cancer care. **Methods:** An interdisciplinary team developed an electronic questionnaire assessing trainees' current practices regarding cannabis recommendations in cancer care and their knowledge of its effectiveness and risks compared with conventional care for cancer-related symptoms. We contacted 155 oncology training programs throughout the U.S. and asked that they distribute the survey to their trainees. Primary outcomes were: whether trainees reported discussing or recommending cannabis with/to patients and whether they felt sufficiently informed to make such recommendations. We presented data as proportions and used chi-square tests to compare proportions between groups. **Results:** Forty training programs from 25 states participated; of the 462 trainees in these programs, 187 completed surveys, yielding a response rate of 40%. Of the participants, 52% were female, 53% White, 33% Asian, and 5% Hispanic. One third (34%) graduated medical school before 2015, and 22% attended medical school outside the US. While 24% of trainees reported having received training regarding medical cannabis, only 12% felt sufficiently informed to make cannabis recommendations. Despite this, 91% reported having discussed cannabis with patients, and 58% reported recommending cannabis clinically to more than five patients in the prior year. Many viewed it as useful adjunctive therapy that was at least as effective as conventional treatments for: anorexia/cachexia (72%), nausea/vomiting (45%), and pain (41%). Over half (55%) believed that cannabis was beneficial to patients at the end of life; 31%, patients in active treatment; 11%, cancer survivors; 20%, the elderly with cancer and 16%, young adults with cancer. Peer-reviewed material (30%), lectures or webinars by another physician (29%), and patients and their families (22%) were the most commonly cited sources of information regarding medical cannabis. Oncologists who reported at least one area of focus as supportive/palliative care were more likely to feel sufficiently informed to make recommendations than oncologists without this focus (17% vs. 4%, $P = 0.01$); no other demographic or practice characteristics were associated with feeling sufficiently informed (all $P > 0.10$). **Conclusions:** Although most oncology trainees discuss cannabis use with their patients, the majority do not feel sufficiently informed about its use in cancer care. This represents an unmet need in contemporary oncology training, trainee satisfaction, and patient care. Research Sponsor: None.

11029 **Poster Session**

Cancer specialists in the VA as early adopters of clinical genetic services. *First Author: Maren Theresa Scheuner, San Francisco VA Health Care System, San Francisco, CA*

Background: Genetic testing has become essential to delivery of cancer treatment, risk assessment, surveillance, and prevention. We sought to understand the use of genetic tests by clinicians in the Department of Veterans Affairs (VA). **Methods:** We administered a web-based survey to clinicians at 20 VA facilities with precision oncology programs. We excluded respondents if they were: not at one of the 20 VA facilities; not seeing patients in VA; not a physician, nurse practitioner (NP), physician assistant (PA), or pharmacist; a medical geneticist or specialty was not reported; or if the survey was incomplete. Using multiple logistic regression, we assessed the association between genetic test ordering, genetics referral, and clinician characteristics. **Results:** There were 909 (909/11,442, 8%) eligible respondents with 61% women and 64% under age 55. There were 571 physicians (63%), 200 NPs (22%), 93 pharmacists (10%), and 45 PAs 5(%). There were 361 (40%) primary care providers (PCPs), 90 (10%) cancer specialists, and 458 (50%) non-cancer specialists. Only 21% of clinicians reported feeling prepared to use genetic tests in their practice. In the past year, only 8% had ordered at least one multi-gene cancer test (germline, tumor or both), 12% a pharmacogenetic test, and 0.2%, an exome. Compared to physicians, NPs were 60% less likely (OR = 0.42, 0.23-0.77, p = 0.005), pharmacists, 80% less likely (OR = 0.22, 0.08-0.62, p = 0.005), and PAs, 90% less likely (OR = 0.08, 0.01-0.58, p = 0.01) to have ordered a genetic test. Compared to PCPs, cancer specialists were almost 5 times more likely to order a genetic test (OR = 4.74, 2.57-8.73, $p < 0.0001$); there was no difference in genetic test ordering between PCPs and non-cancer specialists. Among clinicians (n = 72) who had ordered cancer genetic tests, only about two-thirds were confident in knowing the indications for testing; discussing the potential benefits, harms and limitations of testing; understanding the test report; and knowing implications of results on disease management and prevention. Clinicians (n = 106) who had ordered pharmacogenetic tests had lower frequencies of confidence in these tasks. About half (52%) of the cancer specialists had referred patients to genetics in the past year; they were 1.8 times more likely than PCPs to refer (OR = 1.82, 1.10-3.03, p = 0.02), and non-cancer specialists were about 50% less likely than PCPs to refer (OR = 0.46, 0.33-0.64, $p < 0.0001$). **Conclusions:** In the VA, cancer specialists are integrating genetic testing and genetics referral into their practice more than PCPs and other specialists. However, genetic testing is underutilized, and many clinicians remain unprepared to use genetic tests in their practice. These results will inform workforce planning, clinician education, and development of clinical decision support to facilitate genetic risk assessment, informed consent, and ordering of genetic tests. Research Sponsor: Department of Veterans Affairs, Rubin Family Fund.

11030 **Poster Session**

NCI Awardee Skills Development Consortium (NASDC): Applicant profiles. *First Author: Claire F. Verschraegen, The Ohio State University Comprehensive Cancer Center, Columbus, OH*

Background: In 2020, the NCI funded a new educational consortium, NASDC (NCI Awardee Skills Development Consortium**,** RFA-CA-19-010 and -011), through four institutionally granted UE5 awards to deliver a specific course each and a U24 award as a Coordinating Center. The goal is to teach current early-career faculty NCI grantees skills in areas critical for successful independent academic cancer research careers. Courses focus on leadership and socioemotional skills, health disparities, immuno-oncology, and cell and gene therapy. Teaching will initially be virtual, given the COVID pandemic. **Methods:** A steering committee and four working groups were established to build the consortium infrastructure, including the NASDC (osu.edu) website. Clientele are early-career faculty PD/PI of a current NCI-funded grant (K01, K07, K08, K22, K23, K25, R00, R21, DP1, DP2, DP5, R01, R23, R29, R37, R56, RF1, RL1, U01), of whom 454 were directly contacted. Blast emails and social media were also used. We are reporting the characteristics of 154 applicants, who completed the RedCap application online. **Results:** 85% of the applicants are within the first 5 years of a faculty appointment, 87% at the assistant professor rank, and 65% on tenure track. 40% hold an M.D. degree and 72% a Ph.D. 81% are US citizens, 52% females, and 45/33/16/2/4%-11% are White/Asian/Black/Native Americans/Other–Hispanics/Latino. 76% work at NCI-designated comprehensive cancer centers. Mean protected research time is 80%. Non-mutually exclusive fields of research interest are therapeutics (46%), basic science (37%), disparities (34%) prevention (32%), public health (28%), and pediatrics (10%). 66% have received a K-award grant, 13% each an R21 or R00, and 3% an R01. Additionally, 35% had a second NCI grant as PI, 10% a third grant, and 60% had non-NCI grants. Reasons for applying included (1) not quite ready to lead a research team (42%), (2) need for stronger career mentoring (37%), and (3) not being fully confident in research skills (21%). **Conclusions:** Applicants to the new NCI educational consortium (NASDC) have a successful start to their academic career with a third having obtained more than one NCI award. Most applicants work at NCI-designated comprehensive cancer centers. As cancer research continues to evolve and has the potential to address critical health care needs of the nation, NASDC will strive to equip scientists to be leaders, teach advances in technology, and impart confidence in research skills. Research Sponsor: U.S. National Institutes of Health.

11031 **Poster Session**

Efficacy of a fully remote primary lecture series at an academic hematology and oncology fellowship program. *First Author: Sassine Ghanem, State University of New York Downstate Medical Center, Brooklyn, NY*

Background: 615 fellows began training in American combined hematology/oncology fellowship programs in July 2020. These new fellows face a steep learning curve. The coronavirus pandemic has significantly affected how we learn, with programs having to convert most collective learning to a completely virtual format. Research on the efficacy of introductory lecture series in academic hematology/oncology programs is limited especially regarding virtual formats. We introduced a virtual introductory lecture series with the goal of increasing the clinical confidence and knowledge base of first-year fellows. **Methods:** A once weekly remotely-delivered two-hour primer series was designed with lectures given by both third-year fellows and faculty from July-August 2020. Fellows were asked to complete pre & post-test evaluations of each lecture. Evaluations included a combination of knowledge-based questions & self-reported confidence assessment. **Results:** 14 fellows were assigned pre- and post-tests in the study. 1 fellow was excluded due to lack of participation. A total of 123 paired pre and post-tests were compared. Data analysis was performed with SPSS v 24.0 using the paired samples t-test. Pre and post-tests were graded on a scale of 0-100. The pre to post mean difference compares the mean test result of the post tests to that of the corresponding pretests. Questions were divided into 2 groups. The 1st group tested the fellow's medical knowledge regarding the pathology while the 2nd group tested the comfort in the management, diagnosis and treatment. In the statistical analysis, these questions were defined as "Knowledge" and "Comfort" accordingly, the sum as "Complete". A statistically significant improvement in post-test knowledge for fellows of all years was noted with a pre to post test mean difference of 12.52, $P < .0001$. The difference was more pronounced among 1st year fellows with a pre to post test mean difference of 16.84, $P < .0001$. A similar improvement was seen for the comfort in management questions. The post-test comfort pre to post test mean difference was 10.48, $P < .0001$ for fellows of all years and 6.70, $P < .0001$ for first year fellows. **Conclusions:** A remotely-delivered introductory lecture series for fellows in a hematology/oncology training program increases both clinical knowledge and clinical confidence in fellows of all years of training. Research Sponsor: None.

				95% CI		
		Answer Mean	Pre to Post Mean Difference	Lower	Upper	p value
All Years	Pretest Complete	58.49	10.82	9.66	11.99	<.0001
	Post Test Complete	69.31				
First Year	Pretest Complete	43.71	8.37	6.67	10.07	<.0001
	Post Test Complete	52.08				
All Years	Pretest Knowledge	64.88	12.52	8.47	16.56	<.0001
	Post Test Knowledge	77.40				
First Year	Pretest Knowledge	58.95	16.84	10.75	22.92	<.0001
	Post Test Knowledge	75.79				
All Years	Pretest Comfort	57.19	10.48	9.34	11.63	<.0001
	Post Test Comfort	67.67				
First Year	Pretest Comfort	40.73	6.70	5.12	8.28	<.0001
	Post Test Comfort	47.43				

11032 **Poster Session**

Factors associated with open access publishing costs in oncology journals. *First Author: Alex Koong, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The open access (OA) publishing model represents an exciting opportunity to facilitate dissemination of scientific information to global audiences. In contrast to many traditional models, which require readers to pay subscription fees or rely upon institutional subscriptions for article access, the OA model grants free access to all consumers. However, OA publication is often associated with significant article processing charges (APCs) for authors, which may thus serve as a barrier to publication. In this investigation, we aimed to identify journal-level factors associated with OA publication costs in oncology journals. **Methods:** We identified oncology journals using the SCImago Journal & Country Rank database. All journals under the "Oncology" category that offer an OA publishing option with APC data openly available were included. For all journals, we searched journal websites and tabulated journal characteristics, including APC amount (USD), OA model (hybrid vs full), journal 2-year impact factor (IF), H-index, number of citable documents, primary treatment modality (surgery, radiation, medical, non-specific), treatment site (e.g. breast, etc), and continent of origin. Pearson correlation was used to evaluate univariate linear relationships between variables; for variables with significant correlation, we generated a multiple regression model to identify journal characteristics independently associated with OA APC amount. **Results:** Of 367 oncology journals screened, 266 met final inclusion criteria. The median APC was 2810 USD (range 0 – 5200). On univariate linear correlation regression testing, journals with the full OA model ($p < 0.001$), higher journal IF ($p < 0.001$), higher H-index ($p < 0.001$), greater number of published articles ($p < 0.001$), and those from North America or Europe ($p < 0.001$) tended to have higher OA publishing costs. When these co-variates were analyzed in a multiple regression model, only full OA status ($p < 0.001$), higher IF ($p < 0.001$), and North American or European origin ($p < 0.001$) persisted as independently associated with greater OA APC. **Conclusions:** Large APCs may serve as a barrier to OA publication and therefore create or exacerbate disparities among scientific investigators seeking to share their research. In this investigation, we find that OA publication costs are greater in oncology journals that utilize the hybrid OA model, have higher IF, and are based in North America or Europe. These findings may inform targeted action to help the oncology community fully appreciate the benefits of open science. Research Sponsor: None.

11033 **Poster Session**

How to teach Breast ERAS protocols: Surgical residents' perspectives and perioperative practices for mastectomy patients. *First Author: Kristen Jogerst, Mayo Clinic, Phoenix, AZ*

Background: Breast enhanced recovery after surgery (ERAS) protocols emphasize multimodal analgesia to decrease pain and expedite home recovery, but variability remains for same-day discharge and pain management. The purpose of this qualitative study is to examine how residents learn and apply breast surgery ERAS protocols, how they conceptualize pain management for breast surgery patients, and what influences their decision to discharge a patient home on the day of surgery. **Methods:** A semi-structured interview guide was adapted from existing instruments in the pain management qualitative literature. Surgical residents who rotated on the breast surgery service within the previous 12 months were interviewed by a single researcher. Interviews were recorded, transcribed, de-identified, and independently inductively coded by two researchers. A codebook was developed and refined using the constant comparative method until interrater reliability (Cohen's kappa) reached greater than 0.9. Codes were grouped into coding categories and explored for thematic analysis. **Results:** Twelve interviews were completed with plastic and general surgery residents. Participants spanned postgraduate years 1-4. Preferred discharge narcotic regimens for mastectomy patients ranged from 5-30 tablets of 5mg oxycodone and participants rarely reported the same quantity. Ultimately, 365 primary codes were collapsed into 26 parent codes, with a Cohen's kappa of 0.93. Six emerging themes were identified. Three themes describe how participants learned through a mixture of templated care, formal education, and informal experiential learning. Two themes delineate how residents would teach breast surgery ERAS protocols: by emphasizing buy-in and by connecting the impetus behind ERAS with the implementation in daily workflow. One theme illustrates the patient-centered culture and how that impacts postoperative management and same-day discharges. **Conclusions:** Residents learn breast surgery ERAS and postoperative pain management from imitating their seniors, observing patient encounters, completing templated orders, and translating concepts from other ERAS services, more so than from a formal lecture. When implementing new same-day discharge protocols for mastectomy patients, it is important to consider how informal learning and local culture influence postoperative pain management and discharge rates. Research Sponsor: None.

11034 **Poster Session**

Factors associated with successful publication of abstracts in women malignancies: Are we closing the gender gap? *First Author: Ankita Kapoor, Rochester General Hospital, Rochester, NY*

Background: We aimed to determine abstract characteristics associated with successful peer-reviewed publication after presentation at ASCO annual meeting in the women's malignancy category (breast & gynecologic cancer). Awareness of this could help meeting organizers & attendees understand factors associated with impactful abstracts. **Methods:** All oral & poster abstracts (OA: n = 53 & PA: n = 527) in Breast (Loco/Regional/Adjuvant & Metastatic) & Gynecologic cancers category (2017 & 2018 meeting) were included. Subsequent publication was confirmed by searching PubMed by title, names of first & last authors for abstracts published by January 2021. Time to online publication, US or foreign journal publication & impact factor (IF) were recorded. We also recorded number of authors, single/ multi-institution studies & gender of first/ last author, which was confirmed by viewing biography details on their institutional websites. Descriptive analysis was performed & association between above factors & publication matrix was analyzed using multiple logistic regression model, Chi-square and t-test. **Results:** 45/53 OA (85%) & 269/527 PA (51%) were published in peer-reviewed journals. Median number of authors for published PA was 12 vs 11 for unpublished ($p = 0.24$). Females (F) presented 34% (18/53) OA & 49.3% (260/527) PA. 55% (143/260) PA presented by female authors & 47.1% (126/267) presented by male (M) authors ($p = 0.073$) were published. No difference in publication between single vs multi-institution studies ($p = 0.76$) for PA was noted. Average time to journal publication for OA & PA was 15.45 (SD +/- 3.37) & 17.73 (SD +/- 1.27) months (mo) respectively. Mean IF for OA was 27.95 (SD+/- 6.18) while for PA was 10.96 (SD+/- 1.75). For published OA, 33% (15/45) had female first & 29% (13/45) had female last authors. For published PA, 50.2% (135/269) had female first while only 37.5% (101/269) had female last authors. There was no association between gender of last author to IF ($p = 0.39$), single vs multi-institution study ($p = 0.48$) or time to publication ($p = 0.44$) for PA. **Conclusions:** More than 75% of OA & 50% of PA were successfully published regardless of gender, number of authors or institutions involved. We observe a slight disparity in senior authorship for females and although this was not statistically significant, we are encouraged that the gap is closing in first authorship. Research Sponsor: None.

Variable (Published)	OA (%/SD/IQR) n = 45/53	PA (%/ SD/IQR) n = 269/527
U.S. journals	25/45 (55.5 %)	108/269 (40.1 %)
Median number of authors	17 (14-20)	12 (8-17)
Multi-institution study	44/45 (97.7 %)	206/269 (76.5 %)
M first/ last author	23/45 (51 %)	85/269 (31.5 %)
F first/ M last author	9/45 (20 %)	83/269 (31 %)
M first/ F last author	7/45 (16 %)	49/269 (18.2 %)
F first/ last author	6/45 (13 %)	52/269 (19.3 %)
F first author: mean publication time (mo)	19.64 +/- 4.43	18.50 +/- 1.70
M first author: mean publication time (mo)	15.75 +/- 4.03	18.95 +/- 1.81

11035 **Poster Session**

The Johns Hopkins Molecular Tumor Board Precision Oncology elective for Medical Oncology fellows. *First Author: Kristen Marrone, Johns Hopkins University School of Medicine, Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: The accelerated impact of next generation sequencing (NGS) in clinical decision making requires the integration of cancer genomics and precision oncology focused training into medical oncology education. The Johns Hopkins Molecular Tumor Board (JH MTB) is a multi-disciplinary effort focused on integration of NGS findings with critical evidence interpretation to generate personalized recommendations tailored to the genetic footprint of individual patients. **Methods:** The JH MTB and the Medical Oncology Fellowship Program have developed a 3-month precision oncology elective for fellows in their research years. Commencing fall of 2020, the goals of this elective are to enhance the understanding of NGS platforms and findings, advance the interpretation and characterization of molecular assay outputs by use of mutation annotators and knowledgebases and ultimately master the art of matching NGS findings with available therapies. Fellow integration into the MTB focuses on mentored case-based learning in mutation characterization and ranking by levels of evidence for actionability, with culmination in form of verbal presentations and written summary reports of final MTB recommendations. A mixed methods questionnaire was administered to evaluate progress since elective initiation. **Results:** Three learners who have participated as of February 2021 were included. Of the two who had completed the MTB elective, each have presented at least 10 cases, with at least 1 scholarly publication planned. All indicated strong agreement that MTB elective had increased their comfort with interpreting clinical NGS reports as well as the use of knowledgebases and variant annotators. Exposure to experts in the field of molecular precision oncology, identification of resources necessary to interpret clinical NGS reports, development of ability to critically assess various NGS platforms, and gained familiarity with computational analyses relevant to clinical decision making were noted as strengths of the MTB elective. Areas of improvement included ongoing initiatives that involve streamlining variant annotation and transcription of information for written reports. **Conclusions:** A longitudinal elective in the JHU MTB has been found to be preliminarily effective in promoting knowledge mastery and creating academic opportunities related to the clinical application of precision medicine. Future directions will include leveraging of the MTB infrastructure for research projects, learner integration into computational laboratory meetings, and expansion of the MTB curriculum to include different levels of learners from multiple medical education programs. Continued elective participation will be key to understanding how best to facilitate adaptive expertise in assigning clinical relevance to genomic findings, ultimately improving precision medicine delivery in patient care and trial development. Research Sponsor: None.

11036 **Poster Session**

Incorporating HER2/HER3 targeted therapies across solid tumors: Assessing the impact of digital education on clinician practice patterns. *First Author: Tariqa Ackbarali, PlatformQ Health Education, Needham, MA*

Background: Improved understanding of the interactions between HER2 and HER3, the heterogeneity of HER-expressing disease, and mechanisms of resistance to anti-HER2 therapy has led to increasing number of treatment options to address clinical needs. Tumor types of interest, impacted by HER2/HER3 expression and pathophysiology were breast cancer, non-small cell lung cancer (NSCLC), gastric cancer, and colorectal cancer (CRC). Increasing competency in these areas is deemed critical to clinician's ability to individualize treatment plans and improve patient outcomes. **Methods:** A 2-hour CME activity was broadcast live-online in September 2020 and remains on-demand through September 2021 at OMedLive.com. The educational initiative was divided into one hour addressing HER2 and HER3, testing guidelines, resistance mechanisms and emerging data elucidating recent and ongoing clinical trials across NSCLC, gastric cancer, and CRC. The second hour focused on individualizing metastatic HER2+ breast cancer, HER2-low breast cancer as an emerging subtype, and management of side effects. Knowledge and competence questions were administered pre-, immediate post-, and 2 mos. post-activity. Behavioral impact questions were also asked at follow-up. Data from these questions were analyzed to determine engagement and clinical impact. **Results:** To date, 448 clinicians participated in the activity. Across the seven CME test questions, improvements in knowledge and competence were observed in the clinical applications of HER2-directed agents and HER3 antibody drug conjugates (ADCs), first-line standard of care for HER2+ breast cancer, and adverse event management for HER2 ADCs. At 2-mos. follow-up, 67% reported improved behavioral impact on both clinical practice and patient experience and outcomes. Clinicians provided specific write-in examples of these changes, noting improved patient-reported outcomes, improved treatment adherence, improved competence developing treatment plans, and increased understanding of HER2/HER3 pathophysiology. Updated and expanded results will be shared. **Conclusions:** The activity was successful in improving clinician understanding of the relationship between HER2/HER3, pathophysiology across tumor types, and applications of emerging targeted therapies. Open-ended responses to behavioral impact questions illustrated clear improvements in clinician-reported patient experience and outcomes, clinical practice management, and knowledge of emerging HER2/HER3 therapies and their uses across multiple solid tumors. Research Sponsor: Daiichi Sankyo, Inc.

11037 **Poster Session**

Supporting the mental well-being of healthcare professionals during a pandemic. *First Author: Ana Maria Lopez, Sidney Kimmel Cancer Center at Thomas Jefferson University, Philadelphia, PA*

Background: Burnout amongst healthcare professionals has been well-documented as a phenomenon that compromises the quality and viability of patient-centered care, particularly in oncology. Due to the extraordinary demands of the pandemic, burnout has emerged as a public health crisis that warrants immediate attention to preserve the wellbeing of healthcare staff. At the onset of the pandemic, The Sidney Kimmel Cancer Center (SKCC) at Jefferson, an urban NCI-designated cancer center, translated its support offerings to virtual events. Initially, healthcare providers (HP) sought support by attending patient programs. In response, SKCC initiated virtual programming to support the well-being and needs of the HP team. **Methods:** Within weeks of the state shutdown due to the pandemic, programs were initiated to address HP self-reported distress: Coping Effectively and Mindfulness Moments Each 30-minute session was facilitated by a licensed psychologist and social worker. Coping Effectively offers strategies from evidence based treatment including Dialectical Behavior Therapy, Acceptance and Commitment Therapy, and Cognitive Behavioral Therapy, to cope with distress and burnout. Mindful Moments draws from Mindfulness Based Stress Reduction practices including observing breath and guided meditations. These programs have been offered consistently throughout the pandemic. Schwartz Rounds, geared towards supporting the human side of healthcare, provided "hot" topic moderated discussions, four of which focused on the pandemic These discussions allow for HP to come together to discuss difficult topics and emotions impacting a variety of professionals. All programming was evaluated with a single question to measure the impact of the session on reducing distress. Each program began and ended with a poll asking, "How distressed do you currently feel?" Attendees respond on a Likert scale from 0 to 10, in which10 indicated the highest level of distress. **Results:** Since March 31st, 340 staff have attended Mindful Moments and 236 staff have attended Coping Effectively. From March 2020-February 2021, 382 attendees measured their distress before and after attending a staff program. Schwartz Rounds hosted 471 HP from a variety of disciplines. Participants were asked to complete an evaluation following rounds. 31% of program participants' completed an evaluation form and 89% rated the program exceptional/very good. **Conclusions:** Despite the challenges of COVID-19, the pivot to virtually create programs to support staff during the pandemic was swift and thoughtful. The increased attendance and the feedback from evaluations are promising indicators of decreasing burnout amongst HP. How Distressed do you Currently Feel? (Average Score scale 1-10) Research Sponsor: None.

	Coping Effectively through Covvid-19	Mindful Moments for Professionals
N=	236	340
PRE	5.37	5.28
POST	**2.92**	**3.5**

11038 **Poster Session**

Impact of the COVID-19 pandemic on the wellbeing of international fellows training in hematology/oncology at the Princess Margaret Cancer Centre (PMCC). *First Author: Carlos Stecca, Princess Margaret Cancer Center, Toronto, Canada*

Background: The COVID-19 pandemic has led to significant disruptions across all levels of medical training. International fellows in subspecialty training programs are essential members of the frontline physician workforce, who may be facing additional and unique challenges being far away from their home country. We aimed to understand the impact of the pandemic on the wellbeing of current international fellows in the Hematology/Oncology training program. **Methods:** We conducted an online survey of 52 international fellows at the PMCC from July 6-August 10, 2020. There were 60 questions divided into 4 sections: demographics, wellbeing assessment using the validated Short Warwick Edinburgh Mental Wellbeing Scale (SWEMWBS), fellowship specific questions (personal and professional) and coping strategies using the validated brief COPE scale. **Results:** Response rate was 46% (n = 24). Relevant demographics include: married (65%), male (54%), age between 31-35 years (48%), have children (48%), and home country from Asia (48%). Mean SWEMWBS score was 21, indicating lower overall wellbeing than the general population (23.6). Compared to pre-COVID-19, many reported a decline in their wellbeing (63%), sense of guilt for not being with their family (45%) or helping their country (41%), stress in personal relationships (26%), fatigue (50%), sleep disorders (38%) and loss of interest in daily activities (38%). Personal events were altered by almost 80% and 20% plans to extend their fellowship. According to the Brief-COPE scale, most fellows used more adaptive coping mechanisms (mean score 39.2) as opposed to maladaptive ones (mean score 21.8). **Conclusions:** The ongoing COVID-19 pandemic has negatively affected the overall wellbeing of international fellows. Understanding the specific challenges and coping mechanisms of international fellows may help Institutions develop better targeted strategies to promote their overall wellbeing, professional development and high-quality patient care during these unprecedented times. Research Sponsor: None.

11039 **Poster Session**

Impact of *#ASCO* Twitter impressions on the oncology community. *First Author: Gilberto Morgan, Department of Medical and Radiation Oncology, Skåne University Hospital, Lund, Sweden*

Background: The oncology community is embracing social media (SM) platforms like Twitter to gain exposure to research, to network, and to engage in real-time discussions. The emergence of SM activity around the ASCO annual meetings has dramatically increased over the past 5 years, with factors such as the COVID-19 pandemic further accelerating use of digital platforms. This growth in SM engagement within the oncology community has previously been presented by totaling the quantity of tweets within a given time frame. Here, we explore the impact of specific trends through impression data. **Methods:** To evaluate activity trends among certain oncology stakeholders, we utilized an SM analytics platform, Symplur, to conduct a content analysis around ASCO conferences (2016-2020) using hashtags (#ASCOyy) as the search criterion. We focused our analysis on trends in impressions, defined by the theoretical maximum number of Twitter users a given tweet could have directly reached in a follower's timeline. We gathered impressions data to quantitatively assess overall ASCO engagement and evaluate topics of interest, and to discover common ASCO themes and reach within specific stakeholder groups. **Results:** Our results show the largest increase in impressions was during #ASCO20, despite a plateauing effect seen in the actual number of tweets (Table). The cumulative number of impressions for #ASCO16 was 468.2 million compared with approximately 1.12 billion for #ASCO20. Differentiating this result from the number of tweets related to ASCO, there was stabilization in the absolute number from #ASCO17 onward. When compiling impressions by doctors and by patient advocates, a similar trend emerged, with the most impressions captured during #ASCO20 (Table). **Conclusions:** As SM use continues to expand in the oncology community, stakeholders have turned to their digital voice to express views and opinions. The impact of impressions versus absolute number of tweets will continue to grow with a stakeholder's follower count, thus building on the digital presence in oncology. Research Sponsor: Eisai Inc.

		#ASCO16	#ASCO17	#ASCO18	#ASCO19	#ASCO20
Cumulative impressions (millions)	**Total**	468.2	504.8	595.1	583.4	1125.8
	Doctors	66.6	134.9	121.6	139.4	187.1
	Patient advocates	15.6	20.5	10.7	18.9	26.2
Number of tweets (thousands)		89.0	116.7	104.8	112.9	98.1

11040 **Poster Session**

OCEAN (wOmen's Career choicEs About oNcology) Study: Motivations to pursue or not pursue academic oncology. *First Author: Grace Blitzer, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI*

Background: Although women outnumber men in US medical school enrollment, women constitute < 50% of faculty in academic oncology. This study aimed to determine factors affecting women oncologists' decisions to pursue academic versus non-academic oncology in Hematology/Oncology (HO), Pediatric Oncology (PO), Radiation Oncology (RO), and Surgical Oncology (SO), and to characterize the challenges women oncologists face. **Methods:** A survey was designed to collect cross-sectional data on factors affecting career choices among US women oncologists. The survey was distributed via email and social media. Data were collected anonymously and analyzed using t-tests for continuous variables and Chi-squared tests for categorical variables. **Results:** Six hundred sixty-seven women oncologists responded: 245 (45.3%) specialized in HO, 173 (25.9%) RO, 88 (13.2%) PO, 56 (8.4%) SO, and 48 (7.2%) other. Four-hundred twenty-two (63.2%) women identified as an academic oncologist (AO); 245 (36.8%) women identified as a non-academic oncologist (non-AO). Approximately 1/4 of women oncologists reported their partner (156, 23.5%) or family (176, 26.4%) extremely or moderately impacted their decision whether to pursue academic practice. There was no difference in the timing of childbearing between AO and non-AO. AO perceived the biggest sacrifice of pursuing academics to be time with loved ones (181, 42.9%). Non-AO perceived the biggest sacrifice for AO to be pressure for academic promotion (102, 41.6%), which was the third most common response (44, 18.0%) among AO. Thirty-three (7.9%) AO and 5 (2.0%) non-AO reported feeling that they rarely or never have a sense of belonging in their work environment ($p < 0.01$). AO and non-AO had significantly different perceptions on how their gender impacted their ability to obtain a chosen job ($p < 0.01$), with 100 (23.8%) AO and 52 (21.2%) non-AO reporting a negative or somewhat negative impact, and 116 (27.6%) AO and 101 (41.2%) non-AO reporting a positive or somewhat positive impact. More than half of women surveyed (230 AO, 54.6%; 123 non-AO, 50.6%; $p = 0.61$) felt that they were somewhat or much less likely to be promoted compared to male colleagues. The majority of women reported they would choose the same career path again (71% of AO, 69% of non-AO); however, 92 (21.9%) of AO responded that they were likely or very likely to pursue a career outside academics in the next 5 years. **Conclusions:** While partners/family have a substantial impact on 1 in 4 women oncologists, this does not differ between AO and non-AO. Significantly more non-AO find their gender to have positively impacted their ability to obtain their chosen job. In contrast, a meaningful number of AO report a poor sense of belonging and perceived discrimination in obtaining jobs and being promoted; 1 in 5 are considering leaving academia. Academic oncology remains at high risk for continued gender inequality if the culture is not addressed. Research Sponsor: University of Wisconsin School Medicine and Public Health.

11041 **Poster Session**

Specialty representation on national comprehensive cancer network guideline committees. *First Author: Bismarck Odei, Ohio State University Wexner Medical Center, Columbus, OH*

Background: Among the National Comprehensive Cancer Network (NCCN) guidelines, the existence of Category 1 evidence for cancer management decisions remains low, resulting in the reliance on multispecialty perspective to determine optimal treatment approach. Multiple studies suggest that the specialty composition of oncological teams is important in the trajectory of decision-making. Consequently, we sought to determine if there was adequate representation of radiation oncologists (ROs) on NCCN committees (NCMs). **Methods:** NCMs with Category 1 or 2A recommendations for radiotherapy use were identified. Committee members were documented including specialty, academic rank, and committee role. H-index and gender was assessed for each member. A minimum arbitrary threshold of < 10% was used to define underrepresentation of ROs. Univariate and multivariate (MVA) logistic regression identified factors predictive of underrepresentation. **Results:** Of 57 assessed guidelines, 38 (66.7%) NCMs recommended radiation as Category 1 or 2A from which a total of 1284 committee members were identified. Median committee size was 33 (range 29-38). Overall, 42.2% were Medical Oncologists (MOs), 23.9% were Surgical Oncologists (SOs), and 11.5% were ROs [22.4% were a mix of Radiologists, Pathologists, other specialty physicians, and non-physician members like Patient Advocates]. ROs constituted 4.4% of NCM Chairs (MOs: 68.9%, SOs: 13.3%, Other: 13.3%); 29% of Vice Chairs (MOs: 35.5%, SOs: 35.5%); and 5.9% of the discussion writing committee (MOs: 70.6%, SOs: 23.5%). The representation of ROs was highest for Head/ Neck Cancer NCM (38.8%) and Prostate Cancer NCM (25.8%). 42% of the NCMs recommending radiation had < 10% representation of ROs; 17% of guidelines recommending radiation had 1 or less RO including 4 NCMs which did not have a single RO committee member. On univariate analysis, factors predictive of RO underrepresentation were low SO representation ($p = 0.038$) and low median H-index of the NCM ($p = 0.013$); low proportion of full professors trended towards significance ($p = 0.060$). On MVA, median H-index had a negative association with RO underrepresentation ($p = 0.038$) —no association was found to rank, gender or specialty. **Conclusions:** Our study shows alarmingly low representation of ROs among NCCN committees which include radiation as a Category 1 or 2A recommendation. This can both limit the discussion during guideline development and negatively impact the diversity of perspectives in management recommendations. Efforts to ensure more proportional representation of ROs on NCCN guideline committees are warranted including exploring potential barriers to committee leadership. Research Sponsor: None.

11042 **Poster Session**

Hematology/medical oncology fellow responses to the initial development of an antiracism curriculum. *First Author: Erica C. Nakajima, Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Baltimore, MD*

Background: While the American Council on Graduate Medical Education (ACGME) set up a Planning Committee for Diversity in GME in 2018, no formalized milestones or training mandates have been announced. The nation-wide protests for racial justice following the senseless killings of Breonna Taylor, Ahmaud Arbery and George Floyd further brought to the forefront the need for immediate action to address widespread inequities across graduate medical education, our healthcare system and society as a whole. Therefore, the Johns Hopkins Hematology/Medical Oncology Fellowship Program focused on creating an anti-racism curriculum to foster dialogue on systemic racism and discrimination, grounded in the institutional and geographic context of our training program. **Methods:** Using the Kern six step curriculum development method, we created a comprehensive anti-racism initiative, which included virtual townhalls with Black alumni of the fellowship, book clubs, readings, and lectures. We sought to deepen the fellowship's awareness of the impact of racism and inequity upon trainees, underrepresented minority oncologists and hematologists, and patients in order to develop initiatives to confront them productively. Trainees received a survey 6 months after the start of the curriculum to assess the impact of the initiatives upon trainees, and inform iterative changes to the curriculum. **Results:** 25 of 34 fellows across all post-graduate years (PGY) completed the survey. Fellows agreed that the curriculum was helpful (68%) and encouraging (60%). Collectively, fellows reported that the curriculum increased their awareness of instances of racism in medicine, caused them to think about next steps that the fellowship could take to address racism, and enabled them to identify available resources for support and further education. Respondents selected community engagement and recruitment of diverse fellowship classes as the most pressing priorities for the program. **Conclusions:** Social justice and anti-racism education belong in the formalized training of our hematology/medical oncology fellows. To this end, our ongoing curricular expansion is focusing on anti-racism training, diverse recruitment and youth mentorship. Collectively, a comprehensive yet program-specific approach facilitates opportunities for learning, engagement and development of the skills necessary to engage in this life-long work for ourselves, our communities and our patients. Research Sponsor: None.

11043 **Poster Session**

Representation trends in radiation oncology training programs in the United States. *First Author: Emilie Garcia, The University of Toledo College Of Medicine and Life Sciences, Toledo, OH*

Background: The ASCO and American Society of Radiation Oncologists (ASTRO) have recently committed to initiatives on increasing URM representation in the radiation oncology workforce. This study aims to assess representation trends in radiation oncology training programs across five academic years in order to understand representation trends and better guide initiatives moving forward. **Methods:** Data on racial and ethnic representation from the ACGME Data Resource Books over a span of five academic years (2015-2020) was included. URM was defined as those who identified as Hispanic, Black, or Native American/Alaskan in concordance with AAMC definition. Chi square testing was used to compare the proportion of residency positions occupied by URM residents by self-identified race and ethnicity in radiation oncology to that of hematology and medical oncology, complex general surgical oncology, and all other specialties. **Results:** A total of 3,315 radiation oncology positions were identified over the study period, 2015 and 2020. 1,938 (58.5%) of radiation oncology residency positions were filled by residents who identified as White, 967 (29.2%) as Asian/ Pacific Islander, 126 (3.8%) as Hispanic, 120 (3.6%) as Black, 7 (0.2%) as Native American/ Alaskan, and 157 (4.7%) as Other. URM representation was 7.6% in total and was relatively stagnant, remaining between 7.3% and 8.0% across study years. Results of chi square comparative analysis demonstrated lower rates of representation in radiation oncology in comparison to hematology and medical oncology as well as all other specialties (Table). **Conclusions:** There is lack of racial and ethnic diversity in radiation-oncology residency training positions in the United States. Over the five-year study period, only 7.6% of trainees identified as URM. URMs have significantly lower rates of representation in radiation-oncology compared to hematology and medical oncology, and other specialties. Efforts to mitigate disparities require a multifaceted approach. Research Sponsor: None.

Specialty	% URM (95% CI)	Comparator	% URM comparator (95% CI)	Total N (both groups)	*P* value
Radiation Oncology	7.6 (6.7-8.5)	Hematology and Medical Oncology	9.0 (8.3-9.6)	10,502	0.024*
Radiation Oncology	7.6 (6.7-8.5)	Surgical Oncology	7.8 (5.4-10.2)	3,788	0.884
Radiation Oncology	7.6 (6.7-8.5)	All Other Specialties	13.1 (13.0-13.2)	518,430	0.000**

Results of chi square comparative analysis for representation in radiation oncology in comparison to hematology and medical oncology, surgical oncology, and all other specialties in total over study period. *denotes significance at $P < 0.05$ **denotes significance at $P < 0.01$.

11044 **Poster Session**

Factors associated with endowed chair allocation in medical oncology divisions and departments in the United States. *First Author: Lena Jia, Washington University School of Medicine, St. Louis, MO*

Background: Despite an increasing number of female physicians in the workforce, a gender disparity remains in many leadership roles in medicine. Endowed chairs can provide a multitude of research and career opportunities; thus, they are coveted positions in academic medicine. We examined factors associated with holding endowed chairs in oncology across the US, with a focus on whether a gender difference existed, as has been demonstrated in top internal medicine departments more generally. **Methods:** In 2019, we identified 95 academic oncology divisions/departments in the US, using the Oncology Division Chiefs & Department Chairs listing in the American Society of Clinical Oncology (ASCO) myConnection forum to define the institutions included. We requested a list of full professors and endowed chairs in those divisions/departments, relying on public data on websites when an institution did not respond. Using public data (e.g., institutional websites, NIH reporter, Scopus, state licensing boards), we collected information on gender, degree, total NIH funding as PIs, H-indices, publication and citation numbers, and graduation year for these individuals. We then created a multivariable logistic regression model to examine if, after controlling for other variables, gender was independently associated with an increased likelihood of holding an endowed chair. **Results:** One thousand thirty-three oncology full professors were identified, 290 (25.6%) of whom held endowed chairs. Overall, and in an adjusted model, greater research productivity (as measured through publications, citations, and h-index) and greater levels of NIH funding were significantly associated with having an endowed chair. Gender was not significantly associated with endowed chair status (21.9% [95% CI:17.2-27.3] of females and 26.8% [23.8-29.9] for males held endowed chairs; $p = 0.11$) on bivariable analysis, nor was it significant in the adjusted multivariable model ($p = 0.50$). Power to detect the observed difference given the total number of professors and their gender distribution was found to be ~53%, suggesting a 47% chance of failing to reject the null hypothesis of equal gender distributions in endowed chairs when the observed difference is as large as estimated. **Conclusions:** Among oncology full professors, gender was not significantly associated with endowed chair status, although the number of professors in this field is too small to definitively rule out a modest gender difference. This finding contrasts with prior work that revealed a more substantial difference by gender that remained significant after controlling for other factors in a study, including all divisions in the Departments of Internal Medicine at top medical institutions. Further work is necessary to understand what specialty-specific and institutional cultural factors may help mitigate challenges in the pursuit of equity, diversity, and inclusion. Research Sponsor: None.

11500 **Oral Abstract Session**

TK216 for relapsed/refractory Ewing sarcoma: Interim phase 1/2 results. *First Author: Joseph Aloysius Ludwig, Sarcoma Medical Oncology, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Ewing Sarcoma (ES) is a rare cancer of the young with very few treatment options in the relapsed/refractory (R/R) setting. Fusions of the EWS gene and one of five different ETS transcription factors are dominant drivers of ES. TK216 was designed to bind ETS proteins directly, disrupt protein-protein interactions, and inhibit transcription factor function. TK216 plus vincristine (VCR) exerted synergistic activity in non-clinical models. Here, we report updated interim results of the Phase 1/2 trial of TK216 ± vincristine in R/R ES. **Methods:** TK216 was administered by continuous IV infusion to adult and pediatric patients (pts) with R/R ES using a 3+3 design. Dosing duration of 7 days was later extended to 10 and 14 days. Dose limiting toxicity was evaluated during Cycle 1. VCR could be added after Cycle 2. The MTD for the 14-day infusion was 200 mg/m^2/d, which was selected as the recommended Phase 2 dose (RP2D) for the Expansion cohort, with VCR started in Cycle 1. **Results:** Thirty-two R/R pts in 9 dose and schedule escalation cohorts, and 31 pts in the Phase 2 Expansion cohort were enrolled. Thirty-five pts were treated at the RP2D. Mean age was 30.6 years and 61% were males. Median prior treatment regimens for recurrent/metastatic ES were 3 (range 0-13). Median time from initial diagnosis of ES to study start was 3.5 years (range 0.3-18.1). Prior procedures included surgery (84%) and radiation (81%). At study entry, all pts had metastases with sites being bone only (13%), pleuropulmonary only (39%), and other metastatic (47%). As of the 20JAN2021 safety cutoff, the most common AEs observed in 62 treated pts, regardless of causality, included anemia (n = 34), neutropenia (n = 30) and fatigue (n = 25). Myelosuppression observed was transient, reversible, and responsive to growth factors. No deaths were attributed to TK216. As of the 06FEB2021 efficacy cut-off, 28/35 pts treated at the RP2D were evaluable for efficacy: Complete response (CR) 7.1%, stable disease (SD) 39.3%, progressive disease (PD) 53.6%, for an overall clinical benefit (CR+PR+SD) rate of 46.4%. SD median duration was 113 days (range 62-213). Three tumor responses were notable. One pt had regression of the target lesion after 2 cycles of TK216 alone, then after 6 cycles of TK216 + VCR therapy a residual non-target lesion was removed, for a surgical CR, without PD at 24 months on study. A second pt had a CR after 6 cycles of combination therapy, without PD at 18 months on study. After 4 cycles of TK216 + VCR therapy, a third pt had a PR of the target lesion, is receiving local therapy for PD of a non-target lesion and remains on study. Pts treated with the RP2D had a longer PFS than those in the dose escalation cohorts. **Conclusions:** TK216 plus VCR was well tolerated and showed encouraging early evidence of anti-tumor activity in this heavily pre-treated/ high tumor burden ES pt population. Clinical trial information: NCT02657005. Research Sponsor: Oncternal Therapeutics, Inc, Other Foundation.

11501 **Oral Abstract Session**

Efficacy of dose intensification in induction therapy for localized Ewing sarcoma: Italian Sarcoma Group (ISG) and Associazione Italiana Ematologia ed Oncologia Pediatrica (AIEOP) ISG/AIEOP EW-1 study. *First Author: Roberto Luksch, Pediatric Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: The role of dose intensification of chemotherapy in Ewing sarcoma (ES) is under evaluation in prospective trials. This is a controlled, randomized phase III study evaluating the impact on event-free survival (EFS) of two arms at different intensity of induction therapy in localized ES at onset. **Methods:** Newly diagnosed localized ES patients aged 2-40 were eligible. They were randomized to receive 4-courses induction therapy - 1 every 21 days - either with a standard arm (arm A) as per ISG/SSGIII protocol (Ferrari S, et at, Ann Oncol. 2011;22(5):1221) or with an intense arm B, consisting of vincristine 1,5mg/sqm+ doxorubicin 80mg/sqm+ifosfamide 9g/sqm for each course. After induction, patients underwent surgery and/or radiotherapy,followed by an adaptive treatment. Good responders received standard courses chemotherapy: arm A pts received 9 courses, while arm B pts received 5 courses. Poor responders in both arms received 4 courses followed by high-dose busulfan/melphalan+autologous stem cell rescue. The primary outcome measure was EFS for the 2 arms in the intention-to-treat population. Kaplan-Meier curves compared with log-rank test and Cox model were performed to assess differences between study arms. A secondary outcome was toxicity differences, assessed by means of the Fisher's exact test. Initial sample size was 230 pts, type I error rate 5%, power 80%. **Results:** Between 2009 and 2019, 234 patients were randomized (arm A-115; arm B-119). M:F ratio was 1.8; median age 14 years (range 2-40); tumour site extremity in 55%, axial/pelvis in 45%; tumour volume $<$ 200ml in 31% and $\geq$200ml in 69%. A good response was obtained in 56% in arm A and 60% in arm B. Median follow-up was 68 months. EFS was not significantly different between arms; HR: 0.85; 95% CI: 0,51-1,41, 5-year EFS (95% CI) was 73% (64-82%) in arm A and 75% (67-83%) in arm B ($p = 0.526$). Good responders in arm A and in arm B and poor responders in arm B had comparable results: 5-year EFS (95% CI) was 80% (71-91%), 77% (67-88%), and 72% (59-86%), respectively, while poor responders in arm A showed a worse, not statistically significant (p = 0.164) performance (63%; 50-78%). Subgroup analyses showed similar outcome for age, tumour site and volume in both arms. Hematological, gastrointestinal, and cardiovascular grade $\geq$3 toxicities were more pronounced in arm B ($p < 0.05$). **Conclusions:** Intense induction therapy with arm B did not improve 5-year EFS when compared with the standard arm A. The higher toxicity observed in arm B than in arm A was counterbalanced, in good responders, by a similar outcome with a shorter treatment plan. For poor responders, with almost 30 patients per arm event-free and with $<$ 48-month FUP, better 5-year EFS in arm B than in arm A was observed but needs further observation. Clinical trial information: NCT02063022. Research Sponsor: None.

11502 **Oral Abstract Session**

Association of treatment delays with an unfavorable outcome in patients with localized Ewing sarcoma: A retrospective analysis of data from the GPOH Euro-E.W.I.N.G.99 trial. *First Author: Uta Dirksen, Pediatrics III, West German Cancer Center, University Hospital Essen, German Cancer Consortium (DKTK), Essen, Germany*

Background: Outcome in EwS has improved by the implementation of dose or time intense systemic treatment. Aim of the study was evaluate whether treatment delays have impact on outcome of patients with localized Ewing sarcoma (EWS). **Methods:** Data from 692 patients with a tumor of the extremities, the pelvis, the chest wall and the trunk registered in the international database of the German Society for Pediatric Oncology and Hematology (GPOH) and treated in the Euro-E.W.I.N.G. 99 trial (NCT00020566) were analyzed. All patients underwent surgical treatment after induction chemotherapy. The optimal interval cut-off values for survival analyses were calculated with receiver operating characteristics curves. Hazard ratios (HR) were estimated with respective 95% confidence intervals (CI) in multivariate Cox regression models. **Results:** As per protocol, patients were to receive six cycles of VIDE induction chemotherapy in 21-day intervals. The duration between induction cycles as per protocol was fulfilled in only 5% of patients. In 72% of patients, the average interval duration between induction chemotherapy cycles was 25 days. Median interval between day 1 of the first induction chemotherapy cycle and definitive tumor surgery was 141 (IQR, 133 – 153) days in patients receiving six VIDE cycles prior to surgery. The optimal cut-off value for survival analyses in these patients amounted to 150 days. Patients with a duration of induction chemotherapy $>$ 150 days were at higher risk to develop an event (HR, 1.546; 95% CI, 1.103 – 2.166) and had a higher risk of death (HR, 1.574; 95% CI, 1.095 – 2.262), compared to patients with a duration of induction chemotherapy $<$ 150 days. Patients with delays during the induction chemotherapy also experienced a significant delay between VIDE 6 and surgery (36 vs. 27 days, $p < 0.001$) and were treated significantly more often at smaller low-volume centers (63% vs. 48%, p = 0.005). Patients with a prolonged interval $>$ 21 days between surgery and day one of postoperative chemotherapy were at a higher risk to develop an event (HR, 1.406; 95% CI, 1.011 – 1.955), and also had a significantly higher rate of postoperative complications (26% vs. 11%, $p < 0.001$), compared to patients with a shorter interval. **Conclusions:** Delays between induction chemotherapy and surgery and between surgery and consolidation chemotherapy are independently associated with a poor outcome in patients with localized EWS. Our results also underscore the need to treat EWS patients in larger and experienced sarcoma centers. The implementation of new and standardized methods in the operative strategy and optimized supportive care during systemic therapy are required to reduce perioperative morbidity and treatment delays. Research Sponsor: German Cancer Aid.

11503 **Oral Abstract Session**

P10015/SARC033: A phase 2 trial of trametinib in patients with advanced epithelioid hemangioendothelioma (EHE). *First Author: Scott Schuetze, University of Michigan, Ann Arbor, MI*

Background: EHE is a rare vascular cancer arising in liver, lung, soft tissue and bone. The natural history of metastatic disease varies considerably from indolent growth over years to rapid growth with fatal outcome in months. Treatment of patients (pts) with metastatic EHE with antiangiogenic therapy induces tumor response in a minority of pts, and median PFS is 6-12 months. TAZ-CAMTA1 translocation results in activation of MAPK pathway and is an oncogenic driver in EHE. We sought to evaluate the effect of MEK inhibition using trametinib in pts with unresectable EHE. **Methods:** A phase 2 trial of trametinib 2 mg daily was conducted in pts with EHE though the Experimental Therapeutics Clinical Trials Network supported by NCI in collaboration with SARC. Additional support was provided by the EHE Rare Cancer Charity and the EHE Foundation. Pts had to have evidence of objective tumor progression or EHE-related pain requiring narcotics for relief prior to enrollment. Presence of TAZ-CAMTA1 translocation was analyzed by fusion-FISH after enrollment. Primary trial endpoint was objective response rate (ORR) per RECIST1.1 with at least 1 objective response required in the 1st 13 pts to expand enrollment to 27. The trial was amended after stage 1 to continue enrollment to 27 pts with TAZ-CAMTA1 detected by FISH with goal of $>$4 objective responses in this group. Secondary objectives were PFS and OS rates, safety and change in pt-reported global health and pain scores per PROMIS questionnaires. **Results:** 43 pts were enrolled between 6/2017 – 9/2020 across 10 sites and 41 started therapy. TAZ-CAMTA1 fusion was detected in 26, not detected in 7, test failed in 5 and was not performed due to insufficient tumor in 5. Median pt age was 54 (range 22-81 yrs) and 11 were $>$65 yrs; 25 were female; ECOG was 0 in 23, 1 in 16 and 2 in 3 pts. Most pts experienced reduction in tumor size. ORR per RECIST was 7% (3/41); in pts with TAZ-CAMTA1 detected, the ORR was 0% (0/26). Mean pain intensity and interference scores had a statistically significant improvement and global quality of life scores did not statistically change after 4 weeks of therapy. 17 pts remained on treatment $>$ 6 months and 7 $>$ 12 months. 25 pts stopped trametinib due to EHE progression, 6 died during treatment, 6 withdrew from treatment, 3 stopped drug due to adverse event and 1 is on treatment. The most common AEs related to trametinib were rash, fatigue, nausea/vomiting, diarrhea, alopecia and edema; Grade $>$3 AEs included anemia, dyspnea, hypoxia, hypotension, syncope and dermatitis. **Conclusions:** To our knowledge, this is the largest prospective clinical study focused on pts with EHE. Although the trial did not meet the ORR goal, stable disease $>$ 6 months was seen in 40% of pts, and EHE-related pain improved on treatment. Trametinib was associated with expected cutaneous and GI adverse effects. Additional pt-reported outcomes and biomarkers of inflammation are undergoing analysis. Clinical trial information: NCT03148275. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

11504 **Oral Abstract Session**

SPEARHEAD-1: A phase 2 trial of afamitresgene autoleucel (Formerly ADP-A2M4) in patients with advanced synovial sarcoma or myxoid/round cell liposarcoma. *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: This phase 2, open-label trial (SPEARHEAD-1; NCT04044768) is designed to evaluate the efficacy, safety, and tolerability of afamitresgene autoleucel in 45 patients (pts) with advanced/metastatic synovial sarcoma or Myxoid/Round Cell Liposarcoma (MRCLS). **Methods:** Eligible pts are HLA-A*02 positive with MAGE-A4-expressing tumors. Pts undergo leukapheresis for collection of autologous T-cells for processing and manufacture into afamitresgene autoleucel cells. Pts were treated with afamitresgene autoleucel doses between $1–10 \times 10^9$ transduced T-cells after receiving lymphodepleting chemotherapy. The primary endpoint is overall response rate per RECIST v1.1 by independent review. An independent Data Safety Monitoring Board reviews ongoing safety and benefit: risk during the interventional phase. **Results:** As of Feb 4, 2021, 32 pts received afamitresgene autoleucel. Of these pts, 59% were male, 87.5% had synovial sarcoma, the median age was 43 yrs (range: 24–73), and they had a median of 3 prior systemic lines of therapy. The MAGE-A4 antigen expression level (histoscore) ranged from 112–300, and the transduced cell dose ranged from 2.7–9.9 x 10^9. At the data cutoff, 25 pts were evaluable for preliminary efficacy (23 with synovial sarcoma and 2 with MRCLS) and 7 pts (5 with synovial sarcoma and 2 with MRCLS) had insufficient follow-up (<8 weeks follow-up and/or awaiting first scan). Of the 25 evaluable pts, the investigator-assessed responses were: complete response (2 pts), partial response (8 pts), stable disease (11 pts), and progressive disease (4 pts). All responses were confirmed. Nine of the 10 responders had ongoing response at the data cutoff and 3 responders had MAGE-A4 antigen histoscores <200. The most common AEs of any grade (>30% pts) were neutropenia, lymphopenia, nausea, cytokine release syndrome, leukopenia, fatigue, pyrexia, and anemia. Cytokine release syndrome of any grade occurred in 19/32 pts; 95% of those events were ≤Grade 2. No immune effector cell-associated neurotoxicity syndrome (ICANS) has been reported to date. Cytopenia (≥G3) at 4 wks post-infusion was observed in 6 pts (anemia 3 pts, neutropenia 2 pts, and thrombocytopenia 1 pt). **Conclusion**: These preliminary data demonstrate afamitresgene autoleucel is efficacious and well tolerated in heavily pre-treated pts. Objective responses are reported across a wide range of MAGE-A4 antigen levels and deep responses have been observed. Initial durability data is encouraging. Preliminary response data in SPEARHEAD-1 is comparable to the findings of the prior Phase 1 trial [1]. To date, the safety profile of afamitresgene autoleucel has been favorable, with mainly low-grade cytokine release syndrome and tolerable/reversible hematologic toxicities. [1]. Van Tine BA, et al. CTOS; November 18-21, 2020; Virtual. Clinical trial information: NCT04044768. Research Sponsor: Adaptimmune Limited.

11505 **Oral Abstract Session**

A phase III study (APROMISS) of AL3818 (Catequentinib, Anlotinib) hydrochloride monotherapy in subjects with metastatic or advanced synovial sarcoma. *First Author: Brian Andrew Van Tine, Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO*

Background: AL3818 (Catequentinib, Anlotinib) is a novel, orally administered, small molecule tyrosine kinase inhibitor. The primary objective of this Phase 3 study is to evaluate the efficacy of AL3818 monotherapy in patients (pts) with synovial sarcoma (SS) comparing with dacarbazine in randomization setting. **Methods:** Patients with a diagnosis of synovial sarcoma requiring second line or further line treatment were eligible for enrollment. The regimen was a 21-day cycle with oral AL3818 administered on 14 days on and 7 days off. This phase 3 trial is randomized in 2:1 ratio of AL3818 comparing to dacarbazine with option of crossover after PD of dacarbazine treatment. Progression free survival (PFS) with Log Rank test is the primary endpoint and this trial for SS is currently completed enrolled in US and Italy. **Results:** Total 79 pts initiated treatment and are evaluable, 52 received AL3818 as treatment arm (T), and 27 received dacarbazine (D) as control arm (C). Arms T/C median ages were 40.5/42.0 years (range: 18-70+) and 20/16 (38.5%/59.3%) were male. Overall, PFS was 2.89 months (95% CI: 2.73 – 6.87) for AL3818 and 1.64 (95% CI: 1.45 – 2.70) for D. The PFS of study met the primary endpoint with a p-value of 0.0015 and a HR of 0.449 (95% CI: 0.270– 0.744). At the month 4, 6, and 12, the percentages of progression free patients for AL3818 were 48.1%, 42.3% and 26.9%; and for D were 14.85%, 11.1% and 3.7%. For grade 3 treatment-related adverse events, 12(23.1%) of pts experienced for AL3818 and 7(25.9%) of pts experienced for D. The most common AL3818 related grade 3 AEs were diarrhea (5.8%) and hypertension (3.8%). **Conclusions:** This phase III trial demonstrates improved disease control and superior progression free survival for AL3818 vs dacarbazine in advanced SS. In addition, the study further confirms the acceptable benefit-risk profile of AL3818 from the prior randomized Phase 2b soft tissue sarcoma study (NCT02449343). AL3818 is a meaningful treatment option for pts with advanced SS. Clinical trial information: NCT 03016819 Clinical trial information: NCT03016819. Research Sponsor: Advenchen Laboratories.

11506 **Oral Abstract Session**

NCI protocol 10250: A phase II study of temozolomide and olaparib for the treatment of advanced uterine leiomyosarcoma. *First Author: Matthew Ingham, Columbia University Irving Medical Center, New York, NY*

Background: Uterine leiomyosarcoma (uLMS) is an aggressive sarcoma subtype with frequent metastatic relapse. After failure of front-line chemotherapy, remaining options provide limited benefit (trabectedin: ORR 11%, mPFS 4.0 mos; pazopanib: ORR 11%, median PFS 2.9 mos; dacarbazine: ORR 9%, mPFS 1.5 mos). Recent molecular studies suggest uLMS harbors characteristic defects in the homologous recombination (HR) DNA repair pathway, including somatic biallelic *BRCA2* deletion in 10%, implicating potential sensitivity to PARP-inhibitor based treatment approaches. In preclinical uLMS models in which temozolomide (T, an oral equivalent to dacarbazine) or the PARP inhibitor olaparib (O) showed limited single agent activity, the combination of T + O was highly effective in inhibiting uLMS tumor growth and promoting apoptosis. **Methods:** NCI protocol #10250 is a single-arm, open-label, multi-center phase II study evaluating T + O in advanced uLMS. Pts had progression on ≥ 1 prior line and ECOG PS ≤ 2. Pts received T 75 mg/m^2 PO daily + O 200 mg PO BID days 1-7 in 21-day cycles. Primary endpoint was ORR. A one-stage binomial design was used. If ≥ 5/22 responded, the treatment was considered promising (95% power; $\alpha = 0.06$). All pts underwent paired tumor biopsies. Correlative assays to evaluate for HR deficiency (whole exome sequencing/RNAseq, RAD51 foci formation) and for intrinsic PARP inhibitor resistance (SLFN11 expression) will be correlated with response. **Results:** 22 patients were evaluable (median age 55, median prior treatment lines 3). Median follow-up was 10.8 mos. Primary endpoint, ORR within 6 mos of initiating treatment, was 23% (5/22). Overall ORR was 27% (6/22). Median PFS was 6.9 mos (95% CI: 5.4 mos – not estimable (NE)). Median duration of response (DOR) was 12.0 mos (95% CI: 9.5 mos – NE). Hematologic toxicity was common (grade 3/4 neutropenia, 77%; thrombocytopenia 32%) but manageable with dose modification. Correlative assays are ongoing with plans to present at the meeting. An immunohistochemical assay for RAD51 foci has been adapted for uLMS samples and clearly distinguishes *BRCA2*- deleted and wild-type tumors. **Conclusions:** NCI 10250 met the prespecified primary efficacy endpoint of ORR in a population of patients with heavily pre-treated uLMS. Responses are durable (median DOR 12 mos). Correlative assays are being completed to evaluate whether uLMS tumors with HR deficiency or with preserved SLFN11 expression are most sensitive to T + O and may underlie durable responses. A randomized study of the combination is planned. Clinical trial information: NCT03880019. Research Sponsor: U.S. National Institutes of Health, Conquer Cancer Foundation of the American Society of Clinical Oncology.

11507 **Oral Abstract Session**

PD1 inhibition in soft-tissue sarcomas with tertiary lymphoid structures: A multicenter phase II trial. *First Author: Antoine Italiano, Early Phase Trials Unit, Institut Bergonié, Bordeaux, France*

Background: PD1 inhibition has shown limited activity in all comers clinical trials including patients with advanced soft-tissue sarcomas (STS). In the PEMBROSARC study, objective response rate, progression-free (PFS) and overall survival (OS) were respectively 2.1%, 1.4 and 7.1 months respectively (Toulmonde et al. Jama Oncol 2017). We have recently shown that the presence of tertiary lymphoid structures (TLS) may represent a biomarker to select patients who are more likely to benefit from immunotherapy (PetitPrez et al., Nature 2020). We report here the first clinical trial investigating the efficacy of PD1 inhibition in TLS-positive STS. **Methods:** PEMBROSARC is an open-label multicenter phase II study of pembrolizumab in combination with low-dose cyclophosphamide in pts with STS selected based on the presence of TLS. TLS status has been assessed centrally has previously described (PetitPrez et al., Nature 2020). Eligible patients received pembrolizumab 200mg IV q21 days and cyclophosphamide 50 mg BID 1week on, 1 week off. All patients had confirmed progressive disease at inclusion based on central review of two imaging performed at less than 6 months interval. The primary efficacy endpoint was 6-month non-progression (as per RECIST evaluation criteria v1.1). Based on the following hypotheses: 15% 6-month non-progression rate (H0), 40% acceptable 6-month non-progression rate (H1), 5% type I error rate, 90% power, a total of 29 assessable patients were necessary and 8 patients or more had to be progression-free at 6 months to reach the first endpoint. **Results:** 240 patients were screened for TLS status between September 2018 and January 2020 in 7 centers of the French Sarcoma Group. Among them, 48 were found to be TLS+ as per central review and 35 were included in the study. The three most frequent histological subtypes were: well-differentiated/dedifferentiated liposarcoma (n = 13); UPS (n = 6), and leiomyosarcoma (n = 4). 30 patients were eligible for efficacy. Of those, as per central imaging review, 13 patients (43.3%) had tumor shrinkage resulting in partial response in 8 patients (26.7%) and stable disease in 5 cases (16.7%). 10 patients had progressive disease. Twelve patients were progression-free at 6 months (40.0% 95%CI = [22.7 – 59.4]).Median PFS and OS were 4.1 months (95%CI, 1.4-9.6) and 14.5 months (95%CI, 8.5- 18.3 months), respectively. **Conclusions:** With an objective response and a 6-month non-progression rates of 26.7% and 40% respectively versus 2.1% and 4.2% in all comers, the PEMBROSARC study confirms that selection based on TLS status is an efficient approach to tailor immunotherapy in STS patients. Clinical trial information: NCT02406781. Research Sponsor: MSD.

11508 **Oral Abstract Session**

Phase II trial of pegylated arginine deiminase in combination with gemcitabine and docetaxel for the treatment of soft tissue sarcoma. *First Author: Brian Andrew Van Tine, Siteman Cancer Center, Washington University in St. Louis, St. Louis, MO*

Background: Soft tissue sarcoma (STS) is dependent on extracellular arginine as it often lacks expression of argininosuccinate synthase 1 (ASS1), the urea cycle enzyme needed to produce intracellular arginine. PEGylated arginine deiminase (ADI-PEG 20) is an extracellular arginine-degrading enzyme that causes ASS1 deficient tumors to enter the starvation state. Preclinical data demonstrated that addition of docetaxel (D) with ADI-PEG20 upregulates expression of the transporter for gemcitabine (G), overcoming transporter level resistance, and causing increased cell death. In vivo modeling demonstrated that the combination of ADI-PEG20 with G+D was superior to G+D alone. Therefore, we performed a phase 2 trial testing the addition of ADI-PEG20 to G+D. **Methods:** We performed an investigator-initiated, phase 2, multicenter, multi-arm clinical trial of ADI-PEG20 with G (90minute infusion)+D in STS, Ewing's, osteosarcoma and small cell lung cancer. We are reporting Arm A, the STS arm. Eligible patients had STS that would be standardly treated with G+D that had progressed on at least one prior line of therapy with measurable disease by RECIST1.1 and had adequate organ function Based on a historic median PFS of 6.2 months for G+D, we targeted to enroll N = 75 patients in cohort A to detect a 2.8 month improvement with 80% power at a 5% alpha level. Primary endpoint was progression-free survival (PFS). Secondary endpoints included overall survival (OS), clinical benefit rate (CBR), safety, tolerability, cancer related mortality, and correlation with ASS1 expression by IHC. We evaluated PFS by Kaplan-Meier method and estimated overall response rate (ORR). **Results:** 75 patients were treated and deemed evaluable. The trial underwent two dose reductions by the data safety monitoring board due to prolonged neutropenia and thrombocytopenia preventing the use of day 8 G+D, consistent with preclinical mechanism of action data showing that ADI-PEG 20+D enhanced G uptake. Originally, the G dose was 900mg/m2 reduced first to 750mg/m2 then to 600mg/m2. D was dose reduced at the time of the second dose reduction from 75mg/m2 to 60mg/m2. ADI-PEG20 was given at a fixed intramuscular dose (36 mg/m2) weekly. The need for two dose reductions affected the PFS. The PFS/OS (months) were for the 600mg/m2 group (n = 31) was 6.0/N.D., leiomyosarcoma (LMS) (N = 33) 7.2/22.5, liposarcoma 5.1/17.4, and other (N = 36) 2.8/15.0. Responses were 8% complete (6/75) (3 LMS, 1 synovial and 2 angiosarcoma), 17% partial (13/75), and 43% stable disease (32/75), for an ORR of 25% (19/75) and CBR of 68% (51/75). There was a trend for ASS1 negative tumors to benefit more than ASS1 positive tumors. **Conclusions:** The combination of ADI-PEG20 with G+D can be safely and effectively given at a dose of 600mg/m2 G and 60mg/m2 D. Future randomized trials of ADI-PEG20 with G+D are planned. Clinical trial information: NCT03449901. Research Sponsor: U.S. National Institutes of Health, Polaris.

11509 **Clinical Science Symposium**

Molecular predictors of response to selinexor in advanced unresectable de-differentiated liposarcoma (DDLS). *First Author: Christopher James Walker, Karyopharm Therapeutics Inc, Newton, MA*

Background: Patients (pts) with recurrent inoperative DDLS have a poor prognosis and limited treatment options. Selinexor is an oral, selective inhibitor of nuclear export (SINE) compound approved for previously treated pts with myeloma and diffuse large B-cell lymphoma. SEAL was a Phase 2-3 randomized, double-blind, study of selinexor versus placebo in pts with progressive DDLS and 2-5 prior systemic therapies. SEAL showed significantly prolonged progression-free survival (PFS, HR = 0.70, p = 0.0228) with well managed toxicity. A biomarker predictive of clinical activity could be used to optimize selection of pts with DDLS for selinexor. **Methods:** Pts were randomized 2:1 for Phase 3: 188 received twice weekly selinexor (60mg) and 97 received placebo. Three exploratory biomarker analyses (RNA sequencing of biopsies) from selinexor-treated pts were performed: discovery set of sensitive (n = 8) or resistant (n = 9) tumors; a validation set of pts with favorable (n = 19) or poor (n = 14) tumor control based on PFS, and paired lesions from a pt who harbored both a responsive and resistant lesion. Tumor biopsies from 24 pts on placebo with short (< 5 months, n = 18) and long (> 6 months, n = 6) PFS were RNA sequenced. Gene expressions were compared using a negative binomial distribution with DeSeq2. Pathway analyses were performed using Gene Set Enrichment Analysis (GSEA) with MSigDB Cancer Gene Neighborhoods. **Results:** RNA sequencing analysis comparing 17 sensitive and resistant tumors identified 114 differentially expressed genes (adjusted p-values < 0.05). Expression of *CALB1*, which encodes the calcium-binding protein calbindin, was significantly lower in sensitive tumors (adjusted P [P_{adj}] = $7.5x10^{-20}$), and expression of *GRM1*, which encodes a metabotropic glutamate receptor that activates phospholipase C, was higher in selinexor sensitive tumors (P_{adj}= 0.003). These findings were confirmed in an independent validation set (P_{adj} = 0.01 – 0.02). In the pt with paired sensitive and resistant lesions, *CALB1* expression was 52-fold lower in the sensitive tumor. In a comparison of placebo-treated pts, neither *CALB1* or *GRM1* was differentially expressed between pts with short or long PFS, indicating they are markers of response to selinexor treatment, rather than general markers of disease aggressiveness. Gene set enrichment analyses revealed that selinexor sensitive tumors in the discovery and validation sets showed upregulation of cancer genes related to SNRK and the netrin 1 receptor tumor suppressor DCC. The resistant tumors showed upregulated EIF3S2 translation initiator-related genes. **Conclusions:** Selinexor sensitive DDLS tumors showed low expression of *CALB1* and high *GRM1*. If validated, pts with DDLS whose tumors match this expression profile are especially likely to benefit from selinexor. Clinical trial information: NCT02606461. Research Sponsor: None.

11510 **Clinical Science Symposium**

Prognosis value of S45F mutation of CTNNB1 in desmoid-type fibromatosis (DF): Prospective analysis of 500 consecutive patients (pts) from ALTITUDES trial. *First Author: Nicolas Penel, Department of Medical Oncology, Centre Oscar Lambret and Lille University Hospital, Lille, France*

Background: DF rare locally aggressive fibroblastic non-metastasizing tumor, with an unpredictable course. Its management remains challenging, there is a current shift in standard of care from large surgical resection (SR) to active surveillance (AS). Most of DF display somatic mutation of CTNNB1, with three major hotpots: S45F, T41A and S45P. The poor prognosis of S45F is a matter of debate (Timbergen et al. Ann Surg 2019). **Methods:** ALTITUDES (NCT02867033) is a nationwide prospective registry of DF, diagnosed from January 2016 to December 2020 and confirmed by central pathological review. CTNNB1 mutations were identified by NGS. Primary endpoint was event-free survival (including disease progression or relapse). We have selected pts managed by AS, SR or systemic treatments as front-line. Pt undergoing R2 resection and then managed by follow-up were part of AS group. Prognostic factors were assessed using univariate and multivariate Cox Model. **Results:** From the 630-pts enrolled in ALTITUDES, 500 (79.3%) were eligible for the present analysis. Exclusion criteria were diagnosis before 2016 in 13 pts, multiple DF in 33 pts, 39 pts without CTNNB1 mutation analysis, and 45 pts receiving other treatments. The study population included 349 females (69.8%), the median age was 40 years (range 1-89). Abdominal wall was the predominant primary site: 161 pts (32.2%). In 430 (86.0%) cases, there was a CTNNB1 mutation, including, S45F in 56 cases (11.2%). In 70 cases (14.0%), we did not identify CTNNB1 mutation. The front-line managements were AS in 361 pts (72.2%), SR with R0/R1 margins in 57 cases (11.4%) and systemic treatments in 82 pts (16.5%). The median follow-up was 23 months (Range, 0.4-55). Overall, progression or relapse occurred in 128 pts (25.6%). We observed a significant EFS-difference between treatment groups, both in univariate and multivariate analysis with, compared to AS, a better outcome in patients with SR and worse outcome in patients who had received a systemic treatment (p = 0.01 in multivariate analysis). The risk of event was significantly associated with the tumor size, with a HR = 1.46 in tumors larger than 50 mm compared to smaller tumors (95%CI, 1.01-2.10, p = 0.04). We did not observe any significant association between the CTNNB1 mutational status and the outcome: compared to patients with another mutation, the hazard ratio associated with a S45F mutation was HR = 0.84 (95%CI, 0.48-1.46, p = 0.53) in multivariate analysis. Age, gender, location (abdominal wall versus other) were not associated with EFS. **Conclusions:** In this large prospective study, S45F was not an independent poor prognostic factor in DF. Size and front-line treatment drive both the outcome. The understanding and prediction of natural course of DF require further studies. Research Sponsor: Ligue contre le Cancer.

11511 **Clinical Science Symposium**

Inflammatory indexes neutrophils/lymphocytes, platelets/lymphocytes and red-cell distribution width (RDW) as prognostic biomarkers in advanced solitary fibrous tumors (SFT) treated with pazopanib: Correlative study of GEIS-32 trial. *First Author: Javier Martin Broto, Virgen del Rocio University Hospital, Institute of Biomedicine Research (IBIS)/CSIC/ Universidad de Sevilla, Seville, Spain*

Background: Pazopanib (P) was assessed prospectively in a phase 2 study in SFT resulting in a longer progression free survival (PFS) and overall survival (OS) compared to historical controls treated with chemotherapy. No statistical correlation was found between angiogenic factors and P in its pivotal phase III sarcoma trial. In the last two years, a soaring interest on the prognostic and predictive value of inflammatory indexes such as neutrophil/lymphocyte (NLR) and platelet/lymphocyte (PLR) is emerging in sarcomas. A retrospective analysis of inflammatory indexes of patients who entered the GEIS-32 (NCT02066285) trial was performed. In that trial advanced SFT patients were treated with P from front-line. **Methods:** All eligible patients who entered in the typical- and malignant-SFT cohort of the GEIS-32 trial were included in this analysis. To determine NLR and PLR, baseline values of platelets ($10e^9$/L), neutrophils ($10e^9$/L) and lymphocytes ($10e^9$/L) were obtained from complete blood count tests. Additionally, RDW (standardized as 1 = upper value of normal range) values at baseline were also determined. The impact of NLR, PLR and RDW on OS, PFS and Choi response were analyzed by univariate and multivariate analysis. MAXSTAT was used to determine optimal cut-off points for overall survival. Metastasis free interval (MFI), mitotic count and ECOG were also analyzed, among others. **Results:** Sixty-seven out of 70 enrolled SFT patients, median age 63-y and 57% female, were considered for this analysis. The median follow-up from treatment initiation was 20.0 months. High standardized RDW value at baseline (cut-off 1.03) was significantly associated with worse OS [10.7 months (95% CI 3.8-17.5) vs 49.8 months (95% CI 9.4-90.2), p $<$ 0.001] and worse PFS [8.8 months (95% CI 0.9-7.0) vs 9.8 months (7.4-12.3), p = 0.001]. High PLR (cut-off 242) significantly correlated with worse OS [10.7 months (95% CI 5.2-16.2) vs 49.8 months (95% CI 14.6-85.0), p $<$ 0.001] and worse PFS [4.5 months (95% CI 2.0-7.0) vs 10.1 months (95% CI 6.3-13.9), p = 0.005], and high NLR (cut-off 3.78) was significantly associated with worse OS [11.7 months (95% CI 3.5-19.8) vs NA, p $<$ 0.001] and worse PFS [4.5 months (95% CI 1.9-7.0) vs 10.8 months (95% CI 8.7-12.9), p = 0.010]. Independent variables in multivariate analysis were NLR, RDW, MFI and mitosis for PFS; while RDW and ECOG for OS (see table). Further, NLR and mitosis were independent factors for Choi progressive disease (as best response). **Conclusions:** High NLR and RDW values were independent biomarkers of worse outcome in advanced SFT patients treated with pazopanib. Research Sponsor: None.

	Factor	HR	95% CI	P
PFS	MFI	2.1	1.0-4.1	0.042
	NLR	2.8	1.3-5.9	0.008
	RDW	2.8	1.3-6.3	0.012
	MITOSIS	5.0	2.3-10.4	< 0.001
OS	RDW	7.4	2.4-23.0	0.001
	ECOG	8.8	1.9-40.5	0.005

11512 **Clinical Science Symposium**

Large scale multiomic analysis suggests mechanisms of resistance to immunotherapy in leiomyosarcoma. *First Author: Galina Lagos, Columbia University Medical Center, New York, NY*

Background: Leiomyosarcomas (LMS) have been reported to have immunohistochemical (IHC) and gene expression signatures suggestive of an immune-responsive tumor microenvironment. Despite this, immune checkpoint inhibitors have demonstrated minimal activity in LMS. We examined molecular profiles of LMS specimens from multiple institutions to explore mechanisms of immunotherapy (IO) resistance. **Methods:** LMS specimens (n = 1115), including 701 uterine (uLMS) and 414 soft tissue site (stLMS) samples, underwent next-generation sequencing (NGS) of DNA (592-gene panel or whole exome) and RNA (whole transcriptome, n = 537) at Caris Life Sciences (Phoenix, AZ). A threshold of 10 mut/Mb was used to identify high tumor mutational burden (TMB-H). IHC was performed for PD-L1 (SP142; 2+|5% positive). Deficient mismatch repair (dMMR)/high microsatellite instability (MSI-H) was tested by IHC and NGS, respectively. RNA expression was analyzed using Gene Set Enrichment Analysis and Microenvironment Cell Populations-counter, with results compared to melanoma (n = 1255) as a representative immunogenic tumor type. P-values were adjusted for multiple hypothesis testing. **Results:** TMB-H was observed in 3.8% (n = 41) of LMS specimens, with a median of 5 mut/Mb (IQR 3.3-6.7). dMMR/MSI-H was rarely detected (1.5%, n = 17), whereas 8.2% (n = 88) were positive for PD-L1 expression. uLMS and stLMS did not differ in TMB-H (3.4 vs 4.5%, p = 0.277), PD-L1 expression (8.6 vs 7.4%, p = 0.322), or dMMR/MSI-H (2.0 vs 0.7% p = 0.207). stLMS demonstrated upregulation of immune-related gene sets, including interferon γ (p = 0.035) and α (p = 0.033) response, inflammatory response (p = 0.038), interleukin-6/STAT3 signaling (p = 0.030), and TNFα signaling (p = 0.026) compared to uLMS. Immune cell infiltration was increased in stLMS over uLMS, most notably for CD8 T-cell and B-cell abundance ($>$ 2-fold increase, $p < 0.0001$). Compared to melanoma, all LMS had lower abundance of CD8 T cells, cytotoxic lymphocytes, and B-cells ($>$ 2-fold decrease, $p < 0.0001$). Fibroblasts were more prevalent in LMS relative to melanoma (3.2-fold increase, $p < 0.0001$). Interestingly, while higher CD8 T-cell infiltration was positively associated with dMMR/MSI-H among LMS specimens (p = 0.032), TMB-H and PD-L1 expression were associated with lower CD8 T-cell infiltration ($p < 0.01$). **Conclusions:** Only a small proportion of LMS are TMB-H or MSI-H, suggesting that the neoantigen burden in LMS may be insufficient to promote a robust anti-tumor response, even in the presence of PD-L1 positive tumor cells. Traditional predictive biomarkers of response to IO are unlikely to be useful in LMS. Furthermore, both uLMS and stLMS have an immune microenvironment characterized by a high fibroblast and low T cell abundance relative to melanoma. Future IO trials in LMS should focus on combination therapies that may reverse the observed T-cell exclusion/desmoplastic phenotype. Research Sponsor: None.

11513 **Poster Discussion Session**

A phase II trial of sitravatinib, a multireceptor tyrosine kinase inhibitor, in patients with advanced well-differentiated/dedifferentiated liposarcoma. *First Author: Jay Oza, Columbia University Irving Medical Center, New York, NY*

Background: Well-differentiated/dedifferentiated liposarcoma (WD/DD LPS), a sarcoma of adipocytic origin, lacks effective treatment options for advanced disease. Pazopanib, a receptor tyrosine kinase (RTK) inhibitor active upon angiogenic RTKs, is approved for non-adipocytic sarcomas but failed to show activity in LPS. In a phase 2 study, pazopanib provided a progression-free rate at 12 weeks of 26% in LPS. Our preclinical work implicated IGF1R, MET, and PDGFRα/ß in liposarcomagenesis. Sitravatinib (S) is a novel, orally available, potent, small molecule RTK inhibitor active upon these and related targets. In preclinical WD/DD LPS models, S demonstrated significant activity *in vitro* and *in vivo* and appeared superior in efficacy to pazopanib, imatinib and crizotinib. **Methods:** We performed a phase II, single-arm, multi-center, Simon 2-stage study to evaluate S in adult pts with unresectable/metastatic WD/DD LPS who had received ≥ 1 prior line of systemic therapy and had evidence of disease progression $\leq$ 12 wks prior to enrollment. Pts received S 120 mg PO daily in continuous 21-day cycles. Primary endpoint was the progression-free rate at 12 wks (PFR_{12}). Secondary endpoints were objective response rate (ORR), progression free survival (PFS) and safety/tolerability. Based upon historical controls, $PFR_{12} \leq 20\%$ was considered inactive whereas $PFR_{12} \geq 40\%$ was considered promising. If $\geq$ 3/13 met PFR_{12} in stage 1, the study proceeded to full accrual. If $\geq$ 9/29 met PFR_{12} overall, S was considered promising. Design provided 85% power with α= 0.10. A subset of pts underwent paired biopsies. **Results:** 29 pts initiated treatment and are evaluable. Median age was 62 yrs (range: 28-88). 16 (55%) were male. 28/29 had DD LPS. 3 pts remain on treatment and 26 pts have discontinued (22 for disease progression, 2 for adverse events). In the first stage, 5/13 pts met the PFR_{12} endpoint; therefore, the study proceeded to full accrual. Overall, 12/29 pts (41%) were progression-free at 12 weeks and the study met the primary endpoint. ORR by RECIST was 3.4%. Median PFS was 11.7 weeks (95% CI: 5.9 - 35.9 wks). 12/29 (41%) of pts experienced grade 3 treatment-related adverse events. Common S-related grade 3 AEs were hypertension (24%), fatigue (7%) and hyponatremia (7%). There were 2 grade 4 events (hypertension, reversible posterior leukoencephalopathy syndrome). Hypertension was easily managed with medication. A subset of pts underwent paired tumor biopsies that will be analyzed using next generation sequencing and reverse phase protein array. **Conclusions:** S met the predefined efficacy endpoint with 12/29 pts (41%) progression-free at 12 weeks, indicating clinically meaningful activity potentially superior to pazopanib. The drug was well tolerated. Further study of S in WD/DD LPS is warranted. Clinical trial information: NCT02978859. Research Sponsor: Mirati Therapeutics.

11514 **Poster Discussion Session**

Phase 1 trial of seclidemstat (SP-2577) in patients with relapsed/refractory Ewing sarcoma. *First Author: Damon R. Reed, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Ewing sarcoma (ES), a rare bone and soft tissue sarcoma mainly of adolescents and young adults, is characterized by a chromosomal translocation resulting in a fusion oncoprotein. Lysine specific demethylase 1 (LSD1) has been shown to associate with the fusion oncoprotein and promote oncogenic transcriptional activity making LSD1 an attractive target for ES treatment. Seclidemstat is a novel, selective, reversible oral LSD1 inhibitor capable of inhibiting both LSD1's catalytic and scaffolding functions. This is the first report of an LSD1 inhibitor in a Phase 1 trial focused exclusively on ES. **Methods:** SALA-002-EW16 is a Phase 1 trial of single agent seclidemstat in patients (pts) with relapsed or refractory (R/R) ES. This report describes the completed monotherapy dose escalation. Pts $>$ 12 years received oral SP-2577 twice daily in 28-day cycles under fasting conditions at the assigned dose level. The primary objective was safety and tolerability. Secondary objectives include to determine maximum-tolerated dose (MTD), recommended Phase 2 dose (RP2D), preliminary efficacy, pharmacokinetics, and pharmacodynamics. **Results:** As of December 30, 2020, 27 pts with R/R ES were enrolled. Pts received escalating doses of SP-2577 at 75 (n = 1), 150 (n = 2), 300 (n = 4), 600 (n = 6), 900 (n = 8), or 1200 mg PO BID (n = 6). The median age was 25 years (range 15–68), 63% were male, and pts had received a median of 3 (range 2–12) prior systemic therapies. There were no treatment-related deaths. The most common ($>$ 5%) grade 3 treatment-related adverse events (TRAEs) were vomiting (15%), abdominal pain (11%), and hypokalemia (11%). One pt (4%) with grade 3 pancreatitis reported a grade 4 AE of elevated lipase. All remaining grade 3 TRAEs, including hematological TRAEs, were reported in only one pt each. Four pts discontinued study for an AE (weight loss, pancreatitis, vomiting, abdominal pain). Three pts had a dose reduction. The first cycle dose-limiting toxicities were gastrointestinal-related AEs observed in 2 pts at 1200 mg BID. Thus, the MTD/RP2D was established as 900 mg BID. Peak plasma concentrations occurred at a median of 4 hours (h) post-dose and median terminal half-life was 6 h; exposure was dose proportional through 900 mg BID. One pt at 600 mg BID achieved a reduction in target lesions starting at end of C2 with further target lesion tumor shrinkage through end of C4 and C6 (maximum 76% tumor shrinkage) with coincident new non-target lesion appearance at end of C2. Of pts evaluable for response at the end of C2 (12 pts), two additional pts (16.7%) at 600 mg BID and 900 mg BID had overall stable disease. **Conclusions:** Seclidemstat has a manageable safety profile with proof-of-concept preliminary activity in heavily pretreated pts with relapsed/refractory ES. These data support the planned Phase 2 expansion of seclidemstat as single agent and in combination with chemotherapy in ES and other sarcomas that share similar translocations. Clinical trial information: NCT03600649. Research Sponsor: Salarius Pharmaceuticals Inc, Other Foundation, Other Government Agency.

11515 **Poster Discussion Session**

Outcomes in the dedifferentiated liposarcoma cohort of SAR-096, a phase II trial of ribociclib in combination with everolimus in advanced dedifferentiated liposarcoma (DDL), and leiomyosarcoma (LMS). *First Author: Margaret von Mehren, Fox Chase Cancer Center, Philadelphia, PA*

Background: Dedifferentiated liposarcoma (DDL) is characterized by ring chromosomes of chromosone12, which includes amplification of MDM2 and CDK4. Exposure to CDK4 inhibitors in Rb+ leiomyosarcoma (LMS) cell lines leads to decreased cell proliferation, and increased senescence, and G0/G1-phase arrest. When combined, ribociclib a CDK4 inhibitor and everolimus, an mTOR inhibitor show synergistic growth inhibition in multiple tumor models. We hypothesized that this combination could lead to increased disease control in patients with DDL. **Methods:** This study enrolled patients (pts) into one of two cohorts: DDL or Rb+ LMS. LMS pts were required to have 1 prior line of therapy; DDL pts required no prior therapy. There were no limits to prior therapies in either group. Measurable disease by RECIST 1.1 was also required. Ribociclib was given at 300 mg daily for 21/28 days and everolimus was given continuously at 2.5 mg daily in 28 day cycles. The primary endpoint was progression free rate at 16 weeks. A Simon two-stage design was utilized and if at least 8 out of 24 pts were progression free at 16 weeks, the treatment was declared promising for the cohort. Here in we present data on the DDL cohort. **Results:** To date, 21 DDS pts, median age of 63 (range 40-79), of which 43% (n = 9) female were treated. Median prior lines of therapy was 1 (range 0-6). Of 19 pts with complete data, 8 (42%) met the primary endpoint of non-progression at 16 weeks. Confirmed partial response was seen in 2 pts (10%). Median PFS was 16 weeks, and stable disease occurring as best response in 11 (55%) pts. Grade 3-4 toxicities were uncommon except for lymphopenia (24%) and neutropenia (33%); no episode of neutropenic fever were observed. There was one death on study secondary to myocardial infarction, considered possibly related to therapy. Results of optional tissue biopsies pre and on therapy obtained to assess pharmacodynamic changes in PTEN, pAKT, CDK4, Rb and pS6 will be presented. **Conclusions:** The combination of ribociclib and everolimus demonstrates activity in DDL with prolonged stable disease ($>$16 weeks) meeting the primary protocol endpoint. Notably partial responses were also observed. The combination was well tolerated with acceptable side effects. Updated outcomes will be presented. Clinical trial information: NCT03114527. Research Sponsor: Novartis, Fox Chase Cancer Center.

11516 **Poster Discussion Session**

Eribulin and gemcitabine in previously treated patients with advanced liposarcoma or leiomyosarcoma: A multicenter, single-arm, phase 2-trial. *First Author: Chang Gon Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Eribulin and gemcitabine have shown encouraging efficacy in soft-tissue sarcoma (STS) as a monotherapy. Here, we evaluated the activity and safety of combined use of eribulin and gemcitabine in two most common histologic types of STS, liposarcoma and leiomyosarcoma. **Methods:** In this non-randomized, multi-center phase 2 study, patients were included if they had progressive disease after one or two prior chemotherapy including doxorubicin. Patient were given eribulin 1.4 mg/m^2 and gemcitabine 1,000 mg/m^2 on day1 and day 8 every 3 weeks. The primary endpoint was progression-free survival rate at 12 weeks ($PFSR_{12wks}$) with null and alternative hypothesis of $PFSR_{12wks} \leq 20.0\%$ and $\geq 40.0\%$, respectively. **Results:** Of 37 patients included, 22 had leiomyosarcoma, and 15 had liposarcoma. At 12-weeks after treatment, 16 and (72.7%) 11 (73.3%) patients in leiomyosarcoma and liposarcoma were progression-free. Overall $PFSR_{12wks}$ was 73.0%, satisfying the primary endpoint. Objective response rate, disease control rate, median progression-free survival, and median overall survival were 16.2%, 78.4%, 23.9 weeks, and 88.9 weeks, without any statistical differences according to histologic subtypes. No new safety signals and treatment-related death were observed. **Conclusions:** Eribulin and gemcitabine showed promising activity and manageable safety profile in patients with STS of liposarcoma and leiomyosarcoma histology. Updated outcomes for ongoing patients will be presented. Clinical trial information: NCT03810976. Research Sponsor: None.

11517 **Poster Discussion Session**

Phase (Ph) 1b/2 evaluation of olaratumab in combination with gemcitabine and docetaxel in advanced soft tissue sarcoma (STS). *First Author: Steven Attia, Mayo Clinic, Jacksonville, FL*

Background: Doxorubicin (doxo) remains standard first-line therapy for advanced STS. Doxo in combination with olaratumab (O) demonstrated superior clinical activity compared to doxo alone in a Ph 2 trial (NCT01185964), although this was not confirmed in the subsequent Ph 3 trial (NCT02451943). Gemcitabine (G) plus docetaxel (D) is a second line therapy for advanced STS. Here, we report a concurrent Ph 2 study that explored a second-line addition of O to G and D for advanced STS (ANNOUNCE 2 NCT02659020). **Methods:** Adult patients (pts) with unresectable locally advanced or metastatic STS, $\leq$ 2 prior lines of systemic therapy, and ECOG PS 0-1 were eligible. Pts were enrolled from 2 cohorts: O-naïve and O-pretreated. In both cohorts, pts were randomized 1:1 to either O, G plus D or placebo (PBO), G plus D. Pts received 21-day cycles of O (20 mg/ kg cycle 1 and 15 mg/kg other cycles, day (d) 1 and d8), G (900 mg/m^2, d1 and d8) and D (75 mg/m^2, d8). Pts continued treatment until progression, toxicity, or withdrawal. Randomization was stratified by histology (leiomyosarcoma [LMS] vs non-LMS), prior systemic therapy, ECOG PS, and prior pelvic radiation. The primary objective was overall survival (OS) in the O-naïve population using an alpha level of 0.20. Secondary endpoints included OS (O-pretreated) and other efficacy parameters, as well as safety and pharmacokinetics (PK). **Results:** 167 pts were enrolled in the O-naïve cohort and 89 pts in the O-pretreated cohort. Baseline patient characteristics were well balanced. OS for O-naïve pts was 16.8 vs 18.0 months (m) (hazard ratio [HR] = 0.95, 95% CI: 0.64-1.40; p = 0.78) for the investigational vs control arm, respectively. Other efficacy outcomes are presented in the table. Safety was manageable across treatment arms. PK parameter estimates for O were consistent with previous studies. **Conclusions:** There was no statistically significant difference in OS between the two arms in the O-naïve population. However, while not statistically significant, the combination of O, G and D demonstrated favorable OS in the O-pretreated cohort, and PFS and objective response rate (ORR) in both cohorts. For O-naïve pts, a clinically meaningful progression-free survival (PFS) improvement was observed. Further investigations in specific histological subtypes are ongoing. Clinical trial information: NCT02659020. Research Sponsor: Eli Lilly.

	O-Naïve					O-Pretreated				
Cohort	O+G+D N = 81		Control N = 86		HR (95% CI)/ p-value*	O+G+D N = 46		Control N = 43		HR (95% CI)/ p-value*
Endpoint		95% CI		95% CI			95% CI		95% CI	
OS, median m	16.8	15.3, 25.4	18.0	13.2, 22.9	0.95 (0.64, 1.40)/0.78	19.8	14.2, -	17.3	10.8, 20.3	0.67 (0.39, 1.16)/0.15
PFS, median m	7.6	5.1, 8.5	4.4	2.9, 6.9	0.69 (0.48, 1.01)/0.06	5.5	2.8, 8.7	4.2	2.2, 6.9	0.83 (0.49, 1.40)/0.48
ORR, %	32.1	22.2, 43.4	23.3	14.8, 33.6	0.19	30.4	17.7, 45.8	14	5.3, 27.9	0.06

CI = confidence interval; N = total number of pts *Log-rank p-value (2-sided).

11518 **Poster Discussion Session**

Updated results of European Organization for Research and Treatment of Cancer (EORTC) phase 2 trial 1202 cabazitaxel in patients with metastatic or inoperable locally advanced dedifferentiated liposarcoma. *First Author: Roberta Sanfilippo, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: Treatment options for patients with unresectable and/or metastatic dedifferentiated liposarcoma (DDLPS) are limited. The most effective agents include doxorubicin, ifosfamide, trabectedin and eribulin, but, in general, objective response rates (ORR) and progression free survival (PFS) are modest. Cabazitaxel exerts its effect through inhibition of microtubular disassembly and has been shown to be relatively safe, effective and well-tolerated. EORTC 1202 assessed whether cabazitaxel demonstrated sufficient antitumor activity in patients with metastatic or inoperable locally advanced DD LPS to justify further investigation in a phase III setting. **Methods:** This was an international multi-center, open label single arm phase II trial. The clinical cut-off date for the primary analysis was performed on August 31, 2020. Data base lock was performed on February 2, 2021. Eligible patients with metastatic or inoperable locally advanced DD LPS, after a centralized pathological review, were treated with cabazitaxel 25mg/m^2 IV infusion over 1 hour every 21 days. Primary endpoint was PFS rate at 12 weeks assessed by local investigator per RECIST 1.1. Based on a Simon two-stage design, at least 4 out of 17 (Stage 1) and 11 out of 37 (Stage 2) eligible and evaluable patients who are progression-free at 12 weeks were needed. Currently, a centralized radiological assessment is ongoing. **Results:** Forty patients were registered by 10 institutions in 4 countries between March 2015 and March 2019, with 2 patients being ineligible. One patient was still on treatment at the clinical cut-off date. The number of cycles ranged from 1 to 30, with a median of 5; 26 patients (65%) received at least 4 cycles of cabazitaxel. PFS at 12 weeks was 55% (conditional 1-sided 95% CI 40.8-100), achieving the primary study endpoint. The median FU was 21.6 months, median PFS was 6 months and median OS 21 months. RR was 8% with one CR and two PR. Twenty-three(60.5%) pts had a SD. Disease control (PR+SD) was achieved in 26 patients (68%). The most common cabazitaxel -related grade >3 adverse events in all 40 registered patients were Neutrophil count decreased (50%), febrile neutropenia (25%), fatigue (12.5%), and anemia (10%). There were no cabazitaxel-related deaths. **Conclusions:** EORTC 1202 met its primary endpoint, with 21/38 pts (55%) being progression-free at 12 weeks. Results of this trial confirm activity of cabazitaxel in patients with metastatic or inoperable locally advanced DD LPS and looks interesting if compared to the other available options and experimental drugs recently reported in this patient population. Clinical trial information: NCT01913652. Research Sponsor: Sanofi Aventis.

11519 **Poster Discussion Session**

Phase II study of atezolizumab in advanced alveolar soft part sarcoma (ASPS). *First Author: Abdul Rafeh Naqash, Developmental Therapeutics Clinic/Early Clinical Trials Development Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD*

Background: ASPS constitutes < 1% of soft tissue sarcomas and frequently presents in adolescents and young adults. There are no approved therapies for ASPS. We are currently evaluating the clinical activity of atezolizumab (atezo), an anti-PD-L1 antibody, in patients (pts) with advanced ASPS. **Methods:** This is a multicenter, open-label, single-arm phase II study where atezo is administered at a fixed dose of 1200 mg in adults or 15 mg/kg (1200 mg max) in pediatric pts age $\geq$2 once Q21 days. The primary objective is to determine the objective response rate (ORR) of atezo using RECIST 1.1. Secondary objectives include duration of response and correlating response with the immune effects of atezo in blood and paired tumor biopsies (pre- and post-treatment). Tumor specimens were analyzed with multiplex immunofluorescence immuno-oncology panels to quantify CD8+, PD-1+, and PD-L1+ cells/mm^2 in the tumor microenvironment. CD8+ density was calculated as the total number of CD8+ cells divided by the entire area (mm^2) of the tumor and invasive margins of the biopsy. **Results:** As of February 4, 2021, 44 pts have been enrolled. The median age in the study was 31 years (range, 12–70) with equal male: female distribution. 54.5% of pts were Caucasian. Baseline ECOG $\leq$1 was present in 97.7%. The median time on study was 11.5 months (range, 0.8–40.3 months). At data cutoff, response evaluation was available for 43 pts with an ORR of 37.2% (16/43). One pt experienced a complete response and 15 pts experienced a partial response (PR), of which 14 were confirmed. The median time to confirmed response was 3.5 months (range, 2.1–14.9 months). The median duration of confirmed response was 16.5 months (range, 4.9–38.1 months). Stable disease (SD) was present in 58.1% (25/43). One or more grade 3 adverse events potentially related to atezo were identified in 16.3% (7/43) pts. These include diarrhea, hypothyroidism, transaminitis, anemia, vertigo, extremity pain, myalgia, pneumonitis, rash, and stroke (n = 1 each). No grade 4 or 5 events have been reported. Among 8 cases with evaluable biopsy pairs, both baseline and C3D1 specimens in all cases demonstrated CD8+ T cell infiltration and PD-L1 expression. PD-1 expression was detected at baseline in 5 cases and at C3D1 in 7 cases. In 6 cases (3 SDs and 3 PRs), treatment did not change CD8+ cell density. In the other 2 cases (both PRs), CD8+ density increased > 3x above baseline by C3D1. Analysis of T cell activation using pharmacodynamic response biomarkers, along with whole exome and RNA-seq to evaluate the genomic and transcriptomic landscape of ASPS, are ongoing. **Conclusions:** Atezo is well tolerated and demonstrates promising single agent activity with durable responses in advanced ASPS. Preliminary tumor biomarker analysis confirms the presence of multiple PD-1/PD-L1 immune checkpoint (IC) components, indicating that advanced ASPS is an ideal candidate for therapeutic IC inhibition. Funded by NCI Contract No HHSN261200800001E. Clinical trial information: NCT03141684. Research Sponsor: U.S. National Institutes of Health.

11520 **Poster Discussion Session**

High clinical activity of pembrolizumab in chordoma, alveolar soft part sarcoma (ASPS) and other rare sarcoma histotypes: The French AcSé pembrolizumab study from Unicancer. *First Author: Jean-Yves Blay, Centre Léon Bérard, Lyon, France*

Background: AcSé Pembrolizumab is a Phase 2, non-randomized parallel arms, open-label, multicentric study from Unicancer investigating the efficacy and safety of pembrolizumab monotherapy in different cohorts of patients with rare cancers (NCT03012620). Here we report the results of pembrolizumab in the rare sarcoma cohort. **Methods:** Selected histotypes were all rare sarcomas patients (pts) (incidence $< 0.2/100,000$/year). Main inclusion criteria were age > 18, ECOG PS$\leq$1 and advanced or metastatic disease resistant to standard treatment. Patients received pembrolizumab 200 mg IV as a 30-minute infusion on Day 1 of every 21-day cycle for a maximum of 2 years. The primary endpoint was the confirmed objective response rate according to RECIST v1.1 at 12 weeks. Secondary endpoints included clinical benefit rate, duration of response, progression-free survival (PFS), overall survival (OS), and safety. Five groups of pts were distinguished, namely chordoma, alveolar soft-part sarcoma (ASPS), desmoplastic small round cell tumor (DSRCT), smarca4 deficient malignant rhabdoid tumor (SMRT), and other histotypes. **Results:** 98 patients including 34 with chordoma, 14 ASPS, 11 SMRT, 8 DSCRT and 31 with other histotypes, were included from July 2017 to December 2020. The median number of cycles was 5 (range, 1 to 35) with 78 (79.6%) patients who discontinued the trial after a median of 4 cycles. There were 6 (7.3%) partial response (PR) at 12 weeks. The best response was CR in 1 patient (1%), PR in 14 patients (14.3%), and stable disease (SD) in 33 (33.7%). Median duration of response was 8.2 months [IQR, 4.1 to 9.0]. The occurrence of best response depended on the histotype, with 3 (8.8%) responses in chordoma, 7 (50%) in ASPS, 3 (27%) in SMRT, 1 (12.5%) in DSCRT and 1 (3.2%) in other histotypes ($p = 0.0011$). At the data cut off, median PFS was 2.75 months, and median OS was 19.7 months on the overall population. Outcomes differed according to the histotype group, with the 12 months PFS rates at 31.2% (chordoma), 35.7% (ASPS), 18.2% (SMRT), 0% (DSCRT) and 3.3% (other), respectively ($p < 0.0001$), and median PFS at 6.6 (chordoma), 7.5 (ASPS), 1.1 (SMRT), 2.1 (DSCRT) and 2.1 months (other), while 1-year OS rates were 76.6% (chordoma), 85.7% (ASPS), 36.4% (SMRT), 17.5% (DSCRT) and 42.9% (other) with median OS only reached for SMRT (2.4 months), DSRCT (10 months), and the other histotype group (7.1 months) ($p = 0.004$). The side effect profile of pembrolizumab was similar to other tumor type. **Conclusions:** Pembrolizumab is safe and well tolerate in this pop od STS pts, AcSé study reports high levels response rate and prolonged activity in selected subtypes of rare sarcomas. Clinical trial information: NCT03012620. Research Sponsor: La Ligue Nationale contre le Cancer, Other Foundation, Pharmaceutical/Biotech Company.

11521 **Poster Discussion Session**

Safety and efficacy of letetresgene autoleucel (lete-cel; GSK3377794) in advanced myxoid/round cell liposarcoma (MRCLS) following high lymphodepletion (Cohort 2): Interim analysis. *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Cancer testis antigen NY-ESO-1 is expressed in multiple tumor types, including 80–90% of MRCLS [1,2]. Overall response rates (ORRs) to MRCLS treatment are low (1L, <20%; 2L, <10%) [2]. Lete-cel, an autologous T-cell therapy, targets NY-ESO-1/LAGE-1a+ tumors using a genetically modified, high-affinity T-cell receptor. High-dose lymphodepletion (LD) was linked with better responses in synovial sarcoma [3]; the current study tested this hypothesis in MRCLS. **Methods:** This open label, pilot study evaluates lete-cel efficacy and safety in advanced MRCLS following low-dose (Cohort 1 [C1]; 30 mg/m^2 fludarabine [flu] x 3d + 600 mg/m^2 cyclophosphamide [cy] x 3d) or high-dose (Cohort 2 [C2]; 30 mg/m^2 flu x 4d + 900 mg/m^2 cy x 3d; initiated based on C1 data) LD. Key eligibility: age $\geq$18 y; HLA-A*02:01; A*02:05, or A*02:06; advanced high-grade NY-ESO-1+ MRCLS ($\geq$30% of cells 2+/3+ by IHC); prior anthracycline; measurable disease; specified washouts; and active/chronic/intercurrent illness restrictions. Stages include screening, leukapheresis, lete-cel manufacture, LD, lete-cel infusion (1– 8 $\times$ 10^9 transduced T cells), follow-up. Response is assessed at wk 4, 8, 12, and 24, then every 3 mo to disease progression/death/withdrawal. The primary efficacy endpoint is investigator-assessed ORR by RECIST v1.1. In C1 (n=10 patients [pts]), lete-cel was well tolerated and linked with 2 confirmed partial responses (PR; ORR, 20%) and stable disease (SD) in 8 pts. Planned interim analysis for C2, shown here, was done once all 10 treated pts had $\geq$3 post-baseline disease assessments or progressed/died/withdrew. Efficacy data will be correlated with transduced cell kinetics and pharmacodynamics marker profiles. **Results:** Durable (1.0–7.8 mo) PR (4/10 pts [ORR, 40%]; 2 ongoing) and prolonged (2.7–10.6 mo) SD (5/10 pts; 3 ongoing) with tumor regression were observed. Treatment-emergent cytopenias occurred in all pts. All experienced T-cell related cytokine release syndrome (5 serious adverse events; 30% Grade 3), with onset $\leq$5d of infusion and median duration 7.5d. Graft-vs-host disease, immune effector cell–associated neurotoxicity syndrome, pancytopenia, or aplastic anemia were not reported. **Conclusions:** A single lete-cel infusion after high LD showed antitumor activity in advanced MRCLS and a manageable safety profile consistent with other lete-cel studies. The trial is active but no longer recruiting (NCT02992743). MRCLS is included in a separate, ongoing lete-cel study (NCT03967223). References: 1. D'Angelo SP, et al. *J Clin Oncol* 2018;36:15_suppl, 3005. 2. Pollack SM, et al. *Cancer Med* 2020;9(13):4593–602. 3. D'Angelo SP, et al. *J Immunother Cancer* 2020;8:P298. Funding: GSK (208469; NCT02992743). Editorial support was provided by Eithne Maguire, PhD, of Fishawack Indicia, part of Fishawack Health, and funded by GSK. Clinical trial information: NCT02992743. Research Sponsor: GlaxoSmithKline (208469).

11522 **Poster Discussion Session**

A phase II, open-label, randomized trial of durvalumab (D) with olaparib (O) or cediranib (C) in patients (pts) with leiomyosarcoma (LMS). *First Author: Olubukola Ayodele, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: The use of immune checkpoint blockade (ICB) in non-inflamed (cold) tumors is associated with limited clinical efficacy. Combination of ICB with certain molecularly targeted agents (MTA) is hypothesized to increase tumor immunogenicity by recruiting tumor infiltrating lymphocytes in cold tumors, such as LMS. Here, we present the results of LMS cohort treated on the DAPPER study (NCT03851614). **Methods:** LMS pts with ECOG 0-1 were randomized to either D+O (arm A), or D+C (arm B). In a 28-day cycle, D 1500mg i.v. q4w with either O 300mg bid po qd or C 20mg po qd 5d/week were administered. Overall response rates (ORR) were determined using RECISTv1.1. Evaluation of tumor kinetics (TK) was performed by calculating tumor growth rate (TGR) of target lesions on CT images at baseline and on-treatment, adjusted to account for the time difference between scans. TGR is expressed as % tumor growth/week (Ferte C et al. CCR, 2014). Additionally, paired FFPE samples (from baseline and on-treatment biopsies) were assessed using multispectral fluorescent immunohistochemistry (IHC) panel: CD3, CD8, CD20, CD68, FOXP3 and cytokeratin. Tumor areas were identified by a pathologist and immune cells were quantified using InForm image analysis software. **Results:** 25 metastatic LMS pts were randomized to arm A (n = 11) or B (n = 14) over 21 months. Median age was 53 years, 96% were females and 60% of pts had $\geq$3 lines of therapy. In 23 evaluable pts, no responses were seen, 7 pts had stable disease (SD) while 16 has progressive disease (PD). TK analysis was evaluable for 18 pts (arm A = 8, B = 10). 5/8 pts (62.5%) in arm A and 6/10 pts (60%) in arm B showed decreased TK (defined as $TGR^{baseline} > TGR^{on\text{-}treatment}$). In 4/5 (80%) pts who had deceleration of TK in arm A, SD was maintained for $\geq$6 months. The reduction in TGR on treatment, compared to baseline was significant in arm A but not in arm B (measured as median % tumor growth/week of 0.5 vs 5.1, 95% CI 0.2-4.3, $p = 0.035$ in arm A; and 1.3 vs 2.9, 95% CI 0.2-2.7, $p = 0.088$ in arm B). The median PFS of arm A and B were 9 (95% CI 3-12.8) and 4 (95% CI 2.2-4.6) months respectively. There were no statistically significant differences in tumor-infiltrating immune cells when comparing baseline and on-treatment biopsies from arm A or B. In arm A, one pt with SD > 6 months had a 2.5-fold increase in CD8 (CD3+CD8+) T cells and a 7.6-fold increase in macrophages (CD68+). **Conclusions:** D+O or D+C resulted in stable disease in 30% of pts, mostly on arm A (D+O). TK analysis may identify pts with prolonged SD on treatment. Although a cold-to-hot immunophenotype change was not generally seen, changes in tumor infiltrating immune cell subsets were observed in one patient with prolonged stable disease. These findings support further molecular and immunophenotype characterization in LMS patients treated with D+O or D+C. Clinical trial information: NCT03851614. Research Sponsor: Princess Margaret Cancer Centre.

11523 **Poster Discussion Session**

Demographics, outcomes, and risk factors for patients (Pts) with sarcoma and COVID-19: A multi-institutional cohort analysis. *First Author: Michael J Wagner, University of Washington, Fred Hutchinson Cancer Research Center, Seattle Cancer Care Alliance, Seattle, WA*

Background: Sarcoma pts often receive aggressive, highly immunosuppressive therapy and may be at high risk for severe COVID-19. Demographics, outcomes and risk factors for pts with sarcoma and COVID-19 are unknown. We aimed to describe the course of COVID-19 in sarcoma pts and to identify factors associated with adverse outcomes. **Methods:** The COVID-19 and Cancer Consortium (NCT04354701) is an international registry of pts with cancer and COVID-19. Adult pts ($\geq$18 years old) with a diagnosis of sarcoma and laboratory confirmed SARS-CoV-2 were included from 50 participating institutions. Data including demographics, sarcoma diagnosis and treatment, and course of COVID-19 infection were analyzed. Primary outcome was the composite rate of hospitalization or death at 30 days from COVID-19 diagnosis. Secondary outcomes were 30 day all-cause mortality, rate of hospitalization, O2 need, and ICU admission. Descriptive statistics and univariate Fisher tests are reported. **Results:** From March 17, 2020 to February 6, 2021, N=204 pts were included. Median follow up was 42 days. Median age was 58 years (IQR 43-67). 97 (48%) were male. 30 (15%) had ECOG performance status $\geq$2. 104 (51%) received cancer treatment, including surgery or radiation, within 3 months of COVID-19 diagnosis. 153 (75%) had active cancer, of whom 34 (22%) had lung metastases. 100 (49%) pts met the composite primary endpoint; 96 (47%) were hospitalized and 18 (9%) died within 30 days from COVID-19 diagnosis. 64 (31%) required oxygen, and 16 (8%) required ICU admission. Primary endpoint rates were similar for pts who received cytotoxic chemotherapy (38/58, 66%) or targeted therapy (16/28, 57%). Pts with higher rates of the primary endpoint included patients $\geq$60 years old (59% vs 40%, OR 2.04, 95% CI 1.12-3.74, p=0.016), pts with ECOG PS $\geq$2 vs 0-1 (90% vs 41%, OR 12.2, 95% CI 3.44-66.8, p<0.001), pts receiving any systemic therapy within 3 months of COVID-19 diagnosis (62% vs 39%, OR 2.65, 95% CI 1.43-4.97, p=0.001), and pts with lung metastases (68% vs 42%, OR 2.77, 95% CI 1.19-6.79, p=0.013). Primary endpoint rates were similar across sarcoma subtypes (Table). **Conclusions:** This is the largest cohort study of pts with sarcoma and COVID-19 to date. Sarcoma pts have high rates of complications from COVID-19. Older patients, those with poor performance status, those recently receiving systemic cancer therapy, and those with lung metastases appear to have worse outcomes. Research Sponsor: U.S. National Institutes of Health.

Sarcoma type	Pts*, n	Age 60+, n (%)	Recent systemic cancer therapy, n (%)	Composite outcome, n (%)
Soft tissue sarcoma, NOS	48	18 (38)	25 (52)	23 (48)
GIST	33	27 (82)	21 (64)	15 (45)
Liposarcoma	23	15 (65)	6 (26)	10 (43)
Osteosarcoma	19	*	5 (26)	9 (47)
Leiomyosarcoma	10	*	*	*
Pleomorphic sarcoma	10	*	*	5 (50)
Ewing sarcoma	9	0	*	*
Myxofibrosarcoma	9	7 (78)	*	*
Other types	45	-	-	-

+2 pts had 2 different sarcomas. *<5 pts in subgroup.

11524 **Poster Discussion Session**

Randomized, double-blind, placebo (PL)-controlled, phase III trial of pimitespib (TAS-116), an oral inhibitor of heat shock protein 90 (HSP90), in patients (pts) with advanced gastrointestinal stromal tumor (GIST) refractory to imatinib (IM), sunitinib (SU) and regorafenib (REG). *First Author: Yoshitaka Honma, National Cancer Center Hospital, Tokyo, Japan*

Background: Pimitespib (PIM) is a novel class of orally active selective HSP90 inhibitors. KIT and PDGFRA are clients of HSP90 for their functional stability; therefore, HSP90 is a rational therapeutic target on GIST in pts with acquired resistance, such as secondary mutation in *KIT*, to approved tyrosine kinase inhibitors. A phase II trial showed clinical activity of PIM in pts with advanced GIST refractory to standard treatments whose medical need remains unmet. This phase III trial evaluated the efficacy and safety of PIM for this unmet clinical need. **Methods:** Eligible pts had histologically confirmed advanced GIST refractory to IM, SU, and REG, ≥1 measurable lesion, and ECOG performance status 0 or 1. Pts were randomized 2:1 to receive either PIM 160 mg once daily on a 5-days-on/ 2-days-off schedule or PL. Pts eligible for unblinding at the time of progressive disease were allowed to crossover to open-label PIM. The primary endpoint was progression-free survival (PFS) by blinded central radiological review based on modified RECIST 1.1. Secondary endpoints included overall survival (OS), PFS in the pts crossed over to PIM (secondary PFS), and safety. Crossover-adjusted OS was derived using the rank preserving structural failure time (RPSFT) model. Exploratory endpoints included pharmacogenomics (PGx). **Results:** From Oct 2018 to Apr 2020, 86 pts were randomized to receive either PIM (n = 58) or PL (n = 28). Baseline characteristics were well balanced between the two arms. Median PFS was 2.8 months (mo) (95% CI: 1.6–2.9) for PIM vs. 1.4 mo (95% CI: 0.9–1.8) for PL. The hazard ratio (HR) for PFS was 0.51 (95% CI: 0.30–0.87) ($p = 0.006$, stratified log-rank test). Median OS was 13.8 mo (95% CI: 9.2–not reached) for PIM vs. 9.6 mo (95% CI: 5.5–not reached) for PL (HR for OS 0.63; $p = 0.081$), with 60.7 % of PL pts crossed over to PIM; secondary PFS was 2.7 mo (95% CI: 0.7–4.1). The RPSFT-adjusted median OS of PL was 7.6 mo (adjusted HR for OS 0.42; $p = 0.007$). Furthermore, the results of PGx analysis suggested that PIM was also effective in pts with secondary *KIT* mutation detected from blood samples. The most common (> 5%) grade 3 or higher adverse events (AEs) in PIM/PL were diarrhea (13.8%/0%), anemia (6.9%/10.7%), decreased appetite (6.9%/0%), and tumor hemorrhage (5.2%/0%). AEs leading to PIM/PL study discontinuation were observed in 4/2 pts (6.9%/7.1%), respectively. **Conclusions:** This randomized trial demonstrated that PIM significantly improved PFS with OS prolongation in pts with advanced GIST refractory to IM, SU, and REG, as a HSP90 inhibitor for the first time. PIM was tolerated and AEs were manageable. With a mechanism of action different from that of standard therapies, PIM has the potential to be a new standard treatment in GIST. Clinical trial information: JapicCTI-184094. Research Sponsor: Taiho Pharmaceutical.

11525 **Poster Session**

Giant cell tumor of bone: Effect of longer dosing intervals of denosumab on tumor control and bone related complications. *First Author: Cindy Jiang, University of Michigan, Ann Arbor, MI*

Background: Giant cell tumor of bone (GCTB) is a benign but locally aggressive bone neoplasm characterized by osteoclast activation causing destructive osteolysis. Denosumab, a human monoclonal antibody against RANK ligand, has emerged as an effective treatment option when surgery is not recommended, but can cause significant bone toxicity. Current standard dosing is every 4 weeks after 3 weekly loading doses. As patients (pts) with GCTB are often young adults, frequent denosumab administration long-term may be burdensome and associated with increased risk of complications. We assessed whether alternative, longer dosing intervals are associated with differences in efficacy or bone toxicity. **Methods:** Retrospective chart review was conducted on GCTB pts over 18 years old at University of Michigan who received at least 1 year of standard denosumab treatment. Pts were identified using a free-text medical record search engine with keywords “giant cell tumor” and “denosumab” until August 2020. We compared bone-related adverse effects and tumor control in pts who continued denosumab every 4 weeks versus longer treatment intervals. Decision to increase interval between doses was based on provider and pt discussion and preference as part of routine medical care. **Results:** 37 GCTB pts were identified; 51% female and 49% male. Average age was 41 years (range 22-73). Most common primary location was lower extremity (38%), followed by pelvis (35%), upper extremity (14%), spine (8%), and head/neck (5%). Metastasis were present at start of treatment in 14% of pts, involving lung (n = 4) and spine (n = 1). Pts received median of 71 (range 15-139) total doses of denosumab. Dosing interval was increased in 38% (n = 14). With the first interval change, 43% changed to every 6 weeks, 29% every 8 weeks, and 29% every 12 weeks dosing. Most common final dosing interval was 12 weeks (n = 8). 6 pts (16%) had bone complications after mean of 56 doses. This included osteonecrosis of the jaw (n = 4), atypical fracture (n = 1), and non-healing dental wounds (n = 2). All pts with bone complications were treated on the monthly dosing schedule, but there was no statistically significant difference compared to longer intervals (p = 0.22). Pts with GCT progression (n = 10) were either no longer receiving therapy or had missed denosumab doses. There was no statistically significant difference in PFS with standard vs. interval increased dosing (p = 0.97). However, 5-year PFS was superior with interval increased vs standard dosing (p = 0.036). **Conclusions:** Increasing the interval of denosumab dosing for GCTB provided similar tumor control as compared to standard dosing and is potentially associated with less bone toxicity and more convenience for afflicted pts. Further larger scale studies are needed to better define the optimal interval of denosumab administration in GCTB and the effect on efficacy, toxicity, and associated health care expense. Research Sponsor: None.

11526 **Poster Session**

Efficacy and safety of JMT103 in patients with giant cell tumor of bone: A multicenter, single-arm, open-label, phase Ib/II study. *First Author: Xiaohui Niu, Department of Orthopedic Oncology Surgery, Beijing Ji Shui Tan Hospital, Peking University, Beijing, China*

Background: JMT103 is a novel, fully humanized IgG4 monoclonal antibody targeting RANKL, inhibiting osteoclastogenesis and osteoclast-mediated bone resorption. A multicenter, single-arm, open-label, phase Ib/II study was conducted to evaluate the efficacy and safety of JMT103 in patients (pts) with Giant cell tumor of bone (GCTB). **Methods:** Eligible pts (ECOG: 0-2) were adults with pathologically confirmed unresectable GCTB or their planned surgery is associated with severe morbidity. Pts with active dental or jaw condition requiring oral surgery, other anti-tumor therapies, anti-RANKL antibody or concurrent use of bisphosphonates were excluded. 2 mg/kg JMT103 was administrated subcutaneously every 4 weeks with a loading dose on days 8 and day 15 of the first 4 week of therapy. The primary endpoint was tumor response, defined as elimination of at least 90% giant cells or objective response of the target lesion assessed by radiologic imaging as per Modified Inverse Choi density/size (ICDS) or the Modified European Organization for Research and Treatment of Cancer (EORTC) criteria within 12 weeks. Secondary endpoints included safety profile, change of pain score using Brief Pain Inventory-Short Form, and suppression of bone-resorption biomarkers. **Results:** 38 pts (14 males) were enrolled between June 3 and December 24, 2020. The median age was 31 years (range 18-57). Lesions sites included lower extremities (39.5%), upper extremities (31.6%), spine (21.1%) and pelvis (13.2%). Among 32 pts with at least 1 efficacy evaluation within 12 weeks, 26 (81.3%, 95% CI: 63.6-92.8) had a tumor response by at least one response criteria. All 7 pts who underwent histological assessments had a tumor response. 25 of 32 pts assessed by radiology had a tumor response. As per ICDS criteria, 23 of 32 (71.9%) had a response; as per EORTC criteria, 15 of 17 (88.2%) had a response. 21 of 26 (80.8%) pts who complained of pain at baseline experienced reduced pain during the treatment. The median reductions in bone-resorption biomarkers were 71.8% (IQR 67.7-82.4) for uNTx/Cr ($p < 0.001$) and 81.4% (IQR 68.3-84.7) for sCTx ($p < 0.001$) at day 8. Of all 38 pts who were included in safety analyses, treatment-related adverse events (TRAEs) occurred in 14 pts. The most common TRAEs were hypophosphatemia (18.4%), hypocalcemia (7.9%) and blood bilirubin increased (7.9%). 1 patient (2.6%) was reported a grade 3 AE but it was not related to the treatment; other AEs were grade 1–2. **Conclusions:** JMT103 demonstrated encouraging anti-tumor efficacy and manageable safety profile in pts with unresectable GCTB or at high risk of severe morbidity after surgery. Clinical trial information: NCT04255576. Research Sponsor: Shanghai JMT-Bio Technology Co., Ltd.

11527 **Poster Session**

ABCB1/P-glycoprotein (Pgp) expression as stratification factor for treatment of patients with non-metastaticextremity high-grade osteosarcoma: A merged analysis of an Italian (ISG) and a Spanish (GEIS) sarcoma groups' multicentric prospective trials. *First Author: Emanuela Palmerini, IRCCS Istituto Ortopedico Rizzoli, Bologna, Italy*

Background: Overexpression of ABCB1/P-glycoprotein (Pgp) predicts poor outcome in retrospective osteosarcoma series.Two prospective trials with Pgp expression and post-induction histologic response as stratification factors were activated in Italy (ISG/OS-2) and Spain (GEIS-33). **Methods:** Patients ≤ 40 years with extremity non-metastatic high-grade osteosarcoma were eligible. Analysisi of Pgp expression from diagnostic biopsy was centralized. Preoperatively, all patients received methotrexate, adriamycin, cisplatinum (MAP). Surgery was performed at week 8. All patients received a dose of adriamycin following surgery. In case of Pgp overexpression (Pgp+), mifamurtide (2 mg/m2 twice/week for 3 months then weekly for 6 months) was added after surgery, with 4 consecutive cycles of ifosfamide 3 gr/m2/day, day 1-5 (HDIFO) in case of poor histologic response (necrosis < 90%) to MAP. Patients without overexpression of Pgp (Pgp-) received MAP postoperatively, regardless the pathological response. From March 2013, an amendment increased high dose methotrexate cumulative dose from 60 g/m2 (5 cycles) to 120 mg/m2 (10 cycles). The post-amendment regimen was adopted in the observational prospective study by GEIS. Here we present the merged analysis of ISG/OS-2 patients treated post-amendment and GEIS-33. **Results:** From March 2013 to April 2018, 274 patients were included. Median age was 14 years (range 4-38), male/female: 163/111; 90 were Pgp-, 164 were Pgp+, 20 not evaluable. With a median follow-up of 48 months (1.3-78.5 months), the 3-year EFS and OS were 71.9% (95%CI 66-76.9) and 88% (95%CI: 83.2-91.5) respectively, with no inferior survival for Pgp positive patients and improved survival for good responders (Table). **Conclusions:** In this prospective uncontrolled study with a risk-adapted strategy for non-metastatic osteosarcoma, survival is superior to that of all ISG/GEIS previous series. The 3-year EFS of 71.9% compares favorably with other reports. Pgp+ patients performed well in this study, in which mifamurtide and HDIFO were added after a poor response to MAP.Clinical trial information: NCT01459484; NCT04383288. Research Sponsor: This work was supported by the Associazione Onlus ‘il Pensatore: Matteo Amitrano’, the Associazione Mario Campanacci and the Carisbo Foundation Call for Translational and Clinical Medical Research.

	n	% 3-yrs EFS (95% CI)	p
Pgp			0.2951
Negative	90	68.2% (56.9-77.0)	
Positive	163	75.6% (68.1-81.5)	
Necrosis			0.0004
Good (> 90% necrosis)	122	81.6% (73.2-87.7)	
Poor (≤90% necrosis)	149	64.2% (55.8-71.5)	
Necrosis in Pgp -			0.0566
Good (MAP)	38	75.7% (56.8-87.2)	
Poor (MAP)	51	61.6% (46.5-73.6)	
Necrosis in Pgp +			0.0117
Good (mifamurtide+MAP)	74	84.4% (73.6-91.1)	
Poor (mifamurtide+HDIFO)	88	69.1% (58.3-77.7)	

*Not available in 3 patients.

11528 **Poster Session**

Activity of erlotinib in patients (pts) with advanced chordoma: A retrospective study. *First Author: Olivier Mir, Institut Gustave Roussy, Villejuif, France*

Background: Chordoma is a rare tumor with no approved therapy. Preclinical studies have shown expression of EGFR and activated EGFR family kinases (EGFR, HER2 and HER4). Erlotinib and other anti-EGFR agents (gefitinib and cetuximab) have shown clinical activity in advanced chordoma in single case reports or small series. We aimed to evaluate the activity of erlotinib in a larger, homogeneous series of pts with advanced chordoma. **Methods:** We retrospectively reviewed the electronic medical records of consecutive adult pts with advanced chordoma progressive over 6 months (+/- 2 weeks, according to RECIST 1.1), treated with erlotinib (150 mg daily) at Gustave Roussy (Villejuif, France) following multidisciplinary tumor board discussion, from January 2010 to January 2021. All cases were confirmed by an expert pathologist. Response was evaluated according to RECIST 1.1, and survival was estimated using the Kaplan-Meier method. **Results:** Thirty-one pts [median age : 60 years (range : 32-88), median PS : 2 (range : 1-3), 30 males)] were identified. Twenty-seven (87%) had locally advanced disease; the median number of metastatic sites was 1 (range : 1-2) in the remaining 4 pts. Primary tumor site was sacral (25), lumbar (3) or cervical (3). All pts but 6 had undergone prior surgery, and 29 (94%) had undergone radiotherapy of the primary tumor. Eight pts had received previous systemic treatments (imatinib in 4, sorafenib and regorafenib in 2 each). Best tumor response by RECIST 1.1 was PR (4 pts, 13%), SD (14 pts, 45%) or PD (13 pts, 42%). Median PFS was 6.2 months (95%CI : 4.5-9.8), and median OS was 15.9 months (95%CI : 10.6-20.2). Fourteen pts (45%) remained progression-free after 1 year, and three (10%) after two years under erlotinib. Grade 3 diarrhea occurred in 4 pts (13%) and grade 3 skin rash in 13 pts (42%). Twelve pts (39%) required dose reduction to 100 mg daily due to multiple grade 2 toxicities. Ongoing studies are exploring whether candidate biomarkers such as EGFR and HER2 expression or amplification, and their mutational status could help predicting the benefit of erlotinib in pts with advanced chordoma. **Conclusions:** Erlotinib has clinically meaningful but unpredictable activity in advanced chordoma. Molecular profiling would probably be of high interest in this setting. This series may serve as a benchmark for future clinical trials in chordoma. Research Sponsor: None.

11529 **Poster Session**

GEIS 39: Phase II trial of nabpaclitaxel for the treatment of patient with multiply relapsed/refractory desmoplastic small round cell tumor (DSRCT) and Ewing sarcoma (EwS). *First Author: Jaume Mora, Pediatric Surgery Department, Hospital Sant Joan de Déu, Universitat de Barcelona, Barcelona, Spain*

Background: Nab-paclitaxel (albumin-bound paclitaxel) has shown preclinical activity against pediatric solid tumors. Preclinical data in EwS PDX models suggested high activity of nab-paclitaxel in tumors expressing high-levels of SPARC. Tumoral SPARC facilitates the accumulation of albumin in the tumor and increases the effectiveness of albumin-bound paclitaxel. Nab-paclitaxel utilizes albumin to deliver paclitaxel via caveolin-mediated endocytosis which is expressed in the EwS cells surface. We hypothesized that SPARC can be a predictive biomarker for nab-paclitaxel in EwS and DSRCT that could potentially be relevant for a better design of clinical trials and personalized treatments using nab-paclitaxel. **Methods:** Main endpoint of GEIS-39 was the overall response rate (ORR) assessed by RECIST 1.1 criteria with centralized pathology and imaging review. Secondary objectives included safety according to the CTCAE 4.0 criteria. Patients aged $\geq$ 6 months and $\leq$ 40 years, with relapsed/refractory DSRCT were eligible after having received at least one previous poly-chemotherapy line; EwS must have received at least two standard chemotherapy lines. Prior taxane therapy was accepted. Central pathology review selected for tumors with $>$ Grade 3 (intense and diffuse) expression of SPARC by immunohistochemistry to be eligible. Nab-paclitaxel was administered as follows: age $\geq$ 21 and $\leq$ 40 years: 125 mg/m2 days 1, 8 and 15 in cycles of 28 days; age $\geq$ 6 months and $\leq$ 20 years: 240 mg/m2 days 1, 8 and 15 in cycles of 28 days. A 30% ORR was anticipated with a sample size of 25 patients needed to test the hypothesis. Stopping rule was set at 1 response within the first 16 treated pts. If 5 or more successes were observed in 25 pts, the results of the trial will warrant further investigation. **Results:** Twenty-nine patients were enrolled from June 2017 until October 2019, 11 DSRCT and 18 EwS. Median age was 32 years (range 14-69), and 5 females and 24 males were included, having received a median of 3 previous systemic treatment lines. Patients received a median of 3 cycles of nab-paclitaxel (range 1-17). In the EwS cohort an ORR of 33.3% (all partial responses, median duration 2 months) and 16.7% of stabilizations were achieved. No objective responses were observed among DSRCT pts, but 27.3% of pts achieved a stabilization. Overall, median progression free survival was 2.8 months and median overall survival 12.1 months, with no significant differences between DSRCT and EwS cohorts. Most common grade 3 toxicities were neutropenia (20.7%) and diarrhea (10.3%). **Conclusions:** Single agent nab-paclitaxel in biomarker selected EwS patients, but not in DSRCT, provided clinically meaningful activity that deserves further development. Nab-paclitaxel had a manageable adverse event profile. Clinical trial information: 2016-002464-14. Research Sponsor: Celgene.

11530 **Poster Session**

Outcome of patients with recurrent/refractory osteosarcoma enrolled in three recent phase II trials: A report from the Children's Oncology Group. *First Author: Seema Rao, Baylor College of Medicine, Houston, TX*

Background: Based on seven prior Phase 2 Children's Oncology Group (COG) trials, the 4-month event-free survival(EFS) and associated confidence interval for relapsed osteosarcoma with measurable disease according to RECIST was determined to be 12% (95% CI 6 - 19%). Three prospective clinical trials were conducted using this historical benchmark to detect activity defined by an EFS improvement of double the upper confidence interval. This report summarizes the outcome of these studies, describes whether the historical data remains an accurate baseline, and considers implications for future phase II trial study design in relapsed osteosarcoma measurable according to RECIST. **Methods:** We conducted an analysis of outcome for patients with recurrent/refractory osteosarcoma enrolled in three recent prospective COG phase II trials; AOST1321 (unresected cohort), AOST1322 and AOST1521 that used EFS at 4 months as the primary endpoint. Patients were eligible if they had osteosarcoma that had recurred or become refractory after standard therapy and had measurable disease according to RECIST. We assessed whether risk of an EFS event is modified by age, sex, race/ethnicity, number of prior chemotherapy regimens, or time to first relapse. **Results:** In each of the three phase II trials (unresected group of AOST1321, AOST1322, AOST1521), the drugs tested (denosumab, eribulin and glembatumumab) were concluded to be not effective due to a failure of the patient populations to meet the prespecified active 4-month progression free survival endpoint. The 4-month EFS for the 57 evaluable patients enrolled on these trials was 7% (95% CI 2 – 16%), similar to the 4-month EFS for 96 patients in the previous seven phase II trials of 12% (95% CI 6 - 19%). The combined EFS at 4 months for all 10 studies is 10% (95% CI 6 – 15%).There was no significant difference in EFS across trials based on age, sex, ethnicity, number of prior treatment regimens, consistent with prior analysis. Data from AOST1321 and AOST1521 were analyzed to determine the impact of time to first recurrence on EFS. Two different quantifications were applied: 1 year or less versus 2 or more years; and 2 years or less versus 3 years or more. Neither categorization was statistically significant. **Conclusions:** The EFS at 4 months in the three new phase II trials is similar to the previous seven phase II single arm trials. The combined analysis of 153 patients from 10 trials tightens the confidence interval, moving the upper 95% CI to 15%. Modification to future study designs could be considered based on this updated analysis. EFS at 4 months remains a robust primary endpoint. Single-arm trials using this endpoint based on the historical benchmark have accrued rapidly and allowed assessment of multiple novel agents in osteosarcoma. The negative trial results and continued poor outcome highlight the need for new approaches for relapsed osteosarcoma. Clinical trial information: NCT02097238, NCT02470091, NCT02487979. Research Sponsor: Children's Oncology Group statistics and Data Center Grant/ Chair's Grant.

11531 **Poster Session**

Comparison of treatment effect and long-term outcomes for pediatric and adult Ewing sarcoma patients in British Columbia, Canada. *First Author: Omar Hajjaj, BCCA Vancouver, Vancouver, BC, Canada*

Background: Treatment of Ewing Sarcoma (EWS) is challenging. While it is known to be sensitive to chemotherapy and radiation, the number of lines of therapy available are limited. This disease affects pediatric patients (PP) more often than adults (AP), and reported outcomes are worse for AP onset EWS in the literature. It is unclear if this is due to difference in the biology of disease in AP compared to PP, or if this is due to differences in treatment approach. Furthermore, optimal treatments and real world impact of treatment is unclear in both the PP and AP populations. This study identifies the features of therapy received by AP and PP with EWS in a large, mutli-institutional cohort, and provides real world evidence for the expected outcomes in both AP and PP with EWS. **Methods:** A cohort study analysis of the Sarcoma Outcomes Unit database at BC Cancer was conducted to identify patients diagnosed with EWS in British Columbia from January 1, 2000 to December 31, 2018. Data on the frequency, amount, and regimen of chemotherapy were collected. Baseline Charlson comorbidity index, age at diagnosis, progression free survival and overall survival were collected. **Results:** 108 patients with EWS were identified, 66 AP and 42 PP Median age at diagnosis for adults was 37 (19-86) and median age for diagnosis of pediatric patients was 14 (1-18). Real world median PFS and OS for AP were 23 mos and 79 mos, and for the PP were 32 mos and NE. Five year overall survival was 54% in AP and 77% in PP. Overall, there was no difference in the number of lines of therapy received between PP and AP, but the type of therapy was more dose-dense in the PP than in the AP, (85% vs 28% for dose dense chemo). 5 year overall survival was longer for PP who received dose dense regimens compared to non-dose dense regimens (HR 0.87), but was not different in the AP receiving dose dense regimens (HR 0.95), even when controlling for comorbidities. The most common chemotherapy regimen for AP was Vincristine, Adriamycin, cyclophosphamide alternating with Ifosfamide and Etoposide q3weeks, whereas in the pediatric population the most common chemotherapy regimen was the same but alternating q2weeks. **Conclusions:** The treatment plans for PP with EWS were more often dose dense compared to the AP. Outcomes for PP were vastly better than for APs, despite overall similarities in the number of lines of therapy and types of agents used. Given the lack of difference between dose dense and non-dose dense regimens for APs, this is not the likely cause of difference in survival between PPs and APs. Extrapolating pediatric protocols to the adult setting may not be appropriate given the differences in outcomes. Further work to identify effective therapies and predictive biomarkers in this disease are needed, and my further identify reasons for discrepant outcomes in pediatric and adult populations. Research Sponsor: None.

11532 **Poster Session**

Genomic alterations and associated pathway abnormalities in Ewing sarcoma. *First Author: Adam Rock, Harbor-UCLA Medical Center, Torrance, CA*

Background: Ewing Sarcoma (ES) is an aggressive, translocation-associated, bone cancer associated with a poor prognosis in the recurrent or metastatic setting. ES is identified by the canonical balanced reciprocal chromosomal translocation involving EWSR1 and ETS transcription factors. Secondary somatic alterations in ES are rarely described and genomic alterations (GA) affecting various molecular pathways may work synergistically with ETS-FL1 translocations to promote oncogenesis. Alterations in fibroblast growth factor receptor 4 (FGFR4), a receptor tyrosine kinase protein that functions in cellular processes, have been observed to affect carcinogenesis. Moreover, the FGFR4-Gly388Arg (G388R) single nucleotide polymorphism (SNP) is found to increase the risk of cancer with mouse embryonic fibroblasts derived from knock-in strain of homologous Fgfr4 G385R mice exhibiting a transformed phenotype. We sought to further evaluate the frequency of FGFR4 G388R SNP in relation to other identifiable pathway alterations observed with Comprehensive Genomic Profiling (CGP). **Methods:** Next generation sequencing (NGS) analysis was obtained in the context of clinical care with clinical status, outcomes, and source acquisition (primary tumor, metastasis, or recurrence) unknown to Foundation Medicine. CGP, FoundationOne Heme, evaluated GAs including base substitutions, indels, amplifications, copy number alterations, gene fusions and rearrangements. 189 samples were assayed by hybrid-capture based CGP, including 406 DNA-sequenced genes in addition to 265 RNA-sequenced genes commonly reported to be rearranged in cancer, as previously described. Tumor mutational burden was assessed from a minimum 1.4 Mb sequenced DNA. Microsatellite instability (MSI) status was determined by a novel algorithm analyzing 114 specific loci. **Results:** The median age of evaluated patients was 20 (range 0-70) with the number of alterations averaging 7 per patient. Pathways noted to be altered in the presence of FGFR388R SNP occurred frequently with the following pathways most observed: MAPK (33%), WNT (32%), NOTCH1 (20%), HRR (19%), Histone/chromatin remodeling (18%). FGFR388R SNP was observed in more than half (51%) of evaluated samples. Most affected pathways irrespective of FGFR388R SNP status included: MAPK (n = 89), HRR (n = 75), and PIK3 (n = 64). All evaluated samples were TMB low ($<$ 10 mut/mb) and Microsatellite Stable. **Conclusions:** Secondary GAs affecting major pathways were observed in high frequency, often co-occurring with the FGFR4 G388R SNP. Secondary alteration of known oncogenic pathways may contribute to sarcoma formation in ES potentially informing further therapeutic strategies in the future. Research Sponsor: None.

11533 **Poster Session**

Accumulation of genome-wide somatic loss of heterozygosity (LOH) as a prominent feature of advanced malignant soft tissue tumors and association with the BRCAness status, suppression of immune responses, and lower survival rates. *First Author: Katsuhito Takahashi, Kameda Medical Center, Center for Multidisciplinary Treatment of Sarcoma, Department of Sarcoma Medicine, Kamogawa, Japan*

Background: Malignant soft tissue tumor is a rare cancer with few therapeutic options. Recent genomic analysis revealed widespread CNA and the cumulative burden of cancer-related pathogenic germline mutations/variants, their clinical and therapeutic significance were unknown. **Methods:** We recruited 155 patients with advanced malignant soft tissue tumors (135 female and 20 male, mean age 51 at analysis, 100 LMS, 19 LPS, 4 ESS, 3 UPS, 3 AS, 3 MPT, 3 GIST and others) with confirmed metastasis/recurrence and information on familial cancer burden. Whole exome sequencing was performed in both blood and tumor samples as described in 2018ASCO. The copy number of BRCA2 gene was determined by the MLPA method. Tumor immune microenvironment was assessed by immunohistochemistry. The MSI status was analysed by PCR. **Results:** We analyzed the LOH status in 595 COSMIC genes and found that genome-wide accumulation of somatic LOH of polygenic germline mutations/variants. Patients with more than 33% LOH genes (n=102) in the total of somatic and LOH mutations showed significantly lower OS rates compared with those (n=53) with less LOH genes (5-year survival rates; 49 vs 75%, p=0.010), which constitute 78% of LMS (n=78/100) and 26% of LPS (n=5/19). Total of 41 patients (26%, n=41/155) including 33 LMS (33%, n=33/100) showed LOH in the BRCA2 locus with hemizygous VUS. Those patients with BRCA2 LOH (n=41) showed significantly lower OS rates compared with those without BRCA2 LOH (n=114) (5-year survival rates; 43 vs. 64%, p=0.019). Neither TMB nor the MSI status was associated with LOH. In contrast, accumulation of somatic LOH (mean LOH values of 71.7 vs. 15.7%) was clearly and negatively associated with CD8+T-cell immune infiltrates (T-cells; 44±23 vs 555±180/mm^2, n=7, p=0.016), CD20+B-cell accumulation in tertiary lymphoid structures (TLS) (TLS; 0.57±0.43 vs. 20.1±6.1/tumor, n=7, p=0.008) and low levels of neutrophil-to-lymphocyte ratio (NLR) (NLR; 3.63±0.45 vs. 1.71±0.17, n=7, p=0.002), hallmarks of the immunological response to tumors. **Conclusions:** This study suggests that in advanced malignant soft tissue tumors, accumulation of genome-wide LOH of germline mutations/variants is associated with the BRCAness status and suppression of the immune responses to tumors, and thus influences therapeutic response and survival of the patients. Research Sponsor: Promotion fund for genomic medicine of rare cancers by Japan Sarcoma Association.

11534 **Poster Session**

A phase Ib/II study of selinexor in combination with imatinib in patients with advanced gastrointestinal stromal tumor (GIST): SeliGIST/GEIS-41 trial. *First Author: Cesar Serrano, Vall d'Hebron Institute of Oncology, Vall d' Hebron University Hospital, Barcelona, Spain*

Background: KIT or PDGFRA oncogenic activation drives GIST progression throughout the disease course. Accordingly, currently approved agents in metastatic GIST focus on the therapeutic suppression of these receptors. However, the clinical benefit after imatinib (IM) progression is still modest, suggesting the co-operation of KIT/PDGFRA-independent mechanisms in GIST cell survival. Selinexor is an oral, selective inhibitor of XPO1-mediated nuclear export, and preclinical studies evidenced antitumoral activity in GIST as single agent and in combination with IM in both IM-sensitive and IM-resistant models. **Methods:** The phase Ib portion studied IM 400 mg daily plus weekly selinexor in patients (pts) with IM-resistant, advanced GIST. Prior intolerance to IM was not allowed. A standard 3+3 dosing schema was utilized to determine the recommended phase II dose (RP2D) of this combination. Investigator-assessed response was evaluated every 8 weeks using RECIST 1.1. **Results:** At data cutoff of Sep 25, 2020, 12 pts were enrolled and received treatment with IM 400 mg and selinexor once weekly at dose levels (DL) 1 (60 mg), DL2 (80 mg) and DL3 (100 mg). Median age 57 (range 46-77), 42% female, median prior therapies 4 (range 2-7). Although only 1/6 pts developed a dose limiting toxicity (DLT) at DL3, the RP2D was defined at DL2 (IM 400 mg daily and selinexor 80 mg once weekly) based on activity data in the DL2 and the need for dose reductions in 5/6 pts at DL3 after the DLT window. All pts were evaluable for toxicity and response. One DLT occurred at DL3 (G3 nausea). Non-DLT G3/4 toxicities were anemia (1/12 pts), neutropenia (1/12 pts), vomiting (1/12 pts) and fatigue (2/12 pts). Common G1/2 toxicities were nausea (11/12 pts), vomiting (10/12 pts), neutropenia (5/12 pts) and anemia, fatigue, diarrhea, and periorbital edema (4/12 pts each). No unexpected toxicities were observed. Overall response rate in the 12 pts evaluable for response was 67% (95% CI 0.349-0.901), with 2 pts achieving PR (17%) and 6 pts SD (50%) as the best response. Clinical benefit rate (CBR = CR, PR, SD) $\geq$ 16 weeks was 42% (95% CI 0.157-0.723). Median progression free survival was 3.5 months (95% CI 1.7-7.3). Four pts remain on trial at data cutoff. **Conclusions:** IM and selinexor combination is well-tolerated and has clinical activity in heavily pretreated GIST pts. The trial is currently exploring selinexor as single agent in the IM-resistant GIST population. Clinical trial information: NCT04138381. Research Sponsor: Karyopharm Therapeutics, Spanish Group for Sarcoma Research (GEIS).

11535 **Poster Session**

Chromosomal complexity as a biomarker to de-escalate adjuvant imatinib treatment in high-risk gastrointestinal stromal tumor. *First Author: Kjetil Boye, Oslo University Hospital, Oslo, Norway*

Background: Gastrointestinal stromal tumors (GISTs) are characterized molecularly by oncogenic *KIT* or platelet-derived growth factor alpha (*PDGFRA*) mutations. Malignant progression of primary GISTs occurs through stepwise accumulation of additional chromosomal aberrations, such as losses of chromosome arms 14q, 22q, 1p, 15q and Xp. After surgical resection of primary GIST, three years of adjuvant imatinib treatment is recommended for patients with an estimated high risk of recurrence. Still, nearly half of high-risk patients are cured by surgery alone, indicating that selection of patients could be improved. We hypothesized that high-risk GISTs with few chromosomal aberrations had a favorable outcome, and might not benefit from adjuvant therapy. The aim of the study was to investigate if chromosomal complexity could be used as a biomarker in de-escalation of adjuvant imatinib treatment. **Methods:** GIST patients undergoing surgical resection of their primary tumor between 1998 and 2020 were identified in the sarcoma database at Oslo University Hospital. All samples with available karyotype analysis made on fresh tumor tissue were included. Karyotypes were categorized as simple if they had $\leq$5 chromosomal changes, and complex if there were $>$ 5 chromosomal aberrations. **Results:** Chromosomal aberrations were detected in 226 tumors, of which 181 (80.1 %) were gastric. The most frequent resulting imbalances were loss of 14q (75.9 %), 22q (43.5 %), 1p (36.6 %), and 15q (29.6 %). One-hundred and thirty-six tumors (60.2 %) had simple karyotypes whereas 90 (39.8 %) were complex. Cytogenetically complex tumors were larger ($P<$ 0.001), had a higher mitotic count ($P=$ 0.009), and were more often non-gastric ($P<$ 0.001). There was a strong association between chromosomal complexity and risk classification according to the modified NIH criteria ($P<$ 0.001). Thirty-eight of 58 (65.5 %) high-risk tumors were karyotypically complex compared to 37 of 144 (25.7 %) tumors that were not high-risk. In the high-risk group, 17 patients experienced disease recurrence, of whom one had a simple and 16 had a complex tumor karyotype. Estimated 5-year recurrence-free survival (RFS) for patients with simple tumor karyotypes was 94 % compared to 51 % for patients with cytogenetically complex tumors ($P=$ 0.004). Adjuvant and/or neoadjuvant imatinib treatment was administered to 40 high-risk patients with a median treatment duration of 33 months (range 2-60 months). A complex karyotype was associated with poor RFS both in patients with ($P=$ 0.016) and without ($P=$ 0.046) adjuvant imatinib. **Conclusions:** Chromosomal complexity was strongly associated with poor RFS in localized, high-risk GIST. Recurrences were infrequent for tumors with simple karyotypes, indicating that de-escalation of adjuvant imatinib treatment should be further explored in patients with cytogenetically simple GISTs. Research Sponsor: The South-Eastern Norway Regional Health Authority.

11536 **Poster Session**

Intra-patient dose escalation (IPDE) of ripretinib after disease progression in patients with advanced gastrointestinal stromal tumor (GIST): Analyses from the phase 3 INVICTUS study. *First Author: John Raymond Zalcberg, Monash University, Melbourne, VIC, Australia*

Background: Ripretinib is a switch-control tyrosine kinase inhibitor that broadly inhibits KIT and PDGFRA kinase signaling. In the INVICTUS study (NCT03353753), patients with advanced GIST (≥4th-line) receiving ripretinib had a median progression-free survival (mPFS) of 6.3 months vs 1.0 month for patients receiving placebo (HR = 0.15, p <0.0001). In an earlier phase 1 dose escalation study, the maximum tolerated dose was not reached with doses up to 200 mg twice daily (BID). Here, we report efficacy, safety, and pharmacokinetic data for IPDE patients initially randomized to ripretinib from the phase 3 INVICTUS study based on data as of 10 Aug 2020. **Methods:** A total of 129 patients were randomized 2:1 to ripretinib 150 mg once daily (QD; n = 85) or placebo (n = 44). Patients receiving ripretinib 150 mg QD who had progressive disease (PD) as assessed by blinded independent central review (BICR) using mRECIST were given the option for IPDE to 150 mg BID. Tumor response assessments were performed every 28 days for 4 cycles and every 56 days thereafter (including after IPDE). The primary endpoint was PFS. For this exploratory analysis, PFS1 for IPDE patients was defined as the time from randomization to PD; PFS2 for IPDE patients was the time from the first dose of ripretinib 150 mg BID to PD or death. PFS1 and PFS2 were based on BICR. **Results:** Of 85 patients treated with ripretinib 150 mg QD, 43 patients with BICR PD dose escalated to 150 mg BID. Baseline characteristics of IPDE patients at time of study entry were similar to those observed in the original ripretinib QD arm and similar to the 22 patients with BICR PD who either remained on 150 mg QD or discontinued treatment. IPDE patients had a mPFS1 of 4.6 months (95% CI, 2.7–6.4) and a mPFS2 of 3.7 months (95% CI, 3.1–5.3); mPFS2/mPFS1=80%. The IPDE dosing period was well tolerated without the emergence of new safety concerns. The most common new or worsening (unchanged or improving grades not included) treatment-emergent adverse event (TEAE) for IPDE patients during the BID period was abdominal pain (30.2% all grades and 7% Grade 3–4 vs 41.9% and 4.7% in QD period, respectively). The most common Grade 3–4 TEAE in the BID period was anemia (14% vs 2.3% in QD period). IPDE from QD to BID resulted in an approximately 2-fold increase in the steady state trough concentration. **Conclusions:** Similar to the phase 1 study wherein IPDE to 150 mg BID following PD provided clinical benefit with a mPFS1 of 5.5 months and mPFS2 of 4.6 months (mPFS2/mPFS1=84%) for patients with ≥4th-line GIST, these analyses from INVICTUS indicate that IPDE to ripretinib 150 mg BID can also provide additional meaningful clinical benefit and a similar tolerability profile to the 150 mg QD regimen for patients with ≥4th-line GIST that progressed following treatment with ripretinib 150 mg QD. Clinical trial information: NCT03353753. Research Sponsor: Deciphera Pharmaceuticals, LLC.

11538 **Poster Session**

Next generation sequencing of sarcomas: Response to crizotinib in two cases with MET amplification. *First Author: Adrienne I. Victor, University of Rochester, Rochester, NY*

Background: Sarcoma subtypes are often defined by recurrent molecular alterations. The purpose of this study is to review the utility of next generation sequencing (NGS) in sarcoma patients and report clinical outcomes to matched therapies. **Methods:** The records of all patients seen at the University of Rochester Medical Center (URMC) with sarcoma and NGS profiling between 8/2013 and 3/2020 were reviewed. Responses to agents targeting reported alterations were analyzed. In patients with fluorescent-in-situ hybridization (FISH) testing, fusion events by NGS were compared with FISH results. All highlighted pathogenic alterations on the NGS profile report as well as variants of uncertain significance (VUS) were recorded. **Results:** Seventy-five patients met inclusion criteria. Of these, 25 received a treatment based on identified alterations; 1 had a complete response (CR), 4 had partial responses (PR), and 4 experienced disease stabilization (SD). We identified two patients with MET amplified sarcoma that responded to treatment with crizotinib. One other patient with a diagnosis of leiomyosarcoma was found to have an unusually high total mutational burden (TMB) and experienced complete pathologic response to dual checkpoint blockade. In 4 cases, testing resulted in a change in subtype diagnosis. Several rare and novel fusions were identified; a sarcoma with TPM4-NTRK3 fusion responded to larotrectinib, while a sarcoma with PML-JAK1 fusion did not respond to ruxolitinib, and a sarcoma with IL7R-BCL2 fusion progressed on venetoclax. Table summarizes matched therapies in responders. **Conclusions:** NGS profiling led to a targeted therapy with a clinical benefit rate of 12% in this cohort. NGS profiling led to a change in diagnosis in 5% of this cohort. Multi-institutional collaborations to track outcomes of matched therapy would help determine the utility of therapies in rare cancers and unusual alterations. Research Sponsor: None.

Histology	Alterations	Matched therapies and Response
Leiomyosarcoma	High TMB (49 Mut/Mb)	Ipilimumab + Nivolumab – CR, ongoing 1.5+ yrs
Undifferentiated pleomorphic sarcoma	MET: amplification - 8 copies	Crizotinib – PR/CR, ongoing 6+ yrs
Malignant peripheral nerve sheath tumor	NTRK3: TPM4-NTRK3 fusion	Larotrectinib – PR, 3+ yrs
Malignant peripheral nerve sheath tumor	TSC2: A736V NF2: E108*	Temsirolimus + cyclophosphamide + vinorelbine – PR, 13 mo. Everolimus - PD
Inflammatory myofibroblastic tumor	ALK: DCTN1-ALK fusion	Crizotinib - PR, 3 mo. Alectinib - PD
Sarcoma, NOS	SMARCB1: A240fs*28	Palbociclib – SD, 6 mo. Tazemetostat – SD, 2 yrs
Chordoma	PIK3CA: M1043I, amplification	Everolimus – SD, 6 mo.
Undifferentiated sarcoma NOS	MET: amplification – 6 copies	Crizotinib – SD, 3 mo.
Undifferentiated pleomorphic sarcoma	NF1: rearrangement exon 9	Trametinib – SD, 2 mo.

11539 **Poster Session**

Deciphering the molecular landscape and the tumor microenvironment of perivascular epitheloid cell neoplasma (PEComa). *First Author: Andreas Seeber, Department of Internal Medicine V (Hematology and Oncology), Medical University of Innsbruck, Comprehensive Cancer Center Innsbruck, Innsbruck, Austria*

Background: PEComa is a rare mesenchymal neoplasm composed of perivascular epithelioid cells. Due to its rarity, diagnosis is challenging and no standardized treatment guidelines have been established. A subgroup of PEComas are characterized by a loss of function mutation in *TSC1/2* that activates the PIK3-Akt-mTOR pathway. In the majority of patients, however, the molecular landscape and the composition of the tumor microenvironment (TME) remain largely unclear. Thus, we conducted this study to elucidate the genetic landscape of PEComas. A comparative analysis was performed with melanoma as a representative immunogenic tumor type. **Methods:** Thirty-five PEComa specimens were centrally analysed at the Caris Life Sciences laboratory. NextGen DNA sequencing (NextSeq, 592 gene panel or NovaSeq, whole-exome-sequencing), whole-transcriptome RNA sequencing (NovaSeq) and immunohistochemistry (Caris Life Sciences, Phoenix, AZ) were performed. Gene expression profiling (GEP) was performed by unsupervised hierarchical clustering. RNA deconvolution analysis was performed using the Microenvironment Cell Populations (MCP)-counter method to quantify immune cell populations (Becht 2016, Genome Biology). **Results:** The most common mutations detected in this cohort were *TP53* (47%), *ATRX* (32%), *TSC1/2* (11%/29%) and *MSH3* (17%). Interestingly, *TP53* mutations occurred less frequently (25 vs 60%, p = 0.055) in *TSC1/2*-mutated (*TSC1/2-mt*) compared to *TSC1/2*-wildtype (*TSC1/2*-wt) tumors, whereas *MSH3* (25%, n = 1/4) and *ERCC2* (14%, n = 2/14) mutations were exclusively observed in *TSC1/2*-mt cases. *TSC1/2* mutations and other mTOR signalling pathway alterations, including two TFE gene fusion transcripts, were mutually exclusive. Of note, we found that 33.3% (n = 2) of *TSC2*-mt tumors were associated with high PIK3-Akt-mTOR pathway expression, while 100% (n = 3) of *TSC1*-mt tumors demonstrated lower expression. Deficient mismatch repair/microsatellite instability-high and high tumor mutational burden were rare (2.9%, n = 1 each) and observed concurrently in absence of PD-L1 expression. Overall, PD-L1 expression was observed in 21.9% (n = 7) of patients. An exploratory comparison with melanoma revealed that PEComa TMEs were characterized by a significant increase of NK cells and fibroblasts, as well as a relevant decrease of $CD8^+$ T cells and B cells. **Conclusions:** Within this study we discovered a heterogeneous molecular landscape with a high prevalence of *TSC1/2* mutations that were in part associated with transcriptional up-regulation of the PIK3-Akt-mTOR pathway. Furthermore, the relatively immune-cold TME compared to melanoma suggests increased lymphocyte infiltration may be required to increase the efficacy of immune checkpoint inhibitors for PEComa. Research Sponsor: None.

11540 **Poster Session**

Whole-genome sequencing to improve sarcoma diagnosis and patient care. *First Author: Luuk J. Schipper, Netherlands Cancer Institute, Department of Molecular Oncology, Amsterdam, Netherlands*

Background: With more than 70 different histological subtypes, accurate classification sarcomas is challenging. Although pathognomonic genetic events aid accurate classification, large-scale molecular profiling is generally not incorporated in regular diagnostic workflows for sarcoma patients. We hypothesized that whole genome sequencing (WGS) optimizes clinical care of sarcoma patients by detection of pathognomonic and actionable variants, and of underlying hereditary conditions. **Methods:** WGS of tumor and germline DNA was incorporated in the diagnostic work-up of 83 patients with a (presumed) sarcoma as part of the WIDE (Whole genome sequencing Implementation in standard Diagnostics for Every cancer patient) study in a tertiary referral center. WGS results were reported back to the pathologist and treating clinician. Clinical follow-up data were collected prospectively to assess impact of WGS on clinical decision making. **Results:** WGS analysis had impact on multiple levels. First, in 14% of cases (12/83 patients), the genomic profile led to a revision of the diagnosis (table). All patients had undergone multiple diagnostic procedures (mean number: 4) and pathologist assessments (mean: 6) before WGS analysis was performed. Secondly, actionable biomarkers with therapeutic potential were detected for 36/83 patients and finally, 8 pathogenic germline variants were present. Taken together, WGS had implications for clinical decision making in 52% of patients with (presumed) sarcomas. **Conclusions:** WGS is an important extension of the diagnostic arsenal of pathologists and has contributed to change of care in 52% of patients with sarcomas. Given the diagnostic complexity and high unmet need for new treatment opportunities in sarcomas we advocate the use of WGS for sarcoma patients early in the disease course. Clinical trial information: NL68609.031.18. Research Sponsor: ZonMw, the Netherlands Organisation for Health Research and Care innovation.

Diagnostic revisions after WGS analysis.

Study number	(Preliminary) diagnosis without WGS	Diagnosis after WGS	Revision based on
342	Sarcomatoid mesothelioma vs. sarcoma	Malignant Peripheral Nerve Sheath Tumor (MPNST)	Genomic profile (including lack of NF2 and BAP1 driver events)
483	Adenocarcinoma of unknown primary	Synovial sarcoma	SS18–SSX1 fusion
663	Osteosarcoma/UPS	Spindle cell/sclerosing rhabdomyosarcoma (SCSRMS)	FUS–TFCP2 fusion
711	Ewing sarcoma of soft tissue	Soft Tissue Myoepithelial Carcinoma	EWSR1–POU5F1 fusion
810, 986	Embryonal rhabdomyosarcoma, alveolar rhabdomyosarcoma	SCSRMS	MYOD p.L122R
821, 1016, 1025	Melanoma vs. sarcoma, interdigitating dendritic cell sarcoma, MPNST	Melanoma	High ML/UV-signature, TERT promoter
822	Dedifferentiated liposarcoma	RTx-associated second primary	Lack of MDM2/CDK4 co-amplification
881	Wild type GIST	KIT^{mt} GIST	Large KIT exon 11 deletion
1065	Carcinoma of unknown primary	Desmoplastic Small-Round-Cell Tumor	EWSR1–WT1 fusion

11541 **Poster Session**

The sarcoma microbiome as a diagnostic and therapeutic target. *First Author: Gabriel Tinoco, The Ohio State University, Columbus, OH*

Background: Sarcoma is a heterogeneous group of malignant tumors that consist of distinct histological and molecular subtypes, each with unique features. Despite immunotherapy's promise in many cancers, immunotherapeutic approaches for sarcoma have had variable response rates. Evaluating the tumor microbiome is a promising new approach that aims to improve our understanding of the immunogenicity of sarcoma subtypes, leading to improved treatment options and better clinical outcomes. **Methods:** We utilized The Cancer Genome Atlas (TCGA) and Genome Tissue Expression (GTEx) database to obtain RNA sequencing (RNAseq) data to identify microbes in sarcoma samples (all subtypes available). Due to the large number of sarcoma subtypes, we focused on three groups: dedifferentiated liposarcoma (DDLPS), leiomyosarcoma (LMS) and "other," representing all other sarcoma subtypes. We utilized ExoTIC, "Exogenous sequences in Tumors and Immune cells," a tool recently developed by Dr. Daniel Spakowicz and Dr. Xaiokui Mo. ExoTIC takes raw RNAseq reads and carefully aligns to both human and non-human reference genomes to identify low-abundance microbes. Models of association were analyzed based on each of the three groups as well as all the samples: "All" group. We performed Cox proportional hazards regression to identify the microbes associated with overall survival (OS). **Results:** We evaluated 97 LMS, 56 DDLPS and 100 "other" RNAseq samples (Table). ExoTIC identified 1304 microbes, of which 431 were statistically associated with OS in the "All" group. Of these, 50 microbes were statistically associated only with DDLPS, 54 only with LMS (e.g., Candida dubliniensis, Mycobacterium avium, Streptococcus sp. Z15), and 46 with "other." The presence of no organism was associated with improved survival. Median hazard ratios were largest in DDLPS (2.3), followed by "other" (2.1) and LMS (1.9). Only 18 microbes were found in the DDLPS, LMS and "All" groups, including Bacillus sp., Streptococcus lutetiensis, Clostridium tetani, and Pseudomonas sp. LTJR-52. Each was negatively correlated with survival with a median hazard ratio of 2.5. **Conclusions:** We found a specific relationship between microbial presence and histological sarcoma subtype (DDLPS, LMS), which also statistically correlated with OS. Assessing individual characteristics of a sarcoma histological subtype with its particular microenvironment (e.g., microbes) can lead to personalized treatment insights and improvements in outcomes. Our future research will consist of validating and correlation of the microbial profile of sarcoma subtypes with clinical outcomes retrospectively and prospectively. Research Sponsor: None.

	Overall
n	253
Histology (%)	
DD LPS	56 (22.1)
LMS	97 (38.3%)
Other	100 (39.5)
Age (mean (SD))	60.79 (14.67)
Sex = Male (%)	117 (46.2)
Race (%)	
White	222 (87.7)
Black or African-American	17 (6.7)
Asian	6 (2.4)
Not reported	8 (3.2)
Vital Status = Deceased (%)	95 (37.5%)

11542 **Poster Session**

Phase 1 trial of autologous dendritic cell vaccination with imiquimod immunomodulation in children and adults with refractory sarcoma. *First Author: Aditi Dhir, University of Miami Miller School of Medicine/ Sylvester Comprehensive Cancer Center, Miami, FL*

Background: Sarcomas are rare, heterogeneous, and aggressive neoplasms that often affect otherwise healthy individuals. Patients with advanced or metastatic sarcomas have dismal outcomes. Immunotherapy presents promising new modalities to help treat sarcomas. One such therapy, autologous dendritic cell (DC) vaccines, using antigen-loaded DCs, intensify the adaptive immune response by enhancing T-cell activity and inducing tumor cell death through apoptosis and cytolysis. We present the results of a phase 1 study of DC vaccine for refractory sarcomas. **Methods:** A phase 1 dose-escalation study of autologous DC vaccination was conducted in children and adults with recurrent/refractory sarcomas who underwent surgical resection of a primary or metastatic tumor between 2014-2019. A 5+3 dose-escalation schema was chosen to determine safety and recommended phase 2 dose. Patient monocytes were collected by pheresis and incubated with GM-CSF plus IL-4 to generate immature DCs which were then loaded with autologous tumor lysates from the patient's surgical resection. Three dose levels, 3, 6, and 12 million DCs per treatment were tested. The DC product was administered intradermally in imiquimod-treated skin to complete in situ maturation. Treatment consisted of four weekly injections of the DC product, followed by four monthly "boosters" of tumor lysate. The primary and secondary endpoints included safety/feasibility and preliminary clinical efficacy, respectively. **Results:** Nineteen patients were enrolled with a median age 50 years (13-75 years) and 47% female. Seven patients were treated on dose level 1 and six each on dose level 2 and 3. Thirteen patients received all planned injections while the remaining six patients progressed during treatment. There was no treatment related dose limiting toxicity. Grade 1-2 fever, headache, arthralgia, injection site reaction attributable to treatment were noted in four patients. There were no adverse events $>$ grade 2. Disease progression before or after completion of study treatment was noted in 15 patients with a median PFS of 9.5 months (95%CI 5.6-28.7). The two-year PFS and OS was 36.8% and 68.1%, respectively. There were seven deaths due to disease, one patient was discharged to hospice and two patients have been lost to follow up. Five patients are currently receiving alternative therapy. Four patients remain in follow up without evidence of disease progression including three patients (pleomorphic myxofibrosarcoma, pleomorphic myosarcoma, and leiomyosarcoma) who are disease free over two years from initiating study therapy and one pediatric patient (Ewing sarcoma) disease free for over one year. **Conclusions:** Autologous DC vaccine with imiquimod immunomodulation for patients with relapsed/refractory sarcomas is feasible and well-tolerated. Refinement to augment initial and sustained antitumor activity is needed. Clinical trial information: NCT01803152. Research Sponsor: None.

11543 **Poster Session**

Results of NC-6300 (nanoparticle epirubicin) in an expansion cohort of patients with angiosarcoma. *First Author: Richard F. Riedel, Duke University Medical Center, Durham, NC*

Background: NC-6300 is a polymeric micelle exhibiting increased tumor accumulation compared to small-molecule epirubicin through enhanced pharmacokinetics and controlled release within the tumor through a pH-sensitive linker conjugated to epirubicin. In a phase 1b trial, which accrued twenty-nine patients with various types of sarcoma as well as solid tumors, observed dose-limiting toxicities included thrombocytopenia, stomatitis, lung infection, and febrile neutropenia. The maximum tolerated dose and the recommended phase 2 dose were determined to be 185 mg/m^2 and 150 mg/m^2, respectively. The objective response rate (ORR) in soft tissue sarcoma subset (n = 17) was 18% with both angiosarcoma patients achieving partial response. To further evaluate the anti-tumor activity of NC-6300 in angiosarcoma, we conducted an expansion cohort of 10 additional angiosarcoma patients. **Methods:** Eligible patients, at least age 18 years old, with histologically confirmed angiosarcoma, including cutaneous and non-cutaneous variants, not amenable to curative treatment with surgery or radiotherapy were included. No more than two lines of prior systemic therapy were allowed. NC-6300 was administered at the dose of 150 mg/m^2 intravenously on Day 1 of a 21-day cycle. Treatment was continued until disease progression or unacceptable toxicity. Disease assessment was performed every 6 weeks using RECIST v1.1. The primary endpoint was median progression-free survival (mPFS). **Results:** Ten patients (cutaneous: 2 pts; non-cutaneous: 8 pts) were enrolled and deemed evaluable. Median line of prior systemic treatment in the advanced disease setting was 1.0 and seven patients (70%) received prior anthracycline therapy. Objective response rate (ORR) was 30% (cutaneous: 1 pt, non-cutaneous: 2 pts) and mPFS was 5.4 months (95% CI: 1.2-NA). Across all angiosarcoma patients included in the phase 1 portion and expansion cohort (phase 1b portion: 2 pts, expansion cohort: 10 pts), ORR and mPFS was 42% and 7.3 months (95%CI: 3.3-NA), respectively. All patients enrolled in the expansion cohort experienced grade 3/4 AEs and no treatment related death was observed. Most frequent grade 3/4 AEs were neutropenia without fever (80%), thrombocytopenia (40%), anemia (20%) and leukopenia (20%). AEs led to NC-6300 dose reduction and medication withdrawal were seen in 70% and 10% of patients, respectively. **Conclusions:** Promising anti-tumor activity was observed in this cohort of patients with cutaneous and non-cutaneous angiosarcoma. The safety profile of this expansion cohort was consistent with previous clinical study results of NC-6300. Our study results warrant further development of NC-6300 for angoisarcoma. Clinical trial information: NCT03168061. Research Sponsor: NanoCarrier Co., Ltd.

11544 **Poster Session**

Long-term evaluation of the novel radioenhancer NBTXR3 plus radiotherapy in patients with locally advanced soft tissue sarcoma treated in the phase II/III Act.In.Sarc trial. *First Author: Sylvie Bonvalot, Institut Gustave Roussy, Villejuif, France*

Background: NBTXR3, a novel radioenhancer activated by radiotherapy (RT) demonstrated superior efficacy, as preoperative treatment, in patients with locally advanced soft tissue sarcoma (LA STS), compared to RT alone. Primary endpoint of pCR rate was 16% vs 8% (p=0.044) and R0 margin rate was 77% vs 64% (p=0.042) (Bonvalot et al. *Lancet Oncol.* 2019). No modification of the early safety profile of RT was observed, leading to market authorization. Here we report on the long-term safety, limb function and quality of life. **Methods:** This phase II/III randomized (1:1), international trial included adult patients with LA STS of the extremity or trunk wall, requiring preoperative RT (NCT02379845). Patients were treated with either a single intratumoral injection of NBTXR3 (volume equivalent to 10% of tumor volume, at 53.3g/L) plus EBRT (arm A), or EBRT alone (arm B) (50 Gy in 25 fractions), followed by surgery. The primary and main secondary efficacy endpoints were previously reported. Safety of NBTXR3+RT, as preoperative treatment, was evaluated as secondary endpoint. We present the safety analyses done in the "all treated population", with data recorded during at least a two-year follow-up. Important parameters related to HR-QoL, including functional outcome were studied using the EQ-5D, RNLI, TESS and MSTS questionnaires. **Results:** Patients had at least two-year follow-up and the lost to follow-up rate was very low (1.9%). RT-related SAEs were observed in 11.2% (10/89) vs 13.3% (12/90) in A vs B. Post-treatment AEs, any grade, were observed in 51.7% (46/89) vs 57.8% (52/90) and serious post-treatment AEs in 13.5% (12/89) vs 24.4% (22/90) of patients in A vs B. Second primary cancer was observed in 1 patient in arm A and 6 patients in arm B. Long-term safety continues to demonstrate that NBTXR3 plus RT has no impact on post-surgical wound complications (24.7% vs 36.7%, A vs B). Furthermore, the evaluation of radiation late toxicities in limbs such as fibrosis (4.5% vs 7.7%), arthrosis (2.2% vs 0.0%) and edema (6.7% vs 2.2%) that may alter limb function showed no difference between arms. Accordingly, HR-QoL evaluation yielded no difference in functional outcome. In addition, the intratumoral injection of NBTXR3 did not induce cancer cell seeding at the former tumor site. Finally, sequelae or chronic tissue disturbances at the former tumor localization were similar in both treatment arms, confirming that the increase of energy dose deposit and the physical presence of NBTXR3 did not impact post-treatment limb functions. **Conclusions:** The long-term safety results demonstrate that the addition of NBTXR3 to EBRT neither added toxicity nor modified the bystander effect of RT. The results presented here associated with the efficacy data reported previously reinforce the favorable benefit-risk ratio of the use of NBTXR3 in patients with LA STS. Clinical trial information: NCT02379845. Research Sponsor: Nanobiotix, SA and PharmaEngine Inc.

11545 **Poster Session**

Efficacy and safety of nivolumab and trabectedin in pretreated patients with advanced soft tissue sarcomas (STS): Preliminary results of a phase II trial of the German Interdisciplinary Sarcoma Group (GISG-15, NitraSarc) for the non-L sarcoma cohort. *First Author: Daniel Pink, Klinik und Poliklinik für Innere Medizin C, Hämatologie und Onkologie, Transplantationszentrum, Palliativmedizin, Universität Greifswald and Klinik für Hämatologie, Onkologie und Palliativmedizin-Sarkomzentrum, HELIOS Klinikum Bad Saarow, Bad Saarow, Germany*

Background: Single-agent PD-1 inhibitors have modest activity in the treatment of most STS. Potential strategies to increase efficacy include combination therapies targeting the tumor microenvironment. Considering that apart from direct growth inhibition and death of malignant cells, trabectedin (Tr) also induces macrophage depletion and/or different immunologic effects, suggesting a possible synergistic effect of combined Tr plus anti-PD-1 treatment. We therefore aimed to evaluate the efficacy and safety of combined Tr and nivolumab (Ni) as a second-line treatment in STS. **Methods:** The prospective, explorative, two group, non-randomized phase II NiTraSarc trial enrolled pretreated patients (pt) with advanced STS (Group A: lipo- or leiomyosarcomas, Group B: non-L-sarcomas). Pt were initially treated with 3 cycles of Tr 1.5 mg/m^2, followed by the combination of Tr 1.5 mg/m^2 + Ni 240 mg ("late combination cohort" (LCC)) for up to 16 cycles. After positive results of a preplanned interim analysis, pt received the combination therapy starting with cycle 2 ("early combination cohort" (ECC)). 92 pt were recruited to the trial (55 in Group A, 37 in Group B). Primary efficacy endpoint is progression-free survival rate after 6 months (PFSR6) according to RECIST v.1.1. This is a first analysis of the primary efficacy endpoint in Group B based on a modified intention-to-treat (mITT) population of evaluable 36 pt: 23 and 13 pt from the LCC and ECC, respectively. **Results:** The most common Group B subtypes comprised undifferentiated pleomorphic/not otherwise specified sarcoma (UPS/NOS, 13pt) and fibromyxoid sarcoma (FMS, 6pt). After a median follow-up of 5 months (m) PFSR6 was 13.9% for all pt, 8.7% in LCC and 23.1% in ECC. Median duration of disease stabilization (DoDS) was 4m in all pt, the LCC and the ECC. Two pt had a partial response (PR), 10 had disease stabilization (SD), while 13 pt progressed, and 11 had missing data. By subtype: PR- UPS/NOS=2 (DoDS 12.7m/12.5m). SD: UPS/NOS=3, epithelioid=2, synovial=2, FMS=1, fibrosarcoma=1, other=1. All 36 pt experienced at least one adverse event (AE) reaching a total of 579 AEs, 141 (24.4%) of which were considered to be grade ≥3 treatment-related AEs. The main grade ≥3 AEs were: leukopenia (47.2% of pt), neutropenia (41.7% of pt), thrombocytopenia (33.3% of pt), increased ALT (30.6% of pt), and anemia (27.8% of pt). **Conclusions:** Tr+Ni was well tolerated and showed activity in at least some patients with non-L-sarcomas (mostly UPS/NOS) especially in the ECC. Analyses of the collected data, including PD-L1 expression profile, with the goal to establish whether Tr+Ni should be further pursued in these patients, are ongoing. ClinicalTrials.gov Identifier: NCT03590210; EudraCT: 2017-001083-38. Clinical trial information: NCT03590210. Research Sponsor: University Medicine Greifswald, Germany, Pharmaceutical/Biotech Company.

11546 **Poster Session**

Recurrence and disease-specific survival after 10-year disease-free interval in patients with primary retroperitoneal liposarcoma: Implications for long-term surveillance. *First Author: Mark Archer Eckardt, Department of Surgery, Yale School of Medicine, New Haven, CT*

Background: Surveillance imaging of patients with retroperitoneal liposarcoma (RP-LPS) following surgical resection is based on a projected risk of locoregional and distant recurrence. The duration of surveillance is not well defined as the long-term natural history of RP-LPS after treatment is poorly understood. We evaluate a cohort of RP-LPS patients—without evidence of disease 10 years following initial resection—to assess the long-term risk of recurrence and disease-specific survival (DSS). **Methods:** The prospectively maintained UCLA Sarcoma Database was used to identify RP-LPS patients who demonstrated 10-year progression-free survival (10yr-PFS) after initial diagnosis and treatment. Patients in the 10yr-PFS cohort were subsequently evaluated for recurrence and DSS. Time intervals start at date of initial surgical resection. Cox proportional hazards models were used to determine factors associated with recurrence and DSS. **Results:** From 1972-2010, 76 patients with RP-LPS had at least 10 years of follow-up. Of these, 37 (49%) demonstrated 10yr-PFS. Median follow-up was 15 years (range 10-35 years). Among the 10yr-PFS patients, 43% (16/37) developed a recurrence >10 years *after* the initial surgery, and 19% (7/37) died of disease. Neither long-term recurrence nor DSS were significantly associated with age, sex, tumor size, LPS subtype, surgical margin, or peri-operative treatment with radiation or chemotherapy (Table). **Conclusions:** Patients with primary RP-LPS treated with surgical resection +/- multimodality therapy have a long-term risk of recurrence and disease-specific death that is unacknowledged by current surveillance imaging guidelines. Among the patients with a 10yr-PFS, 43% developed a recurrence and 19% died of disease. These findings suggest a need for lifelong surveillance imaging in patients with RP-LPS. Research Sponsor: None.

Factors associated with RP-LPS recurrence & DSS in patients with 10yr-PFS.

Characteristic	Totaln (%) or median (range)	RecurrenceHR (95% CI)Univariate Cox model	p value	SurvivalHR (95% CI)Univariate Cox model	p value
LPS Subtype					
-WD	22 (59.5)	Reference	Reference	Reference	Reference
-DD	13 (35.1)	0.98 (0.32-3.05)	0.986	1.12 (0.22-5.69)	0.885
-Myxoid	2 (5.4)	8.77 (0.87-88.80)	0.066	-	-
Surgical Margin					
-R0	30 (81.1)	Reference	Reference	Reference	Reference
-R1	7 (18.9)	0.71 (0.15-3.37)	0.667	3.13 (0.32-30.43)	0.325
Size (cm)	22.0 (10.0-51.0)	1.02 (0.98-1.07)	0.387	0.95 (0.86-1.05)	0.329
Chemotherapy	5 (13.5)	3.65 (0.93-14.38)	0.064	0.71 (0.08-6.22)	0.759
Radiation	15 (40.5)	1.06 (0.37-3.07)	0.916	2.85 (0.49-16.63)	0.244

11547 **Poster Session**

Efficacy and safety of anlotinib plus TQB2450 in patients with advanced soft tissue sarcoma: A multicenter, single armed, phase 1b trial. *First Author: Jiayong Liu, Beijing Cancer Hospital, Beijing, China*

Background: Anlotinib, a multitargeted tyrosine kinase inhibitor, had been prove to be effective for the treatment of advanced or metastatic soft tissue sarcoma(STS) faild anthracycline chemotherapy. With the lack of prospective data of combination of PDL-1 inhibitor and antiangiogenic agent, we designed a phase 1b study to investigated the efficacy and safety of anlotinib plus TQB2450 in patients with STS. **Methods:** Eligible patients (age 18-70, ECOG 0-1, with histopathologically confirmed advanced STS, at least one measurable lesion according to RECIST 1.1, and previously received front-line anthracycline chemotherapy) were included and received anlotinib (12mg qd, D1-14, 21d/cycle) plus TQB2450 (1200 mg, IV, D1, 21d/cycle) until disease progression or intolerable toxicities.The primary endpoint was objective response rate (ORR) , secondary endpoints included safety, overall survival (OS), progression-free survival (PFS), disease control rate (DCR). **Results:** From January 2019 to January 2021, 30 pts were enrolled1, 12 alveolar soft part sarcoma and 18 others (7 synovial sarcoma, 4 leiomyosarcoma, 5 undifferentiated pleomorphic sarcoma, 1 fibrosarcoma and 1 epithelioid sarcoma). ORR by RECIST was 36.7% , DCR was 83.3%, 11/30 pts had PR, 14/30 (46.7%) had SD, 5/30 (16.7%) PD. Median PFS was 9.6 m in all pts and 4.9m. in non-ASPS, respectively. Median OS in non-ASPS was 10.27m, while mOS in all pts and both mPFS and mOS in ASPS had not been reached. Notably, to ASPS pts, ORR was 75%, and DCR was 100%. The most common 1-2 grade treatment-related adverse reaction (TRAE) was hypothyroidism (19/30,63.3%), hypercholesterolemia (16/30, 53.3%) and hypertriglyceridemia (16/30, 53.3%), the most common ≥3 grade TRAEs were hypertriglyceridemia (3/30, 10%). 6 SAE (20%) occurred, including 2 pneumothorax, 1 Immune associated hapatic injury, 1 hypotension, 1 Immune myocarditis and 1 diabetic ketoacidosis. **Conclusions:** The combination of anlotinib and TQB2450 showed promising activity in second-line treatment of advanced STS, especially in ASPS, with well tolerance and acceptable toxicity. Research Sponsor: China International Medical Foundation (No. Z-2014-06-15331).

11548 **Poster Session**

The impact of multimodality therapies in marginally inoperable soft tissue sarcomas (STS): The Toronto Sarcoma Program (TSP) experience. *First Author: Olga Vornicova, Department of Medical Oncology, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: The mainstay therapy of operable STS remains surgery, which may include (neo)adjuvant therapies. Within the TSP, marginally inoperable STS are often treated with sequential chemo (CTX) and radiation (RT) therapy, followed by surgery (SX). Herein we present our experience of multi-modality therapies for marginally inoperable STS patients (pts). **Methods:** This was a dual-center, single program, retrospective review. Pts were included if deemed to have marginally inoperable primary or recurrent STS, as determined at the TSP tumor board. Pts included must have had CTX with the intent of having RT and SX after. Pts demographics, treatment details and clinical outcomes data were collected. Relapse free survival (RFS) and overall survival (OS) were estimated using the Kaplan-Meier method. Multivariate analysis of the influence of disease characteristics and treatment on outcomes was assessed using Cox regression. **Results:** From June 2005 to May 2019, 75 pts were identified. Median age was 52 years (range 16-72). Pts were predominantly male (55%). Histological subtypes included dedifferentiated liposarcoma (29%), leiomyosarcoma (27%), synovial sarcoma (19%) and others (25%). Primary tumor was located in the retroperitoneum (48%), extremity (23%), pelvis (12%), thorax (9%), and other sites (8%). All pts had doxorubicin and ifosfamide CTX (median 4 cycles; range 1-6), while RT dose delivered was 50.4Gy/28 fractions in 58 (77%) of cases. Twenty three pts (31%) achieved partial response, 40 pts (53%) had stable disease and 12 pts (16%) had progression of disease (PD) on CTX, of which half (8%) did not undergo further treatment. Nine pts (12%) underwent CTX followed by SX due to significant response, 9 pts (12%) underwent CTX and RT without SX due to persistent tumor unresectability or PD. The final 50 pts (67%) completed multi-modality treatment (CTX, RT & SX). Overall, 59 pts (79%) had SX; negative margins were achieved in 53 (71%). 19 pts (25%) had postoperative complications, causing death in 2 pts (2.7%). With a median follow-up of 72 months, median RFS and OS were 26.9 months (95% CI: 0-86.0), and 65 months (95% CI: 13.5-116.4). Extremity location was associated with superior RFS (median not reached [NR], HR 0.28 95% CI 0.09-0.83, p = 0.022), and OS (median NR, HR 0.29 95% CI 0.09-0.90, p = 0.032). Receipt of RT was associated with superior RFS (median NR, HR 0.23 95% CI 0.10-0.52, p < 0.001); and OS (median NR, HR 0.21 95% CI 0.09-0.50, p < 0.001). Pts who had PD after CTX were associated with poor outcomes - RFS (median 4.7 months, HR 2.03 95% CI 0.61-6.76, p = 0.24); and OS (median 21.9 months, HR 2.48 95% CI 0.73-8.47, P = 0.144). **Conclusions:** Multi-modality approach resulted in successful resection for most pts with marginally inoperable STS. Extremity location and RT administration were associated with better RFS and OS, while progression on CTX confers worse survival outcomes. Research Sponsor: None.

11549 **Poster Session**

A phase 1b study of avelumab plus DCC-3014, a potent and selective inhibitor of colony stimulating factor 1 receptor (CSF1R), in patients with advanced high-grade sarcoma. *First Author: Evan Rosenbaum, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Select sarcomas are infiltrated with immunosuppressive myeloid cells. DCC-3014 is an inhibitor of the CSF1R kinase that decreases tumor infiltrating myeloid cells in preclinical models. We hypothesized that DCC-3014 combined with the anti-PDL1 inhibitor avelumab would be safe and tolerable, decrease immunosuppressive myeloid cells, and increase cytotoxic T cells. **Methods:** This investigator initiated, open label, single center, phase I study of DCC-3014 plus avelumab in patients (pts) with unresectable or metastatic sarcoma utilized a standard 3+3 dose escalation design. DCC-3014 was administered on days 1-3 (loading dose of 20, 30, or 50 mg) followed by oral daily maintenance (10, 14, or 20 mg) in 28-day cycles; 800 mg of IV avelumab was administered q2weeks. The primary endpoint was to determine the recommended phase 2 dose (RP2D). Secondary endpoints defined the adverse event (AE) profile and assessed clinical efficacy. Peripheral blood $CD14^{+}Lin^{-}HLA\text{-}DR^{lo}$ myeloid-derived suppressor cells (MDSCs) were measured by flow cytometry. **Results:** 13 pts were treated; median age was 61 (range 32 – 71), 8 were female, and median prior lines of therapy was 5 (range 2 – 10). Histologic subtypes included leiomyosarcoma (LMS, n = 7), undifferentiated pleomorphic sarcoma (2), dedifferentiated liposarcoma (LPS, 2), synovial sarcoma (1), and pleomorphic LPS (1). The Table lists treatment-related AEs (TRAEs) of any grade (G) occurring in ≥ 10% of pts and all G ≥ 3 TRAEs, sorted by frequency. All pts had at least 1 TRAE. Seven pts (54%) had a G ≥ 3 TRAE. Most TRAEs were either G ≤ 2 or expected on-target effects of CSF1R inhibition. 1 of 6 pts on the highest dose level had a dose limiting toxicity (G4 elevated AST with abdominal pain) that resolved with treatment cessation. The highest dose level was declared the RP2D. Best objective response by RECIST 1.1 was stable disease in 3 pts; 2 had LMS and were treated at the highest dose level. At baseline, the mean proportion of monocytes in peripheral blood samples with an MDSC phenotype was 12.2% (range 7.1 – 19.9). 5 of 7 pts with serial blood samples had decreased circulating MDSCs (mean decrease of 26.9% from baseline to last time point). **Conclusions:** DCC-3014 combined with avelumab was safe and tolerable. Study therapy decreased circulating MDSCs in select patients; T cell analyses will be reported. Study expansion at the RP2D is ongoing. Clinical trial information: NCT04242238. Research Sponsor: Deciphera Pharmaceuticals, Inc. and EMD Serono, Inc., an affiliate of Merck KGaA, Darmstadt, Germany, as part of an alliance between Merck KGaA and Pfizer, Conquer Cancer Foundation of the American Society of Clinical Oncology, Other Foundation.

TRAE	G1	G2	G3	G4
AST/ALT increased	4 (31)	5 (38)	3 (23)	1 (8)
CPK increased	1 (8)	4 (31)	1 (8)	2 (15)
Amylase increased	1 (8)	6 (46)	1 (8)	0
Lipase increased	4 (31)	1 (8)	1 (8)	0
Creatinine increased	5 (38)	0	0	0
Periorbital edema	5 (38)	0	0	0
Anorexia	3 (23)	1 (8)	0	0
Fatigue	2 (15)	2 (15)	0	0
Troponin I increased	3 (23)	0	0	0
Headache	3 (23)	0	0	0
Neutrophil decreased	1 (8)	2 (15)	0	0
Anemia	1 (8)	1 (8)	1 (8)	0
Fever	2 (15)	0	0	0
Flu like symptoms	2 (15)	0	0	0
Hypertension	0	0	1 (8)	0

All values represent number of pts (%).

11550 **Poster Session**

Preliminary results of phase 2 trial of preoperative image guided intensity modulated proton radiation therapy (IMPT) with simultaneously integrated boost (SIB) to the high-risk margin for retroperitoneal sarcomas (RPS). *First Author: Thomas F. DeLaney, Massachusetts General Hospital, Boston, MA*

Background: RPS often have local recurrence (LR) after surgery. Preoperative radiation (RT) to 50.4 Gy can reduce LR risk but is not uniformly effective, especially after (+) margin resections. Therefore, we conducted a multi-institutional, prospective Phase II study to assess efficacy and tolerability of preop IMPT with selective dose escalation to 63 GyRBE to the posterior RPS margin (clinical target volume [CTV] 2) at high risk for (+) margins to further reduce the risk of LR. This dose was tolerable in a prior phase I study (DeLaney T et al, 2017, PMID:28740917). **Methods:** Primary RPS patients (pts) >18 years received preop IMPT, 50.4 GyRBE in 28 fractions (fx) of 1.8 GyRBE to CTV1 (tumor plus adjacent tissue at risk of subclinical disease) with SIB to CTV2 to 63.0 GyRBE in 28 fx of 2.25 GyRBE. Pts with high-grade tumors could get chemotherapy(CTX) prior to IMPT. To avoid treatment delay, 11 fx of IMRT x-rays could be substituted for IMPT. Pts had restaging and surgery 4-8 weeks after IMPT. Primary study endpoint was local tumor control. Secondary endpoints included clinical and pathologic response, surgical margin status, and disease-free and overall survival. **Results:** We accrued 60 pts from January 2016 to February 2021. Histology: 35 liposarcoma(LPS) (19 dediff and 16 well diff), 22 leiomyosarcoma(LMS), and 3 undifferentiated pleomorphic sarcoma. IMPT was delivered per protocol in all pts. 51 pts have had surgery, 5 are awaiting surgery, and 4 had no surgery due to metastases(DM) on preop imaging. 22 pts had (+) margins. 2 pts had > 75% necrosis. With 23-month median (range 1-52 months) follow-up after start of RT, there were two LRs. A dediff LPS pt had a well diff LPS LR 26 months postop, resected, and is disease-free. A renal vein/IVC LMS pt treated with CTX and IMPT had LR and DM 4 months postop and died from disease. Surgical Clavien-Dindo morbidity scores: 0(21) , 1(9), 2(8), 3a (4), 3b(4), 4a(2), 4(b)1, 5(2); the periop deaths were from sepsis(pneumonia) and duodenal ulcer. The grade 3-4 periop morbidity included abscess(3), treated by catheter(2) or operative(1) drainage, prolonged hospital stays (2 pts with IVC LMS), small bowel obstruction (1), and late sigmoid colon anastomotic failure (1). Readmissions for lymphopenia(1), pneumoperitoneum (1), and volume overload (1). One late neuropathy was seen in a Type II diabetic pt with transient postop weakness after femoral nerve dissection who later had significant lower extremity weakness 3.75 years postop. Study was amended to reduce IMPT dose in diabetic pts. **Conclusions:** Preoperative IMPT with selective dose escalation to 63 GyRBE to the high risk posterior RPS margin is feasible. Early local control results with this approach appear promising. Some peri-operative morbidity was noted but appears to be in the expected range for RPS resections. Clinical trial information: NCT01659203. Research Sponsor: U.S. National Institutes of Health.

11551 **Poster Session**

Durvalumab and pazopanib in patients with advanced soft tissue sarcoma: A single-center, single-arm, phase 2 trial. *First Author: Hyo Song Kim, Division of Medical Oncology, Department of Internal Medicine, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, South Korea*

Background: Based on the central role played by the vascular endothelial growth factor receptor (VEGFR) in immunosuppression, we assessed the activity and safety of VEGFR inhibitor pazopanib plus anti-PD-L1 blockade durvalumab in soft tissue sarcoma (STS). **Methods:** We did a single-arm, single-center, phase 2 study that enrolled patients with metastatic or locally advanced STS aged 19 years or older, ECOG PS 0-1, with at least one measurable lesion, and received at least one previous line of systemic therapy. Patient were given pazopanib 800 mg orally daily and durvalumab 1500 mg intravenously for 60 min every 3 weeks. The primary endpoint was investigator-assessed objective response. **Results:** Between September 2019 and October 2020, 47 participants were enrolled, of whom 46 (97.9%) were evaluable for the efficacy analyses. With a median follow up of 12.3 months, complete and partial response (PR) was achieved in 1 (2.2%) and 12 (26.1%) patients, resulting in 28.3 % of objective response rate. Median time to achieve PR was 1.4 months and median duration of response was 11.0 months. The most common treatment-related adverse events of any grade include fatigue (20 [42.6%]), anorexia (17 [36.2%]), diarrhea (17 [36.2%]), and AST elevation (16, [34.0%]). Thirty-one patients (67.3%) had progressive disease, and the median progression free survival was 8.6 months (95% CI 3.6-13.6). **Conclusions:** Durvalumab and pazopanib showed encouraging activity in patients with advanced STS. Molecular predictors with whole exome and RNA sequencing will be presented. Clinical trial information: NCT03798106. Research Sponsor: None.

11552 **Poster Session**

Immune-desert tumor microenvironment in SMARCA4-deficient thoracic sarcomas with limited efficacy of immune checkpoint inhibitors. *First Author: Justine Gantzer, Medical Oncology Department, ICANS, Strasbourg, France*

Background: SMARCA4-deficient thoracic sarcomas (SDS) are rare and aggressive sarcomas characterized by inactivating *SMARCA4* mutations, with no approved treatment to date. Previous data linking SWI/SNF deficiency with tumor immune microenvironment (TME) are contradictory. While an immunogenic microenvironment and efficacy of immune checkpoint inhibitors (ICI) were described in SMARCA4-deficient small cell carcinoma of the ovary, the TME phenotype of SDS is unknown; in addition, response of patients to ICI is lacking. **Methods:** All consecutive patients diagnosed with SDS between 2016 and 2019 in Strasbourg University Hospital were included and clinical outcomes collected. Immunostainings for immune cell markers, immune checkpoints and tertiary lymphoid structures (TLS) were assessed on available samples. Validation was performed using an independent transcriptomes dataset of SDS (n = 12), not otherwise specified (NOS) non-small cell lung cancer (NSCLC) with/without *SMARCA4* mutations (n = 14) and undifferentiated thoracic sarcoma (n = 5). Finally, chemokines (CXL9 and CXCL10) and PD-L1 expressions were assessed in NSCLC and thoracic fibroblast cell lines, treated with/without interferon gamma (IFNG). **Results:** Nine patients were identified and had all metastatic disease at presentation, with a median overall survival of 1.8 months (0.3-NR). Among them, 4 received ICI as part of their treatment. Out of 11 evaluated tumors samples, all but one case showed no TLS, consistent with an immune desert TME phenotype charted by low densities of CD3+ T-cells, CD8+ T-cells, CD20+ B-cells from one side and high density of CD68+ macrophage-cells from the other side. Conversely, the unique tumor with TLS aggregate showed an immune-rich TME phenotype associated with high mutational tumor burden. While the patient with TLS harboring tumor showed an exceptional long-lasting response, the 3 remaining patients without TLS had progressive disease at best response to ICI. Using an independent cohort, unsupervised clustering using immune cell scores identified two clusters tightly associated with cell ontogeny of cancer subtypes and immunity; while cluster 1 (C1) was enriched for NOS NSCLC independently from *SMARCA4* status (n = 9/10; 90%) (p = 0.001), C2 was enriched for SDS (n = 11/12; 91.7%) (p = 0.005) and undifferentiated thoracic sarcomas (n = 5/5; 100%) (p = 0.0005). Finally, SMARCA4 loss of function experiments revealed upregulation of chemokines (CXL9 and CXCL10) and PD-L1 expression in the NSCLC cell line with no effect on thoracic fibroblast cell line. **Conclusions:** SDS harbor an immune desert TME phenotype with limited efficacy to ICI, similar to other sarcomas. Our data suggest that TME of SMARCA4-driven tumors might vary according to the cell of origin. Further studies are needed to understand the interplay between SWI/SNF mutations, cell ontogeny and immunity. Research Sponsor: None.

11553 **Poster Session**

ESMO Magnitude of Clinical Benefit Scale (MCBS): An evaluation of systemic treatment trials for soft tissue sarcomas (STS). *First Author: Abdulazeez Salawu, Princess Margaret Cancer Centre, University of Toronto, Toronto, ON, Canada*

Background: Patients with STS have poor prognosis in the metastatic setting. Although some treatment options are associated with improved outcomes, such as progression-free (PFS) or overall survival (OS), the overall magnitude of clinical benefit can be unclear. The ESMO MCBS is a validated and reproducible tool developed to quantify the clinical benefit of treatments evaluated in trials (www.esmo.org/guidelines/esmo-mcbs). Herein, we report the application of ESMO MCBS to systemic treatment trials involving metastatic STS patients. **Methods:** A systematic search of Medline, Embase and Cochrane databases for adult phase II and III trials in advanced STS (01/1998 to 12/2020) was carried out. Gastrointestinal stromal tumor trials were excluded. Outcomes, including but not limited to OS, PFS, objective response rate (ORR), toxicity and quality of life (QoL) data were extracted and analyzed. Studies with outcomes that met the criteria for ESMO MCBS v1.1 were evaluated to generate a score of 1 to 5 (score of $\geq$ 4: substantial benefit). MCBS scoring of each study was performed by at least 2 co-authors for consensus. **Results:** Among 3454 abstracts screened, a total of 140 Phase II and 28 phase IIII trials were identified. A total of 41 studies fulfilled the criteria for ESMO MCBS scoring. These include 5 phase III studies, as well as 9 randomized and 27 single-arm phase II trials. Fifteen studies involved specific histology, while remaining 26 studies were of all STS subtypes. Chemotherapy, alone or in combination was evaluated in 29 trials, while molecular-targeted agents (MTA) and immune checkpoint inhibitors (IO) were evaluated in 11 and 3 studies, respectively (Table). The median MCBS score was 2 (range 1-4), regardless of drug class or combination. Only 3 studies, all randomized in design, had a MCBS score of 4. All three trials were in the 2nd line setting or beyond, where there is no standard control treatment. None of the trials, irrespective of drug class had a score of 5 and no study showed evidence of significant improvement in QoL. The observed MCBS scores were low, partly because the trials evaluated mainly comprise single-arm studies without QoL assessments, restricting to a maximum MCBS score of 3. **Conclusions:** Most systemic therapy trials in advanced STS did not confer substantial clinical benefit when evaluated using MCBS. Although randomized phase 3 trials remain the gold standard of treatment evaluation, clinical benefit evaluation of STS trials using tools such as MCBS may be useful. Incorporation of QoL evaluation, even in single-arm studies should be prioritized in metastatic STS trials. Research Sponsor: None.

Frequency of MCBS scores by drug class.

ESMO MCBS Score		1	2	3	4	5	Total
Chemo	Single agent	5	4	1	2	-	12
	>1 agent	1	7	6	1	-	15
MTA		2	5	2	-	-	9
IO	Single agent	-	1	-	-	-	1
	>1 agent	-	1	-	-	-	1
IO + MTA		-	1	-	-	-	1
Chemo + MTA		-	2	-		–	2
Totals		**8**	**21**	**10**	**2**	**0**	**41**

11554 **Poster Session**

First-in-human administration of CEB-01, a novel drug delivery implant matrix, in patients with recurrent or locally advanced retroperitoneal soft tissue sarcoma (RPS) after surgery: Preliminary safety and pharmacokinetics report. *First Author: José Antonio Gonzalez, Hospital de la Santa Creu i Sant Pau, Surgery Department, Barcelona, Spain*

Background: RPS local recurrence after radical surgery (SX) is frequent and a major cause of death. Locally delivered CHT by a biocompatible and biodegradable implant matrix (CEB-01) loaded with SN-38 and placed in the surgical bed during SX may increase local control and survival in RPS patients with reduced systemic toxicity. **Methods:** This is a multicentre, open label, first-in-human phase 1 trial comprising a dose-escalation phase (3 cohorts with total SN-38 doses of 9, 18 and 36 mg respectively), followed by an expansion cohort at the recommended phase 2 dose (RP2D). Recurrent or locally advanced RPS patients candidates for local surgery, with no option of systemic treatment, ECOG < 2, life expectancy > 6 months, and normal organ function are eligible. Primary objective is to determine RP2D, defined as the dose level at which less than 33% of patients present dose limiting toxicity (DLT) in a minimum of 6 at-risk patients during the first two weeks after SX. DLT is defined as any Grade $\geq$3 toxicity. Secondary objectives include safety, time to recurrence, biomarkers, pharmacokinetics (PK) and quality of life (QoL). Here we report preliminary safety, efficacy, and PK data for the initial patients enrolled. **Results:** First cohort of 9 mg SN-38 was completed in february 2021, with the inclusion of three patients with dedifferentiated liposarcoma, (grade 2-3) Patients were male, age 65 to 74, with ECOG of 0-1. Optimal SX were performed for recurrent/metastatic disease (2 patients) or locally advanced disease (1 patient) with complete (R0) and optimal (R1) outcomes. There were no surgical complications attributed to the SN-38 treatment . One patient suffered from grade 2 (Dindo Clavien classification) intestinal subocclusion due to SX complication resolved with medical treatment at day 5. Frequency and severity of adverse events (AE) was low. All the patients presented transitory abdominal discomfort and seroma. AEs consisted of one catheter infection and one hypomagnesemia, both grade 3. Only one treatment related AE (TRAE) consisting of alopecia grade 1 was reported. There were no DLTs observed during the first administrations of CEB-01 (9 mg SN38). SN38 and its glucuronidated SN-38 systemic levels were low, reaching a peak (Cmax) of 0.60 and 3.3 ng/mL at 2 and 6 hours respectively, and were detectable 27 days after CEB-01 implantation in the surgical bed, at 0.1 and 0.6 ng/mL respectively. **Conclusions:** CEB-01 biocompatible and resorbable implant matrix loaded with SN38 has proven to be safe upon first human administrations in RPS patients, with scarce low grade AEs and TRAE. Preliminary PK indicates low, prolonged, systemic SN-38 exposure as expected. Currently the second cohort of this trial is open for recruitment. Clinical trial information: NCT04619056. Research Sponsor: CEBIOTEX.

11555 **Poster Session**

Multiomic analysis to reveal distinct molecular profiles of uterine and nonuterine leiomyosarcoma. *First Author: Tabitha Copeland, Rutgers-Robert Wood Johnson Medical School/CINJ, New Brunswick, NJ*

Background: Leiomyosarcoma (LMS) is a rare group of mesenchymal malignancies found in the uterus, retroperitoneum, skin, or other soft-tissue sites. Treatment for LMS is extrapolated from trials including both uterine (uLMS) and non-uLMS subtypes, although whether they respond similarly and have similar outcomes from treatment is not clear. We examined the molecular composition of LMS by site of origin to better inform future drug development and trial design. **Methods:** We reviewed 1115 specimens with LMS histology tested by Caris Life Sciences for targeted exome (NextSeq, 592 gene panel), whole exome, and whole transcriptome sequencing (NovaSeq). Specimens were stratified into uLMS, rpLMS (retroperitoneal), and otherLMS (non-uterine/retroperitoneal) subgroups based on tumor origin sites. Genomic data was analyzed for mutations, copy number aberrations, and fusions. RNA expression profiling included evaluation of individual genes and gene set enrichment analysis (GSEA). P-value adjustment performed by the Benjamini-Hochberg procedure. **Results:** The study cohort was comprised of 62.9% uLMS (n = 701), 14.9% rpLMS (n = 166) and 22.2% otherLMS (n = 248) specimens. Overall, LMS specimens most frequently harbored *TP53* (64%, n = 612), *ATRX* (30%, n = 219), *RB1* (22%, n = 156), and *MED12* (16%, n = 94) mutations, with these genes accounting for 74.4% (n = 1044) of all observed pathogenic/likely pathogenic mutations. *RB1* mutations were significantly less common in uLMS (15%) compared to rpLMS (30%, $p < 0.05$) and otherLMS (33%, $p < 0.01$), whereas *MED12* mutations were almost exclusive to uLMS (22% vs 1% rpLMS, 3% otherLMS, $p < 0.05$). *MAP2K4* copy number amplification were more common in rpLMS (22%, $p < 0.001$) and otherLMS (14%, $p < 0.182$) compared to uLMS (7%), with frequent co-amplification of nearby genes (*FLCN*, *GID4*, *SPECC1*, *GAS7*, *PER1*, and *AURKB*) located at chr17p11-13. Actionable gene fusions involving *ALK* (2.1%, n = 11), *FGFR1* (0.2%, n = 1), and *NTRK1/2* (0.2%, n = 1 each) were rare overall, with similar prevalence across subtypes. Genomic alteration rates were not significantly different between rpLMS and otherLMS subtypes. RNA expression profiling identified significant upregulation of PI3K/AKT/mTOR, DDR, WNT/Beta-Catenin pathway genes in non-uLMS. GSEA indicated several immune-related gene sets were enriched in rpLMS and otherLMS compared to uLMS. **Conclusions:** Comprehensive molecular profiling suggests that LMS originating from the uterus represents a molecularly distinct disease compared to other primary sites of origin. We identified key genomic patterns which have potential for targeted therapy. These data provide insight for the framework of future clinical trials designed to separate uLMS from non-uLMS histologies, although further subdivision does not appear to be warranted. Research Sponsor: Caris Life Sciences.

11556 **Poster Session**

The efficacy and safety of anlotinib in refractory/recurrent/advanced pediatric solid tumors: A retrospective study. *First Author: Suying Lu, Sun Yat-sen University Cancer Center, Guangzhou, China*

Background: Refractory and recurrent advanced pediatric solid tumors are short of effective treatment and with a dismal outcome, thus an urgent need for novel and effective treatment. The aim of the study is to evaluate the efficacy and safety of anlotinib, a novel and oral multi-target receptor tyrosine kinase inhibitor, in refractory or recurrent advanced pediatric solid tumors. **Methods:** The retrospective, single-institutional, observed study was conducted in Sun Yat-sen University cancer center in China. Refractory, recurrent, or advanced pediatric solid tumors patients treated with anlotinib between 2018 to 2020 were evaluated. **Results:** Forty-one patients and thirty patients were enrolled in the study to evaluated efficacy and safety, respectively. The objective response ratio (ORR) was 12.2% (95%CI 1.7-22.7): complete response (n = 0) and partial response (n = 5) (Table). The disease control rate (DCR) was 65.9% (95%CI 50.7-81). The median progression-free survival (PFS) was 2.87 months (95%CI 0.86-4.88). According to anlotinib treatment schedule, all patients were divided into three groups: anlotinib monotherapy (A, n = 16), anlotinib combined with immune checkpoint inhibitor treatment (A + ICI, n = 6), anlotinib combined with salvage chemotherapy (A + SC, n = 19). The ORR, DCR and median PFS for three groups were 6.3% (95%CI 7.1-19.6), 56.3% (95%CI 28.9-83.6), 2.43months, 16.7% (95%CI 26.2-59.5), 66.7% (95%CI 12.5-120.9), 1.13months, 15.8% (95%CI 2.3-33.8), 73.7% (95%CI 51.9-95.5), 2.87months, respectively. There was no significantly difference between three groups in aforementioned response index. The incidence rates of any grade and grade 3-4 adverse events were 80% and 20%, respectively. Bleeding (20%), hand-foot syndrome (13.3%), and diarrhea (13.3%) were the most common adverse events. Grade 3-4 adverse events include hypertension, hand-foot syndrome, diarrhea, anemia, and thrombocytopenia. There was no adverse events-related death. **Conclusions:** For heavily pretreated pediatric solid tumors, anlotinib may be an effective treatment with tolerable adverse events. Further prospective randomized controlled clinical study is warranted. Research Sponsor: None.

Treatment responses to anlotinib in refractory/recurrent advanced pediatric solid tumors.

Clinical evaluations	All patients	Group A	Group A+ICI	Group A+SC
Total, n	41	16	6	19
CR, n	0	0	0	0
PR, n (%)	5 (12.2%)	1 (6.3%)	1 (16.7%)	3 (15.8%)
SD, n (%)	22 (53.7%)	8 (50%)	3 (50%)	11 (57.9%)
PD, n (%)	14 (34.1%)	7 (43.8%)	2 (33.3%)	5 (26.3%)
ORR (%, 95% CI)	12.2%, 1.7-22.7	6.3%, 7.1–19.6	16.7%, 26.259.5	15.8%, 2.3-33.8
DCR (%, 95% CI)	65.9%, 50.7-81	56.3%, 28.9-83.6	66.7%, 12.5-120.9	73.7%, 51.9-95.5

Abbreviations: A, anlotinib monotherapy; ICI, immune checkpoint inhibitor; SC, salvage chemotherapy; CR, complete response; PR, partial response; SD, stable disease; ORR, objective response rate; DCR, disease control rate.

11557 **Poster Session**

Early results of intratumoral INT230-6 alone or in combination with ipilimumab in subjects with advanced sarcomas. *First Author: Matthew Ingham, Columbia University Irving Medical Center, New York, NY*

Background: Patients have limited treatment options following initial chemotherapy failure. INT230-6, a novel formulation of cisplatin (CIS) and vinblastine (VIN) with an amphiphilic cell penetration enhancer, is designed for intratumoral (IT) administration. Study IT-01 (BMS # CA184-592, NCT 03058289) evaluates INT230-6 alone or in combination with ipilimumab (IPI), an antibody to CTLA-4. INT230-6 dosing is set by a % of the volume of the tumor to be injected. The product has been shown to disperse throughout an injected tumor and diffuse into cancer cells. Cell death leads to recruitment of dendritic and T cells, the effect of which may be augmented by CTLA-4 inhibition as evidenced by increased efficacy of the combination in preclinical models. Historically, checkpoint inhibitors have limited activity in sarcoma. Considering the large volume of drug injected and retained in the tumor, coupled with immune infiltration on biopsies, RECIST response methodology may not capture the benefits of INT230-6 treatment. **Methods:** IT-01 is an open-label phase 1/2 study that is enrolling adult subjects with locally advanced, unresectable or metastatic sarcoma. INT230-6 was administered IT Q2W for 5 doses alone or with IPI 3mg/kg IV Q3W for 4 doses. The study objectives are to assess the safety and efficacy of IT INT230-6 alone and in combination with IPI. **Results:** 16 heterogenous sarcoma subjects (13 monotherapy, 3 IPI combination) having a median of 3 prior therapies (0, 8) were enrolled to date. The INT230-6 dose was up to 145 mL (72.5 mg of CIS, 14.5 mg VIN) in a single session (an amount of each agent in excess of standard IV doses). The most common ($>$ 20%) related TEAEs in sarcoma subjects (n = 16) were localized pain (63%), fatigue (38%), decreased appetite (31%), nausea (31%), and vomiting (25%) most of which were low grade; with only grade 3 TEAE above 5% being anemia (13%). There were no related grade 4 or 5 TEAEs. In 11 evaluable monotherapy subjects, the disease control rate (DCR = CR+PD+SD) was 82%. Basket studies of sarcomas, including chordoma, with Royal Marsden Hospital index (RMHI) scores of 2 or higher report median overall survival (mOS) of 4 months. In this study 75% of monotherapy subjects had a RMHI score of 2 and preliminary estimates of mOS was 21.3 (4.67, NA) months. Pilot immunohistochemistry analysis of 5 paired (pre- and 28 days post-dose) biopsy samples showed substantial tumor necrosis, reduction of viable cancer, a decreased cancer proliferation as measured by Ki67, and increased TILs. **Conclusions:** Preliminary data shows that INT230-6 administered intratumorally alone or in combination with ipilimumab is well-tolerated in this small, heterogenous sarcoma population. The preclinical cancer cell death and immune infiltration mechanism of action appears to translate to sarcoma subjects. There are early signs of efficacy, DCR and potentially OS, that need to be confirmed in randomized studies. Clinical trial information: 03058289. Research Sponsor: Intensity Therapeutics, Inc.

11558 **Poster Session**

Regorafenib (R) in advanced solitary fibrous tumor (SFT): Results from an exploratory phase II clinical study. *First Author: Silvia Stacchiotti, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: R showed antitumor activity in a PDX model of dedifferentiated SFT (D-SFT), inducing a superior tumour growth inhibition than with other antiangiogenic agents (A), such as pazopanib (P) and axitinib (A). The efficacy of P and A in patients (pts) with advanced typical- (T-)/ malignant- (M-)SFT has been already confirmed in phase 2 clinical trials, but not in D-SFT. An exploratory phase 2 study was designed to investigate the activity of R in advanced SFT. **Methods:** An investigator-initiated exploratory phase 2 trial was started in December 2015 at the Istituto Nazionale Tumori, Milan, Italy, to evaluate the activity of R, 160 mg OD, 3 weeks on/1 week off, until progression or limiting toxicity. in $>$ 18 years old pts with advanced SFT. The target sample size was 16 evaluable pts; at least 3 responses were requested to reject the null hypothesis of 5% in favour of an alternative hypothesis of 30% (with type-I and type-II error rates fixed at the 10% level). Eligible pts had to have evidence of progression. Prior treatment with A was allowed. Centralized pathologic review was performed, distinguishing T-SFT, M-SFT and D-SFT subtypes. The primary end-point was the overall response rate (ORR) by Choi. Secondary end-points were ORR by RECIST, progression-free survival (PFS), overall survival (OS). **Results:** Enrolment was completed in February 2021. Eighteen pts were enrolled (D-SFT = 4; M-SFT = 13; T-SFT = 1). Four pts were naïve, 14 were pre-treated [12 with antiangiogenics (4 with $>$ 1 prior antiangiogenic line); 11 with cytotoxic agents]. Three pts are ongoing, 13 completed their treatment (11 = progression, 1 = toxicity, 1 = other). Fourteen pts are evaluable for response by Choi and RECIST (1 = screening failure; 1 = early discontinuation for toxicity before radiologic assessment; 2 = too early). A definitive dose reduction was required in 5 of 14 evaluable (35.7%) pts. The ORR by Choi was 42.9% (exact binomial 95% Confidence Interval [CI]: 17.7%-71.1%), with 6/14 (42.9%) partial responses (PR), 5/14 (35.7%) stable disease (SD) and 3/14 (21.4%) progressions (PD). Best responses by RECIST were: 1/14 (7.1%) PR, 10/14 (71.4%) SD, 3/14 (21.4%) PD. 5/6 pts responsive by Choi were pre-treated with another antiangiogenic. No responses were seen in the 3 D-SFT pts. At a m-FU of 23 months, m-PFS by Choi was 3.68 (IQR: 2.73-8.54) months, with 23.4% pts progression free at 1 year. m-PFS by Choi in responsive pts was 5.62 (IQR: 2.89 – 8.54) mos. Median OS was 15.7 (IQR: 7.35-not reached) months. **Conclusions:** R did not show a higher activity in D-SFT compared to P and A. The response rate was in the range observed with other A, but m-PFS was shorter. This may be due to discrepancies in pt populations and a high-rate of dose reductions with R. However, responses to R were seen also in pts previously treated with other A and almost one fourth of pts benefited from R for more than a year. Clinical trial information: 2015-002629-21. Research Sponsor: None.

11559 **Poster Session**

A pilot study of the feasibility and utility of a fitness tracker to correlate activity level with patient reported outcomes (PROs) in sarcoma patients undergoing systemic therapy. *First Author: Elizabeth J. Davis, Vanderbilt University, Nashville, TN*

Background: The feasibility and utility of wearable devices is unknown in sarcoma patients (pts). Objective assessment of activity level, body composition, and PROs facilitate understanding of the tolerability and toxicity of cancer treatment. **Methods:** From 6/11-10/12/2020, we enrolled sarcoma pts receiving systemic therapy to a prospective study evaluating activity levels and sleep via a Fitbit Charge 3, body composition with the Inbody 570, and PROs using NIH PROMIS short forms (fatigue, pain, physical function, and sleep disturbance), the Generalized Anxiety Disorder Scale, and the Patient Health Questionnaire Depression Scale. Time on study was 12-16 weeks depending upon treatment. The Fitbit was worn continuously. Body composition and PROs were assessed every 3-4 weeks. Feasibility was defined as successful device wearing and data syncing. Data was collected through a cloud-based application, Fitabase. **Results:** 22 pts were approached and enrolled. Two pts did not complete the first study assessment due to disease progression and were excluded from analysis. 50% of pts were female. 90% of pts were white. Median age was 47 yrs (range 20-81). The most common histologies were Ewing sarcoma and leiomyosarcoma. 89.5% (17/19) of pts wore the Fibit for $>$3 weeks; median time was 68 days (5-112). 95% (19/20) of pts were able to sync data. Median step count was 2614 steps (376-19806). High step counts, defined as greater than the median, were associated with improved sleep (p=0.14) and physical function (p=0.22), and decreased pain (p=0.15), but these associations were not statistically significant. Low step counts, defined as lower than the median, were associated with skeletal muscle mass loss (p=0.22), but this was not statistically significant. **Conclusions:** Incorporating a fitness tracker is feasible in sarcoma pts receiving systemic therapy. It provides longitudinal, objective evaluation of activity levels and sleep patterns. Correlation of activity level with sleep, body composition, and PROs was limited due to small numbers; however, a larger prospective pilot study is ongoing. Research Sponsor: U.S. National Institutes of Health.

Pt characteristics, activity, & sleep.

Characteristic	N=20 (%)
Female	10 (50)
Median age in years (range)	47 (20-81)
Race	
White	18 (90)
Black	1 (5)
Other	1 (5)
ECOG (baseline/end of study)	
0	16 (80)/ 12 (60)
1	4 (20)/ 8 (40)
Histology	
Ewing sarcoma	7 (35)
Leiomyosarcoma	4 (20)
Undifferentiated pleomorphic sarcoma	3 (15)
Other*	6 (30)
Treatment goal	
Curative	11 (55)
Palliative	9 (45)
Median days Fitbit worn (range), n=19	68 (5-112)
Success wearing Fitbit	
<20 days	2 (10.5)
>20 days	17 (89.5)
Success syncing Fitbit	19 (95)
Median steps per day (range)	2614 (463-19806)
Median sleep in minutes (range), n=18	463 (87-617)

*Angiosarcoma, malignant peripheral nerve sheath tumor, myxofibrosarcoma, osteosarcoma, solitary fibrous tumor, and synovial sarcoma.

11560 **Poster Session**

A patient reported outcomes of treatments for desmoid tumors: An international natural history study. *First Author: Danielle Braggio, The Desmoid Tumor Research Foundation, Suffern, NY*

Background: The Desmoid Tumor Research Foundation (DTRF) launched the natural history study (NHS) in 2017. At this time, there are no standard-of-care options for this rare sarcoma. The treatments, clinical descriptors, and the patient reported outcomes to pharmacologic agents are described here within. **Methods:** The web-based natural history study launched September 2017 in collaboration with the National Organization of Rare Disorders. It contains 15 surveys covering diagnostics, disease, treatment, care management, and quality of life. Treatment types included in the DTRF NHS were pharmacology, surgery, radiation, high-intensity focused ultrasound (HiFU), and active surveillance (watch and wait). **Results:** While surgery was once the primary intervention for desmoid tumor patients, the NHS participants reported that 47.6% had received active surveillance or no systemic treatment at diagnosis. This is most common for desmoid tumors located in abdominal wall (54/103; 52.4%). There were 87 reported cases of complete surgical resection, 38 incomplete resections, and 23 bowel resections. 9 amputations were reported; 8 participants reported recurrent disease following the removal of the limb. The non-surgical interventions, such as radiation and HiFU, were mostly described for participants with chest wall tumors (15 pts) and joints/extremities (10 pts). Many options for systemic therapies were described including sorafenib (44/284; 15.5%), sulindac (36/284; 12.7%), and anti-hormonal agents tamoxifen and toremifene (34/285; 10.9%) were described. Targeted agents, such as gamma secretase inhibitor, pazopanib, and sorafenib, were greater in the United States than the non-US country participants (21% vs 9%). Multiple lines of treatments were reported by 81 participants, surgery is greatest as the first intervention for all tumor locations (49/81, 60%), with the exception of those with head/neck tumors who received chemotherapy (6/11, 55%). Analysis has started to evaluate the efficacy of systemic treatments from these NHS data. The table describes the participant reported outcomes of anti-hormonal agents, chemotherapeutics, non-steroidal anti-inflammatories, and targeted agents. Both chemotherapies and targeted agents were reported to have 38.1% response rates from the participants with 34.3% and 23.8% of participants reported progressive disease on therapy, respectively. **Conclusions:** Desmoid tumor NHS study participants reported the use of many treatment modalities demonstrating a range of frequency of use by tumor location and efficacy. Data collection through the DTRF NHS is ongoing. Research Sponsor: The Desmoid Tumor Research Foundation, Other Government Agency, U.S. National Institutes of Health, National Organization of Rare Disorders (NORD).

	Tumor Shrinking/ Changing structure	Continued growth	Unknown Response
Anti-hormonal agents	8 (8.2%)	19 (18%)	26 (19.3%)
Chemotherapies	37 (38.1%)	36 (34.3%)	48 (35.6%)
Non-steroidal anti-inflammatories	15 (14.5%)	25 (23.8%)	49 (36.3%)
Targeted agents	37 (38.1%)	25 (23.8%)	12 (8.9%)

11561 **Poster Session**

Treatment patterns, and survival of patients with metastatic undifferentiated pleomorphic sarcoma: A National Cancer Database (NCDB) study. *First Author: Hussain I Rangoonwala, Creighton University School of Medicine, Omaha, NE*

Background: Undifferentiated Pleomorphic Sarcoma (UPS) is regarded as one of the most common types of soft tissue sarcoma. Although prior studies have highlighted its metastatic potential, there have been no database studies that delineate the clinical/social characteristics and outcomes in UPS patients with metastatic disease. Utilizing the National Cancer Database (NCDB), we want to observe the complex interplay between treatment approaches and non-biologic modifiers. **Methods:** 737 patients diagnosed with metastatic UPS above the age of 17 years between 2004 and 2015 were identified utilizing the NCDB. Patients were identified with ICD-O-3 morphologic code 8830/3. Demographic factors (Race/ethnicity, biological sex, Median household income/education at zip code level, facility type, insurance) were studied in relation to the type of treatment they received: No treatment; chemotherapy only; chemotherapy and radiation therapy; chemotherapy and surgery; chemotherapy, surgery, and radiation; radiation therapy and/or surgery; and other treatments. Survival tables were utilized to generate 1-year and 3-year survival rates, and Kaplan-Meier method with associated log-rank list was used to examine the differences in unadjusted survival. **Results:** Approximately 17% of our cohort were left untreated, whereas 83% received treatment. Patients who were untreated were likely to be older, on Medicare, and had a Charlson-Deyo (CD) score of 2 or above. Patients who were more likely to receive treatment were younger educated males with private insurance, residing in areas of higher income, and receiving care at an academic program. Patients who only received chemotherapy were more likely to belong to areas with lower income and had a CD score of 0. Patients who received a combination of chemotherapy, surgery, and radiation therapy were more likely to belong to areas of high income, private insurance owners, and received care at an academic facility. Patients who received chemotherapy with surgery and without radiation therapy were more likely to be younger males from areas of highest income, and received care at an academic facility. Patients who had better unadjusted survival were younger educated patients on private insurance or Medicaid, with distant lymph nodes metastases at diagnosis, who received a combination of chemotherapy, radiation therapy and surgery at an academic program. Patients who had poorer unadjusted survival were untreated older patients on Medicare, and with bone metastases. **Conclusions:** This is one of the most comprehensive studies involving patients with metastatic UPS that analyzes demographic variables in relation to the treatment approach. Some of the major determinants that influence outcomes in these patients included age, insurance status, treatment at academic facility, CD score, and type of metastases at diagnoses. Research Sponsor: None.

11562 **Poster Session**

A phase 2 study using ipilimumab, nivolumab, and trabectedin for previously untreated metastatic soft tissue sarcoma. *First Author: Erlinda Maria Gordon, Sarcoma Oncology Center, Santa Monica, CA*

Background: Sarcoma cells are most immunogenic earlier in the disease course and before treatment when the immune system can recognize and destroy them. Hypothesis: Immune checkpoint inhibitors would be most effective when given to previously untreated patients with metastatic soft tissue sarcoma. **Methods:** Eligible patients for this Phase 2 study are previously untreated patients $\geq$ 18 years of age with unresectable or metastatic soft tissue sarcoma, with measurable disease by RECIST v1.1. Immune checkpoint inhibitors Ipilimumab (I) and Nivolumab (N) were given with Trabectedin (T), a marine derived alkaloid with defined doses of I (1 mg/kg i.v. q 12 weeks), N (3 mg/kg i.v. q 2 weeks), and T (1.2 mg/m2 i.v. q 3 weeks). Primary endpoints: (1) Objective response rate by RECIST v1.1 via CT scan or MRI, (2) Progression-free survival (PFS): from first day of treatment to disease progression or death due to any cause; otherwise, it is censored at the time of last follow-up, and (3) Overall survival: from first day of treatment to death due to any cause; otherwise, it is censored at the time of last follow-up. **Results:** There were eighty-two evaluable subjects, having completed the first cycle of I, N, and T and have had a CT or MRI scan at the 6-week follow-up period. Best Overall Response by RECIST v1.1 = 7 CR (2 surgical CR), 9 PR, 54 SD, and 12 PD. Disease control rate was 85.4%. The median PFS was >6.4 (range: 0-32) months; 6-month PFS rate: 57.3%. The median OS was >12.0 (0-38) months; 6-month OS rate: 78.8%. Safety analysis: The most common Grade 3 TRAEs include increased ALT (26), anemia (11), increased AST (9), and fatigue (8). Common Grade 4 TRAEs include thrombocytopenia (2), increased AST (2), increased ALT (2), and increased CPK (2). There was one Grade 5 TRAE of rhabdomyolysis (1). **Conclusions:** Taken together, these results suggest that first-line combinatorial therapy with I, N, and T are (1) synergistic, and (2) may be equal or superior to, and safer than, standard first line therapy for advanced/metastatic soft tissue sarcoma. Clinical trial information: NCT03138161. Research Sponsor: Bristol-Myers-Squibb.

11563 **Poster Session**

Results of the phase 1b soft-tissue sarcoma (STS) portion of the global randomized, double-blind, placebo-controlled study of tazemetostat (TAZ) plus doxorubicin (DOX) as frontline therapy for advanced epithelioid sarcoma (ES). *First Author: Sant P. Chawla, Sarcoma Oncology Research Center, Santa Monica, CA*

Background: ES is a rare, aggressive subtype of STS for which cytotoxic chemotherapy has limited effectiveness. TAZ, an FDA-approved EZH2 inhibitor, has shown single-agent clinical activity and a favorable safety profile in patients with metastatic or locally advanced ES. In preclinical studies, TAZ has shown synergistic antitumor activity with DOX, which is often used as frontline treatment for STS. Here, we present results of the phase 1b study (NCT04204941), designed to assess the recommended phase 3 dose (RP3D), safety, and efficacy of TAZ + DOX in patients with advanced STS. **Methods:** The open-label, phase 1b portion of this study enrolled adult patients with previously untreated advanced STS. A standard 3 + 3 design was used to assess TAZ 400 mg, 600 mg, and 800 mg orally twice daily in combination with DOX (75 mg/m^2 intravenously on day 1 of each cycle, for up to 6 cycles) as frontline therapy. Dose-limiting toxicities (DLTs) were predefined in the protocol. The RP3D of TAZ was determined by Scientific Review Committee review of the safety and pharmacokinetic data from the phase 1b trial, with a target DLT rate of $<$ 33%. **Results:** As of February 1, 2021, 16 patients are enrolled, including 2 with ES; 10 are still receiving TAZ + DOX and 6 have discontinued (5 due to disease progression, 1 due to patient withdrawal). The median age was 49.5 years (range, 2982) and all had unresectable STS. Median (range) time on treatment was 13 (0.151.1+) weeks across all dose levels evaluated. Two DLTs, both of febrile neutropenia, were observed, one in the TAZ 600 mg + DOX cohort (n = 1/6, 17%), and one in the TAZ 800 mg + DOX cohort (n = 1/3, 33%). When used in combination with DOX, the RP3D of TAZ was 800 mg. Grade 3 or 4 treatment-related treatment-emergent adverse events (TR-TEAEs) occurred in 13/16 (81.3%) patients. The most common ($\geq$ 20%) TR-TEAEs were neutropenia (n = 11, 69%), anemia (n = 10, 63%), fatigue (n = 10, 63%), stomatitis (n = 9, 56%), nausea (n = 8, 50%), febrile neutropenia (n = 7, 44%), constipation (n = 6, 38%), vomiting (n = 6, 38%), and decreased appetite (n = 5, 31%). TR-TEAEs were defined as attributable to either study agent. **Conclusions:** The combination of TAZ + DOX was generally well tolerated in this dose finding study in patients with advanced STS. The RP3D to be tested in the phase 3 randomized, double blind, placebo controlled study is TAZ 800 mg twice daily + DOX. The safety profile of this combination is consistent with the respective safety information for TAZ and for DOX. The TR-TEAEs include known toxicities of DOX or TAZ. Further comparison with DOX + placebo in the phase 3 trial will aid in assessing efficacy and safety of the combination of TAZ + DOX. The global phase 3 confirmatory trial will enroll patients with ES who have unresectable disease and have had no prior systemic therapy. Clinical trial information: NCT04204941. Research Sponsor: Epizyme, Inc.

11564 **Poster Session**

Retrospective world-wide registry on the efficacy of immune checkpoint inhibitors in alveolar soft part sarcoma: Updated results from sixty patients. *First Author: Nadia Hindi, Institute of Biomedicine Research (IBIS)-Universitary Hospital Virgen del Rocio/CSIC/Universidad de Sevilla, Seville, Spain*

Background: Alveolar soft-part sarcoma (ASPS) is a highly metastasizing ultra-rare sarcoma subtype, frequently affecting young adults. Conventional cytotoxic drugs are not effective in ASPS, but antiangiogenics demonstrated significant improvement in tumor burden reduction and PFS in the only ever conducted comparative trial. Immune checkpoint (PD-1/PD-L1) inhibitors (ICI) are emerging promising drugs in the therapy of ASPS, from small reported retrospective and prospective series. A world-wide registry has been set up with the aim of exploring the efficacy of ICI in ASPS. **Methods:** Data from adult patients (pts) diagnosed with ASPS and treated with PD- 1/PD-L1 inhibitors for advanced disease in expert sarcoma centers from Europe, Australia and US was retrospectively collected. IRB approval was obtained. Demographics, data related to treatments and outcome were considered. Radiologic assessment was based on RECIST 1.1. Progression-free (PFS) and overall survival (OS) were calculated with Kaplan-Meier method. An updated analysis of this series is presented here. **Results:** Sixty ASPS pts (27 female/33 male) with a median age at diagnosis of 25y (range 3-61) were registered. Primary tumor arose in limbs in 47 pts (78%) and 41 pts (68%) were metastatic at diagnosis. 52/60 pts (87%) had received previous systemic therapy (including chemotherapy in 19 pts and antiangiogenics in 47pts), with a median of one previous line (0-6). All pts received ICI for metastatic disease. Immunotherapy regimens consisted of monotherapy in 31 pts (52%) and combination in 29 pts (48%) (23 with an antiangiogenic agent). 29/60 pts (48%) received ICI within a clinical trial. Among the 52 evaluable pts, there was 1 complete response (CR) and 20 partial responses (PR) (ORR 40.4%). After a median follow-up of 21 months -mos- (range 4-59), 37/60 pts have progressed to ICI, with a median PFS of 13.4 mos (95% CI 10.1-16.7). Eleven pts received a subsequent line of ICI with a median PFS of 26 mos (95%CI 0-57). 16 pts have died, being the median OS from ICI initiation 38 mos (95% CI 33-43). The 12-mos and 24-mos OS rates were 94% and 70% respectively. **Conclusions:** This registry constitutes the largest available series of ASPS treated with immune check-point inhibitors. Our results suggest that treatment with ICI provide long-lasting disease control and prolonged OS in pts with advanced ASPS, an ultra-rare entity with limited active therapeutic options. The results on subsequent ICI lines suggest a lack of cross-resistance among different ICI therapies. Research Sponsor: None.

11565 **Poster Session**

Palbociclib (P) in patients (pts) with soft tissue sarcoma (STS) with *CDK4* amplification: Results from the Targeted Agent and Profiling Utilization Registry (TAPUR) study. *First Author: Scott Schuetze, University of Michigan, Ann Arbor, MI*

Background: TAPUR is a phase II basket study evaluating anti-tumor activity of commercially available targeted agents in pts with advanced cancers with genomic alterations. Results in a cohort of STS pts with *CDK4* amplification treated with P are reported. **Methods:** Eligible pts had advanced STS, no standard treatment options, measurable disease, ECOG PS 0-2, and adequate organ function. Genomic testing was performed in CLIA-certified, CAP-accredited site selected labs. Pts received P at 125 mg orally once daily for 21 days, followed by 7 days off until disease progression. Pts matched to P had *CDK4* amplification and no *RB* mutations. Simon 2-stage design tested the null disease control (DC) - defined as partial (PR), complete response (CR) or stable disease at 16+ weeks (SD 16+) - rate of 15% vs. 35% (power = 0.85; α = 0.10). If $\geq$2 of 10 pts in stage 1 have DC, 18 more pts are enrolled. If $\geq$7 of 28 pts have DC, the null DC rate is rejected. Secondary endpoints are progression-free survival (PFS), overall survival (OS) and safety. **Results:** 29 pts (66% male) with STS with *CDK4* amplification were enrolled from July 2016 to Nov 2019. 1 pt was not evaluable and excluded from efficacy analyses. Demographics and outcomes are summarized in Table. One pt with partial response (PR) and 12 pts with SD16+ were observed for DC and objective response (OR) rates of 48% (95% CI: 31%, 62%) and 3.7% (95% CI: 0.1%, 19%), respectively, and the null DC rate of 15% was rejected ($p<0.001$). 9/13 pts with DC continued on treatment for >32 weeks. 14 pts had at least one grade 3-4 AE at least possibly related to P with the most common being low WBC/platelets. Other grade 3 AEs included increased alanine aminotransferase, anemia, and fatigue. **Conclusions:** Monotherapy P demonstrated antitumor activity in heavily pre-treated pts with STS with *CDK4* amplification. Additional study is warranted to confirm the efficacy of P in pts with STS with *CDK4* amplification. Clinical trial information: NCT02693535. Research Sponsor: Pfizer.

Demographics (N=29) and efficacy outcomes (N=28).		
Median age, yrs (range)		**64 (41, 85)**
ECOG PS, %	0	28
	1	72
Prior systemic regimens, %	1-2	48
	≥3	52
DC rate, % (OR or SD16+) (95% CI)		48 (31, 62)
OR rate, % (95% CI)		3.7 (0.1, 19)
Median PFS, wks (95% CI)		16.1 (11.6, 28.1)
Median OS, wks (95% CI)		68.7 (31.0, inf)
1 year OS, % (95% CI)		53.6 (38.0, 75.6)

11566 **Poster Session**

Critical impact of radiotherapy protocol compliance and quality in the treatment of retroperitoneal sarcomas: Results from the 62092-22092 STRASS trial. *First Author: Rick L.M. Haas, The Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: The EORTC 22092-62092 STRASS trial failed to detect a superiority of neoadjuvant radiotherapy in patients with retroperitoneal sarcoma as compared to surgery alone. As radiotherapy (RT) was the experimental treatment, a comprehensive quality assurance program (RTQA) has been included in the study protocol in order to detect and correct potential RT deviations. We report here the overall trial RTQA results and its potential impact on patient's outcomes in this international phase III trial. **Methods:** Plans from all patients randomized to the experimental preoperative RT arm were submitted to a multidisciplinary RTQA team, consisting of medical physicists and radiation-oncologists. Target volume parameters and tumor dose coverage were prospectively reviewed by the RTQA team but not all plans were made compliant. In order to evaluate the impact on oncological outcomes, a composite endpoint, overall RT compliance status, was created; patients were classified into two major groups: RT compliant (RC) group and non-compliant (NRC) group, defining whether RT was as concisely per protocol or not. This composite endpoint combined the information related to PTV coverage, target delineation, total dose received and overall treatment time. Both abdominal recurrence-free survival (ARFS) and OS were compared between RC and NRC patients using Cox's proportional hazard model adjusted for age, sex, WHO performance status, tumor grade, histological subtype and tumor size at baseline (millimeters). **Results:** After final review, 75.2% (94 out of 125) of patients had compliant RT plans (65.6% were already compliant at first submission to RTQA team and 9.6% were made compliant after review). Most patients in the NRC (77.4%) had deviations linked to incorrect target volume delineations. 3-year ARFS was 67.2% (95% Confidence interval (CI): 58.0 – 77.8%) and 48.4% (34.3 – 68.2%) for RC and NRC group, respectively (adjusted HR: 2.64, 95% CI: 1.38 – 5.07, p = 0.003). Corresponding OS at 3 years was 89.9% (95% CI: 83.6 – 96.3%) and 75.4% (95% CI: 61.9 – 91.8%) in the RC and NRC group with a trend in favor of RC (adjusted HR: 2.76, 95% CI: 0.91 – 8.43, p = 0.074). **Conclusions:** To our knowledge, this is the first RTQA evaluation of a phase III sarcoma trial. The data suggests a significant benefit in terms of ARFS and a trend for OS in favor of the RT compliant group. RTQA in prospective clinical trials, investigating new RT techniques, dose levels and indications, continues to be an important and integral part of trial designing. Funding Source: EORTC, EORTC Cancer Research Fund, EUROSARC FP7 278472 and Kom op tegen Kanker (Stand up to Cancer), the Flemish Cancer Society. Research Sponsor: EORTC, EORTC Cancer Research Fund, EUROSARC FP7 278472 and Kom op tegen Kanker, the Flemish cancer society.

11567 **Poster Session**

A phase 2 study of talimogene laherparepvec, nivolumab, and trabectedin (TNT) in advanced sarcoma. *First Author: Neal Shiv Chawla, City of Hope Comprehensive Cancer Center, Duarte, CA*

Background: Combination trabectidin (T) and nivolumab (N) has been shown to be a safe and effective therapy in soft tissue sarcoma (STS). Intratumoral injection of talimogene laherparepvec (TVEC) has a local oncolytic effect, and increases immune response via enhanced recruitment of antigen presenting cells, and thereby cytotoxic immune response. This study aims to determine if the addition of TVEC to combination trabectedin and nivolumab is effective and safe in advanced sarcoma. **Methods:** Eligible patients include patients $\geq$ 18 years of age with locally advanced unresectable or metastatic STS, measurable disease by RECIST v1.1, and at least one accessible tumor for TVEC intratumoral injection. N (3 mg/kg i.v. q 2 weeks), T (1.2 mg/m^2 i.v. q 3 weeks) and TVEC (1x10e^8 PFU/ml q 2 weeks depending on tumor size) were administered. A test dose of TVEC (1x10e^6 PFU/ml) was initially given, followed three weeks later by full dose TVEC. Primary endpoint: Progression-free survival (PFS); Secondary endpoints: (1) Best overall response during treatment period, (2) PFS rate at 6 and 9 months, (3) Overall survival (OS) rate at 6, 9, and 12 months, (4) Incidence of conversion from unresectable to resectable tumor, and (5) Incidence of treatment-related adverse events. Interim. **Results:** There were 36 evaluable subjects under the Modified Intention-to-Treat (MITT) population, having completed the first cycle of TNT and a CT or MRI scan at the 6-week follow-up period. The most common histological subtypes include leiomyosarcoma (9), liposarcoma (5), spindle cell sarcoma (3), pleomorphic sarcoma (2), Ewing's sarcoma (2), and other (5). Median number of prior lines of therapy was 4 (range 1-8). Best Overall Response by RECIST v1.1 = 3 PR, 27 SD, 5 PD. One patient, with previously unresectable disease was taken for resection and was found to have 100% necrosis on surgical pathology. Disease control rate (CR+PR+SD) was 86.1%. The median PFS was 5.5 (range: 1-18) months; 6-month PFS rate: 62.1%. Median PFS on therapy immediately preceding this trial was 2.0 months (range = 1-14 months). There were 47 evaluable subjects for OS analysis under the Intention-to-Treat (ITT) population having received at least one dose of T and N. The median OS was 9.0 (range 0-20) months; 6-month OS rate: 73%. Safety analysis: There were 47 evaluable subjects under the ITT population. 28% of these patients experienced ^{3}1 SAE. The most common grade 3/4 TRAEs include anemia (12), increased ALT (8), fatigue (4), thrombocytopenia (4), neutropenia (4). There were no grade 3/4 TVEC injection site reactions. 22% of patients in the MITT cohort remain on study. **Conclusions:** These results suggest that combination therapy with TNT appears to be as effective as standard therapy, with no new safety signals seen. Furthermore, median PFS exceeded that of the immediately preceding lines of therapy in this heavily pre-treated cohort. As data matures, further data will be reported. Clinical trial information: NCT03886311. Research Sponsor: Partial funding by Amgen.

11568 **Poster Session**

Evaluation of homologous recombination deficiency (HRD) score and immuno-tumor microenvironment (iTME) as biomarkers of soft tissue sarcoma (STS) survival and response to immune checkpoint inhibitor therapy. *First Author: Chenlu Zhang, Department of Oncology, Zhongshan Hospital, Fudan University, Shanghai, China*

Background: Soft tissue sarcoma (STS) are highly heterogenous in both histology and underlying genetic alterations, resulting in heterogenous outcomes of standard therapy. With recent stride of immunotherapies in oncology it is crucial to find the optimal match of the new therapies to disease subtypes. HRDScore and iTME parameters are two top candidate biomarkers to predict clinical outcomes in complex diseases such as STS. **Methods:** We prospectively profiled 102 Chinese STS patients who had received more than 1 line of prior treatment, mainly chemo-drugs. We then classified the patients according to their HRDScore (calculated from WES data using the Richardson method, ref. Telli M.L. et al. Clin. Cancer Res. 2016) and iTME parameters (calculated from RNAseq data using CIBERSORT method). Lastly, we tested the correlation of HRDScore or iTME with patient survival and clinic outcomes of anti-PD-1/L1 based combination therapy. **Results:** The histological subtypes of the patients included 32 LMS, 44 LPS, and 26 others (such as UPS, clear cell, myxofibrosarcoma, uterus LMS etc.). The top mutation genes (frequency > 5%) included TP53 29%, KMT2C 16%, NOTCH2 9%, ATRX 8%, NF1 8%, RB1 8% and PTEN 6%. The patients could be classified to HRD-high or HRD-low (HRDScore > or < = 42). Alternatively, unsupervised clustering of iTME revealed three patient subgroups (named iTME-I, -II, and -III). While all the three groups are characterized by a generally suppressed immune environment, iTME-I have high proportion of M0 macrophages and median M2 macrophages; iTME-II have high proportion of M2 macrophages but low M0 cells; and iTME-type III are low in both M0 and M2 cells. No significant M1 cells present in all the three iTME groups. Patient survivals were correlated with the iTME types but not HRDScore in Kaplan-Meyer analysis. The trend of survival time was iTME-III > iTME-II > iTME-I, with an HR = 0.156 for iTME-III over iTME-I (p = 0.008, log-rank test). Treatment response of anti-PD-1/L1 based combination therapies also showed a positive correlation to iTME-III, but not HRDScore although the small sample size prevented a definitive conclusion. Clinical evaluation of the 22 patients who received anti-PD-1/L1 therapy showed 1 PD (20%) and 4 SD/PR (80%) in iTME-III, 4 PD (40%) and 6 SD/PR (60%) in iTME-II, and 1 PD (33%) and 2 SD (67%) in iTME-I. **Conclusions:** iTME is a better biomarker than HRDScore in STS for survival and treatment outcomes. Differential Infiltration of M0 and M2 macrophages can distinguish patients with different survival and response to anti-PD-1/L1 combination therapy. The iTME subtypes may be used for treatment screen of combination immunotherapy but larger and randomized clinical studies are required to validate the discovery. Research Sponsor: None.

11569 **Poster Session**

Prospective cohort study of Kaposi sarcoma treated under real-world conditions in Malawi. *First Author: Edwards Kasonkanji, Research, Lilongwe, Malawi, Malawi*

Background: Kaposi sarcoma (KS) is the leading cancer in Malawi (34% of cancers). Outside of clinical trials, prospective KS studies from sub-Saharan Africa (SSA) are few and limited by loss to follow up. We conducted a prospective KS cohort study of standard of care bleomycin/vincristine (BV) at Lighthouse HIV clinic, in Lilongwe, Malawi. **Methods:** We enrolled pathologically confirmed, newly diagnosed, HIV+ KS patients from Feb 2017 to Jun 2019. We collected clinical and treatment characteristics, toxicity, and outcomes of KS with follow-up censored Jun 2020. Patients were treated with bleomycin (25 mg/m^2) and vincristine (0.4 mg/m^2) every 14 days for a planned maximum of 16 cycles. STATA v13.0 was used to calculate descriptive statistics and Kaplan Meier survival analysis. Toxicity was graded using NCI CTCAE v5.0. **Results:** We enrolled 138 participants, median age 36 (IQR 32-44) and 110 (80%) male. By ACTG staging, 107 (78%) were T1 (tumour severity), 46 (33%) were S1 (illness severity) and 46 (33%) had Karnofsky performance status ≤70. Presenting symptoms included edema in 69 (53%), visceral disease in 9 (7%), and oral involvement in 43 (33%). Prior to KS diagnosis, 70 (51%) participants were aware of being HIV+ for median 17 months (IQR 6-60) and had been on ART for median 16 months (IQR 6-60). Median CD4 count was 197 (IQR 99-339), median HIV-viral load was 2.6 log copies/mL (IQR 1.6 – 4.8) and 57% were HIV-suppressed (< 1000 HIV copies/ml). The median number of cycles was 16 (IQR 7-16). 62 (45%) participants missed at least one dose due to stock out. Amongst patients with missed doses, the median number was 3 (IQR 2-4) for bleomycin and 2 (IQR 1-3) for vincristine. 14 (10%) participants experienced at least one reduced dose due to toxicity. 5 (4%) participants suffered grade ≥3 anaemia, 13 (9%) grade ≥3 neutropenia, and one participant had grade 4 bleomycin-induced dermatitis. There was no reported grade ≥3 bleomycin lung toxicity or vincristine-induced neuropathy. Of 115 evaluable participants, responses at the end of therapy were: complete response in 52 (45%), partial response in 27 (23%) stable disease in 5 (4%), and progressive disease in 31 (28%). Median duration of follow-up was 20 months. At censoring, 69 (50%) were alive, 36 (26%) dead, and 33 (24%) lost to follow-up. Overall survival is shown Table as crude and worst-case scenario; worst-case assumes all participants lost to follow up died. **Conclusions:** Here, we present one of the most complete characterizations of KS presentation and treatment from SSA. As in other studies from the region, the majority of patients presented with advanced disease, chemotherapy stock-outs and loss to follow up were common, and mortality was high. Studies are planned to understand the virologic characteristics, improve therapies, and better implement existing therapies. Research Sponsor: U.S. National Institutes of Health.

Crude Survival, % (95% CI)	
1 year	76 (67-83)
2 year	70 (60-78)
Worst Case Scenario, % (95% CI)	
1 year	60 (51-67)
2 year	52 (42-60)

11570 **Poster Session**

Active surveillance in primary desmoid tumor (DT): A prospective observational study. *First Author: Chiara Colombo, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: In recent years evidence of long term stabilization and spontaneous regression of primary sporadic DT resulted in a paradigm shift towards more conservative approaches. We present herein the results of an observational study aimed at prospectively assess the behavior of primary sporadic DT initially managed by active surveillance and its relation to *CTNNB1* mutational status. **Methods:** This is an Italian prospective, multicenter, observational study (NCT 02547831) to evaluate primary sporadic DT behavior in patients (pts) >16 years with primary naive or incompletely resected and measurable disease, at any site, with *CTNNB1* mutational status available. Pts were assessed by contrast enhanced MRI or CT scan at baseline, at 3, 6, 9, 12 months, then every 6 months until the third year. Tumor changes were assessed by RECIST. In case of dimensional or symptomatic progression active treatment could be proposed on an individualized basis*CTNNB1* mutational status was obtained in all patients by Sanger and deep sequencing was performed in wild-type cases. Primary end-point was progression-free survival (PFS) at 3 yrs. Treatment-free survival (TFS) was also analyzed. PFS and TFS were calculated using survival analysis methods, including Kaplan-Meier plots, log-rank test for survival curves comparison, and Cox proportional-hazard multivariable regression (age, size, anatomic site and *CTNNB1* mutational status). **Results:** From April 2013 to February 2018 108 pts were included (82% female, 18% male); median age was 39 (interquartile range, IQR 34-48) and median size 50 mm (IQR, 40-80 mm). Tumor location was: 4/108 (4%) = head&neck, 25/108 (23%) = trunk, 59/108 (55%) = abdominal wall, 3/108 (3%) = intra-abdominal, 17/108 (16%) = extremities. *CTNNB1* mutations were as follow: T41A 54/108 (50%), S45F 13/108 (12%), WT 20/108 (19%), other mutations 21/108 (19%). At a m-FU of 32.3 months, the 3-year PFS was 54.5% (95% CI, 44.9%-66.1%). 42/108 (39%) pts showed a RECIST progression, with equal distribution among the different anatomic sites. None of the variables analyzed were associated to PFS. Spontaneous regression was initially observed in 27/108 (25%) patients, while it followed dimensional progression in another 33/108 (30%). 35/108 (32%) pts received active treatment, 18/42 (43%) after RECIST progression and 17/66 (26%) after symptomatic progressions. TFS at 36 months was 65.9% (95% CI, 57.3%-75.9%). S45F mutation, larger tumor size and extremity location were associated to a shorter TFS. No dimensional or symptomatic progression were observed after 36 months of FU. **Conclusions:** Active surveillance was marked by spontaneous regressions in 60/108 (55%) pts. An active treatment was needed in 32%. If no events occur after 3 yrs of FU, more relaxed FU schedules can be considered given the low risk of subsequent progression. Attention should be paid to patients with DT located to the extremity and/or carrying a S45F mutation. Clinical trial information: NCT 02547831. Research Sponsor: Ricerca Finalizzata- Ministero della Salute.

11571 **Poster Session**

Growth rate and site of pulmonary metastasis to predict lung relapse and overall survival in patients affected by bone and soft tissue sarcomas (B-STS). *First Author: Lorenzo D'ambrosio, Ospedale Cardinal Massaia, Asti, Italy*

Background: Despite surgically resectable pulmonary metastases may lead to cure patients with B-STS (Chudgar NP 2017), a substantial proportion of patients will eventually relapse. Presently, patient selection is based on unique organ involvement, number of metastases, interval between previous surgery and pulmonary progression or relapse. We assessed the impact of anatomical site of metastasis into the lung (as if the pleural site might ease further tumor spreading) and nodule growth rate as additional predictive/prognostic factors of lung progression-free survival (L-PFS) and overall survival (OS). **Methods:** In our prospectively collected database, we retrospectively evaluated patients operated for B-STS pulmonary progression at 3 different centers from 2005 to 2019. Beyond patients' clinical features at both baseline and disease progression in the lungs, we focused on whether the relapse occurred into the parenchyma or nearby the pleura (Welter S 2012); secondly, we estimated lung metastasis growth rate, defined as tumor doubling time (TDT) (Nakamura T 2011). Statistical analyses were carried out with IBM SPSS (v. 20.0). Survival outcomes were estimated by Kaplan-Meier method. Hazard ratios (HR) were estimated by Cox regression. Multivariate analysis was performed for both L-PFS and OS according to Cox proportional hazard model. All tests were 2-sided with their corresponding 95% confidence intervals (CI95%). **Results:** We identified 138 patients who underwent lung metastasectomy [(F=66 (48%); median age at surgery 50 (14-78)]. Median PFS and L-PFS were 8.7 months (CI95% 6.6-10.9) and 8.6 months (CI95% 6.2-11.0), respectively. Median OS was 40.6 months (CI 95% 32.8-48.5). Univariate analysis showed a statistically significant impact of the following variables for both L-PFS and OS: ECOG 0, nodule number <3, being disease-free after first-line treatment, no pleural involvement, and TDT >40 days. Disease-free interval ≤ 24 months and absence of metastases at diagnosis showed significant correlation with L-PFS and OS, respectively. At multivariate analyses the following variables retained statistical significance for L-PFS: TDT >40 days (HR 0.53, CI95% 0.31-0.93, p=0.028); nodule number <3 (HR 0.54, 95%CI 0.29-0.99, p=0.048), no pleural involvement (HR 0.39, CI95% 0.22-0.70, p=0.001); and for OS: TDT >40 days (HR 0.36, CI95% 0.18-0.72, p=0.004), nodule number <3 (HR 0.35, 95%CI 0.18-0.71, p=0.004), no pleural involvement (HR 0.49, CI95% 0.24-0.98, p=0.045), and ECOG 0 (HR 0.29, 95%CI 0.14-0.59, p=0.001). **Conclusions:** Acknowledging its retrospective nature and the need for an external validation, our series highlights the key-role of the anatomical site of relapse within the lung and the impact of tumor growth rate. If confirmed, these two clinical parameters should be factored in the decision making on performing pulmonary metastasectomy. Research Sponsor: None.

11572 **Poster Session**

Immune contexture in high-risk soft tissue sarcomas (STS): A planned analysis of the ISG-STS-1001 randomized trial. *First Author: Sandro Pasquali, Department of Surgery, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

Background: The characteristics of immune contexture and its prognostic and predictive value in STS is left to be understood. This planned analysis of the ISG-STS-1001 trial, which compared neoadjuvant anthracycline + ifosfamide (AI) vs a histology-tailored (HT) chemotherapy (ChT), was aimed at characterizing the immune contexture after neoadjuvant ChT and investigating any association with the risk of recurrence. **Methods:** Patients registered in the ISG-STS-1001 study (ID: NCT01710176) were included if they had tumor tissue available for Tissue MicroArray (TMA), which was performed in the area of the surgical specimen with the highest lymphocyte infiltrate. The following markers were analyzed with IHC and measured quantitatively: CD3, CD8, PD1, GranzymeB, Foxp3, CD20, CD163, and PDL1. The T-Distributed Stochastic Neighboring Entities (t-SNE) analysis was used to account for the co-expression of IHC markers in each tumor. The prognostic value of each marker for disease-free survival (DFS) was assessed. **Results:** This analysis was conducted in 256 of 435 study patients. AI and HT neoadjuvant ChT did not result in any different distribution of immune contexture. Conversely, differences were observed between 'complex' karyotype STS (ck-STS: LMS, MPNST, UPS, MFS, pleomorphic liposarcoma, and pleomorphic rhabdomyosarcoma) and 'simple' karyotype STS (sk-STS: MLPS and SS). Ck-STS were enriched in both CD3+ and CD8+ cells compared to sk-STS. These cells displayed an heterogeneous distribution and were dispersed inside the tumor nest, keeping direct contact with sarcoma cells. Ck-STS also displayed an enrichment in Granzyme B+, and CD163+ cells. PDL1+ cells were occasionally identified and were more frequent in ck-STS, suggesting an immune-related expression. Most STS were negative for CD20+ cells, however, when present these cells were highly represented and organized in tertiary lymphoid-like structure. The t-SNE generated plot clustered tumors, the 'cold' mainly including sk-STS and the 'hot' mainly composed by ck-STS. In the 'hot' group, a cluster of tumors displayed an immune infiltrate enriched with a high number of CD3, CD8, GranzymeB, PD-1, and PDL-1+ cells. When the prognostic value of the immune markers was investigated, the presence of CD20+ cells was the only independent prognostic factor for DFS (HR=0.68, 95%CI 0.52-0.91) in a histology-stratified estimate adjusting for tumor size in cm (HR=1.07, 95%CI 1.03-1.12) and patient age (HR=1.0, 95%CI 0.97-1.02). **Conclusions:** Immune contexture differed across sarcoma histologies after neoadjuvant ChT, rather than across the two study arms, with ck-STS being marked by a rich immune contexture. While a CD20+ infiltrate was found to be an independent prognostic factor for a better outcome, further analyses are in progress on the prognosis of patients with the richest immune contexture. Clinical trial information: NCT01710176. Research Sponsor: EUROSARC FP7 278472, LYRICAN (INCA-DGOS-INSERM 12563), DEPGYN (RHU4).

11573 **Poster Session**

VAC temporization pending final margins after suprafascial myxofibrosarcoma excision to reduce the rate of local recurrence. *First Author: Mitchell Stephen Fourman, Massachusetts General Hospital, Boston, MA*

Background: The microinvasive nature of suprafascial myxofibrosarcoma complicates the accuracy of intraoperative margin assessment, and tumor bed resections after soft tissue reconstruction are unreliable. For the past 3 years we have temporized the excised tumor bed with a wound VAC, delaying soft tissue coverage until final negative margins were achieved. Here, we compare the oncologic/surgical outcomes of suprafascial myxofibrosarcomas managed with VAC temporization (VT) with single-stage excision/reconstruction (SS). **Methods:** We retrospectively studied suprafascial myxofibrosarcomas managed from 1/1/2000 to 1/1/2019 who received neoadjuvant or adjuvant radiation and had at least 2-years of oncologic follow-up at a tertiary referral cancer center. Our primary outcome was local recurrence. Comparisons were performed using Fisher's Exact Test or Students t-test. A p-value < 0.05 was considered significant. **Results:** Fifty-three patients (18 VAC temporized, 35 single stage) were included. While VT patients were older (74.9 ± 10.2 vs. 63.9 ± 13.6, p = 0.003), treatment groups did not significantly differ with respect to comorbidity, tumor volume, stage and grade. VT patients had significantly fewer local recurrences (5.6% vs. 28.6% after SS, p = 0.048) and R1 resections that required an unplanned readmission for tumor bed re-excision (0% vs. 37.1% after SS, p = 0.002). VT required more total surgeries (2.8 ± 0.9 vs. 1.8 ± 0.9 for SS, p = 0.0002). Post-operative infectious and wound complications were equivalent (Table). **Conclusions:** Our VAC temporization strategy had a significantly lower LR than SS treatment. While high quality multi-institutional validation is required, VT may represent a paradigm shift in the management of myxofibrosarcoma. Research Sponsor: None.

Cohort oncologic and surgical outcomes.

	Full Cohort (n = 53)	VAC Temporized (n = 18)	Single Stage (n = 35)	P-Value
R0 Margins after Sentinel Management	11 / 53 (20.8%)	18 / 18 (100%)	24 / 35 (68.6%)	***0.01**
Total # Oncologic Surgeries	1.9 ± 0.9	2.8 ± 0.9	1.8 ± 0.9	***0.0002**
Superficial Infection (Antibiotics Only)	5 / 53 (9.4%)	1 / 18 (5.6%)	4 / 35 (11.4%)	0.65
Deep Infection Requiring OR	5 / 53 (9.4%)	3 / 18 (18.2%)	2 / 35 (5.7%)	0.32
Thromboembolic Event (DVT/PE)	1 / 53 (1.9%)	0 / 18 (0%)	1 / 35 (2.9%)	> 0.99
Operative Wound Revision / Flap	7 / 53 (13.2%)	3 / 18 (18.2%)	4 / 35 (11.4%)	0.68
Unplanned Flap	5 / 53 (9.4%)	1 / 18 (4.5%)	4 / 35 (11.4%)	0.65
Local Recurrence	10 / 53 (18.9%)	1 / 18 (5.6%)	10 / 35 (28.6%)	* **0.048**
Distant Recurrence	6 / 53 (11.3%)	1 / 18 (9.1%)	5 / 35 (14.3%)	0.65
Tumor-Related Death	5 / 53 (9.4%)	1 / 18 (9.1%)	4 / 35 (11.4%)	0.65
PROMIS-10 Physical Subscore at Max Follow-Up	52.0 ± 11.3	50.3 ± 10.5 (n = 16)	51.7 ± 9.5 (n = 16)	0.38
PROMIS-10 Mental Subscore at Max Follow-Up	51.9 ± 9.3	52.1 ± 9.4 (n = 16)	53.9 ± 9.5 (n = 16)	0.91

11574 **Poster Session**

Patient reported outcomes in patients with desmoid type fibromatosis. *First Author: Vikas Garg, All India Institute of Medical Science (AIIMS), New Delhi, India*

Background: Desmoid type fibromatosis (DTF) is a rare benign neoplasm with infiltrative growth and high local recurrences. Due to long disease course, unpredictable growth pattern, and low mortality, using only survival outcomes may be inappropriate. In this study we assessed the impact of DTF on health related quality of life (HRQoL). **Methods:** This was a cross-sectional study done in patients with DTF. The study participants were asked to fill the EORTC QLQ-C30, GAD-7 and *PHQ-9 questionnaires* to assess HRQoL, anxiety and depression. Outcomes were also compared with healthy controls. **Results:** 204 subjects (102 DTF patients and 102 healthy controls) were recruited. Study parameters have been summarized in Table. Appendicular skeleton (limbs + girdle) was most commonly involved in 59 % patients and abdominal wall or mesentery was involved in 22.5 %. Patients have received median of 2 lines of therapy. 54 % patients were currently on sorafenib and 41 % were under active surveillance. Mean global health status in DTF patient 65.58 ± 22.64, was significantly lower than healthy controls. Similarly, DTF patients scored low on all functional scales except cognitive functioning. Symptom scale showed significantly higher symptom burden of fatigue, pain, insomnia and financial difficulties. Anxiety & depression was observed in 39.22 % and 50 % of DTF patients respectively. DTF patients had higher rates of mild, moderate and severe anxiety and depression compared to healthy controls. No difference was observed based on site of disease. **Conclusions:** DTF patients have significant symptom burden, poor functioning, and heightened anxiety and depression. Patient reported outcomes should be routinely used to assess treatment efficacy in DTF patients. Research Sponsor: None.

Difference in HRQoL between healthy controls & DTF patients.

Parameter	Healthy Controls (n=102)	Fibromatosis (n=102)	p value
Female	58.80 %	64.71 %	0.74
Age in years(Mean ± SD)	32.54 ± 9.68	32.73 ± 11.40	0.54
PHQ9	3.14 ± 4.34	05.73 ± 05.25	**0.0001**
GAD7	2.86 ± 3.72	04.52 ± 04.53	**0.005**
Global health status	81.43 ± 17.83	65.58 ± 22.64	**<0.0001**
Symptom scales			
Fatigue	15.79 ± 17.96	31.32 ± 24.10	**<0.0001**
Pain	10.77 ± 17.33	34.60 ± 28.30	**<0.0001**
Insomnia	9.14 ± 19.41	21.88 ± 28.32	**0.0002**
Financial difficulties	6.20 ± 20.30	29.07 ± 34.98	**<0.0001**
Functional scales			
Physical functioning	90.24 ± 13.94	76.23 ± 19.35	**<0.0001**
Role functioning	87.72 ± 17.25	72.85 ± 27.25	**<0.0001**
Emotional functioning	83.59 ± 20.35	67.57 ± 23.98	**<0.0001**
Cognitive functioning	87.73 ± 18.47	87.08 ± 20.17	0.80
Social functioning	91.57 ± 16.37	79.07 ± 26.92	**<0.0001**

TPS11575 **Poster Session**

Phase II trial of olaparib in combination with ceralasertib in patients with recurrent osteosarcoma. *First Author: Suzanne J. Forrest, Dana-Farber/ Boston Children's Cancer and Blood Disorders Center, Boston, MA*

Background: Osteosarcoma is the most common primary bone tumor, occurring in children, adolescents, and young adults. In contrast to advances in treatment for most childhood cancers, there have been no significant improvements in osteosarcoma outcomes in the past 40 years. Forty percent of osteosarcoma patients will, at some point, have advanced disease which has a very poor outcome with a 5-year overall survival of approximately 20%. Genomic alterations and signatures associated with sensitivity to treatment with DNA damage response (DDR) inhibitors are observed frequently in osteosarcoma. Many osteosarcomas have a unique mutational signature (signature 3) similar to that seen in BRCA1 deficient cancer and response to PARP inhibitors has been seen in osteosarcoma cell lines. Additionally, ATRX, a protein involved in the alternative lengthening of telomeres (ALT), is often inactivated in osteosarcoma. Defects in the ALT pathway may sensitize tumor cells to ATR inhibitors and osteosarcoma cell lines have been shown to be sensitive to ATR inhibition. In vitro susceptibility of osteosarcoma cell lines to ATR and PARP inhibitors, the presence of mutations in genes involved in DDR and the presence of signature 3 in a subset of osteosarcomas serves as the basis for the development of this trial. **Methods:** This is an ongoing open label, multicenter, phase II clinical trial to evaluate the clinical activity of PARP inhibitor, olaparib, in combination with ATR inhibitor, ceralasertib, in 2 cohorts of patients aged 12-40 with recurrent osteosarcoma (NCT04417062). Patients with unresectable disease are enrolled into Cohort 1. Patients with resectable disease limited to the lung are enrolled into Cohort 2. Patients in both cohorts receive olaparib 300mg orally twice a day on days 1-28 and ceralasertib 160 mg orally once a day on days 1-7 of a 28-day cycle (adult maximum tolerated dose for the combination). For patients in Cohort 2, study treatment also includes surgical resection of lung metastases at protocol-specified timepoints. Patients can remain on treatment for up to 2 years if they have not progressed. For Cohort 1, the primary objective is to determine whether the combination treatment improves the 4-month event-free rate as compared to a historical benchmark from Children's Oncology Group (COG) trials using a Simon's two-stage design. In the first stage, ≥3 of 19 patients must be event-free at 4 months to proceed to stage 2. Enrollment into Cohort 2 continues as long as Cohort 1 enrollment is ongoing. For Cohort 2, the primary endpoint is the submission of paired pre- and post-treatment tumor samples for correlative studies. Secondary endpoints include objective response rate, event-free survival, and overall survival. Integrated correlative studies will assess tumor tissue for biomarkers of treatment response and measure circulating tumor DNA longitudinally. Enrollment began November 24, 2020 and is ongoing. Clinical trial information: NCT04417062. Research Sponsor: The Osteosarcoma Institute.

TPS11576 **Poster Session**

REGOSTA: A randomized, placebo-controlled, double-blinded, multicenter study evaluating the efficacy and safety of regorafenib (REGO) as maintenance therapy after first-line treatment in patients (pts) with osteosarcoma (OS) and non-osteosarcomas (non-OS) of bone (non-Ewing, non-chondrosarcomas and non-chordomas). *First Author: Florence Duffaud, La Timone University Hospital, Marseille, France*

Background: Pts with OS and non-OS of bone are treated with a multimodal sequence therapy of neoadjuvant chemotherapy (CT), surgery and adjuvant CT, followed by a close surveillance until recurrence. At recurrence, the prognosis remains poor with objective response rates of 3-29%, and a median Progression-Free Survival (PFS) of less than 4 months in OS. There is a clinical need to reduce the risk of recurrence after the initial treatment sequence. The REGOBONE study reported a significant clinical benefit of regorafenib compared to placebo in patients with relapsed OS (median PFS: 16.4 versus 4.1 weeks). **Methods:** This multicenter trial is ongoing to study the efficacy and safety of maintenance REGO in pts > = 16 years, with complete remission after initial treatment sequence of their bone sarcoma. 168 pts will be randomly allocated in a 1:1 ratio to receive either oral REGO or its matching placebo (control arm) at a daily dose of 120mg, continuously and for a maximum of 12 months. Randomization will be stratified according to the following risk factors: metastases (mets) at diagnosis and/or poor response to neoadjuvant CT versus no mets at diagnosis and good response to neoadjuvant CT. The primary objective is to compare the efficacy (Relapse-Free Survival) between the 2 arms. The expected 3-year RFS rates are 55% in the control arm and 74.6% in the REGO arm (HR = 0.5). 66 events will provide 80% power to show significant improvement in RFS, using a 2-sided log-rank test at a 5% level. Secondary endpoints include Time to Treatment Failure, Overall Survival, Quality of Life, safety profile, and compliance to treatment. Radiological endpoints will be evaluated using the RECIST 1.1. Translational objectives will be to identify predictive biomarkers for efficacy of REGO as maintenance therapy using liquid biopsies. As of Feb 1st, 2021, 3 patients have been randomized. 15 sites of the French Sarcoma Group will participate. Clinical trial information: NCT04055220. Research Sponsor: Bayer Healthcare.

TPS11577 **Poster Session**

Phase 1 expansion trial of the LSD1 inhibitor seclidemstat (SP-2577) with and without topotecan and cyclophosphamide (TC) in patients (pts) with relapsed or refractory Ewing sarcoma (ES) and select sarcomas. *First Author: Damon R. Reed, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL*

Background: Several sarcomas possess chromosomal translocations in *FET* family members (*FUS, EWSR1,* and *TAF15)* responsible for cancer development. Sarcomas caused by *FET* family gene rearrangements include ES, desmoplastic round cell small tumors (DSRCT), myxoid liposarcoma (ML), and several others. Lysine specific demethylase 1 (LSD1) is a critical protein for sarcoma development and progression through its colocalization and/or association with several *FET* family oncogenic transcription factors. This suggests that pharmacologic inhibition of LSD1 may be a therapeutic strategy. Seclidemstat (SP-2577, Salarius Pharmaceuticals) is an oral, first-in-class, small molecule with reversible, noncompetitive inhibition of LSD1 (IC_{50}: 25–50 nM). *In vitro* and *in vivo* data demonstrate seclidemstat, or analogs, modulate EWS/ETS transcriptional activity, down-regulating oncogene expression and up-regulating tumor-suppressor gene expression, leading to significant tumor growth inhibition in ES mouse xenograft studies. Seclidemstat has shown in *in vitro* ES cell lines near additivity efficacy when added to TC. In *in vitro* studies of other *FET*-translocated sarcomas, including ML (FUS/DDIT3 fusion) and clear cell sarcoma (EWS/ATF1 fusion), seclidemstat showed anti-proliferative activity. In an ongoing Phase 1 trial investigating single agent seclidemstat in advanced solid tumors (NCT03895684), three pts with metastatic *FET*-translocated sarcomas had a median progression-free survival of 5.7 months (range: 4.3–7.2) with a best response of stable disease despite having a median of 5 (range: 1–7) prior therapies. **Methods:** This dose expansion Phase 1 study (NCT03600649) assesses seclidemstat at 900 mg PO BID, the recommended Phase 2 dose, in two expansion cohorts: a single agent expansion in select sarcoma pts (n = 30) and a safety lead-in dose escalation and expansion (n = 24) of seclidemstat combined with TC in pts with ES. Pts must be ≥12 years old, have ECOG performance status of 0 or 1, with a life expectancy > 4 months. In the select sarcoma cohort, pts must have ML (n = 15) or other sarcomas with FET family translocations (n = 15) including DSRCT. One to 3 prior lines of therapy are allowed. In the ES combination cohort, up to 2 lines of prior therapy are allowed. Primary objective is safety/tolerability and secondary objective is efficacy. The trial is currently recruiting across 8 locations in the United States. Clinical trial information: NCT03600649. Research Sponsor: Salarius Pharmaceuticals Inc, Other Foundation, Other Government Agency.

TPS11578 **Poster Session**

A phase 2 study of belinostat and SGI-110 (guadecitabine) for the treatment of unresectable and metastatic conventional chondrosarcoma. *First Author: Jay Oza, Columbia University Irving Medical Center, New York, NY*

Background: Conventional chondrosarcoma (cCS) accounts for ~25% of primary bone cancers and is the second most common primary bone tumor after osteosarcoma. Surgical resection is the primary treatment for localized disease. No FDA approved therapy exists for advanced disease and chemotherapy has marginal efficacy with ORR < 12%. IDH1/2 mutation is seen in 50% of cases. Epigenetic dysregulation is central to oncogenesis in both IDH1/2 mutant and wild-type CS. Pre-clinical studies from our group show that combination treatment with HDAC and DNMT inhibitors is significantly more effective at suppressing the growth of CS models in vitro and in vivo compared to either therapy alone. The combination regimen mediates anti-tumor effects on CS by induction of apoptosis, induction of tumor suppressor genes (eg. E-cadherin), the induction of interferon responsive genes (eg. IRF7, OASL, ISG15, DDX58) and reversal of global hypomethylated state. Based on these findings we have designed a phase 2 clinical trial with an HDAC inhibitor (belinostat) and a DNMT inhibitor (guadecitabine) in patients with advanced cCS. **Methods:** NCI # 10330 is a single-arm, multi-center, Simon 2-stage, phase 2 clinical trial evaluating belinostat and guadecitabine in patients with advanced cCS. Eligible patients will have biopsy proven cCS which is measurable by RECIST v1.1 and amenable to biopsy, ECOG PS ≤ 2, any number of prior treatments (including none). Patients will receive guadecitabine 45 mg/m^2 SC followed by belinostat 1000 mg/m^2 IV once daily on days 1-5 of a 28-day cycle. A safety lead-in and continuous toxicity monitoring rule will be applied. The primary endpoint will be ORR. Since chemotherapy is associated with an ORR of 8-12% and targeted agents have shown an ORR of 0% in cCS, we will consider an ORR of 8% as inactive while an ORR of 28% will suggest promising activity. A Simon 2-stage design is employed. The design calls for 26 patients. If ≥ 2 responses are observed among 13 patients in stage I, the study will proceed to full accrual. If ≥ 5 responses are seen among 26 patients, the study treatment is considered promising. This design has 85% power with α of 0.054 to test for a response rate of 8% vs 28%. Secondary objectives include safety, tolerability and PFS. All patients will undergo pre-treatment and on-treatment tumor biopsies. Paired tissue will be used for correlative analysis including: 1) whole exome sequencing/RNAseq to evaluate changes in gene expression in response to treatment, 2) multiplex IHC to interrogate the effect of combination therapy on tumor immune microenvironment and 3) a global DNA methylation assay to better understand the changes in epigenetic landscape in response to treatment. This study is open throughout the ETCTN (NCT04340843). Six of the planned 26 patients in the safety lead-in have been enrolled without DLT. Further accrual is on hold pending completion of the safety lead-in. Clinical trial information: 04340843. Research Sponsor: U.S. National Institutes of Health.

TPS11579 **Poster Session**

A multicenter, open-label, uncontrolled phase II study of ONO-4538 for cutaneous angiosarcoma (Angio Check study). *First Author: Yasuhiro Fujisawa, University of Tsukuba Hospital, Tsukuba, Japan*

Background: Cutaneous angiosarcoma (CAS) is a rare sarcoma and advanced cases face a complex treatment regimen and dismal prognosis. Several cytotoxic agents (anthracycline, taxane, and gemcitabine) and targeted therapies (bevacizumab and sorafenib) have been tested for advanced disease in clinical trials with poor results. Since CAS commonly develops in elderly patients, high-grade adverse events from treatment may not be ideal and thus therapies featuring durable response and low comorbidity are in great demand. Recent studies suggest that CAS has a distinct genomic profile, including higher tumor mutational burden (TMB), compared to angiosarcomas developed in other sites. Moreover, we have shown that CAS with higher PD-1/L1 in the tumor microenvironment had statistically better overall survival compared with those without, indicating CAS susceptibility to immune checkpoint blockade therapy. However, to date, reports of immune checkpoint inhibitors for CAS are nonexistent. **Methods:** The present study is a phase 2, multicenter, single-arm clinical trial of ONO-4538 (nivolumab, 480 mg IV every 4 weeks) for patients with unresectable or metastatic CAS refractory to first-line paclitaxel. Twenty-three patients with advanced CAS will be enrolled at 11 sites in Japan with a primary objective to assess the confirmed response rate (H0 p < 5%, H1: p > 20%) to nivolumab. Secondary endpoints include PFS, OS, time to response, and adverse events. A correlative aim includes assessing tissue biomarkers using whole-genome sequencing (1023 genes including interferon-gamma associated genes and other known factors associated with response to immune checkpoint inhibitors) for association with response to nivolumab. The study started in April 2020 and remains open with 7 patients enrolled at time of Clinical trial information: UMIN000043039. Research Sponsor: Ono pharmaceutical Co. Ltd.

TPS11580 **Poster Session**

A randomized phase II trial of second-line treatment for advanced soft tissue sarcoma comparing trabectedin, eribulin and pazopanib (2ND-STEP, JCOG1802). *First Author: Makoto Endo, Kyushu University Hospital, Fukuoka, Japan*

Background: Soft tissue sarcomas (STS) are a rare type of malignancy, which comprises of a variety of histologies. Chemotherapy is the standard treatment for patients with advanced STS. Doxorubicin alone or in combination with ifosfamide is widely accepted as the first-line chemotherapy for advanced STS. While a combination with gemcitabine and docetaxel is regarded as a standard regimen of the second-line chemotherapy after failure of doxorubicin-based first-line regimen, the efficacy is not sufficient. Trabectedin, eribulin, and pazopanib are the candidates of the second-line chemotherapy for advanced STS, although there is no clear evidence showing which is better among those agents. The purpose of this clinical trial conducted by Bone and Soft Tissue Tumor Study Group of Japan Clinical Oncology Group (JCOG) is to determine the most promising regimen among trabectedin, eribulin and pazopanib as the test arm regimen in the future phase III trial of the second-line treatment for patients with advanced STS. **Methods:** The study, JCOG1802, is a multicenter, selection design, randomized phase II trial comparing trabectedin (1.2 mg/m^2 IV, every 3 weeks), eribulin (1.4 mg/m^2 IV, days 1 and 8, every 3 weeks) and pazopanib (800 mg PO, everyday) for patients with unresectable or metastatic STS refractory to doxorubicin-based first-line chemotherapy. Eligibility criteria include 16 year-old or older, unresectable and/or metastatic STS, an exacerbation within 6 months prior to registration, histological diagnosis of STS other than Ewing sarcoma, well-differentiated liposarcoma and myxoid liposarcoma, a history of chemotherapy for STS other than doxorubicin-based regimen, ECOG (Eastern Cooperative Oncology Group) performance status 0 to 2, and sufficient organ function. Primary endpoint is progression-free survival (PFS), and secondary endpoints include overall survival, disease-control rate, response rate, and adverse events. To select the most promising regimen in median PFS (3 months in the worst regimen and 4 months in the best regimen) with a probability of at least 80%, a total of 120 patients will be enrolled from 37 institutions in Japan. After JCOG1802, a subsequent phase III trial comparing the winner of this study and a combination of gemcitabine and docetaxel will be planned. The study was activated at December 5, 2019 and 22 of planned 120 patients have been enrolled as of February 15, 2021. Clinical trial information: jRCTs031190152. Research Sponsor: Japan Agency for Medical Research and Development, Other Government Agency.

TPS11581 **Poster Session**

ENVASARC: A pivotal trial of envafolimab, and envafolimab in combination with ipilimumab, in patients with advanced or metastatic undifferentiated pleomorphic sarcoma or myxofibrosarcoma who have progressed on prior chemotherapy. *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Metastatic undifferentiated Pleomorphic Sarcoma (UPS) and the genetically related myxofibrosarcoma (MFS) are soft tissue sarcoma (STS) subtypes with poor prognoses. While responses to front line chemotherapy can approach 20%, efficacy remains limited in the 2nd line setting and beyond. Pazopanib, the only approved treatment in the refractory setting, has demonstrated an objective response rate (ORR) of 4%. Envafolimab is a single domain PD-L1 antibody administered rapidly by subcutaneous (SQ) injection that is being studied in two additional pivotal trials: microsatellite instability-high (MSI-H) cancer and biliary tract cancer. The activity of envafolimab appears to be similar to other PD-1 antibodies administered i.v. Envafolimab demonstrated a 32% objective response rate (ORR) in MSI-H colorectal cancer patients who failed three approved chemotherapeutics, similar to the ORR of 28% and 33% with nivolumab and pembrolizumab in these patient populations, respectively. The rationale for the ENVASARC trial is based on the previously reported activity of checkpoint inhibition in UPS/MFS. Single agent pembrolizumab demonstrated a 23% ORR, while the combination of nivolumab and ipilimumab demonstrated a 29% ORR in refractory UPS/MFS. **Methods:** ENVASARC (NCT 04480502) is a pivotal multicenter (at ~25 U.S. centers) open-label, randomized, non-comparative, parallel cohort study of treatment with envafolimab 300 mg every 3 weeks by SQ injection (cohort A; n = 80) or envafolimab 300 mg every 3 weeks by SQ injection combined with ipilimumab 1 mg/kg every 3 weeks i.v. for four doses (cohort B; n = 80) in patients with locally advanced, unresectable or metastatic UPS/MFS who have progressed on one or two lines of prior therapy. The primary objective of each of parallel cohort is to demonstrate an ORR with a lower limit of the 95% confidence interval that excludes 5.0% in each cohort. If ≥ 9 responders are observed of the 80 patients enrolled in each cohort, then the lower bound of the 95% confidence interval will exclude 5.0%. Secondary endpoints include duration of response (DOR), PFS and OS. Key inclusion criteria: ≤ 2 prior lines of therapy (neoadjuvant and adjuvant therapy excluded), ECOG ≤ 1. Clinical trial information: NCT 04480502. Research Sponsor: TRACON Pharmaceuticals.

TPS11582 **Poster Session**

IGNYTE-ESO: A master protocol to assess safety and activity of letetresgene autoleucel (lete-cel; GSK3377794) in HLA-A*02+ patients with synovial sarcoma or myxoid/round cell liposarcoma (Substudies 1 and 2). *First Author: Sandra P. D'Angelo, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Letetresgene autoleucel (lete-cel; GSK3377794) is an autologous T-cell product using a genetically modified T-cell receptor to target cancer cells expressing the cancer testis antigen New-York esophageal squamous cell carcinoma 1 (NY-ESO-1). Lete-cel is currently being investigated alone and in combination in multiple tumor types [1,2]. NY-ESO-1 is expressed in 70–80% of synovial sarcoma (SS) and 80–90% of myxoid/round cell liposarcoma (MRCLS) tumors [3,4], suggesting these tumors may be prime lete-cel targets. This master protocol design (IGNYTE-ESO; NCT03967223) enables evaluation of multiple cell therapies in multiple tumor types and treatment stages in separate substudies, beginning with lete-cel in Substudies 1 and 2 for SS and MRCLS. **Methods:** Substudy 1 is a single-arm study assessing lete-cel in treatment-naïve patients (pts; ie, anthracycline therapy-naïve for metastatic disease) with advanced (metastatic/unresectable) NY-ESO-1+ SS or MRCLS as a first line of therapy (n=10 planned). Substudy 2 is a pivotal, single-arm study assessing lete-cel in pts with NY-ESO-1+ SS or MRCLS who progressed after anthracycline therapy (n=70 planned). Key eligibility criteria are age ≥10 y and NY-ESO-1 and HLA-A*02 positivity. Exclusion criteria include prior NY-ESO-1–specific/gene therapy, allogeneic stem cell transplant, and central nervous system metastases. Screened pts undergo leukapheresis for lete-cel manufacture, lymphodepletion, lete-cel infusion, and follow-up (FU). Long-term FU (15 y) may be done under a separate protocol. The Substudy 2 primary endpoint is overall response rate (ORR) per RECIST v1.1 assessed by central independent review. Substudy 1 is not testing any formal hypotheses; statistical analysis will be descriptive. Substudy 2 is comparing ORR with the historical control assuming at least 90% power with 0.025 one-sided type I error. Secondary endpoints include efficacy (time to/duration of response, disease control rate, progression-free survival), safety (adverse event [AE] frequency/severity, serious AEs, AEs of special interest), and pharmacokinetic (maximum transgene expansion [C_{max}], time to C_{max}, area under the time curve from zero to time *t* as data permit). Enrollment began in December 2019. References: 1. Reckamp KL, et al. *Ann Oncol* 2019;30(Suppl_5):v602–v660. 2. Rapoport A, et al. *J Clin Oncol* 2020 38:15_suppl, TPS8555. 3. D'Angelo SP, et al. *Cancer Discov* 2018;8(8):944–957. 4. D'Angelo SP, et al. *J Clin Oncol* 2018 36:15_suppl, 3005. Funding: GSK. Editorial support was provided by Eithne Maguire, PhD, of Fishawack Indicia, part of Fishawack Health, and funded by GSK. Previously presented at BSG 2021 (P914542). Clinical trial information: NCT03967223. Research Sponsor: GlaxoSmithKline (208467).

TPS11583 **Poster Session**

A randomized phase II trial of cabozantinib combined with PD-1 and CTLA-4 inhibition in metastatic soft tissue sarcoma. *First Author: Vanessa Anne Eulo, Washington University in St. Louis, St. Louis, MO*

Background: Soft tissue sarcomas (STS) are rare malignancies with poor prognosis in the metastatic setting. Current standard therapy includes anthracycline based chemotherapy. Cabozantinib is a multikinase inhibitor that has demonstrated efficacy in solid tumors such as renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC). A phase II study of cabozantinib in advanced STS is underway. Cabozantinib in combination with immune checkpoint blockade has shown clinical benefit in several tumor types including HCC, RCC, non-small cell lung cancer, and urothelial carcinoma. Since cabozantinib may alter PD-1 expression in regulatory T-cells and promote an immune permissive environment, we hypothesize that combining cabozantinib with immune checkpoint inhibition is a therapeutic strategy that will be more effective than cabozantinib alone. Additionally, the design of the trial will allow assessment of whether pretreatment with cabozantinib will enhance the efficacy of nivolumab and ipilimumab alone. **Methods:** This is an open label, multicenter, randomized phase II clinical trial of cabozantinib (60mg orally daily as a single agent, 40mg in combination) with or without combination Ipilimumab (ipi, 1mg/kg IV every 3 weeks for 4 doses) and Nivolumab (nivo, 3mg/kg IV every 3 weeks for four doses, then 480mg IV every 4 weeks) in patients (pts) with unresectable or metastatic STS refractory to up to two lines of chemotherapy. 105 pts with non-translocation driven sarcomas will be enrolled at three US sites and randomized 2:1 to the combination group. Pts will be stratified by prior pazopanib use and balanced for histologies. Patients who progress on arm A will cross over to combination therapy (arm B). The primary efficacy endpoint is objective response rate (ORR) by RECIST 1.1. 35 patients in Cohort A (cabozantinib alone) and 70 patients in Cohort B (cabozantinib plus ipi/nivo) will be required to detect an increase of the ORR from 10% in cohort A to 30% in cohort B with 81% power with a one-sided alpha level of 10%. Key eligibility criteria include: at least 18 years of age, ECOG performance status of 0 or 1, ≤2 prior lines of therapy and measurable disease. Exclusion criteria include: translocation-driven sarcoma except alveolar soft part sarcoma (ASPS), prior immunotherapy, and chronic use of corticosteroids or other immunosuppression. Secondary endpoints are safety, overall and progression free survival, disease control rate, and response rate to ipilimumab and nivolumab after cabozantinib pretreatment. Mandatory tumor biopsies pre-treatment and at 6 weeks will be obtained. Peripheral blood will be collected for circulating immune phenotyping. Enrollment will occur at 3 participating institutions and is expected to be completed in 2022. Clinical trial information: NCT04551430. Research Sponsor: Exelixis, Bristol Myers Squibb.

12000 **Oral Abstract Session**

Randomized trial of remote cancer symptom monitoring during COVID-19: Impact on symptoms, QoL, and unplanned health care utilization. *First Author: Kathi Mooney, Huntsman Cancer Institute at the University of Utah, Salt Lake City, UT*

Background: Unplanned health care utilization due to poorly controlled cancer symptoms is common and important to avoid during the Covid-19 pandemic. In a randomized trial we evaluated whether remote symptom monitoring and management utilizing Symptom Care at Home (SCH), would reduce symptom burden, improve quality of life, and decrease unplanned health care use in cancer patients receiving active treatment. **Methods:** Patients (n = 252) receiving chemotherapy and/or radiation therapy were randomized to the SCH intervention (n = 128) or usual care (UC) (n = 124). Daily, those in the intervention group, utilized the SCH system to report the presence and severity of 9 common symptoms during treatment. For symptoms endorsed, SCH participants received immediate, tailored automated self-management coaching. Symptoms at moderate to severe levels were automatically reported to oncology nurse practitioners who called the SCH patients to improve symptom management based on a decision support dashboard. Participants from both groups were assessed at baseline and monthly for up to 5 months on symptom burden (MDASI), mental health well-being and social isolation (PROMIS; HADS) and Health-related Quality of Life (HRQoL) (Penedo Covid-19 HRQoL subscale). Unplanned health care use was extracted from the EHR. Descriptive statistics examined equivalency between groups. Mixed effects models with random intercepts were utilized to examine group differences over time with post-hoc analyses to determine specific timepoint differences. **Results:** Participants did not differ on demographic or baseline measures. On average participants were 61 years of age, predominantly female (61%) and white (93%). A variety of cancers were represented with colon, breast and ovarian most common and 60% had stage 3 or 4 disease. Longitudinal mixed effects models found significant effects for lower symptom burden (p = .018) and better HRQoL (p = .007) for SCH participants versus UC at months 1 and 2 with improvements subsiding over the remaining months. Mental health wellbeing and social isolation were not significantly different. There were a total of 71 unplanned health care episodes with 28 for SCH and 43 for UC. Unplanned episode types included: unplanned clinic visit- 3 SCH vs 2 UC; ED visit- 10 SCH vs 16 UC and unplanned hospitalizations-15 SCH vs 25 UC. More SCH participants had no unplanned health care episodes than UC participants ($\chi 2$ 4.08; p = .04). **Conclusions:** Remote monitoring and management of patients' cancer and treatment-related symptoms during the Covid-19 pandemic reduced symptom burden and improved quality of life during the first two months of monitoring. Unplanned health care utilization trended lower for those remotely monitored. Extending care to the home during the pandemic can decrease demand on the health care system and improve cancer patients' symptom experience. Clinical trial information: NCT04464486. Research Sponsor: U.S. National Institutes of Health.

12001 **Oral Abstract Session**

I'm being forced to make decisions I have never had to make before': Oncologists and the conundrums created by COVID-19. *First Author: Chithra R. Perumalswami, University of Michigan, Ann Arbor, MI*

Background: The COVID-19 pandemic has created conundrums for physicians. This study examines the experiences of oncologists who engage in complex decision-making regarding the use of chemotherapy in seriously ill persons in the context of the COVID-19 pandemic. **Methods:** Between January 2020 and August 2020, the authors conducted semi-structured, in-depth individual interviews with 22 purposefully sampled oncologists from practices enrolled in the Michigan Oncology Quality Consortium. Transcripts were double-coded and reconciled by consensus using qualitative data analysis software for thematic analysis. **Results:** Among the thematic clusters we identified, one was related to conundrums created by the COVID-19 pandemic. In this presentation, we report the results pertaining to three themes within this cluster: (1) the ethical dilemmas faced by oncologists due to the COVID-19 pandemic, (2) the need for both patients and oncologists to manage uncertainty and emotions, and (3) the importance and complexity of integrating technology and communication for seriously ill persons. Oncologists grappled with several conundrums including resource scarcity, resource allocation, delays in care, a duty to promote equity and non-abandonment, high levels of uncertainty and fear, and the importance of advanced care directives and end-of-life care planning. Non-abandonment featured as a coping mechanism for increased stress, and integration of communication with telemedicine was frequent and necessary. **Conclusions:** This study offers an in-depth exploration of the conundrums faced by oncologists due to the COVID-19 pandemic and how they navigated them. Optimal decision-making for seriously ill persons with cancer during the COVID-19 pandemic must include open acknowledgement of the ethical dilemmas faced, the heightened emotions experienced by both patients and their oncologists, and the urgent need for integrating technology with compassionate communication in determining patient preferences. Research Sponsor: U.S. National Institutes of Health, Center for Bioethics and Social Sciences in Medicine, University of Michigan.

12002 **Oral Abstract Session**

Feasibility of a virtual hybrid resistance and balance training program for older patients with cancer and its preliminary effects on lower body strength and balance. *First Author: Schroder Sattar, University of Saskatchewan, Regina, SK, Canada*

Background: Falls are a major issue among older patients with cancer and can lead to interruption in cancer treatment. Ample evidence shows resistance and balance training can prevent falls in older adults; however, there is a paucity of evidence regarding exercise on fall prevention in the older cancer population, who often have unique risk factors for falls. Given the new reality of the COVID-19 pandemic, minimizing group gatherings and its associated risks is imperative for older patients, who are a vulnerable population. This study sought to investigate the feasibility of an 8-week, virtual exercise program and its preliminary effects on lower body strength and balance in community-dwelling cancer patients. **Methods:** Study participants were recruited for this pretest-posttest intervention study using consecutive sampling over a one-year period from the Cross Cancer Institute in Edmonton, Alberta. The intervention entailed leg muscle strengthening and balance training exercises that progressed in difficulty as outlined by the Otago program, and involved a virtual component (facilitated live by a certified exercise physiologist via Zoom meeting platform once a week) and independent at-home training component (twice a week). Lower body strength and balance were assessed using the 5-times chair-stand and the 4-stage balance test, respectively, and were analyzed using the Wilcoxon Signed Rank test. **Results:** Twenty-seven older patients (mean age 70.1, range 65-76) participated. The most common cancer sites were breast (48%) and prostate (41%). One participant withdrew due to personal reasons unrelated to the program. The remaining 26 participants completed the intervention. Attendance rate for the virtual component was 97.6% and independent component 84.7%. Participants perceived the program as rewarding and enjoyable (100%), felt this program prepared them to exercise on their own (92%), were confident to continue exercising on their own (81%), and would recommend the program to other patients (100%). At baseline, 33% (n = 9) $\geq$1 fall over the past 6 months. A statistically significant improvement in lower body strength was detected post-intervention ($p = .001$), whereas no difference was detected in balance ($p = .059$). **Conclusions:** This virtual, hybrid resistance and balance training program was feasible, overwhelmingly accepted by our older participants, and appeared effective in improving lower body strength. Findings from this study may have potential to inform design of a larger, randomized multi-site study. Research Sponsor: CIHR Project Seed Grant.

12003 **Oral Abstract Session**

Prospective validation of genetic predictors of aromatase inhibitor-associated musculoskeletal symptoms (AIMSS) in a racially diverse cohort: Results from ECOG-ACRIN E1Z11. *First Author: Vered Stearns, The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins School of Medicine, Baltimore, MD*

Background: AIMSS are common and frequently lead to early discontinuation of adjuvant AI therapy. Single nucleotide polymorphisms (SNPs) in candidate genes have been associated with AIMSS and AI discontinuation. The primary objective of E1Z11 was to validate previously identified associations between 10 specific SNPs in candidate genes and AI discontinuation due to AIMSS in a community-based, racially diverse cohort. **Methods:** Postmenopausal women with hormone receptor-positive stage I-III breast cancer enrolled onto a prospective multi-site cohort study, the majority through the NCI Community Oncology Research Program (NCORP). Participants received anastrozole 1 mg oral daily, and completed patient-reported outcomes (PROs) at baseline, 3, 6, 9, and 12 months. AIMSS was defined as >20% increase in Stanford Health Assessment Questionnaire (HAQ) score over baseline occurring within 1 year of AI therapy. We projected 40% would develop AIMSS and 25% would discontinue AI treatment within 1 year, informing a planned enrollment of 1000 women with a fixed number per strata (600 Caucasian, 200 African-American [AA] & 200 Asian) to provide 80% power to detect an effect size of 1.5-4. SNPs include ESR1 (rs2234693, rs2347868, rs9340835), CYP19A1 (rs1062033, rs4646), TCL1A (rs11849538, rs2369049, rs7158782, rs7159713), and HTR2A (rs2296972). Hardy-Weinberg equilibrium (HWE) was evaluated within each racial subset. SNP genotypes were coded as additive effects on the log odds ratio by coding as 0, 1 or 2 for the count of the minor allele. A Cochran-Armitage trend test was used with a 1-sided alpha of 0.0025 (Bonferroni correction for 10 tests). **Results:** We enrolled 999 evaluable women (616 Caucasian, 184 AA, 199 Asian). Genotyping was successful in 974 (98%). AIMSS developed in 43%, and AI therapy was discontinued in 12% within 1 year. While more AA and Asians developed AIMSS compared to Caucasians (48% vs 38%, p=0.017; 50% vs 38%, p=0.004), AI discontinuation rates were similar across racial groups. HWE was satisfied for all SNPs at the 5% alpha level, except for TCL1A/rs11849538 (p=0.002) in the AA cohort. None of the 10 SNPs were significantly associated with AI discontinuation or development of AIMSS in the overall population, or in any of the 3 cohorts. **Conclusions:** Although AIMSS were more common in AA and Asians, AI discontinuation rates were similar in the 3 cohorts. We were unable to prospectively validate 10 SNPs in 4 genes previously associated with AI discontinuation due to AIMSS. Future analyses will include other predictors of AIMSS, PROs, and additional genetic markers for the entire cohort and by race. Support: NCI UG1CA189828, UG1CA233196, UG1CA233277, UG1CA233320, UG1CA233178, UG1CA233160, UG1CA232760, UG1CA233341, UG1CA233329, U10CA180821, UG1CA189821, UG1CA189830, U10CA180888, UG1CA189859, UG1CA189863, UG1CA189971. Clinical trial information: NCT01824836. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

12004 **Oral Abstract Session**

Pharmacogenomics of cisplatin-induced neurotoxicities: Hearing loss, tinnitus and peripheral sensory neuropathy. *First Author: Xindi Zhang, Department of Medicine, University of Chicago, Chicago, IL*

Background: Cisplatin is an essential component of first-line chemotherapy for many cancers, but causes neurotoxicity, including hearing loss (CisHL), tinnitus (CisTinn), and peripheral sensory neuropathy (CisPNeuro). However, few opportunities exist to identify risk factors and comorbidities for cisplatin-induced neurotoxicities among large numbers of homogenously treated patients without the confounding effect of cranial radiotherapy. **Methods:** Within a well-characterized clinical cohort of 1,680 cisplatin-treated testicular cancer survivors, linear and logistic regression analysis were utilized to analyze associations of CisHL (n = 1,258), CisTinn (n = 1,217), and CisPNeuro (n = 1,653) with non-genetic risk factors. Genome-wide association studies and gene-based analysis were performed on each phenotype. **Results:** Cisplatin-induced neurotoxicities (CisHL CisTinn, CisPNeuro), adjusting for age and cisplatin dose, were interdependent. Survivors with these neurotoxicities experienced more hypertension (CisTinn: OR = 2.62, $p < 0.0001$; CisHL: $\beta = 0.25$, $p = 8.5 \times 10^{-4}$; CisPNeuro: OR = 1.86, $p < 0.0001$) and were more likely to report their health as poor (CisTinn: OR = 0.54, $p < 0.0001$; CisHL: $\beta = -0.11$, $p < 0.0001$; CisPNeuro: OR = 0.61, $p < 0.0001$). Persistent vertigo was significantly associated with both CisTinn (OR = 7.18, $p < 0.0001$) and CisPNeuro (OR = 4.29, $p < 0.0001$). In addition, CisTinn was significantly associated with hypercholesterolemia (OR = 1.78, p = 0.01). Importantly, gene-based association analyses identified significant associations between CisTinn and *WNT8A* (n = 1,037, $p = 2.52 \times 10^{-6}$), encoding a signaling protein important in germ cell tumors; and marginal significance between CisHL and *TXNRD1* (n = 1,071, $p = 4.21 \times 10^{-6}$), thioredoxin reductase-1, which plays a key role in redox regulation. In silico analysis showed high expression levels of *TXNRD1* were significantly correlated with cellular resistance to cisplatin in central nervous system tumor cells (Spearman Rho = 0.35, p = 0.04; $R^2 = 0.14$, p = 0.03), indicating *TXNRD1* is protective for cisplatin-induced cytotoxicity. Previously, rs62283056 in *WFS1* found to be significantly associated with CisHL (n = 511; subset of current population), was marginally significant in an independent replication cohort (p = 0.06; n = 606; subset of current population). **Conclusions:** Cisplatin-induced neurotoxicities are significantly associated with multiple clinical characteristics, including hypertension and self-reported poor health. *WNT8A and TXNRD1* are notable risk factors for CisTinn and CisHL, respectively. Future studies should further investigate these genes and their potential impact on chemotherapy strategies. This study, based on the largest number of testicular cancer survivors investigated to date, highlights the clinical importance of these iatrogenic toxicities and their associated risk factors. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

12005 **Oral Abstract Session**

Polymorphisms rs4673 and rs28714259 as predictors of anthracycline-mediated cardiotoxicity in patients with breast cancer. *First Author: Dmitry Yu. Gvaldin, National Medical Research Centre for Oncology, Rostov-on-Don, Russian Federation*

Background: Numerous pharmacogenetic studies have led to the identification of genetic polymorphisms associated not only with the development of cardiovascular disease, but also increase the risk of complications due to the use of anthracycline drugs, widely used in the treatment of cancer. The purpose of this study was to study the frequency of rs4673 and rs28714259 and possible associations with the risk of cardiovascular changes in patients with breast cancer during anthracycline therapy (anthracycline-mediated cardiotoxicity — AMC). **Methods:** The study included 256 Caucasian patients (median age - 55 years) with a diagnosis of breast cancer without diagnosed cardiovascular changes, who were treated with anthracyclines at the National Medical Research Center of Oncology in 2019-2020. For genotyping of rs4673 and rs28714259, DNA was extracted from blood using DNA-sorb-B (AmpliSens, Russia) and HRM-PCR was performed on a CFX96 amplifier (Bio-Rad, USA). The presence of polymorphisms was confirmed by Sanger sequencing on a Genetic Analyzer 3500 (ABI, USA). **Results:** During the follow-up period 21 (8.2%) patients were diagnosed with signs of subacute (changes developed within several weeks after the last course of therapy) or early chronic AMC (changes developed within a year after completion of anthracycline therapy). In the group of patients without AOC the allelic frequency of rs4673 (c.214T > C *CYBA*) was 0.38, the frequency of genotypes C/C – 0.4, C/T – 0.43, and T/T – 0.17. In the same group, the frequency of the A allele rs28714259 was 0.07, the frequency of the G/G genotypes – 0.87, G/A – 0.13, and A/A – 0. The prevalence of genotypes T/T rs4673 and allele G rs28714259 in a cohort of Russian patients differed from the European population (p = 0.014 and p = 0.05, respectively). The risk of cardiovascular changes on the background of anthracycline therapy increased in the presence of the rs4673 polymorphic allele by 6.49 times, in the case of the G/A and A/A rs28714259 genotypes - by 3.27 times. The results of the ROC-analysis suggested high quality of the tests based on the dominant models rs4673 and rs28714259 (AUC was 71.9% and 76.3% correspondingly). **Conclusions:** In this study the prognostic efficiency of the genetic markers rs4673 and rs28714259 was shown for the prompt detection of the risks of AMC development in the management of cancer patients. However, population characteristics should be taken into consideration for risk assessment. Research Sponsor: None.

12006 **Oral Abstract Session**

Does early palliative care reduce end-of-life hospital costs? A propensity-score matched, population-based, cohort study. *First Author: Hsien Seow, McMaster University, Hamilton, ON, Canada*

Background: Few studies describe how early versus late palliative care affects end-of-life health services costs. The aim of this study was to investigate the impact of early vs not-early palliative care among cancer decedents on the combined costs of receiving aggressive care (ED/hospitalization) and supportive care (home care/physician home visit). **Methods:** Using linked administrative databases, we created a retrospective cohort of cancer decedents between 2004 -2014 in Ontario, Canada. We identified those who received early palliative care (palliative care service used in the hospital or community 12 to 6 months before death [exposure]). We used propensity score matching to identify a control group of not-early palliative care, hard matched on age, sex, cancer type and stage. The propensity score included region, year, treatment, etc. We examined differences in median costs (including hospital, ED, physician, and home care costs) between pairs in the last month of life. **Results:** We identified 144,306 cancer decedents, of which 37% received early palliative care in the exposure period. After propensity score matching, we created 36,238 pairs of decedents who received early and not-early palliative care. After matching the early and not-early groups had equal distributions of age, sex, cancer type (24% lung cancer) and stage (25% stage 3 or 4). Among those who received early palliative care, 56.3% used hospital in-patient care in the last month, whereas 66.7% of the control group (not-early palliative care) used in-patient care; considering only inpatient hospital costs, those receiving early palliative care used a median of $2,894 in the last month of life compared to the control group of $5,311 ($p < 0.001$). Overall median costs in the last month of life for patients in the early palliative care vs the control group was $11,129 vs. $10,598 ($p < 0.001$). **Conclusions:** In our population-based, propensity-score matched, cohort study of cancer decedents, receiving early palliative care reduced the median overall health system costs, especially via avoiding hospitalizations in the last month of life. Research Sponsor: Canadian Centre for Applied Research in Cancer Control (ARCC).

12007 **Oral Abstract Session**

Palliative care and coping in patients with acute myeloid leukemia receiving intensive induction therapy: A mediation analysis of data from a randomized trial. *First Author: Thomas William LeBlanc, Duke University School of Medicine, Durham, NC*

Background: Patients with acute myeloid leukemia (AML) receiving intensive induction chemotherapy experience significant symptoms, quality of life impairment, anxiety, and depression. We previously showed that integrated palliative care improves quality of life (QOL), anxiety and depression during induction, but the mechanism of these benefits is unexplained. **Methods:** We conducted a non-blinded, multi-site randomized trial of integrated palliative and oncology care (IPC) (n = 86) vs usual care (n = 74) for hospitalized patients with AML receiving induction therapy. IPC patients were seen by palliative care clinicians at least twice weekly while hospitalized. Patients completed the Functional Assessment of Cancer Therapy-Leukemia scale, the Hospital Anxiety and Depression Scale, and the Brief COPE questionnaire, to assess QOL, mood, and coping at baseline and weeks 2, 4, 12, and 24. To facilitate analysis, we categorized coping strategies into approach-oriented (active coping, positive reframing, and acceptance) or avoidant (denial, or self-blame), per prior studies. We used linear regression models adjusting for baseline scores to assess the effect of the intervention on coping at week 2. We used causal mediation regression models to examine whether changes in coping during the initial hospitalization mediated intervention effects on QOL, depression and anxiety symptoms at week 2, when patients feel worst during induction. **Results:** We enrolled 160 of 235 (68.1%) eligible patients. Those randomized to IPC reported more approach-oriented coping (B = 1.85, 95%CI 0.62-0.38, P = 0.004) and less avoidant-oriented coping (B = -0.70, 95%CI -1.28, -0.11, P = 0.020) at week 2. Intervention effects on approach-oriented coping were sustained up to week 24 (B = 0.36, 95%CI 0.68, 0.09, P = 0.010), but not on avoidant-oriented coping (B = -0.01, 95%CI -0.28-0.05, P = 0.163). Changes in approach-oriented coping and avoidant-oriented coping during hospitalization partially mediated the intervention effects on week 2 QOL (indirect effect = 6.58, 95%CI 2.14, 13.63), depression (indirect effect = -1.08, 95%CI -2.05, -0.27), and anxiety symptoms (indirect effect = -0.52, 95%CI -1.25, -0.04). Changes in approach- and avoidant-oriented coping accounted for 78% of the total palliative care intervention effect on QOL; 66% of the intervention effect on depression; and 35% of the intervention effect on anxiety. **Conclusions:** IPC as part of induction chemotherapy for AML facilitates active coping strategies for patients, while reducing avoidant coping. Improvement in coping skills accounts for a substantial proportion of the effect from a palliative care intervention on QOL, depression, and anxiety symptoms. These findings offer important insights into the mechanism by which palliative care may enhance patient-reported outcomes in patients with AML. Clinical trial information: NCT02975869. Research Sponsor: Cambia Health Foundation.

12008 **Oral Abstract Session**

Disparities in end-of-life inpatient care received by patients with metastatic cancer, 2010 to 2017. *First Author: Stephanie Deeb, Icahn School of Medicine at Mount Sinai, New York, NY*

Background: Many patients with metastatic cancer receive high-cost, low-value care near the end of life. We examined interventions during terminal hospitalizations for patients with metastatic cancer to identify those with high likelihood of receiving futile care. **Methods:** A retrospective population-based cohort analysis of encounter-level data from the National Inpatient Sample was conducted, including records from 2010-2017 for patients ages ≥18 with metastatic cancer who died during hospitalization. We fit multivariable binomial logistic regression models to examine associations between exposures, including patient demographics, and the main outcome of aggressive, low-value, and high-cost medical care (Table). **Results:** Out of 321,898 hospitalizations among patients with metastatic cancer, 21,335 (6.6%) were terminal. Of these, 65.9% were white, 14.1% Black, 7.5% Hispanic, 58.2% were insured by Medicare or Medicaid, and 33.2% were privately insured. Overall, 63.2% were admitted from the Emergency Department (ED), 4.6% received systemic therapy, and 19.2% received invasive ventilation. Median total charges were $43,681. Black patients and publicly insured patients had higher likelihoods of admission from the ED and receiving ventilation, as well as higher total charges; similar trends emerged among patients of Asian race and Hispanic ethnicity. Patients hospitalized at urban teaching hospitals had higher likelihoods of receiving systemic therapy, ventilation, and incurring higher total charges (Table). **Conclusions:** Metastatic cancer patients of racial and ethnic minority groups and those with Medicare or Medicaid were more likely to receive low-value, aggressive interventions at the end of life. Further studies are needed to determine the underlying causes of these disparities in order to implement prospective interventions and advance appropriate end-of-life care. Research Sponsor: U.S. National Institutes of Health, Icahn School of Medicine at Mount Sinai.

		ED admission		Systemic therapy		Invasive ventilation		Total charges[c]	
Factors[a]		OR[b]	p[b]	OR	p	OR	p	OR	p
Race	WNH	1.00		1.00		1.00		1.00	
	BNH	1.39 (1.27-1.52)	<0.0001	0.78 (0.64-0.96)	0.020	1.59 (1.44-1.75)	<0.0001	1.23 (1.13-1.34)	<0.0001
	Hispanic	1.45 (1.28-1.64)	<0.0001	0.97 (0.76-1.23)	0.77	1.14 (0.99-1.30)	0.063	1.50 (1.34-1.69)	<0.0001
	API	1.43 (1.20-1.72)	<0.0001	0.92 (0.65-1.31)	0.66	1.20 (0.98-1.45)	0.073	1.35 (1.13-1.60)	0.00076
Payer	Public	1.00		1.00		1.00		1.00	
	Private	0.47 (0.44-0.51)	<0.0001	1.05 (0.90-1.22)	0.56	0.75 (0.69-0.82)	<0.0001	0.64 (0.59-0.68)	<0.0001
Location/ teaching	Rural	1.00		1.00		1.00		1.00	
	UT	1.09 (0.97-1.23)	0.13	2.79 (1.84-4.24)	<0.0001	2.91 (2.40-3.54)	<0.0001	3.81 (3.34-4.35)	<0.0001

[a]WNH = White, non-Hispanic; BNH = Black, non-Hispanic; API = Asian or Pacific Islander; public = Medicare or Medicaid; UT= urban teaching hospital [b]Odds ratio (95% confidence interval); two-tailed p [c]Dichotomized according to whether median total charges were greater than median for overall cohort.

12009 **Clinical Science Symposium**

A symptom-adapted physical activity intervention during induction chemotherapy for older adults with acute myeloid leukemia (AML) to maintain physical function. *First Author: Heidi D. Klepin, Comprehensive Cancer Center, Wake Forest Baptist Health, Winston Salem, NC*

Background: Older adults are at risk for physical function decline during therapy for AML. Impaired physical function after induction therapy is associated with shorter survival Interventions designed to maintain function may improve treatment outcomes. We piloted a physical activity (PA) intervention among older adults receiving intensive chemotherapy for AML designed to prevent functional decline. **Methods:** Single institution randomized pilot study of PA vs. usual care. Eligibility included age ≥60 years, newly-diagnosed AML, ambulatory, planned intensive induction chemotherapy. Intervention participants were offered a PA session five days/week tailored daily to symptoms and conditions during the induction hospitalization. Session options were: 1) Standard (ward-based), walking + balance trahining + resistance exercises; 2) Intermediate (room-based), upper-body ergometer + balance training + resistance exercises; 3) Low-intensity (bed-based), upper-body ergometer + resistance exercises. Behavioral counseling sessions to establish PA goals and overcome barriers were conducted weekly during hospitalization and continued monthly by phone for 6 months. Assessment of physical function occurred at baseline, weekly during hospitalization (approximately 4-6 weeks), 3 months, and 6 months. The primary functional outcome of interest was the Short Physical Performance Battery (SPPB; 5 repeat chair stands, gait speed, balance tests; score 0-12 higher indicates better function). Clinically significant change in physical function was defined as ≥1.0 on the SPPB. Proportions of those that declined, remained stable, or improved on the SPPB were compared by group using an exact test for trend. **Results:** Among 96 eligible patients 70 enrolled (recruitment rate 73%, average participation 3 sessions/week). The mean age was 72.1±6.3 years, 70% were male. Mean baseline SPPB score was 7.0±3.8. In the surviving intention to treat population (N = 66), more intervention participants, compared to controls, maintained or improved their SPPB score (38% vs. 25%) during induction hospitalization (p = 0.278). Among those who achieved remission (N = 42), function was maintained or improved in a greater proportion of intervention participants (55%) compared to controls (23%), p = 0.047. Maintenance or improvement in SPPB from baseline to last follow-up (3 or 6 months post enrollment) was 62% vs 54% for intervention versus control among the intention to treat cohort (N = 50) and 67% vs. 55% among those who achieved remission (N = 40). **Conclusions:** A symptom adapted PA intervention with behavioral counseling during induction chemotherapy shows promise in preventing clinically meaningful decline in physical function among older adults with AML who achieve remission. Continued maintenance intervention may sustain benefits. Clinical trial information: NCT01519596. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

12010 **Clinical Science Symposium**

The effects of geriatric assessment on oncologist-patient communication regarding functional status and physical performance in older adults with cancer: A secondary analysis of a 541-subject nationwide URCC NCORP (NCI Community Oncology Research Program) cluster randomized trial. *First Author: Marielle Jensen-Battaglia, James P. Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY*

Background: Despite high prevalence of functional status (FS) and physical performance (PP) impairments among older adults with cancer, standardized assessments and interventions are not routinely used in oncology care. This study characterized how oncologist knowledge of Geriatric Assessment (GA) results influenced conversations and GA-guided recommendations addressing FS and PP concerns. **Methods:** Data were from a NCORP funded (UG1CA189961) nationwide cluster randomized controlled trial (ClinicalTrials.gov: NCT02107443; PI: Mohile), with inclusion criteria: age ≥70, stage III/IV solid tumor or lymphoma with palliative treatment intent, and ≥1 GA domain impairment. All subjects underwent baseline GA including standardized FS ([instrumental] activities of daily living) and PP (Timed Up and Go, Short Physical Performance Battery, Older Americans Resources and Services Physical Health scale, falls in past 6 months) measures. Oncologists in Intervention arm practices received full GA results and validated recommendations for each patient, while those in the usual care (UC) arm were only notified of depression or severe cognitive impairment. One clinical encounter per patient within 4 weeks of GA was audio-recorded, transcribed and blind coded using a priori content-analysis scheme to categorize conversations and oncologist response (dismissed, acknowledged, or addressed with recommendation) by GA domain. Frequencies, raw and adjusted (for site using generalized linear mixed models) proportions were compared using the Chi square test. **Results:** 541 patients (mean age: 77, range 70-96) were included. More FS and PP conversations occurred in Intervention (PP=532, FS=164) than UC (PP=183, FS=87) arm (p<.0001). The adjusted proportion of all patients having one or more FS or PP conversations reached 85.8% in the Intervention arm but only 58.6% in UC (p<.0001). Intervention oncologists were more likely to address FS and PP concerns than UC oncologists (42.6% vs 16.5%, p=0.0003), and to use referrals (Intervention=23.5%, UC=5.0%, p<.0001) or information (Intervention=22.3%, UC=3.8%, p=0.0006) to address them. **Conclusions:** Providing oncologists a GA report with recommended interventions enhances oncologist-patient communication regarding FS and PP-related concerns in older adults with advanced cancer. FS and PP-related issues were more likely to be addressed by those oncologists receiving the GA report, demonstrating the utility of GA as a tool in creating tailored interventions for FS and PP concerns. Our findings support use of GA as an important tool in caring for patients with impairments in physical performance and function. Funding: NIH/NCI UG1CA189961, T32CA102618. Clinical trial information: NCT02107443. Research Sponsor: U.S. National Institutes of Health.

12011 **Clinical Science Symposium**

Comprehensive geriatric assessment and management for Canadian elders with Cancer: The 5C study. *First Author: Martine Puts, University of Toronto, Toronto, ON, Canada*

Background: Comprehensive Geriatric Assessment (CGA) is recommended by ASCO for older adults with cancer undergoing chemotherapy to identify issues that can interfere with treatment delivery and optimize functional status and quality of life. However, few randomized controlled trials have been completed so far. Our objective is to evaluate the effectiveness of CGA on improving quality of life for older adults receiving cancer treatment. **Methods:** Eligible patients were aged 70+, diagnosed with a solid tumour, lymphoma or myeloma, referred for first/second line chemotherapy, speaking English/French, and with an Eastern Collaborative Oncology Group Performance Status 0–2. The CGA was done by a nurse and geriatrician followed by monthly phone calls by the study nurse for 6 months. Patients were randomly assigned (1:1) to receive either the intervention (CGA plus follow-up by geriatric trained team in addition to usual oncology care) or usual care alone. All participants received a monthly healthy aging booklet for attention control. Randomization was stratified by center and treatment intent (curative/adjuvant versus palliative). Our primary outcome was health-related quality of life (HRQOL) assessed with the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 global health scale (items 29 and 30). Secondary outcomes include functional status (Instrumental Activities of Daily Living). Outcome data collection was completed monthly for the first 6 months, then at 9 and 12 months. For the primary outcome we used a pattern mixture model using an intent-to-treat approach (at 0, 3, and 6 months). The last data collection took place March 8 2021. **Results:** From May 2017 to March 2020, 351 participants from 8 hospitals across Canada were enrolled. All patients were seen on or after day 1 of treatment for the intervention per patient request. Patient characteristics at baseline were similar in both arms. The average age was 75.7 (SD = 4.8), 60.4% was male and 54.3% had treatment with palliative intent. Change in HRQOL scores did not differ by arm (p = .80). Neither group exceeded the MCID of 10 points. There was also no difference in IADL between the groups (p = 0.82). **Conclusion:** CGA was not effective in improving quality of life for older adults receiving cancer treatment in this study. CGA may need to be performed prior to treatment initiation to achieve benefits. Clinical trial information: NCT03154671. Research Sponsor: 705046.

12012 **Clinical Science Symposium**

Barriers and facilitators of geriatric assessment implementation in daily oncology practice: A qualitative study applying a theoretical implementation framework. *First Author: Ayumu Matsuoka, Division of Behavioral Sciences, Research Center for Public Health Sciences, National Cancer Center, Tokyo, Japan*

Background: Geriatric assessment (GA) is recommended in various guidelines for older adults with cancer, but is not widely used in daily practice. This study aims to identify multi-level barriers and facilitators of GA implementation in daily oncology practice, based on a theoretical implementation framework. **Methods:** We conducted 20 semi-structured interviews with healthcare providers and managers in 14 hospitals treating older adults with cancer in Japan. The Consolidated Framework for Implementation Research (CFIR) was used to guide the collection and analysis of interview data using a deductive approach. CFIR consists of 5 major domains (I. intervention characteristics, II. outer setting, inner setting, . individual characteristics, and V. process), including 39 constructs. Differences in the constructs influencing GA implementation between hospitals where GA is routinely performed (high implementation, HI) and hospitals where GA is not performed or performed only in clinical trials (low implementation, LI) were explored. **Results:** Among constructs identified as barriers or facilitators of GA implementation, 15 multi-level constructs greatly differed between 5HI and 5LI, including 4 constructs from intervention characteristics, 6 from inner setting, 1 from individual characteristics, and 4 from process. In HI, GA was self-administered (I. adaptability), or administered on a mobile app with interpretation (I. design quality and packaging). In HI, healthcare providers strongly perceived the need to change the practice for older adults (III. tension for change), and recognized GA as fitting in with existing workflow as part of their jobs (III. compatibility). In LI, they did not realize the need to change practice, and rejected GA as an extra burden on their heavy workload. In HI, the usefulness of GA was widely recognized by healthcare providers (IV. knowledge and beliefs about the intervention), GA was given high priority (III. relative priority), had strong support from hospital directors and nursing chiefs (V. leadership engagement), and multiple stakeholders were successfully engaged, such as healthcare providers, especially nurses (V. key stakeholders), directors and nursing chiefs (V. opinion leaders), and those who dedicated themselves to implementing GA (champions). **Conclusions:** This is the first study to reveal the multi-level barriers and facilitators of GA implementation in daily oncology practice. The findings highlight the need to focus not only on individual or intervention characteristics, but also on the inner setting and the process of implementing GA. Our findings suggest future strategies, such as devising the administration of GA using technology, conducting local needs assessment and consensus discussions about the usefulness and priority of GA, and engaging multiple stakeholders. Research Sponsor: None.

12013 **Clinical Science Symposium**

Effects of metabolic syndrome on cognitive outcomes in long-term survivors of childhood cancer. *First Author: Tyler Alexander, St. Jude Children's Research Hospital, Memphis, TN*

Background: Childhood cancer therapy increases risk for cognitive impairment and other chronic conditions, which also may impact cognition. We assessed the unique impact of metabolic syndrome (MetS) on cognition in survivors participating in the St. Jude Lifetime Cohort Study. **Methods:** Participants included 4058 survivors of childhood cancer (53.9% female; mean [SD] age 30.1 [10.5] years at evaluation; 22.6 [10.1] years from diagnosis) who completed clinical evaluation and cognitive testing. MetS criteria followed Adult Treatment Panel III guidelines (at least 3 of: hypertension, high triglycerides, abdominal obesity, low high-density lipoprotein [HDL], high fasting glucose). Multivariable log-binomial regression models assessed risk of cognitive impairment associated with MetS stratified by survivors who did (n = 2301) or did not (n = 1757) receive central nervous system (CNS)-directed therapy. Mediation analysis assessed effects of MetS and physical activity in cranial radiotherapy (CRT)-associated cognitive impairment. Models were adjusted for age, sex, follow-up time and treatment exposures. **Results:** MetS was associated with increased risk of impaired attention (relative risk [RR] 1.34 95% confidence interval [CI] 1.07-1.66), processing speed (RR 1.25 CI 1.11-1.41) and executive function (RR 1.18 CI 1.01-1.37) in survivors with CNS-directed therapy and academic achievement (RR 1.84 CI 1.18-2.89), attention (RR 1.43 CI 1.10-1.87), and processing speed (RR 1.46 CI 1.21-1.75) in those without CNS-directed therapy. MetS components associated with cognitive impairment included abdominal obesity (memory RR 1.34 CI 1.13-1.59; processing speed RR 1.41 CI 1.24-1.59; executive function RR 1.21 CI 1.05-1.39) and low HDL (intelligence RR 1.26 CI 1.06-1.49; attention RR 1.27 CI 1.03-1.57; processing speed RR 1.17 CI 1.01-1.35; executive function RR 1.20 CI 1.05-1.37) in survivors with CNS-directed therapy. In survivors treated without CNS-directed therapy hypertension (academic achievement RR 1.49 CI 1.18-1.88; intelligence RR 1.34 CI 1.02-1.76; attention RR 1.42 CI 1.12-1.79; memory RR 1.45 CI 1.14-1.84; processing speed RR 1.30 CI 1.08-1.55; executive function RR 1.32 CI 1.08-1.62) and abdominal obesity (academic achievement RR 1.71 CI 1.07-2.72; processing speed RR 1.23 CI 1.02-1.49; executive function RR 1.38 CI 1.09-1.75) were associated with impairment. In mediation analyses, direct effects of CRT were identified, as were indirect effects through physical activity (processing speed $\beta = 0.035$ $p < 0.01$; attention $\beta = 0.03$ $p < 0.01$; executive function $\beta = 0.172$ $p < 0.01$). **Conclusions:** MetS increases risk of cognitive impairment in survivors, particularly abdominal obesity, hypertension and low HDL. Physical activity appears to partially mediate impact of CRT on cognitive outcomes and is an important target for interventions to lower impairment risk. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

12014 **Clinical Science Symposium**

Association between learning and memory problems and health outcomes after blood or marrow transplantation (BMT): A BMT survivor study (BMTSS) report. *First Author: Donna Murdaugh, University of Alabama at Birmingham, Birmingham, AL*

Background: Cognitive impairment after BMT for hematologic malignancies typically involves processing speed, attention and working memory. Survivors perceive these deficits as learning and/or memory problems. However, limited information exists regarding learning/memory problems experienced by survivors several years after BMT. We addressed this gap using the BMTSS. **Methods:** BMTSS is a retrospective cohort study examining long-term outcomes of individuals who survived ≥2y after BMT performed between 1974 and 2014 at three transplant centers. Study participants completed a 255-item questionnaire covering diagnosis by a healthcare provider of health conditions (including learning/memory problems), sociodemographic characteristics, and functional status. We used a nested matched case-control study design. Cases consisted of individuals with learning/memory problems developing after BMT (n = 543). Each case was matched to a BMTSS participant without memory problems (controls: n = 543) using the following criteria: cancer diagnosis, race/ethnicity, type of BMT (allogeneic or autologous), and time from BMT. Multivariable conditional logistic regression analysis was used to identify clinical factors (age at BMT, stem cell source, chronic graft vs. host disease [cGvHD], total body irradiation [TBI], fatigue, pain) and demographic factors (household income, education, sex) associated with learning/memory problems. We also examined the association between learning/memory problems and instrumental activities of daily living (IADL). Analyses were stratified by type of BMT. **Results:** For all survivors (n = 1,086), mean age at BMT was 40.7y and at study participation was 53.3y (18-85); 47% of the study population was females; 78% were non-Hispanic whites; 31% reported an annual household income < $50k. Primary diagnoses included leukemia (50%), lymphoma (36%), and other (14%); 55% received an allogeneic BMT (36% developed cGvHD); 54% received TBI; and 68% received peripheral blood stem cells. Allogeneic BMT survivors with fatigue (odds ratio [OR] = 2.2, 95% CI, 1.4-3.3; p = 0.001), significant pain (OR = 1.8, 95% CI, 1.1-2.9; p = 0.02) and < college education (OR = 1.6, 95% CI, 1.1-2.5; p = 0.02) had higher odds of reporting learning/memory problems. Autologous BMT survivors exposed to TBI (OR = 2.8, 95% CI, 1.4-5.4; p = 0.003) and reporting significant pain (OR = 1.7, 95% CI, 1.0-2.9; p = 0.05) had higher odds of reporting learning/memory problems. Learning/memory problems were associated with increased odds of impairments in IADL in both autologous (OR = 2.1, 95% CI, 1.1-4.0; p = 0.03) and allogeneic (OR = 2.0, 95% CI, 1.2-3.3; p = 0.01) BMT survivors. **Conclusions:** Modifiable risk factors, such as fatigue and pain, can be targeted to mitigate the learning/memory problems and improve the functional outcomes of BMT survivors. Research Sponsor: Leukemia and Lymphoma Society, U.S. National Institutes of Health.

12015 **Clinical Science Symposium**

Effect of physical exercise on cognitive function after chemotherapy in patients with breast cancer: A randomized controlled trial (PAM study). *First Author: Emmie W. Koevoets, Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht University, Utrecht, Netherlands*

Background: Chemotherapy is associated with cognitive problems. Physical exercise is a promising intervention. We investigated whether exercise improves cognition in chemotherapy-exposed breast cancer (BC) patients 2-4 years after diagnosis. **Methods:** In the PAM study, we randomized chemotherapy-exposed BC patients with self-reported and test-confirmed cognitive problems to an exercise or control group. The 6-month exercise intervention consisted of 2 hours of supervised aerobic and resistance training and two hours of Nordic/power walking. Memory function measured with the Hopkins Verbal Learning Test-Revised (HVLT-R) was our primary outcome. Further measurements included online neuropsychological tests (Amsterdam Cognition Scan; ACS), self-reported cognitive complaints (MDASI-MM, EORTC QLQ C-30 cognitive functioning), physical fitness (VO_{2peak}), fatigue (MFI, EORTC fatigue), quality of life (QoL; EORTC), anxiety (HADS) and depression (HADS, PHQ9). HVLT-R total recall was analyzed with a Fisher exact test for clinically relevant improvement of ≥5 words. Other outcomes were analyzed using multiple regression analyses adjusted for baseline and stratification factors. An hypothesis driven but not pre-specified analysis in patients with high baseline EORTC fatigue levels (≥39) was performed. **Results:** We randomized 181 patients to the exercise (n = 91) or control group (n = 90). Two-third of the patients attended ≥ 80% of the exercise program and physical fitness significantly improved compared to the control patients (VO_{2peak}1.4 ml/min/kg, 95% CI 0.6; 2.2). No difference in favor of the intervention group was seen on the primary cognitive outcome or other cognitive tests. However, significant beneficial intervention effects were found for self-reported cognition (MDASI-MM Severity (-0.7, -1.2;-0.1)), fatigue (general fatigue (-2.2, -3.3; -1.1), physical fatigue (-3.3, -4.4; -2.2), mental fatigue (-1.0, -2.0; 0.0), reduced motivation (-1.1, -2.0; -0.2) and reduced activity (-2.1, -3.2; -1.1)), QoL (summary score (4.0, 1.2; 6.7), global health status (5.8, 1.1; 10.6), role functioning (7.2, 1.3; 13.1) and social functioning (5.9, 0.2; 11.6)) and depression (PHQ9 (-1.16, -2.19; -0.13)). In high-fatigued patients, exercise did show significant positive effects on objective cognitive function (ACS Reaction Time (-26.8, -52.9; -0.6) and ACS Wordlist Learning (4.4, 0.5; 8.3)). **Conclusions:** A 6-month exercise intervention did not improve objectively measured cognitive function in chemotherapy-exposed BC patients with cognitive problems. However, self-reported cognitive function, physical fitness, fatigue, QoL and depression did improve. Unplanned analysis indicated a small positive effect of exercise on cognitive functioning in high-fatigued patients. Clinical trial information: NTR6104. Research Sponsor: KWF kankerbestrijding.

12016 **Clinical Science Symposium**

Phase II study of exercise and low-dose ibuprofen for cancer-related cognitive impairment (CRCI) during chemotherapy. *First Author: Michelle Christine Janelsins, University of Rochester Medical Center, Rochester, NY*

Background: CRCI is a debilitating consequence of cancer and its treatment, including difficulties in attention, memory, and executive function. Though CRCI can develop during the course of chemotherapy, interventions targeting CRCI during chemotherapy have not been investigated. Inflammation contributes to CRCI and thus reducing inflammation may ameliorate CRCI. Using a biobehavioral approach, we investigated 2 promising interventions that reduce inflammation: exercise and low-dose ibuprofen. **Methods:** This is a Phase II RCT with a 2:2 factorial design. Eligible participants were patients with cancer receiving chemotherapy who self-reported cognitive difficulties. Participants were stratified by disease type (breast cancer; gastrointestinal cancer; other) and were randomized to 1 of 4 groups for 6 weeks: exercise alone (+ placebo), ibuprofen alone, exercise + ibuprofen, or placebo only. The exercise intervention, delivered by an exercise physiologist, was Exercise for Cancer Patients (EXCAP), an individually tailored, home-based prescription of walking and resistance band training. Ibuprofen/placebo was over-encapsulated for blinding; 200mg was taken 2 times per day. Participants completed 7 cognitive assessments probing attention, memory, and executive function including the Trail Making Test (TMT) and self-report (FACT-Cog) at baseline and post-intervention. ANCOVA, controlling for baseline, assessed overall Arm effects at post-intervention. **Results:** Of the 110 who consented to the study, 86 participants (mean age=54; 88% female; 76% breast cancer, 21% GI; 73% Stage I-III) completed baseline assessments and were randomized to one of four study arms. Ninety percent (78/86) of those completed post-intervention. Average pill compliance across all 4 groups was balanced and averaged 90.8%. Participants in the exercise and exercise + ibuprofen arms increased 2,414 and 1,073 steps respectively compared to those in placebo and ibuprofen arms increased only 464 and 412 steps respectively from pre- to post-intervention. No study-related adverse events occurred. Intent to treat ANCOVA analyses revealed a significant improvement in attention (TMT) in exercise alone compared to placebo (21.57 seconds better; p=0.003), ibuprofen alone compared to placebo (11.27 seconds better; p=0.0475), and trend for exercise + ibuprofen (7.98 seconds better; p=0.122). Those participating in both exercise arms exhibited significant improvements in the FACT-Cog Comments from Others subdomain ($p<0.05$). **Conclusions:** Exercise and low-dose ibuprofen during chemotherapy improved attention in patients with cancer receiving chemotherapy. Exercise improved self-reported cognitive functioning. These results suggest possible treatment options for ameliorating CRCI during chemotherapy. Phase III trials are needed to confirm these findings. K07CA16888; DP2CA195765. Clinical trial information: NCT01238120. Research Sponsor: U.S. National Institutes of Health.

12017 **Poster Discussion Session**

Effects of yoga, cognitive behavioral therapy, and a behavioral placebo on sleep: A nationwide multicenter phase III RCT in cancer survivors. *First Author: Po-Ju Lin, University of Rochester Medical Center, Rochester, NY*

Background: Patients commonly experience impaired sleep throughout cancer treatment and for years into survivorship. Impaired sleep may mediate other cancer-related symptoms and can lead to the inability to complete daily activities and lower quality of life. More effective non-pharmacological treatment options for impaired sleep are needed. We conducted a nationwide, multicenter, phase III randomized controlled trial (RCT) comparing the effects of yoga (Yoga for Cancer Survivors; YOCAS), cognitive behavioral therapy for insomnia (CBT-I), and a behavioral placebo on impaired sleep in cancer survivors. **Methods:** This RCT was conducted via the URCC NCORP Research Base. Participants were cancer survivors 2-60 months post-treatment with insomnia. They were randomized to 1) YOCAS (75-min session biweekly for 4 wks), 2) CBT-I (90-min session weekly for 8 wks), and 3) behavioral placebo (survivorship health education per ASCO guidelines; 75-min session biweekly for 4 wks). Sleep efficiency, sleep duration, wake after sleep onset (WASO), and sleep latency were assessed via actigraphy at baseline and post-intervention. Actigraphs were worn on the non-dominant wrist 24 hours a day for 7 days. Linear mixed models were used to assess intervention effects on sleep outcomes. **Results:** 740 survivors were enrolled (93% female, mean age 56±11 years, 73% breast cancer). Results revealed significant group differences among survivors in the 3 arms in sleep efficiency, sleep duration, and WASO (all $p<0.05$), but not in sleep latency ($p>0.05$). YOCAS and CBT-I subjects maintained sleep efficiency (mean change= -0.8% and -0.03%, respectively, all $p>0.05$) while behavioral placebo subjects significantly reduced sleep efficiency (mean change= -3.4%, $p<0.01$). When controlling for baseline, YOCAS and CBT-I subjects demonstrated better sleep efficiency compared to behavioral placebo subjects at post-intervention (all $p<0.05$). YOCAS subjects also maintained sleep duration (mean change= -3.5 minutes, $p>0.05$) while CBT-I and behavioral placebo subjects significantly reduced sleep duration (mean change= -20.3 minutes and -26.6 minutes, respectively, all $p<0.01$). When controlling for baseline, YOCAS subjects demonstrated longer sleep duration compared to CBT-I and behavioral placebo subjects at post-intervention (all $p<0.05$). There were no significant within-group changes in WASO over time in the 3 arms. When controlling for baseline, CBT-I subjects demonstrated a trend toward lower WASO compared to YOCAS (p=0.07) and behavioral placebo (p=0.05) subjects at post-intervention. **Conclusions:** Both YOCAS and CBT-I maintained sleep efficiency and/or sleep duration among cancer survivors. Oncologists should consider prescribing yoga and CBT-I for treating impaired sleep in cancer survivors. Funding: NCI UG1CA189961, R01CA181064, T32CA102618. Clinical trial information: NCT02613364. Research Sponsor: U.S. National Institutes of Health.

12018 **Poster Discussion Session**

Long-term results from a randomized blinded sham- and waitlist-controlled trial of acupuncture for joint symptoms related to aromatase inhibitors in early stage breast cancer (S1200). *First Author: Dawn L. Hershman, Columbia University Irving Medical Center, New York, NY*

Background: Musculoskeletal symptoms are the most common side effect of aromatase inhibitors (AIs) among breast cancer (BC) survivors. We previously reported that true acupuncture (TA) resulted in better pain outcomes than either sham acupuncture (SA) or wait-list controls (WC) at 6 weeks with durable effects through 24 weeks, with minimal toxicity. We now report the 52-week outcomes. **Methods:** We conducted a SWOG multicenter randomized controlled trial among postmenopausal women with early-stage BC. Patients taking an AI for ≥30 days and reporting a worst pain score of ≥3 out of 10 using the Brief Pain Inventory-Worst Pain (BPI-WP) were eligible. Subjects were randomized 2:1:1 to TA vs. SA vs. WC. Both the TA and SA protocols consisted of a 12-week intervention, with 2 sessions per week for 6 weeks, followed by 1 session per week for 6 additional weeks. At 24 weeks, all subjects remained blinded to intervention arm but were offered 10 sessions of true acupuncture. Endpoints included BPI scores, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) for hips and knees, the Modified Score for the Assessment of Chronic Rheumatoid Affections of the Hands (M-SACRAH), PROMIS Pain Inventory Short Form (PI-SF), and Functional Assessment of Cancer therapy Endocrine Symptoms (FACT-ES). **Results:** Among 226 patients registered, 110 were randomized to TA, 59 to SA and 57 to WC. Baseline characteristics were similar among the arms. At 52 weeks, follow-up assessments were available for 91 (82.7%) TA, 53 (89.8%) SA, and 47 (82.5%) WC patients. In a linear regression adjusting for the baseline score and stratification factors, 52-week mean BPI-WP scores were 1.08 points lower (correlating with less pain) in the TA compared to SA arm (95% CI: 0.24-1.91, p = .01), and were 0.99 points lower in the TA compared to WC arm (95% CI: 0.12-1.86, p = .03). The proportion of patients experiencing a clinically meaningful (>2) reduction (i.e. improvement) in BPI-WP was 64% for TA compared to 45% on SA and 53% on WC. Patients randomized to TA had reduced BPI pain interference at 52 weeks compared to SA (adjusted difference = 0.58, 95% CI: 0.00-1.16, p = .05) but not compared to WC (adjusted difference = 0.33, 95% CI: -0.28-0.93, p = .29). Also, at 52 weeks, patients randomized to TA had improved PROMIS PI-SF T-scores compared to SA (adjusted difference = 2.35, 95% CI: 0.07-4.63, p = .04) but not compared to WC (adjusted difference = 1.28, 95% CI: -1.09-3.66, p = .29). No statistically significant differences were observed in other measures. **Conclusions:** Women with breast cancer receiving AI therapy and treated with 12 weeks of TA for joint symptoms had reduced levels of worst pain compared to control patients, an effect that was durable through one year despite completion of protocol acupuncture at 12 weeks, and the offering of acupuncture to all participants at 24 weeks. Clinical trial information: NCT01535066. Research Sponsor: U.S. National Institutes of Health.

12019 **Poster Discussion Session**

Complementary and alternative medicine (CAM) use in cancer patients of immigration background. *First Author: Alex Wu, Maimonides Cancer Center, Brooklyn, NY*

Background: Cancer patients are more likely to use complementary and alternative medicine (CAM) than non-cancer patients for immune enhancement and symptom relief. Cancer patients with immigration background may seek out CAM use more readily due to the influence from their cultural background. **Methods:** We carried out a prospective questionnaire study surveying the use of 21 CAM types to cancer patients between 10/23/2015 and 10/31/2020, to evaluate the association of CAM use with patients' age, sex, cancer types, stages, race/ethnicity, birthplace, immigration duration, first language, marital status, levels of poverty, education and anxiety. **Results:** 658 patients were included in this analysis. The median age was 62 years old. The prevalence of CAM use was 66.11%. CAM use was higher in females (71.98%) than the males (54.34%) ($p = 1.13 \times 10^{-5}$), and higher in patients ≥ 38 years old (67.09%) than < 38 years old (46.88%) (p = 0.0215). Patients of African American descent (both US born and foreign born) (n = 198) had statistically higher CAM use (72.73%) than the Caucasians and Others (including Middle-Eastern, Multi-Racial and Others) (n = 266) (63.53%) (p = 0.0371). There was no difference of CAM use between the US born patients (n = 301, CAM use 68.77%) and the immigrants (n = 347, CAM use 63.98%) as a whole; however, Asian born immigrants (n = 106) had statistically less CAM use (53.77%) than the US born and other non-Latin American born (n = 397, CAM use 66.50%) (p = 0.0161), while the Latin-American born had a trend towards higher CAM use (74.83%, P = 0.0608). The number of years living in the US by the immigrants did not have an association with CAM use. Among psychosocial economic factors, married patients had a lower CAM use (61.23%) than the unmarried group (defined as divorced, separated, widowed, or single status, 70.85%) (p = 0.0102). The levels of education, poverty and anxiety did not show a statistical difference in relation to CAM use. Earlier stages of disease had numerically higher CAM use than stage 4 patients, and patients with breast and GYN cancers had higher CAM use (72.30%, p = 0.00252), consistent with the data on the higher CAM use in females. Prayer and spirituality and Dietary medicine were the 2 most common CAM types used (25.91% and 16.12%, respectively). African Americans of the combined US and Non-US origin showed the highest rate of using Prayer and spirituality (84.72%), versus Hispanics (71.19%), Caucasians (53.85%), and Asians (40.32%). Chiropractic therapy was exclusively used by Caucasian CAM users (9.38%). **Conclusions:** Among cancer patients of multi-ethnic groups with immigration background served in a community hospital in Brooklyn, New York, CAM use appeared to be higher in the African American patients, and lower in the patients born in Eastern Asia, as compared to the US born, or to Caucasians. Cultural roots appeared to be a strong influencing factor among all the medical and socioeconomic factors. Research Sponsor: None.

12020 **Poster Discussion Session**

The comparative effectiveness of direct oral anti-coagulants and low molecular weight heparins for prevention of recurrent venous thromboembolism in cancer: The CANVAS pragmatic randomized trial. *First Author: Deborah Schrag, Dana-Farber Cancer Institute, Boston, MA*

Background: Previous randomized trials in cancer patients suggest that DOACs are non-inferior to LMWH for preventing recurrent VTE but have higher risk of bleeding. However, the balance of benefits and burdens remains uncertain. Objective: The CANVAS pragmatic trial compared recurrent VTE, bleeding and death in cancer patients following an initial VTE treated with either DOAC or LMWH therapy. **Methods:** CANVAS was an unblinded hybrid comparative effectiveness non-inferiority trial, with randomized and preference cohorts. Between 12/16 and 4/20, 671 participants were randomized and followed for 6-months. Between 12/16 and 12/17, 140 participants declined randomization, chose their preferred anticoagulant and were followed for 6-months. The preference cohort was closed when predetermined stopping criteria were met. Final follow-up was 11/30/20. Randomized patients were assigned 1:1 to receive either a DOAC or a LMWH. If assigned to LMWH, transitions to warfarin were allowed. Physicians and patients could choose among any DOAC or LMWH. Doses were suggested based on FDA-approved labeling but not mandated. Patients from 67 practices in the US with any invasive solid tumor, lymphoma, multiple myeloma or CLL and a diagnosis of symptomatic or radiographically detected VTE within 30 days of enrollment were eligible. The 1° analysis was conducted in the randomized modified-into to treat popululation, (all subjects who received study drug). The 1° outcome was recurrent VTE. The aim was to establish noninferiority of anticoagulation with a DOAC as defined by the upper limit of the 2-sided 90% CI for the difference in the event rate at 6 months of $< 3\%$. Secondary outcomes included death and bleeding. Hypothesis testing included only the randomized cohort but propensity score adjusted results for the preference and combined cohorts are also shown. **Results:** The non-inferiority criteria for recurrent VTE was met. **Conclusions:** Among adult cancer patients with VTE, the use of a DOAC compared with a LMWH resulted in a noninferior risk of recurrent VTE with no differences in rates of bleeding or death in randomized patients. Clinical trial information: NCT02744092. Research Sponsor: PCORI CER-1503-29805.

CANVAS event rate at 6 months.

Cohort	Endpoint	DOAC	LMWH	Difference (0.90 CI[2])
Randomized Cohort[1]		(N = 330)	(N = 308)	
	Recurrent VTE	6.1%	8.8%	-2.7% (-6.1%, 0.7%)
	Major Bleeding[3]	4.6%	4.6%	0.0% (-2.7%, 2.7%)
	Mortality	21.5%	18.4%	3.1% (-2.1%, 8.3%)
Preference Cohort[4]		(N = 107)	(N = 30)	
	Recurrent VTE	7.5%	4.1%	3.3% (-3.1%, 9.7%)
	Major Bleeding[3]	11.5%	3.0%	8.5% (1.2%, 15.8%)
	Mortality	16.3%	23.8%	-7.5% (-18.8%, 3.8%)
Combined Cohort		(N = 437)	(N = 338)	
	Recurrent VTE	6.4%	7.8%	-1.3% (-4.4%, 1.7%)
	Major Bleeding[3]	5.4%	4.4%	1.0% (-1.5%, 3.6%)
	Mortality	20.5%	19.3%	1.2% (-3.5%, 6.0%)

1. analysis for hypothesis tesing 2. CI: Confidence interval 3. CTCAE grade 3-5 4. Adjusted by propensity score weighting.

12021 **Poster Discussion Session**

Incidence of venous thromboembolism in advanced lung cancer and efficacy and safety of direct oral anticoagulant: A multicenter, prospective, observational study (Rising-VTE/NEJ037 Study). *First Author: Yukari Tsubata, Department of Internal Medicine, Division of Medical Oncology & Respiratory Medicine, Shimane University Faculty of Medicine, Izumo, Japan*

Background: Venous thromboembolism (VTE) is a well-known kind of cancer-associated thrombosis and a common complication of malignancy. However, little is known about the incidence of VTE and the effectiveness of direct oral anticoagulants (DOACs) associated with lung cancer chemotherapy. **Methods:** The Rising-VTE/NEJ037 study was a multicenter, prospective, observational study with 40 participating Japanese institutions. A total of 1,021 patients diagnosed with lung cancer that was unsuitable for radical resection or radiation were enrolled and followed up for two years. The diagnosis of VTE was confirmed through a central review by two radiologists. Patients with VTE at the time of lung cancer diagnosis started treatment with edoxaban. The primary endpoint of this trial was the rate of newly diagnosed VTE after enrollment or the recurrence rate 6 months after the start of treatment with edoxaban. **Results:** Of the 1,021 enrolled patients, data were available for 1,008 patients. The median age was 70 years (range: 30-94 years), and 70.8% were males. Eighty-six percent of patients had non-small cell lung cancer, and 13.6% had small cell lung cancer. Histological types included adenocarcinoma (N = 641, 63.6%), squamous cell carcinoma (N = 187, 18.6%), and others (N = 42, 4.2%). Sixty-two patients (6.2%) had VTE at the time of lung cancer diagnosis, and 42 patients (4.2%) developed VTE during two years follow-up, making a total of 104 patients (10.3%). No cases of VTE recurrence were found 6 months after the start of treatment with edoxaban. Major and minor bleeding occurred in 95 patients (9.4%) and increased to 23% in the edoxaban treatment group. The two-year survival probability was 0.43 in the non-VTE group and 0.48 in the VTE with edoxaban treatment group, showing no difference. **Conclusions:** This study shows a high cumulative incidence of VTE, suggesting that attention should be paid to VTE during treatment for lung cancer. Treatment with edoxaban was highly effective in preventing recurrence of VTE, and there was no difference in survival with or without VTE, but treatment should be considered more carefully because of the high bleeding rate associated with DOAC. Clinical trial information: jRCTs061180025. Research Sponsor: Daiichi Sankyo Co., Ltd.

12022 **Poster Discussion Session**

Assessing the risk of severe post-treatment (tx) cancer-related fatigue (CRF) among breast cancer survivors (BCS) in the CANcer TOxicity (CANTO) cohort. *First Author: Antonio Di Meglio, Gustave Roussy, Villejuif, France*

Background: CRF is among the most common and troublesome symptoms experienced by BCS. While preventing severe post-tx CRF is a major survivorship need, limited tools exist to predict this risk. We aimed to describe the long-term prevalence rates and to identify BCS that are more likely to develop severe CRF. **Methods:** CANTO is a multicenter, prospective clinical study of stage I-III BCS (NCT01993498). Longitudinal data were collected at diagnosis (dx), 0.5 (T1), 1 (T2) and 3 (T3) years post-tx. The primary outcome of interest was severe post-tx global CRF (score $\geq$ 40/100, EORTC QLQ-C30). Secondary outcomes were physical, emotional and cognitive dimensions of CRF (QLQ-FA12). Multivariable logistic regression models retained associations with severe CRF by bootstrapped Augmented Backwards Elimination, validated using 10-fold internal cross-validation and overoptimism-corrected AUC. **Results:** Among 6619 BCS, mean age at dx was 56.5 years (SD 11.5), mean BMI was 25.9 Kg/m^2 (SD 5.4), 53.3% and 80.8% received chemotherapy (CT) and hormonotherapy (HT), respectively. Prevalence rates of severe global CRF were 25.0% (dx), 35.6% (T1), 34.0% (T2) and 31.6% (T3). Severe post-tx global CRF was consistently associated with higher BMI, worse insomnia and pain, and severe pre-tx CRF. Receipt of CT increased odds of severe CRF at T1, whereas associations of HT with CRF emerged at T2 and T3 (Table). The estimated risk of severe CRF at T3 was 14% for a BCS with BMI 23.0 Kg/m^2 and no concomitant symptoms at dx, whereas it was 82% for a BCS with BMI 32.0 Kg/m^2, severe insomnia, pain and pre-tx CRF, receiving HT. Anxiety and depression at dx were consistently retained in models of severe post-tx emotional and cognitive CRF (all $p < .05$). **Conclusions:** Over 1/3 BCS endured persistent, severe global CRF, particularly those that were medically more fragile and reported heavier pre-tx symptom burden. A transient impact of CT on CRF was evident on the short aftermath of tx, whereas exposure to HT seemed to affect CRF on the longer run. Consistent factors flag BCS whose risk of severe CRF is high and who should be upfront targeted and aggressively helped. Dimension-specific risk factors can guide prevention of distinct CRF symptoms. Clinical trial information: NCT01993498. Research Sponsor: Career Catalyst Research grant from Susan G. Komen to Ines Vaz-Luis (CCR17483507), Conquer Cancer Foundation of the American Society of Clinical Oncology.

Models of severe global CRF.

	T1	T2	T3
	OR* (95% CI)	OR* (95% CI)	OR* (95% CI)
BMI, additional 5 units	1.22 (1.16-1.34)	1.16 (1.05-1.22)	1.10 (1.05-1.22)
Insomnia**, additional 10 points	1.05 (1.03-1.07)	1.04 (1.02-1.07)	1.04 (1.01-1.07)
Pain**, additional 10 points	1.10 (1.07-1.15)	1.15 (1.11-1.19)	1.17 (1.10-1.21)
Severe pre-tx CRF, vs no	3.00 (2.53-3.57)	3.31 (2.75-4.00)	2.18 (1.74-2.72)
CT, vs no	1.27 (1.10-1.47)	NR	NR
HT, vs no	NR	1.30 (1.06-1.59)	1.43 (1.13-1.81)
Corrected AUC	0.74 (0.72-0.75)	0.75 (0.73-0.76)	0.71 (0.69-0.72)

OR= Odds Ratio; CI= Confidence Interval; NR= Not Retained; *Adjusted by age, menopause, smoke, socioeconomic, psychological, tumor and tx; **QLQ-C30.

12023 **Poster Discussion Session**

Health concerns in long-term survivors with ovarian cancer: Results of Expression VI–Carolin meets HANNA–Holistic Analysis of Long-term survival with Ovarian Cancer—The international NOGGO, ENGOT and GCIG survey. *First Author: Hannah Woopen, NOGGO and Department of Gynecology, European Competence Center for Ovarian Cancer, Charité, University Medicine of Berlin, Campus Virchow Klinikum, Berlin, Germany*

Background: So-called long-term survivors (LTS) may be cured from cancer but still experience a wide range of long-term side effects. Aim was to analyze the main concerns in long-term survival to improve follow-up care. **Methods:** Within the study Carolin meets HANNA (www.carolinmeetshanna.com) long-term survivors with ovarian cancer (LTS) were recruited since 11/2016. Long-term survival was defined as an ovarian cancer diagnosis more than five years ago. **Results:** Until 02/2021 1,044 long-term survivors with ovarian cancer could be recruited. Median survival time at recruitment was 11 years (range 5-43 years). More than half had been diagnosed with advanced stage ovarian cancer (58.6% FIGO III/IV). Almost half have developed recurrent disease (43.4%). 26.0% were under cancer treatment at recruitment. Health status was rated very good or good by 52.0% while 20.3% report a bad or very bad health status. Almost half of the LTS have current concerns/long-term side effects (46.1%). Main concerns are fatigue (23.9%), pain (21.6%), polyneuropathy (16.9%), gastrointestinal symptoms (16.6%) and memory problems (15.5%). 42.8% still regard themselves as cancer patients. Health status and distress did not differ between LTS 5-10 years after diagnosis and $>$ 10 years after diagnosis ($p = 0.59$ and $p = 0.0843$ respectively). Patients with a history of recurrence and those under current treatment had a worse health status and more health concerns. LTS without recurrence reported fatigue in 18.4%, pain in 19.2%, polyneuropathy in 13.1%, gastrointestinal problems in 13.4% and memory problems in 14.4%. Fatigue, polyneuropathy, nausea and concentration problems improve with the time of survival. However, fatigue is still present in 21.1% after ten years survival time. There was no significant difference in pain between 5-10 (20.1%) and $>$ 10 years (22.0%) survival time. In this cohort 94.2% receive regular follow-up care including CA125 testing in 77.0%, clinical examination in 54.3%, transvaginal ultrasound in 55.1%, abdominal ultrasound in 43.9%, mammogram in 50.5% and further radiological examinations such as CT scans in 53.4%. **Conclusions:** Follow-up care in ovarian cancer is usually delivered within the first five years after diagnosis. However, our analyses show the high frequency of health concerns in LTS despite the high frequency of follow-up care in this cohort. Therefore, specialized survivorship care should be offered beyond the typical five years of follow-up care with a focus on long-term side effects. Research Sponsor: German Ovarian Cancer Foundation, Astra Zeneca GmbH, Janssen-Cilag GmbH, Pfizer Pharma GmbH, Tesaro.

12024 **Poster Discussion Session**

Simplifying survivorship care planning: A randomized controlled trial comparing three care plan delivery approaches. *First Author: Claire Frances Snyder, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Survivorship care plans (plans) have been promoted to smooth the transition from active cancer treatment to survivorship. However, the time and resources involved in plan completion and delivery have been barriers to implementation. This randomized controlled trial aimed to identify the simplest, most effective approach for implementing survivorship care planning. **Methods:** Stage 1-3 breast, colorectal, and prostate cancer patients aged 21+ who were completing acute treatment were recruited from one urban-academic and one rural-community cancer center. Participants were randomized, stratified by recruitment site and cancer type, 1:1:1 to (a) mailed plan (mail), (b) plan delivered during one-time transition visit (one-visit), or (c) plan delivered during transition visit plus a 6-month follow-up visit (two-visit). Health service use (visits, tests/procedures, non-oral medications) was collected from participants and medical records for 18 months and compared to the plan recommendations. Logistic regression, adjusting for cancer type and recruitment site, was used to evaluate the primary outcome of adherence to recommendations for all health service use categories by intervention arm. Descriptive analyses compared care receipt for each health service use category separately (i.e., visits, tests/procedures, non-oral medications). **Results:** Of 378 participants randomized (n = 126 mail; n = 125 one-visit; n = 127 two-visit), 316 (84%) were analyzable for the primary outcome (n = 107 mail; n = 105 one-visit; n = 104 two-visit): 164 (52%) recruited from the urban-academic and 152 (48%) from the rural-community site; 137 (43%) breast, 112 (35%) prostate, 67 (21%) colorectal cancer; mean age 62 years. For the primary outcome, there was no difference across arms in the proportion of participants who received all plan-recommended care: 45.2% mail, 50.5% one-visit, 42.7% two-visit (p = 0.60). We did not find significant interactions by recruitment site or cancer type. There were also no differences in receipt of recommended care by category of health service use. The proportion of participants who had the recommended number of visits was 53.4% mail, 54.8% one-visit, 53.7% two-visit (p = 0.99). The proportion undergoing recommended tests/procedures was 78.8% mail, 77.2% one-visit, 73.0% two-visit (p = 0.62). The proportion receiving recommended non-oral medications was 66.7% mail, 75.0% one-visit, 73.7% two-visit (p = 0.87). **Conclusions:** This study found no significant difference in receipt of recommended follow-up care by plan delivery approach. Across study arms, survivors were more likely to receive recommended tests/procedures and non-oral medications but less likely to have the recommended number of visits. Feasibility and other factors may determine the best survivorship care planning approach. Clinical trial information: NCT03035773. Research Sponsor: Patient-Centered Outcomes Research Institute.

12025 **Poster Discussion Session**

Racial disparities in follow-up care of early-stage lung cancer survivors. *First Author: Jyoti Malhotra, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ*

Background: Follow-up care and surveillance in lung cancer survivors is essential formanagement of treatment- and disease-related symptoms as well as for the early detection of cancer recurrence. To investigate if race impacts receipt of follow-up care in lung cancer survivors, we conducted a cross-sectional study in lung cancer survivors recruited through the New Jersey State Cancer Registry (NJSCR). **Methods:** Between May 2019 and December 2019, survivors of early-stage NSCLC were identified and recruited from the NJSCR. Participants were eligible if they had surgery for stage I or II NSCLC between 2014 and 2017 and, completed all treatment at least one year prior to enrollment. Eligible participants were asked to complete a paper survey questionnaire and medical record release form sent to them by mail. The survey had questions about demographics, smoking, cancer history and treatment, quality of life, follow-up care, barriers to care and informational needs. Study measures were compared between the groups using t-test or chi-square test as applicable. **Results:** Of the 482 survivors contacted, 23% (n = 114) mailed back the survey questionnaire. Of the 112 survivors who returned a completed survey; 78 (70%) were non-Hispanic (NH) Whites and 34 (30%) were NH Blacks. Mean age was 67 years, 61% were female, 92% had cancer in remission. 82% of participants reported receiving a surveillance scan (CT or PET) within one year of completing the study survey. More NH White survivors received a scan within a year compared to NH Black survivors (89% vs 64%; p = 0.006). Also, 88% of survivors reported that they were informed of the need for follow-up care by their provider with more NH White survivors reporting receiving this information (94%) compared to NH Blacks (71%; p = 0.002). About 57% of the survivors reported receiving a written treatment summary and 92% reported being seen by a physician within the past year; no racial differences in these measures were noted.There was also no racial difference in receipt of age-appropriate cancer screening; 66% and 80% reported receiving regular colon and breast cancer screening, respectively. A significantly higher percentage of NH Blacks reported currently smoking compared to NH Whites (16% vs 12%). The most significant barriers to care for both populations were concern for out-of-pocket costs (26% NH Whites, 19% NH Blacks), non-coverage of test (14% NH Whites, 10% NH Blacks) and lack of insurance (8% NH Whites, 16% NH Blacks). **Conclusions:** Significant racial disparity was identified between NH Blacks and NH Whites in receipt of surveillance scans, guidance about follow-up care and smoking cessation. The most significant barriers to follow-up care was lack of insurance in NH Blacks and financial concerns about cost and coverage of tests in NH Whites. Future interventions to increase survivorship care should target these specific needs in survivor populations. Research Sponsor: American Cancer Society.

12026 **Poster Discussion Session**

Real-world outcomes in older adults treated with immunotherapy: A United Kingdom multicenter series of 2,049 patients. *First Author: Anna Claire Olsson-Brown, Clatterbridge Cancer Centre, Liverpool, United Kingdom*

Background: Immune checkpoint inhibitor (ICI) therapy is now commonly used in a range of tumours and settings. Most data relating to outcomes and rates of immune-related adverse events (irAE) is derived from clinical trial or registry populations and small case series. Limited data exist for patients aged > 75 years. Here we present a multi-centre, real-world analysis of the outcomes and incidence of irAEs in older adults managed within a single comprehensive public health service. We also compare these outcomes to younger patients in the same cohort. **Methods:** A retrospective analysis of 2049 patients treated with ICIs was undertaken across 12 centres. All patients were managed within the UK National Health Service outside of a trial setting between June 2016 and September 2018. Patients received either ICI monotherapy (MT) or duel combination ICI therapy (CT) for malignant melanoma (MM), non-small cell lung cancer (NSCLC) or renal cell cancer (RCC). Data were collected using a standardised, collection tool. IrAEs ≥ grade 2 or all-grade endocrinopathies were recorded as per the Common Terminology Criteria for Adverse Events (V5) (CTCAE). Statistical analyses were performed using T-tests, Mann-Whitney and Chi-squared. Kaplan-Meier analysis and log-rank test were used for overall survival (OS) analysis. **Results:** 409 (20%) of patients were aged > 75 years(a), 1413 (69%) aged 50-75(b) and 227 (11.1%) aged < 50(c). There was no difference in sex, ethnicity or PD-L1 status (in the NSCLC cohort) between groups. Older patients were less likely to receive combination therapy (3%(a) v 13%(b) v 34%(c), p < 0.001). There was no difference in median OS across age groups in the cohort as a whole (p = 0.822) or for the individual tumour groups when treated with single agent ICI. Across the total cohort patients aged > 75 had no increased risk of any irAE (35%(a) v 33%(b) v 41%(c),p = 0.074). However there was an increase in irAEs in older patients treated with MT (36%(a) v 26(b) v 25%(c), p = 0.011) However there was no difference in the > 75s with regard to severe (G3/4) toxicity, toxicity type, admission or discontinuation due to toxicity in the aPD-1 group. In the overall cohort younger patients were more likely to develop irAEs and be admitted. **Conclusions:** Patients aged > 75 years treated with anti-PD1 therapy in the standard of care setting derive similar survival benefit to younger patients. There was no increase in ≥G3 toxicity. Our data support the safety of single agent aPD-1 ICI therapy in older adults and provide reassurance relating to the impact of toxicity. Research Sponsor: None.

	< 50 years	50-75 years	> 75 years	p-value
Any G3+ toxicity	9 (26%)	115 (37%)	36 (27%)	0.097
Median time to toxicity (days, range)	68 (33, 142)	83 (40, 151)	78.0 (34, 146)	0.52
Admission rate	16(43%)	130 (40%)	41 (31%)	0.12
Median length of stay (days)	5.0 (3.0, 10.0)	7.0 (4.0, 15.0)	7.0 (5.0, 15.0)	0.30
Discontinuation due to toxicity	10 (7%)	118 (10%)	41 (11%)	0.49

12027 **Poster Discussion Session**

Immunotherapy toxicity in patients over 65 years. *First Author: Miriam Mendez, Hospital Puerta de Hierro, Majadahonda, Spain*

Background: Cancer patients increasingly present an advanced age at diagnosis; 50% of the new cases are over 65 years old, being underrepresented in clinical trials. The safety of immunotherapy has not been adequately evaluated in the subgroup of elderly patient. In this population, with more comorbidities, adverse events may be less well tolerated and have more serious consequences. **Methods:** A retrospective observational study was developed, including all patients treated with immunotherapy at our center between January 2015 to February 2020. Of the total (279 patients), the analysis was performed with the 105 patients ≥65 years of age who had received at least one cycle (in routine clinical practice or within an unblinded clinical trial). All clinical and radiological data of the patients were collected. **Results:** From the total, the majority had a lung carcinoma or melanoma, treated with nivolumab or pembrolizumab either in first or second line. 63% had died at the time of the analysis. The frequency of toxicities: digestive (15%), pneumonitis (12%) and endocrine (9%). We divided the population into 65-75 years (76 patients) or > 75 years (29 patients), analyzing the frequency of toxicity and deaths secondary to it. Those > 75 years had more digestive toxicity (25% vs 11%), but less pneumonitis (3% vs 15%). There were 7 deaths (6%) related to treatment: 2 patients with ipilimumab-nivolumab (28%), 2 nivolumab (28%), 2 pembrolizumab (28%), and 1 ipilimumab (16%). 5 patients were > 75 years old (median 78 years) presenting a higher mortality rate in relation to toxicity (4% vs 20%, p 0.02) and a worse median survival (29 vs 23 months). The fatal toxicities were: 3 neurological (2 meningoencephalitis and 1 acute diffuse axonal denervation), 2 hepatic, 1 hemophagocytic syndrome and 1 myocarditis. **Conclusions:** The most frequent toxicity was digestive, but those that led to death were neurological, hepatic, hematological and cardiac. In our series, neurological and cardiac adverse events accounted for 57% of immunotherapy deaths in older patients. Our data warn that patients over 75 years have a higher risk of death from immune-mediated events. In addition, these would be mainly neurological and cardiac, which represents a diagnostic and treatment challenge for oncologists. Research Sponsor: None.

	N (%)
Tumor Histology	
Lung carcinoma	70 (67%)
Melanoma	14 (13%)
Bladder carcinoma	13 (12%)
Hepatocellular carcinoma	3 (3%)
Kidney carcinoma	2 (2%)
Head and neck carcinoma	1 (1%)
Colorectal carcinoma	1 (1%)
Gastric carcinoma	1 (1%)
Treatment	
Nivolumab	45 (43%)
Pembrolizumab	24 (23%)
Atezolizumab	12 (11%)
Chemotherapy +Nivolumab	11 (10%)
Nivolumab + Ipilimumab	10 (9%)
Ipilimumab	3 (3%)
Situation	
Dead	66 (63%)
Alive without immunotherapy	28 (27%)
Alive with immunotherapy	10 (9%)
Toxicities	
Digestive	15 (15%)
Pneumonitis	12 (12%)
Endocrine	9 (9%)
Cutaneous	8 (8%)
Urological	5 (5%)
Neurological	3 (3%)
Rheumatological	2 (2%)
Cardiac	1 (1%)
Haematological	1 (1%)

12028 **Poster Discussion Session**

Can patients with advanced malignancy and poor performance status benefit from nivolumab plus ipilimumab as a palliative treatment? *First Author: Omar Khaled Abughanimeh, University of Nebraska Medical Center, Omaha, NE*

Background: Performance status (e.g. Eastern Cooperative Oncology Group [ECOG] score) is a predictive tool used to determine whether a patient may benefit from cytotoxic chemotherapy. The toxicity profile of immunotherapy is different, and less is known about whether performance status (PS) is similarly associated with toxicity and benefit. Nonetheless, most clinical trials for immune checkpoint inhibitors have excluded patients with poor PS. Emerging data by our group and others has linked poor PS with lack of response and decreased survival with anti-PD-1/L1 agents, but whether combination therapy abrogates the poor outcomes of PD1 only therapy is unknown. **Methods:** We conducted a retrospective cohort study of patients with metastatic cancer who received ipilimumab plus nivolumab at our institution between January 2014-December 2020. We compared outcomes between those with good PS (Group A, ECOG PS 0-1) and poor PS (Group B, ECOG PS $\geq$ 2). Our primary outcomes were overall survival (OS) and incidence of grade 3-4 immune-related adverse events (irAEs). Other outcomes included objective response rates and need for hospitalization. We utilized the Kaplan-Meyer method for time to survival analysis and exact Pearson Chi-squared testing for response, toxicity, and hospitalization analysis. **Results:** A total of 129 patients were identified with a mean age of 59.9 years. Among them were 73 males (57%) and 56 females (43%). Malignant melanoma was the most common malignancy (39%) followed by renal cell carcinoma (27%), small cell lung cancers (10%), non-small cell lung cancers (9%), and the rest with other histologies. 113 patients (87.6%) were in group A and 16 (12.4%) in group B. Across all tumor types, patients in Group B had significantly worse OS compared to group A (HR 0.24 [0.13-0.48], P = < 0.0001). Group B similarly had higher rates of hospitalization compared to group A (94% vs 56%, P = 0.0048). Interestingly, irAEs were not driving these hospitalizations, with a trend toward lower rates of irAEs in the poor PS group (19% vs 46% in Group A, P = 0.057). The overall response rate in group B was numerically lower (6% vs 26% in group A, p = 0.1). **Conclusions:** Our study showed that using ipilimumab plus nivolumab in patients with poor PS was associated with significantly poorer OS and higher rates of hospitalizations. irAEs were not increased in the poor PS group, suggesting a lack of treatment efficacy seemed to driving these poor outcomes. Extrapolation of clinical trial data for ipilimumab-nivolumab to a broader population including those with poor PS should be done with caution. Unfortunately, our data showed that most patients with poor PS were not adequately palliated with ipilimumab-nivolumab. Research Sponsor: None.

12029 **Poster Session**

The impact of advance care planning on hope among patients with advanced cancer. *First Author: Michael Cohen, UPMC Cancer Center - Magee-Womens Hospital, Pittsburgh, PA*

Background: Providers often cite a fear of giving up hope as a reason they defer advance care planning (ACP) among patients with advanced cancer. We sought to determine whether engagement in ACP impacts patient's hope. **Methods:** This is a secondary analysis of a randomized controlled trial of primary palliative care in advanced cancer. Patients who had not completed ACP at baseline were included in the analysis. ACP was assessed in the forms of an end of life conversation with one's oncologist (EOL conversation) and completion of a living will/advance directive (AD). Measurements were obtained at baseline and 3 months. Hope was measured using the Herth Hope Index (HHI, range 12-48, higher scores indicate higher hope). ACP was measured with patient responses to a validated ACP questionnaire that queried (1) if they had had an EOL conversation with their provider and (2) if they had completed a living will or advance directive. Multivariate regression was performed to control for baseline HHI score, study randomization and age, religious importance, education, marital status, socioeconomic status, time since cancer diagnosis, pain/symptom burden (ESAS), and anxiety/depression score (HADS)—all variables known to be associated with ACP and/or hope. **Results:** A total of 672 patients with advanced cancer were enrolled in the overall study. The mean age was 69±10, and the most common cancer types were lung (36%), GI (20%) and breast/GYN (16%). In this group, 378 (56%) had not had an EOL conversation at baseline, of whom 29% (111/378) reported having an EOL conversation by 3 months. Hope was not different between patients who had or did not have an EOL conversation over the study period (ΔHHI 0.20 ± 5.32 vs -0.53 ± 3.80, p=0.136). After multivariable adjustment, hope was significantly increased in patients who had engaged in an EOL conversation (adjusted mean difference in ΔHHI 0.95 (95%CI 0.08-1.82), p=0.032). Similarly, of 216 (32%) patients without an AD at baseline, 31% (67/216) patients had subsequently completed one. Unadjusted hope was not different between those who had and had not completed an AD (ΔHHI 0.20 ± 3.89 vs -0.91 ± 4.50, p=0.085). After adjustment, hope was significantly higher in those who completed an AD (adjusted mean difference in ΔHHI 1.31 (95%CI 0.13-2.49), p=0.030), (Table). **Conclusions:** Our results demonstrate that hope is not decreased after engagement in ACP and may, in fact, be increased. These findings may provide reassurance to providers who are apprehensive about having these important and difficult conversations. Unadjusted and adjusted change in hope for those patients who had and had not had completed an EOL conversation or AD. Research Sponsor: U.S. National Institutes of Health.

EOL CONVERSATION	Mean Difference	95% CI	P-Value (Difference)
Unadjusted	-0.21	(-1.36, 0.92)	0.707
Adjusted	0.95	(0.08, 1.82)	0.032
ADVANCE DIRECTIVE			
Unadjusted	1.14	(-0.35, 2.63)	0.134
Adjusted	1.31	(0.13, 2.49)	0.030

12030 **Poster Session**

Predicting dying from lung cancer: Urine metabolites predict the last weeks and days of life. *First Author: Seamus Coyle, Waterford Regional Hospital, Waterford, Ireland*

Background: Recognising dying is difficult. We believe there is a predictable biological process to dying and previously demonstrated that urinary volatile organic compounds change in the last weeks and days of life of patients with lung cancer. We further analysed our urine samples using a different metabolomic platform, Liquid Chromatography QTOF Mass Spectrometry (LC-QTOF-MS). **Methods:** We prospectively collected urine samples from people with lung cancer many of whom were in the last 4 weeks of life. The samples were analysed using a LC-QTOF-MS. Volcano plots identified metabolites that changed 2 fold for different time periods (0-28 days, 0-14 days, 0-7days, 0-5 days and 0-3 days). All metabolites were also grouped into weeks. A One-way ANOVA between the groups identified metabolites that changed significantly. Cox regression with Least Absolute Shrinkage and Selection Operator (LASSO) logistic regression was used to analyse the data and create a statistical model. **Results:** 234 urine samples from 112 patients were analysed by LC-QTOF-MS. 90 metabolites were identified that increase or decrease in the last weeks or days. Pathway Analysis using MetaboAnalyst demonstrated a number of biochemical pathways affected during different time intervals; 0-2 weeks and 0-3 days before death. Cox LASSO regression analysis was performed for the last 28 days. A model using 21 metabolites, prognosticates for each day in the last 28 days with high AUC values (88-90%). Patients can be categorized into high, medium and low risk of death. A Kaplan-Meier survival analysis demonstrated the groups were well separated. **Conclusions:** The results confirm urine metabolites predict when people with lung cancer are in the last weeks and days of life. Our model, using 21 metabolites, prognosticates for each of the last 28 days of life and is approximately 88% -90% accurate. This is the only model able to prognosticate for the last week or days of life. Research Sponsor: Wellcome Trust UK, North West Cancer Research UK.

12031 **Poster Session**

Outcomes among patients with cancer previously identified as being at risk for 30-day mortality using augmented intelligence. *First Author: Ajeet Gajra, Cardinal Health, Dublin, OH*

Background: An augmented intelligence (AI) tool using a machine learning algorithm was developed and validated to generate insights into risk for short-term mortality among patients with cancer. The algorithm, which scores patients every week as being at low, medium or high risk for death within 30 days, allowing providers to potentially intervene and modify care of those at medium to high risk based on established practice pathways. Deployment of the algorithm increased palliative care referrals in a large community hematology/oncology practice in the United States (Gajra et al, JCO 2020). The objective of this retrospective analysis was to evaluate the differences in survival and healthcare utilization (HCU) outcomes of patients previously scored as medium or high risk by the AI tool. **Methods:** Between 6/2018 – 10/2019, the AI tool scored patients on a weekly basis at the hematology/oncology practice. In 9/2020, a chart review was conducted for the 886 patients who had been identified by the algorithm as being at medium or high risk for 30-day mortality during the index period, to determine outcomes (including death, emergency department [ED] visits, and hospital admissions). Data are presented using descriptive statistics. **Results:** Of the 886 at-risk patients, 450 (50.8%) were deceased at the time of follow-up. Of these, 244 (54.2%) died within the first 180 days of scoring as at-risk, with median time to death 68 days (IQR 99). Among the 255 patients scored as high risk, 171 (67.1%) had died, vs. 279 (44.2%) of the 631 patients who were scored as medium risk ($p < 0.001$). Of the 601 patients who were scored more than once during the index period as medium or high risk, 342 (56.9%) had died, vs. 108 (37.9%) of the 285 who were scored as at risk only once ($p < 0.001$). A total of 363 patients (43.1%) had at least 1 ED visit, and 346 patients (41.1%) had at least 1 hospital admission. There was no difference in the proportion of patients scored as high risk compared with those scored as medium risk in ED visits (104 of 237 [43.9%] vs. 259 of 605 [42.8%], p = 0.778) or hospital admissions (100 of 237 [42.2%] vs. 246 of 605 [40.7%], p = 0.684, respectively). Compared with patients scored as medium or high risk only once during the index period, patients who were scored as at-risk more than once had more ED visits (282 of 593 [47.6%] vs. 81 of 249 [32.5%], $p < 0.001$) and hospital admissions (269 of 593 [45.4%] vs. 77 of 249 [30.9%], $p < 0.001$). **Conclusions:** This follow-up study found that half of the patients identified as at-risk for short-term mortality during the index period were deceased, with greater likelihood associated with high risk score and being scored more than once. Over 40% had visited an ED or were admitted to hospital. These findings have important implications for the use of the algorithm to guide treatment discussions, prevent acute HCU and to plan ahead for end of life care in patients with cancer. Research Sponsor: Cardinal Health.

12032 **Poster Session**

Intensity of end-of-life care for gynecologic cancer patients by primary oncologist specialty. *First Author: Katherine Hicks-Courant, University of Pennsylvania, Philadelphia, PA*

Background: The impact of primary oncologist specialty, medical oncology (MO) versus gynecologic oncology (GO), on intensity of care at the end of life (EOL) in elderly patients with gynecologic cancer is unclear. **Methods:** This retrospective cohort study used Surveillance, Epidemiology and End Results (SEER) Medicare data. Subjects were fee-for-service Medicare enrollees over 65 years old, who had seen a GO or MO in an outpatient setting in the last year of life and died of a gynecologic cancer between 2006 and 2015. The primary oncologist was defined as the provider with the majority of outpatient visits in the last year of life. The primary outcome was intensity of care at the EOL, a composite score defined by receipt of chemotherapy in the last 14 days of life, death in the hospital, enrollment in hospice for less than three days, more than one ED visit, more than one hospital admission, spending more than 14 days in the hospital, or any ICU admission in the last 30 days of life. Simple and multivariable linear regression analyses were conducted to evaluate for differences in EOL care outcomes by primary oncologist specialty. Linear regressions were repeated after creating a more similar control group through nearest-neighbor propensity score matching, with and without replacement. **Results:** Of 12,189 subjects, 63% were primarily treated by a MO and only 27% by a GO for EOL care. Most died of ovarian cancer (55.1%), followed by uterine (31.4%), cervical (6.9%), and other cancers (6.7%). Compared to GO patients, MO patients were younger, more likely to be white, married, not dual-eligible, higher stage, and to die of ovarian cancer. Overall, 55.4% (95% CI 54.73-56.49) received intense care at the EOL. Although both specialties engaged in high levels of intense EOL care, the adjusted rates for GO (54.03%; 95% CI 52.28-55.77) were significantly less compared to MO (56.53%; 95% CI 55.36-57.69; p=0.023) in unadjusted and adjusted analyses of the entire and propensity-matched cohorts (Table). **Conclusions:** Approximately 2/3 of women with gynecologic cancer will receive EOL care from a MO, compared to 1/3 from a GO. Both specialists engage in high levels of intense EOL care in over half of their patients, although GO less so. Future work should focus on identifying approaches to reduce high-intensity EOL care, which may include additional training or incorporation of palliative medicine into cancer care. Research Sponsor: None.

Difference in composite rate of high-intensity care by primary outpatient oncology type.

	Medical Oncologist		Gynecologic Oncologist		
Entire cohort	**n**	**% intense EOL care**	**n**	**% intense EOL care**	**p-value**
Simple	7,705	56.51	4,484	54.06	0.028
Multivariable	7,705	56.53	4,484	54.03	0.023
Propensity-score matched cohort, with replacement					
Simple	2,697	57.58	4,484	54.06	0.010
Multivariable	2,697	57.5	4,484	54.11	0.010
Propensity-score matched cohort, without replacement					
Simple	4,484	56.85	4,484	54.06	0.023
Multivariable	4,484	56.8	4,484	54.11	0.021

12033 **Poster Session**

Personalized delirium sedation goal (PDSG): Balancing comfort and communication in the last days of life. *First Author: David Hui, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Management of patients with agitated terminal delirium is challenging as clinicians try to find a balance between adequate sedation to maximize comfort while retaining communication abilities. A novel approach to tailor care is to ask caregivers for a PDSG by setting an individualized target for sedation. In this study, we examined PDSG using (1) clinical vignettes and (2) as a clinical response criteria in patients enrolled onto a randomized clinical trial. **Methods:** This is a pre-planned secondary analysis of a double-blind randomized clinical trial examining the sedative effect of chlorpromazine and/or haloperidol in patients with agitated terminal delirium refractory to low dose haloperidol (clinicaltrials.gov: NCT03021486; *Lancet Oncol* 2020 21:7 989-998). At baseline, caregivers and bedside nurses were independently asked to select the PDSG for 6 patient vignettes that differed by level of agitation (high vs. moderate), ability to communicate (yes or no), and survival (days vs. weeks). There were 5 choices for PDSG, corresponding to RASS scores of 0 (no sedation), -1 to -2, -3, -4 and -5 (deep sedation). Respondents were also asked to select the PDSG for the enrolled study patient, which were assessed against actual RASS scores over the first 24 hours to determine a response. We examined the association between PDSG levels and various patient and respondent characteristics with multi-level cumulative logits models. **Results:** 68 patients were enrolled and 45 received the masked study interventions (median survival 73 h [95% CI 49,106 h]). 42 caregivers and 40 nurses provided PDSG data. For the case vignettes, 7-31% of caregivers and 20-55% of nurses chose RASS -4 or -5 as PDSG. PDSG was significantly lower for patients who were unable to communicate (odds ratio [OR] 3.1-4.4, $P < 0.0001$), patients with only days of survival vs. weeks (OR 1.7, 95% confidence interval [CI] 1.2-2.5; $P = 0.002$) and if the respondent was a bedside nurse (OR = 2.5, 95% CI 1.8-3.6; $P < 0.0001$). For study patients, 12 (29%) of caregivers and 13 (33%) of nurses selected RASS -4 or -5 as PDSG. After the first 2 hours, 40-61% of patients achieved RASS scores that were within ±1 point of caregiver's PDSG, with no significant difference detected among treatment groups ($P = 0.45$). PDSG for study patients was significantly lower if the respondent perceived severe distress related to agitation (OR = 4.4, 95% CI 1.1-17.2; $P = 0.03$), particularly if the respondent was a bedside nurse (OR = 4.8, 95% CI 1.4-16.2; $P = 0.01$). **Conclusions:** PDSG represents a novel response criterion to tailor care for patients with agitated terminal delirium. Lighter sedation was preferred by caregivers compared to nurses, particularly for patients with less agitation, ability to communicate, and longer expected survival. These findings may allow clinicians to better tailor the level of sedation for patients with restlessness/agitation in the last days of life. Clinical trial information: NCT03021486. Research Sponsor: U.S. National Institutes of Health.

12034 **Poster Session**

Incidence and risk factors for euthanasia or physician-assisted suicide in oncology patients: A systematic review. *First Author: Wei Liu, Department of Radiation Oncology, London Health Sciences Centre, London, ON, Canada*

Background: In a growing number of jurisdictions, oncology patients may choose euthanasia or physician-assisted suicide (EPAS). A 2016 systematic review reported that 75% of U.S. and over 70% of Dutch and Belgian EPAS cases involved oncology patients. In the Netherlands and Belgium, the percentage of deaths among oncology patients via EPAS has been increasing. We investigated the incidence and risk factors for EPAS and EPAS requests in oncology patients. **Methods:** A systematic review was performed following PRISMA guidelines. PubMed, Embase and Cochrane databases were searched for articles from January 2000 to April 2020. Search terms were related to suicide, euthanasia, assisted dying, assisted death, right to die, mercy killing, and cancer. Eligible studies reported incidence and/or risk factors for EPAS/EPAS request based on at least 50 oncology patients. Eligibility for inclusion was independently reviewed by two authors, with discrepancies adjudicated by a third. Data obtained included: study type, country, cancer diagnosis, number of eligible patients, inclusion criteria, follow-up length, incidence of EPAS or EPAS request, and odds ratios (OR) for risk factors for EPAS and EPAS request. ORs and p values were extracted from studies whenever possible and were otherwise calculated based on the data provided using chi-squared test. **Results:** The search strategy identified 6519 results. 25 abstracts were selected for full-text review and 10 studies were included for analysis. All studies reported incidence of EPAS/EPAS request and 6 studies reported risk factors for EPAS/EPAS request. Six studies were from the Netherlands, 3 from Belgium, and 1 from Canada. Inclusion period for studies spanned from 1996 to 2018. Half of the included studies were prospectively conducted. Incidence of EPAS in cancer patients ranged from 7% to 15% and EPAS requests ranged from 8% to 27%. Factors significantly associated ($p<0.05$) with EPAS or EPAS request in any study are shown in the Table. **Conclusions:** Up to 15% of oncology patients choose euthanasia or physician-assisted suicide. Potentially modifiable symptoms including severe nausea, vomiting, and pain are significantly associated with EPAS in oncology patients. Research Sponsor: None.

Factors significantly associated with EPAS request or EPAS.

Risk Factor	Paper	EPAS Request OR	EPAS OR	Patients included
Advance euthanasia directive	Ruijs '14	34.9		64
Charlson Comorbidity Index >1	Pardon '12	3.6	9.1	105
Severe nausea	Georges '05		5.8	170
Treatment goal: Palliation	Pardon '12	5.0	5.6	104
Severe vomiting	Georges '05		5.1	170
Severe pain	Georges '05		4.7	170
Treatment of severe pain	Georges '05		4.7	170
Depressed mood at inclusion	van der Lee '05	4.3		137
Treatment of severe nausea	Georges '05		4.2	170
Help needed with housekeeping	Ruijs '14	3.8		60
Higher education (post-secondary)	Ruijs '14	3.7		64
Severe coughing	Georges '05		3.5	170
Severe feeling unwell	Georges '05		2.6	170

12035 **Poster Session**

Code status and outcomes in patients with cancer and COVID-19: A COVID-19 and cancer consortium (CCC19) registry analysis. *First Author: Elizabeth Trice Loggers, Fred Hutchinson Cancer Research Center, Seattle, WA*

Background: In-hospital mortality among patients with cancer (pts) and COVID-19 infection is high. The frequency of, and factors associated with, do-not-resuscitate (DNR) or do-not-intubate (DNI) orders at hospital admission (HA), and their correlation with care, has not been well studied. In November 2020, we began collecting this information for pts who were hospitalized at initial presentation in the CCC19 registry (NCT04354701). **Methods:** We investigated: 1. the frequency of, and factors associated with, DNR/DNI orders at HA; 2. change in code status during HA; and 3. the correlation between DNR/DNI orders and palliative care consultation (PC), mortality or length of stay (LOS). We included hospitalized, adult pts with cancer and COVID-19 from 57 participating sites. Reported characteristics include age, ECOG performance status (PS), and cancer status. Comparative statistics include 2-sided Wilcoxon rank sum and Fisher's exact tests. **Results:** 744 pts had known baseline and/or changed code status (CS); most (79%) maintained their baseline CS (Table). Those with DNR±DNI orders at HA were older (median age 79 vs 69 yrs, $p<0.001$) and more likely to have: ECOG PS 2+ vs 0-1 (45% vs 22%, OR 3.95, $p<0.001$), metastatic disease (45% vs 35%, OR 1.72, p=0.005) and progressing cancer (32% vs 16%, OR 2.69, $p<0.001$), but equally likely to have received systemic anticancer therapy in the prior 3 months (38% vs 45%, p=0.15). N=192 pts with a change in CS from full to DNR±DNI were younger (median age 73), had better PS (37% ECOG PS 2+), and were less likely to have progressing cancer (23%) than those with DNR±DNI orders at baseline. However, their LOS was significantly longer, median 9 vs 6 days, $p<0.001$. Compared to those with DNR±DNI orders at HA, pts whose CS changed to DNR±DNI were more likely to die, OR 2.94, 95% CI 1.76-4.97, $p<0.001$. PC was obtained in 106 (14%) pts and associated with transition to DNR±DNI in 47 (44%), affirmation of admission CS in 58 (55%), and reversal in 1 (1%). Median LOS for pts receiving PC was 11 vs 6 days, $p<0.001$. **Conclusions:** In our sample, the majority of patients with cancer and COVID-19 were full code at hospital admission. DNR±DNI status, whether at baseline or assigned during the hospital course, was associated with worse prognosis. Longer length of stay for patients changing code status and/or receiving palliative care consultation was observed likely suggesting earlier palliative care consultation is an important, but likely underutilized component in the care of patients with cancer and COVID-19. Research Sponsor: P30 CA068485.

Initial code status	N (%)	Change in code status during hospital admission	N (%)	LOS, median (IQR)	30-day Mortality, N (%)
Full code	585 (79)	Full code	393 (67)	6 (4-10)	19 (5)
		DNR only	54 (9)	12 (6-18)	38 (70)
		DNI±DNR	138 (24)	8 (5-15)	119 (86)
DNR only	42 (6)	Full code	1 (2)	19	1 (100)
		DNR only	41 (98)	6 (4-10)	23 (56)
		DNI±DNR	0		
DNI±DNR	117 (15)	Full code	0		
		DNR only	1 (1)	2	0
		DNI±DNR	116 (99)	7 (4-11)	73 (63)

12036 **Poster Session**

Inequity in location and quality of death of advanced cancer patients by immigrant status. *First Author: Ana Isabel Tergas, Columbia University College of Physicians and Surgeons and New York-Presbyterian Hospital, New York, NY*

Background: Most cancer patients prefer to die at home, a location associated with better quality of death (QoD) and caregiver outcomes. A number of studies demonstrate disparities in end-of-life (EoL) care among immigrant vs non-immigrant populations in the U.S. This study aims to evaluate how immigrant status affects location and QoD among patients with advanced cancer in the U.S. **Methods:** Data were derived from Coping with Cancer, a federally funded multi-site prospective study of advanced cancer patients and caregivers. The analytic sample of patients who died during the study observation period was weighted (N_w=308) to reduce statistically significant sociodemographic differences between immigrant (N_w=49) and non-immigrant (N_w=259) groups. Immigrant status was determined by patient self-report. Primary outcomes were location of death (intensive care unit, hospital, nursing home, inpatient hospice, home), death at preferred location (yes/no, as per caregiver report in post-mortem interview), and poor QoD (composite score of post-mortem caregiver ratings for patient psychological distress, physical distress, and quality of life in the last week of life). **Results:** As compared to non-immigrants, immigrants were more likely to die in a hospital as opposed to home [AOR 3.33; 95% CI (1.65-6.71); p=0.001] and less likely to die where they preferred [AOR 0.42, 95% CI (0.20-0.90); p=0.026]. As shown in Table, values-inconsistent aggressive EoL care mediated the effect of immigrant status on death at the patient s preferred location. Further, immigrants were more likely to have poor QoD [AOR 5.47; 95% CI (2.70-11.08); p<0.001]. In particular, among patients who preferred symptom-directed, comfort EoL care, immigrants as opposed to non-immigrants were more likely to have poor QoD [AOR 9.53, 95%CI (4.05-22.40); p<0.001]. **Conclusions:** Immigrants, as compared to non-immigrants, are more likely to die in hospital settings, less likely to die at their preferred location, and more likely to have poor QoD. These findings are consistent with previously described inequities in EoL care of immigrants and highlight the importance of determining the potential causes and solutions to ensure immigrants receive values-congruent care. Research Sponsor: U.S. National Institutes of Health.

Values-inconsistent aggressive end-of-life (EoL) care as a mediator of the effect of immigrant status on death at preferred location (weighted sample; N_w=291).

	Values-Inconsistent Aggressive EoL Care, Y/N				Death at Preferred Location, Y/N (Model A)				Death at Preferred Location, Y/N (Model B)			
Predictor	AOR	(95% CI)		p	AOR	(95% CI)		p	AOR	(95% CI)		p
Immigrant, Y/N	3.42	1.64	7.14	<0.01	0.42	0.20	0.90	0.03	0.63	0.27	1.45	0.28
Values Inconsistent Aggressive EoL Care, Y/N									0.13	0.07	0.26	<0.01

Notes: All AOR s adjusted for patient sex and level of education AOR s for Death at Preferred Location also adjusted for post-mortem survey respondent (i.e., formal or informal caregiver).

12037 **Poster Session**

Prognostic understanding, hospitalization, and hospice use among older patients with advanced cancer. *First Author: Kah Poh Loh, University of Rochester Medical Center, Rochester, NY*

Background: Poor prognostic understanding of curability is associated with lower hospice use in patients with advanced cancer. Little is known if this holds true for older adults specifically. In addition, prognostic understanding are variably assessed and defined in prior studies. We evaluated the associations of poor prognostic understanding and patient-oncologist discordance in both curability and survival estimates with hospitalization and hospice use in older patients with advanced cancer. **Methods:** We utilized data from a national geriatric assessment cluster-randomized trial (URCC 13070: PI Mohile) that recruited 541 patients aged ≥70 with incurable solid tumor or lymphoma considering any line of cancer treatment and their oncologists. At enrollment, patients and oncologists were asked about their beliefs about cancer curability (options: 100%, > 50%, 50/50, < 50%, 0%, and uncertain) and estimates of patient's survival (options: 0-6 months, 7-12 months, 1-2 years, 2-5 years, and > 5 years). Non-0% options were considered poor understanding of curability (uncertain was removed from the analysis) and > 5 years was considered poor understanding of survival estimates. Any difference in response options was considered discordant. We used generalized estimating equations to estimate adjusted odds ratios (AOR) assessing associations of poor prognostic understanding and discordance with hospitalization and hospice use at 6 months, adjusting for covariates and practice clusters. **Results:** Poor prognostic understanding of curability and survival estimates occurred in 59% (206/348) and 41% (205/496) of patients, respectively. Approximately 60% (202/336) and 72% (356/492) of patient-oncologist dyads were discordant in curability and survival estimates, respectively. In the first 6 months after enrollment, 24% were hospitalized and 15% utilized hospice. Poor prognostic understanding of survival estimates was associated with lower odds of hospice use (AOR 0.30, 95% CI 0.16-0.59) (Table). Discordance in survival estimates was associated with greater odds of hospitalization (AOR 1.64, 95% CI 1.01-2.66). **Conclusions:** Prognostic understanding may be associated with hospitalization or hospice use depending on how patients were queried about their prognosis and whether oncologists' estimates were considered. Research Sponsor: U.S. National Institutes of Health.

	Adjusted Odds Ratio	95% Confidence Interval
Hospitalization		
Poor understanding of curability	0.77	0.49-1.21
Poor understanding of survival estimates	0.74	0.50-1.08
Discordance in curability	0.87	0.50-1.53
Discordance in survival estimates	1.64	1.01-2.66
Hospice Care		
Poor understanding of curability	0.76	0.51-1.12
Poor understanding of survival estimates	0.30	0.16-0.59
Discordance in curability	0.78	0.50-1.22
Discordance in survival estimates	1.27	0.73-2.20

12038 **Poster Session**

Impact of the G8 score on the outcome of a cohort of elderly patients with solid or hematological malignancies. *First Author: Federica Biello, Division of Oncology, Department of Translational Medicine, University of Eastern Piedmont, Maggiore Hospital, Novara, Italy*

Background: Elderly cancer patients may have important benefits from innovative treatments. However, they are often barred from clinical trials because of highly selective eligibility criteria, or due to biased and subjective physician standpoints including reluctance to invite elderly patients and fear of excessive toxicity. Indeed, geriatric assessment has been increasingly recognized as predictive and prognostic instrument to detect frailty in older adults with cancer. In this perspective, the G8 score is a simple and reproducible instrument to identify elderly patients who should undergo full geriatric evaluation. The aim of our study was to evaluate the impact of frailty assessment by the G8 screening tool on the outcome of onco-hematological patients. **Methods:** Between January 2017 and December 2020 the G8 screening tool was administered to patients, aged >65 years, referred to our center for solid and hematological malignancies. G8 score was assessed at the time of first access. The primary endpoint was overall survival. Multivariate analysis was performed according to G8 score, age, tumor type, stage and treatment. **Results:** In the observation period, 430 patients were screened for frailty by G8; median age was 77 years (65-92); of these, 331 (77%) had a G8 score <14. Pts with solid tumors were 310 (72%), 175 (57%) of whom had metastatic diseases; 227 (73%) had a G8 score <14. Pts with hematological malignancies were 120 (28%), 100 (83%) of whom had a G8 score <14. Systemic therapy was administered to 336 patients (78%). At a median follow up of 7.2 months (range 1 to 52) 101 pts (24%) were dead. Median overall survival (mOS) was 27 months (1-52+).Patients with solid tumors, classified as frail by a G8 score <14 had a 3-fold risk of death compared with those with G8 > 14 (OR 3.26, CI 95 1.5-7.2, p = 0.003). Conversely, this increased risk was not observed in hematological malignancies (OR 1.4, CI 95 0.4-4.6, p = 0.57). By multivariate analysis, G8 score was associated with a worse prognosis only in patients with solid tumors. **Conclusions:** Our analysis suggest that elderly frail patients with solid tumors have a significantly increased risk of death as compared to elderly fit patients. Conversely, no impact of frailty, as assessed by a G8 score < 14, was evident in elderly patients with hematological malignancies. Research Sponsor: None.

12039 **Poster Session**

Effect of a geriatric management unit on the outcomes of hospitalized older adults with cancer in Mexico. *First Author: Gretell Henriquez Santos, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico*

Background: Geriatric assessments and interventions improve the outcomes of hospitalized older adults with cancer, but their implementation in developing countries is limited. We studied the effect of a specialized geriatrician-led inpatient geriatric management unit compared with a conventional internal medicine ward on the outcomes of hospitalized Mexican older adults with cancer. **Methods:** This retrospective study included patients aged ≥65 with solid tumors who had a cancer-related hospitalization at a public academic center in Mexico City between March 2015 and October 2018. Patients hospitalized in the geriatric management unit (cases) were paired in a 1:2 fashion with those in internal medicine wards (controls). Pairing was done by age (+/- 5 years), tumor type, and admission date (+/- 3 months). We studied the effect of being hospitalized in the geriatric management unit on length of stay (LOS), incidence of delirium, hospital-acquired complications, and in-hospital mortality. Multivariate logistic regression models for each outcome were created using variables which were significant on univariate analysis. **Results:** 300 patients (100 cases, 200 controls, median age 75) were included. The most common tumors were gastrointestinal (GI) (53%) and genitourinary (25%). Both groups were comparable regarding baseline comorbidities (Charlson index 8.5 vs. 7.7, p = 0.99) and illness severity at admission (NEWS2 score 2.6 vs. 2.3, p = 0.82). No difference in median LOS was found between cases and controls (9.1 vs. 9.5 days, p = 0.34). Diagnosis of a GI tumor (OR 3.4, 95% CI 1.3-5.5), hospital-acquired complications (OR 4.9, 95% CI 2.5-7.3), and delirium (OR 5.5, 95% CI 2.3-8.7) were associated with longer LOS. 14% of patients in both groups had delirium. Hospitalization in the geriatric management unit reduced the risk of delirium (OR 0.35, 95% CI 0.1-0.9), while a higher Charlson index (OR 1.2, 95% CI 1.0-1.4), NEWS2 score (OR 1.2, 95% CI 1.1-1.4), and hospital-acquired complications (OR 7.3, 95% CI 2.9-18.5) increased it. 34% of patients developed hospital-acquired complications. Diagnosis of a GI tumor (OR 1.9, 95% CI 1.1-3.3) and higher NEWS2 score (OR 1.2, 95% CI 1.1-1.4) increased the risk of hospital-acquired complications. No differences in in-hospital mortality were seen between cases and controls (12% vs. 10%, p = 0.59). A higher NEWS2 score at admission (OR 1.4, 95% CI 1.2-1.7) and delirium (OR 10.7, 95% CI 3.2-36.3) increased the risk of death. **Conclusions:** Among older Mexican adults hospitalized for a cancer-related diagnosis, receiving care in a geriatric management unit led to a significant decrease in the risk of delirium. No improvements were seen in LOS, complications, or in-hospital mortality, which were associated with tumor and patient-related characteristics. Geriatric co-management can lead to improved geriatric outcomes in developing countries with limited resources. Research Sponsor: Fundación Carlos Slim.

12040 **Poster Session**

Characteristics of elderly-specific oncology trials registered in ClinicalTrials.gov. *First Author: Bian Wu, Cancer Center, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China*

Background: Clinical trials dedicated to the elderly cancer patients are essential to help to define optimal cancer therapy for this rapidly growing population. Our study aimed to analyze the characteristics and the evolution of elderly-specific oncology trials registered in ClinicalTrials.gov. **Methods:** A dataset of 61120 oncology trials registered in ClinicalTrials.gov between Jan 1th, 2000 and Dec 17th, 2019 was downloaded. Interventional trials were identified and systematically reviewed to validate classification into elderly-specific (at least using a chronological landmark to define the elderly) and age-unspecified trials. Cancer type and other registration information were extracted. Characteristics of elderly-specific trials were compared with characteristics of age-unspecified trials. Chronological shifts in elderly-specific trials between 2000 to 2009, and 2010 to 2019 were analyzed. **Results:** Of the 49273 trials eligible for analysis, only 791 (1.6%) were elderly-specific. The most frequently used threshold to define the old was 60 years (36%), followed by 70 years (28%) and 65 years (26%). More than half of the elderly-specific trials were phase 2 (56.8%) trials and enrolled 100 or fewer participants (59.4%). Compared with age-unspecified trials, elderly-specific trials were less likely to be funded by industry (28.3% vs 37.1%; $p < 0.001$), and more likely to be conducted in Europe (42.1% vs 24.5%, $p < 0.001$). During the two time periods between 2000 to 2009, and 2010 to 2019, the proportion of elderly-specific trials of all the oncology trials remained stable (1.57% vs 1.62%). The proportion of treatment-oriented trials decreased from 91.9% to 71.4% ($p < 0.001$) while supportive care-oriented trials increased from 1.9% to 13.2% ($p < 0.001$). Industry-funded elderly-specific trials decreased from 34.0% to 25.6% ($p = 0.014$). Concerningly, the use of clinically meaningful end points in elderly such as disease-specific survival, patient-reported outcomes (PROs) and functional status as a primary end point were uncommon (0.5%, 8.0%, and 6.9%, respectively). However, the use of PROs as a primary end point tended to increase in the second time period, from 2.4% to 10.5% ($p < 0.001$). There was no correlation between the number of trials for a given cancer type and relative incidence and mortality. 336/791 (42.5%) of the trials were conducted for patients with blood cancer, although the incidence and mortality of blood cancer were relatively low. The most common solid cancer types were breast cancer (13.9%), lung cancer (10.0%), and colorectal cancer (7.8%). **Conclusions:** Although the majority of all new cases of cancer occur in the elderly population, elderly-specific trials account for only a minority of all oncology trials. Our study helps us to better understand the current state of elderly-specific trials and provides insights for future development that can improve the care of elder patients with cancer. Research Sponsor: None.

12041 **Poster Session**

Association between baseline geriatric domains and survival in older adults with chronic lymphocytic leukemia (CLL). *First Author: Julia Rice, Massachusetts General Hospital, Boston, MA*

Background: CLL is a disease that commonly affects older adults. Although the value of geriatric assessment is increasingly being recognized in older adults with cancer, few studies have examined the relationship between baseline geriatric domains and clinical outcomes in older adults with CLL. **Methods:** We conducted a secondary data analysis of 369 adults diagnosed with CLL and treated in a phase 3 randomized trial of patients age ≥65 with bendamustine plus rituximab versus ibrutinib plus rituximab versus ibrutinib alone. We evaluated geriatric domains of functional status (activities of daily living [ADL], instrumental activities of daily living [IADL], Timed Up and Go, and number of falls in last 6 months), psychological status (Mental Health Inventory), social activity (Medical Outcomes Study [MOS] Social Activity Survey), cognition (Blessed Orientation Memory Concentration Test), social support (MOS Social Support Tangible and Emotional/Informational subscales), and nutritional status (> 5% weight loss in the preceding 6 months). We examined associations among baseline geriatric domains with overall survival (OS) and progression-free survival (PFS) using multivariable Cox regression models. **Results:** The median age of patients was 71 years (range: 65-89). Most were male (67.1%) and had an ECOG performance status of 0 or 1 (96.9%). In multivariable models, the following geriatric domains were significantly associated with OS: better functional status (ADL score: HR 0.67, $p = 0.012$; IADL score: HR 0.98, $p = 0.007$); social activity score (HR 0.97, $p = 0.004$); and nutritional status (HR 2.58, $p = 0.008$). Similarly, functional status (ADL score: HR 0.77, $p = 0.028$; IADL score: HR 0.99, $p = 0.007$); social activity score (HR 0.97, $p < 0.001$); and nutritional status (HR 2.87, $p < 0.001$) were all associated with PFS. Additionally, the number of impaired geriatric domains was also associated with OS (HR 1.50, $p = 0.004$) and PFS (HR 1.45, $p < 0.001$). Timed Up and Go, number of falls in last 6 months, psychological status, cognition, and social support were not significantly associated with clinical outcomes. **Conclusions:** Geriatric domains of functional status, social activity, and nutritional status were associated with OS and PFS in this cohort of older adults with CLL. These findings highlight the importance of assessing geriatric domains to identify high-risk patients with CLL who may benefit from additional support during their treatment. Research Sponsor: None.

12042 **Poster Session**

Concerns and difficulties associated with the COVID-19 pandemic among older adults with cancer in Mexico. *First Author: Sofia Sánchez-Román, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Delegacion Tlalpan, Mexico*

Background: The COVID-19 pandemic has impacted the well-being of people not only due to the disease but also because of stay-at-home orders, social distancing, unemployment, and different kinds of loses. Older adults have particularly suffered during the pandemic, with increased health-related concerns and anxiety leading to increased vulnerability. However, little is known about the effects of the pandemic on older adults with cancer living in developing countries. They are facing issues related to their diagnosis and treatment, as well as the effects of the pandemic on their care and on the well-being of their families. To improve care for this vulnerable population, we studied the concerns and difficulties associated with COVID-19 among older Mexican adults with cancer. **Methods:** We included patients age ≥65 with the 10 most common tumors in Mexico according to GLOBOCAN and within 3-24 months of cancer diagnosis at two public hospitals in Mexico City. Patients were contacted telephonically and asked to complete a survey reporting the difficulties encountered during the COVID-19 pandemic and to rate their concerns associated with cancer care management using a 0-10 Likert-type scale, with higher ratings meaning increased concerns. Focused interviews were used to describe the individual experience of selected patients and their relatives related to COVID-19 and cancer care. **Results:** Between April 20, 2020 and December 1, 2021, 67 patients (mean age 71.9, min 65, max 90; 35.8% female; 62.7% living with a partner) were included. The most common tumors were prostate (43%), colon (16%), and lung (12%). 46% had Stage IV disease, and 61% had a life expectancy of more than a year. Twenty-five percent of patients reported encountering at least one difficulty in obtaining cancer care due to the COVID-19 pandemic. 43% of the patients reported difficulties with accessing follow-up cancer care; 39% reported issues with obtaining medications, including chemotherapy; and 34% reported problems obtaining medical care in general, including oncology visits. Regarding concerns, 33% of the patients reported being very worried or extremely worried about the COVID-19 pandemic. The most relevant concerns were related to getting infected with COVID-19 (or having a family member who became infected) (mean rating 7.9, SD 2.9); not being able to pay for cancer treatments or medical care (mean rating 6.9, SD 3.5); and worsening of cancer due to delayed care during the pandemic (mean rating 6.6, SD 3.7). **Conclusions:** A significant proportion of older adults with cancer in Mexico faced difficulties obtaining cancer treatment and follow-up care during the COVID-19 pandemic. Their most relevant concerns included getting infected, financial losses, and progression of disease. Creating systems to provide continued cancer care for vulnerable populations in developing countries is essential to face the COVID-19 pandemic. Research Sponsor: Conquer Cancer Foundation of the American Society of Clinical Oncology.

12043 **Poster Session**

Evaluating the role of baseline geriatric assessment in predicting adherence to oral targeted therapies and outcomes in older adults with non-Hodgkin lymphoma. *First Author: Othman Salim Akhtar, Roswell Park Comprehensive Cancer Center, Buffalo, NY*

Background: Oral targeted therapies (OTT) have transformed the treatment landscape of Non-Hodgkin lymphoma (NHL). However, measuring, defining and optimizing adherence to OTT remains a challenge. Prior studies have reported variable adherence rates (12-100%) to OTT in cancer patients (pts), with suboptimal adherence associated with inferior outcomes. In older adults (OA), geriatric syndromes (GS) such as polypharmacy and cognitive impairment can impact adherence. While geriatric assessment (GA) can predict chemotherapy-related toxicity in OA, its utility in NHL pts on OTT is unknown. In this pilot study, we evaluate the role of GA in predicting adherence and outcomes in NHL pts on OTT. We also report the feasibility of using MEMS Cap, an electronic event monitoring system, to measure adherence in this population. **Methods:** Pts ≥70 years (yrs) with NHL, initiating/receiving OTT were included. A GA was performed at baseline; pt, disease, and OTT characteristics were recorded. Pts were followed monthly for the first 3 months (mos), then every 3 mos for 1 year. Primary endpoint was treatment adherence rate, measured using both subjective [brief adherence rating scale (BARS)] and objective (pill counts and MEMS cap) methods. Progression free survival (PFS) was measured from time of therapy initiation to disease progression or death. **Results:** Of the 54 pts screened, 25 were enrolled. Median age was 77 yrs (71-93 yrs), 21 pts had chronic lymphocytic leukemia, 3 had mantle cell lymphoma and 1 had marginal zone lymphoma. Most frequently used OTT were ibrutinib (n = 17) and venetoclax (n = 5). Most pts (72%) were on OTT at study entry. Median time on therapy was 16.4 mos (1.9-44.6 mos). GS included cognitive impairment (28%), depression (24%), polypharmacy (92%) and recent falls (12%); 48% pts had ≥2 GS. Nine pts (36%) had impaired 4-meter gait speed and/or timed-up-and-go; 20 pts (80%) had an adjusted CIRS-G score of ≥6. So far, pts have completed a median follow up of 3.3 mos. BARS was the most consistent measure of adherence used (63/63 visits, 100%). MEMS Cap and pill counts were used at 13% and 8% visits respectively. Only 5 pts used the MEMS Cap, mostly due to packaging incompatibility (44%-pill box, 32%-blister packs). Median adherence was 100% (range, 70%-100%) with no pts missing > 7 days of prescribed doses. Five pts (20%) required dose interruptions, mostly due to adverse events. Six pts discontinued therapy and 2 pts died of unrelated causes. Median PFS was not reached. Chronological age and presence of a GS were not associated with adherence rate or outcomes. **Conclusions:** Despite presence of ≥2 geriatric syndromes in 48% of older adults with NHL on OTT, self-reported adherence remains high (> 99%) in this group. The MEMS Cap device has poor applicability in measuring adherence to OTT due to pill package incompatibility and increasing use of virtual/tele visits. Research Sponsor: Roswell Park Alliance Foundation.

12044 **Poster Session**

Pre-existing geriatric conditions in older adults with poor prognosis cancers. *First Author: Mazie Tsang, University of California San Francisco, San Francisco, CA*

Background: Older adults with poor prognosis cancers are more likely to experience toxicity from cancer-directed therapies. Although geriatric assessment (GA) reduces chemotherapy toxicity by detecting pre-existing conditions, GA can be difficult for oncologists to perform because of limited time and resources. We aim to determine the prevalence of pre-existing geriatric conditions that could be detected if GA were performed during routine oncology care. **Methods:** We used the Health and Retirement Study (HRS) linked with Medicare (1998-2016) to identify adults age >65 with poor prognosis cancers (median overall survival < 1 year). The HRS is a biennial nationally representative survey that asks about pre-existing geriatric conditions. Using the interview prior to the cancer diagnosis, we determined the presence of conditions included in GA: functional status (i.e. difficulty with climbing stairs, walking one block, getting up from a chair, bathing or showering, taking medications, and managing money), falls and injurious falls, unintentional weight loss, self-rated health, social support, mentation, advanced care planning, use of pain or sleep medications, and mobility. To identify groups with the highest prevalence of pre-existing geriatric conditions, we stratified results by age (adjusted for gender) and gender (adjusted for age). **Results:** Our study included 2,121 participants. At the time of cancer diagnosis, mean age was 76, 51% were female, 79% were non-Hispanic White, 26% had lung cancer, 14% had a GI cancer, and 60% had other metastatic cancers. Mean time between the HRS interview and cancer diagnosis was 12.7 months. The median overall survival of the entire cohort was 9.6 months with a 45% 1-year survival rate. The adjusted prevalence of pre-existing geriatric concerns were as follows: 65% had difficulty with climbing several flights of stairs, 27% had difficulty with walking one block, 47% had difficulty getting up from a chair after sitting down, 12% had difficulty in bathing or showering, 6% had difficulty taking medications, 11% had difficulty in managing money, 35% had a fall in the last 2 years with 12% of participants reporting injury after their fall. Those who were aged 85 +, vs those aged 65-74, had higher rates of conditions indicative of cognitive impairment (e.g. 12 vs 4% had difficulty taking medications, p = 0.000, 26% vs 6% had difficulty managing money, p = 0.000) and physical impairments (e.g. 54% vs 30% had falls, respectively, p = 0.000). Rates of geriatric conditions indicative of physical impairment were higher in women vs men (e.g. 72% vs 58% had difficulty climbing stairs, p = 0.000 and 52% vs 41% had difficulty getting up from a chair, p = 0.000). **Conclusions:** Patients with poor prognosis cancers have high rates of pre-existing geriatric conditions that can be detected by GA. Geriatric assessments could find important impairments that could be addressed prior to cancer therapy to reduce adverse effects. Research Sponsor: T32-AG000212.

12045 **Poster Session**

Trajectories of functional status among older adults receiving treatment for gastrointestinal (GI) malignancies: A report from the CARE study. *First Author: Smith Giri, University of Alabama at Birmingham, Alabama, AL*

Background: Preservation of functional independence while undergoing treatment is of utmost importance to older adults with cancer, in addition to being associated with healthcare utilization and survival. Yet, such data are not readily available from published clinical trials. We sought to examine functional status trajectories and risk factors associated with functional decline among older adults receiving treatment for GI malignancies. **Methods:** This study included older adults (≥60y) treated at the UAB GI oncology clinic and enrolled in a prospective Cancer and Aging Resilience Evaluation (CARE) registry. All patients completed a geriatric assessment (GA) that included an assessment of activities of daily living (ADL) and instrumental activities of daily living (IADL). Participants were approached for a repeat assessment three months after baseline GA. Change in functional status was classified as one or more points decline or improvement in IADL and/or ADL from baseline to follow up. We measured the proportion with functional decline or improvement and constructed 95% confidence interval (95%CI) using binomial exact methods. We built multivariable logistic regression models to study the impact of baseline predictors on functional decline. Putative risk factors included age, sex, race/ethnicity, cancer type & stage, baseline CARE frailty index, fatigue, pain, malnutrition and CT-based muscle mass indices (Skeletal Muscle Index [SMI] and Skeletal Muscle Density [SMD]) at the time of diagnosis. **Results:** This study included 184 patients. The median age at first visit was 68y (IQR 64-74); 55% were males, 71% white. Primary cancer diagnoses included colorectal cancer (29%), pancreatic cancer (28%) and other GI cancers (43%); 73% presented with advanced stage disease (III/IV). Most patients were receiving first line therapy (91%), with systemic chemotherapy (95%). The median duration between the baseline and follow up assessment was 109 days (IQR 84-154 days). Overall, 38% (95%CI, 30-45%) experienced a functional decline, whereas functional improvement was seen in 22% (95%CI, 16-29%). In a multivariable analysis, baseline frailty (odds ratio [OR] = 2.37; 95%CI, 1.05-5.38; p =0.03) was associated with significantly increased odds of functional decline; a trend towards increased odds was seen for pancreatic cancer (OR = 2.23; 95%CI, 0.90-5.53; p= 0.08; reference group: colorectal cancer). **Conclusions:** One in three older adults with GI malignancies experienced functional decline while a quarter experienced functional improvement in the first 3 months following treatment. Baseline frailty was associated with higher odds of functional decline. Early identification of such patients may allow targeted interventions to preserve functional independence and optimize quality of life of older adults with cancer. Research Sponsor: U.S. National Institutes of Health.

12046 **Poster Session**

Impact of geriatric assessment (GA) based frailty index (CARE-Frailty Index) on mortality and treatment-related toxicity among older adults with gastrointestinal (GI) malignancies. *First Author: Smith Giri, University of Alabama at Birmingham, Alabama, AL*

Background: Older adults with cancer are at increased risk of treatment-related toxicity and mortality. A comprehensive geriatric assessment (GA) may uncover aging associated vulnerability and identify those at greatest risk of adverse outcomes. We studied the association between a novel frailty index and treatment-related morbidity and mortality among older adults with GI malignancies. **Methods:** Older adults (≥60y) referred for initial consultation at the UAB GI oncology clinic between 9/2017 to 12/2020 were enrolled in a prospective Cancer and Aging Resilience Evaluation (CARE) registry. All participants underwent a patient-reported GA at baseline as previously described *(Williams et al J Geriat Oncol 2020).* Using this information, we constructed a 44-item frailty index using a deficit accumulation approach. Vital status was acquired by linking with death records and chart review. In a subgroup of patients continuing care at UAB, we collected information on toxicity for the first 6 months of treatment via chart review using CTCAE v5.0. We used Kaplan Meier Methods and log-rank test to compare survival distributions, and a multivariate cox regression to adjust for potential confounders. We compared the toxicity rates across frailty subgroups using risk ratio (RR) calculated from general linear models. **Results:** Of 765 consecutive older adults referred to GI oncology clinic, 590 (77%) had available data to measure frailty index. Median age at enrollment was 68y; with 59% males and 72% White. Common cancer types included colorectal (30%) and pancreatic cancer (26%); mostly with advanced stage disease (stage III 28%; IV 46%). Overall, 168 (28%) were characterized as pre-frail and 230 (39.3%) as frail. As compared to non-frail, those who were frail were more likely to be Black (33% vs 20%; p < 0.01) and have pancreatic cancer (33.6% vs 21.8%; p < 0.01). Over a median follow up of 22 months, 212 (36%) patients had died. The 2y overall survival among non-frail, pre-frail and frail patients was 71%, 63% and 51%, respectively (log rank p value < 0.001). In a multivariate cox regression, as compared to non-frail patients, frailty was associated with worse OS (HR 1.75; 95% CI 1.13-2.70; p = 0.01) after adjusting for age, sex, race, cancer stage, cancer type, line of therapy and performance status. In a subset of 168 patients with available data, baseline frailty was associated with increased risk of ≥grade 3 non-hematologic toxicity (RR 2.23; 95% CI 1.27-3.92; p < 0.01) but not ≥grade 3 hematologic toxicity (RR 1.03; 95% CI 0.67-1.58; p = 0.90) as compared to non-frail patients **Conclusions:** The CARE-Frailty Index is a novel frailty index built on the principle of deficit accumulation using a patient-reported GA, and appears to be a robust predictor of survival and may predict treatment related toxicity among older adults with GI malignancies. Research Sponsor: U.S. National Institutes of Health.

12047 **Poster Session**

The association between geriatric assessment, body composition measures, and treatment-related toxicity in elderly cancer patients: A prospective cohort study. *First Author: Shlomit Strulov Shachar, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel*

Background: Treatment decisions in older adults with cancer are confounded by limited evidence due to their under-representation in clinical trials and as associations between geriatric assessment findings, body composition measures, treatment-related toxicity, and treatment effectiveness have yet to be fully elucidated. We investigated the relationship between geriatric assessment results, skeletal muscle measures, and treatment-related toxicity in older adults with cancer. **Methods:** This prospective single-center cohort study included patients with cancer > 65 years of age with advanced lung, breast, or genitourinary (GU) cancer who received systemic treatment (chemotherapy, biologic therapy, immunotherapy, or combination), and had available CT scans. Patients completed the Comprehensive Geriatric assessment (CGA) and 36-item Carolina Frailty Index (CFI) was calculated to classify them as robust (< 0.2), pre-frail (0.2-0.35), or frail (> 0.35). For each patient, skeletal muscle area (SMA) and density (SMD) were analyzed from CT scan L3 lumbar segments using Slice-O-Matic software. SMA and height (m^2) were used to calculate skeletal muscle index (SMI). Skeletal muscle gauge (SMG) was created by multiplying SMI x SMD. Sarcopenia was defined as having SMI < 41 cm^2/m^2 for males and < 38 cm^2/m^2 for females. The associations between study variables and the occurrence of at least one adverse event (AE) grade ≥2 were analyzed using the Pearson's chi-squared test. The study was approved by the IRB of Rambam Health Care Campus. All patients signed an informed consent. **Results:** Overall, 51 patients (recruited between 5/2015 and 1/2020) were included in the final analysis. Median (interquartile [IQR]) age was 72 (68-76) years; 59% were male; 51%, 28%, and 22% had lung, breast, and GU cancer respectively. The most common treatment received was doublet chemotherapy (49%). All patients except 3 (6%) completed the CGA and CFI was calculated; 29%, 26%, and 39% were classified as robust, pre-frail, and frail, respectively. Median (IQR) SMG was 1251 (1104-1497) AU; median (IQR) SMI was 42 (39-48) cm^2/m^2; 31% were defined as sarcopenic. Overall, 45% of patients experienced at least one AE grade ≥2; 24% experienced at least one AE grade≥3. No statistically significant association was found between treatment-related toxicity and sex, age, tumor type, treatment, or CFI category. Yet, having low SMG (categorically, by tertile) was significantly associated with having at least one AE grade≥2 (p = 0.03) as was being sarcopenic (p = 0.02). **Conclusions:** Low SMG and sarcopenia are associated with treatment-related toxicity in older patients with cancer. Further research and better understanding of this association could help optimize treatment decisions (e.g., choice of regimen, dosing) and interventions in this population. Research Sponsor: Israel Cancer Association.

12048 **Poster Session**

Change in the comprehensive geriatric assessment scores at day 30 post-cancer treatment in geriatric oncology patients. *First Author: Toufic Tannous, Roger Williams Medical Center/Boston University School of Medicine, Providence, RI*

Background: The comprehensive geriatric assessment (CGA) is a multidimensional tool for assessing the functional, cognitive, nutritional and frailty status of patients above 65 years of age with cancer. It includes several components: patient health questionnaire (PHQ-9), timed up and go (TUG), mini mental status exam (MMSE), mini nutritional assessment (MNA), Poly Pharmacy (PP), activities of daily living (ADL), instrumental activities of daily living (IADL) and comorbidities. Previous studies showed that some baseline CGA scores (pre-treatment) are predictors of mortality. However, to our knowledge, there has been no study evaluating the change of those scores in response to treatment at different time periods. We sought to evaluate the evolution of the CGA scores after 30 days post-treatment. **Methods:** We conducted a single institution, prospective cohort registry of patients with solid cancers aged 65 or older in Rhode Island from 2013-2018. All patients underwent a CGA before starting treatment (day 0) and post-treatment (day 30). Treatment included surgery, chemotherapy, radiation, or any combination. Baseline demographic characteristics as well as CGA components were abstracted. TUG, MMSE, PHQ-9, IADL, PP, BMI, MNA and ADL performed at day 0 and 30 were collected. The mean for each score was obtained at both days. Student T test was used to test for significance for nominal data and Chi square test for ordinal data. A P value of less than 0.05 was deemed statistically significant. **Results:** 283 patients were enrolled. The mean age was 76 (+-6.86) of which 54% were females. 92% of patients were white and 8% were black. Colorectal and lung cancer were among the most common. The mean Charleston comorbidity index was 12.3 (+-3.2). The mean BMI decreased from 26.92 (+-5.84) at day 0 to 26.1 (+-5.45) at day 30 ($p < 0.01$). The mean IADL decreased from 5.93 (+-2.03) to 5.2 (+-2.12) ($p < 0.01$). At day 0, one patient had impaired ADLs compared to 7 patients at day 30 ($p = 0.03$). PHQ-9, MMSE, MNA, TUG and PP scores did not significantly differ at day 30 post treatment (Table). **Conclusions:** The ADL, IADL and BMI scores showed a statistically significant change at Day 30, indicating deteriorating scores in those patients. Our study showed that ADL, IADL and BMI were the only variables that worsened at day 30 post-treatment compared to PHQ-9, MMSE, MNA, TUG and PP. This suggests that they may be used as early markers of clinical deterioration in geri-onc patients undergoing treatment. More studies are needed to assess their prognostic significance. Research Sponsor: None.

CGA variables	Day 0	Day 30	P
BM	26.92 (+-5.84)	26.1(+-5.45)	<0.01
IADL	5.93(+-2.03)	5.2(+-2.12)	<0.01
PHQ-9	5.02(+-4.3)	5.13(+-3.82)	0.72
MMSE	27.01(+-3.38)	26.91(+-3.11)	0.63
MNA	4.96(+-3.44)	5.23(+-2.81)	0.5
TUG	10.23(+-2.52)	10.11(+-1.78)	0.74
PP	51	62	0.12
ADL	1	7	0.03

Mean score and SD sum of all the patients who had PP sum of all the patients with impaired ADL.

12049 **Poster Session**

Associations of quality of social support and beliefs in curability among older adults with advanced cancer. *First Author: Lee Kehoe, University of Rochester Medical Center, Rochester, NY*

Background: Prior studies suggest that social support plays a role in disease understanding of older patients with advanced cancer. In this study, we examined the association of quantity and quality of social support with belief in curability among older patients with advanced incurable cancer. **Methods:** We performed a secondary analysis of a cluster-randomized geriatric assessment trial (URCC 13070: PI Mohile) that recruited older adults (≥70) with advanced incurable cancer and caregivers. At enrollment, patients completed the Older Americans Resources and Services (OARS) Medical Social Support form to measure both quantity (number of close friends and relatives) and quality of social support. Quality of social support was measured using twelve questions, each ranged from 1 (none of the time) to 5 (all of the time). Higher cumulative scores indicated greater quality of support. For beliefs in curability, patients were asked, What do you believe are the chances that your cancer will go away and never come back with treatment? Responses were 0%, <50%, 50/50, >50%, and 100%. Ordinal logistic regression was used to investigate the association of social support with beliefs in curability, adjusting for adjusting for age, gender, education, race, number of Geriatric Assessment (GA) impairments, cancer type, and locality (rural versus urban). **Results:** We included 347 patients; mean age was 76.4 years, 91% were white, 52% were male, 46% had household income <$50,000, and 55% had high school degree or higher. For every unit increase in OARS Medical Social Support score, the odds of believing in curability decreases by 36.4% [Adjusted Odds Ratio (AOR) 0.733, 95% Confidence Interval (CI): (0.555, 0.969)], after controlling for covariates. Quantity of social support was not associated with belief in curability [AOR 1.033 95% CI: (0.921, 1.156)]. **Conclusions:** Our study revealed that older patients with advanced cancer who felt more supported by their social network were more likely to report that their cancer was not curable. Interventions that improve quality of social support may also affect disease understanding. Funding: Patient-Centered Outcomes Research Institute (PCORI) 4634 and NIH K24 AG056589 to SGM, NCI UG1CA189961, T32CA102618, NCI K99CA237744 to Loh. Research Sponsor: U.S. National Institutes of Health, Patient-Centered Outcomes Research Institute (PCORI).

12050 **Poster Session**

Perceived physical fatigability improves after an exercise intervention among breast cancer survivors: A pilot randomized clinical trial. *First Author: Yujia (Susanna) Qiao, University of Pittsburgh, Pittsburgh, PA*

Background: Among breast cancer populations, exercise interventions resulted in positive but relatively small improvements on fatigue, which may have been masked by using single-item, non-specific measures of global fatigue. Perceived fatigability – whole-body tiredness anchored to standardized tasks/activities of specific intensity and duration – accounts for self-pacing bias as an individual likely titrates their usual activities and exertion level to avoid exhaustion. We examined whether this novel fatigability measure could replace global fatigue in an exercise intervention trial in breast cancer survivors. **Methods:** This pilot single-center randomized clinical trial of 49 breast cancer survivors was conducted from 2015-17, among which 41 participants (exercise = 22, control = 19) completed the trial and reported their perceived physical fatigability and global fatigue at the first (V1) and the last visit (V3). Perceived physical fatigability was measured using the 10-item, self-administered Pittsburgh Fatigability Scale (PFS) scored 0-50, higher PFS Physical scores = greater fatigability. Global fatigue was assessed with a single question I have a lack of energy scored 0 not at all to 4 very much from the Functional Assessment of Cancer Therapy-Endocrine Subscale (FACT-ES). The exercise intervention consisted of three one-on-one training sessions over 6-14 weeks, plus two optional email/phone consultations. The trainer developed a personalized, home-based exercise program with a goal of achieving the recommended ≥150 minutes/week of moderate to vigorous exercise based on ACSM guidelines. Those randomized to the control group met the trainer for V1 and again 6-14 weeks later at V3, but no exercise prescription was provided. We computed mean differences in perceived physical fatigability and global fatigue between V3 and V1 and compared by intervention groups. **Results:** Among the 41 women in the study (mean age = 54.9±9.8 years; 80% white), sociodemographic and clinical characteristics were similar by intervention groups, except for antiestrogen use. Post-intervention changes (mean ± SE) in PFS Physical scores were -4.4±1.4 (-22.5%) in the exercise group and 0.2±1.4 (+1.0%) in the control group ($p = .022$), whereas change in global fatigue scores were -0.64±0.23 in the exercise group and 0.00±0.22 in the control group ($p = .054$). **Conclusions:** These findings add to mounting evidence that an exercise intervention reduces fatigue among breast cancer survivors. Importantly, the PFS showed a clinically meaningful reduction after the exercise intervention that was masked when using global fatigue as the measurement. Therefore, the PFS serves as a more sensitive instrument to measure perceived physical fatigability and can better evaluate patient-reported outcomes in future cancer trials, especially those focused on cancer survivorship. Clinical trial information: NCT 02770781. Research Sponsor: U.S. National Institutes of Health, Other Foundation.

12051 **Poster Session**

Patient experience of early high grade symptomatic adverse events on early phase clinical trials using the PRO-CTCAE. *First Author: Geoffrey Alan Watson, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: There are limited data describing the patients' experience of symptomatic adverse events (syAEs) on early phase clinical trials. This information is critical to understand the tolerability of experimental agents. The patient reported outcome version of the CTCAE (PRO-CTCAE) evaluates syAE components such as severity and interference in daily life. The aim of this study was to correlate clinician reported early, high grade (grade 3-4) AEs with patients' reported experience of these toxicities. **Methods:** Advanced solid tumor patients (pts) enrolled on early phase clinical trials at Princess Margaret Cancer Centre were surveyed electronically using the full library of 78 items for PRO-CTCAE v1.0, which was administered at baseline (prior to therapy), mid-cycle 1, and mid-cycle 2. AEs on study were recorded by physicians using the CTCAE v4.0. Worst responses for severity items are severe' and very severe' and for interference items are quite a bit' and very much'. A logistic regression model was used to assess the association between CTCAE grade and PRO-CTCAE severity and interference. **Results:** A total of 292 pts were approached in phase 1 clinics from May 2017 to January 2019, and 219 pts were included in the analysis: median age 60 years (range 18-82), 111 (51%) were male; all were ECOG ≤1. A total of 140 pts (64%) received combination therapy (immunotherapy and targeted therapy), and 73 pts (33%) had received ≥3 previous lines of treatment. In terms of patient reported syAEs, a total of 114 pts (52%) reported a symptomatic AE as either severe or very severe at any timepoint and 79 pts (36%) reported a syAE with an interference that was either quite a bit' or very much'. With regards to clinician reported AEs, a total of 82 pts (37%) had a clinician reported grade 3 or 4 syAE, and of these 34 pts (41%) reported these as either severe or very severe; and 26 pts (32%) found these AEs interfered with daily life either quite a bit' or very much'. Additionally 137 pts (66%) had a clinician reported grade 1 or 2 syAE, and of these 39 pts (28%) reported these as either severe or very severe; and 19 (14%) found these AEs interfered with daily life either quite a bit' or very much'. Higher grade clinician reported syAEs (CTCAE grade 3-4 vs 1-2) was associated with higher patient reported severity levels (odds ratio, OR = 1.78, 95% CI 1-3.16, $p = 0.049$), and was associated with higher patient reported interference levels (OR = 2.88, 95% CI 1.47-5.64, $p = 0.002$). **Conclusions:** A majority of patients had a very negative experience of syAEs on a phase I trial. Higher grades of clinician reported AEs correlated with greater severity and interference with daily living. Future phase I studies could incorporate the PRO-CTCAE and other PRO tools which could inform the tolerability of experimental regimens and enhance the description of symptomatic AEs. Research Sponsor: None.

12052 **Poster Session**

Overall and progression-free survival in young breast cancer patients with low muscle mass and density. *First Author: Rebecca Sheaff Greiner, Atrium Health Levine Cancer Institute, Charlotte, NC*

Background: Low muscle mass (skeletal muscle index, SMI) and density (skeletal muscle density, SMD) are associated with chemotherapy toxicity and shorter survival in women with breast cancer. This has not been studied specifically in women ≤ 40 years at diagnosis. They have different body compositions and more aggressive cancers than older women. We compared pre-treatment muscle measures in survivors and non-survivors and investigated their association with overall survival (OS) and progression-free survival (PFS). **Methods:** This case-control study included 112 women aged ≤ 40 years at diagnosis. Women with pre-treatment CT scans from 2009-2018 were identified; non-survivors were matched with survivors by age, year of diagnosis and disease characteristics. Body composition was determined by CT analysis. Measures were compared between the groups using Kruskal-Wallis tests. Kaplan-Meier methods summarized OS and PFS and the associations of muscle characteristics with OS and PFS were examined by univariate Cox proportional hazard models. **Results:** Median age was 35 years; median follow-up was 8.2 years. 75% had Stage II or III disease and 21% Stage IV disease. 33% were sarcopenic (SMI < 40) and 16% had low SMD (HU <37.8). Non-survivors had more intermuscular fat (IMAT), reduced SMD, and reduced skeletal muscle gauge (SMG). Sarcopenia was not associated with OS; however, sarcopenia was associated with shorter PFS. The median skeletal muscle gauge was 1973; low skeletal muscle gauge (SMG <1973) was associated with both shorter OS and PFS. Median IMAT was 1.6, and high IMAT (≥1.6) was associated with shorter OS and PFS. **Conclusions:** Low muscle mass (sarcopenia) at breast cancer diagnosis was associated with shorter PFS and low muscle density (low SMG and higher IMAT) was associated with shorter OS and PFS in women ≤ 40 years. These sub-optimal muscle characteristics may indicate an overall reduced state of health and/or decreased ability to tolerate treatment, thus reducing survival. Future research should determine the significance of muscle changes throughout treatment and establish standards for improved muscle health. Research Sponsor: Atrium Health Foundation.

	SURVIVORS (N=56) Med [Min, Max]	NON-SURVIVORS (N=56) Med [Min, Max]	P - value
A Pre-treatment muscle characteristics			
BMI (kg/m^2)	26.6 [20, 49]	27.9 [19, 63]	0.57
SMI (cm^2/m^2)	44.8 [34, 69]	42.3 [34, 75]	0.29
IMAT (intermuscular adipose cm^2/m^2)	1.5 [0.4, 6]	1.8 [0.5, 13]	0.02
SMD (HU)	49.1 [30, 62]	45.5 [27, 71]	0.03
SMG (SMI X HU)	2102 [1421, 3273]	1905 [908, 4310]	0.04
B. Survival Estimates	**OS HR [95% CI]; P-value**	**PFS HR [95% CI]; P-value**	
Sarcopenia (SMI < 40)	1.5 [0.9, 2.5]; P=0.16	1.8 [1.1, 2.9]; P=0.02	
Low SMG (< 1973)	1.8 [1.0, 3.0]; P=0.03	1.8 [1.1, 2.9]; P=0.01	
High IMAT (IMAT ≥1.6)	2.0 [1.2, 3.4]; P=0.01	1.7 [1.0, 2.7]; P=0.04	

12053 **Poster Session**

COVID-related anxiety is prevalent and accurately reflects serious COVID risks in breast cancer patients. *First Author: Marisa C. Weiss, Breastcancer.org, Ardmore, PA*

Background: A current cancer diagnosis is a risk factor for serious COVID-19 complications (CDC). In addition, the pandemic has caused major disruptions in medical care and support networks, resulting in treatment delays, limited access to doctors, worsening health disparities, social isolation; and driving higher utilization of telemedicine and online resources. Breastcancer.org has experienced a sustained surge of new and repeat users seeking urgent information and support. To better understand these unmet needs, we conducted a survey of the Breastcancer.org Community. **Methods:** Members of the Breastcancer.org Community were invited to complete a survey on the effects of the COVID-19 pandemic on their breast cancer care, including questions on demographics, comorbidities (including lung, heart, liver and kidney disease, asthma, diabetes, obesity, and other chronic health conditions); care delays, anxiety due to COVID-related care delays, use of telemedicine, and satisfaction with care during COVID. The survey was conducted between 4/27/2020-6/1/2020 using Survey Monkey. Results were tabulated and compared by chi square test. A p-value of 0.05 is considered significant. Data were analyzed using Stata 16.0 (Stata Corp., Inc, College Station, TX). **Results:** Our analysis included 568 breast cancer patients of whom 44% had ≥1 other comorbidities associated with serious COVID-19 complications (per CDC) and 37% had moderate to extreme anxiety about contracting COVID. This anxiety increased with the number of comorbidities (p=0.021), age (p=0.040), and with a current breast cancer diagnosis (p=0.011) (see table). Anxiety was significantly higher in those currently diagnosed, ≥65, or with ≥3 other comorbidities, compared to those diagnosed in the past, age <44, or without other comorbidities. **Conclusions:** Our survey reveals that COVID-related anxiety is prevalent at any age regardless of overall health status, but it increased with the number of other comorbidities, older age, and a current breast cancer diagnosis. Thus, reported anxiety is proportional to the risk of developing serious complications from COVID. Current breast cancer patients of all ages—especially with other comorbidities—require emotional support, safe access to their providers, and prioritization for vaccination. Research Sponsor: None.

	Anxiety Level			
	No Anxiety	**Slightly/Somewhat**	**Moderately/Extremely**	**P-value**
Breast Cancer				0.011
Past	33 (11.6)	164 (58.0)	86 (30.4)	
Current	28 (10.0)	134 (47.5)	120 (42.5)	
Other Comorbidities				0.021
0	43 (13.5)	170 (53.5)	105 (33.0)	
1	14 (8.1)	99 (57.2)	60 (34.7)	
2	3 (5.2)	24 (41.4)	31 (53.5)	
3	1 (9.1)	3 (27.3)	7 (63.6)	
4	0 (0)	2 (40.0)	3 (60.0)	
Age				0.04
25-34	0 (0)	4 (57.1)	3 (42.9)	
35-44	6 (12.0)	31 (62.0)	13 (26.0)	
45-54	19 (14.1)	74 (54.8)	42 (31.1)	
55-64	25 (13.7)	96 (52.5)	62 (33.9)	
65+	11 (5.8)	92 (49.0)	85 (45.2)	

12054 **Poster Session**

High intensity interval training safety and efficacy in patients with advanced NSCLC receiving systemic treatment: Results of a prospective trial. *First Author: Myriam Nait Ajjou, CHUM, Montreal, QC, Canada*

Background: Patients with advanced NSCLC experience fatigue and physical deconditioning altering their quality of life. Safety and feasibility of high intensity exercise in advanced NSCLC has not been explored yet. **Methods:** We report the results of a single-center, prospective two-arm study. Patients with advanced NSCLC actively receiving systemic therapy or having completed treatment less than 2 months prior to enrollment were included. Patients were allocated to either an intervention arm consisting of kinesiologist supervised high intensity interval training (HIIT) at 2 sessions per week for a total of 12 weeks; or a control arm of home exercise guided by an informative pamphlet. All patients were evaluated at baseline, 6 and 12 weeks by a kinesiologist. Quality of life (QoL) exercise surveys and measurement of strength were measured. **Results:** Sixty patients were enrolled between January 2018 and March 2020. The study was interrupted due to COVID-19. Thirty-two patients were included in the exercise program and 28 patients in the control group. Both groups were balanced in respect to baseline characteristics. A total of 32 (53%) patients went off protocol, 13 (18%) patients stopped due to symptomatic disease progression which included 2 (3%) deaths, 2 (3%) stopped due to COVID-19 preoccupations and the remaining patients withdrew for other reasons. 42 (70%) patients were evaluated at 6-weeks and 28 (47%) completed the 12-week follow-up, with equal distribution in each group. There were no significant difference at 12 weeks in the physical assessment nor the overall QoL scores between both groups: FACT-L on 135 points (+4.1 vs +1.7, p = 0.342) and FACIT on 52 points (+3 vs -0.2, p = 0.832). Patients in the exercise group demonstrated a significant improvement at 12 weeks in the Lung Cancer Symptoms domain on 28 points (22.3 vs 19.8, p = 0.015) as well as the Physical Wellbeing domain on 28 points (23.6 vs 20.6, p = 0.056) compared to the control group, respectively. No significant exercise related complications were reported. After the study, 9 of the 14 patients (64%) who completed the HIIT program continued to exercise virtually with a kinesiologist in contrast to none in the control group. **Conclusions:** This study demonstrated the safety and potential benefit of a HIIT program on lung-specific and physical wellbeing in patients with advanced NSCLC on active treatment. This study provides further support on the role of supervised physical exercise in patients living with cancer. Clinical trial information: 16.229. Research Sponsor: None.

12055 **Poster Session**

Predictors of receiving survivorship care plans and visits. *First Author: Christine M. Duffy, Lifespan Cancer Institute, Providence, RI*

Background: While the Commission on Cancer has eliminated strict quotas for accreditation, Survivorship Care Plans (SCPs) and/or Survivorship Care Visits (SCV) at treatment completion are encouraged. However, who receives a SCP or SCV, whether it impacts care, and impact of distress on care is unknown. We examined the provision of survivorship care at the Lifespan Cancer Institute (LCI) to determine (1) clinical and distress thermometer scores (DTS) association with SCPs and SCVs; (2) impact of SCV visits on specialty referrals, and (3) demographic and clinical predictors of receipt of SCP and SCV. **Methods:** We retrospectively reviewed EMR records on 1,960 patients at LCI between 2014-2017 for SCPs and SCVs and extracted demographics, treatment variables, and distress scores. We used T-test or Wilcoxon rank test and Chi-square tests for evaluating the bivariate associations of SCP and SCV with continuous and categorical factors respectively. We fit logistic regression models to assess the adjusted effect of these factors on receipt of SCP and SCV independently. All analyses were performed in R v4.0.2. **Results:** The mean age was 63.9 (SD=11.8), 67% were female, 51.2% were married or partnered. Breast (38.8%), lung (17.6%), and prostate (13.7%) were the most common cancers. DTS were recorded in 64% with mean of 3.88(SD=3.05): distress was higher in women (4.36, SD=3.01), breast cancer pts (4.53, SD=3.07), gyn (4.22, SD=3.07) , pancreatic (4.12, SD=3.41) and anal cancers (4.52, SD=3.47) and in those with Stage IV disease (5.33, SD=3.43). SCPs were completed in 740 (37.8%) patients and of those 65.9% had a SCV. SCV were associated with more specialty referrals for psychiatry, physical therapy, nutrition, and sexual health but not smoking cessation or fiscal services. DTS were associated with increased referral to psychiatry only. The adjusted models (table) showed odds of receiving a SCP were higher in those younger, and having breast cancer v all other cancers, with prostate having lowest odds. For receipt of SCV, odds were higher in those younger, female, and having breast cancer, with prostate and lung having the lowest odds. **Conclusions:** Gender, age and type of cancer are significant predictors of receipt of SCP and SCV. SCP and SCV patterns may represent patient preferences, but practice patterns and unconscious biases may also play a part suggesting areas for further research and outreach. Research Sponsor: None.

	SCP adjusted	SCV adjusted
Age	0.98 (0.97, 0.99)**	0.97 (0.96, 0.99)**
Male	0.85 (0.55, 1.30)	0.52 (0.30, 0.91)*
Partnered	1.25 (0.97, 1.61)	1.23 (0.93, 1.62)
Stage III or IV	1.33 (0.94, 1.86)	1.39 (0.93, 2.06)
Lung	0.13 (0.08, 0.19)**	0.08 (0.04, 0.14)**
Prostate	0.05 (0.02, 0.09)**	0.08 (0.03, 0.18)**
Colon cancer	0.12 (0.07, 0.22)**	0.26 (0.14, 0.46)***
Non-colorectal	0.15 (0.10, 0.25)**	0.19 (0.11, 0.33)***
Gynecologic	0.15 (0.10, 0.25)**	0.14 (0.08, 0.25)**

**p-value < 0.001;
*p-value< 0.05.

12056 **Poster Session**

Weight management following endometrial cancer treatment: A pilot trial to evaluate the efficacy of the profile by Sanford program. *First Author: Maria Bell, Sanford Health, Sioux Falls, SD*

Background: Excess weight and weight gain are risk factors for endometrial cancer and cancer recurrence following treatment for women with endometrial cancer. Conversely, weight loss among women with obesity has been shown to reduce endometrial cancer risk. Intensive behavioral weight management programs may be an effective method to improve health and reduce weight following treatment. **Methods:** Twenty-two women following endometrial cancer treatment (age = 59.4 ± 11.5; weight = 241.3 ± 46.3; BMI = 40.5 ± 7.8; time since last treatment 19 ± 17.4 months) were enrolled in a behavioral weight management program and followed for 12 months and 28 matched controls (age = 58.4 ± 11.5; weight = 246.9 ± 60.3; BMI = 41.6 ± 8.6) were assessed over 12 months. The program consists of weekly health coaching meetings to discuss nutrition, activity, and behavior change topics. The nutrition plan targets ≥4 cups of vegetables per day, a lean and green' grocery meal, complimented with meal replacement foods to provide a nutritionally complete meal plan. Cost of participant membership, coaching, and meal replacements were covered for 6 months and available to purchase for months 7-12. **Results:** The treatment group completed 28.3 ± 14.1 appointments throughout 12 months resulting in an average weight change of -31.2 ± 17.3 pounds (-13.3 ± 7.4%) at 6 months and -36.1 ± 27.6 pounds (-15.3 ± 11.4%) at 12 months (all $p<0.001$). Controls had a weight change of -3.9 ± 18.4 pounds (-2.3 ± 7.6%) at 12 months which was significantly different than the treatment group ($p<0.001$). BMI was significantly reduced in the treatment group at 6 months (-4.8 ± 4.5, $p<0.001$) and 12 months (-5.2 ± 5.9, $p<0.001$) and significantly different than in the control group at 12 months (-0.9 ± 3.2, $p=0.007$). **Conclusions:** This behavioral weight management program with health coaching and structured nutrition provided clinically significant weight loss that was sustained to 12 months. Future research should examine long-term enrollment in the Profile by Sanford program with reduction in endometrial cancer recurrence. Research Sponsor: Profile by Sanford.

	Treatment (n=22)	Control (n=28)	p-value
Age	59.4 ± 11.5	58.4 ± 11.5	0.758
Baseline Weight	243.1 ± 46.3	246.9 ± 60.3	0.799
Baseline BMI	40.5 ± 7.8	41.6 ± 8.6	0.622
Weight at 12 months	200.2 ± 46.3	243.1 ± 70.1	0.014
Weight change (pounds) at 12 months	-36.1 ± 27.6	-3.9 ± 18.4	<0.001
Weight change (percent) at 12 months	-15.3 ± 11.4	-2.3 ± 7.6	<0.001
BMI at 12 months	34.0 ± 7.4	40.7 ± 10.4	0.013
BMI change at 12 months	-5.2 ± 5.9	-0.9 ± 3.2	0.007

12057 **Poster Session**

Predictors of early readmission to hospital and mortality in patients with malignant ascites: Analysis of the nationwide readmissions database. *First Author: Omid Yazdanpanah, Wayne State University, Detroit, MI*

Background: Malignant ascites accounts for 7 percent of ascites cases in the United States. It is a common manifestation of several solid tumors and is associated with poor prognosis with median survival of 3 months. Moreover, patients with malignant ascites are at risk of recurrent hospitalizations. Hospital readmissions are costly for health-care system and are regarded as a quality of care index. Nevertheless, predictive factors for hospital readmissions and mortality in patients with malignant ascites are limited. Understanding these factors can expedite development of strategies to reduce the readmission and health-care costs. **Methods:** Utilizing the Nationwide Readmissions Database (NRD), we conducted a retrospective cohort study on patients admitted with malignant ascites between 2016 and 2018 across the United States. We used multivariable logistic regression to determine the predictors of unplanned 30-days readmissions and mortality among patients with malignant ascites. **Results:** Out of 130,648 patients hospitalized with malignant ascites, 15,756 individuals (12.1%) were readmitted within next 30 days. Predictors of early readmission included pulmonary embolism (OR 2.40; 95% CI 1.55-3.74), complicated diabetes (OR 1.28; 95% CI 1.05-1.56) and having Medicaid insurance (OR 1.34; 95% CI 1.11-1.62). In-hospital mortality for patients with malignant ascites was 14.1%. The comorbidities associated with increased mortality were liver disease (OR 1.87; 95% CI 1.77-1.97), pulmonary embolism (OR 1.60; 95% CI 1.34-1.90), renal failure (OR 1.39; 95% CI 1.27-1.52), and congestive heart failure (OR 1.27; 95% CI 1.16-1.38). Patients with Medicaid insurance also had higher mortality (OR 1.21; 95% CI 1.12-1.32) among the payers. **Conclusions:** One in eight patients with malignant ascites was readmitted to the hospital within 30 days of discharge. By examining the risk factors leading to readmission, this study helped to identify the subpopulations of patients likely to become more ill. The strong association of pulmonary embolism with readmission and in hospital mortality suggests the benefit of prophylactic anticoagulation. Furthermore, higher readmission and mortality rate within Medicaid insurance population can open a new window in studying health care disparities. Research Sponsor: None.

12059 **Poster Session**

The GET FIT trial (NCT01635413): A randomized controlled trial of strength training versus Tai Ji Quan for fall prevention among female cancer survivors. *First Author: Kerri M. Winters-Stone, Oregon Health & Science University, Portland, OR*

Background: Women with cancer are significantly more likely to fall than women without cancer but there are not yet any evidence-based fall prevention strategies that specifically target cancer survivors. The GET FIT trial compares the efficacy of two distinct types of exercise, strength training vs. tai ji quan, to prevent falls in women finished with chemotherapy. **Methods:** We conducted a 3 group, single-blind, parallel design, randomized controlled trial in older, inactive women cancer survivors treated with chemotherapy. Women were randomly assigned to 1 of 3 intervention groups: 1) strength training, 2) tai ji quan or 3) a placebo control group (stretching) that trained 2x/week for 6 months. Additional follow-up occurred 6 months after formal training stopped. The primary outcome was fall rate across 6-and 12 months; secondary outcomes, reflective of training fidelity, were maximal leg strength (by 1-repetition maximum) and dynamic postural control (by computerized dynamic posturography), collected at 0, 3, and 6 months. **Results:** 442 women (mean age 62.4 + 6.3 yrs.) were enrolled and randomly assigned to study groups. Over the 6 months prior to enrollment, 21% of the sample (n = 94) reported at least one fall (of which, 37% (n = 35) reported two or more falls)), and 12% (n = 51) reported at least one injurious fall. Retention across the 12 months study period was 88%, while adherence to the study interventions over 6 months averaged 73%, 71%, and 74% for the strength, tai ji quan and stretching (control) groups, respectively. 26% of the sample (n = 99 of 382) reported at least one fall during the intervention and 27% (n = 102) reported falls during follow up. Using regression models, there were no significant differences in the odds of having at least one fall during the intervention period (1-6 months) or across the entire follow-up period (1-12 months) between the control and either the strength or tai ji quan groups. At 6 months, the strength group showed a greater increase from baseline in maximal leg strength (+14.3 kg, 95% CI: 11.4-17.1) than the control group (+7.5 kg, 95% CI: 4.6-10.4, p = 0.002). Whereas, the tai ji quan group showed a greater increase in dynamic postural control (+2.42%, 95% CI: 1.36-3.48) compared to the control group (+0.35%, 95% CI: -0.69-1.38, p = 0.007). **Conclusions:** Despite evidence for fidelity of strength and tai ji quan training to improve muscle strength and postural control, respectively, neither program significantly lowered fall rates over a placebo control group. It is possible that the dose of exercise was too low and/or the sample was not at high risk of falls. The etiology of fall risk in women cancer survivors needs to be better understood as it may differ from risk factors in older adults. Future trials should consider patient-centered, tailored fall-prevention interventions for cancer survivors based on identified fall risk factors. Clinical trial information: NCT01635413. Research Sponsor: U.S. National Institutes of Health.

12060 **Poster Session**

Complementary and alternative medicine use among cancer patients at two cancer centers in Brazil. *First Author: Eliza Dalsasso Ricardo, Hospital Alemão Oswaldo Cruz, São Paulo, Brazil*

Background: Complementary and alternative medicine (CAM) use is relatively common among cancer patients. Data regarding CAM use in Brazil is scarce. We sought to define CAM use among cancer patients and investigate factors that might influence it. **Methods:** We conducted a cross-sectional survey of adults diagnosed with any cancer type who came to appointments at two cancer centers in Brazil from January 2020 to January 2021. Unadjusted and adjusted analyses were conducted by using Logistic Regression models to determine the association of covariates with binary outcome. Statistical analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC). All tests were 2-sided, and $P < 0.05$ was considered significant. **Results:** In total, 319 patients who consented to the face-to-face interview were included and all of them completed the questionnaires. Most patients (52.4%) were between 51 and 70 years-old, 59,6% were female, 85,2% were from the private service and 67% had college graduate/baccalaureate. Most cancer types were from gastrointestinal tract (31,4%), breast (20.4%), lung (12.3%) and genitourinary type. More than 85% of the participants were on any active cancer treatment. The prevalence of current CAM use was 34.2% and 50.2% of the patients did not believe CAM has anti-cancer properties. Two-thirds of the participants have never discussed about CAM with their oncologists. Only 4.1% of the respondents would abandon conventional cancer treatment in order to use just CAM. Among CAM users, 55% referred multiple therapies use. Of those therapies, spiritual surgery was the most prevalent one. There was a significant higher proportion of females reporting CAM use (p = 0,008) as well as a higher proportion of CAM use among private patients (p = 0,008). **Conclusions:** CAM use was common among our study population, especially spiritual surgery. Women and private patients were more prone to use CAM. Although most patients would not abandon conventional treatment, many of them have never discussed about CAM with their oncologists. Research Sponsor: None.

12061 **Poster Session**

Brief relaxation training effects on long-term endocrine therapy adherence among women with breast cancer. *First Author: Molly Ream, University of Miami, Coral Gables, FL*

Background: Despite life-saving potential, many women struggle to adhere to adjuvant endocrine therapy (AET) for their early-stage, hormone receptor-positive breast cancer. Prior research has demonstrated that emotional distress is a barrier to AET adherence. The current study aimed to test the long-term effects of two 5-week post-surgical group-based stress management interventions, cognitive behavioral therapy (CBT) and relaxation training (RT), versus an attention-matched health education (HE) control on AET adherence at long-term follow-up. **Methods:** We conducted long-term follow-up (median = 8 years, range = 7-11 years) of a cohort of women who enrolled in a randomized controlled trial of CBT vs. RT vs. HE shortly after surgery for stage 0-3 breast cancer.We measuredadherence with the Endocrine Therapy Medication Usage Questionnaire (ETMUQ) given at long-term follow-up. First, we established adherence factors on the ETMUQ via confirmatory factor analysis. We then used structural equation modeling to regress these factors on study arm, controlling for patient age, stage of disease, and treatments received (chemotherapy/radiation). **Results:** The sample was predominately middle-aged (M= 54.81, SD= 10.19), White (41.5%) and Hispanic (42.2%), partnered (62.2%) with stage 1 (57.0%) or stage 2 (25.9%) disease. Of the women who completed long-term follow-up (N = 59, 44.7% of original sample); more than half (n = 30; 50.8%) reported having at least some problems with adherence. There was an effect of intervention group on adherence, such that women receiving RT (n = 15) had significantly better adherence than those receiving CBT (n = 20) on the factor measuring Forgetfulness/Inconsistency ($B(SE)$ = .57 (.34), p= .001), and marginally better adherence than those receiving CBT on the factor measuring Intentional Nonadherence ($B(SE)$ = .60 (.33), p = .062). There was no such effect when comparing RT or CBT to HE (n = 24). **Conclusions:** Women receiving RT were less likely to forget to take their AET and marginally less likely to intentionally miss doses of AET in the long-term compared to women receiving CBT. Future research could investigate the mechanism by which RT may improve adherence. For example, RT may reduce somatic symptoms related to AET or improve a patients' self-efficacy to cope with these symptoms thereby reducing intentional non-adherence. In addition, RT may improve patients' attention and awareness leading to less forgetfulness. Clinical trial information: NCT02103387. Research Sponsor: U.S. National Institutes of Health.

12062 **Poster Session**

Multifactorial analysis of cancer patients' willingness for COVID-19 vaccination. *First Author: Paris A. Kosmidis, Care Across, London, United Kingdom*

Background: Public health authorities advocate vaccinations for the general population, including cancer patients and survivors. Since the onset of the COVID-19 pandemic, its vaccine has been eagerly awaited, but the extent of cancer patients' willingness to get vaccinated is not clear. As health promotion is crucial for these individuals, it is important to measure and analyze their willingness to receive the vaccine. **Methods:** A few days after the regulatory approval for the first COVID-19 vaccine, the CareAcross online interactive platforms were used to evaluate the willingness of patients to get vaccinated. Through an online survey, within a few hours, 1106 cancer patients selected either Yes, I plan to get the vaccine or No, I will not get the vaccine. The patients were from the UK, Germany, France, Spain or Italy; they had been diagnosed with breast, lung, prostate or colorectal cancer. Their responses were analyzed to determine how their cancer diagnosis (including date, metastatic status, and other aspects), and their country of origin, affected their reported willingness to get vaccinated. **Results:** Overall, 70.6% of patients indicated willingness to get the vaccine (WTV), and 29.4% reported the opposite (NWTV). The strongest determinant of WTV was the patient's country of origin: patients in the UK, Spain, Italy, Germany and France reported WTV of 84.1%, 64.2%, 58.7%, 47.4% and 38.3%, respectively. The next strongest determinant was the time elapsed since the patient's diagnosis: for the largest population with available diagnosis date (451 UK patients), the average time since diagnosis for patients with WTV vs NWTV was: breast, 3.5 vs 2.5 years; lung, 1.6 vs 1.4 years; prostate, 2.4 vs 3.3 years; colorectal, 1.9 vs 1.5 years. Among patients from other countries with available diagnosis date: as the time since diagnosis increased, among 148 Italian patients WTV gradually increased; among 94 Spanish patients, WTV substantially decreased; among 85 French patients, WTV gradually decreased; among 50 German patients, WTV substantially increased. There was no significant correlation of WTV percentages with cancer type; metastatic status; triple negative vs non-triple negative among breast cancer patients; non-small cell vs small cell among lung cancer patients. **Conclusions:** Despite long-standing efforts of the scientific community for health promotion through the COVID-19 vaccine, a substantial percentage of cancer patients reported no willingness to get vaccinated. This appeared to depend on each patient's country of origin, and the time elapsed since their diagnosis. This patient input was collected shortly after the first vaccine's approval. With increasing evidence of efficacy and safety through more vaccinations of citizens and patients, willingness is expected to increase. We are in the process of conducting a follow-up survey to track these changes and update the results to be reportable during ASCO. Research Sponsor: None.

12063 **Poster Session**

Integration of a polygenic risk score of kidney function with cumulative cisplatin dose and time variables for the prediction of serum platinum levels. *First Author: Megan Shuey, Vanderbilt University Medical Center, Nashville, TN*

Background: Platinum levels are measurable in the serum for decades after cisplatin therapy and higher levels may be related to chemotherapy-induced toxicities. Since cisplatin is cleared exclusively by the kidney, we hypothesized that a genetic predictor of kidney function, an estimated glomerular filtration rate polygenic risk score (eGFR PRS), would significantly associate with serum platinum levels and could improve prediction models. **Methods:** Within a large well-characterized, multicenter clinical cohort of cisplatin-treated testicular cancer survivors (TCS), we conducted analyses on all patients with genetic data and serum platinum levels. Genotyping was performed on the HumanOmniExpressExome chip and standard QC measures were included. Serum platinum concentrations were quantified by inductively coupled plasma mass spectrometry. For all TCS, time since therapy (TIME) and cumulative cisplatin dose were collected. The eGFR PRS was developed from the Chronic Kidney Disease Genetics (CKDGen) consortium meta-analysis summary statistics using PRS-CS. Using principal component analysis, we restricted the analysis to TCS of genetically determined European ancestry, then calculated the genome-wide PRS for all participants. We performed Cox regression analyses to evaluate prediction models of serum platinum that included cumulative dose and TIME, as well as a model including eGFR PRS. Data are presented as median (interquartile range). **Results:** 901 patients were included in our analysis with a median diagnosis age of 31 (26 - 38) years, cumulative cisplatin dose of 400 (300-400) mg/m^2, and time since first cisplatin dose of 4.6 (2.3-9.5) years. The median serum platinum level for all TCS was 305 (121-981) ng/L. When stratified into quartiles by eGFR PRS, TCS in the lowest quartile had a median serum platinum level of 316 (139-1014) ng/L while TCS in the highest had a median of 268 (106-731) ng/L. Comparison of two Cox regression models for serum platinum prediction, one including only cumulative dose and TIME as predictors and a second including dose, TIME, eGFR PRS, and an eGFR PRS*TIME interaction term, we determined the model including eGFR PRS had a lower AIC (14350 vs 16180) suggesting a more parsimonious model. Further, eGFR PRS was a significant independent predictor of serum platinum levels (p = 0.02) and the impact of eGFR PRS varies over time (eGFR PRS*TIME, p = 0.05). **Conclusions:** The genetic predictor of kidney function circumvents the use of renal function measures that may have been impaired by initial cisplatin administration. It is a significant independent predictor of serum platinum levels and consistent with expectation: TCS with higher genetically predicted kidney function had lower serum platinum levels. Our results suggest kidney function inferred by genetics may improve the prediction of serum platinum levels. Research Sponsor: U.S. National Institutes of Health.

12064 **Poster Session**

Patient preferences for cancer survivorship care: Results of an online survey. *First Author: Deanna J. Attai, David Geffen School of Medicine at UCLA, Los Angeles, CA*

Background: Nearly 17 million cancer survivors live in the United States. Workforce shortages are projected to diminish the number of available medical oncologists (MOs) to care for newly diagnosed patients with cancer and for the growing number of cancer survivors. Models of survivorship care include oncologist-led, primary care-led, and shared care approaches. Recent proposals recommend a risk-stratified approach to care, guided by individual and cancer-specific factors, but there is little evidence regarding patient preferences for non-oncologist survivorship care. **Methods:** We developed a survey in partnership with patient advocates. The primary endpoints were patient-reported comfort with survivorship care by a primary care provider (PCP) or in a dedicated survivorship clinic. We distributed the survey to online, cancer-specific patient communities from June to August 2020. Logistic regression analyses were adjusted for patient age, race and ethnicity, insurance, and cancer type and stage. **Results:** Of 1166 responses, 975 surveys were complete and available for analysis. Respondents were primarily women (91%), white (92%), and US residents (73%); 78% had a college or graduate degree. Two-thirds had private insurance. Thirty-six different cancer types were reported; 61% of respondents had breast cancer, and 25% were treated for more than one type of cancer. Most respondents (83%) had nonmetastatic disease, 74% reported experiencing late effects of cancer therapy, and almost all (93%) had a PCP. Only 21% of respondents were comfortable seeing a PCP (versus MO) for survivorship care, including cancer follow-up, side effect management, and monitoring for recurrence or progression. About half (55%) were comfortable with follow-up in a survivorship clinic instead of with their MO. Multivariable analyses showed no significant associations between age, race or ethnicity, insurance, cancer type, or stage at diagnosis and comfort with follow-up care from a PCP or in a survivorship clinic. In analyses restricted to the 439 respondents with a history of early-stage breast cancer, the 239 (54%) who were within 1 to 5 years of diagnosis were less comfortable with PCP versus MO follow-up, compared with the 52 (12%) who were $>$ 15 years from diagnosis (OR 0.40; 95% CI 0.20–0.75; p= 0.004). In this sub-analysis, time from diagnosis was not associated with comfort being seen in a survivorship clinic. **Conclusions:** In our study, most patients with a history of cancer were not comfortable receiving follow-up care from their PCP. It is often recommended that survivors of early-stage breast cancer transition to primary care for follow-up and surveillance, but our study revealed comfort with this approach only many years after diagnosis. While both PCP survivorship training and patient confidence in PCP follow up is needed, preferences of cancer survivors should be considered in designing new models of survivorship care. Research Sponsor: None.

12065 **Poster Session**

The rate and risk of secondary pelvic malignancies (SPM) in patients treated with definitive radiation for locally advanced rectal cancer. *First Author: Kathryn Ries Tringale, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: With a rising incidence of younger patients diagnosed with rectal cancer, the long-term toxicity of cancer-related therapy is becoming even more relevant. Risk of SPM is a known potential consequence of both chemotherapy (chemo) and radiation therapy (RT), yet the rate of SPM in patients with rectal cancer is still not defined. We sought to further investigate factors associated with and outcomes of SPM after RT for rectal cancer. **Methods:** Patients diagnosed with stage II-III rectal cancer treated with chemo and/or RT from 1995-2019 were included in a retrospective study. Patients treated with palliative intent and those who survived < 5 years from treatment were excluded. RT-associated SPM was defined as a cancer occurring $^{3}5$ years after RT completion. Cumulative incidence (CI) of SPM was analyzed using a landmark analysis at 5 years with death as a competing risk. For patients with CT simulation scans available, dosimetric analyses evaluated doses to the organs developing SPM. Kaplan Meier analysis was used to evaluate overall survival among patients who developed an SPM. **Results:** A total of 2,700 patients were included (RT = 978; chemo = 1722). Demographic characteristics were equivalent apart from age, which was higher in the RT group (61 vs 59 years, $p < 0.001$). Five (0.3%) chemo patients developed an SPM, all within 5-10 years after treatment for rectal cancer, vs 48 (4.9%) RT patients. The 8-year CI of developing an SPM in the RT group was 4% (95% CI 2.4-6.2) and increased to 17% at 15 years (95% CI 12.1-21.8) and 21% at 20 years (95% CI 14.8-27.7). Most (89%) RT patients had received chemotherapy (most commonly 5-FU or FOLFOX). The median time to SPM was 108 months (interquartile range [IQR], 84-140). After pelvic RT, the most common SPM histology was endometrial (38%), followed by prostate (31%), bladder (23%), sarcoma (4.2%), and other gynecologic cancers (4.2%). Seven patients had CT simulations for dosimetric analyses: median of maximum dose to the organ with SPM was 5301cGy (IQR, 4928-5427), median of mean dose was 4551 cGy (IQR, 4476-4751). None of the patients who developed endometrial cancer had Lynch syndrome. Median OS for patients with SPM after RT was 5.1 years with 5-yr OS of 58% (95% CI 43-77); 44 out of 48 patients needed at least one treatment modality for their SPM, and 8 received trimodality treatment [surgery, chemo and RT]. **Conclusions:** The CI of SPM increased from 4% at 8 years to 17% at 15 years and 21% at 20 years following pelvic RT for rectal cancer. Endometrial cancer was the most common SPM and survival following treatment of SPM was favorable. These data serve as a foundation for future prospective studies evaluating ways to reduce SPM such as proton therapy. Research Sponsor: None.

12066 **Poster Session**

Impact of using volumetric dosimetry to screen childhood cancer survivors for radiation-related late effects. *First Author: Sally Cohen-Cutler, Children's Hospital Los Angeles, Los Angeles, CA*

Background: Late effects screening guidelines for survivors of childhood cancer treated with radiation therapy currently use irradiated regions (IR) rather than volumetric dosimetry (VD), which more precisely identifies organs-at-risk (OAR). We recently showed that VD reduced mean number of recommended screening diagnostic imaging studies and procedures by 37.0% per patient ($p<0.001$).[1] Here we have incorporated chemotherapy and refined volumetric dosimetry dose thresholds. **Methods:** This was a cross-sectional cohort study of patients (n=132) treated for cancer using computerized tomography-planned irradiation at Children's Hospital Los Angeles from 2000-2016. For each patient, both VD and IR methods were used to determine radiation exposure to the cochlea, heart, lung, breast, and colon. Dose thresholds for VD were based on those supplied in the Children's Oncology Group (COG) Long-Term Follow-Up Guidelines. Relevant chemotherapy exposures were recorded. Under each method, COG Long-Term Follow-Up Guidelines were applied to determine potential chemotherapy- and radiation-related late effects and their correlative screening practices (complete audiologic evaluation, pure tone audiometry, mammogram, breast MRI, echocardiogram, pulmonary functions test, and/or colonoscopy). Identified OAR were compared using Exact McNemar's test. Total numbers of screening practices were computed using VD and IR and compared. **Results:** Median age at end of treatment was 10.6 years (range 1.4-20.4). The most frequent cancer type was brain tumor (45%), followed by bone and soft tissue tumor (39%) and leukemia/lymphoma (16%). Head/brain was the most commonly irradiated region (61%), followed by abdomen (22%). Anthracyclines were received by 25% of patients at < 250 mg/m^2 and by 16% at ≥ 250 mg/m^2. With use of VD, fewer patients were flagged for screening for each organ of interest: cochlea (-21.3%, $p<0.001$), heart (-22.5%, $p<0.001$), lung (-13.8%, p=0.219), breast (-25%, p=0.625), colon (-51.9%, $p<0.001$). Over the lifetime of this cohort, use of VD resulted in recommendations for 1,333 fewer pure tone audiometric tests (-21.5%), 9 fewer complete audiologic evaluations (-16.1%), 4 fewer pulmonary function tests (-13.8%), 112 fewer mammograms (-25.0%) and breast MRIs (-25.0%), 349 fewer echocardiograms (-16.1%), and 275 fewer colonoscopies (-51.9%). **Conclusions:** Use of VD rather than IR significantly reduces guideline-based screening for radiation-related late effects in long-term childhood cancer survivors. This work forms the basis for a comparative cost-effectiveness analysis of these two approaches. (1) Cohen-Cutler et al, Cancer Medicine, 2020. Research Sponsor: The Hoag Family Foundation Fellowship.

12067 **Poster Session**

Safety of using hormone replacement therapy in breast cancer survivors: A systematic review and metanalysis. *First Author: Francesca Poggio, Breast Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy*

Background: Improvements in breast cancer (BC) care have led to increased survival of patients; hence, more attention to long-term treatment-related adverse events and quality of life (QoL) is required. Symptoms of spontaneous and treatment-induced menopause significantly affect the QoL and adherence to endocrine therapy among BC survivors, with potential negative implications on outcome. Use of systemic hormone replacement therapy (HRT) to mitigate menopause-associated symptoms is not recommended to reduce the burden of these side effects being historically associated with an increased risk of disease recurrence. This systematic review and metanalysis aimed to estimate the effect of HRT on risk of disease recurrence in BC survivors. **Methods:** A systematic search of Pubmed and Embase libraries up to January 15, 2021, was conducted in order to identify randomized controlled trials (RCTs) investigating the risk of disease recurrence with the use of HRT in BC survivors. We used the random-effect model to calculate the overall risk of recurrence, reported as pooled hazard ratio (HR) with 95% confidence intervals (CI). Moreover, we performed a subgroup analysis to estimate the risk of recurrence according to hormone receptor status. The Higgins I^2 index was computed to assess the heterogeneity between studies. The likelihood of publication bias was assessed by Egger's test. **Results:** Four RCTs were found and three were included in the metanalysis (n = 3.973 patients); one study (n = 100 patients) was excluded due to the impossibility to extract the HR for disease recurrence. Overall, 1.990 patients were randomized to receive HRT (estrogen-progesteron combination or tibolone), while 1.983 patients were included in control groups (placebo or no HRT). As compared to control group, HRT significantly increased the risk of BC recurrence (HR 1.49, 95% CI 1.15-1.93, $p = 0.002$). The heterogeneity between the studies was low (39%, $p = 0.194$), and no publication bias was found ($p = 0.537$). Two studies reported the HR according to hormone receptor status. At the subgroups analysis, the risk of BC recurrence with the use of HRT was significantly increased in hormone receptor-positive patients (HR 1.8, 95% CI 1.15-2.82, $p = 0.010$) but not in those with hormone receptor-negative tumors (HR 1.25, 95% CI 0.83-1.88, $p = 0.290$). **Conclusions:** Use of HRT significantly increases the risk of recurrence in BC survivors, particularly in those with hormone receptor-positive disease. Therefore, this approach remains contraindicated in this setting. Alternative interventions to mitigate menopause-related symptoms should be proposed to these patients. Research Sponsor: None.

12068 **Poster Session**

Associations between preexisting nociplastic pain and early discontinuation of aromatase inhibitor therapy in breast cancer. *First Author: Elizabeth Joyce, University of Michigan Health System, Ann Arbor, MI*

Background: Aromatase inhibitors (AI) are recommended for at least five years to reduce risk of breast cancer recurrence in postmenopausal women with hormone receptor-positive disease. Despite the potential benefit, up to 50% of patients discontinue AI early, primarily because of musculoskeletal side effects. Some patients, including those with fibromyalgia and other chronic pain conditions, have preexisting pain that arises from altered nociception without clear evidence of tissue or peripheral nerve damage, called nociplastic or centralized pain. We hypothesized that preexisting nociplastic pain is associated with early discontinuation of AI therapy due to toxicity. **Methods:** Patients diagnosed with breast cancer between 2012-19 and who enrolled in the Michigan Genomics Initiative (MGI) were identified. Patients who were female, had hormone receptor-positive breast cancer, had not received neoadjuvant therapy, and who initiated adjuvant AI therapy were included in the analysis. Prior to breast cancer surgery patients completed surveys about pain in the affected breast and overall worst pain (Brief Pain Inventory [BPI]), nociplastic pain (2011 Fibromyalgia Survey [FS], which assesses widespread pain plus somatic symptom severity), and anxiety (PROMIS Anxiety 4a v.1). Demographics, cancer characteristics, and treatment history, including date and reason for discontinuation of AI therapy, were abstracted from the medical record. Patients were censored at date of last oncology follow-up. Univariate and multivariable analyses were conducted to assess relationship between age, BMI, surgical site pain, overall worst pain, FS score, anxiety, and time to discontinuation of initial AI medication. **Results:** Of 207 analyzed patients, the average age was 61 years, average BMI was 30.3 kg/m^2, 181 (87%) were postmenopausal at the time of breast cancer diagnosis, and 31% received chemotherapy. The majority were prescribed anastrozole (n=196); 6 took letrozole and 5 took exemestane. Average scores prior to surgery were 1.5/10 for worst pain, 0.2/10 for surgical site pain, 4.2/31 for FS score, and 54.1/100 for anxiety. On univariate analysis, only use of exemestane (HR 5.55, $p<.001$) and use of letrozole (HR 3.11, $p<.001$) were associated with shorter time to ET discontinuation; age, BMI, surgical site pain, worst pain, FS score, and anxiety were not statistically significantly associated with time to AI discontinuation. On multivariable analysis, only higher FS score was statistically significantly associated with time to AI discontinuation (HR 1.11, p=.021). **Conclusions:** Greater pre-existing nociplastic pain was associated with early discontinuation of AI therapy. For these patients, early interventions that target centralized pain, or treatment with tamoxifen instead of AI therapy, may be appropriate in order to reduce risk of nonpersistence with AI therapy. Research Sponsor: None.

12069 **Poster Session**

Prevalence and predictors of peripheral neuropathy after chemotherapy: Outcomes from the Detroit Research on Cancer Survivorship (ROCS) cohort. *First Author: Kalyan Sreeram, Ascension St. Vincent Hospital, Indianapolis, IN*

Background: Increased life expectancy for cancer survivors following advances in treatment has led to a greater likelihood of developing long-term complications. Among them is chemotherapy-induced peripheral neuropathy (CIPN), which adversely impacts the functional capacity of survivors. We assessed prevalence and predictors of CIPN in a cohort of African-American (AA) cancer survivors. **Methods:** The study population included 633 breast, colorectal, prostate and lung cancer survivors who received chemotherapy and participated in the Detroit Research on Cancer Survivorship (ROCS) study. Presence of CIPN was based on self-reported pain, numbness or tingling in the hands or feet, occurring either for the first time or worsening after chemotherapy. If participants reported continued CIPN at the time of survey, their symptoms were reported as persistent. CIPN severity was self-reported as mild, moderate or severe. Logistic regression analysis was used to evaluate socio-demographic and clinical factors (including 12 common comorbid conditions) associated with CIPN prevalence, persistence and severity. **Results:** Overall, 67% of the cohort reported CIPN at a mean time of 25.3 months (range 2-74 months) after cancer diagnosis, and 51% reported persistent CIPN. The distribution of CIPN severity consisted of 32.2% with mild, 30.8% with moderate, and 36.9% with moderate to severe symptoms. Diagnosis of primary breast (OR 3.99, 95% CI 1.52-10.46) or colorectal cancers (OR 5.24, 95% CI 2.17-12.69) conferred greater CIPN prevalence relative to a diagnosis of prostate cancer. The presence of each additional comorbid condition among those outlined in the survey also conferred a 20% greater prevalence of CIPN (OR 1.2, 95% CI 1.03-1.39). Similar trends were seen among those who reported persistent CIPN. Using age $>$ 65 at diagnosis as the reference group, age $<$ 50 (OR 2.64, 95% CI 1.43-4.88) and age 51-64 (OR 1.96, 95% CI 1.14-3.35) resulted in an increased risk of moderate or severe compared to mild CIPN. **Conclusions:** In the Detroit ROCS cohort, CIPN was reported in two-thirds of cancer survivors receiving chemotherapy. Out of them, more than one-third reported moderate to severe symptoms, more commonly seen among those age $<$ 65. Consideration of CIPN as a prominent long-term complication of cancer treatment should play a role in treatment decisions and development of new chemotherapy regimens. Research Sponsor: None.

12070 **Poster Session**

Late cardiac events and their impact on overall survival in patients receiving an allogeneic stem cell transplant. *First Author: Christine Auberle, Washington University School of Medicine in St. Louis, St. Louis, MO*

Background: There is limited data on the impact of cardiac disease on long term outcomes of allogeneic stem cell transplant (alloSCT). We sought to describe the importance of adverse cardiac events on long term outcomes of alloSCT. **Methods:** We performed a retrospective analysis of pts who underwent alloSCT from 2007 to 2017 and survived at least one year after transplantation. Late cardiac events were defined as occurring at least one year after transplant. Data was obtained through electronic medical records and the transplant database at Siteman Cancer Center. Univariate Cox proportional hazards model was used to assess the effect of baseline characteristics on cardiac events and overall survival. Time-dependent Cox model was used to determine the effect of cardiac events on overall survival. Gray's sub-distribution methods, while accounting for death as a competing risk, were used to calculate the incidence of cardiac events. **Results:** 804 pts met our criteria (58.7% male, average age 49.7 years). Median duration of follow up was 59.3 months. Most pts were transplanted for acute myeloid leukemia (49.9%) and had a match-related or unrelated donor (56.1%). The majority received myeloablative conditioning (74.4%), and 34.6% received total body irradiation (TBI). The most common late cardiac events were an elevated troponin (20.9%), elevated brain natriuretic peptide (BNP) or N-terminal pro-BNP (16.9%), shock (15.3%), and reduced left ventricular ejection fraction (LVEF) defined as $<$ 45% (10.4%). Pts were at significantly increased hazard of developing late cardiac events if they were of male sex (HR 1.29, P = 0.026), had pre-existing diabetes (HR 1.45, P = 0.022), pre-existing atrial fibrillation or flutter (HR 1.77, P = 0.008), history of congestive heart failure (HR 1.82, P = 0.032) or increasing age at time of transplant (HR 1.02, P $<$ 0.001). Primary disease for alloSCT, donor type, TBI and myeloablative conditioning regimen had no significant association with late cardiac events. The cumulative incidence of developing any cardiac event in the period 1-5 years after transplant was 28.2% with a cumulative incidence of shock at 13.6%, reduced ejection fraction at 8.7% and an atrial arrythmia at 7.1%. Most cardiac events were associated with an increased risk of death (Table). **Conclusions:** Cardiac events after alloSCT have a substantial impact on overall survival. Efforts to optimally manage cardiac disease after alloSCT are likely to have a major benefit, and cardiac protection should be a major focus for post-alloSCT follow up. Research Sponsor: Mentors in Medicine Program, Division of Medical Education, Department of Internal Medicine at the Washington University School of Medicine.

The effect of cardiac events on risk of death.

Cardiac event	Hazard Ratio (HR)	95% CI
Troponin elevation	10.7*	8.4-13.5
Percutaneous coronary intervention	1.6	0.7-3.7
Atrial arrythmia	10.6*	7.7-14.6
LVEF < 45%	5.8*	4.3-7.9
Elevated NT pro-BNP	5.2*	3.7-7.3
Shock	19.0*	14.7-24.4
Pericarditis	7.5*	3.9-14.7
Pericardial effusion	5.2*	3.3-8.3

*Statistically significant.

12071 **Poster Session**

Feasibility and first results of digital patient-reported outcomes measures (PROMs) data collection for patients with localized prostate cancer at diagnosis. *First Author: Geraldine Pignot, Institut Paoli-Calmettes, Marseille, France*

Background: Patient-reported outcomes measures (PROMs) allow optimal evaluation of side effects of treatments and their impact on quality of life. In localized prostate cancer, these PROMs are an interesting tool for comparing the impact of different treatments. The objective of our study was to evaluate the feasibility of a PROMs assessment using a digital application and to analyze the functional outcomes at 1, 3 and 6 months for urinary continence and sexuality. **Methods:** Since May 2019, patients treated for localized prostate cancer in our center, regardless of the treatment choice, have been offered inclusion in a digital prospective program. PROMs questionnaires (EPIC-26, Q50 PR25, EQ- 5D and PRO-CTCAE) were sent via a dedicated digital application, before treatment (T0), at 1 month (M1), 3 months (M3), 6 months (M6) and 1 year. Program adherence was assessed by the proportion of patients who logged in to the app and the proportion of patients who responded to questionnaires. The first results, at T0, M1, M3 and M6, were analyzed for urinary continence and erectile function, and compared according to age, baseline characteristics and treatment strategy. **Results:** Between May 2019 and December 2020, 324 patients were included in the program. Thirty patients (9.3%) did not log into the app and 29 (8.9%) logged in but did not respond to the PROMs questionnaires sent out. The adherence rate was not related to age or treatment strategy. In the end, 265 patients (81.8%) answered the PROMs questionnaires, including 185 patients treated by surgery, 11 by brachytherapy, 15 by radiotherapy, 24 by radio-hormonotherapy and 30 under active surveillance. Before treatment (T0), 15.8% (42/265) of patients reported having urine leakage (at least once a week) and 41.5% (110/265) having poor or no erections. At M1, M3, and M6, the incontinence rate was 50.8%, 37.8% and 28.7% respectively, and the erectile dysfunction rate was 73.3%, 74.1% and 70.1% respectively. Sexual recovery was strongly associated with baseline erectile function (T0); patients with good sexual function at diagnosis had an erectile dysfunction rate of 53.8% at 1 month (versus 89.9% for patients with pre-existing sexual dysfunction, p $<$ 0.001), and 51.1% at 3 months (versus 84.0%, p $<$ 0.001). Age was not associated with continence or sexuality recovery. Patients treated with surgery had significantly poorer functional outcomes in terms of continence (p $<$ 0.001) and sexuality (p $<$ 0.001) compared to other strategies. **Conclusions:** The implementation of PROMs using a digital application achieves an adherence rate of over 80%. The incontinence rate decreases rapidly over the 6 months following treatment, while erectile dysfunction rate remains stable over time. Early side effects are more common after surgery, requiring appropriate supportive strategies. Research Sponsor: ARS (AAP Pertinence des Soins).

12072 **Poster Session**

Treatment-specific risk of second malignancies in five-year survivors of diffuse large B-cell lymphoma. *First Author: Yvonne M. Geurts, Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Due to the historically less favorable prognosis of diffuse large B cell lymphoma (DLBCL), the burden of second malignant neoplasms (SMNs) has been rarely studied in DLBCL survivors. However, radiotherapy and chemotherapy may increase SMN risk among DLBCL patients. Anthracyclines may increase the risk of hematological malignancies, but it is not clear whether they also increase solid cancer risk. **Methods:** We established a multicenter cohort of 2,384 5-year DLBCL survivors treated at ages 15-60 years with radiotherapy and/or immunochemotherapy between 1989 and 2012. Observed numbers of SMNs were compared with expected cancer incidence in the general population to compute standardized incidence ratios (SIRs), absolute excess risks (AERs, per 10.000 person-years) and cumulative incidence. Treatment specific incidence was compared with general population rates and assessed within the cohort using Cox regression. **Results:** Most DLBCL patients received alkylating agents (95%), anthracycline-containing chemotherapy (95%) or radiotherapy (61%); 46% received rituximab. Median follow-up was 13.3 years; 17% of patients was followed ≥20 years. In total, 308 5-year survivors developed an invasive SMN (SIR 1.6; 95% confidence interval (CI), 1.4 to 1.8), translating into 56.2 excess cancers per 10.000 person-years (see Table for specific sites). In 20-year survivors of DLBCL, the SIR was 1.8 (95% CI 1.3-2.6). The 20-year cumulative incidence of any SMN was 18.7% (95% CI 16.5-21.0%). The SIR for any SMN was higher in patients $<$40 years at first treatment (SIR ≤40 years: 2.8, SIR $>$40 years: 1.4; p$<$0.001). Treatment specific results will be presented at ASCO21. **Conclusions:** DLBCL survivors experience higher risk of SMNs than the general population. Identification of patients at increased risk could improve follow-up care. Research Sponsor: Dutch Cancer Society.

SIRs, AERs and 20-year cumulative incidence of selected SMNs*.

Second malignancy site	Number of patients	SIR (95% CI)	AER 10.000 person-years	20-year cumulative incidence (95% CI)
Any cancer	308	1.6 (1.4-1.8)	56.2	18.7 (16.5-21.0)
Any solid cancer	263	1.5 (1.3-1.7)	41.9	16.4 (14.3-18.6)
Head & Neck	18	2.5 (1.5-4.0)	5.3	1.0 (0.6-1.8)
Gastrointestinal tract	63	1.5 (1.1-1.9)	10.0	4.1 (3.0-5.4)
Esophagus	10	2.2 (1.0-4.0)	2.6	0.4 (0.2-0.9)
Stomach	10	3.2 (1.5-5.9)	3.3	0.6 (0.3-1.2)
Colorectal	24	0.9 (0.6-1.4)	-0.9	1.6 (1.0-2.6)
Bronchus and lung	53	2.1 (1.6-2.8)	13.7	3.1 (2.3-4.1)
Melanoma skin cancer	14	1.4 (0.8-2.4)	2.0	1.0 (0.5-1.7)
Bone, joint and soft-tissues	6	3.5 (1.3-7.7)	2.1	0.4 (0.1-0.9)
Bladder	10	1.9 (0.9-3.5)	2.3	0.5 (0.2-1.0)
Female breast	29	1.2 (0.8-1.7)	5.2	4.2 (2.7-6.2)
Hodgkin lymphoma	6	10.6 (3.9-23.1)	2.6	0.4 (0.2-0.8)
Acute myeloid leukemia	15	7.0 (3.9-11.5)	6.3	0.7 (0.4-1.2)

*Only first invasive cancers. Excludes Kaposi sarcoma. Includes myelodysplastic syndrome. AER, absolute excess risk; CI, confidence interval; SIR, standardized incidence ratio.

12073 **Poster Session**

Overall and cardiac-specific mortality following serious cardiovascular events in survivors of childhood cancer: A report from the Childhood Cancer Survivor Study (CCSS). *First Author: Wendy Bottinor, Virginia Commonwealth University, Richmond, VA*

Background: The direct impact of a major cardiovascular (CV) event on mortality among childhood cancer survivors is not well described. We hypothesized that mortality following a major CV event would be higher among survivors compared with siblings and that mortality would be influenced by primary cancer treatment. **Methods:** The CCSS cohort has conducted longitudinal follow-up of 25,658 survivors of childhood cancer and 5,051 siblings. All-cause and CV-cause specific mortality after a first event of heart failure (HF), coronary artery disease (CAD), or stroke occurring at least 5 years after cancer diagnosis, was estimated using the Kaplan-Meier method. The relative hazards (HR) and 95% confidence intervals (CI) between survivors and siblings as well as the influence of demographic (sex, age, race/ethnicity) and cancer treatment factors were estimated via Cox regression. **Results:** In total, 1780 survivors and 91 siblings experienced a serious CV event. Total deaths included 706 survivors (271 cardiac causes, 381 non-cardiac causes, 54 unknown causes) and 14 siblings. Survivors were a median age of 31.5 years (range 6.5-61.5) and 20.0 years (range 5.0-44.6) since cancer diagnosis at time of CV event. After a CV event, estimated 10- and 20-y all-cause mortality was significantly higher among survivors than siblings (Table). The HR for all-cause mortality was significantly higher among survivors than siblings after HF (HR 5.2, CI 2.1-13.0), CAD (HR 4.2, CI 2.0-9.0), and stroke (HR 4.6, CI 1.5-14.6). HF and stroke-specific mortality were not significantly increased among survivors versus siblings, in contrast to CAD-specific mortality (HR 3.5, CI 1.1-11.0). Among survivors, heart dose from radiotherapy (per 10 Gy) was associated with increased all-cause and cause-specific mortality after HF (HR 1.2, CI 1.0-1.3; HR 1.3, CI 1.0-1.7), all-cause mortality after CAD (HR 1.2, CI 1.0-1.3), and cause-specific mortality after stroke (HR 2.5, CI 1.2-4.9). Brain dose from radiotherapy was associated with increased all-cause mortality (HR 1.1, CI, 1.0-1.2, per 10 Gy) after stroke. Anthracycline dose was not associated with increased overall or cause-specific mortality risk after a CV event. **Conclusions:** After a CV event, mortality is higher among survivors than siblings. In survivors, mortality is primarily driven by non-cardiac causes. CAD and prior radiotherapy exposure to the heart and brain also influenced mortality. Research Sponsor: Childhood Cancer Survivor Study.

Kaplan-Meier estimates of all-cause mortality probability after a CV event.

		HF	CI	CAD	CI	Stroke	CI
10-y mortality	Survivors	30%	0.26-0.33	36%	0.31-0.40	29%	0.25-0.33
	Siblings	14%	0.00-0.25	14%	0.02-0.25	4%	0.00-0.11
20-y mortality	Survivors	48%	0.44-0.53	63%	0.56-0.69	41%	0.35-0.45
	Siblings	14%	0.00-0.25	14%	0.02-0.25	19%	0.00-0.38

Log-rank tests comparing survivor and sibling survival curves all had P<0.001.

12074 **Poster Session**

Anthracycline exposure and breast cancer risk in female Hodgkin lymphoma survivors. *First Author: Suzanne I.M. Neppelenbroek, Department of Epidemiology, Netherlands Cancer Institute, Amsterdam, Netherlands*

Background: Female Hodgkin lymphoma (HL) survivors treated with chest radiotherapy (RT) at a young age have a strongly increased risk of breast cancer (BC). Recently concern has been raised that anthracyclines may also increase BC risk, based on studies in childhood cancer survivors with/without a history of chest RT. So far, the association between anthracyclines and BC risk has not been examined in cancer survivors treated at adolescent/adult ages. Now that RT dose and volumes are decreasing, the potential contribution of anthracyclines to BC risk is an important issue. **Methods:** We assessed BC risk in a cohort of 2314 female 5-year HL survivors, treated at ages 15-50 years and diagnosed between 1965 and 2008 in 20 Dutch hospitals. Treatment factors were time-dependently included in the analysis, focusing on the effect of anthracycline exposure on BC risk. **Results:** After a median follow-up of 18.8 years, 258 women developed invasive BC or ductal carcinoma in situ as a subsequent malignancy. The 30-year cumulative incidence was 15.0% (95% Confidence Interval (CI) 12.8-17.4%). Mantle field RT (or other RT involving both axillae) was associated with increased risk of BC (Hazard ratio (HR) 1.9; 95% CI 1.2-2.8) compared to no supradiaphragmatic RT or RT to the neck only (Table 1). Gonadotoxic treatment (>4.2 g/m^2 procarbazine or pelvic RT) significantly decreased this risk. In a multivariable analysis, anthracycline exposure was associated with increased BC risk (HR 1.8; 95% CI 1.3-2.5) in patients who received a cumulative dose of >200 mg/m^2. Among patients exposed to gonadotoxic treatment, the HR of BC associated with >200mg/m^2 anthracyclines was 3.8 (95% CI 2.0-7.2), with a trend for higher risk with higher anthracycline dose (HR 1.58 per 100mg/m^2 anthracycline, p<0.001). **Conclusions:** Our results suggest an association of anthracyclines with BC risk in HL survivors. Also when accounting for the protective effect of gonadotoxic treatment on RT-associated BC risk, anthracyclines significantly contributed to a higher BC risk. Research Sponsor: KWF Dutch Cancer Society.

Cox PH regression model of anthracycline exposure and breast cancer risk.

	Number of patients N=2314	Events (%) N=258	Hazard ratio (95% CI)
Anthracyclines			
No anthracyclines	994	172 (17.3%)	1.0
35-200 mg/m^2 (median: 150 mg/m^2)	471	21 (4.5%)	1.5 (0.9-2.5)
>200 mg/m^2 (median: 245 mg/m^2)	793	64 (8.1%)	1.8 (1.3-2.5)
Unknown	56	1 (1.8%)	0.3 (0.0-2.0)
Supradiaphragmatic RT			
No supradiaphragmatic RT	356	20 (5.6%)	1.0
Incomplete mantle field	968	48 (5.0%)	0.9 (0.5-1.5)
Full mantle field	990	190 (19.2%)	1.9 (1.2-3.1)
Gonadotoxic therapy			
No procarbazine or pelvic RT	1213	160 (13.2%)	1.0
No pelvic RT & <=4.2 g/m^2 procarbazine	453	43 (9.5%)	0.8 (0.5-1.2)
No pelvic RT & >4.2 and <8.4 g/m^2 procarbazine	331	35 (10.6%)	0.7 (0.4-1.0)
No pelvic RT & >=8.4 g/m^2 procarbazine	124	9 (7.3%)	0.4 (0.2-0.9)
Pelvic RT	193	11 (5.7%)	0.3 (0.1-0.6)

RT: radiotherapy; adjusted for age at first treatment.

12075 **Poster Session**

Predictors of falls after starting an exercise program: A secondary analysis in inactive, female cancer survivors participating in the GET FIT trial. *First Author: Deanne Tibbitts, Oregon Health & Science University, Portland, OR*

Background: Women treated for cancer are more likely to fall than women without a cancer history. Exercise is a fall prevention strategy for older adults that we are testing in the GET FIT trial as a fall prevention approach in women cancer survivors. Increasing physical activity, though, could acutely increase the risk of falls in inactive survivors with known fall risk related to treatment. Knowing who might be at risk prior to beginning an exercise program would inform additional safety precautions during exercise. **Methods:** We conducted a secondary analysis of baseline data from the GET FIT trial that enrolled inactive, older women who had completed chemotherapy for cancer. Women completed objective (muscle strength, static postural control, range of motion, physical functioning) and self-report (fall history, comorbidities, presence of neuropathy symptoms, pain severity, depressive symptoms, cognitive functioning, perceptions of lower extremity functioning, disability, fear of falling, demographic, and clinical characteristics) measures at baseline. Falls were prospectively collected during the 6 month intervention using monthly self report. Potential predictors of falls were included if univariate tests revealed significant differences between fallers and non-fallers. To identify the strongest predictors of falls, we used an automated model selection and multimodel inference approach to perform an exhaustive model search. **Results:** Baseline data were available for 415 participants with known faller status at the end of the intervention, of whom 31.3% (n = 130) reported at least one fall. The average age of the sample was 62.1±6.4 years and consisted mostly of non-Hispanic white, married, highly educated, overweight or obese women treated for breast cancer. Fallers (1+ falls) and non-fallers significantly differed on measures of fall history, comorbidities, pain, neuropathy, fear of falling, disability, perceived lower extremity functioning, cognitive functioning, depression, and postural control. The best model of faller status (per BIC) included postural control (p = 0.004), perceived lower extremity functioning (p = 0.072), and fear of falling (p = 0.030). Odds of ≥1 fall during the intervention increased by 1.72 (95% CI: 1.05-2.83) times for a 0.1-point decrease in postural control, 1.11 (1.04-1.19) times for a 0.1-point increase in fear of falling, and 1.02 (1.00-1.03) times for a 1-point decrease in perceived lower extremity functioning. **Conclusions:** Women cancer survivors with poor balance, poor self-rated functioning, and a fear of falling may need to take additional fall precautions when starting an exercise program. Clinical trial information: NCT01635413. Research Sponsor: U.S. National Institutes of Health.

12076 **Poster Session**

Factors associated with weight gain during endocrine therapy for breast cancer. *First Author: Anna-Carson Uhelski, Johns Hopkins University School of Medicine, Baltimore, MD*

Background: Weight gain is common after a breast cancer diagnosis. The incidence of and risk factors for weight gain during adjuvant endocrine therapy (ET) are poorly described. Limited data support an association between emergent symptoms and weight gain after a breast cancer diagnosis. **Methods:** We enrolled women with stage 0-III breast cancer initiating ET in a prospective clinic-based cohort. We assessed symptoms with the FACT-ES and PROMIS pain interference, depression, anxiety, fatigue, sleep disturbance and physical function measures at baseline (BL), 3, 6, 12, 24, 36, 48 and 60 months (mo). We defined emergent symptoms at 3 and/or 6 mo as worsening of 4 points from BL on PROMIS measures and 5 points from BL on the FACT-ES. We abstracted weight and menopausal status from charts. The primary outcome of this secondary analysis was weight gain (dichotomized as ≥5% vs < 5% of body weight compared to BL) through 60 mo. We evaluated the association between weight gain during ET and menopausal status. We also evaluated the associations between clinicodemographic factors and emergent symptoms with weight gain and if these associations differed by menopausal status. We performed logistic regression modeling with GEE to account for the longitudinal design. We identified a multivariable model for the set of factors associated with weight gain among pre-menopausal women taking ET. **Results:** 309 of 321 participants with BL and ≥1 follow-up (FU) weight were included. 263 (85%) had stage I-II disease, 99 (32%) were pre-menopausal, 259 (84%) were White and 32 (10%) were Black. Prior to ET, 45% had mastectomy, 66% had radiation, and 28% received chemotherapy. 4% of pre- and 82% of post-menopausal participants initiated an aromatase inhibitor (AI); all others initiated tamoxifen (Tam). 17% of pre-menopausal participants received ovarian suppression. At BL, 75% of Black and 59% of White participants were overweight/obese. With a median FU of 56 mo, 51% of pre- and 34% of post-menopausal participants gained ≥5% body weight (OR 1.09, 95% CI 1.07-1.13, p < 0.001). For each PRO measure, > 20% of participants had emergent symptoms. Worsening of physical function and pain interference scores at 3 and/or 6 mo were differentially associated with weight gain according to menopausal status (interaction p-values ≤0.05). On multivariate analysis, factors associated with weight gain among pre-menopausal participants were ET (AI vs Tam) (OR 2.8, 95% CI 0.90- 8.77, p = 0.08), prior mastectomy (OR 2.06, 95% CI 0.89-4.77, p = 0.09), emergent pain interference (OR 2.49, 95% CI 0.99-6.24, p = 0.05) and race (White vs other) (OR 7.13, 95% CI 1.29-39.4], p = 0.02). **Conclusions:** Weight gain during ET for breast cancer is more frequent among pre-menopausal than post-menopausal women. Worsening pain soon after ET initiation, receipt of AI, prior mastectomy and race may identify pre-menopausal women at risk for weight gain for whom prevention strategies are a priority. Research Sponsor: Susan G Komen.

12077 **Poster Session**

Long-term quality of life of cancer survivors: A case-control study. *First Author: Joaquin Ponce-Zepeda, UC Irvine Douglas Hospital, Orange, CA*

Background: There were extensive reports in literature about the debilitating health experienced by cancer patients during treatment. This study examined how the quality of life of cancer survivors changed over time. **Methods:** The National Health and Nutrition Examination Survey (NHANES) is a program of studies designed to assess the health and nutritional status of adults and children in the U.S. This study involved participants in NHANES from 2000-2020. Participants who reported having had a cancer diagnosis were matched one to one with participants who reported no cancer diagnosis by age, gender, race, year of recruitment into NHANES, and comorbidities. Quality of life measures including self-reported general/physical/mental health, examinations, and laboratory tests were compared between cancer cases and matched controls using paired t tests. **Results:** This study included 5,166 pairs of cancer cases and matched controls. Mean age was 66 (± 15 years). Male 47% and female 53%. White 69%, Black 14%, Hispanic 12%, others 5%. Most common comorbidities were hypertension (56%), arthritis (50%), diabetes (19%), and thyroid (18%). About 38% of cancer cases had survived in 1-5 years; 22% in 6-10 years; 39% in 10+ years. Most prevalent cancers were skin (28%), breast (15%), and prostate (15%). Compared to controls, cancer cases who had survived in 1-5 years reported higher rates of poor general health (38% vs. 27%, $p < .0001$), hospitalizations (31% vs. 17%, $p < .0001$), mental health visits (9% vs. 7%, $p = .0204$). There were no significant differences in general health and healthcare utilization between cancer cases who survived > 5 years and controls. There were no clinically meaningful differences in laboratory tests and examinations between cancer cases and controls regardless of survival time. **Conclusions:** During the first 5 years after cancer diagnosis, survivors reported worse health than controls. As survival time extended, there was no difference between cancer cases and controls. The debilitating health reported during the first 5 years could not be explained by examinations and laboratory tests alone. Future research should explore neurochemical and hormonal markers to investigate adverse effects of cancer treatment on long-term quality of life. Research Sponsor: None.

12078 **Poster Session**

Investigating the prevalence and risk of chemotherapy-induced neuropathy among cancer patients. *First Author: Philip Jordache, University of Chicago, Chicago, IL*

Background: Neuropathy is a common side effect of some chemotherapies. Clinical and other factors may confer neuropathy risk, but rates and risk factors across neuropathy-causing chemotherapies are incompletely understood. **Methods:** We examined 15 chemotherapy drugs known to confer neuropathy. Within a broad population of cancer patients who underwent treatment with these agents at the University of Chicago Medicine between 2012-2018, we determined prevalence of chemotherapy-induced neuropathy, defined as patients with initiation of a neuropathy treatment medication (amitriptyline, carbamazepine, duloxetine, gabapentin, or pregabalin) after starting chemotherapy. We then analyzed chemotherapy-induced neuropathy risk for different drugs and based on clinical demographic factors. **Results:** We analyzed 7,866 patients (65.3% White, 53.7% Female, 27.6% Black/African-American, 5.6% Hispanic or Latino, 3.1% Asian/Mideast Indian, 2.4% More than one Race, 0.2% American Indian or Alaska Native, 0.2% Native Hawaiian/Other Pacific Islander). The overall prevalence of chemotherapy-induced neuropathy was 24.3% across our patient population. Black/African-American patients had an increased risk of chemotherapy-induced neuropathy compared to the rest of the patient cohort (OR 1.4, 95% CI 1.3-1.6, $P = 1.6e-10$). Females also exhibited an increased risk of chemotherapy-induced neuropathy compared to males (OR 1.2, 95% CI 1.1-1.3, $P = 1.5e-3$). **Conclusions:** Certain chemotherapy agents confer substantial risk of chemotherapy-induced neuropathy, and risk is increased in Blacks and females. Future work will investigate additional risk-modifying factors including the potential role of germline polymorphisms on chemotherapy neuropathy risk. Research Sponsor: None.

Chemotherapy drug	Total patients taking chemotherapy drug*	Patients initiated on at least 1 neuropathy treatment-related medication after chemotherapy start	Proportion initiated on neuropathy treatment-related medication after chemotherapy start out of total patients taking chemotherapy drug
Vincristine	473	106	106/473 = 22.4%
Bortezomib	274	61	61/274 = 22.3%
Cisplatin	1,109	216	216/1,109 = 19.5%
Oxaliplatin	1,376	242	242/1,376 = 17.6%
Paclitaxel	3,209	527	527/3,209 = 16.4%
Docetaxel	1,196	190	190/1,196 = 15.9%
Vinblastine	150	23	23/150 = 15.3%
Lenalidomide	427	63	63/427 = 14.8%
Carboplatin	3,099	434	434/3,099 = 14.0%
Vinorelbine	145	17	17/145 = 11.7%
Ixabepilone	11	1	1/11 = 9.1%
Cabazitaxel	102	8	8/102 = 7.8%
Pomalidomide	98	7	7/98 = 7.1%
Eribulin	151	9	9/151 = 6.0%
Carfilzomib	156	5	5/156 = 3.2%
TOTAL	**7,866**	**1,909**	**1,909/7,866 = 24.3%**

*Patients receiving multiple chemotherapies are listed for each individual drug received.

12080 **Poster Session**

Effect of an e-home based symptom management and mindfulness training program on quality of life in breast cancer survivors: A randomized clinical trial. *First Author: Karis Kin-Fong Cheng, National University of Singapore, Singapore, Singapore*

Background: The first five years post-treatment for breast cancer are a critical phase, when the survivors may face a multitude of physical and psychosocial problems. We aimed to develop an e-home based symptom management and mindfulness training program to support women with breast cancer in transition to survivorship and to determine its effect on the endpoints including quality of life, symptom distress, psychosocial adjustment, and psychological morbidity. **Methods:** This parallel 4-arm, superiority randomized clinical trial together with a process evaluation using semi-structured interview recruited women who had completed cancer treatment for stage 0 to 3 breast cancer between 6 months to 5 years previously, from November 2016 through March 2020 at two tertiary hospitals. A total of 593 women were eligible, of these, 402 refused to participate and 191 women were randomized. However, 19 subjects withdrew from the study without completion of baseline assessments. Hence, 172 subjects were included in the intention-to-treat analysis (e-home based breast cancer survivorship program, experimental group; n = 44), comparison group 1 (online symptom management program only; n = 41), comparison group 2 (online mindfulness training program only; n = 44) or the usual care group (n = 43). The e-home based breast cancer survivorship program involved 5 weekly online education module regarding self-management strategies of common symptoms + various online self-administered mindfulness exercises. The primary endpoint included change of Quality of Life-Cancer Survivor Scale (QoL-CS) score measured at 8, 12 and 24 weeks from baseline. Secondary endpoints were changes of Social Support Questionnaire, Breast Cancer Survivor Self-Efficacy Scale, Memorial Symptom Assessment Scale, Psychosocial Adjustment to Illness Scale, Fear of Recurrence Scale, Hospital and anxiety Depression Scale, and Five Facet Mindfulness Questionnaire scores. **Results:** Of 172 subjects, mean ± SD age was 51.2 ± 9.4 years; 118 (77.7%) were in the first two years of cancer treatment completion; 165 (98.2%) underwent surgery; and 111 (73.5%) treated with adjuvant chemotherapy. All demographic and clinical characteristics were comparable among the four groups ($p > .05$). There was no between-group difference in the primary endpoint; QoL-CS scores among groups at 8, 12 and 24 weeks from baseline ($p > .05$). Secondary endpoints were also not different among groups ($p > .05$). Two main themes; positive impact and gap/barrier, emerged from process evaluation data. **Conclusions:** In women who were in the first five years post-breast cancer treatment, an e-home based multidimensional cancer survivorship program did not affect outcomes. Nevertheless, the interview data revealed a positive experience in regards to the home-based approach in cancer survivorship care program. Clinical trial information: NCT02931864. Research Sponsor: Singapore Cancer Society Cancer Research Grant.

12081 **Poster Session**

Association of cancer treatment with excess heart age among young breast cancer survivors. *First Author: Jacqueline B Vo, National Cancer Institute, Rockville, MD*

Background: Young women with breast cancer may be at increased risk for premature development of cardiovascular disease (CVD) in part due to their cancer treatment. Limited data are available on CVD risk among young breast cancer survivors. **Methods:** Women aged 30-40 years at diagnosis with stage 0-III breast cancer enrolled in a prospective cohort study of women diagnosed with breast cancer at ≤40 were eligible for inclusion in this analysis. Data were obtained from serial surveys and electronic medical records at breast cancer diagnosis and 5-year follow-up. We calculated excess heart age, which incorporates a CVD risk-based score (calculated using age, systolic blood pressure, blood pressure medication, diabetes, smoking, body mass index) to estimate the difference in years between an individual's chronological age and their CVD-risk adjusted age. Multivariable logistic regression models (adjusting for age at diagnosis, stage, and race) were fitted to evaluate associations between treatment (radiation, endocrine therapy, anthracyclines, and trastuzumab) and having a change in excess heart age ≥2 years from baseline to 5 years. **Results:** Among 372 young breast cancer survivors, mean age at diagnosis was 36.6 (SD 2.89), 93% were white, and 79% were diagnosed with stage I or II breast cancer. Mean excess heart age was .32 (SD: 6.16) years at baseline, which declined to -.07 (SD 6.64) at 5-year follow-up (p=.17). At 5 years, 31% (n=114) of women experienced an increase of at least 2 years in their excess heart age since diagnosis, and their mean excess heart age was 4.34 years (range -9 to 30). In multivariable analyses, receipt of trastuzumab was associated with higher odds (OR: 1.68, 95% CI: 1.02-2.77) of experiencing an increase of ≥2 years in excess heart age between diagnosis and 5 years of follow-up. Endocrine therapy, anthracyclines, and radiation were not significantly associated with a change in excess heart age of ≥2 years at 5 years post-diagnosis. **Conclusions:** At 5 years post-diagnosis, approximately 1/3 of young breast cancer survivors experienced a change from baseline in their excess heart age of ≥2 years. Further research is warranted to confirm findings regarding trastuzumab and excess heart age, and potential effects on longer-term cardiac outcomes in this population. Extended follow-up of this cohort may further quantify CVD risk over time. Research Sponsor: Breast Cancer Research Foundation/Susan G. Komen.

Association of treatment with change in excess heart age of ≥2 years from diagnosis to 5-year follow-up.

Cancer Treatment	Odds Ratio	95% CI Lower	95% CI Upper	Standard Error	P
Anthracyclines	1.31	.74	2.35	.39	.354
Trastuzumab	1.68	1.02	2.77	.43	**.040**
Radiation therapy	.75	.44	1.28	.20	.296
Endocrine therapy	.86	.52	1.40	.21	.532

12082 **Poster Session**

Perceptions of prognosis in caregivers of multiple myeloma (MM) patients. *First Author: Yael N. Shapiro, Massachusetts General Hospital, Boston, MA*

Background: Caregivers of patients with cancer play a critical role in supporting patients when making informed decisions about their medical care. Although MM patients and their caregivers face an incurable illness, data describing caregiver perceptions of the patient's prognosis and factors associated with accurate prognostic perceptions are lacking. **Methods:** We conducted a cross-sectional, multisite study of caregivers of MM patients between 6/2020-1/2021. Eligible caregivers were identified by the patient as the primary caregiver and enrolled in 1 of 3 cohorts based on lines of therapy: 1) caregivers of newly diagnosed patients receiving first-line therapy; 2) 2-3 lines; 3) ≥4 lines. Caregivers completed the Perception of Treatment and Prognosis Questionnaire to assess their perceptions of the illness and prognosis. We also used the CareGiver Oncology Quality of Life (QOL) questionnaire, the Hospital Anxiety and Depression Scale, the Post-Traumatic Stress Disorder Checklist–Civilian Version, and the Brief COPE to assess caregiver QOL, psychological distress, and coping strategies. We used a multivariate logistic regression analysis to examine whether caregiver factors (i.e. demographics), line of therapy, QOL, psychological distress, or coping were associated with caregiver perceptions of the patient's prognosis. **Results:** We enrolled 113 caregivers of MM patients (newly diagnosed (n=39), 2-3 lines (n=37), and ≥ 4 lines (n=37)). Overall, 89.2% (99/111) of caregivers reported that it is extremely' or very' important to know about the patient's prognosis and the majority (58.0%, 65/112) stated that they had received adequate information regarding the patient's prognosis. Caregivers reported that prognostic information was extremely' or very' helpful in making decisions about treatment (93.3%, 97/104), preparing for the future (88.2%, 90/102), and coping with the disease (85.6%, 89/104). Most caregivers (84.7%, 94/111) reported that the oncologist told them the patient's cancer was incurable. In contrast, only 53.6% (59/110) of caregivers reported that they thought the patient's cancer was incurable and 48.6% (52/107) acknowledged that the patient is terminally ill. In a multivariate analysis, we found that the use of positive reframing coping (OR=0.71, 95%CI=0.52-0.97, P=0.033) was associated with lower odds of reporting an accurate perception of prognosis. Caregiver demographics, line of therapy, QOL, and psychological distress were not associated with their perceptions of the patient's prognosis. **Conclusions:** Although the majority of caregivers of MM patients report that knowing the patient's prognosis is extremely important, a substantial minority still have significant misperceptions of the patient's prognosis. Interventions are needed to promote effective coping and enhance caregiver perceptions of the patient's prognosis to facilitate informed decision-making in this population. Research Sponsor: None.

12083 **Poster Session**

The moderating role of informal caregiver's involvement on the relationship between patient activation and adherence to treatment: Implications for self-management intervention in cancer care. *First Author: Chiara Acquati, University of Houston, Houston, TX*

Background: With increasing demands for a more active role on the part of individuals with cancer and their families in cancer care, patient activation (PA) is emerging as a key factor to promote self-management, adherence to treatment, and satisfaction with treatment planning. The present work investigated the relationship between patient activation and treatment decision making. Given the role informal caregivers play on patient-reported outcomes, it was additionally assessed whether caregiver involvement acted as a moderator of this relationship. **Methods:** Survey data collected from 504 cancer survivors recruited through online consumer panels were utilized. The survey contained questions concerning treatment options, quality of life, adherence to treatment, next to presence and involvement of informal caregivers. Additionally, the Patient Activation Measure (PAM), sociodemographic and clinical questions were included. A path analysis Structural Equation Modeling (SEM) controlling for covariates was used to examine the relationship between Patient Activation Measure (PAM), caregiver involvement, and the identified outcomes. Moderator analysis was conducted using multiple group SEM. **Results:** Respondents were mostly women (57.1%), non-Hispanic white (72.9%), middle aged or older adults (68% ≥ 55 y.o.) The four largest cancer type groups were prostate (16.3%), early stage breast (9.7%), gynecological (8.9%), and colorectal cancer (8.3%). Most of the respondents were diagnosed more than 4 years earlier (52.0%). Participants were evenly split between those who received care at an academic cancer center (29.4%) and those treated at community hospital (31.7%). Patient activation was significantly associated with treatment planning being reflective of survivors 'goals and values ($p < 0.001$); adherence to treatment ($p = 0.011$); and satisfaction ($p < 0.001$). Caregiver's involvement significantly moderated the association between activation and adherence to treatment. **Conclusions:** Patient activation was positively associated with all three selected outcomes. However, for cancer survivors reporting low rates of caregiver involvement, patient activation was not associated with treatment adherence. Research is needed to deliver and test patient activation interventions inclusive of informal caregivers to improve self-management. Research Sponsor: In collaboration with CancerCare.

12084 **Poster Session**

Dermatologic diagnoses in oncology patients of color on anticancer therapy: Five-year retrospective review of outpatient dermatology consultations. *First Author: Britney N. Wilson, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Dermatologic toxicities from cancer treatments affecting patients from racial and ethnic minority backgrounds or skin of color (SOC) patients is an understudied area of research. These patients are also significantly underrepresented in therapeutic clinical trials, limiting complete understanding of toxicities associated with cancer therapies. Current treatment algorithms for dermatological adverse events (dAE) also do not take into account possible biologic differences in different skin types affecting toxicity presentation and treatment response. In this study we summarize the demographic, clinical, and treatment characteristics of oncology patients from racial and ethnic minority backgrounds who developed dermatologic adverse events related to cancer therapies. **Methods:** We performed a retrospective review of all SOC patients (Asian, Black, Hispanic) on active cancer therapy who received outpatient dermatology consultation at Memorial Sloan Kettering Cancer Center from January 1, 2014 to December 31, 2019. Electronic health record information for 2917 patients was obtained. A computational keyword-based text analysis of medical chart text, developed in consultation with a board-certified dermatologist, was performed to determine dermatologic diagnoses categories for each patient. All analyses were conducted using R statistical programming software, version 4.2.06. **Results:** There were 2917 outpatient dermatology consultations. Our population consisted of 1992 (68.29%) females and 925 (31.71%) males with a mean age of 53 (range 0-97). There were 35.55% Black, 41.28% Asian, 1.02% (30) Native American or Alaskan Native, 0.17% (5) Native Hawaiian or Other Pacific Islander. 729 were Hispanic ethnicity of which 641 were Caucasian. A total of 4,026 dermatologic diagnoses occurred in the study population. Bacterial infections were the most commonly observed, occurring in 15% of patients. Nail disorders were the second most common dAE, occurring in 14% of the study population, followed by eczema/eczematous reactions at 9%. In all racial groups, eczema/eczematous reactions, nail disorders, and dermatomyositis were in the top five most common observed dAEs. Asian patients made up the largest proportion of those who had morbilliform rash dAEs (55%) while Black patients made up the largest proportion of those with hyperpigmentation dAEs (54%) and vascular insufficiency dAEs (47%). **Conclusions:** The findings from our study indicate that pigmentary changes, bacterial infections, eczema/eczematous reactions, and nail disorders are the most common dAE types that occurred in our group of SOC patients. We hope to use this information to aid in the development of specific management strategies within the field of supportive oncodermatology to meet the needs of minority patient populations. Research Sponsor: None.

12085 **Poster Session**

Depression, chronic pain, and high-impact chronic pain among cancer survivors. *First Author: Nosayaba Osazuwa-Peters, Duke University School of Medicine, Durham, NC*

Background: The majority of the 17 million individuals living with a cancer diagnosis in the United States have experienced pain, either from the disease itself or from its treatment. Pain negatively impacts psychosocial quality of life and is associated with poorer overall outcome. However, the impact of pain on daily living differ among cancer survivors, and there is a paucity of research on chronic pain, especially high-impact chronic pain (HICP) in this growing population. We estimated the prevalence of chronic pain, and HICP among cancer survivors, and described the association between depression and these outcomes. **Methods:** This study used data from the 2015-2017 National Health Interview Survey. Outcomes of interest were chronic pain, defined as pain on most days or every day in the past six months, and HICP, defined as chronic pain that limited life or work activities on most days or every day during the past six months. Weighted, adjusted multivariable logistic regressions estimated association between depression and chronic pain and HICP among cancer survivors, while controlling for age, gender, marital status, education, employment, health insurance, smoking status, number of doctor's visit, general health, and comorbidities. **Results:** Among 49,326 survey respondents, 11.7% (n = 5,335) had a cancer diagnosis. An estimated 43.6% of cancer survivors reported chronic pain; and 19.2% reported HICP. We found an association between depression and both chronic pain and HICP in unadjusted analyses. In the adjusted models, cancer survivors depressed within the last month had more than double the odds of reporting both chronic pain (aOR = 2.32; 95% CI 1.75, 3.07) and HICP (aOR = 2.12; 95% CI 1.50, 3.01). Other factors associated with both chronic pain and HICP among cancer survivors included being a current smoker ($aOR_{chronic\ pain}$ = 1.63; 95% CI 1.14, 2.34; aOR_{HICP} = 1.83; 95% CI 1.18, 2.84) and being unemployed ($aOR_{chronic\ pain}$ = 1.44; 95% CI 1.10,1.90; aOR_{HICP} = 3.10; 95% CI: 2.00−4.81). Cancer survivors with ≥2 comorbidities also had 55% increased odds of reporting chronic pain (aOR = 1.55; 95% CI 1.17,2.04) compared with those without comorbidities. **Conclusions:** Over 40% of cancer survivors may have a history of chronic pain, and survivors reporting being depressed are significantly more likely to report both chronic pain and HICP. The association between depression and pain in cancer survivors calls for personalized management of chronic pain, especially in cancer survivors with a history of depression. Research Sponsor: None.

12086 **Poster Session**

Radiofrequency ablation for palliative treatment of osseous metastases results in rapid, significant, and durable improvements in pain relief and quality of life: Results from the OPuS One trial. *First Author: Jason Levy, Northside Hospital, Atlanta, GA*

Background: Patients with bone metastases may experience pain and decreased quality of life. Standard of care therapies such as radiation therapy could take weeks for pain relief and carry a risk of radiation induced fracture. Minimally invasive percutaneous radiofrequency ablation (RFA) have been shown in small observational studies to be an alternative treatment for bone metastases. We report the results of the OPuS One trial evaluating RFA for the palliative treatment of patients with painful bone metastases. **Methods:** OPuS One (NCT03249584) was a multicenter prospective trial. 218 subjects with painful bone metastases ($\geq$ 4/10 worst pain scores, Brief Pain Inventory [BPI], at target treated site) were enrolled from 15 sites. RFA was performed under image guidance at one or two locations. Vertebral augmentation was followed based on physician's discretion. Subjects' pain (BPI) and quality of life (EQ-5D) scores were calculated in subjects at three days, one week, and one, three, six, and 12 months post RFA. Rate of complete (0 pain score at treated site with no concomitant analgesic increase) and partial responders ($\geq$ 2 pain score reduction without analgesic increase or analgesic reduction of $\geq$ 25% from baseline) were calculated. Device-, procedure-, and/or therapy-related adverse events (AEs) were collected. **Results:** 206 subjects, 113 (55%) female and 93 (45%) males (mean age was 63.7 years) were treated with RFA. Most common primary cancers were breast (23%), lung (23%), and kidney (10%). 184 (89%) subjects were treated for metastatic lesions involving the thoracolumbar spine and 22 (11%) subjects were treated for iliac crest, periacetabulum, sacrum or mixed vertebral and pelvic location. 99% (262/264) of RFA procedures were technically successful and 97% were followed by vertebral augmentation. Subjects reported significant improvement in worst pain from baseline at 7.8 to 5.5, 4.7, 3.6, 3.2, 2.4, and 2.6 at three days, one week and one, three, six, and 12 months post RFA, respectively ($p < 0.0001$ for all visits). Significant improvements were also seen in average pain ($p < 0.0001$ for all visits), pain interference ($p < 0.0001$ for all visits), and quality of life scores ($p < 0.0001$ for all visits). Overall response rates were 53%, 58%, 61%, 63%, 70%, and 75% at three days, one week, one month, three months, six months, and twelve months post RFA, respectively. Six AEs were reported with three as serious: intra-abdominal fluid collection, pneumonia and respiratory failure. 82 deaths were reported during the study, none were related to the device, therapy, and/or procedure. No skeletal related events were reported. **Conclusions:** In a large prospective multicenter trial, OPuS One, RFA provided rapid, significant, and durable improvements in pain relief and quality of life up to 12 months. Clinical trial information: NCT03249584. Research Sponsor: Medtronic.

12087 **Poster Session**

Receipt of palliative care (PC) in acute myeloid leukemia (AML) using data from the National Cancer Database (NCDB). *First Author: Bryan Chan, Georgetown University Medical Center, Lombardi Comprehensive Cancer Center, Washington, DC*

Background: AML is an aggressive disease with high mortality and significant impact on quality of life. Palliative care (PC) services have become integral in managing patient's symptoms during treatment as well as at the end of life. We hypothesize that socioeconomic factors such as achieving higher levels of education, and higher incomes, increases the odds of receiving PC. **Methods:** This is a retrospective analysis using NCDB data of 124,988 newly diagnosed non-M3 AML patients over 18 yrs from 2004-2016. Unadjusted and multivariate adjusted logistic regression analysis (MVA) evaluated the impact of socioeconomic variables on the receipt of PC. In the MVA, we adjusted for demographic variables and facility characteristics including facility type, facility volume, age, sex, race, Hispanic origin, income, education, urban/rural residence, Charlson-Deyo score, great circle distance, Medicaid expansion status state group, and insurance status. Patients with Medicaid expansion $<$ 39yrs were excluded due to low patient numbers. **Results:** For the 124,988 patients, median age was 63 years (range 18-90) with 54% males and 86% White. 25% of patients lived in regions with the highest education level defined as $<$ 6.3% of adults over 25 without a high school diploma. 35% of patients had a household income bracket of $\geq$ $63,333. A total of 3% of patients received PC. MVA showed that patients within the highest income bracket of $\geq$ $63,333 were less likely to have used PC services (OR 0.82, $p < 0.01$). More educated patients residing in regions with $<$ 6.3% of adults without a high school diploma had higher odds of receiving PC treatment compared with patients with less education (OR 1.23, $p < 0.01$). Residence in states with Medicaid expansion in January 2014 or later was associated with greater utilization of PC services (Jan 2014 expansion states: OR 1.33 and late expansion states/after Jan 2014: OR 1.43, $p < 0.01$) compared to residence in non-expansion states. No difference was seen across races; except Hispanics with decreased use of PC services(OR 0.8, $p = 0.022$). **Conclusions:** In this large cohort, a small percentage of patients received PC. Higher education was associated with higher likelihood of using PC, while, surprisingly, higher income was associated with a lower likelihood of PC. Additionally, the higher use of PC services with Medicaid expansion suggests a broad impact of public health insurance in providing increased access to PC services. Research Sponsor: None.

12088 **Poster Session**

Marijuana use among US adults with cancer: Findings from the 2018-2019 Behavioral Risk Factor Surveillance System. *First Author: Min Jee Lee, Southern Illinois University School of Medicine, Springfield, IL*

Background: Cancer survivors experiencing adverse effects from their cancer and treatment report decreased symptom burden with marijuana use. An increasing number of U.S. states have legalized marijuana use for both medical and recreational purposes. This study aimed to assess the prevalence of current marijuana use and to identify the factors associated with its use among US adults with cancer living in 17 U.S. states and territories. **Methods:** Data from the 2018-2019 Behavioral Risk Factor Surveillance System Marijuana Use module were analyzed. In 2018, 13 states (California, Florida, Idaho, Maryland, Minnesota, Montana, New Hampshire, North Dakota, Ohio, South Carolina, Tennessee, West Virginia, and Wyoming) and 2 territories (Guam and Puerto Rico) participated in the optional marijuana use module. In 2019, 12 states (California, Idaho, Illinois, Maryland, Minnesota, New Hampshire, North Dakota, South Carolina, Tennessee, Utah, West Virginia, and Wyoming) and 1 territory (Guam) participated in the optional marijuana use module. The analytic sample included 13,174 adults with cancer. The analysis was weighted to account for BRFSS's complex survey design. The primary outcome was current marijuana use (in the past 30-days). Multivariable logistic regression was used to identify demographic, socioeconomic, clinical, and behavioral factors associated with marijuana use among US adults with cancer. **Results:** Overall, 9.2% of adult cancer survivors (n = 13,174; weighted 5.7 million; 37.9% men) reported marijuana recently current use, 51.3% of whom used it for medical reasons only, with 65.2% reporting smoking as the main method of administration. Adult cancer survivors were significantly more like to use marijuana if they were younger (odds ratio [OR] for 55-64 versus 18-44 years old: 0.60; 95% CI: 0.38-0.93; $P < 0.01$); male (OR for female versus male: 0.65; 95% CI: 0.48-0.87; $P < 0.01$); non-Hispanic Black race/ethnicity (OR: 2.00; 95% CI: 1.21-3.33; $P < 0.01$); having depression (OR: 1.58; 95% CI: 1.17-2.14; $P < 0.01$) and current (OR: 3.23; 95% CI: 2.20-4.74; $P < 0.01$) or former tobacco smoker (OR: 2.40; 95% CI: 1.70-3.38; $P < 0.01$) and binge drinker (OR: 2.25; 95% CI: 1.53-3.29; $P < 0.01$). **Conclusions:** Among a large cohort of US adults with cancer, marijuana use was commonly reported and certain subgroups were at higher risk for marijuana use. Health professionals should identify the risk factors for elevated marijuana use, especially as more states legalize medical and recreational marijuana use despite uncertain health risks. Research Sponsor: None.

12089 **Poster Session**

Exploration of optimal paracentesis volume for terminally ill patients with malignant ascites. *First Author: Tetsuya Ito, Department of Palliative Care, Japanese Red Cross Medical Center, Tokyo, Japan*

Background: Malignant ascites (MA) often causes distressing symptoms especially for terminally ill cancer patients. Control of such symptoms is generally difficult when it becomes refractory to standard antitumor therapies. Paracentesis is the most common treatment modality which provides rapid and temporary symptom relief, while it requires frequently repeated treatment to maintain symptom control. The optimal procedure is often a balance between the potential for symptom improvement and the known risks of adverse events such as hypotension and renal impairment. However, there are limited data regarding the optimal amount of fluid to be removed. The aim of this study was to explore the efficacy (paracentesis interval and symptom relief) and safety (adverse events) of paracentesis by the drainage volume. **Methods:** This is part of a multicenter prospective observational study (EASED study). Consecutive adult patients with advanced cancer admitted to 23 participating palliative care units were eligible. We analyzed patients with MA who received paracentesis. We compared paracentesis-free survival (PFS) using Cox regression among 3 groups with different paracentesis volumes: minimum: $<$ = 1500 mL, small: 1500-2500 mL, and moderate: $>$ 2500 mL, with adjustment for potential confounders: age, sex, the Karnofsky Performance Status, and variables of which P-values were $<$ 0.1 in univariate analysis. Trend of the difference in abdominal distention numerical rating scale (NRS) before and after paracentesis and adverse events were compared among 3 groups. Under missing at random assumption, missing values were imputed using multiple imputation. **Results:** A total of 1926 patients were enrolled and 673 patients developed MA at admission. Of these, 586 patients never received paracentesis during their PCU stay. Thus, the population for analysis consisted of 87 patients. Median PFS was 7 days. Compared with a moderate volume, small-volume paracentesis was not a significant risk for shorter PFS (HR: 1.14, 95%CI: 0.69-1.93), while a minimum volume was a significant risk for shorter PFS (HR: 2.34, 95%CI: 1.25-4.39). The spline-based hazard ratio curve indicated that a dose-response of the ascites drainage volume to PFS was not likely when more than 2,000 mL of ascites was removed. Abdominal distension NRS significantly decreased after paracentesis (median: 7.5 to 4.0, $p < 0.0001$), while the difference did not significantly increase as the volume of paracentesis rose ($p = 0.61$). No severe adverse event was observed. **Conclusions:** Even small-volume paracentesis could alleviate abdominal distension of terminally ill cancer patients with MA without shortening the paracentesis interval compared with moderate-volume paracentesis. Small-volume paracentesis was an effective and safe treatment for such patients. Our findings may help physicians estimate an optimal volume of paracentesis for each patient with MA. Research Sponsor: JSPS KAKENHI Grant Number JP20K16567.

12090 **Poster Session**

Neuropathy severity at the time of oxaliplatin treatment alteration in patients with colon cancer (Alliance A151912). *First Author: Daniel Louis Hertz, University of Michigan College of Pharmacy, Ann Arbor, MI*

Background: Clinical guidelines recommend altering chemotherapy treatment by decreasing, delaying, or discontinuing dosing in patients (pts) experiencing chemotherapy-induced peripheral neuropathy (CIPN). There are few data available on clinical use of treatment alteration including the severity of CIPN at the time of alteration. Our objective was to investigate the incidence of oxaliplatin treatment alterations and CIPN severity at that time. **Methods:** This was a retrospective analysis of pts with colon cancer scheduled to receive oxaliplatin-containing combination chemotherapy on the N08CB trial of intravenous calcium and magnesium for prevention of CIPN. Dose alterations were not mandated by the N08CB protocol. Clinicians assessed CIPN using NCI-CTCAE V.4.0; pts used the sensory subscale of the EORTC-QLQ Chemotherapy-Induced Peripheral Neuropathy 20 (CIPN8). Pts were classified as 1) completed oxaliplatin treatment without alteration, 2) dose reduction or delay due to CIPN, 3) discontinuation due to CIPN, 4) discontinuation due to other AE, or 5) discontinuation for another reason. Comparisons focused primarily on pts with alteration due to CIPN (groups 2 and/or 3) compared with pts completing treatment without alteration (group 1) using chi-squared and Kruskal-Wallis tests. **Results:** In this analysis of 350 N08CB pts, 135 (39%) completed oxaliplatin without treatment alteration, 70 (20%) had a dose reduction (n=66) or delay (n=4) due to CIPN and 35 (10%) discontinued early due to CIPN. Pts who experienced alterations due to CIPN were younger (p=0.0249) and more likely to be female (p=0.008). Clinician-assessed CIPN severity was greater in pts at the time of dose reduction or delay compared with CIPN severity at the end of treatment in pts with no alteration ($p<0.0001$). Pt-assessed CIPN severity was not different in pts who completed treatment without alteration compared to pts who had a dose reduction or delay (p=0.88) or a discontinuation (p=0.37). CIPN8 scores at cycle 4 were higher (worse) in pts who eventually had any alteration (i.e., reduction, delay, or discontinuation) compared to pts who completed treatment without any alteration (median CIPN8 11.5 vs. 7.7, p=0.023). **Conclusions:** Treatment alterations due to CIPN are relatively common in pts receiving adjuvant oxaliplatin for colon cancer and are associated with clinician-assessed but not pt-reported CIPN severity. Rapid CIPN8 increases early in treatment are indicative of increased likelihood of a future oxaliplatin treatment alteration, indicating a potential use of early monitoring and intervention. Support: UG1CA189823; https://acknowledgments.alliancefound.org. Clinical trial information: NCT01099449 (NCCTG N08CB). Research Sponsor: U.S. National Institutes of Health, Alliance Foundation https://acknowledgments.alliancefound.org.

12091 **Poster Session**

Assessing duration of breakthrough chemotherapy-induced nausea and vomiting (CINV): A pooled study analysis of NEPA versus aprepitant. *First Author: Rudolph M. Navari, World Health Organization Cancer Care Program, Birmingham, AL*

Background: The historical standard clinical trial endpoint for preventing chemotherapy-induced nausea and vomiting (CINV) has been assessment of complete response (CR: no emesis and no rescue medication use) over five days. Recent evaluations focused on the duration of breakthrough CINV suggest that long duration of CINV results in more lost work time and impaired activity and is also a strong predictor for CINV in subsequent cycles. A recent pooled analysis of three similarly designed registration trials of NEPA, a fixed oral combination NK_1 receptor antagonist (RA) (netupitant)/5-HT_3RA (palonosetron), showed significantly higher CR rates during the delayed phase (≥24-120h) for NEPA compared to an aprepitant (APR) regimen. In this post-hoc analysis, we evaluated the extent and duration of breakthrough CINV in these pooled studies. **Methods:** Chemotherapy-nave patients who received cisplatin-based chemotherapy and antiemetic prophylaxis of either a single dose of NEPA plus dexamethasone (DEX) or a 3-day APR/5-HT_3 RA/DEX regimen from three randomized, double-blind pivotal trials were included. Patients without a CR were defined as treatment failures. Extent of CINV was evaluated using proportions of patients with treatment failure, emesis, and significant nausea (defined as >25 mm on a 100 mm visual analog scale). Over the 5-day overall phase, duration was categorized as 1-2, and ≥3 days. Pearson s chi-square test was employed to compare risks between treatments for each duration category in each of the previously mentioned endpoints. **Results:** Among all 621 NEPA and 576 APR patients, a significantly greater proportion of APR patients experienced treatment failure, emesis, and significant nausea for ≥3 days. Specifically, among patients with treatment failure, 31% (41/134) who received NEPA and 43% (61/143) who received APR experienced breakthrough CINV for ≥3 days. **Conclusions:** Expanding on data suggesting single-day NEPA is more effective than 3-day APR in preventing delayed CINV, NEPA is also more effective in minimizing the extent and duration of CINV in patients with breakthrough emesis and nausea. Research Sponsor: Helsinn Healthcare.

CINV Extent and Duration	NEPA + DEX (N = 621)	APR/5-HT_3 RA + DEX (N = 576)	P-value
TREATMENT FAILURE			
1-2 days	93 (15%)	82 (14.3%)	0.736
≥3 days	41 (6.6%)	61 (10.6%)	**0.013**
EMESIS			
1-2 days	85 (13.7%)	79 (13.8%)	0.969
≥3 days	40 (6.5%)	55 (9.6%)	**0.045**
SIGNIFICANT NAUSEA			
1-2 days	73 (11.8%)	76 (13.2%)	0.437
≥3 days	54 (8.7%)	71 (12.4%)	**0.038**

12092 **Poster Session**

Province-wide analysis of patient reported outcomes for stage IV non-small cell lung cancer. *First Author: Michael Chandra Tjong, Princess Margaret Cancer Centre, Toronto, ON, Canada*

Background: Stage IV NSCLC patients have significant disease and treatment-related morbidity. In Ontario, Canada, cancer patients complete Edmonton Symptom Assessment System (ESAS) questionnaires, a tool that elicits patients' self-reported severity of common cancer-associated symptoms at clinical encounters. ESAS domains are: anxiety, depression, drowsiness, appetite, nausea, pain, shortness of breath, tiredness and well-being. The purpose of this study is to examine moderate-to-severe symptom burden in the 12 months following a diagnosis of stage IV NSCLC. **Methods:** Using administrative databases and unique encoded identifiers, stage IV NSCLC diagnosed between January 2007 and September 2018 were evaluated for symptom screening with ESAS in the 12 months following diagnosis. Proportion of patients reporting moderate-to-severe score (i.e. ESAS ≥4) in each domain within 12 months were calculated. Patients reporting moderate-to-severe within the different ESAS domains of were plotted over time. Multivariable (MV) Poisson regression models with potential covariates such as age, sex, Elixhauser comorbidity index, income quintiles, and lung cancer treatments received were constructed to identify factors associated with moderate-to-severe symptoms. **Results:** Of 22,799 stage IV NSCLC patients, 13,289 (58.3%) had completed ESAS (84,373 unique assessments) in the year following diagnosis. Patients with older age, high comorbidity, and not receiving active cancer therapy were less likely to complete ESAS. Most (94.4%) reported at least 1 moderate-to-severe score. Most prevalent moderate-to-severe ESAS symptoms within 12 months after diagnosis were tiredness (84.1%), lack of wellbeing (80.7%), low appetite (71.7%), and shortness of breath (67.8%); nausea was the least prevalent (34.6%). Most symptoms peaked at diagnosis and persisted in the year after diagnosis. On adjusted MV analyses, patients with high comorbidity, low income, and urban residency were associated with increased moderate-to-severe symptoms. Moderate-to-severe scores in all ESAS symptoms were associated with delivery of radiotherapy within 2 weeks prior, while moderate-to-severe nausea, drowsiness, tiredness, low appetite, and lack of wellbeing were associated with delivery of systemic therapy within preceding 2 weeks. **Conclusions:** In this population-based analysis of stage IV NSCLC PROs in the year following diagnosis, moderate-to-severe symptoms were highly prevalent and persistently high, underscoring the need to address supportive requirements in this at-risk population. Research Sponsor: Ontario Institute of Cancer Research Grant.

12093 **Poster Session**

Noninferiority study evaluating dexamethasone (DEX)-sparing regimens administered with NEPA, a fixed combination of netupitant and palonosetron, for the prevention of chemotherapy-induced nausea and vomiting (CINV) caused by high-dose cisplatin. *First Author: Luigi Celio, Oncology Unit, ASST del Garda, Desenzano del Garda Hospital, Brescia, Italy*

Background: Corticosteroids such as DEX continue to play a key role for the prevention of CINV. Although they are generally considered safe when used in combination with other anti-emetic agents, corticosteroids can cause a range of side effects. To reduce the overall exposure to DEX in patients receiving cisplatin-based chemotherapy, we evaluated the non-inferiority of DEX on day 1, with or without low-dose DEX on days 2 and 3, combined with oral NEPA, a fixed combination of the NK_1 receptor antagonist (RA), netupitant and 5-HT_3 RA, palonosetron, compared with NEPA plus the guideline-recommended use of 4-day DEX (reference arm). Non-inferiority was met for both DEX-sparing regimens and the reference arm for the primary endpoint of complete response (CR: no emesis and no rescue use) during the overall (0-120h) phase post-chemotherapy. In this analysis secondary efficacy endpoints were evaluated for the single-dose DEX-sparing group versus the 4-day DEX arm. **Methods:** In this analysis from an open-label, multicenter study (ClinicalTrials.gov NCT04201769) chemotherapy-nave patients undergoing high-dose cisplatin (≥70 mg/m^2) received either NEPA and DEX (12 mg) on day 1 only or NEPA and DEX [12 mg on day 1 plus 4 mg twice daily on days 2-4 (DEX4)]. Efficacy endpoints included complete protection (CR plus no significant nausea), no emesis, and no significant nausea (<25 mm on a 100 mm visual analog scale) during the acute (0-24h), delayed (>24-120h) and overall phases. The non-inferiority margin was set at -15% difference (DEX1 minus DEX4). **Results:** One-hundred fifty-two patients, 76 in each arm, were included. Non-inferiority was met for the DEX1 arm and the DEX4 reference arm for all efficacy endpoints (Table). **Conclusions:** A simplified regimen of NEPA plus single-dose DEX offers comparable CINV prevention throughout 5 days post-chemotherapy with the advantage of sparing patients additional doses of DEX in the high emetic risk setting of cisplatin-based chemotherapy. Clinical trial information: NCT04201769. Research Sponsor: None.

Endpoint time period post-chemotherapy	NEPA + DEX1 (N = 76) % of patients	NEPA + DEX4 (N = 76) % of patients	Risk Difference (DEX1 minue DEX4) %	95% CI
Complete protection				
Acute (0-24h)	90.8	89.5	1.3	-8.2 to 10.8
Delayed (>24-120h)	73.7	67.1	6.6	-7.9 to 21.1
Overall (0-120h)	73.7	67.1	6.6	-7.9 to 21.1
No emetic episodes				
Acute	96.1	98.7	-2.6	-7.7 to 2.4
Delayed	92.1	97.4	-5.3	-12.3 to 1.8
Overall	92.1	97.4	-5.3	-12.3 to 1.8
No significant nausea				
Acute	93.4	97.3	-3.9	-10.6 to 2.7
Delayed	77.6	76.3	1.3	-12.1 to 14.7
Overall	77.6	76.3	1.3	-12.1 to 14.7

12094 **Poster Session**

A randomized, double-blind, multicenter, phase III study of fosnetupitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving doxorubicin-cyclophosphamide/epirubicin-cyclophosphamide (AC/EC) based highly emetogenic chemotherapy: CONSOLE-BC. *First Author: Junji Tsurutani, Showa University, Tokyo, Japan*

Background: Fosnetupitant (FN) is a phosphorylated pro-drug of netupitant that has high binding affinity and selectivity for the neurokinin 1 receptor and a long half-life of 70 h. Recent studies have reported that fosaprepitant (FA) has a risk for developing injection site reactions (ISRs) in patients with breast cancer who receive doxorubicin-cyclophosphamide/epirubicin-cyclophosphamide (AC/EC)-based treatments. Previous studies have shown that FN may have a low risk of ISRs and could potentially address this unmet medical need. The present study (JapicCTI-194691) was intended to evaluate the safety profile, including ISRs, of FN in patients receiving AC/EC treatment. For exploratory purposes, we set the FA group as the exploratory arm. A separate pivotal phase 3 study (JapicCTI-194611) was conducted to verify the efficacy and safety of FN compared with FA in patients receiving cisplatin-based chemotherapy. **Methods:** Patients scheduled to receive AC/EC were randomly assigned 1:1 to receive FN 235 mg or FA 150 mg in a double-blind manner, in combination with intravenous palonosetron (PALO) 0.75 mg and dexamethasone (DEX) 9.9 mg on day 1. The stratification factors were age class ($<$ 55 years vs. $\geq$55 years) and site. The primary endpoint was the incidence of treatment-related adverse events (TRAEs) of FN. In addition, the ISRs were investigated as secondary endpoints. Efficacy outcomes were also evaluated as secondary endpoint. **Results:** Between April 2019 and March 2020, total 102 patients were enrolled in the study. Fifty-two patients were randomized to the FN group and 50 to the FA group, and all of them were treated with the study drug and evaluated for safety. The baseline characteristics were generally balanced, except for the history of motion sickness (54.9% vs. 44.9%) and non-smokers (78.4% vs. 63.3%) in the FN and FA groups, respectively, which are considered as risk factors for chemotherapy-induced nausea and vomiting. The primary endpoint, the incidence of TRAEs was 21.2% (n = 11) (95% CI 11.1% – 34.7%) in the FN group, which was similar to that in the FA group [22.0% (n = 11) (95% CI 11.5% - 36.0%)]. Any cause or treatment-related ISRs were observed in 5.8% (n = 3) and 0% (n = 0), respectively, in the FN group and 26.0% (n = 13) and 10.0% (n = 5), respectively, in the FA group. The overall (0–120 h) complete response (no emetic event and no rescue medication) rate standardized by age category was 45.9% (n = 23) in the FN group and 51.3% (n = 25) in the FA group. **Conclusions:** The safety of FN in combination with PALO and DEX was favorable. Risk of ISR by FN was quite low in the AC/EC setting. Clinical trial information: JapicCTI-194691. Research Sponsor: Taiho pharmaceutial Co., Ltd.

12095 **Poster Session**

The PROVIEW+ tool: Developing and validating a tool to predict risk of poor performance status and severe symptoms in cancer patients over time. *First Author: Hsien Seow, McMaster University, Hamilton, ON, Canada*

Background: There are numerous predictive cancer tools that focus on survival. However, no tools predict risk of low performance status or severe symptoms, which are important for patient decision-making and early integration of palliative care. The aim of this study was to develop and validate a model for all cancer types that predicts the risk for having low performance status and severe symptoms. **Methods:** A retrospective, population-based, predictive study using linked administrative data from cancer patients from 2008-2015 in Ontario, Canada. Patients were randomly selected for model derivation (60%) and validation (40%). The derivation cohort was used to develop a multivariable logistic regression model to predict the risk of having the reported outcomes in the subsequent 6 months. Model performance was assessed using discrimination and calibration plots. The main outcome was low performance status using the Palliative Performance Scale. Secondary outcomes included severe pain, dyspnea, well-being, and depression using the Edmonton Symptom Assessment System. Outcomes were recalculated after each of 4 annual survivor marks. **Results:** We identified 255,494 cancer patients (57% female; median age of 64; common cancers were breast (24%) and lung (13%)). At diagnosis, the risk of having low performance status, severe pain, well-being, dyspnea, and depression in 6-months is 1%, 3%, 6%, 13% and 4%, respectively for the reference case (i.e. male, lung cancer, stage I, no symptoms). Generally these covariates increased the outcome risk by $>$ 10% across all models: obstructive lung disease, dementia, diabetes; radiation treatment; hospital admission; high pain; depression; Palliative Performance Scale score of 60-10; issues with appetite; or homecare. Model discrimination was high across all models. **Conclusions:** The model accurately predicted changing cancer risk for low performance status and severe symptoms over time. Providing accurate predictions of future performance status and symptom severity can support decision-making and earlier initiation of palliative care, even alongside disease modifying therapies. Research Sponsor: Canadian Institutes for Health Research.

12096 **Poster Session**

Cannabidiol (CBD) use among cancer survivors. *First Author: Chasse Margot Bailey-Dorton, Atrium Health Levine Cancer Institute, Charlotte, NC*

Background: Cannabidiol (CBD) is a non-psychoactive component of cannabis touted for various therapeutic effects. The Federal Drug Agency has only approved one prescription CBD product for treatment of severe epilepsy. On December 17, 2020 the Federal Trade Commission announced legal consequences for deceptively marketed CBD products in the rapidly expanding market of various CBD products; the products' unsupported claims included CBD as a cancer treatment. Little is known about survivors use of CBD. This study explores the prevalence and nature of CBD use by cancer survivors. **Methods:** A link to an anonymous, electronic survey was posted on the Levine Cancer Institute and SherryStrong (Martin Truex Jr. Foundation: philanthropy for ovarian cancer) Twitter and Facebook social media platforms. Data were managed in REDCap, a secure, web-based, electronic data capture tool. Survey responses were summarized and described with frequencies and compared using Fisher's Exact tests; $p < 0.1$ was considered statistically significant. **Results:** N = 295 self-selected respondents were White (95%), female (86%), middle aged (45-64 years) (58%) and in the US (95%). Ninety percent indicated current (85%) or past (15%) use of CBD product; a third of these participants (N = 102) identified as cancer survivors. Gynecologic (31%) and breast (30%) cancers were the most recorded malignancies, and 38% report active treatment. Most survivors indicated using CBD products daily (77%) for a year or less (79%) and spent @$30 a week on products (70%). Common uses for CBD were easing pain (66%), anxiety (50%), and sleep (50%)—14% reported treating or preventing cancer. 41% learned about CBD from family/friends, fewer learned from the Internet (21%) or local store (11%). Only 12% received information from a physician. Liquid drops (58%) and topicals (19%) were popular products and reported side effects were sparse—sedation and/or euphoria were indicated by 10% and 2%, respectively. Over 82% of cancer survivors indicated that CBD product helped their conditions. CBD use to ease anxiety and stress declined with age; 71% of young survivors (aged 18-44) sought anxiety relief versus 45% and 36% of middle age (aged 45-64) and seniors (aged 65+), respectively (p = 0.05), and 58% of young survivors pursued stress relief versus 39% of middle age and 21% of seniors (p = 0.08). More young (25%) and middle age (37%) survivors indicated spending over $30 on products weekly than seniors (7%) (p = 0.08). No differences were seen in CBD use between cancer survivors by gender or treatment status. **Conclusions:** Cancer survivors commonly use CBD, yet infrequently under the guidance of a physician. Survivors largely rely on word of mouth and internet information about CBD. Despite lack of standardization of production and labeling of CBD products, the majority of patients reported positive improvements in symptoms. Future research should explore strategies to educate cancer patients and providers in safe CBD use. Research Sponsor: None.

12097 **Poster Session**

Effectiveness of a nurse-led, screening-triggered, early specialized palliative care intervention program for patients with advanced lung cancer: A multicenter randomized controlled trial. *First Author: Yoshihisa Matsumoto, Department of Palliative Medicine, National Cancer Center Hospital East, Kashiwa, Japan*

Background: The integration of palliative care into standard cancer treatment during the early phase of the disease can improve cancer patients' quality of life (QOL). The current study examined the effectiveness of a nurse-led, screening-triggered, early specialized palliative care intervention program for patients (pts) with advanced lung cancer. **Methods:** Pts with advanced lung cancer undergoing initial chemotherapy were randomized (1:1) to the intervention group (IG) or the usual care group (UG) between January 2017 and September 2019. The intervention, which was triggered using by a brief, self-administered screening tool, comprised comprehensive need assessments, counseling, and service coordination by advanced-leveled nurses. The primary endpoint was the change from baseline of the Functional Assessment of Cancer Therapy -Lung Trial Outcome Index (TOI) at week 12, and the secondary endpoints were TOI at week 20, depression (Patient Health Questionnaire-9), anxiety (Generalized Anxiety Disorder-7), and survival. **Results:** Pts were randomly allocated (102 for each group). The median age was 69 y (range, 27-91) and 77.5% were male. Seventy-two pts had extensive disease small-cell lung carcinoma and 132 Pts had stage IV non-small cell lung carcinoma. Because there was not a significant time-by-group interaction, we estimated main effects and the IG did not show a significant improvement in TOI from the baseline at week 12 and 20 compared to the UG (Mean group difference [the same applies hereafter] 2.13; 90% CI: -0.70, 4.95; P = .107, one-tailed). However, when we considered time-by-group interaction effects exploratorily, the IG did show significant improvement in TOI from baseline at week 20 compared to the UG (3.58; 90% CI: 0.15, 7.00; P = 0.043). There was no significant difference in change from baseline depression and anxiety between the two groups either at week 12 (depression −0.38; 95% CI: -1.81, 1.05; $P = 0.60$, anxiety -0.18; 95% CI: -1.45, 1.09; $P = 0.78$) or at week 20 (depression -1.27; 95% CI: -2.79, 0.25; $P = .10$, 1.26; 95% CI: -2.61, 0.09; $P = .067$). The 1-year survival rates were 49.5% (95% CI: 39.3, 58.9) in the IG and 43.4% (95% CI: 33.6, 52.8) in the UG. **Conclusions:** This trial failed to show statistical superiority of nurse-led, screening-triggered, early specialized palliative care intervention program over usual care, however, it's possible delayed clinical benefits of improvement in QOL (TOI), depression and anxiety were suggested. The study design that some pts in the IG received later or no intervention, may dilute the difference of intervention between group differences. Further investigation, including the mixed method approach adopted in this study, is needed to uncover mediating factors for the effect of this low-cost, novel model of early palliative care. Clinical trial information: UMIN000025491. Research Sponsor: the Japan Agency for Medical Research and Development (AMED), Other Government Agency.

12098 **Poster Session**

Efficacy of olanzapine combined with the standard triplet antiemetic therapy for cisplatin-based chemotherapy: A sub-analysis of a randomized, double-blind, placebo-controlled trial (J-FORCE). *First Author: Yukiyoshi Fujita, Division of Pharmacy, Gunma Prefectural Cancer Center, Gunma, Japan*

Background: In a randomized, double-blind, placebo-controlled trial (J-FORCE), we previously reported the efficacy of olanzapine (OLZ) 5 mg plus triplet antiemetic therapy for cisplatin (CDDP)-based chemotherapy-induced nausea and vomiting (CINV) in the delayed phase (24–120 h after CDDP treatment). Here, we report the results of a pre-planned subgroup analysis of this trial (in which risk factors were used as the allocation factors). This analysis was designed to determine which patients benefit more from OLZ. **Methods:** Subgroup analysis was performed on complete response (CR: no emesis and no rescue medication) in the acute (within 24 h of CDDP treatment) and delayed phase and time to treatment failure (TTF: time from CDDP treatment to the first vomiting or use of rescue medication). Data from 705 patients in the efficacy analysis population (354 in the OLZ group and 351 in the placebo (PLA) group) were analyzed by sex (male/female), age (≥55 years/ < 55 years), and CDDP dose (≥70 mg/m^2/ < 70 mg/m^2). For CR, we calculated point estimates of differences between groups and 95% confidence intervals and performed a Mantel-Haenszel test. We used the Kaplan-Meier method for the analysis of TTF, and comparisons between groups were made using a log-rank test. **Results:** Delayed CR (OLZ versus PLA) and risk difference (RD) of delayed CR following OLZ treatment were significantly greater than following PLA in the following subgroups: male (83.1% versus 70.5%, RD 12.6%, p = 0.001), female (70.9% versus 56.4%, RD 14.5%, p = 0.021), age ≥55 years (78.7% versus 67.6%, RD 11.1%, p = 0.003), age < 55 years (81.0% versus 57.4%, RD 23.6%, p = 0.005), and CDDP ≥70 mg/m^2 (78.8% versus 65.3%, RD 13.5%, p < 0.001). TTF of all subgroups (male/female, ≥55 years/ < 55 years, and ≥70 mg/m^2/ < 70 mg/m^2) was significantly longer in the OLZ group than in the PLA group (HR 0.493, p < 0.001; HR 0.612, p = 0.022; HR 0.586, p < 0.001; HR 0.401, p = 0.005; HR 0.546, p < 0.001; HR 0.543, p = 0.031, respectively). **Conclusions:** Our results suggest a benefit of OLZ 5 mg plus triplet therapy regardless of risk factors for CDDP-based CINV. Clinical trial information: UMIN000024676. Research Sponsor: Japan Agency for Medical Research and Development.

		Olanzapine (n = 355)	Placebo (n = 351)	Difference	95% CI	p value
Sex	Male (n = 471)	197 (83.1%)	165 (70.5%)	12.6%	5.0–20.6	0.001
	Female (n = 234)	83 (70.9%)	66 (56.4%)	14.5%	2.2–26.3	0.021
	Difference	12.2%	14.1%		p value: 0.793	
Age	≥55 yrs. (n = 581)	229 (78.7%)	196 (67.6%)	11.1%	3.9–18.2	0.003
	< 55 yrs. (n = 124)	51 (81.0%)	35 (57.4%)	23.6%	7.3–38.3	0.005
	Difference	-2.3%	10.2%		p value: 0.158	
CDDP dose	<70 mg/m^2 (n = 179)	72 (80.0%)	60 (67.4%)	12.6%	-0.3–25.0	0.0564
	≥70 mg/m^2 (n = 526)	208 (78.8%)	171 (65.3%)	13.5%	5.9–21.0	< 0.001
	Difference	1.2%	2.1%		p value: 0.902	

12099 **Poster Session**

A phase III, randomized, double-blind, multicenter, active control study of fosnetupitant for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving cisplatin-based highly emetogenic chemotherapy (HEC): CONSOLE. *First Author: Yoshimasa Shiraishi, Research Institute for Diseases of the Chest, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan*

Background: Fosnetupitant (FN) is a phosphorylated pro-drug of netupitant that has high binding affinity for the neurokinin-1 (NK-1) receptor and a long half-life of 70 h. This phase 3 study is the first head-to-head study to compare two NK-1 receptor antagonists, FN and fosaprepitant (FA), in combination with palonosetron and dexamethasone for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients receiving highly emetogenic chemotherapy (JapicCTI-194611). **Methods:** Patients scheduled to receive cisplatin (≥70 mg/m^2) -based chemotherapy were randomly assigned 1:1 to receive FN 235 mg or FA 150 mg, in combination with palonosetron 0.75 mg and dexamethasone (9.9 mg on day 1, 6.6 mg on days 2-4). The stratification factors were sex, age category (<55 vs. ≥55 years), and site. The primary endpoint was the complete response (CR; no emetic events and no rescue medication) rate, stratified by sex and age category, during the overall phase (0-120 h) to show the non-inferiority (margin, -10%) of FN to FA. The secondary endpoints were: CR rate, complete protection rate, total control rate, no nausea rate, no emetic events rate in each period [i.e., acute (0-24 h), delayed (24-120 h), overall, 0-168 h and 120-168 h], time to treatment failure, and safety, including injection site reactions (ISRs). Assessment of efficacy was continued until 168 h after the initiation of cisplatin. Some eligible patients were evaluated for safety and efficacy of FN for up to four cycles. **Results:** Between February 2019 and March 2020, total 795 patients were enrolled in the study. The study drug was administered to 785 patients (n=392 in FN vs. n=393 in FA), and all of them were evaluated for efficacy and safety. Baseline characteristics were generally balanced between the two groups. The adjusted overall CR rate was 75.2% in FN vs. 71.0% in FA [MH common risk difference, 4.1%; 95% CI, -2.1% to 10.3%), thus demonstrating non-inferiority of FN to FA. Regarding the other secondary endpoints of efficacy until 168 h, FN was favorable against FA, especially the CR rate during 0-168 h (73.2% in FN vs. 66.9% in FA) (Table). The incidence rates of treatment-related adverse events were 22.2% in FN vs. 25.4% in FA, whereas those of ISRs with any cause or with treatment-related were 11.0% or 0.3% in FN vs 20.6% or 3.6% in FA, respectively (p<0.001). **Conclusions:** FN demonstrated non-inferiority to FA, with a favorable safety profile and lower risk for ISRs. For the period beyond 120 h after initiation of chemotherapy, FN may have the potential to improve the prevention of beyond delayed CINV. Clinical trial information: JapicCTI-194611. Research Sponsor: Taiho Pharmaceutical Co., Ltd.

CR rate by period.

	FN (n=392)	FA (n=393)
Acute (0-24 h)	93.9%	92.6%
Delayed (24-120 h)	76.8%	72.8%
Overall (0-120 h)*	75.2%	71.0%
0-168 h	73.2%	66.9%
120-168 h	86.5%	81.4%

* Stratified by sex and age category.

12100 **Poster Session**

The equivalency study of novel current standard 3-drugs combination regimen (ondansetron, dexamethasone and olanzapine) to netupitant containing regimen for preventing high dose cisplatin induce nausea and vomiting treatment, double blind placebo control trial. *First Author: Chalermchai Lertanansit, Division of Medical Oncology, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand*

Background: Prevention of chemotherapy-induced nausea and vomiting (CINV) is vital in cancer treatment. Here, we compared the efficacy of netupitant-containing regimen; composed of NEPA, dexamethasone, and olanzapine (NEPAs), which is recommended for preventing CINV from high-emetogenic chemotherapy (HEC) to standard 3-drugs; ondansetron, dexamethasone, olanzapine for preventing CINV from high-dose cisplatin (≥75 mg/m^2). **Methods:** This randomized, double-blind, placebo-control trial randomly assigned untreated patients who were received high-dose cisplatin in a 1:1 ratio to either NEPAs or standard 3-drugs combination regimen. Dose of dexamethasone in NEPAs regimen was modified after preplanned interim safety analysis to increase from 4 to 8 mg per day on days 2-4. The stratification factors were concurrent treatment with radiation and sex. The primary endpoint was the overall complete response (CR) rate defined as no vomiting and no use of rescue antiemetic drugs. The protocol allowed crossover to NEPAs for those who received standard 3-drugs and did not reach CR in the first cycle. We collected outcome in the first 2-cycle of treatment. **Results:** Between January 2019 and December 2020, hundred patients were randomly assigned to either NEPAs (n = 51) or in-house standard 3-drugs (n = 49). Demographic characteristics were well-balanced in both arms. Total events in both arms were 101 events for NEPAs and 78 events for standard 3-drug. Overall CR rate were 70% and 69% in NEPAs and standard 3-drugs, (p-value 0.87) respectively. According to emesis phase, CR in acute (0-24 hrs.) and delay phase (24-120 hrs.) were not different in both arms; 91% vs. 89% and 72% vs. 71% in NEPAs and standard 3-drugs respectively. However, mean nausea VAS score was significantly lower in NEPAs (1.63 vs. 2.02, p-value = 0.001). The ad hoc subgroup analysis shown similar efficacy between before and after protocol amendment of NEPAs regimen in term of delay emesis CR rate; 70.9% vs. 73.9% (p-value 0.73). **Conclusions:** The NEPA-containing regimen did not show superiority compare to standard 3-drug in terms of complete response rate for CINV prevention among patients receiving high-dose cisplatin. Furthermore, the dexamethasone dosage of 4 vs. 8 mg per day might not affect the efficacy of delay emesis of the NEPAs regimen. Clinical trial information: TCTR20190508001. Research Sponsor: Chulalongkorn University for CV and Medical Oncology Research funding to ST.

Baseline demographic and clinical characteristics of the study patients.

	Arm A (N = 49]	Arm B (N = 49]	*p*-value
Age	52 (23-69)	53 (21-70)	0.46
- < 60 yr	40 (81.6%)	37 (75.5%)	
- > 60 yr	9 (18.4%)	12 (24.5%)	
Sex			1.00
- Male	33 (67.3%)	33 (67.3%)	
- Female	16 (32.7%)	16 (32.7%)	
With or without RT			1.00
- with radiation	33 (67.3%)	33 (67.3%)	
- without radiation	16 (22.7%)	16 (22.7%)	
Median dose of cisplatin —mg [range]	125 [100-171]	125 [100-162]	0.51

12101 **Poster Session**

The effectiveness of a provincial symptom assessment program in reaching adolescents and young adults with cancer: A population-based cohort study. *First Author: Sumit Gupta, The Hospital for Sick Children, Toronto, ON, Canada*

Background: Symptom control is prioritized by cancer patients and may improve overall survival. Several jurisdictions have thus launched population-wide initiatives to assess symptoms at regular intervals. In Ontario, Canada, for example, all cancer patients are screened using the Edmonton Symptom Assessment System (ESAS) at every outpatient visit. Few studies have examined symptom burdens in adolescents and young adults (AYA). Previous work suggests that AYA symptoms differ from those in older patients, and that general screening tools may not be appropriate. Despite this, whether current symptom screening initiatives reach AYA with cancer are unknown. We therefore determined 1) Whether AYA with cancer were participating in ESAS screening, and 2) Which AYA were at highest risk of not being screened. **Methods:** We identified all Ontario AYA diagnosed with cancer at age 15-29 years between 2010-2018 and treated in adult centers. Patients were linked to population-based databases to identify all cancer-related outpatient visits in the year following diagnosis and whether visits involved completion of an ESAS form. Each patient's first year was divided into two-week periods. For each period, AYA were considered either unscreened if they had a cancer-related visit but no ESAS score, or screened if they had a cancer-related visit with at least one ESAS score. Periods without cancer-related visits were not considered, given no potential for ESAS screening during such periods. Covariates included age at diagnosis, sex, cancer type, neighbourhood income quintile, and institution type [regional cancer centre (RCC) vs. community]. Multivariable logistic regression models were implemented under a generalized estimating equations approach to account for individual-level correlation. **Results:** The final cohort included 5,435 AYA. Within any given two-week period, only 36-45% of AYA attending cancer-related outpatient visits were screened. In adjusted analyses, age and sex were not associated with being screened. However, AYA living in the lowest income quintile neighbourhood were less likely to be screened [odds ratio (OR) 0.86, 95th confidence interval (95CI) 0.77-0.97; p = 0.01] compared to those in the highest. Patients with hematologic malignancies were least likely to be screened (OR 0.77, 95CI 0.67-0.88; p < 0.001), as were AYA attending community centers (OR 0.48, 95CI 0.42-0.55; p < 0.001). **Conclusions:** Despite a population-wide symptom assessment program, only a minority of AYA are screened. Though patients with hematologic cancers suffer from particularly high symptom burdens, they were less likely to be screened. Interventions targeting AYA are required to increase uptake, particularly among those in disadvantaged neighborhoods or attending community hospitals. Studies of AYA-specific symptom assessment tools are also warranted. Research Sponsor: Terry Fox Research Institute.

12102 **Poster Session**

Association between allostatic load, symptom burden and mortality in E1A11 trial for myeloma. *First Author: Samilia Obeng-Gyasi, The Ohio State University, Columbus, OH*

Background: Allostatic load (AL) conceptualizes the effects of chronic psychosocial adversity on physiologic dysregulation. To date, studies have shown an association between elevated AL and higher disease-specific and overall mortality among cancer patients; however, none have focused on multiple myeloma (MM) patients. We aim to understand the relationship between baseline AL, symptom burden, and mortality among patients enrolled in the E1A11 therapeutic trial in MM. **Methods:** ECOG-ACRIN E1A11 was a phase III RCT comparing induction with Bortezomib (Arm A) versus Carfilzomib (Arm B) in conjunction with Lenalidomide +Dexamethasone. AL included 7 biomarkers: BMI, alkaline phosphatase, creatinine, C-reactive protein, white blood cell count, albumin and creatinine clearance. AL7 was a composite summary score with a point was assigned for each biomarker value in the highest quartile, except for albumin and creatinine clearance, where a point was assigned for values in the lowest quartile. Endpoints included symptom burden at baseline and ~1 month, non-completion of induction therapy, and overall survival (OS). Functional Assessment of Cancer Therapy Multiple Myeloma (FACT-MM) items assessed patient-reported symptom burden, including fatigue (item HI7), pain (GP4), and bother by side effects of treatment (GP5) on a 5-point Likert scale. Multivariable logistic regressions assessed the effect of AL7 (ranging 0-7) on high-pain, -fatigue, and -bother (QOL score $>=3$ vs <3), and non-completion of induction therapy. The effect of AL7 on OS was assessed using multivariable Cox regression. Regression covariates included study arm, age, sex, race, ECOG performance status, and the target symptom burden score at baseline. **Results:** The study cohort included 1087 patients. Mean baseline AL7 was 1.8 (±1.4). In adjusted analysis, a unit increase in AL7 was associated with a greater odds of high pain (OR 1.15, 95%CI [1.04-1.27]) and high fatigue (OR 1.19, 95%CI [1.07-1.32]) at baseline, which did not persist at ~1 month (pain OR 0.96, 95%CI [0.84-1.10]; fatigue OR 1.03, 95%CI [0.91-1.16]). There was no association between AL7 and high side effect bother at baseline (OR 1.06, 95% CI [0.83-1.35]) or at ~1 month (OR 1.06, 95%CI [0.90-1.24]). There was no association between AL7 and induction non-completion (OR 1.07, 95%CI [0.96-1.18]). Notably, each unit increase in AL7 was associated with higher mortality (HR 1.26, 95%CI [1.14-1.39]). **Conclusions:** Despite its association with fatigue and pain at baseline, AL7 was not associated with these symptoms at ~1 month nor induction non-completion. However, elevated baseline AL7 was associated with poorer OS. AL composite score at baseline, which we interpret as a measure of physiological dysregulation associated with adverse social factors, may have implications on clinical outcomes within clinical trials despite presumed equal treatment access. Research Sponsor: U.S. National Institutes of Health, Pharmaceutical/Biotech Company.

12103 **Poster Session**

Implementation of electronic patient-reported outcomes for symptom monitoring in a large multi-site community oncology practice. *First Author: Debra A. Patt, Texas Oncology, Dallas, TX*

Background: Among patients receiving chemotherapy, symptomatic adverse event monitoring with electronic patient-reported outcomes (ePRO) is associated with improved clinical outcomes, satisfaction, and compliance with therapy. Standard approaches for ePRO implementation are not established warranting evaluation in community cancer practices. Objective: Evaluate implementation of ePRO symptom monitoring across a large multi-site community oncology practice network. **Methods:** Patients initiating a new systemic therapy at one of 210 practice sites in the Texas Oncology Practice were invited to use in the Navigating Cancer ePRO platform, with rolling implementation from July-December 2020. Participating patients received a weekly prompt by text message or email (patient choice) to self-report common symptoms and well-being via web or smartphone. Severe self-reported symptoms triggered a real-time notification alert to nursing triage to address the symptom. Enrollment and compliance were systematically tracked weekly with evaluation of barriers and facilitators to adoption and sustainability. **Results:** 4375 patients planning systemic treatment enrolled and participated, with baseline characteristics are shown in Table 1. 73% (1841/2522) of enrolled patients with follow up completed at least one ePRO assessment, and among these individuals, 65% (8762/25061) of all available weekly ePRO assessments were completed. Over a 10-week period, compliance with weekly symptom reporting declined from 72% to 52%. Patients on oral therapy had higher compliance rates overall. Barriers currently being addressed include lack of a second reminder text/email prompt, inconsistent discussion of reported ePROs by clinicians at visits, and COVID-related changes in workflow. Facilitators included patient and staff engagement on the importance of PROs for symptom management. **Conclusions:** ePROs can be effectively implemented in community oncology practice. Utilization of ePROs is high, but diminishes over time without attention to barriers. Ongoing work to address barriers and optimize compliance are underway. Research Sponsor: None.

Baseline patient characteristics.	
Age	
Median (range) age, years	65
Age ranges, n (%)	
<25	17 (0.3)
25-34	98 (2.2)
35-44	297 (6.8)
45-54	595 (13.6)
55-64	1127 (25.8)
65-74	1341 (30.7)
75-84	735 (16.8)
85>	165 (3.8)
Sex, n (%)	
Female	2681 (61.3)
Male	1694 (38.7)
Race, n (%)	
White	3176 (72.6)
Black/African American	285 (6.5)
Asian	72 (1.6)
Hawaiian/Pacific Islander	7 (0.2)
American Indian / Alaska Native	5 (0.1)
Missing / Unknown	795 (18.2)
Multiple races reported	35 (0.8)
Ethnicity, n (%)	
Non-Hispanic/Latino	3264 (74.6)
Hispanic/Latino	758 (17.3)
Missing / Unknown	353 (8.1)
Location, n (%)	
Clinic location in rural area	238 (5.4)
Distance to clinic ≥ 20 mi	1060 (24.2)
Collection Method, n (%)	
SMS	3639 (82.9)
Email	342 (7.8)
Clinic Collect	406 (9.3)

12104 **Poster Session**

CD4+ T-cell count eligibility by HIV status among participants receiving immunotherapy for cancer diagnoses. *First Author: Thomas A Odeny, National Cancer Institute, National Institutes of Health, Bethesda, MD*

Background: The Food and Drug Administration recommends that patients living with HIV (PLWH) with a CD4+ T cell count (CD4) ≥350 cells/μL should generally be eligible for any cancer clinical trial, but there has been a reluctance to enter patients with lower CD4 counts. Patients with relapsed or refractory cancers may also have low CD4 due to initial cancer therapies, irrespective of HIV status. Immune checkpoint inhibitors (ICI) are safe among PLWH with advanced cancer receiving antiretroviral therapy and CD4 >100 cells/μL. We examined the outcomes of immunotherapy trials by HIV and CD4 status among patients receiving ICI for relapsed/refractory cancers. **Methods:** We conducted a retrospective cohort study of participants who received ICI for relapsed/refractory cancers in 2 trials (1 specifically in PLWH with CD4 >100 only) from the National Cancer Institute. Primary outcomes were to assess relationship between HIV status and baseline CD4 (<350 vs ≥350 cells/μL) and other characteristics. We stratified 3-year survival by CD4 in PLWH and HIV-negative participants with HPV-related cancers. The Kaplan-Meier method was used to estimate survival rates. **Results:** Eighty-three participants were included: 26 (31.3%) were HIV-positive and received pembrolizumab and 57 (68.7%) were HIV-negative and received bintrafusp alfa. HIV-negative participants had relapsed HPV related malignancies (cervix, anal, head and neck) whereas participants with HIV had both viral and non-viral associated cancers (Table). While the median screening CD4 was significantly lower among PLWH than HIV-negative participants, there was no difference in the proportion with CD4 <350 (p=0.1). When restricted to HPV related malignancies, 3-year survival rates were 32.2% for CD4 <350 and 21.2% for CD4 ≥350 (p=0.7). **Conclusions:** In this retrospective study of ICI clinical trials in relapsed and refractory malignancies, there was no significant difference in baseline CD4 (<350 vs ≥350 cells/μL) by HIV status; 50% of HIV-negative participants had CD4<350 cells/μL. Patients with HIV should be included in ICI studies, and CD4 thresholds lower than 350 cells/μL should be considered as to not unfairly exclude PLWH with cancer. Research Sponsor: U.S. National Institutes of Health.

		HIV+ N=26	HIV- N=57	Unadjusted p-value
CD4+ cells/μl	<350	18 (69%)	23 (50%)	0.11
	≥350	8 (31%)	23 (50%)	
CD4+ cells/μL		227 (164, 375)	356 (260, 470)	0.02**
Sex	Male	25 (96%)	21 (37%)	<0.001
	Female	1 (4%)	36 (63%)	
Cancer type	HPV-related cancers	5 (19%)	57 (100%)	<0.001
	Other	21 (81%)	0	
Age (years)		53.2 (47.7, 61.1)	58.7 (48.2, 64.8)	0.37
Absolute neutrophil count, X1000/μL		3.0 (2.1, 4.7)	4.0 (3.0, 5.3)	0.07
Absolute lymphocyte count, X1000/μL		1.0 (0.8, 1.4)	0.9 (0.6, 1.4)	0.42

* Data are presented as n (%) or *median (inter-quartile-range) ** Two-sample Wilcoxon rank-sum (Mann-Whitney) test.

12105 **Poster Session**

A multicenter analysis of the outcome of cancer patients with neutropenia and COVID-19 infection optionally treated with granulocyte colony-stimulating factor (G-CSF). *First Author: Ana M. Jimenez-Gordo, Medical Oncology Department, Hospital Universitario Infanta Sofía, San Sebastián De Los Reyes, Spain*

Background: Infection by SARS-CoV-2 can turn into an acute respiratory infection. Approximately 15% of patients will develop a distress syndrome responsible in most cases of mortality. A host hyperinflammatory response induced by a cytokine storm, is the main cause of this severe complication. Chemotherapy myelosuppression is associated with higher risk of infections and mortality in cancer patients. There have been no previous reports about the clinical management of patients with neutropenia and concomitant COVID-19. Herein, we present a multicenter experience in several hospitals during COVID-19 outbreak in neutropenic cancer patients infected by SARS-Cov-2. **Methods:** Retrospective clinical data were collected from clinical reports. Protocol was approved by a Clinical Research Ethics Committee (HULP: PI-4194). Inclusion criteria were cancer patients with neutropenia (<1500 cells/mm3) and concomitant COVID-19 infection. Comorbidities, tumor type and stage, treatment, neutropenia severity, filgrastim (G-CSF), COVID-19 parameters and mortality were analyzed. Exploratory analysis included a description of all data collected and bivariate analyses among different pairs of variables, including their impact in mortality in this cohort. In addition, multivariable logistic regression was used to predict respiratory failure and death as a function of multiple variables. **Results:** Among 943 patients with cancer screened in 14 hospitals in Spain, eighty-three patients (8%) had a febrile neutropenia and COVID-19 infection**.** Lung (26%), breast (22%), colorectal (13%) and digestive non-colorectal (17%) cancers were the main locations and most patients had advanced disease (67%). Fifty-three (63%) of patients included died because respiratory failure. Neumonia was presented in 76% of patients, bilateral in 47% and 12% of all patients had thrombotic events. The median of neutrophils was 650cls/mm3 and 49% received G-CSF with a median of days on treatment around 4,5 days. Among all variables related with mortality in neutropenic cancer patients with COVID-19 infection, we found that the number of days with G-CSF showed a significant trend toward worse outcome and higher mortality. In particular, a logistic regression model was developed to predict respiratory failure, as a function of the number of days of G-CSF treatment. As adjusting covariates, sex, age, treatment purpose (palliative vs curative, to adjust for patient status), tumor type, and the lowest level of neutrophils in the patient (to adjust for neutropenic status) were used. A significant effect was obtained for the days of G-CSF treatment (OR = 1.4, 95% CI [1.03, 1.92], p-value = 0.01). **Conclusions:** Our findings suggest that a prolonged G-CSF treatment could be disadvantageous for these cancer patients with COVID-19, with a higher probability of worse outcome. Research Sponsor: None.

12106 **Poster Session**

The impact of a web-based prognostic intervention on physicians' prognostic confidence. *First Author: David Hui, University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Clinicians often hesitate to discuss prognosis with patients because of prognostic uncertainty. The use of validated prognostic models may enhance prognostic confidence and/or prognostic accuracy. Prognostic confidence is a novel concept that has not been well studied and may support prognosis-based decision making. We examined the impact of a web-based prognostic intervention on physicians' prognostic confidence. **Methods:** In this prospective study, palliative care specialists estimated the prognosis of patients with advanced cancer seen at an outpatient supportive care clinic using the temporal, surprise and probabilistic questions for 6 m, 3 m, 2 m, 1 m, 2 w, 1 w and 3 d survival. They then reviewed information from a web-based prognostic calculator (www.predictsurvival.com) that provided survival predictions from 7 validated prognostic scores, including the Palliative Prognostic Score, Palliative Prognostic Index, and Palliative Performance Status. The clinicians then provided their prognostic estimates post-intervention. The primary outcome was prognostic confidence (0-10 numeric rating scale, where 0 = not at all, 10 = most confident) before vs. after the study intervention. Secondary outcomes included (1) confidence to share the prognosis with patients, (2) confidence to make prognosis-based care recommendations (agreement = strongly agree or agree) and (3) prognostic accuracy. With 220 patients, we had 80% power to detect an effect size of 0.66 with 2-sided α 0.05. We compared the pre-post data using the Wilcoxon signed-rank test for the primary outcome and McNemar test for secondary outcomes. **Results:** 216 patients with advanced cancer (mean age 61, 50% female) were included and 154 (71%) died. The median (IQR) actual survival was 90 (39, 178) days; the median (IQR) predicted survival before and after intervention were 90 (60, 90) and 80 (60, 90) days, respectively. Prognostic confidence significantly increased after the intervention (pre vs. post: median 6 vs. 7, $P < 0.001$). A significantly greater proportion of clinicians reported that they felt confident enough about their prognostic estimate to share it with patients (44% vs. 74%, $P < 0.001$) and to formulate care recommendations (80% vs. 94%, $P < 0.001$) after the intervention. Prognostic accuracy did not differ significantly before and after the intervention, ranging from 72-100% for the temporal question, 45-97% for the surprise questions and 38%-100% for the probabilistic questions ($P > 0.05$). **Conclusions:** Among patients with advanced cancer seen at a supportive care clinic, the web-based prognostic intervention was associated with greater prognostic confidence and willingness to discuss prognosis, despite not significantly altering clinicians' prognostic estimate or prognostic accuracy. Further research is needed to examine how prognostic tools may be able to augment prognostic discussions and clinical decision making. Research Sponsor: None.

12107 **Poster Session**

Cancer inpatient malnutrition risk, documentation, and ICD-10 coding in an academic medical center. *First Author: Aynur Aktas, Levine Cancer Institute, The Center for Supportive Oncology, Charlotte, NC*

Background: Malnutrition (MN) is common in hospitalized cancer patients but often underdiagnosed. We evaluated the prevalence of MN risk, dietitian documented MN (DDMN), and physician coded malnutrition (PCMN) in a consecutive cohort of cancer inpatients in an academic, community-based medical center. **Methods:** Electronic medical records (EMR) were reviewed for inpatients with a solid tumor diagnosis staged I-IV and admitted to Atrium Health Carolinas Medical Center at least once between 1/1/2016 to 5/21/2019. All data were collected from the first admission EMR encounter closest to the cancer diagnosis date. High MN risk was a score ≥2 on the Malnutrition Screening Tool (MST) completed by an RN at admission. Registered Dietitian (RD) assessments were reviewed for DDMN and grade (mild, moderate, severe). PCMN diagnosis was based on MN ICD-10 codes extracted from the medical coder's discharge summary. Multivariate logistic regression models identified associations between clinic-demographic factors and the prevalence of DDMN and PCMN with stepwise selection. **Results:** N=5,143; 48% females. Median age 63 (range 18-102) years. 70% White; 24% Black, 3% Latino. Most common cancers: thoracic 19% and digestive system (14% other, 11% colorectal). 28% had known stage IV disease. The MST was completed in 79%. Among those with MST ≥2 (N=1,005; 25%), DDMN and PCMN prevalence was 30% and 22%, respectively. In the entire cohort, 8% had DDMN; 7% PCMN; 4% both. Prevalence of MN risk, DDMN, and PCMN by cancer site are in the Table. DDMN (N=420) was mild 2%, moderate 16%; severe 66%; unspecified 16%. On discharge, PCMN (N=360) was mild 10%; moderate 0%; severe 69%; unspecified 21%. Male gender (OR 1.27 [1.01, 1.59]), Black race (OR 1.57 [1.25, 1.98]), stage IV disease (v. I-III) (OR 3.08 [2.49, 3.82]), and primary site were all independent predictors of DDMN (all $p<0.05$); Black race (OR 1.46 [1.14, 1.87]), stage IV disease (OR 2.70 [2.15, 3.39]), and primary site were independent predictors of PCMN (all $p<0.05$). **Conclusions:** 25% of cancer inpatients were at high risk for MN. Primary site, disease stage, and race were independent predictors of a greater risk. MN appears to be under-diagnosed compared to population studies. This is the first study to report the prevalence of MN in a large cancer inpatient database with a representative population. Research Sponsor: None.

Prevalence of MN risk, dietitian documented MN, and physician coded MN by primary site (N=5143).

Primary Cancer Site	N	MST ≥2 (%)	DDMN (%)	PCMN (%)
Pancreas	440	50	19	15
Other Digestive	701	32	12	11
Thoracic	952	31	9	8
Head/Neck	339	28	13	14
Female Genital	403	26	5	4
Colorectal	564	20	9	6
Other	927	14	4	3
Breast	491	13	3	2
Prostate	326	8	2	2

12108 **Poster Session**

Randomized study of electric hand warmer (EHW) versus observation to avoid discomfort during scalp cooling for chemotherapy-induced alopecia (CIA) prevention. *First Author: Luciana Castro G. Landeiro, Núcleo de Oncologia da Bahia-Grupo Oncoclínicas, Salvador, Brazil*

Background: CIA has been reported as the most disturbing adverse event of cancer treatment by most women receiving chemotherapy. Many strategies have been tested to minimize CIA, among which scalp cooling has proven high effectiveness. However, discontinuation rates of this technology vary from 3% to 13%, mostly due to headache, cold sensation and pain. EHW could be used to mitigate these side effects, produce heat on demand and a warming sensation. The primary objective of this study is to evaluated the impact of EHW device on the general comfort of breast cancer patients while on scalp cooling during chemotherapy treatment. **Methods:** Patients were randomly assigned to EHW use or observation. Thermal, sensory and general comfort were measured with pragmatic questionnaires after each chemotherapy infusion: neutral or hot as favorable thermal responses; comfortable and very comfortable as favorable sensory responses; finally, favorable outcomes in both thermal and sensory comfort questionnaires defined a positive result on the general comfort. We evaluated the impact of age (≤ or > 50 years), alopecia (grade 0 or 1/2), chemotherapy regimen (with or without taxanes) and EHW use (yes or no) in the different comfort scales using Logistic Regression (LR) models. **Results:** Forty women with early or locally advanced breast cancer were assigned to EHW (n = 20) or observation (n = 20) during neo(adjuvant) chemotherapy. Median age was 53 years, 67.5% concluded university education, 52.5% had comorbidities. Most patients had stage II disease (55%), largely ER/PR+ HER2- disease (67.5%), followed by triple negative (22.5%), and HER2+ (10%). Most frequent regimen was ACdd-Tdd (42.5%). Thirty-one patients (77.5%) continued scalp cooling during entire chemotherapy regimen (alopecia < grade 3). A favorable thermal response was seen in 79% of EHW applications as compared to 50% in control arm (odds ratio [OR] 3.79, $P < .001$). Sensory comfort was satisfactory in 82% of EHW applications as compared to 74% with control (OR 1.62, $P = .1$). General comfort was favorable in 73% of EHW applications as compared to 44% in control arm (OR 3.4, $P < .001$). Age, alopecia grade and taxane use did not significantly impact on comfort measures. **Conclusions:** Our study suggests that an EHW has a consistent favorable impact on thermal and general comfort of breast cancer patients under scalp cooling technology to prevent CIA. This simple device can improve patient's quality of life and eventually avoid scalp cooling discontinuation due to discomfort. Research Sponsor: Grupo Oncoclinicas.

12109 **Poster Session**

A 10-hour time-restricted eating intervention to address cancer-related fatigue among cancer survivors. *First Author: Amber Kleckner, University of Rochester Medical Center, Rochester, NY*

Background: Cancer-related fatigue is a common, debilitating condition that can persist for months or years after cancer treatment. Time-restricted eating has been shown to improve circadian rhythm and strengthen rest and activity patterns, and therefore could help reduce persistent fatigue. Herein, we evaluated the feasibility of recruiting cancer survivors to a two-week, single-arm, time-restricted eating intervention with a 10-h eating window, assessed safety of the intervention, monitored adherence, and obtained initial estimates of within-group change in patient-reported fatigue. **Methods:** We recruited adults 4-60 months post-cancer treatment who had a fatigue level ≥3 on a scale from 0-10 and who did not already consume food within a 10-h window. Participants were asked to consume all food and beverages within a self-selected 10-h eating window for 14 days; water was allowed at all times. Participants completed a daily diary indicating when they began and stopped eating each day. To assess fatigue, participants completed the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) and the Brief Fatigue Inventory (BFI) at pre- and post-intervention. We report mean±standard deviation and used a t-test to assess differences in pre- vs. post-intervention scores. **Results:** A total of 21 participants consented (20 breast cancer, 1 prostate cancer; 20 female; age 57.7±11.4 years; 1.6±1.1 years post-primary treatment). The study was feasible: 19/21 (90.5%) completed pre- and post-intervention assessments and daily diaries. It was also safe: there were two mild adverse events—one unlikely (insomnia) and one possibly related to the intervention (acute headache) and no severe adverse events. Most of the participants adhered to the intervention; 14/19 (73.7%) ate all of their food within a 10-h window at least 80% of the days, and 16/19 (84.2%) reported an average eating window ≤10 h. Fatigue scores improved a clinically meaningful degree for FACIT-F total score, FACIT-F fatigue subscale, and the BFI total score from pre- to post-intervention per established cutoffs (Table). **Conclusions:** Cancer survivors were willing and able to adhere to a two-week time-restricted eating intervention, and the intervention was safe. Also, fatigue was reduced with moderate to large effect sizes after two weeks of time-restricted eating. Based on our results, a follow-up randomized controlled trial to investigate time-restricted eating to alleviate cancer-related fatigue among cancer survivors is indicated. Funding: NIH/NCI UG1CA189961, T32CA102618. Clinical trial information: NCT04243512. Research Sponsor: U.S. National Institutes of Health.

	Range	Direction	Baseline	Post-intervention	Change	p-value	Effect size
FACIT-F total score	0-160	Higher is better	106.9±14.5	118.2±16.2	11.4±11.3	<0.001	0.79
FACIT-F fatigue subscale	0-52	Higher is better	30.6±7.9	35.5±8.1	4.9±7.5	0.011	0.62
BFI total score	1-10	Lower is better	3.9±1.8	2.5±2.0	-1.4±1.9	<0.001	-0.81

12110 **Poster Session**

Improving cancer pain management in the emergency department: An EMR-based solution. *First Author: Christopher John Coyne, University of California San Diego, San Diego, CA*

Background: Pain is common reason for patients with cancer to seek care in the emergency department (ED). Unfortunately, these patients frequently receive inadequate doses of pain medication, partially due to opioid reduction efforts in the ED, as well as opioid tolerance among those with chronic cancer pain. The purpose of this study was to investigate the effectiveness of an electronic medical record (EMR) based best practice advisory (BPA) at improving analgesic dosing for cancer patients in the ED. **Methods:** We performed a retrospective cohort study on cancer pain at two academic medical centers from 05/18/20 to 10/27/20. The BPA algorithm identified ED patients with cancer that were taking prescription opioids with a morphine equivalent daily dose (MEDD) of at least 100, as calculated by the EMR. If the ED provider ordered opioids for these patients, a BPA alert appeared with a recommended opioid dose based on the patient's individual MEDD. This alert also included pre-set safety orders for O_2 and end tidal CO_2 monitoring as well as naloxone. We compared outcomes based on whether an ED provider accepted or cancelled the BPA recommendation. These outcomes included the change in opioid dose and ED disposition. Continuous variables were compared using the students t-test, while categorical variables were compared with the chi-squared test with an alpha of 0.05. **Results:** Our BPA identified 92 patients that met our criteria, representing 143 BPA alerts. The mean age was 52, 43.5% were female, 54.3% had metastatic disease, and 56.5% presented with a painful chief complaint. Of the ED providers that accepted the BPA, 57.5% increased their dose of opioid medication. BPA usage led to a 33.3% mean increase in medication dosage ($p < .001$). Patients that presented with a painful chief complaint, whose providers utilized the BPA were admitted at a rate of 60.5%, verses a 77.8% admission rate among those whose providers did not utilize the BPA ($p < .01$). No patients required an opioid reversal agent. **Conclusions:** Among cancer patients on chronic opioids presenting to the ED, use of an EMR-based BPA led to more appropriate opioid dosing without the need for opioid reversal agents, and was associated with an overall decrease in hospital admissions. Research Sponsor: None.

12111 **Poster Session**

The impact of cancer-related diarrhea on changes in cancer therapy patterns. *First Author: Pablo C Okhuysen, UT MD Anderson Cancer Center, Houston, TX*

Background: We studied the impact that cancer related diarrhea (CRD) has on cancer therapy and treatment patterns, including persistence, discontinuation, adherence, and switching of chemotherapy and targeted therapies in patients with and without CRD. **Methods:** We performed a longitudinal observational study among adult (> 18 yrs) patients with CRD identified by diagnosis codes or pharmacy claims compared to matched (1:1) non-CRD patients using claims data derived from the IQVIA PharMetrics Plus database. Index date was defined as the date of the first cancer claim, and we re-indexed patients based on CRD claims. Each patient had a 6-month pre-index period and a minimum 3-month follow-up post-index period. To adjust for selection bias and baseline differences, we directly matched the CRD patients to non-CRD patients. Treatment patterns were evaluated and stratified for the first cancer therapy with or without CRD (chemotherapy vs targeted therapy vs both targeted and chemotherapy). Discontinuation was defined as a 30-day gap for chemotherapy and a 14-day gap for targeted therapies from index therapy; switching was a new chemotherapy or targeted therapy prescription within 30 days following discontinuation of index therapy. We computed adherence as the proportion of days covered over the 12-month post-index period and persistence as mean number of days on index therapy. A Cox proportional hazards model was used to estimate the difference in risk of discontinuation of index therapy between CRD and non-CRD cohorts. **Results:** We evaluated a total of 104,135 matched pairs of CRD and non-CRD adult patients with solid or hematologic cancer; each group further grouped by those receiving either chemotherapy (n = 47,220), targeted therapy (n = 2,427), or both treatments (n = 5,313). Patients with CRD discontinued the index therapy more frequently than non-CRD patients for chemotherapy (81.5% vs 62.3%), targeted therapy (69.2% vs 64.3%) or both (96.0% vs 85.5%) ($p < 0.0001$). Also, the overall percentage of discontinuation (82.4% vs. 64.6%) was significantly higher among patients with CRD. The mean time to discontinuation (59.6±54.1 vs. 68.3±76.6 days) was significantly lower ($p < 0.0001$) in patients with CRD. The mean time to switch (72.0± 48.6 vs. 96.9±84.0 days), mean persistence (95.1±98.1 vs. 154.3±142.7 days), and mean adherence (25.5%±37.2 vs. 47.9±41%) were significantly lower (all $p < 0.0001$) among patients with CRD compared to non-CRD. The percentage of patients requiring a dose titration for their index cancer therapy was significantly higher (21.8%) for the CRD cohort versus 8.5% for non-CRD patients ($p < 0.0001$). **Conclusions:** Patients with CRD were 40% (adjusted) more likely to discontinue the index therapy than patients without CRD. The persistence of index cancer therapy and time to switch were also lower for patients with CRD. Strategies to control CRD and continue cancer therapy are urgently needed. Research Sponsor: Napo Pharmaceuticals.

12112 **Poster Session**

Patient-reported benefits and burdens of direct oral-anticoagulants (DOACs) and low molecular weight heparins (LMWHs): The CANVAS pragmatic randomized trial (AFT-28). *First Author: Deborah Schrag, Dana-Farber Cancer Institute, Boston, MA*

Background: Previous randomized trials in cancer patients suggest that DOACs are non-inferior to LMWHs for preventing recurrent venous thromboembolism (VTE). However, patients' perspectives have not been reported. Objective**:** CANVAS compared LMWHs to DOACs for preventing recurrent VTE in cancer patients. Key 2° endpoints were: 1) health-related quality of life (QOL); and, 2) treatment satisfaction. **Methods:** CANVAS was an unblinded hybrid comparative effectiveness non-inferiority trial. Between 12/2016 and 4/2020, 671 participants were randomized and followed for 6-months. Patients were assigned 1:1 to receive either a DOAC or a LMWH. Physicians could select any DOAC or LMWH at standard dosing, and patients assigned to LMWH were allowed to transition to Warfarin. Patients from 67 US practices with any invasive solid tumor, lymphoma, multiple myeloma or CLL and a diagnosis of VTE within 30 days of enrollment were eligible. The 1° analysis was conducted in the randomized modified intent-to-treat population, (all subjects who received assigned treatment). Key 2° endpoints were to establish: 1) non-inferior change in HR-QOL; 2) greater perception of benefit; and 3) lower perception of burden for participants receiving DOACs versus LMWHs. Participants reported QOL at 0, 3 and 6 months on the SF-12 survey. At 3 and 6 months, they also reported satisfaction via the Anti-Clot Treatment Scale (ACTS), which includes a burden and a benefit scale. A 2-point change was pre-specified as significant. **Results:** Neither QOL nor patients' perceptions of treatment benefits differed between groups. However, patients on DOACs reported lower treatment burden compared to those assigned LMWHs. **Conclusions:** Among adult cancer patients with VTE, the use of a DOAC compared with a LMWH resulted in no difference in QOL but higher patient-reported satisfaction stemming from decreased perception of the burden of treatment. Clinical trial information: NCT02744092. Research Sponsor: PCORI CER-1503-29805.

Patient reported outcomes.

Cohort	DOAC	LMWH		
Total	330	308		
N surveyed at 3 mos[1]	212/295 (72%)	197/280 (70%)		
N surveyed at 6 mos[1]	191/294 (65%)	177/278 (64%)		
PRO Endpoint	Mean (SD)	Mean (SD)	Difference (0.90 CI)	p-value
DQOL (Physical) 0 vs. 3 mos	1.9 (9.5)	0.6 (9.6)	1.3 (-0.4, 3.0)	0.21
DQOL (Physical) 0 vs. 6 mos	2.8 (11.5)	1.3 (10.8)	1.6 (-0.6, 3.7)	0.53
DQOL (Mental) 0 vs. 3 mos	0.0 (10.7)	0.7 (10.3)	-0.7 (-2.6, 1.2)	0.23
DQOL (Mental) 0 vs. 6 mos	0.5 (11.4)	0.3 (10.6)	0.1 (-2.0, 2.2)	0.93
Benefits[2] at 3 mos	11.2 (3.1)	10.8 (3.0)	0.4 (-0.1, 0.9)	0.21
Benefits[2] at 6 mos	11.7 (3.0)	11.4 (2.6)	0.3 (-0.2, 0.8)	0.32
Burdens[3] at 3 mos	56.7 (3.9)	53.4 (5.7)	3.3 (2.5, 4.1)	< 0.001
Burdens[3] at 6 mos	56.5 (4.8)	54.5 (5.6)	2.0 (1.1, 2.9)	< 0.001

[1]Respondents among non-deceased participants. [2]The benefit scale has 3 items with scores from 3 to 15. [3]The burdens scale has12 items with scores from 12 to 60. Higher scores signify greater satisfaction (lower burden).

12113 **Poster Session**

Development and validation of a novel patient-reported outcomes (PRO) measure for symptom burden in patients with cancer and COVID-19 infection. *First Author: Loretta A. Williams, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: The symptom burden experienced by patients with cancer who contract the COVID-19 (C19) infection remains to be fully understood. To accurately assess this symptom burden, we developed a valid, reliable patient-reported outcome (PRO) measure of C19 symptoms combined with a known measure of cancer symptom burden. **Methods:** Within the institutional initiative on COVID-19 and cancer named Data-Driven Determinants for COVID-19 Oncology Discovery Effort (D3CODE), patients with cancer and PCR-positive C19 tests were invited to participate in this longitudinal study after providing consent. Pts completed the EQ-5D-5L and the 13 symptom severity and 6 interference items of the core MD Anderson Symptom Inventory (MDASI) plus 14 COVID-specific symptom items generated from literature and expert review. Items were measured on a 0-10 scale, 0 = none to 10 = worst imaginable symptom or interference. Demographic and disease information was collected. Psychometric procedures determined validity and reliability of the MDASI-COVID. **Results:** 600 pts enrolled, mean age 56.5y (range 20 to 91y). 59% female, 80% white. 78% solid tumors, 19% heme cancers. 12.5% required hospitalization for C19. Median number of days between positive C19 test and PRO completion was 17 days. Mean overall health rating on EQ-5D-5L was 78.3 (SD 19.6), best being 100. Highest mean (M) severity symptoms on the MDASI-COVID were fatigue (M 3.45, SD 2.17), drowsiness (M 2.50, SD 2.89), sleep disturbance (M 2.44, SD 2.99), malaise (M 2.37, SD 3.05), and distress (M 2.27, SD 2.90). Most severe ($\geq$ 7) symptoms) reported were fatigue (21.3% of pts), change in taste (14.8%), change in smell (14.4%), malaise (14.3%), sleep disturbance (14.3%), and drowsiness (14%). Internal consistency (Cronbach α) of the 27 symptom items was 0.957, of the 6 interference items was 0.937. Mean severity of the 27 symptom items was significantly correlated with overall EQ-5D-5L health rating (correlation = -0.45, $P < 0.0005$), demonstrating concurrent validity. Mean symptom severity and interference showed known-group validity between patients who required C19 hospitalization (symptom M 2.32, SD 2.09; interference M 3.29, SD 3.02) and those who did not (symptom M 1.69, SD 1.85; interference M 2.20, SD 2.64) (symptom P *0.007*; interference P *0.004*). **Conclusions:** We have validated a novel PRO, the MDASI-COVID, to quantify the combined symptom burden in patients with cancer and COVID-19. This measure allows longitudinal evaluation of COVID-19 on cancer symptom burden and provide clinicians with an accurate tool for ongoing symptom assessment and management. Longitudinal analysis on long-term symptoms related to COVID-19 and cancer are ongoing. Research Sponsor: American Cancer Society.

12114 **Poster Session**

Immune cell counts and perceived cognitive impairment before and after chemotherapy among 544 women with breast cancer. *First Author: Elizabeth Belcher, University of Rochester Medical Center, Rochester, NY*

Background: In a nationwide prospective study, we found that patients with breast cancer had greater perceived cognitive impairment (PCI) before and after chemotherapy compared to controls without cancer. To gain further insight into the role that inflammation plays in cognitive function, we evaluated relationships between immune cell counts and lymphocyte:monocyte ratio with PCI at pre- and post- chemotherapy. **Methods:** Data were collected as part of longitudinal cohort study conducted through the National Cancer Institute Community Oncology Research Program network (NCT01382082). Self-reported PCI was scored at pre-chemotherapy (0-7 days before first chemotherapy) and post-chemotherapy (0-30 days after last chemotherapy) from the PCI sub-scale of the Functional Assessment of Cancer Therapy: Cognitive Function (possible score range 0-72). Immune cell counts were measured by complete blood count with differential at pre- and post- chemotherapy. Lymphocyte:monocyte ratio (LMR) was calculated. Separate linear regression models evaluated the association of immune cell counts and LMR with 1) pre-chemotherapy PCI and 2) post-chemotherapy PCI. Models were adjusted for age, cognitive reserve (reading score), anxiety, and depression. **Results:** PCI and immune cell data were available for 544 patients at pre-chemotherapy and 532 at post-chemotherapy. Subjects had a mean age of 53.1 (SD=10.8). At pre-chemotherapy, higher basophil count and higher LMR were significantly associated with worse PCI (β=5.73, SE=2.37, p<0.05; β=0.047, SE=0.02, p<0.05, respectively). Higher basophil count and higher LMR were also significantly associated with worse PCI at post-chemotherapy (β=5.84, SE=2.92, p<0.05; β=1.01, SE=0.48, p<0.05). **Conclusions:** These data support the hypothesis that inflammation is associated with perceived cognitive function before and after chemotherapy in adults with breast cancer. Targeting inflammatory processes may be beneficial for reducing cancer-related cognitive impairment. Funding: NCI UG1CA289961, T32CA102618, R01CA231014, DP2CA195765. Research Sponsor: National Cancer Institute.

12115 **Poster Session**

Comparison of inpatient outcomes of pathological fractures in metastatic breast cancer and osteoporosis. *First Author: Kriti Ahuja, John H. Stroger, Jr. Hospital of Cook County, Chicago, IL*

Background: In the United States, an estimated 1 in 8 women will be diagnosed with breast cancer during her lifetime. Of those with metastasis, over half have bone metastases leading to risk for pathological fractures. Further, approximately 1 in 4 women over 65 years have osteoporosis of the femur neck or lumbar spine. We performed a retrospective analysis on outcomes in pathological fractures secondary to breast cancer metastasis in comparison to osteoporosis, including disposition at discharge. **Methods:** The Nationwide Inpatient Sample (NIS) database was queried to include all adult women admitted with osteoporotic fractures and pathological fractures due to metastatic breast cancer between 2016 and 2018. T-test was used to compare means of continuous variables and chi-square test to compare proportions of categorical variables. Multivariate analysis of predictors of pathological fractures in women with breast cancer metastatic to bone, as well as mortality, resource utilization and disposition in this group were performed. **Results:** A total of 91,494 fractures, combining osteoporosis and pathological fractures secondary to metastatic breast cancer were identified, of which the latter accounted for 4.9%. Patients with pathologic fractures secondary to metastatic breast cancer were younger (mean age 62.8 vs 79.5 years, $p < 0.0001$) and were more likely to be black (14.6% vs 3.1%, $p < 0.0001$) or Hispanic (8.3% vs 4.7%, $p < 0.0001$). Adjusting for demographic variables and comorbidity burden, pathological fractures secondary to metastatic breast cancer were not associated with a significant increase in inpatient mortality (aOR 1.57, 95% CI 0.84-2.95, p = 0.16), but were independently associated with increased length of hospital stay by 0.7 days per admission (p = 0.01) and higher hospitalization costs by $3,381 USD per admission ($p < 0.01$). Regarding disposition, patients with pathological fractures secondary to breast cancer were less likely to be discharged to a nursing facility (aOR 0.57, 95% CI 0.48-0.68, $p < 0.001$) and were more likely to be transitioned to home health care (aOR 1.46, 95% CI 1.20-1.78, $p < 0.001$). **Conclusions:** In adult women, pathological fractures secondary to breast cancer are less frequent than osteoporotic fractures and were not independent predictors of inpatient mortality. They do however prolong length of stay and increase healthcare costs. Further efforts should focus on risk prediction and prophylactic management of high risk bone lesions in order to enhance patient's quality of life, decrease hospitalization admissions, stay and cost. Research Sponsor: None.

12116 **Poster Session**

The impact of early palliative care on the quality of life of patients with advanced pancreatic cancer: The IMPERATIVE study. *First Author: Christina Kim, Research Institute of Oncology and Hematology, CancerCare Manitoba, Winnipeg, MB, Canada*

Background: Pancreatic cancer (PDAC) is an aggressive, deadly disease. Chemotherapy (CT) can improve survival by months, but symptom burden is heavy and quality of life (QOL) is poor. Early palliative care (EPC) alongside standard oncologic care improves QOL and survival in other types of cancer; however, the impact on QOL and symptom burden in advanced PDAC is not known. The primary objective of this study was to test for improvement in QOL between baseline (BL) and 16 weeks (wks) among patients receiving EPC. A secondary objective was to test for decreased symptom burden between BL and 16 wk. **Methods:** In this prospective case-crossover study, patients >18 years with advanced PDAC received EPC provided by a subspecialist palliative care physician and advanced practice nurse plus standard oncologic care. Ambulatory EPC visits occurred every 2 wks for the first month, then every 4 wks until wk 16, and then as needed. The Functional Assessment of Cancer Therapy – hepatobiliary (FACT-hep) and Edmonton Symptom Assessment System (ESAS) questionnaires were completed at enrollment and every 4 wks until wk 16. Least square means and 95% confidence intervals were computed. A generalized linear mixed model was used to test for statistically significant change in scores between BL and wk 16. A sample size of 20 patients provides 80% power after controlling for covariates; 40 patients were enrolled to account for anticipated attrition and missing data. **Results:** Of 40 patients, 25 (62.5%) were male, 28 (70%) had metastatic disease, 31 (77.5%) had an ECOG performance status of 0-1, 17 (42.5%) had a body mass index (BMI) >25, 35 (89.7%) had an elevated CA19-9 and 31 (77.5%) received CT. Median age was 70.2 (range 63.0-77.5). BL and wk 16 questionnaires were completed by 100% and 70% of patients, respectively. The mean FACT-hep score at BL was 118.8, compared to 125.7 at wk 16, for a mean change of 6.89, [95%CI (-1.69-15.6); p = 0.11]. The mean change from BL to wk 16 for FACT-hep was statistically significant in patients receiving CT, 10.1 [95%CI (0.32-19.8); p = 0.04], patients with metastatic disease, 14.7 [95%CI (5.30-24.1); p = 0.0030] and patients with a BMI >25, 12.5 [95%CI (1.29-23.7); p = 0.03]. The mean ESAS total symptom score at BL was 25.3, compared to 22.7 at wk 16 (p = 0.28). In those with metastatic disease the mean change was statistically significant, -5.73 [95%CI (-11.21 to -0.24); p = 0.04]. **Conclusions:** EPC resulted in improved QOL in pts with PDAC receiving CT and those with a BMI >25, and improved QOL and symptom burden in patients with metastatic disease. Given minimal attrition and high rates of questionnaire completion, our sample size was robust, resulting in strong power. Providing palliative care alongside standard oncologic care results in clinically meaningful improvements. Access to palliative care, shortly after diagnosis, should be available for patients with advanced PDAC. Clinical trial information: NCT03837132. Research Sponsor: CancerCare Manitoba Foundation, Pharmaceutical/Biotech Company.

12117 **Poster Session**

The enduring negative effects of financial toxicity in young adult cancer survivors. *First Author: Bridgette Thom, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Due to disruptions in education, workforce entry, and career development caused by cancer and its treatment, young adult (YA) cancer survivors face financial toxicity (i.e., cancer-related financial distress) at rates higher than older survivors. Financial toxicity in YA survivors is associated with avoiding care and diminished psychosocial well-being, but enduring effects on employment, personal finances, and healthcare use and the association with YA's financial capability are not well studied. **Methods:** This was a cross-sectional survey of a national sample of YAs with cancer (n = 214) recruited online and via mailing lists. It included the Comprehensive Score for Financial Toxicity (COST), demographic/clinical self-report, and questions on medical cost-coping and healthcare use. Financial capability questions considered respondents' knowledge about finances, self-efficacy for managing health expenses, and attitudes and behaviors regarding tracking expenses, budgeting, saving, investing, and bill paying. Multiple linear regression assessed associations among financial toxicity, financial capability, and cost-coping. **Results:** Mean respondent age was 35.4 years (*sd*= 5.40) at survey and 27.5 years (*sd*= 7.23) at diagnosis. Breast cancer (28%) and lymphoma (17%) were the most common diagnoses; most respondents were white (79%) women (87%) with college degrees (74%). Financial toxicity, as measured by COST, was high (mean = 13.9, *sd*= 9.3; possible range 0-44, scores < 26 indicate severe financial toxicity). Nearly all of the sample (96%) had health insurance, but 30% said their insurance does not meet their needs. One-half of the sample lacked confidence to manage health expenses. Cost-coping strategies included skipping/delaying: treatment (23%), survivorship care (35%), or medications (39%); 65% relied on a family member to pay for some/all medical bills. Negative events related to medical expenses included using money from savings (58%), taking on credit card debt (45%), post-cancer credit score decrease (44%), borrowing money to pay bills (42%), debt collection contact (37%), lacking money to pay for basic necessities (23%), loan denial (20%), and thoughts about and/or filing for bankruptcy (15%). In multivariate analyses, greater financial toxicity was associated with lower self-efficacy for managing health expenses (β = -0.88, p = .01), poorer financial behaviors (β = -0.54, p = .001), lower income (β = -5.27, p = .001), and skipping/delaying: treatment (e^{β}= 1.16, p < .001), survivorship care (e^{β}= 1.13, p < .001), or prescribed medication (e^{β}= 1.10, p = .001). **Conclusions:** Our findings illustrate the profound enduring impact of financial toxicity among YAs after cancer treatment. Multilevel interventions are needed to provide YAs the tools to navigate financial aspects of the healthcare system and connect them with resources toward gaining financial independence. Research Sponsor: Chanel Endowment to Fund Survivorship Research.

12118 **Poster Session**

Neuropsychiatric disorders in hospitalized patients undergoing chimeric antigen receptor T-cell therapy for aggressive lymphomas and acute lymphoblastic leukemia: A national study. *First Author: Josephine Emole, Stem Cell Transplantation and Cellular Therapy, Henry Ford Hospital, Detroit, MI*

Background: Chimeric antigen receptor T cell therapy (CART) has shown efficacy in acute lymphoblastic leukemia (ALL), diffuse large B cell lymphoma (DLBCL), and primary mediastinal B cell lymphoma (PMBCL). While neurological toxicities of CART are known, neuropsychiatric disorders (NPD) in patients undergoing CART has not been well described. Our study assessed the prevalence of NPD in hospitalized patients (pts) undergoing CART, and explored association of NPD with clinical variables. **Methods:** Using the National Inpatient Sample database, we conducted a retrospective study of pts with ALL, DLBCL and PMLCL aged ≥ 18 years who underwent CART in 2018. Hospitalizations were selected using International Classification of Disease, Tenth Revision (ICD-10) codes. NPD of interest included anxiety, depression, adjustment disorder, insomnia, psychosis, dementia, bipolar disorder. Delirium was not included in the inventory of NPD since delirium is a neurotoxicity of CART, and inclusion of delirium as NPD would confound results. Patient, disease, and CART complications were extracted from hospitalization records. Regression analyses were used to assess association of NPD with clinical variables. **Results:** 945 CART procedures met the inclusion criteria (56 % males and 60% Caucasians). Majority of CART (88%) were performed for DLBCL and PMBCL. NPD was diagnosed in 31 % of pts. Anxiety was the most common NPD, followed by insomnia and depression. ALL pts were more likely to have NPD compared to pts with lymphoma (52% versus 28%, $p<0.05$). More females had NPD compared to males (40% versus 25%, $p<0.05$). Univariable analysis showed association of NPD with female gender [Odds ratio (OR)=2.03, 95% CI = 1.05-3.93] and ALL (OR=2.76, 95% CI = 1.03-7.43). In a multivariable model, NPD was associated with ALL (OR =3.57, 95% CI= 1.01-12.55), while the association of NPD with female gender was less certain (OR =1.41, 95% CI=0.73 - 2.74). There was no association between NPD and mortality, neurotoxicity, systemic inflammatory response syndrome or hemophagocytic lymphohistiocytosis. **Conclusions:** One in every 3 pts who underwent in-hospital CART for ALL or aggressive B cell lymphoma in 2018 had comorbid NPD. Females and ALL pts were at higher risk for NPD. As CART pts transition into longer follow up and survivorship, ours and similar results should inform the planning and allocation of psychosocial services. Research Sponsor: None.

12119 **Poster Session**

A randomized controlled trial with a cluster of oncologists evaluating of an integrated communication support program for oncologists, caregivers, and patients with rapidly progressing advanced cancer on patient-centered conversation: J-SUPPORT 1704 study. *First Author: Maiko Fujimori, Division of Behavioral Sciences, Research Center for Public Health Sciences, National Cancer Center, Tokyo, Japan*

Background: Communication is an essential aspect of care for patients with progressive serious illnesses. Earlier discussion about patients' values and priorities may lead to empathic communication and more goal-concordant care, and improved quality of life (QOL). This study aims to evaluate the efficacy of a newly developed integrated communication support program for oncologists, patients with rapidly progressing advanced cancer and their caregivers. **Methods:** Oncologists are randomly assigned to the intervention group (IG) or control group (CG). Patients with advanced pancreatic cancer after the start of first-line chemotherapy and their caregivers are allocated to the same group as their oncologists. The IG oncologists receive a 2.5-hour individual communication skills training, and patients and caregivers receive a half-hour coaching intervention to facilitate prioritizing and discussing questions and concerns about care after standard chemotherapy; the CG participants do not receive any training. Conversations during the post-intervention consultation between oncologists, patients and caregivers were audio-recorded, and were assessed on their empathic communication and information sharing performance as primary outcome. Secondary outcomes included the patient psychological distress (HADS), QOL (CoQOLo), satisfaction with communication (CSQ) and trust in oncologist (TiOS) were assessed baseline and after the consultation. **Results:** A total of 26 oncologists (12 intervention; 13 control; 1 excluded before randomization), 230 patients (115 intervention; 115 control), and 127 caregivers (65 intervention; 62 control) in 4 teaching hospitals are enrolled. The intervention resulted statistically significant improvements in the empathetic communication (IG: Mean = 23.4, Standard Error = 0.8; CG: M = 20.3, SE = 0.7; effect, 3.1; 95%CI, 1.0-5.3; P = 0.0063) and in the information sharing (IG: M = 17.6, SE = 0.8; CG: M = 13.2, SE = 0.5; effect, 4.4; 95% CI, 2.5-6.2; $P < 0.0001$). Patients in IG rated more satisfaction with communication using CSQ (effect, 2.4; 95%CI, 1.3, 3.5; P = 0.00023) than those in the CG. There were no differences in HADS total score (effect, 0.1; 95%CI, -1.0, 1.1; P = 0.90), CoQOLo score (effect, 0.4; 95%CI, -0.7, 1.4; P = 0.46) and TiOS score (effect, 0.2; 95% CI, -0.1, 0.6; P = 0.15) between patients in the IG and the CG. **Conclusions:** The program for oncologist and patients with rapidly progressing advanced cancer was effective in improving empathic communication and information sharing about care after standard chemotherapy, and patients' reported satisfaction with communication without increasing psychological distress, but did not affect QOL and trust in oncologists immediately after the consultation. Clinical trial information: UMIN000033612. Research Sponsor: Practical Research for Innovative Cancer Control.

12120 **Poster Session**

Associations between patient-centered communication and quality of life in patients with ovarian cancer. *First Author: Rachel A. Pozzar, Dana-Farber Cancer Institute, Boston, MA*

Background: Patient-centered communication (PCC) occurs when clinicians respond to patients' needs, preferences, concerns, and emotions. The National Cancer Institute (NCI) Framework for PCC in Cancer Care highlights the potential of PCC to improve health-related quality of life (HRQoL), but to date few studies have empirically examined associations between PCC and HRQoL in patients with ovarian cancer. We assessed associations between perceived PCC and HRQoL in patients with ovarian cancer. **Methods:** Cross-sectional, descriptive survey of English-speaking adults with ovarian cancer recruited both online and from one NCI-designated cancer center. We assessed perceived PCC with the Patient-Centered Communication in Cancer Care (PCC-Ca)-36 and HRQoL with the Functional Assessment of Cancer Therapy: General (FACT-G). We used simple linear regression to identify univariate associations between participant characteristics, PCC-Ca-36 total, FACT-G total, and FACT-G subscale (physical, social and family, emotional, and functional well-being) scores. We identified significant predictors of FACT-G total and subscale scores by entering variables associated with each outcome at $p \leq 0.25$ into a multiple linear regression model and using backward elimination. **Results:** One hundred seventy-six participants completed the survey. In multivariable analyses, older age, working (vs. not working), no current treatment (vs. any current treatment), and greater perceived PCC were associated with better overall HRQoL. Working and no current treatment were associated with better physical well-being. Older age, not being cared for by a gynecologic oncologist (vs. being cared for by a gynecologic oncologist), and greater perceived PCC were associated with better social and family well-being. Older age, being recruited online (vs. in clinic), and greater perceived PCC were associated with better emotional well-being. Older age, working, rural residence (vs. not), no current treatment, and greater perceived PCC were associated with better functional well-being (all $p \leq 0.05$). **Conclusions:** Greater perceived PCC was significantly associated with better overall HRQoL and better social, emotional, and functional well-being in this cross-sectional study of patients with ovarian cancer. The NCI Framework for PCC in Cancer Care posits that PCC promotes HRQoL by strengthening the therapeutic alliance, enhancing social support, and improving patient knowledge. Although PCC is theorized to promote patient self-management, PCC was not significantly associated with physical well-being in this sample. Future research should (a) identify mediators of the associations between PCC and HRQoL; (b) examine inter-individual variability in characteristics that may compromise HRQoL; (c) and examine associations between PCC and HRQoL over time. Research Sponsor: American Cancer Society, Other Foundation.

12121 **Poster Session**

A randomized controlled trial of cognitive behavior therapy for reducing anxiety and depressive symptoms in patients with locoregional advanced nasopharyngeal carcinoma. *First Author: Feng Liu, Hunan Cancer Hospital and The Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China*

Background: The purpose of this randomized trial was to compare the efficacy of cognitive behavioral therapy (CBT) versus treatment as usual (TAU) on anxiety and depression, response rates and acute adverse events in patients with locoregional advanced nasopharyngeal carcinoma (NPC) receiving chemoradiotherapy. To the best of our knowledge, this is the first randomized trial evaluating the effect of CBT for depression and anxiety in patients with locoregional advanced NPC treated with chemoradiotherapy. **Methods:** A total of 202 patients with diagnosis of stage III-IVa (8^{th} AJCC) NPC were randomly assigned to receive CBT plus chemoradiotherapy (CBT group, n = 101) or treatment as usual (TAU) plus chemoradiotherapy (TAU group, n = 101). Patients in the CBT group received a series of six CBT sessions for 6 weeks during concurrent chemoradiotherapy. Depression and anxiety were assessed using the Hospital Anxiety and Depression Scale (HADS) score at baseline, the completion of chemoradiotherapy, 1 and 3 months after chemoradiotherapy. Response rates and adverse events were also evaluated. This trial is registered with chictr.org.cn, number ChiCTR2000034701. **Results:** Patients in the CBT group showed significantly less depression and anxiety than patients in the TAU group after the completion of CBT ($P < 0.01$). Complete response (CR) rate was significantly higher in CBT group than in TAU group (100% vs. 93.1% P = 0.014). Compared with the TAU group, the CBT group showed a significantly lower incidence of acute adverse events including anemia, fatigue, mucositis, insomnia and weight losing ($P < 0.05$). **Conclusions:** The addition of CBT to chemoradiotherapy significantly reduced depressive and anxiety symptoms. CBT combined with chemoradiotherapy is associated with improved response rates, with reduced incidence of acute toxic effects in patients with locoregional advanced nasopharyngeal carcinoma. Clinical trial information: ChiCTR2000034701. Research Sponsor: Fund of Cancer Foundation of China (NO.LC2016W05), Fund of Hunan Provincial Science and Technology Department (NO. 2016JJ6088), Natural Science Foundation of Changsha Science and technology Bureau (NO. KP2001024).

12122 **Poster Session**

The association between the coronavirus disease 2019 (COVID-19) pandemic and quality of life and depression symptoms in patients with advanced lung cancer. *First Author: Lauren Heuer, Massachusetts General Hospital, Boston, MA*

Background: It is unclear whether patients with cancer experience greater distress as a result of the COVID-19 pandemic. Thus, we assessed the relationship of the COVID-19 pandemic with quality of life (QOL) and depression symptoms in patients newly diagnosed with advanced lung cancer. **Methods:** We conducted a cross-sectional study of patients with advanced lung cancer enrolled in two multisite randomized supportive care trials. We enrolled adult patients within 12 weeks of diagnosis of advanced lung cancer and an Eastern Cooperative Oncology Group (ECOG) Performance Status from 0 to 3 across 23 institutions in the United States. At the time of enrollment, participants completed the Functional Assessment of Cancer Therapy-Lung (FACT-L), which includes four wellbeing subscales (i.e., physical, social, emotional, and functional) as well as lung cancer symptoms, and the Patient Health Questionnaire-9 (PHQ-9) to assess their QOL and depression symptoms, respectively. We compared QOL and depression symptoms between participants enrolled prior to COVID-19 (i.e., those enrolled in the following time periods: March 2018 to January 2019 and March 2019 to January 2020) and during the COVID-19 pandemic (March 2020 to January 2021). We used linear regression models adjusting for age, race, gender, and time since diagnosis of advanced cancer to examine the relationship between the period of enrollment and patients' QOL and depression symptoms. **Results:** A total of 860 patients were included in this analysis (665 participants enrolled prior to COVID-19 and 195 participants during COVID-19). The two cohorts did not differ significantly with respect to baseline demographic factors [Mean age 65.4 (SD = 11.4), 51.9% female]. In multivariate regression models, enrollment during COVID-19 was not associated with physical (B = -0.16, SE = 0.52, P = 0.763), social (B = -0.48, SE = 0.39, P = 0.217), emotional (B = -0.16, SE = 0.41, P = 0.693), functional (B = -0.83, SE = 0.55, P = 0.128) wellbeing, or lung cancer symptoms (B = -0.11, SE = 0.44, P = 0.806). Enrollment during COVID-19 was not associated with overall QOL (FACT-L: B = -1.32, SE = 1.69, P = 0.436) or depression symptoms (PHQ-9: B = -0.02, SE = 0.45, P = 0.973). **Conclusions:** Despite the prevailing belief that COVID-19 has negatively impacted QOL and distress in patients with cancer, we found no differences in QOL or depression symptoms in patients newly diagnosed with advanced lung cancer during the COVID-19 pandemic compared to those diagnosed prior to the pandemic. These findings suggest that factors other than the COVID-19 pandemic, such as patients' experience with their cancer, contribute to their QOL and depression symptoms. Research Sponsor: Patient Centered Outcomes Research Institute, U.S. National Institutes of Health.

12123 **Poster Session**

Evolution of post-traumatic stress disorder and patient reported-outcomes during the COVID-19 pandemic among cancer patients of the French longitudinal COVIPACT study. *First Author: Florence Joly, Department of Medical Oncology, Centre Francois Baclesse, Caen, France*

Background: Sudden COVID-19 pandemic has enforced social restrictions across the globe, including social distancing, curfews and total lockdowns, which persist in many parts of the world. Beyond these measures, cancer patients have faced up to the threat of the risk of severe COVID-19 infections and the adaptations of medical oncology practices, with potential impact on their psychological well-being. We aimed to follow Post-Traumatic Stress Disorder (PTSD) symptoms and other Patient-Reported Outcomes (PROs) over this period among cancer patients from the French COVIPACT study. **Methods:** The COVIPACT study (NCT04366154) included patients with solid/hematologic malignancy receiving medical treatment during the first lockdown in outpatient departments of two cancer centers. Patients were asked to fulfill validated questionnaires on PTSD symptoms (IES-R), insomnia (ISI), quality of life (FACT-G) and cognition (FACT-Cog) at baseline (M0, first lockdown, Apr/May 2020), 3 months (M3, post-lockdown, Jul/Aug 2020) and 6 months (M6, second lockdown, Oct/Nov 2020). PTSD was defined as an IES-R score $\geq$33 and moderate/severe insomnia as an ISI score $\geq$15. Higher values on the FACT-G (range 0-108) and FACT-Cog (PCI subscale range 0-72) indicated better quality of life and cognition, respectively. Changes in PROs over time were assessed using mixed models for repeated measures. **Results:** Among the 734 patients included in COVIPACT, 579, 347 and 328 completed the questionnaires at M0, M3 and M6, respectively: median age, 64 years, 72% women, 59% metastatic status. Patients were mostly treated for breast (44%), lung, head and neck (20%), digestive (16%) and gynecologic cancers (11%). We observed a J-shaped evolution of PTSD over time, affecting 21.2% of patients during the first lockdown, 13.6% the post-lockdown and 23.6% during the second lockdown (p for time $<$ 0.001). Moreover, patients reported linear deterioration of cognitive function over follow-up (p $<$ 0.001). No change was observed in any dimension of quality of life (p for time = 0.06). 24.3%, 27.1% and 28.1% of the patients reported insomnia at M0,M3 and M6 (p for time = 0.35). At each time, PTSD was associated with more insomnia, worst quality of life and cognitive complain. At all the times, $\geq$50% of patients with PTSD reported insomnia compared to $\leq$23% in non-PTSD patients (p $<$ 0.001). In addition, there was a clinically significant difference of $\geq$16 points on the FACT-G and $\geq$8 points on the FACT-Cog PCI between PTSD and non-PTSD patients (p $<$ 0.001) at the all times. **Conclusions:** More than 20% of patients have developed PTSD during the different periods of lockdown, with strong association with poor quality of life, cognitive complain and insomnia. Psychosocial support promoting emotional resilience should be largely offered to cancer patients to prevent and/or reduce PTSD. Clinical trial information: NCT04366154. Research Sponsor: ARC foundation.

12124 **Poster Session**

Development and validation of the self-efficacy for medical communication scale. *First Author: David B. Feldman, Santa Clara University, Santa Clara, CA*

Background: Most studies of clinician-patient communication use scales created *ad hoc* with unknown validity. To provide a standard measure for future studies, we developed and validated a new scale of clinician-reported skills in communicating difficult news: the Self-Efficacy for Medical Communication (SEMC) scale. **Methods:** Using evidence-based scale development guidelines, we created 16 items sampling a range of communication skills, including Disclose difficult news in manageable chunks, so the patient is not overwhelmed, and Determine how to present information based on the patient's emotional state. Items are rated on Likert scales from 1 (*cannot do at all*) to 10 (*highly certain can do*). We constructed two forms—one assessing communication with patients and one with family—using identical items but replacing patient with family/caregiver. We examined the convergent and discriminant validity of the SEMC (correlations with similar and dissimilar measures) as well as its reliability and factor structure. A total of 221 clinicians working in oncology settings (physicians, nurses, medical students) completed measures online. Convergent measures included medical communication items from past studies; the Self-Perceived Communication Competence Scale to measure communication ability outside the medical realm; and the General Self-Efficacy and Occupational Self-Efficacy scales to measure overall self-efficacy/confidence. Discriminant measures included the Ten Item Personality Inventory to measure personality factors; the Maslach Burnout Inventory to measure job burnout; and the Satisfaction with Life Scale to measure well-being. Finally, the Marlowe-Crowne Social Desirability (MCSD) scale measured motivation to look good in responding to survey questions. **Results:** Mean scores were similar for the patient (126.36) and family (127.09) forms (max score 160), both with excellent reliability (*alphas* = .94, .96, respectively). Because these forms were almost perfectly correlated (r = .95, p $<$ .001), we used only the patient form in subsequent analyses. Factor analysis demonstrated that the SEMC measures a unitary construct (*eigenvalue* = 9.0). Its mean correlation was higher with convergent (r = .46) than discriminant measures (r = .22), supporting its validity. Moreover, its correlation with the MCSD was small (r = .28) and no larger than between the MCSD and other measures, indicating minimal social-desirability effects. Finally, no differences emerged for gender or profession; higher scores did correlate with age (r = .29, p $<$ .001) and years working in oncology (r = .18, p = .01). **Conclusions:** Our findings support the SEMC's validity and reliability. Scores on the patient and family forms were similar, indicating that either may be used. The SEMC provides a useful tool for measuring clinician-rated communication skills in future research, ultimately allowing standardization across studies. Research Sponsor: None.

12125 **Poster Session**

Screened social risk factors & screening acceptability among oncology patients in Philadelphia. *First Author: Jessica Davis, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA*

Background: This pilot study describes the cancer-specific social risk factors (SRFs) of oncology patients on active treatment and the acceptability of using SRF screening to inform care and bolster support during cancer treatment. **Methods:** This is an ongoing cross-sectional survey of adult cancer patients on active treatment at two outpatient cancer centers in the University of Pennsylvania Health System. Since October 2019, 176 patients have completed our two-part, 19-item social risk screening tool (44% response rate; 49% age $>$ 65yo; 45% female; 35% non-white). Survey questions were adapted from other social screening measures (e.g., AHC-HRSN tool, PRAPARE), then pre-tested and modified for our cancer-specific population. Part 1 of our tool covers 12 SRFs in four core domains: technology (e.g., internet accessibility challenges), environmental (e.g., housing instability), emotional (e.g., social isolation), and financial (e.g., ongoing financial toxicity). In part 2, seven acceptability questions cover patients' perceived appropriateness of and comfort with screening, expectations of clinical staff to act on identified SRFs, prior SRF assistance received, interest in receiving SRF assistance (i.e., a proxy for patients' most pressing unmet social needs), willingness to add SRF data to electronic health records (EHR), and comfort sharing findings with other clinicians (e.g., oncologists, primary care physicians, nurses). **Results:** We identified an average of 2.48 SRFs per patient. The five most commonly reported SRFs were ongoing financial toxicity (57%), internet accessibility challenges (46%), social isolation (40%), housing instability (34%), and insufficient internet for telemedicine (29%). The majority of patients thought that SRF screening was appropriate (56%) and many felt comfortable being screened (63%). Half of patients expected cancer center staff to connect them to social resources (50%), fewer wanted staff to just be aware of their SRFs (43%), and a minority did not want staff to know about their SRFs (7%). Many patients had received prior SRF assistance (49%) or were interested in receiving future help (51%). Most patients felt discomfort toward listing SRF results in their EHR (63%) and some felt uncomfortable giving other clinicians access to this data (38%). **Conclusions:** Our study shows that oncology patients contend with SRFs while undergoing treatment and find SRF screening acceptable. These findings support clinical implementation of a cancer-specific social screening tool into routine cancer care, but also bring attention to privacy preferences and limited acceptability of EHR documentation of SRFs. Cancer centers adopting this approach may gain insights into where interventions or resources could be targeted to meaningfully address SRFs, potentially improving clinical outcomes for vulnerable populations. Research Sponsor: Agency for Healthcare Research and Quality, U.S. Academic University Institution.

12126 **Poster Session**

Oncologist phenotypes and associations with response to a behavioral intervention to increase serious illness conversations. *First Author: Eric Li, University of Pennsylvania, Philadelphia, PA*

Background: Interventions to increase serious illness conversations (SICs) between oncologists and patients may improve goal-concordant care, patient mood and quality of life. Randomized studies suggest that behavioral nudges to oncologists may prompt more and earlier SICs. Identifying characteristics of oncologists associated with response to such interventions may clarify barriers to SIC adoption. **Methods:** This was a secondary analysis of a randomized trial showing that machine learning (ML)-based behavioral nudges among 42 oncologist-advanced practice provider (APP) dyads (79 total oncology clinicians total) caring for 14,607 patients in a large academic health system led to a quadrupling of SIC rates (NCT03984773). Latent profile analysis identified oncologist phenotypes based on oncologist, patient, and practice data. We used difference-in-differences analyses among patients with predicted 180-day mortality risk ≥10% (n=2695 [12.6% of cohort]) to test the association between oncologist phenotype and response to the nudge, adjusted for patient and oncologist demographic and practice characteristics. **Results:** Three oncologist phenotypes were identified: 1) Higher-volume specialists 2) Lower-volume specialists; and 3) Higher-volume generalists. Compared with higher-volume specialists and higher-volume generalists, lower-volume specialists had fewer patients per week (9.2 vs 24.3 vs 53.2), fewer days in clinic per week (1.6 vs 2.5 vs 4.4), a higher proportion of new patients per week (34.9% vs 21.0% vs 17.6%), and higher baseline SIC rates (3.9% vs 1.6% vs 0.8%). Lower-volume specialists had a significantly greater response to the intervention than higher-volume specialists and generalists (see Table), demonstrating a nearly six-fold increase in SIC rate from baseline. **Conclusions:** Response to an ML-based behavioral nudge to prompt SICs was driven by specialist oncologists with lower patient volume and greater SIC adoption at baseline, although the nudge was associated with significantly higher SIC rates among all phenotypes. While effective among lower-volume oncologists, nudges to prompt supportive care interventions may have limited impact among higher-volume oncologists. Other strategies, including default involvement of specialty palliative care, may be more effective for higher-volume oncologists. Research Sponsor: National Palliative Care Research Center.

Association between oncologist phenotype and response to nudges.

Phenotype	Oncologists, n (%)	Patients, n (%)	Adjusted probability of SIC, pre-intervention	Adjusted probability of SIC, post-intervention	Difference-in-differences vs higher-volume specialists, absolute percentage points (95% CI)	p-value
Higher-volume specialists	28 (67%)	5755 (66%)	2.3%	7.6%	—	Ref
Lower-volume specialists	5 (12%)	320 (4%)	3.1%	20.7%	12.3 (4.3, 20.3)	0.003
Higher-volume generalists	9 (21%)	3006 (31%)	1.9%	10.7%	3.6 (1.0, 6.1)	0.006

12127 **Poster Session**

Comparing adult child and spousal caregiver burden and potential causes. *First Author: Anny THR Fenton, Dana Farber/Harvard Cancer Center, Boston, MA*

Background: Adult children caring for a parent with cancer comprise a significant segment of caregivers. Demographic trends indicate this caregiving population will grow as the baby boomer generation ages. Yet little is known about adult child caregivers' needs and experiences and how they differ from the well-studied spousal caregiver. This knowledge gap may hinder efforts to ameliorate adult children's caregiver burden and its impact on patients. **Methods:** We analyzed adult child and spousal/partner caregivers' surveys from the Cancer Care Outcomes Research and Surveillance consortium, a multi-regional population-based study of approximately 10,000 persons with newly diagnosed colorectal and lung cancer. We used t-tests and a series of multivariate regression models to assess whether adult child and spousal caregivers' caregiving responsibilities, social/emotional burden, and financial burden (scaled 0-10) differed and examined patient and caregiver characteristics' mediation of variation in burden. **Results:** Compared to spouses/partners (N=1029), adult children (N=230) completed similar levels of caregiving tasks but spent less time (14 vs. 24 hours/week; $p<0.001$). However, adult children experienced higher social/emotional burden (2.9 vs. 2.4; $p<0.01$). In baseline models controlling for patient clinical factors, caregiving characteristics, and caregiver demographics, adult children's average social/emotional and financial burdens were statistically higher than spouses/partners. Additional adjustment for caregivers' childcare responsibilities and employment eliminated social/emotional and financial burden disparities. Additional adjustment to the baseline model for caregiver-patient gender concordance eliminated the social/emotional burden gap. Communication quality was a large and statistically significant predictor of both burdens ($p<0.001$). **Conclusions:** Adult children spend less time caregiving than spouses/partners but experience higher caregiving burden. Adult children's childcare and career responsibilities help explain this increased burden. Gender concordance between caregiver and patient may also contribute to social/emotional burden, adding important context to prior research indicating female caregivers experience the greatest burden. Interventions to improve communication between caregivers and patients have the potential to reduce both adult child and spouses/partners caregiver burden. Research Sponsor: U.S. National Institutes of Health.

Adjusted average caregiver burden for adult child and spousal caregivers.

	Social/emotional burden			Financial burden		
Adjustment	Adult child	Spousal	P	Adult child	Spousal	P
Unadjusted	2.9	2.4	<0.01	3.7	3.4	0.20
Baseline (patient clinical factors, caregiving characteristics, caregiver demographics)	2.8	2.4	0.03	4.0	3.3	<0.01
Baseline + childcare + employment	2.6	2.5	0.54	3.8	3.4	0.10
Baseline + caregiver-patient gender concordance	2.6	2.5	0.56	4.1	3.3	0.01

12128 **Poster Session**

Patient reported sexual concerns in routine cancer care. *First Author: Brittany Lees, Atrium Health, Charlotte, NC*

Background: Sexual health is an important component of overall well-being and can be adversely impacted by chemotherapy, surgery, radiation, in addition to the psychological effects of cancer treatments. Sexual health is challenging to discuss and may be overlooked or avoided during cancer care. **Methods:** Patients presenting for consultation in an outpatient multisite cancer center completed electronic distress screening (EDS) between January 2017 and December 2020. The EDS contains 42 questions; demographic information, cancer symptoms and side effects, and psychosocial factors. The EDS is completed by patients before a clinical encounter for early symptom identification and intervention. We conducted a retrospective data analysis of sexual health concerns (>5; scale 0-10) and evaluated patient characteristics and clinically relevant distress (>4; NCCN Distress Tool), depression risk (>3; PhQ2), and anxiety risk (>3; GAD2). Our primary aim was to identify the prevalence of sexual health concerns. The secondary aim was to examine the relationship between sexual health and emotional well-being. **Results:** 57,375 EDS screens were completed. 13,950 patients (24%) reported sexual concerns or lack of interest in sex (>5) within the last 2 weeks. The frequency of these concerns at specific clinics ranged from 12% to 48%, with the highest rates at Palliative care (39%) and Psycho-Oncology (48%) clinics. Genitourinary (30%), Gynecologic (27%) and Gastroenterology (26%) reported the highest frequency of sexual concerns from cancer site specific clinics. Males reported a higher rate of sexual problems compared to females (30% vs 21%, $p < 0.001$), but a lower rate of relationship concern distress (12% vs 13%, $p < 0.05$). Patients with a risk for depression (n = 9,126) or anxiety (n = 10,809) had higher rates of self-reported sexual concerns than those with a negative screen (44% vs 21% depression, $p < 0.001$; 40% vs 21% anxiety, $p < 0.001$). **Conclusions:** Sexual health is a concern for approximately one-quarter of patients presenting for cancer care. Sexual health concerns were prevalent across cancer sites. Patients with positive screens for anxiety and/or depression have nearly double the rates of reported sexual health concerns. Sexual health is a current unmet need that impacts cancer patients and warrants attention. Research Sponsor: None.

12129 **Poster Session**

The impact of the COVID-19 pandemic on African American cancer survivors living in metropolitan Detroit. *First Author: Jennifer Lynn Beebe-Dimmer, Barbara Ann Karmanos Cancer Institute/Wayne State University, Detroit, MI*

Background: COVID-19 has had profound direct and indirect effects on population health to date and long-term effects are anticipated. Vulnerabilities to the most serious consequences of infection include older age, obesity, African American race and the presence of comorbid conditions. African American cancer survivors represent a particularly high-risk group, therefore understanding the impact of the virus and our strategies to prevent its spread on this patient population is important. **Methods:** The Detroit Research on Cancer Survivors (ROCS) cohort is a unique effort to understand the determinants of poor outcomes in African American cancer survivors. Eligible participants were diagnosed with breast, prostate, colorectal, or lung cancer on or after 1/1/2013, or with endometrial or any other cancer before age 50 on or after 01/01/2016 and were identified through the Metropolitan Detroit Cancer Surveillance System cancer registry. To date, we have enrolled 4173 survivors. Full participation includes completion of a baseline survey, and collection of biospecimens, medical records and tumor tissue, if available. Participants are also followed annually for outcomes and changes in history. A supplemental survey focused on the impact of COVID-19 was offered to enrolled participants beginning in the spring of 2020. The results presented here include data from 890 survivors who also completed the ROCS COVID survey. **Results:** Nearly all (> 99%) survivors reported some change in their daily activities in an effort to reduce the risk of infection. At the time of survey, just over 1/3 of participants reported being tested for the virus and among those, 12% reported positive results. More than 40% of survivors reported some disruption in their access to medical care. A substantial (> 40%) proportion of survivors reported feeling anxious, depressed and/or isolated during the COVID-19 pandemic. Approximately 40% of patients reported changes in health behaviors as a direct result of the pandemic that are known to negatively affect survivorship outcomes (physical inactivity, smoking, alcohol use). Notably, 30% of survivors reported declines in physical activity and these declines were significantly associated with increased anxiety ($p = 0.008$), depression ($p = 0.005$) and poorer health-related quality of life ($p < 0.001$). **Conclusions:** The influence of the COVID-19 pandemic on African American cancer survivors has been substantial, affecting both their physical and mental health and access to needed medical care. Coupled with changes in health behaviors as a direct result of the pandemic, these factors will likely affect outcomes in this high-risk patient population making further study and interventions necessary to mitigate the long-term impact of the pandemic on cancer outcomes. Research Sponsor: U.S. National Institutes of Health.

12130 **Poster Session**

Suicide risk following a new cancer diagnosis among veterans in Veterans Health Administration care. *First Author: Kallisse R. Dent, Serious Mental Illness Treatment Research and Evaluation Center (VHA), Ann Arbor, MI*

Background: Patients diagnosed with cancer are at an increased risk of adverse mental health outcomes including suicidal behavior. Suicide rates among Veterans are 50 percent greater than for non-Veteran US adults. To inform Veterans Affairs (VA) suicide prevention initiatives, it is important to understand associations between cancer and suicide risk among Veterans receiving VA healthcare from the Veterans Health Administration (VHA). Study aims were to assess associations between new cancer diagnoses and suicide among Veterans in VHA care to identify high risk diagnostic subgroups and risk-periods. **Methods:** We used a cohort study design, identifying 4,926,373 Veterans with VHA use in 2011 and either 2012 or 2013 and without a VHA cancer diagnosis in 2011. Incident cancer diagnoses, assessed between first VHA use in 2012-2013 and 12/31/2018, were characterized by subtype and stage using the VHA Oncology Raw Data. Data from the VA/Department of Defense Mortality Data Repository identified date and cause of death. Cox proportional hazards regression, accounting for time-varying cancer diagnosis, was used to evaluate associations between a new cancer diagnosis and suicide risk. An initial model adjusted for VHA regional network and patient age and sex. Cancer subtypes with significant associations with suicide were further assessed using a model that also adjusted for suicide attempts and mental health, tobacco use disorder, and other substance use disorder diagnoses in the prior year. Crude suicide rates following a new cancer diagnoses were calculated among Veterans with new diagnoses, 2012-2018 (N = 240,410). Rates were assessed up to 84 months following diagnosis. **Results:** On average, Veteran VHA users were followed for 6.0 years after their first VHA use in 2012-2013 and for 2.7 years following a new cancer diagnosis. Receipt of a new cancer diagnosis corresponded to a 43% (Adjusted Hazard Ratio [AHR] = 1.43, 95% CI: 1.29, 1.58) higher suicide risk, adjusting for covariates. The cancer subtype associated with the highest suicide risk was esophageal cancer (AHR = 5.93, 95% CI: 4.05, 10.51) and other significant subtypes included head and neck (AHR = 3.44, 95% CI: 2.65, 4.46) and lung cancer (AHR = 2.28, 95% CI: 1.79, 2.90). Cancer stages 3 (AHR = 2.29, 95% CI: 1.75, 3.01) and 4 (AHR = 3.45, 95% CI: 2.75, 4.34) at diagnosis were also positively associated with suicide risk. Suicide rates were highest in the first three months following a diagnosis (Rate = 128.3 per 100,000 person-years, 95% CI: 100.4, 161.6) and remained elevated through the first 12 months. **Conclusions:** Among Veteran VHA users, suicide risk was elevated following a new cancer diagnosis and was especially high in the initial 3 months. Additional screening and suicide prevention efforts may be warranted for VHA Veterans newly diagnosed with cancer, particularly among those diagnosed with esophageal, head and neck, or lung cancer or at stages 3 or 4. Research Sponsor: Department of Veterans Affairs.

12131 **Poster Session**

Family members' attitudes towards disclosure of cancer diagnosis to patients in China. *First Author: Xi Rao, University Medical Center, University of Freiburg, Freiburg, Germany*

Background: Informed consent is very important aspect of treatment, in western countries, a diagnosis of malignancy should be delivered the paient directly. It was the decision of the patient for further disclosure. However, in China, people are always family centered decision making, a diagnosis of cancer is traditionally delivered to the family members, with a protective assumption. We used anonymized questionnaire to investigate the attitude of Chinese people towards to cancer diagnosis disclosure and correlated factors. **Methods:** This is a survey study conducted by a web system named Wenjuan Xing. The study questionnaires were designed in dual English and Chinese. answered by the same person. The regarding questions that answered by the same person are as following: If your close family member is diagnosed with a malignant tumor, would you like to tell him the truth?, If yes/no, what's your reason?. Demographic information include gender, age, economic status, education level, health condition, residential region, occupation, nationality and major reasons. The survey link was placed on Wechat contact of these investigators, social media and also distributed in Oncology Center of a general hospital in Mainland China. The answers of the questions were captured directly online, data can also be exported into excel format for compiled analysis. **Results:** A total of 1470 people completed the survey questions from January to July 2020. The potential factors which influence disclosing diagnosis were registered, 1041 (70.8%) family members are in favor of informing the diagnosis to patients, 429 (29.2%) are not. The main reasons for disclosure diagnosis are it is his or her life, he/she has to be in control' (N=832) and she or he can plan his/her remaining life and leave the world with no regret (N=588). The famliy member who hide the diagnosis worry that paitents could not handle the stress would have poor quality of life (N=295) and die faster(N=323). 1425 (96.9%) people want to know the diagnosis if they have a malignanti tumor, while 45 (3.1%) don't want to know.The univariate analysis revealed educational level, health condition and residential region are correlated to disclosing diagnosis. The logistic regression anaylsis show a significant effort to disclosing diagnosis(OR= 1.9, 95% CI (1.4, 2.7) $P<0.001$) .Interaction and stratified analyses were conducted according to education level and redidential region (P interaction= 0.0406). In the high education level group, people who live in other countries(America, Europe) (P=0.009 OR=29.7 CI 2.3-375.7) more likely to disclose the diagnosis compared to mainland in China. **Conclusions:** The majority of Chinese people want to know the diagnosis. People who have higher education level and live in western countries more likely prefer disclosure of diagnosis to patients. Research Sponsor: None.

TPS12132 **Poster Session**

A phase II study to evaluate the safety and efficacy of OQL011 on VEGFR inhibitor-associated hand-foot-skin reaction in cancer patients. *First Author: Mario E. Lacouture, Memorial Sloan Kettering Cancer Center, New York, NY*

Background: Hand-Foot Skin Reaction (HFSR) is frequently associated with the use of multi-targeted tyrosine kinase inhibitors of the vascular endothelial growth factor receptor (VEGFRi) such as cabozantinib, regorafenib, sunitinib, and lenvatinib. HFSR affects the skin on the palms and soles and is manifested as edema, erythema, hyperkeratosis, and bullae, leading to a decrease in quality of life and interruptions in dosing. The incidence of HFSR differs among VEGFRi, ranging from 5-60% (all grades) and 1-18% (grade 3). To date, there is no FDA approved treatment for HFSR, and marginal benefit has been shown with topical urea or steroids. Although not fully elucidated, the pathogenesis of HFSR has been associated with impaired vascular repair mechanisms, caused by inhibition of VEGF signaling pathways. We hypothesize that topical stimulation of VEGFR through OQL011 will decrease the severity of HFSR symptoms via local upregulation of the VEGF/VEGFR related signaling pathways. **Methods:** NCT04088318 is a phase 2, double-blind, randomized controlled trial to evaluate the safety and efficacy of OQL011 compared to vehicle control in the treatment of moderate to severe HFSR in patients on VEGFRi therapy. Eligible patients will have $\geq$ grade 2 palmar plantar erythrodysesthesia (PPE). The study is expected to enroll 112 patients in two parts. In the first part, 42 patients will apply 0.2% OQL011 topical ointment or vehicle control (2:1 randomization) TID for six weeks. In Part 2, 70 subjects will be randomized into two additional dose levels or vehicle control in a 2:2:1 ratio. The two dose levels selected will be based on the efficacy and safety results of Part 1. The primary efficacy endpoint is improvement of NCI CTCAE v5.0 PPE to grade $\leq$1 by week 3. Photographs of the affected areas will be taken at Day 0, 7, 14, 21 and 42 timepoints. Superiority test will be performed to compare treatment groups, and the exposure-response relationship will be explored. In addition, an investigator global assessment (IGA) for HFSR will be used in this trial to specifically assess skin recovery and is proposed to be a new evaluation tool. The validity of IGA criteria will be evaluated by assessing the inter-rater and intra-rater reliability. The correlation between IGA, NCI CTCAE v5.0 for PPE, and patient reported outcomes including Visual Analog Scale of Pain, Hand-foot Quality of Life questionnaire will also be evaluated. This study began enrolling patients in December 2019 and is ongoing. Clinical trial information: NCT04088318. Research Sponsor: OnQuality Pharmaceuticals (USA) LLC.

TPS12133 **Poster Session**

Olanzapine or dexamethasone, with 5-HT3 receptor antagonist and NK-1 receptor antagonist, to prevent nausea and vomiting induced by cisplatin-based doublet chemotherapy: A non-inferiority, prospective, multi-centered, randomized, controlled, phase III clinical trial. *First Author: Zhigang Liu, The Fifth Affiliated Hospital of Sun Yat-sen University, Zhuhai, China*

Background: Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of cancer treatments, and dexamethasone offers an advantage over placebo for protection against chemotherapy-induced emesis in both acute and delayed phases. However, its side effects are diverse including moderate to severe insomnia, hyperglycemia, dyspepsia and so on, which are gathering increasing concerns. What's more, dexamethasone is not applicable to all cancer patients. The incidence of diabetes mellitus varies in different cancer which can reach up to 55.3%, and dexamethasone might not be a proper anti-emesis choice for them. Besides, dexamethasone delivery is always on debating when patients are receiving immunotherapy. However, all anti-emesis regimen recommended in guidelines are dexamethasone based. Alternative anti-emesis regimen are required. Studies have shown that olanzapine plays an important role in treating delayed, refractory, breakthrough nausea and vomiting. Thus, we initiated this prospective, multi-center, phase III study to validate the dexamethasone-free protocol: the non-inferiority role of applying olanzapine to prevent CINV instead of dexamethasone. **Methods:** This clinical trial started on February 3, 2020 is being conducted in 23 centres. All patients eligible are chemotherapy nave and plan to receive cisplatin-containing regimen. Based on a 70% complete remission rate of previous study, to demonstrate a non-inferiority margin of 10%, 548 patients are required for two arms with the consideration of 5% of drop out and lost to follow-up (80% power,α = 0.05). Study design: Enrolled patients are randomized 1:1 into 2 arms to receive olanzapine or dexamethasone combined with 5-HT3 receptor antagonist (palonosetron, granisetron or ondansetron) and NK-1 receptor antagonist (aprepitant or fosaprepitant) from the first day of chemotherapy. Olanzapine (5mg) is delivered orally per night from day 1 to day 4. Dexamethasone (12 mg) is given orally or intravenously within 30 minutes before cisplatin administrated on day 1; on day 2-4, the orally or intravenously given dose of dexamethasone is 8 mg. The primary endpoint is complete remission rate of vomiting during the whole observation period (0-120 hours from the starting of first course chemotherapy delivery). The secondary endpoints are complete remission rate of vomiting during 25-120 hours from the starting of first course chemotherapy delivery and no nausea rate during the whole observation period. Besides, side effects will be recorded according protocol. Clinical trial information: NCT04437017. Research Sponsor: Beijing Xisike Clinical Oncology Research Foundation.

TPS12134 **Poster Session**

Effect of multimodal intervention care on cachexia in patients with advanced cancer compared to conventional management (MIRACLE): An open-label, phase 2 trial. *First Author: Chi Hoon Maeng, Department of Medicine, Division of Medical Oncology-Hematology, Kyung Hee University Hospital, Seoul, South Korea*

Background: Cancer Cachexia (CC) is a multi-factorial process characterized by progressive weight loss, muscle mass and fat tissue wasting, and adversely affecting the quality of life and survival in patients with advanced stage of cancer. CC has a complex and multi-factorial pathophysiology, and there is no established standard treatment. Once it occurs, it is often irreversible and also difficult to suppress the its progression with any single treatment modality. We are conducting an open-label, parallel, randomized phase 2 trial to investigate the effect on preventing or alleviating cancer cachexia and safety of a multi-modal intervention including anti-inflammation, omega-3-fatty acids, nutritional supplement with counselling, physical exercise, psychiatric intervention as well as bojungikki-tang, which mediates immune-modulation and reverse inflammation-related chronic consumptive wasting condition as a complementary and alternative medicine compared to patients receiving best supportive care. **Methods:** Eligible criteria included patients with recurrent or metastatic gastrointestinal (gastric, colorectal and pancreaticobiliary) as well as lung cancer undergoing active palliative chemotherapy. Patients who have already developed refractory cachexia (ie, low performance status, difficult to take medications orally or visit the hospital to exercise) are excluded. Patients are randomized into experimental arm (Multi-modal intervention care: MIC) versus control arm (Conventional Palliative Care, CPC). MIC are comprised of 1) daily oral medications; ibuprofen 400 mg three times a day, omega-3-fatty acid 1 g twice a day, Bojungikki-tang 3.75g twice a day, oral nutritional supplement (HAMONILAN SOLN) 200 ml twice a day, and 2) clinical interventions; weekly physical exercise (60 minutes per visit), psychiatric assessment on every other week, and nutritional counselling total four times during the study period. CPC included basic nutritional counselling for two times provided by National Health Insurance Service, and megestrol acetate as needed (ie, anorexia $\geq$ Grade 2). All interventions were provided during 12 weeks per subject. Co-primary outcomes are change of total lean body mass and handgrip strength from the baseline. Secondary outcomes included change of fat mass and total body mass, lean body mass, Functional Assessment of Anorexia/Cachexia Treatment (FAACT) score, quality of life assessed by EORTC QLQ-C30, Spleen Qi Deficiency questionnaire (SQDQ), and overall survival. Total 112 patients will be assigned in the two arms (56 in each group). We have started the study in October 2020. At the time of submission, 26 patients were enrolled. Planned period of enrollment is 18 months. Clinical trial information: Clinical Research information Service, CRIS (KCT0004967). Clinical trial information: KCT0004967. Research Sponsor: National Research Foundation of Korea (NRF).

TPS12135 **Poster Session**

Randomized double-blind, placebo-controlled study of topical diclofenac in prevention of hand-foot syndrome in patients receiving capecitabine. *First Author: Atul Batra, All India Institute of Medical Sciences, New Delhi, India*

Background: The pathophysiology of capecitabine induced hand-foot syndrome (HFS) includes activation of cyclooxygenase (COX)-2, leading to an upregulation of the inflammatory cascade. Prophylaxis with oral celecoxib was previously reported to be associated with a significantly lower frequency of HFS (grade 1 [29.0% vs. 72.0%, $p < 0.001$] and grade 2 [11.8% vs. 30.0%, p=0.024]) (1). The findings were confirmed in a phase III trial (2). However, the associated systemic adverse events limit routine prophylactic use. Till date, no clinical trials have assessed the role of topical non-steroidal anti-inflammatory drugs (NSAIDs) in preventing HFS. **Methods:** In this investigator-initiated randomised phase III double-blind, placebo controlled, parallel group trial, a total of 264 patients with any stage breast or gastrointestinal cancer planned to receive capecitabine as a single agent or in combination with other chemotherapy will be randomised (1:1) to 1% topical diclofenac or placebo (base for 1% topical diclofenac) arm at a single tertiary care cancer centre in India. Randomization will be done by stratified (male vs female, and capecitabine mono therapy vs combination) permuted block method using a computer generated random sequence and allocation concealment will be done by using sealed opaque envelopes. In both the arms, patients will be asked to apply 1 fingertip unit (FTU) of topical medication on both surfaces of bilateral hands twice daily for a total duration of 12 weeks or till development of grade 2 or higher HFS, whichever is earlier. The primary objective is to compare the effect of topical diclofenac with placebo in preventing clinically significant HFS (incidence of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 grade 2 or higher HFS). The secondary objectives include comparison of topical diclofenac with placebo on (i) incidence of NCI CTCv5.0 all grade HFS, (ii) time to develop grade $\geq$2 HFS from start of capecitabine, (iii) patient-reported outcomes using HFS-14 questionnaire (iv) adherence with topical application using self-reported adherence diary, (v) capecitabine dose reductions, delays and cessation due to HFS and (vi) safety profile (NCICTCv5.0). The tertiary correlative endpoint is to correlate the occurrence and severity of HFS with serum COX-2 levels and polymorphism of dihydropyrimidine dehydrogenase (DPPD) enzyme. The trial is registered at the Clinical Trial Registry of India (CTRI/2021/01/030592). Till date, we have enrolled 12/264 patients. (1) Zhang RX et al. *J Cancer Res Clin Oncol*. 2011;137(6):953-957. (2) Zhang RX et al. *Annals of oncology*. 2012;23(5):1348-1353. Clinical trial information: CTRI/2021/01/030592. Research Sponsor: Indian Association of Supportive Care in Cancer, Pharmaceutical/Biotech Company.

TPS12136 **Poster Session**

Technology-enhanced palliative care for patients with cancer on phase 1 clinical trials. *First Author: Ishwaria Mohan Subbiah, The University of Texas MD Anderson Cancer Center, Houston, TX*

Background: Patients w advanced cancer participating in Phase I trials carry a high symptom burden from cancer and prior therapies. Our prior work shows patients on phase I trials w multiple active symptoms impacting their immediate quality of life with implications on toxicities and clinical outcomes on subsequent therapy. To identify an effective scalable approach to comprehensive symptom management for patients w adv cancer on phase I trials, we leveraged the increased technology use to design a technology-enhanced symptom management and palliative care intervention (TEC). **Methods:** Patients w adv cancer seen in the phase I clinic will be given the Edmonton Symptom Assessment System (ESAS), a validated patient-reported outcomes (PRO) tool of common cancer symptoms to identify those with a high symptom burden defined as $\geq$4 out of 10 on $>$1 ESAS symptom and a Global Distress Score (GDS) of $\geq$20. The GDS, a validated score of overall symptom intensity derived from the ESAS, is comprised of 6 physical (pain, fatigue, nausea, drowsiness, appetite, shortness of breath) & 2 psychosocial symptoms (depression, anxiety), and overall wellbeing. TEC is an innovative patient-centered care program of strategic vigorous symptom management where standard-of-care clinic visits are complemented by proactive symptom monitoring between clinic visits remotely and through provider-initiated calls. In this pilot randomized study, we will determine the effect sizes of High-Intensity TEC (HI-TEC; q3day remote PRO assessments w preset provider-initiated call bw visits), Low-Intensity TEC (LO-TEC; q5day remote PRO assessments w preset provider-initiated call bw visits), and Standard Palliative Care (no preset provider contact bw visits). Our guiding hypothesis is that a comprehensive, proactive, technology-enhanced symptom management program led by a Palliative Care team can mitigate the high symptom burden of patients with advanced cancers enrolling in phase I trials. The primary objective assesses the effect size of each TEC intervention on the GDS measure of symptom burden prior to C1D1 on phase I trial. Our working hypothesis is that HI-TEC and LO-TEC will be associated with a lower overall symptom burden signifying symptom optimization prior to starting on a phase I trial. Secondary objectives aim to estimate the effect size of TEC on the following: Symptom burden over 12 weeks on a phase I trial using ESAS, quality of life using FACIT-Sp, PRO-CTCAE and patient satisfaction using FAMCARE-P13. clinical outcomes at 6 months including OS, treatment outcomes (interruptions, dose reductions, discontinuation, time on trial) and quality metrics for end-of-life (EOL) (chemotherapy in the last 14 days of life, ICU admit in last 30 days of life, death without hospice or $<$ 3d of hospice). Qualitatively assessment of patients' + caregivers' perceptions of receiving TEC-based cancer care. Clinical trial information: NCI-2020-07465. Research Sponsor: American Cancer Society.

TPS12137 **Poster Session**

Investigating bacterial decolonization for the prevention of radiation dermatitis: A randomized controlled trial and quality of life assessment. *First Author: Karolina Mieczkowska, Department of Medicine, Division of Dermatology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY*

Background: Radiation dermatitis (RD) can be therapy-limiting and detrimental to quality of life for cancer patients receiving radiation therapy (RT). Bacteria play an important role in many inflammatory dermatoses. In an observational clinical study, our group discovered that nasal colonization with bacteria, specifically with *Staphylococcus aureus* (SA), prior to RT was an independent predictor of higher-grade RD (grade $\geq$2). Higher-grade RD patients were also found to have more SA on the irradiated skin after treatment. If successful, bacterial decolonization could be a safe and cost-effective method to prevent RD. **Methods:** This is a randomized controlled trial assessing the efficacy of universal bacterial decolonization in preventing RD. Subject inclusion criteria include patients who are aged $\geq$ 18 years with a diagnosis of a solid tumor of the breast or head and neck with plans for fractionated RT ($\geq$ 15 fractions) with curative intent. Based on previous studies and power analyses, we plan to recruit a total of 80 patients. Patients in the control arm will be treated according to standard of care, including daily application of emollients and gentle bathing. In addition to standard of care, patients in the intervention arm will receive a decolonization regimen consisting of intranasal mupirocin ointment used twice daily and chlorhexidine wash used daily for 5 days prior to the initiation of RT and repeated for 5 days every other week throughout RT. Study evaluations for both groups will include bacterial cultures obtained via superficial swab from the nares, irradiated skin, and contralateral non-radiated skin performed at the beginning, middle, and end of RT. Additionally, standardized photographs of the skin at the radiated site will be performed prior to and at the completion of RT, which will be graded by a dermatologist blinded to study arm. Lastly, at identical timepoints, each patient will complete the SKINDEX-16 questionnaire, a validated quality of life (QoL) assessment. The primary endpoint is development of grade $\geq$ 2 RD, as compared to low-grade RD (grade 0-1), during RT. The secondary endpoint includes the impact of bacterial decolonization on QoL. Pearson's chi square or Fisher's exact tests will be used to compare the incidence rates of higher-grade RD between the interventional arm and control arm to assess if the intervention is associated with a lower incidence rate of higher-grade RD. Paired t-tests will be used to compare the QoL score change from baseline to after RT between the two arms. Linear regression models will be used in both analyses to adjust for covariates. Clinical trial information: NCT03883828. Research Sponsor: Beth N. McLellan MD.

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