Pimicotinib versus placebo for tenosynovial giant cell tumour (MANEUVER): an international, randomised, placebo-controlled, phase 3 trial

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Summary

Background Tenosynovial giant cell tumour (TGCT) is a rare, locally aggressive neoplasm that affects otherwise healthy adults. There are few systemic treatment options, highlighting an unmet need. We report the results of part 1 of the MANEUVER trial, which aimed to evaluate the efficacy and safety of pimicotinib, a highly selective, potent, colony-stimulating factor-1 receptor inhibitor, in patients with TGCT.

Methods MANEUVER is a randomised, placebo-controlled, phase 3 study done in 40 specialised hospitals in Asia, Europe, and North America. Patients aged 18 years and older with unresectable, symptomatic TGCT (patient-reported worse stiffness or worst pain of at least 4 on a scale of 0–10) were randomly assigned (2:1, double-blind) to oral, once-daily pimicotinib 50 mg or placebo for 24 weeks (part 1). An independent statistician used a central interactive web response system to generate the randomisation schedule; stratification was by region (China *vs* non-China). Masking was achieved by using placebo identical in appearance to pimicotinib. In part 1, patients, all investigators, and study funders were masked to treatment assignments. All patients who completed part 1 were allowed to continue to open-label part 2: pimicotinib-treated patients could continue the same dosage and placebo-treated patients could cross over to receive pimicotinib for 24 weeks. Eligible patients who completed part 2 were allowed to continue once-daily pimicotinib long-term in part 3. The primary endpoint was objective response rate (ORR) at week 25 by blinded independent review committee per Response Evaluation Criteria in Solid Tumors version 1.1 in the intention-to-treat population (all randomised patients). Safety was analysed in patients who received at least one dose of study drug. Missing data were not imputed and only observed data were analysed. Trial enrolment is complete; the study is registered at ClinicalTrials.gov (NCT05804045) and is ongoing.

Findings Between April 27, 2023, and March 29, 2024, 126 patients were screened and 94 patients (China [n=45], non-China [n=49]) were randomly assigned to, and received, pimicotinib (n=63) or placebo (n=31). 30 (32%) patients were male and 64 (68%) were female. ORR at week 25 was 54% (34 of 63) in the pimicotinib group and 3% (one of 31) in the placebo group (absolute difference 51% [95% CI 33–63], p<0·0001). Pimicotinib was associated with mainly mild treatment-emergent adverse events, including mostly manageable asymptomatic laboratory abnormalities and clinical events, such as pruritus, facial oedema, rash, periorbital oedema, and fatigue. The only grade 3 or 4 treatment-emergent adverse event occurring in more than 10% of pimicotinib-treated patients was increase in blood creatine phosphokinase, in eight (13%) of 63 patients. The most common treatment-emergent adverse events in the placebo group were fatigue and arthralgia. Dose reductions occurred in five (8%) of 63 pimicotinib-treated patients and treatment discontinuations in one (2%) of 63 pimicotinib-treated patients. There was no cholestatic hepatotoxicity, drug-induced liver injury, or hypopigmentation of skin or hair.

Interpretation Pimicotinib showed robust antitumour activity with clinically meaningful improvements in TGCT-related functional limitations and symptom burden, offering an effective treatment option with a manageable safety profile for this underserved condition.

Funding Abbisko Therapeutics.

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Published Online March 5, 2026 https://doi.org/10.1016/S0140-6736(25)02602-9

See Online/Comment https://doi.org/10.1016/S0140-6736(26)00191-1

For the plain language summary see Online for appendix 1

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Introduction

Tenosynovial giant cell tumour (TGCT) is a locally aggressive, soft tissue tumour originating in the joint synovium, bursae, or tendon sheaths. Previously known as giant cell tumour of the tendon sheath or pigmented villonodular synovitis, TGCT is a rare disease with an estimated annual global incidence of 43 cases per 1 million person-years.[1,2] TGCT is driven by a small number of neoplastic cells overexpressing growth factor colony-stimulating factor-1 (CSF-1), due to genetic

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Research in context

Evidence before this study

For patients with unresectable tenosynovial giant cell tumour (TGCT), systemic treatment might be the only suitable treatment modality. Globally, these patients have few treatment options, emphasising a large unmet need for more effective and tolerable systemic treatments. Less than half of patients treated with pexidartinib in the ENLIVEN trial or vimseltinib in the MOTION trial had an objective tumour response (per Response Evaluation Criteria in Solid Tumours version 1.1). Both trials almost entirely enrolled patients from the USA, Canada, Europe, and Australia; pexidartinib is registered in the USA, Taiwan, and Korea, and vimseltinib is registered in the USA and Europe. In addition, pexidartinib is a multikinase inhibitor with significant risk for serious cholestatic hepatotoxicity or mixed liver injury, or both. We searched PubMed and Embase for original articles and reviews published between Jan 1, 2019, and June 17, 2024, using key terms ("tenosynovial giant cell tumours", "TGCT", "villonodular synovitis", "CSF-1R"). There were few clinical trials using growth factor colony-stimulating factor-1 receptor (CSF-1R) inhibitors with robust efficacy (including quality-of-life domains), well tolerated safety profiles, and generalisability to a diverse global population. There remains a need for highly selective, systemic therapies for a broad population of patients with TGCT, especially given the relatively young age of patients facing this chronic disease with potentially devastating morbidity.

Added value of this study

MANEUVER is the first international, randomised, placebo-controlled, double-blind, phase 3 trial designed to evaluate the efficacy and safety of the CSF-1R inhibitor pimicotinib in patients with TGCT. In adult patients with TGCT who were enrolled at sites in China, Europe, and North America, pimicotinib demonstrated robust tumour shrinkage, early and durable symptomatic benefit, and improved quality of life for patients. These improvements were also seen in prespecified subgroups, including age, sex, Eastern Cooperative Oncology Group performance status, geographical region (China *vs* non-China), disease location, and number of previous surgeries, suggesting that pimicotinib delivers broad efficacy across diverse populations. Pimicotinib had a manageable safety profile and was well tolerated, with low incidences of dose reduction and treatment discontinuation, and there was no evidence of drug-induced liver injury, cholestatic hepatotoxicity, or skin or hair hypopigmentation.

Implications of all the available evidence

Pimicotinib expands treatment options in TGCT and provides an additional, targeted, systemic treatment for patients who are not amenable to surgery. In MANEUVER, pimicotinib as a once-daily, oral treatment showed early and robust efficacy and safety in patients with TGCT. The diverse patient population (approximately equal China *vs* non-China sites) suggests that the study findings would be broadly generalisable. Pimicotinib has potential to address the critical unmet needs of patients with TGCT by offering a highly selective, potent, systemic treatment with broad efficacy and a manageable safety profile, while alleviating pain and improving physical function to enhance quality of life in this life-limiting condition. There are unanswered questions about the use of systemic treatments in TGCT that could be addressed with real-world usage. These include duration of treatment, optimal start and restart times (stop-and-go approach), dosing strategies—such as dose modifications or dose intervals that balance efficacy, safety, and tolerability—treatment sequencing, and impact of CSF-1R inhibitors on family planning.

abnormalities.[2] CSF-1 binds to CSF-1 receptor (CSF-1R), resulting in local recruitment, proliferation, and accumulation of CSF-1R-expressing non-neoplastic inflammatory cells, which comprise most of the tumour.[2]

TGCT affects an otherwise healthy adult population (median age 38 years) with potentially devastating morbidity.[3–5] The high symptom burden of TGCT is characterised by mild to extremely debilitating symptoms.[4,5] In a study from the international TGCT Support Registry, published in 2025, patients indicated pain (92%), swelling (86%), stiffness (83%), and reduced range of motion (85%) as common symptoms.[4] Differential diagnosis of TGCT is challenging, often leading to delays in treatment.[4,6] Although TGCT is not life-threatening, it can cause irreversible joint and bone damage if not treated adequately.[3,7,8]

Surgery has been the primary treatment for controlling TGCT to date. However, in some cases it has resulted in substantial morbidity. There is a risk of postoperative complications, delayed recovery, and disease recurrence (among patients with previous surgery, 72% with diffuse TGCT and 34% with localised TGCT had at least one recurrence).[3,4,7] For patients with unresectable TGCT, systemic treatment might be the only suitable treatment modality.

CSF-1R is a validated therapeutic target for systemic TGCT treatment.[4,9,10] CSF-1R tyrosine kinase inhibitors have transformed the treatment landscape of TGCT. In the ENLIVEN and MOTION pivotal trials, the CSF-1R inhibitors pexidartinib and vimseltinib showed a significant objective response rate (ORR) per Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1 of 39% for pexidartinib and 40% for vimseltinib (both $p<0·0001$ *vs* placebo).[11,12] However, there has been concern over the unfavourable risk–benefit profile of pexidartinib, particularly the risk for severe hepatotoxicity.[9,11,13,14] As of 2026, vimseltinib is registered in the USA and Europe, and pexidartinib is registered in the USA, South Korea, and Taiwan.[9,10,15] Given the absence of consensus for optimal surgical treatment and the limitations with current systemic therapies, there remains a need for the wider availability of highly selective systemic

therapies with broader efficacy and an acceptable safety profile.[4,12]

Pimicotinib is an oral, once-daily, highly selective, and potent tyrosine kinase receptor inhibitor that prevents CSF-1R phosphorylation and subsequent accumulation of non-neoplastic CSF-1R-expressing cells in the tumour.[16–18] In preclinical studies, pimicotinib was shown to be over 40 times more selective for CSF-1R than for other tyrosine kinases in the CSF-1R family (KIT, FLT3, PDGFRα, VEGFR2).[18] This selectivity might limit off-target activity that is often associated with unwanted side-effects.[11,19] In a phase 1 trial of patients with TGCT not amenable to surgery, pimicotinib 50 mg once daily had an ORR of 67·5% at week 25 and 85% at 2-year follow-up (both by RECIST version 1.1) over a median treatment duration of 20·7 months.[20] Patients had durable improvements in joint pain and stiffness, with generally mild treatment-emergent adverse events and no signs of serious liver injuries or hair hypopigmentation.[20] We report here the primary analysis of the double-blind, part 1 phase of the MANEUVER trial, which compared the efficacy and safety of pimicotinib versus placebo in patients with TGCT.

Methods

Study design

MANEUVER is an international, multicentre, randomised, placebo-controlled, double-blind, phase 3 trial conducted at 23 specialised hospitals across China, seven in Europe, and ten in North America. All sites were required to have a medical specialist with knowledge about TGCT, sufficient resources to conduct the study, and comply with the study protocol. Part 1 (presented here) is the 24-week double-blind study, part 2 (ongoing) is the 24-week open-label treatment phase, and part 3 (ongoing) is the long-term open-label extension phase. The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The protocol, amendments, and informed consent forms were approved by the local institutional review board or independent ethics committee at participating sites (appendix 2 pp 3–4) and by the appropriate regulatory authorities. A more detailed description of MANEUVER is published;[16] the protocol and statistical analysis plan are available in appendix 2 (pp 20–226). A key protocol amendment was made during the study, namely to add an open-label extended treatment period (ie, part 3) that provides a longer treatment option for patients who completed part 2. Neither patients nor members of the public were involved directly in the initial design, conduct, or reporting of this trial. The study is registered at ClinicalTrials.gov (NCT05804045) and is ongoing.

Patients

Patients were recruited to the study through a multicentre approach, using specialised hospitals that provided comprehensive care for TGCT, where eligible individuals were identified based on clinical assessments. Eligible patients were aged 18 years or older, and had histologically confirmed, symptomatic TGCT. Symptomatic disease was defined as patient-reported worst stiffness or worst pain of at least 4 (scale of 0 to 10, with 10 being stiffness or pain as bad as imaginable) in the 2 weeks preceding randomisation. Patients were required to have confirmed, unresectable disease, defined as a TGCT lesion that was extensively invasive, located in a complex anatomical site, and could not be completely resected, or when surgery might have caused dysfunction or serious complications, as confirmed by two clinical experts. All patients were also required to have measurable disease per RECIST version 1.1, with at least one lesion measuring at least 2 cm by MRI, and to provide a tumour tissue specimen or histologically confirmed TGCT for central pathological diagnosis. Patients were excluded if they had been treated previously with CSF-1 or CSF-1R inhibitors before randomisation. Previous treatment with multikinase inhibitors that include the CSF-1 or CSF-1R pathway, such as imatinib and nilotinib, was allowed. Full study eligibility criteria are listed in appendix 2 (pp 5–6). Patients self-reported sex (male or female) and race or ethnicity. All patients provided written informed consent to participate in any study-related activity.

Randomisation and masking

Eligible patients were randomly assigned (2:1) to pimicotinib or matching placebo via a central interactive web response system, a service system for masked randomisation and trial supply management that ensured the integrity of study procedures. An independent statistician provided the randomisation schedule. Each patient was assigned a unique randomisation number. Patients were stratified by region (China *vs* non-China). In part 1, patients, study investigators and personnel, central imaging readers, reviewers, and the study funder were masked to assigned treatment. Unmasking for the funder only was allowed after all patients completed part 1 and reached the primary efficacy analysis timepoint at week 25. Data analysis was done after data cleaning and database lock. The appearance of placebo was identical to pimicotinib capsules and contained similar excipients but without the active pharmaceutical ingredient.

See Online for appendix 2

Procedures

Patients received either pimicotinib 50 mg once daily (with no food restrictions) or matching placebo administered orally in 28-day cycles for 24 weeks (six cycles). Patients who had received pimicotinib, completed part 1 (24-week, double-blind treatment period), and still met the study eligibility criteria could continue to part 2 at the same dose they received in part 1; placebo-treated patients could cross over to receive open-label pimicotinib 50 mg once daily for 24 weeks. Patients who completed part 2 and still met the study eligibility criteria could continue to part 3 (open-label treatment extension)

at the same dose they received in part 2. Patients attended two clinic visits (day 1 and day 15) during cycles 1 and 2, and one clinic visit (day 1) during subsequent cycles. Tumour imaging (MRI) was done at screening (baseline), week 13, and week 25, or the end of treatment within 25 weeks, whichever occurred first. Clinical outcome assessments were conducted at baseline (before randomisation), week 13, and week 25 for relative range of motion (assessed by the treating physician, under masked conditions, using a goniometer per the American Medical Association reference standard), and at baseline, week 1, and every 4 weeks for worst stiffness numerical rating scale (NRS) score, Brief Pain Inventory (BPI) worst pain NRS score, physical function (TGCT-specific Patient-Reported Outcomes Measurement Information System–Physical Function [PROMIS-PF]),[21] and health-related quality of life using the 5-level EQ-5D questionnaire (EQ-5D-5L) visual analogue scale score. Clinical evaluations, including vital signs, physical examination, laboratory evaluations, and review of medications (study drug, analgesic use, concomitant medications) were done at each clinic visit. Adverse event reporting was continuous from signed informed consent until, and including, 30 days after the last dose of study drug, and each event was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Investigator discretion for dose interruption, dose reduction, clinically indicated supportive care for disease-related symptoms, and medication for symptom relief (eg, antidiarrhoeals, antiemetics) was permitted.

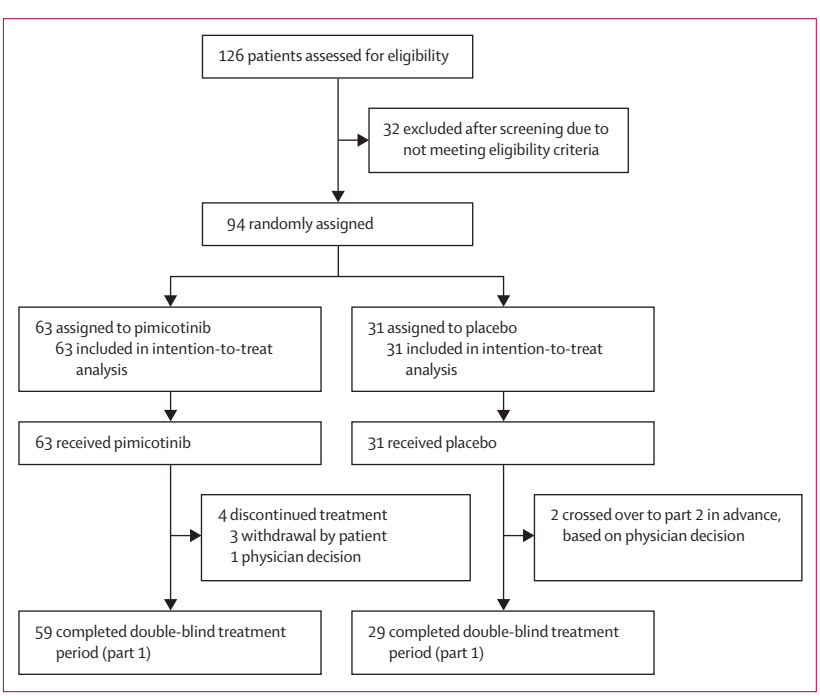


Figure 1: **Trial profile**

Outcomes

The primary endpoint was ORR at week 25 by blinded independent review committee (BIRC) per RECIST version 1.1 in the intention-to-treat (ITT) population. The BIRC comprised three industry radiologists, who had extensive experience with TGCT and tumour volume score. Two radiologists assessed each timepoint for all patients. If there was discordance between them, a third radiologist who was masked to the identity of the two primary readers, was not provided with clinical data, and not involved in the primary radiology review did an independent adjudication review. Key secondary endpoints at week 25 were analysed in the following prespecified hierarchical order: (1) BIRC-assessed ORR based on tumour volume score;[22] and clinical outcome assessments for mean change from baseline in: (2) relative range of motion of the affected joint (relative to reference criteria for the same joint); (3) worst stiffness NRS score; (4) BPI worst pain NRS score; and (5) PROMIS-PF score.

A supportive analysis of key secondary endpoints was the proportion of patients achieving a decrease in BPI worst pain NRS score of at least 30%, without an increase in narcotic analgesic use of at least 30% (BPI-30 responders) at week 25. The threshold to establish a clinically important difference in pain is based on approximately 30% reduction on an 11-point NRS for pain using the self-reported Patient Global Impression of Change scale, a commonly used validated measure for assessing clinically important differences in pain.[23] Health-related quality of life was another secondary efficacy analysis assessed at week 25 as mean change from baseline using the EQ-5D-5L visual analogue scale score. Analysis of data for the additional secondary endpoints (duration of response by BIRC per RECIST version 1.1, duration of response by BIRC per tumour volume score, ORR by investigator per RECIST version 1.1 at week 25, duration of response by investigator per RECIST version 1.1, NCI Patient-Reported Outcomes version of the CTCAE, and pharmacokinetics) and exploratory endpoints listed in the protocol is ongoing and will be reported separately. Safety endpoints including treatment-emergent adverse events were evaluated with NCI CTCAE version 5.0 and included events leading to dose modification, dose interruptions, and treatment discontinuation.

Statistical analysis

The first planned analysis was the primary analysis of this trial and included randomly assigned patients who completed part 1 with a follow-up MRI scan at week 25, withdrew consent, or died. For the primary endpoint, assuming an ORR at week 25 of 40% in the pimicotinib group and 6% in the placebo group, a sample size of 75 evaluable patients provided 90% power to detect a difference between the two groups (Fisher's exact test with a two-sided significance level of α=0·05). The primary endpoint ORR target for pimicotinib was based on 85% of the lower limit of the 95% CI for interim ORR in the

phase 1 study (data not published); the target for the placebo group was the upper 95% CI of the placebo group in ENLIVEN.[11] Primary and key secondary efficacy endpoints were analysed for all randomly assigned patients (intention-to-treat population), and safety was analysed in all patients who received at least one dose of the assigned treatment (safety analysis population). ORRs at week 25 in the ITT population and across subgroups were summarised by treatment group, and exact two-sided 95% CIs were calculated using the Clopper–Pearson method. The primary estimand and estimand for ORR per tumour volume score also accounted for intercurrent events and included any response (RECIST version 1.1) at week 25 regardless of modifications due to toxicity, discontinuation of treatment without disease progression, or before receiving an alternative anticancer therapy (including surgery). For clinical outcomes including range of motion, stiffness, pain, and physical function, intercurrent events were similarly handled as the primary estimand, except when patients received an alternative antitumour therapy (including surgery) in which case data were collected and used regardless (treatment policy strategy).

Key secondary endpoints were tested sequentially in the prespecified order (1–5 listed above) using a hierarchical gatekeeping procedure, whereby they were tested only if the preceding endpoint showed a statistically significant treatment effect. Analysis of the key secondary endpoints, except ORR per tumour volume score, was done using mixed models for repeated measurements, which included change from baseline as the dependent variable, and treatment, baseline, visit, stratification factor of China versus non-China, and treatment by visit interaction, and the baseline by visit interaction as fixed effects; relative range of motion also included joint category as a fixed term. Clinically meaningful changes from baseline to week 25 were established at the individual patient level based on psychometric analyses and exit interviews. The proportion of BPI-30 responders at week 25 was compared between treatment groups. All between-group statistical tests were compared at a two-sided $\alpha=0{\cdot}05$ (Fisher's exact test). Safety data were summarised descriptively. Missing data for all outcomes were not imputed and only observed data were analysed. There was no planned formal interim analysis.

As per the statistical analysis plan, any patients regarded as having protocol deviations were included in the primary and key secondary efficacy endpoint analyses, and in the safety analysis. Statistical analyses were done using SAS software version 9.4. An independent data monitoring committee ensured continuous monitoring of the safety profile and oversaw the conduct of the trial.

Role of the funding source

Abbisko Therapeutics designed and funded the study, provided study drug, and was involved in the collection, analyses, and reporting of data.

Results

Between April 27, 2023, and March 29, 2024, 126 patients with TGCT were screened and 94 patients were randomly assigned to oral pimicotinib 50 mg once daily (n=63) or matching placebo (n=31). 88 (94%) of 94 patients completed part 1 treatment; four (6%) of 63 patients discontinued pimicotinib treatment (three [5%] patients withdrew consent, one [2%] withdrew due to physician

	Pimicotinib (n=63)	Placebo (n=31)	Total (N=94)
Age, years	41·0 (31–52)	36·0 (27–47)	40·0 (30–52)
Sex			
Male	18 (29%)	12 (39%)	30 (32%)
Female	45 (71%)	19 (61%)	64 (68%)
ECOG PS			
0	21 (33%)	12 (39%)	33 (35%)
1	42 (67%)	19 (61%)	61 (65%)
Liver function			
Normal	59 (94%)	29 (94%)	88 (94%)
Mild dysfunction	3 (5%)	2 (7%)	5 (5%)
Moderate dysfunction	1 (2%)	0	1 (1%)
Race			
Asian	32 (51%)	16 (52%)	48 (51%)
White	26 (41%)	11 (36%)	37 (39%)
Black or African American	3 (5%)	2 (7%)	5 (5%)
Other*	2 (3%)	2 (7%)	4 (4%)*
Geographical region			
China	31 (49%)	14 (45%)	45 (48%)
Europe	18 (29%)	10 (32%)	28 (30%)
North America	14 (22%)	7 (23%)	21 (22%)
TGCT type			
Diffuse	53 (84%)	27 (87%)	80 (85%)
Localised	8 (13%)	3 (10%)	11 (12%)
Unknown	2 (3%)	1 (3%)	3 (3%)
Tumour location			
Knee	33 (52%)	14 (45%)	47 (50%)
Ankle	9 (14%)	5 (16%)	14 (15%)
Hip	7 (11%)	6 (19%)	13 (14%)
Foot	4 (6%)	4 (13%)	8 (9%)
Wrist	5 (8%)	2 (7%)	7 (7%)
Other†	5 (8%)	0	5 (5%)
Lower or upper extremity			
Lower	54 (86%)	29 (94%)	83 (88%)
Upper	9 (14%)	2 (7%)	11 (12%)
Previous surgery for TGCT			
0	26 (41%)	12 (39%)	38 (40%)
≥1	37 (59%)	19 (61%)	56 (60%)
Previous systemic treatment for TGCT			
Yes (imatinib)	2 (3%)	4 (13%)	6 (6%)
No	61 (97%)	27 (87%)	88 (94%)

Data are n (%) or median (IQR). ECOG PS=Eastern Cooperative Oncology Group performance status. TGCT=tenosynovial giant cell tumour. *Includes one patient with mixed races of "Black or African American" and "White", and one each who reported as "Colombian", "Caribbean", and "South American". †Includes two patients reported as 'right foot (big thumb)', 'left jaw'.

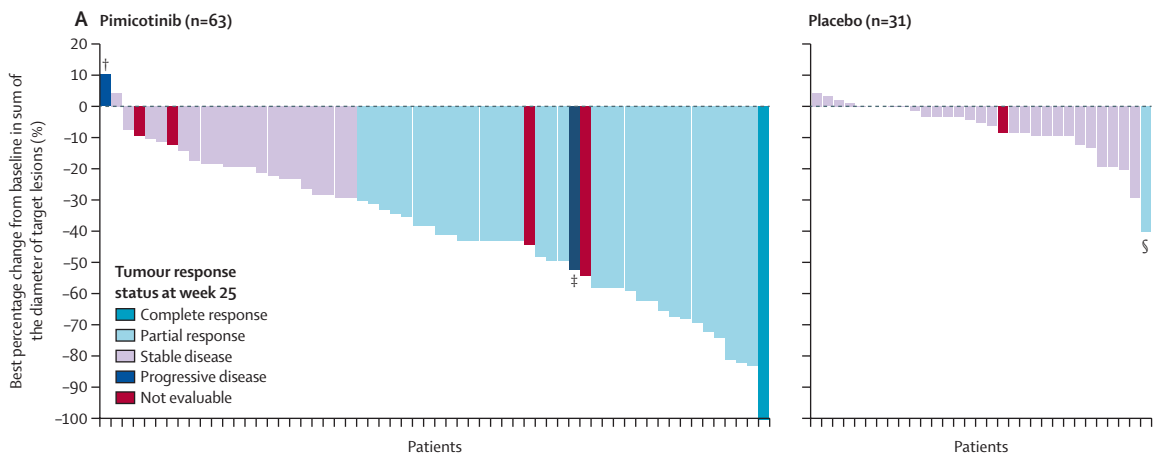
Table 1: **Baseline demographic and disease characteristics (intention-to-treat population)**

	Pimicotinib (n=63)	Placebo (n=31)	Absolute difference, pimicotinib–placebo (95% CI*)	p value
Primary endpoint				
Objective response rate at week 25: BIRC based on RECIST version 1.1†	54% (41 to 67)	3% (0·1 to 17)	51% (33 to 63)	<0·0001‡
Complete response	1 (2%)	0	..	..
Partial response	33 (52%)	1 (3%)§	..	..
Stable disease	20 (32%)	28 (90%)	..	..
Progressive disease	2 (3%)¶	0	..	..
Not evaluable‖	7 (11%)	2 (7%)	..	..
Key secondary endpoints				
Objective response rate at week 25: BIRC based on TVS†	62% (49 to 74)	3% (0·1 to 17)	59% (41 to 70)	<0·0001‡
Complete response	1 (2%)	0	..	..
Partial response	38 (60%)	1 (3%)§	..	..
Stable disease	16 (25%)	28 (90%)	..	..
Progressive disease	1 (2%)	0	..	..
Not evaluable	7 (11%)	2 (7%)	..	..
Relative ROM, at baseline; at week 25**	59 (94%); 56 (89%)	31 (100%); 28 (90%)	..	..
Baseline, mean	70·6 (20·7)	66·1 (21·8)	..	..
Week 25, mean	84·9 (21·4)	67·6 (23·6)	..	..
LS mean change from baseline at week 25††‡‡	15·6 (10·4 to 20·9)	−0·1 (−7·0 to 6·9)	15·7 (7·3 to 24·1)	0·0003
Worst stiffness NRS score, at baseline; at week 25**	63 (100%); 56 (89%)	31 (100%); 29 (94%)	..	..
Baseline, mean	5·3 (1·9)	5·6 (1·7)	..	..
Week 25, mean	2·3 (1·8)	4·8 (2·3)	..	..
LS mean change from baseline at week 25††‡‡	−3·0 (−3·5 to −2·6)	−0·6 (−1·2 to 0·1)	−2·4 (−3·2 to −1·7)	<0·0001
BPI worst pain NRS score, at baseline; at week 25**	63 (100%); 56 (89%)	31 (100%); 29 (94%)	..	..
Baseline, mean	4·8 (2·1)	4·8 (2·6)	..	..
Week 25, mean	2·5 (1·9)	4·4 (2·5)	..	..
LS mean change from baseline at week 25††‡‡	−2·3 (−2·7 to −1·9)	−0·2 (−0·8 to 0·3)	−2·1 (−2·8 to −1·4)	<0·0001
PROMIS-PF score§§, at baseline; at week 25**	62 (98%); 57 (90%)	31 (100%); 29 (94%)	..	..
Baseline, mean	41·2 (7·1)	39·8 (6·0)	..	..
Week 25, mean	46·6 (7·8)	42·6 (7·8)	..	..
LS mean change from baseline at week 25††‡‡	5·6 (4·2 to 7·1)	2·2 (0·2 to 4·2)	3·4 (0·9 to 5·9)	0·0074
Other secondary endpoints				
EQ-5D-5L VAS, at baseline; at week 25**	63 (100%); 58 (92%)	31 (100%); 29 (94%)	..	..
Baseline, mean	71·7 (14·6)	69·0 (14·3)	..	..
Week 25, mean	79·4 (11·6)	70·9 (16·9)	..	..
LS mean change from baseline at week 25††	8·1 (5·8 to 10·5)	0·4 (-3·0 to 3·8)	7·7 (3·6 to 11·9)	0·0004
BPI-30 response rate¶¶ at week 25‡	64% (50 to 75)	16% (5 to 34)	47% (27 to 61)	<0·0001

Data are n (%), % (95% CI), mean (SD), or LS mean (95% CI) unless stated otherwise. BIRC=blinded independent review committee. BPI=Brief Pain Inventory. EQ-5D-5L=5-level EQ-5D questionnaire. LS=least squares. NRS=numerical rating scale. PROMIS-PF=Patient-Reported Outcomes Measurement Information System–Physical Function. RECIST=Response Evaluation Criteria in Solid Tumours. ROM=range of motion. TVS=tumour volume score. VAS=visual analogue scale. *95% CI for ratio difference was derived using the Wilson method. †95% CIs for rates were calculated using the exact Clopper–Pearson method. ‡p values were obtained using Fisher's exact test. §The single placebo responder, who had been receiving imatinib from May 2022 until discontinuation in February 2024 (4 weeks before study treatment initiation), with stable disease as the best overall response, showed a partial response under placebo; the possibility of a spontaneous regression or a delayed effect from imatinib cannot be ruled out. ¶One patient initially had a 52% decrease in tumour size (partial response) by week 13 and then a subsequent 38% increase (progressive disease) at week 25; however, by week 37 the tumour size had reduced by 62% (partial response), and the patient was still on treatment. ‖Patients were non-evaluable in the pimicotinib group due to early discontinuation from part 1 (n=5) or not having an evaluable target lesion (n=2); in the placebo group, patients were non-evaluable due to entering part 2 (open-label pimicotinib) before completing part 1. **Proportion of the total population who completed the outcome assessment at baseline and week 25. ††LS mean and 95% CI values are summarised by treatment groups. Estimated using mixed-model repeated measures with fixed effects for treatment, baseline, visit, stratification factor of China versus non-China sites, and treatment-by-visit interaction, baseline-by-visit interaction; additionally, joint-type category (knee, ankle, and others) was included as a fixed effect for relative ROM. An unstructured variance–covariance matrix was used. ‡‡A hierarchical gatekeeping testing procedure was used to control the family-wise type 1 error rate at a two-sided α level of 0·05. Statistical significance for any subsequent secondary endpoints was not assessed unless the treatment effect on all preceding secondary endpoints was statistically significant. §§The PROMIS-PF scale includes two different sets of topics for upper and lower extremities, which were used for assessment for patients with upper and lower extremity tumours, respectively. ¶¶BPI-30 responder was defined as a patient with a decrease of at least 30% in mean BPI worst pain NRS who did not have an increase of at least 30% in narcotic analgesic use.

Table 2: **Primary and secondary endpoint data at week 25**

decision); two (7%) of 31 patients discontinued placebo treatment due to symptomatic progression (both due to physician decision) and went on to receive open-label treatment with pimicotinib in part 2 (figure 1). Major protocol deviations occurred in 14 (22%) patients in the pimicotinib group and three (10%) patients in the placebo group; patients could have had more than one deviation. In the pimicotinib group, these protocol deviations were



B

	Objective response rate, n/N (%)		Absolute difference (pimicotinib–placebo), % (95% CI)¶
	Pimicotinib group	Placebo group	
Tumour location			
Lower extremity	27/54 (50%)	1/29 (3%)	47% (28–60)
Upper extremity	7/9 (78%)	0/2 (0%)	78%
Disease location			
Knee	16/33 (48%)	0/14 (0%)	48% (22–65)
Others	18/30 (60%)	1/17 (6%)	54% (27–70)
Region			
China	20/31 (65%)	0/14 (0%)	65% (37–79)
Not China	14/32 (44%)	1/17 (6%)	38% (12–56)
Age group, years			
<40	16/29 (55%)	1/17 (6%)	49% (22–66)
≥40	18/34 (53%)	0/14 (0%)	53% (26–69)
Sex			
Male	10/18 (56%)	1/12 (8%)	47% (13–68)
Female	24/45 (53%)	0/19 (0%)	53% (31–67)
Number of previous surgeries			
0	12/26 (46%)	1/12 (8%)	38% (6–57)
≥1	22/37 (59%)	0/19 (0%)	59% (36–74)
Previous systemic therapy			
Yes	1/2 (50%)	1/4 (25%)	25%
No	33/61 (54%)	0/27 (0%)	54% (37–66)
TGCT type			
Localised	5/8 (63%)	0/3 (0%)	63%
Diffuse	28/53 (53%)	1/27 (4%)	49% (30–62)
Unknown	1/2 (50%)	0/1 (0%)	50%
ECOG PS			
0	12/21 (57%)	1/12 (8%)	49% (15–68)
1	22/42 (52%)	0/19 (0%)	52% (30–67)
Overall	**34/63 (54%)**	**1/31 (3%)**	**51% (33–63)**

Figure 2: **Objective response per patient (A) and by patient subgroup (B)***
(A) The bars represent best percentage change in the sum of diameters of target lesions in individual patients during the double-blind study period (until week 25), and the colour coding indicates the objective response achieved at a single time point: week 25. (B) Objective response rate at week 25 by patient subgroup. ECOG PS=Eastern Cooperative Oncology Group performance status. TGCT=tenosynovial giant cell tumour. *By blinded independent review committee based on Response Evaluation Criteria in Solid Tumours version 1.1. †Tumour size increased continuously during the treatment period in this patient, reaching a 43% increase from baseline at week 25 (progressive disease). ‡This patient initially had a decrease in tumour size of 52% (partial response) by week 13 and then a subsequent increase of 38% (progressive disease) at week 25; however, by week 37 their tumour size had reduced by 62% (partial response), and they were still on treatment. §This patient previously received imatinib treatment (9 months before evaluation) and had a partial response at week 25; the patient had no response before discontinuation on the day of consent and was randomly assigned after the protocol-mandated 4-week washout. ¶Subgroups with one treatment group containing fewer than five patients were not subjected to statistical testing and were reported only descriptively.

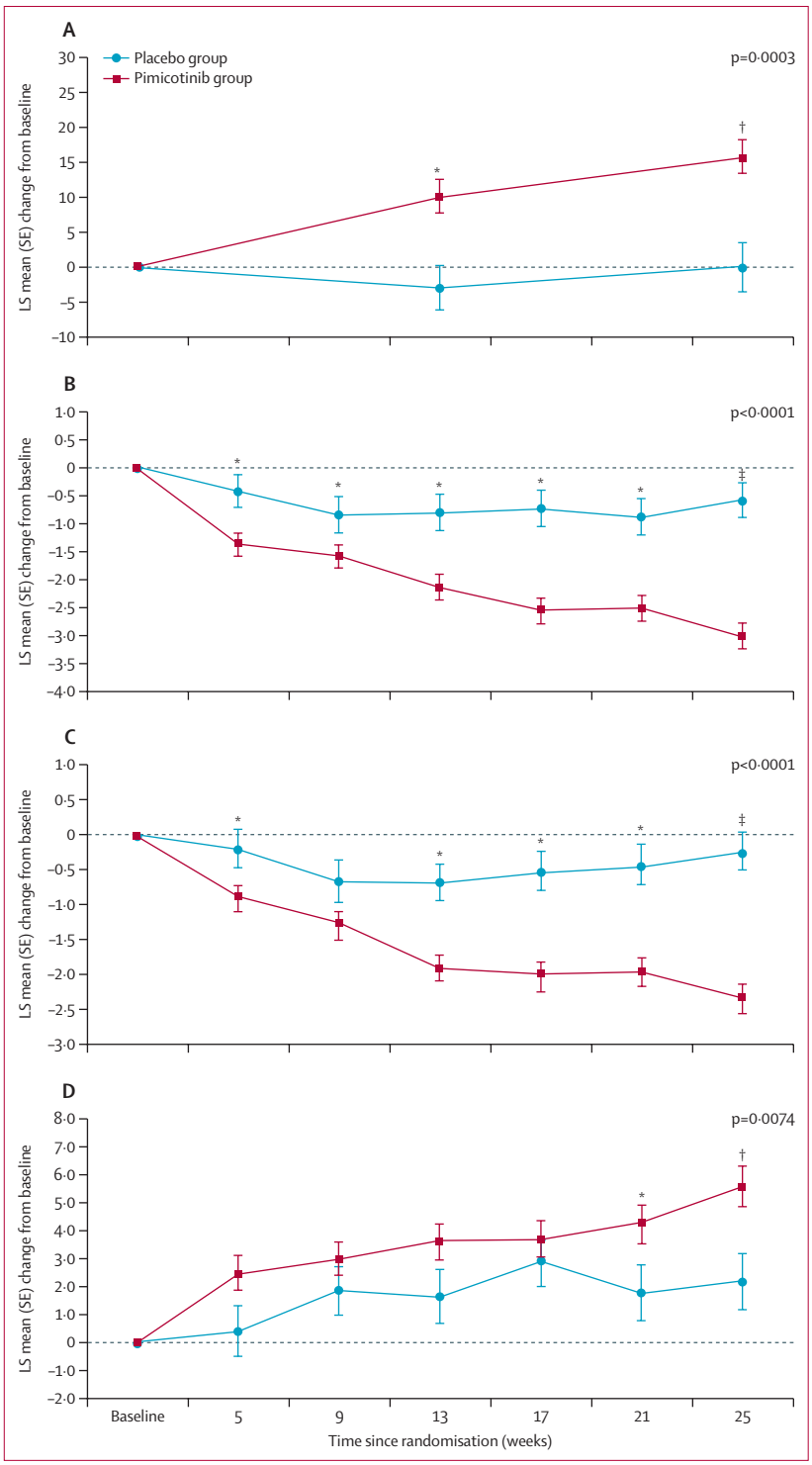


Figure 3: **Change from baseline in clinical outcome assessments in the intention-to-treat population**
Relative range of motion (A), worst stiffness NRS score (B), BPI worst pain NRS score (C), and physical function on the PROMIS-PF T-score (D). BPI=Brief Pain Inventory. LS=least squares. NRS=numerical rating scale. PROMIS-PF=Patient-Reported Outcomes Measurement Information System–Physical Function
*p<0·05 for LS mean group difference at this timepoint; p values are nominal. †p<0·05 for LS mean group difference at week 25; p values are significant (tested in hierarchical order). ‡p<0·0001 for LS mean group difference at week 25; p values are significant (tested in hierarchical order).

due to missing study procedures in 11 (17%) patients, study treatment or investigational medicinal product non-compliance in two (3%) patients, eligibility deviation in two (3%) patients, and investigational medicinal product dispensing or accountability in one (2%) patient. In the placebo group, these protocol deviations were due to missing study procedures in two (6%) patients and other reasons in one (3%) patient. All other amendments were minor, with no expected effect on patients or study outcomes.

The study population was generally representative of patients affected by TGCT (table 1) with baseline demographic and clinical characteristics of patients in both groups being well balanced: median age was 40·0 years (IQR 30–52), 30 (32%) patients were male, 64 (68%) patients were female, 80 (85%) had diffuse TGCT, and 56 (60%) had undergone at least one previous surgery. 88 (94%) patients were systemic treatment-naive. 45 (48%) patients were enrolled in the study in China, 28 (30%) in Europe, and 21 (22%) in North America. The data cutoff date for the primary analysis was Sept 23, 2024.

MANEUVER met its primary endpoint. The ORR at week 25 by BIRC per RECIST version 1.1 was 54% (34 of 63) in the pimicotinib group compared with 3% (one of 31) in the placebo group (absolute difference 51% [95% CI 33–63], p<0·0001, table 2). In the pimicotinib group, one (2%) patient achieved a complete response and 33 (52%) patients had partial responses. The first scheduled study visit for tumour response evaluation by MRI was at week 13, when 26 (41%) patients in the pimicotinib group had an objective tumour response. The one (3.2%) patient who had a response in the placebo arm as discussed above had the response by week 13. 58 (92%) patients in the pimicotinib group had a reduction in tumour size per RECIST version 1.1 during the double-blind study period (compared with 22 [71%] in the placebo group; figure 2A). This effect on tumour reduction was consistent across prespecified subgroups, including age, sex, Eastern Cooperative Oncology Group performance status, geographical region, disease location, and number of previous surgeries (figure 2B).

All key secondary endpoints were met. The ORR at week 25 by BIRC per tumour volume score was 62% (39 of 63) in the pimicotinib group compared with 3% (one of 31) in the placebo group (absolute difference 59% [95% CI 41–70], p<0·0001), consistent with findings based on RECIST version 1.1 (table 2). Completion rates for worst stiffness, worst pain, and physical function were high: 54–63 (86–100%) patients in the pimicotinib group and 28–31 (90–100%) patients in the placebo group (appendix 2 p 7). Statistically significant improvements in change from baseline for all clinical outcome assessments were seen with pimicotinib versus placebo at week 25: relative range of motion (p=0·0003), worst stiffness NRS score (p<0·0001), BPI worst pain NRS score (p<0·0001), and PROMIS-PF (p=0·0074; table 2). Mean scores by clinic visit for all four clinical

outcome assessments are shown in figure 3; p values before week 25 are nominal. Clinically meaningful improvements were observed in all clinical outcome assessments irrespective of tumour response per RECIST version 1.1 and tumour volume score. In addition, pimicotinib showed early improvements across all clinical outcome assessments, with benefits seen in relative range of motion, worst stiffness, worst pain, and physical function at the first scheduled assessments. Improvements in clinical outcome assessments were also observed at various thresholds (appendix 2 pp 8–9). 40 (64%) patients in the pimicotinib group compared with five (16%) patients in the placebo group achieved a BPI-30 response at week 25 (absolute difference 47% [95% CI 27–61], p<0·0001; table 2). Four (6%) patients in the pimicotinib group used concomitant narcotic analgesics compared with six (19%) patients in the placebo group in the BPI-30 analysis. There was significant improvement in EQ-5D-5L visual analogue scale score in the pimicotinib group compared with the placebo group at week 25 (absolute difference 7·7 [95% CI 3·6–11·9], p=0·0004; table 2).

The median duration of exposure was 169 days in both groups (IQR 167–173 in both groups), with a median pimicotinib dose intensity of 94·6% (85·8–99·4). Adverse events, mostly grade 1 or 2, occurred in 63 (100%) patients treated with pimicotinib and 29 (94%) patients who received placebo (table 3). Most of the common (>10% patients) events reported with pimicotinib were asymptomatic, reversible abnormalities in laboratory parameters, including increases in blood creatine phosphokinase, blood lactate dehydrogenase, aspartate aminotransferase, amylase, α-hydroxybutyrate dehydrogenase, and lipase. The most common (>10% patients) clinical events with pimicotinib included pruritus, facial oedema, rash, periorbital oedema, fatigue, nausea, and headache. The most common (>10% patients) treatment-emergent adverse events in the placebo group were fatigue, arthralgia, and increases in blood creatine phosphokinase (table 3; appendix 2 pp 10–11). Elevations in liver function tests (aspartate aminotransferase and alanine aminotransferase) were mild and asymptomatic in both groups (appendix 2 pp 12–13). All adverse events are shown in appendix 2 (pp 14–18).

Grade 3 or 4 treatment-emergent adverse events were reported in 22 (35%) patients in the pimicotinib group, most commonly increased blood creatine phosphokinase, which occurred in eight (13%) patients (table 3; appendix 2 pp 10–11) and increased blood pressure in four (6%) patients. One serious treatment-related adverse event of grade 3 increased blood pressure occurred in one pimicotinib-treated patient who had a medical history of hypertension and white-coat syndrome. No placebo-treated patients had a serious treatment-related adverse event. There were no deaths in the trial.

Five (8%) patients treated with pimicotinib required dose reductions due to adverse events (dermatitis, rash, headache, hypersomnia, fatigue, and increased blood creatine phosphokinase each occurred in one [2%] patient) versus none in the placebo group (table 3). Transient dose interruptions due to adverse events occurred in 34 (54%) patients in the pimicotinib group; these events were primarily serum enzyme elevations,

	Pimicotinib (n=63)		Placebo (n=31)	
	Any grade	Grade 3 or 4	Any grade	Grade 3 or 4
Any treatment-emergent adverse event	63 (100%)	22 (35%)	29 (94%)	1 (3%)
Any treatment-related adverse event	62 (98%)	18 (29%)	18 (58%)	0
Serious adverse event	3 (5%)	0	1 (3%)	0
Treatment related	1 (2%)	0	0	0
Leading to dose modification	36 (57%)	14 (22%)	2 (6%)	1 (3%)
Leading to dose reduction	5 (8%)	0	0	0
Leading to dose interruption	34 (54%)	14 (22%)	2 (6%)	1 (3%)
Leading to trial discontinuation	1 (2%)	0	0	0
Treatment related	1 (2%)	0	0	0
Leading to death	0	0	0	0
Treatment-emergent adverse event occurring in >10% of patients in either group				
Laboratory abnormalities*				
Blood creatine phosphokinase increased	45 (71%)	8 (13%)	5 (16%)	0
Blood lactate dehydrogenase increased	36 (57%)	0	0	0
Aspartate aminotransferase increased	34 (54%)	0	3 (10%)	0
Amylase increased	22 (35%)	0	0	0
α-hydroxybutyrate dehydrogenase increased	16 (25%)	0	0	0
Lipase increased	15 (24%)	2 (3%)	1 (3%)	0
Blood creatine phosphokinase MB increased	12 (19%)	0	1 (3%)	0
Alanine aminotransferase increased	11 (17%)	0	3 (10%)	0
HDL increased	10 (16%)	0	0	0
Blood creatinine increased	10 (16%)	0	0	0
Hypercholesterolaemia	9 (14%)	0	3 (10%)	0
White blood cell count decreased	8 (13%)	0	1 (3%)	0
Apolipoprotein A-I increased	7 (11%)	0	0	0
Blood cholesterol increased	7 (11%)	0	1 (3%)	0
Neutrophil count decreased	7 (11%)	1 (2%)	0	0
Other clinical adverse events				
Pruritus	33 (52%)	2 (3%)	1 (3%)	0
Facial oedema	30 (48%)	0	0	0
Rash	22 (35%)	2 (3%)	0	0
Periorbital oedema	20 (32%)	0	3 (10%)	0
Fatigue	18 (29%)	0	7 (23%)	0
Nausea	17 (27%)	0	2 (6%)	0
Headache	13 (21%)	0	2 (6%)	0
Dizziness	10 (16%)	0	1 (3%)	0
Insomnia	9 (14%)	0	2 (6%)	0
Hypertension	9 (14%)	2 (3%)†	1 (3%)	0
Rash maculopapular	7 (11%)	1 (2%)	2 (6%)	0
Arthralgia	4 (6%)	0	7 (23%)	0

Data are n (%). *Laboratory abnormalities were all asymptomatic and responded well to brief dose interruptions. †Included one patient with a medical history of hypertension, and one patient with abnormal blood pressure at baseline.

Table 3: **Summary of safety data (safety analysis set)**

and the most frequent was increased blood creatine phosphokinase in nine (14%) patients. Non-laboratory adverse events that led to temporary treatment interruptions that occurred in more than 5% of patients included facial oedema in six (10%) patients, rash in five (8%) patients, and periorbital oedema and pruritus each occurred in four (6%) patients (appendix 2 p 19).

Dose interruptions due to adverse events occurred in two (7%) patients in the placebo group (arthralgia and prostate cancer). The mean percentage of intended cumulative dose received was 90% (SD 12·2) for pimicotinib and 98% (5·3) for placebo. Among those who had dose interruptions, 32 (82%) of 39 patients in the pimicotinib group, and two (100%) of two patients in the placebo group had no more than two treatment interruptions. The median duration of dose interruption due to adverse events was 10 days (IQR 7–15) for the pimicotinib group and 13 days (2–24) for the placebo group. One adverse event-related treatment discontinuation was reported as grade 2 fatigue in one (2%) patient in the pimicotinib group.

There was no evidence of cholestatic liver toxicity or drug-induced liver injury, and no reports of skin or hair hypopigmentation.

Discussion

This randomised, placebo-controlled, double-blind, phase 3 trial (MANEUVER) evaluated the efficacy and safety of pimicotinib in a geographically diverse population of patients with TGCT. Pimicotinib showed early, robust, statistically significant, and clinically meaningful antitumour activity in more than half of treated patients with TGCT (ORR 54%).[11,12] By the data cutoff, 58 (90%) of 63 patients in the pimicotinib group had a decrease in tumour size. Pimicotinib antitumour activity was consistent across prespecified subgroups, suggesting broad efficacy.

Patients treated with pimicotinib had early, durable, robust, clinically meaningful, and statistically significant improvements in range of motion, worst stiffness, worst pain, and physical function, regardless of tumour response. Notably, the proportion of patients achieving a BPI-30 response at week 25 was four times higher with pimicotinib than with placebo. The consistently high questionnaire completion rates for patient-reported measures further strengthen these findings.

The potential for TGCT as a life-limiting disease might not be fully realised.[4–7,24] Physical functioning and quality of life domains are especially important given the relatively young age of patients with TGCT.[4,5,7,24] Chronic pain and disability can create heightened emotional and psychological burden.[3,4,7] For patients with TGCT, most of whom are otherwise healthy, high symptom burden might impede routine daily activities (eg, cooking, bathing, exercising, lifting children, running errands) and social participation.[3–5,7] Patients with TGCT might withdraw from family life and social activities, resulting in further isolation.[3–5] These limitations can have substantial implications for work and careers, affecting the livelihood of patients and their families.[3–5,7] Furthermore, patients might have trouble concentrating due to pain or side-effects of pain medications. They might be unable to stand, sit, or operate machinery and vehicles. Some patients might reduce their work hours, change their occupation entirely, or retire early, which can create economic burden and stress.[4,5] The potentially highly debilitating and chronic nature of TGCT affects the physical, emotional, and financial health of patients.[4–7] For patients with TGCT, reducing symptom burden, such as range of motion, worst stiffness, worst pain, and physical function, can meaningfully improve quality of life and empower patients to have better control of their disease.[4,6,7,24]

Currently approved systemic therapies for TGCT include pexidartinib and vimseltinib, depending on regional availability.[10,12] Pexidartinib is a multitargeted kinase inhibitor that primarily targets CSF-1R.[25] Treatment with pexidartinib might pose a risk of fatal cholestatic hepatotoxicity and requires registration in a US Food and Drug Adminstration-mandated Risk Evaluation and Mitigation Strategy programme; drug labeling information was not readily available for South Korea and Taiwan.[9,26] Skin or hair hypopigmentation and the twice-daily dosing regimen with dietary requirements could affect adherence to pexidartinib, which is an especially important consideration given the young age of patients with TGCT.[9,11,13] In fact, patients receiving pexidartinib have identified convenience and side-effects as domains that limit their overall treatment satisfaction.[13] Vimseltinib is a potent CSF-1R inhibitor that is not associated with severe hepatotoxicity; it has a twice-weekly regimen that requires at least 72 h between doses and can be taken without food restrictions.[10,12] There are currently no data directly comparing pimicotinib with pexidartinib or vimseltinib in a global randomised study, in part due to the unavailability of these agents in some regions, including China.[9,10] With this caveat, the diverse population of patients treated with pimicotinib in MANEUVER had a higher ORR at week 25 than that reported in the ENLIVEN (pexidartinib)[11] and MOTION (vimseltinib)[12] trials (39% [ENLIVEN] and 40% [MOTION] ORR all by BIRC per RECIST version 1.1). The multikinase inhibitors imatinib and nilotinib have shown clinical activity in TGCT in a retrospective analysis and a phase 2 study, respectively,[27,28] but not in a randomised study, and neither has received regulatory approval for TGCT.[4] Both imatinib and nilotinib are currently prescribed off-label in clinical practice (as allowed) due to the large unmet need in this disease[4,29] and, in many countries, they remain the only available therapeutic options.[27,30] Emactuzumab, an intravenously administered CSF-1R-targeted monoclonal antibody, is in late-stage clinical investigation for the treatment of TGCT.[31]

In MANEUVER, pimicotinib had a manageable safety profile, with no evidence of cholestatic hepatotoxicity or

drug-induced liver injury, as shown by comprehensive evaluation of liver function. Serum enzyme elevations (eg, liver transaminases) were observed with pimicotinib, as with pexidartinib and vimseltinib. In MANEUVER, the serum enzyme elevations, including increases in blood creatine phosphokinase, blood lactate dehydrogenase, aspartate aminotransferase, amylase, α-hydroxybutyrate dehydrogenase, and lipase, were asymptomatic, reversible, and consistent with the known mechanism of CSF-1 pathway inhibition (depletion of Kupffer cells resulting in decreased clearance of these enzymes, but no signs of organ damage).[32] Consistent with the minimal off-target KIT inhibition with pimicotinib, patients in MANEUVER did not have skin or hair hypopigmentation that was associated with pexidartinib.[11] In addition, there were no events of grade 3 oedema in MANEUVER, which were reported in ENLIVEN and MOTION.[11,12] Notably, the safety profile of pimicotinib reflects additional laboratory parameters due to differences in regional practice (α-hydroxybutyrate dehydrogenase was more commonly measured at sites in China) and differences in specific CSF-1R inhibitor study protocols (MANEUVER evaluated lipase, amylase, and blood concentrations of lactate dehydrogenase). Adverse events were manageable with brief dose interruptions that did not affect treatment adherence or dose intensity. In MANEUVER, the oral, once-daily regimen of pimicotinib was well tolerated, as evidenced by a low rate of dose reductions (five [8%] of 63 patients) and treatment discontinuation (one [2%] of 63 patients). Tolerability of pimicotinib contributes to its favourable safety profile, especially in a chronic, potentially debilitating disease such as TGCT. In comparison, more than a third of patients had to reduce the dose with vimseltinib in the MOTION trial and treatment with pexidartinib required discontinuation in more than 10% of patients in the ENLIVEN study.[11,12] Despite the rate of treatment interruptions in MANEUVER (34 [54%] of 63 patients; median duration 10 days *vs* 13 days for placebo), pimicotinib dose intensity remained high (median 94·6%) during part 1. Dose interruptions were predominantly due to asymptomatic serum enzyme elevations (a class effect of CSF-1R inhibitors) and managed according to protocol-prespecified criteria.[32,33] Additionally, median duration of exposure was 169 days at the end of part 1. The optimal duration of systemic treatment in TGCT is currently unknown. In MANEUVER, the median duration of response was not reached. The broader question of optimal length of time on systemic treatment, benefit-to-risk trade-off with treatment holidays, and best start and stop times is an ongoing area of research interest in TGCT.

Strengths of MANEUVER include a broad patient population from Asia, Europe, and North America that was generally representative of patients with TGCT. The trial enrolled Chinese and non-Chinese patients with TGCT in balanced proportions,[11] which might make the findings generalisable to geographically diverse populations. Another strength of the study is the comprehensive data collection, with high rates of completion of patient-reported outcomes and patient participation, which strengthen the validity of the clinical outcome assessments and the quality of the trial. Limitations of the study include a slight imbalance in the tumour location (upper and lower limb) between groups: this characteristic was not included in the stratification factors and could not be perfectly controlled in this small study. In addition, the inflammatory nature of TGCT might be a limitation when it comes to accuracy of measurement of tumour response, demonstrating high inter-reader variability. This factor was mitigated by independent central reading, which ensured a consistent approach and, when necessary, adjudication.

In conclusion, the pivotal MANEUVER trial supports the use of pimicotinib as a highly selective, potent, convenient therapeutic option that provides early and robust tumour reduction, with a manageable safety profile, in a diverse population of adult patients with TGCT. Patients who received pimicotinib had early, durable, significant, and clinically meaningful improvements in range of motion, stiffness, pain, and physical function—quality of life domains that are highly relevant for this socially and professionally active population, and particularly to those not amenable to surgery.

Contributors

HX, XN, VR, HG, QZ, BS, and XZhu provided the study concept and design; JM-B, AAR, RS, YZ, JS, TL, KKS, CS, SS, JW, GGB, YF, YH, TL, PR, XZha, and GT accessed, verified, and analysed the data. All authors had access and contributed to the interpretation of the trial data, participated in preparation of the manuscript, and approved the final draft submitted for publication. All authors vouch for the completeness and accuracy of the data, and fidelity of the trial to the protocol and statistical analysis plan.

Declaration of interests

VR received consulting fees and honoraria from EMD Serono. JM-B received grants (paid to his institution) from Abbisko Therapeutics, Biosplice, Boehringer Ingelheim, Bristol-Myers Squibb, Cebiotex, Deciphera, Eli Lilly, Immunome, Inhibrx, Karyopharm, Lixte, Pfizer, PharmaMar, Philogen, PTC Therapeutics, Rain Therapeutics, Springworks Therapy, and Synox; consulting fees from Deciphera and PharmaMar; honoraria from Abbisko Therapeutics, Adium, Bayer, Boehringer Ingelheim, Cogent Bioscience, Deciphera, GSK, PharmaMar, and Roche; travel support from PharmaMar; and is the CEO of Sarcoma Research Solutions. AAR received institutional support from 23andMe, Abbisko Therapeutics, AbbVie, Adaptimmune, Amgen, AstraZeneca, Bayer, BioNTech, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Cogent Biosciences, Daiichi Sankyo, Deciphera, Frontier Biopharma, Gilead, GSK, Intensity Therapeutics, Iterion Therapeutics, Karyopharm, Kelun-Biotech, MedImmune, Medison, Merck, Neoleukin Therapeutics, Novartis, Pfizer, Polaris, Roche/Genentech, Rain Therapeutics, and Symphogen; honoraria from Boehringer Ingelheim and Medison; and participated on a data safety monitoring or advisory board for CD40Life and Inhibrx. CS received honoraria from Deciphera, PharmaMar, and Roche; travel support from Bayer, Gilead, and PharmaMar; was a steering committee member for NewBay; and participated in advisory boards for Deciphera and IDRX. SS received grants (paid to her institution) from Abbisko Therapeutics, Daiichi Sankyo, Deciphera, and SynOx Therapeutics; and participated in advisory boards for Daiichi Sankyo, Deciphera, and Merck Serono. GGB received consulting fees from Eli Lilly and PharmaMar; honoraria from Eli Lilly, GSK, Istituto Gentili, MSD, and PharmaMar; travel support from Eli Lilly, Istituto Gentili, and PharmMar; and participated in advisory

boards for Deciphera, GSK, and MSD. PR received research funding (paid to his institution) from Bristol-Myers Squibb, Novartis, Pfizer, Roche; consulting fees from Bristol-Myers Squibb, Genesis, Medison Pharma, MSD, Novartis, Pierre Fabre, and Philogen; honoraria from Bristol-Myers Squibb, Genesis, Medison Pharma, MSD, Novartis, and Pierre Fabre; participated in speakers bureaus for Bristol-Myers Squibb, Genesis, MSD, Novartis, and Pierre Fabre; and travel support from Pierre Fabre. GT participated in advisory boards for Deciphera and SynOx. All other authors declare no competing interests.

Data sharing

The datasets generated and/or analysed during the MANEUVER study will not be publicly shared due to privacy and confidentiality concerns. Deidentified or aggregated data might be made available from the corresponding author upon reasonable request and subject to applicable ethical and regulatory approvals.

Acknowledgments

We thank the patients who agreed to participate in this trial, as well as their families and carers, and the investigating teams at all participating sites. Abbisko Therapeutics designed and funded the study. Merck holds the rights to commercialise pimicotinib worldwide. Merck (CrossRef Funder ID: 10.13039/100009945) funded the medical writing support for this manuscript; the authors critically revised the manuscript and provided substantive input and ultimate approval. Medical writing support, under the direction of the authors, was provided by Trang H Au and Abigail Bailey of the Publications Division of Omnicom Health Medical Communications (formerly Caudex, an IPG Health Company), in accordance with Good Publication Practice (GPP 2022) guidelines. Editorial note: The Lancet Group takes a neutral position with respect to territorial claims in published text.

References

1 Mastboom MJL, Verspoor FGM, Verschoor AJ, et al, and the TGCT study group. Higher incidence rates than previously known in tenosynovial giant cell tumors. *Acta Orthop* 2017; **88:** 688–94.
2 Tap WD, Healey JH. Role of colony-stimulating factor 1 in the neoplastic process of tenosynovial giant cell tumor. *Tumour Biol* 2022; **44:** 239–48.
3 Stacchiotti S, Dürr HR, Schaefer IM, et al. Best clinical management of tenosynovial giant cell tumour (TGCT): a consensus paper from the community of experts. *Cancer Treat Rev* 2023; **112:** 102491.
4 Stern S, McKenzie PF, Bernthal N, et al. Localized and diffuse tenosynovial giant cell tumor: real-world results from a patient observational registry. *Future Oncol* 2025; **21:** 1501–10.
5 Bernthal NM, Spierenburg G, Healey JH, et al, and the TOPP Study Group. The diffuse-type tenosynovial giant cell tumor (dt-TGCT) patient journey: a prospective multicenter study. *Orphanet J Rare Dis* 2021; **16:** 191.
6 Cook NS, Landskroner K, Shah B, Walda S, Weiss O, Pallapotu V. Identification of patient needs and preferences in pigmented villonodular synovitis (PVNS) using a qualitative online bulletin board study. *Adv Ther* 2020; **37:** 2813–28.
7 Riedel RF, Eward W, Verini C, et al. Improving resources and support for patients with tenosynovial giant cell tumor. New York, NY: CancerCare, 2021.
8 Stamatiou A, Nguyen-Ngoc T, Wetterwald L, et al. Overview of pharmacological therapies for diffuse tenosynovial giant cell tumor. *Future Pharmacol* 2023; **3:** 926–37.
9 US Food and Drug Administration. TURALIO® (pexidartinib). US Prescribing Information. 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/211810s009lbl.pdf (accessed Oct 27, 2025).
10 US Food and Drug Administration. ROMVIMZA™ (vimseltinib). US Prescribing Information, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219304s000lbl.pdf (accessed April 9, 2025).
11 Tap WD, Gelderblom H, Palmerini E, et al, and the ENLIVEN investigators. Pexidartinib versus placebo for advanced tenosynovial giant cell tumour (ENLIVEN): a randomised phase 3 trial. *Lancet* 2019; **394:** 478–87.
12 Gelderblom H, Bhadri V, Stacchiotti S, et al, and the MOTION investigators. Vimseltinib versus placebo for tenosynovial giant cell tumour (MOTION): a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2024; **403:** 2709–19.
13 Dai D, Pan I, Freivogel K, Ye X, Tecson K, Tap W. Patient-reported continued benefits of pexidartinib for tenosynovial giant cell tumor based on a real-world study in the United States. *Oncologist* 2025; **30:** oyaf028.
14 Chen D, Yang XW, Fu J, et al. A disproportionality analysis of adverse events caused by pexidartinib from the FDA adverse event reporting system. *Sci Rep* 2025; **15:** 31689.
15 Wagner AJ, Tap WD, Bauer S, et al. Long-term efficacy and safety of pexidartinib in patients with tenosynovial giant cell tumor: final results of the ENLIVEN study. *Oncologist* 2025; **30:** oyae345.
16 Niu X, Ravi V, Shan B, et al. MANEUVER: a phase III study of pimicotinib to assess efficacy and safety in tenosynovial giant cell tumor patients. *Future Oncol* 2024; published online Sept 17. https://doi.org/10.1080/14796694.2024.2396227.
17 Xu H, Zhou Y, Li B, et al. Updated efficacy and safety profile of pimicotinib (ABSK021) in tenosynovial giant cell tumor (TGCT): 1-year follow-up from Phase 1b. Connective Tissue Oncology Society (CTOS) Annual Meeting. Nov 1–4, 2023 (poster 169).
18 Yang S, Zhao B, Zhang M, et al. Abstract LB-288: a highly selective small molecule CSF-1R inhibitor demonstrates strong immunomodulatory activity in syngeneic models. *Cancer Res* 2018; **78** (suppl 13)**:** LB-288 (abstr).
19 Xu H, Zhou Y, Li B, et al. Efficacy and safety profile of pimicotinib (ABSK021) in tenosynovial giant cell tumor (TGCT): phase 1b update. American Society of Clinical Oncology (ASCO) Annual Meeting. June 2–6, 2023 (poster 493).
20 Xu H, Li Y, Zhou Y, et al. Long-term efficacy and safety profile of pimicotinib (ABSK021) in tenosynovial giant cell tumor: phase 1b update. Connective Tissue Oncology Society (CTOS) Annual Meeting. Nov 13–16, 2024 (poster P407).
21 Gelhorn HL, Ye X, Speck RM, et al. The measurement of physical functioning among patients with Tenosynovial Giant Cell Tumor (TGCT) using the Patient-Reported Outcomes Measurement Information System (PROMIS). *J Patient Rep Outcomes* 2019; **3:** 6.
22 Peterfy C, Chen Y, Countryman P, et al. CSF1 receptor inhibition of tenosynovial giant cell tumor using novel disease-specific MRI measures of tumor burden. *Future Oncol* 2022; **18:** 1449–59.
23 Marcus J, Lasch K, Wan Y, Yang M, Hsu C, Merante D. An assessment of clinically important differences on the worst pain severity item of the modified brief pain inventory in patients with diabetic peripheral neuropathic pain. *Pain Res Manag* 2018; **2018:** 2140420.
24 Gelhorn HL, Tong S, McQuarrie K, et al. Patient-reported symptoms of tenosynovial giant cell tumors. *Clin Ther* 2016; **38:** 778–93.
25 Gelderblom H, Wagner AJ, Tap WD, et al. Long-term outcomes of pexidartinib in tenosynovial giant cell tumors. *Cancer* 2021; **127:** 884–93.
26 Dharmani C, Wang E, Salas M, et al. Turalio risk evaluation and mitigation strategy for treatment of tenosynovial giant cell tumor: framework and experience. *Future Oncol* 2022; **18:** 1595–607.
27 Verspoor FGM, Mastboom MJL, Hannink G, et al. Long-term efficacy of imatinib mesylate in patients with advanced tenosynovial giant cell tumor. *Sci Rep* 2019; **9:** 14551.
28 Gelderblom H, Cropet C, Chevreau C, et al. Nilotinib in locally advanced pigmented villonodular synovitis: a multicentre, open-label, single-arm, phase 2 trial. *Lancet Oncol* 2018; **19:** 639–48.
29 Mastboom MJL, Lips W, van Langevelde K, et al. The effect of imatinib mesylate in diffuse-type tenosynovial giant cell tumours on MR imaging and PET-CT. *Surg Oncol* 2020; **35:** 261–67.
30 Spierenburg G, Grimison P, Chevreau C, et al. Long-term follow-up of nilotinib in patients with advanced tenosynovial giant cell tumours: long-term follow-up of nilotinib in TGCT. *Eur J Cancer* 2022; **173:** 219–28.
31 Palmerini E, Veltkamp S, Gelderblom H, et al. 151TiP TANGENT: a phase III, global, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of emactuzumab with tenosynovial giant cell tumor. *ESMO Open* 2025; **10** (suppl 3)**:** 104464.
32 Radi ZA, Koza-Taylor PH, Bell RR, et al. Increased serum enzyme levels associated with Kupffer cell reduction with no signs of hepatic or skeletal muscle injury. *Am J Pathol* 2011; **179:** 240–47.
33 Wang T, Papoutsi M, Wiesmann M, et al. Investigation of correlation among safety biomarkers in serum, histopathological examination, and toxicogenomics. *Int J Toxicol* 2011; **30:** 300–12.