

Management of Newly Diagnosed Symptomatic Multiple Myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013

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Abstract

Multiple myeloma remains an incurable neoplasm of plasma cells that affects more than 20,000 people annually in the United States. There has been a veritable revolution in this disease during the past decade, with dramatic improvements in our understanding of its pathogenesis, the development of several novel agents, and a concomitant doubling in overall survival. Because multiple myeloma is a complex and wide-ranging disorder, its management must be guided by disease- and patient-related factors; emerging as one of the most influential factors is risk stratification, primarily based on cytogenetic features. A risk-adapted approach provides optimal therapy to patients, ensuring intense therapy for aggressive disease and minimizing toxic effects, providing sufficient but less intense therapy for low-risk disease. This consensus statement reflects recommendations from more than 20 Mayo Clinic myeloma physicians, providing a practical approach for newly diagnosed patients with myeloma who are not enrolled in a clinical trial.

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Multiple myeloma (MM) accounts for approximately 1% of all cancers and 10% of hematologic malignancies.¹ The disease is slightly more common in men and in African Americans. Multiple myeloma is at the end of a spectrum of plasma cell disorders, several of which do not require therapy.² Indeed, monoclonal gammopathy of undetermined significance (MGUS) is a generally benign condition, with a transformation rate to symptomatic plasma cell disorders of approximately 1% to 2% annually, and is common, with an incidence of 5% in individuals older than 70 years.^{3,4} Between MGUS and MM is asymptomatic MM (formerly known as smoldering MM), which represents a progression

from MGUS with a greater burden of plasma cells in the bone marrow (>10%) and a higher annual risk of transformation to MM (10% for the first 5 years with subsequent reduction).^{5,6}

Hallmark features of MM are highlighted by the acronym *CRAB*—Calcium elevation, Renal insufficiency, Anemia, and Bone disease—with these clinical manifestations attributable to the plasma cell clone.⁷ Treatment, although not curative, is intended to control the disease and minimize its end-organ effects. Although the disease remains incurable, with the introduction of autologous stem cell transplant (ASCT) and newer agents, such as thalidomide, bortezomib, lenalidomide, and carfilzomib, median overall survival (OS) has increased

from 2 to 3 years a decade ago to greater than 8 years currently.⁸

These advances are a product of a much better understanding of the disease. This has included features of the clone itself, primarily in genetic and genomic studies, revealing multiple genes involved in the development and proliferation of the malignant plasma cells. This has been matched by an appreciation of the importance of the bone marrow microenvironment and its role in supporting and maintaining the malignancy.⁹⁻¹³

These advances have allowed a stratification of the disease that distinguishes patients who will have an aggressive course from those whose disease will be indolent and slow to relapse.^{14,15} When combined with other factors, such as age, renal insufficiency, comorbid status, and patient preference, risk status is another step toward genuinely individualized therapy for patients with myeloma. This is perhaps more important than previously because with many new therapeutic options available, dangers of overtreatment or undertreatment abound; indeed, not providing sufficient therapy for a high-risk patient can lead to poor outcomes, and giving too many drugs (be it in combination or in sequence) to a patient with indolent disease will likely result in excess short- and long-term toxic effects.

MAYO STRATIFICATION OF MYELOMA AND RISK-ADAPTED THERAPY GUIDELINES

Our group has previously published 2 sets of consensus guidelines for newly diagnosed MM known as the Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) in 2007 and 2009.^{16,17} These guidelines are updated more regularly online (<http://mSMART.org>) and reflect the expert opinion of more than 20 myeloma physicians at Mayo Clinic (Minnesota, Arizona, and Florida). The overall purpose is to guide clinicians in the complex world of myeloma by providing practical, easy-to-follow recommendations for initial therapy, transplant, and maintenance therapy. Major updates included in this review are as follows:

1. Risk stratification into 3 groups: high risk, intermediate risk, and standard risk (previously only high risk and standard risk). This update reflects increasing evidence for the therapeutic advantage of bortezomib for patients with the t(4;14) abnormality.
2. Inclusion of more factors in risk stratification. With enhanced evaluation techniques, we have included gene expression profiling (GEP) as a tool to identify high-risk patients.
3. Greater emphasis on delayed ASCT. With improved induction therapies resulting in deeper responses, coupled with enhanced stem cell collection strategies, many patients are now opting to collect their stem cells but not immediately move on to ASCT. Recent evidence has supported this strategy, demonstrating the ongoing benefit of ASCT even when delayed.
4. Maintenance therapy. Several studies have recently been published evaluating the benefit of maintenance therapy (primarily with lenalidomide but also with bortezomib). Although some have advocated its use universally, we retain a risk-adapted approach that balances its benefit with short- and long-term toxic effects.
5. Extended therapy for high- and intermediate-risk patients. Increasing evidence supports the use of more consolidation therapy in patients in higher-risk categories, and this is reflected in longer periods of recommended treatment in these groups.
6. A description of ongoing trends in MM. The treatment of MM is evolving rapidly, with substantial changes in previously held concepts. We summarize some of the major trends that are affecting the field.

For all stages and phases of MM, we strongly recommend clinical trials as the first option for therapy or supportive care. However, when these are not available or when patients may not be eligible, we recommend the strategy set forth in these guidelines. Our approach remains evidence based. As far as possible, we do not consider data from surrogate end points as “evidence of benefit.” In the absence of clear evidence (OS or validated quality-of-life improvement) favoring one approach over another, we generally prefer the least toxic, least expensive option (keeping in line with the first-do-no-harm principle). Our level of caution is highest in standard-risk patients, who have the most to lose in terms of serious toxic effects or quality of life early in the disease course. The grading strategy for these guidelines is outlined in Table 1.

TABLE 1. Classification System for Levels of Evidence and Grades of Recommendations

Level	Type of evidence
I	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
II	Evidence obtained from ≥ 1 well-designed experimental study. Randomized trials with high false-positive or false-negative errors (low power)
III	Evidence obtained from well-designed, quasi-experimental studies, such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series
IV	Evidence from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
V	Evidence from case reports and clinical examples
Grade	Grade for recommendation
A	There is evidence of type I or consistent findings from multiple studies of type II, III, or IV
B	There is evidence of type II, III, or IV and findings are generally consistent
C	There is evidence of type II, III, or IV but findings are inconsistent
D	There is little or no systematic empirical evidence

DIAGNOSIS AND INITIATION OF THERAPY

We previously reported in detail the indications to treat myeloma.¹⁷ Unlike patients with many other malignancies, many patients with indolent or “asymptomatic” MM do not require immediate therapy. It is generally recommended not to commence therapy until there is evidence of end-organ damage, as manifest in the acronym CRAB.¹⁸ There are a few other contexts in which therapy may be indicated before the development of CRAB:

1. Asymptomatic or smoldering MM with bone marrow plasmacytosis greater than 60%. Although the percentage of plasmacytosis is not generally used as a repeated marker of the disease to guide therapy (except for the rarely present nonsecretory myeloma), increasing evidence suggests that at a critical point it is reasonable to initiate treatment as patients will inevitably develop CRAB.¹⁹ Indeed, it is common to inaccurately predict progression to symptomatic MM, and this may result in the patient experiencing a pathologic fracture or other sentinel event that may have been prevented.
2. Markedly abnormal serum free light chain ratio. In contrast to intact immunoglobulin, light chains have a greater propensity to induce renal dysfunction. As a result, it is incumbent on the treating physician to monitor light chains closely in patients with asymptomatic MM; once the involved/uninvolved free light chain ratio is 100 or more, the risk of progression in the next 2 years approaches 80%, and, hence, initiation of therapy should be considered.²⁰

3. Positron emission tomography (PET) or magnetic resonance imaging (MRI) positivity as evidence of early bony involvement or extramedullary disease. Historically, the plain radiograph approach of skeletal surveys has been used to assess the nature of bone disease in MM. However, this modality may detect only late-stage disease, and newer tools may help determine whether there is early active disease that may warrant therapy.²¹ The most commonly used modalities are MRI and PET. Although it is still not routine for all patients to undergo this testing, in patients in whom it is unclear whether active disease is present, MRI or PET may provide useful information to guide therapy.

RISK STRATIFICATION

It is apparent that MM is a very heterogeneous disease, and treating all patients in the same way is too simplistic. Similar to other lymphoproliferative diseases, such as lymphoma, a stratified approach is appropriate to ensure that patients are given therapy that is likely to optimize outcomes and minimize toxic effects. Although 2 historical staging systems exist for myeloma, the Durie-Salmon system²² and the International Staging System,²³ they are not usually used to determine the need for therapy.

Numerous studies have validated multiple biological factors that influence risk and prognosis in myeloma and that may be used to influence the choice of therapy.²⁴⁻²⁶ These factors may be classified into 3 groups: tumor biology,²⁷⁻⁴¹ tumor burden,^{22,23,42,43} and patient-related factors (Table 2).

These factors must be considered in the choice of therapy in patients with MM. To treat patients effectively, it is recommended that all patients undergo cytogenetic evaluation at diagnosis. Although the most information is gained when both conventional cytogenetic and fluorescence in situ hybridization (FISH) testing are performed, not all centers have access to both. With the additional information gained by FISH, it is the preferred modality if both are not available. The incidences of abnormalities of FISH are listed in Table 3.

Owing to cost and current lack of influence on therapy, gene expression profiling (GEP) is neither routinely performed nor recommended in a nonresearch setting. However, as commercial tests are being developed, GEP will likely play a greater role in the management of MM in the future.

By virtue of our experience at Mayo Clinic, along with published results, we have combined these prognostic factors into a risk-adapted approach to patients with myeloma. It is apparent that some patients have an aggressive course with brief periods of disease-free status between therapies, whereas others have a much more indolent course. We termed these categories *high risk* and *standard risk*, respectively. In addition, approximately 10% to 15% of patients carry the t(4;14) abnormality (associated with fibroblast growth factor receptor 3 expression) and have an *intermediate risk* status and tend to be more responsive to bortezomib-based therapy. As a result, these updated mSMART guidelines include these 3 risk categories (Table 4).

It is recognized that many patients and treating physicians will not have access to the plasma cell labeling index or GEP. Although included in mSMART if the data are available, they are not routinely recommended.

Further rationale for a risk-adapted approach is reflected in the differing outcomes in patients in all 3 risk groups (Table 5). Indeed, median OS is different in each group when measured during the past decade in multiple centers. High-risk patients in several contemporaneous studies have median OS of only 3 years, whereas intermediate- and standard-risk patients have OS of 4 to 5 years and 8 to 10 years, respectively.^{41,44-49}

Accordingly, risk stratification has more than academic or prognostic value but differentiates

TABLE 2. Prognostic Factors in Myeloma

Tumor biology factors
Ploidy status
17p- (p53 deletion)
t(14;16)
t(14;20)
t(4;14)
Deletion 13 on conventional cytogenetic testing
Alterations in chromosome 1
t(11;14)
t(6;14)
Lactate dehydrogenase
Plasma cell proliferative rate
Presentation as plasma cell leukemia
High-risk signature in gene expression profiling
Tumor burden factors
Durie-Salmon stage
International Staging System stage
Extramedullary disease
Patient-related factors
Eastern Cooperative Oncology Group performance status
Age
Renal function

TABLE 3. Distribution of Various Abnormalities of FISH Testing and Number of Patients With Overlapping Trisomies

FISH abnormality	Frequency, No. (%)
Trisomies without IgH abnormality	42
IgH abnormality without trisomies	30
t(11;14)	15
t(4;14)	6
t(14;16)	4
t(14;20)	<1
Unknown partner/deletion of IgH region	5
IgH abnormality with trisomies	15
t(11;14)	3
t(4;14)	4
t(14;16)	1
t(6;14)	<1
Unknown partner/deletion of IgH region	7
Monosomy 14 in absence of IgH translocations or trisomy(ies)	4.5
Other cytogenetic abnormalities in absence of IgH translocations or trisomy(ies) or monosomy 14	5.5
Normal	3

FISH = fluorescence in situ hybridization.
Adapted from Kumar,⁴¹ © The American Society of Hematology.

treatment options. In general, more aggressive and continuous therapies will characterize the approach to high-risk patients. It is well-known that these patients will have limited progression-free survival (PFS) if left untreated, and, therefore, we recommend more

TABLE 4. Risk Stratification of Active Multiple Myeloma

High risk	Intermediate risk	Standard risk
FISH Del 17p t(14;16) t(14;20) GEP High risk signature	FISH t(4;14) Cytogenetic del 13 Hypodiploidy PCLI $\geq 3\%$	All others including: FISH t(11;14) t(6;14)

FISH = fluorescence in situ hybridization; GEP = gene expression profiling; PCLI = plasma cell labeling index.

TABLE 5. Incidence and Median Overall Survival by Risk Group

Factor	High risk	Intermediate risk	Standard risk
Incidence (%)	20	20	60
Median overall survival (y)	3	4-5	8-10

continuous therapy approaches. In contrast, standard-risk patients may often have an indolent course and may benefit from the limited toxic effects of being without therapy for periods between treatments. Intermediate-risk patients will benefit from bortezomib-based strategies, which should, therefore, be included in the treatment of these patients. It is too early to know whether this benefit will be seen with other proteasome inhibitors, but it is possible that the newly approved carfilzomib could also be used in this strategy.

Although these factors will “predict” a patient’s risk status and are clear justification to guide therapy, there are some patients in whom their true risk status will not be captured using these tests. Although this review does not discuss relapsed therapy (this is updated at <http://mSMART.org>), patients may later acquire high-risk features or simply behave in a high-risk manner with multiple rapid relapses.

Recommendation: All patients should undergo risk stratification to classify them into standard-, intermediate-, and high-risk groups.

Level of evidence: II

Grade: A

INITIAL THERAPY

Choosing the optimal initial therapy in MM remains a challenge. There are currently at least 5 classes of active agents available for the treatment of myeloma: alkylating agents (melphalan and cyclophosphamide), anthracyclines (adriamycin and liposomal doxorubicin), corticosteroids (dexamethasone and

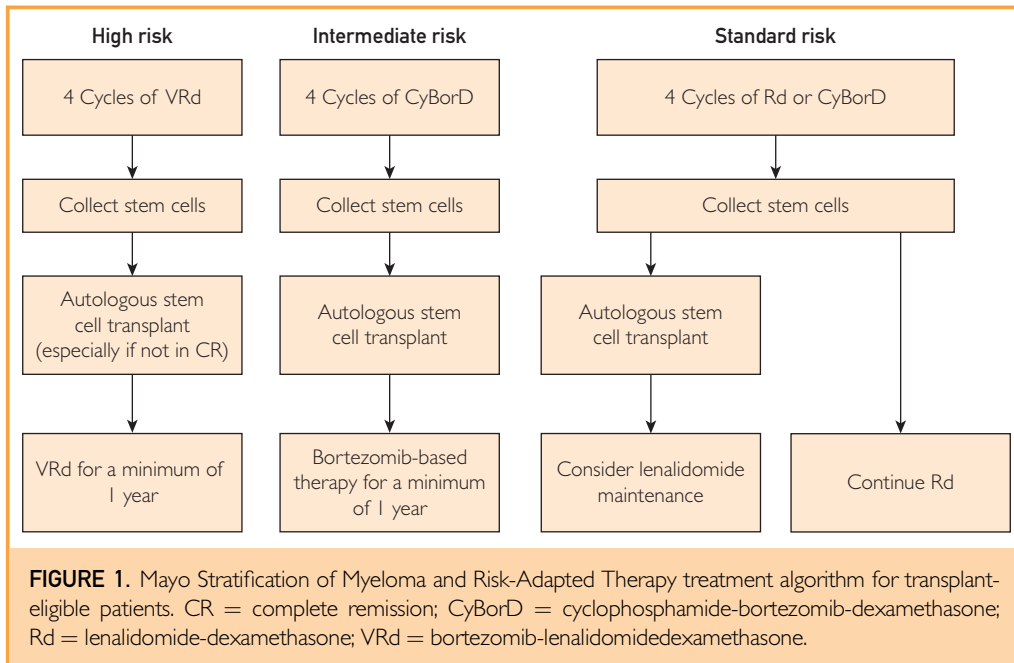
prednisone), immunomodulatory drugs (thalidomide and lenalidomide), and proteasome inhibitors (bortezomib and carfilzomib).

Other less commonly used agents include platinum, vincristine, and etoposide, which are generally used in aggressive combinations, such as DT-PACE (dexamethasone, thalidomide, platinum, adriamycin, cyclophosphamide, etoposide). This now translates to more than 10 agents available to treat MM and the possibility of dozens of combinations. However, few randomized phase 3 trials can genuinely guide the clinician, and even those available mostly report only response rates (RRs) and PFS, not OS. The choice of therapy, therefore, is very much guided by the availability of agents, the comfort of the treating provider, and consensus among experts. These factors are then considered in the context of each individual patient, their age, and their comorbidities. We herein recommend that risk stratification can provide the framework to facilitate the optimal therapy for patients to yield the best long-term outcomes. The following recommendations are summarized in Figures 1 and 2.

TRANSPLANT-ELIGIBLE PATIENTS

High-dose chemotherapy with autologous stem cell support remains the standard of care in eligible patients based on a series of randomized trials that found improved PFS and OS.⁵⁰⁻⁵⁶ However, this recommendation is now being challenged with novel therapies that have significantly improved the depth and duration of response in initial therapy of MM. However, until it is proved that strategies excluding ASCT are superior, it is likely that ASCT will remain the mainstay of therapy for eligible patients with MM. We, therefore, continue to divide patients into transplant eligible and ineligible. Our general approach is to consider patients with a physiologic age of 70 years or younger for ASCT.

Patients who undergo ASCT generally receive 4 cycles of therapy; although the intent is usually to have achieved at least a partial response (PR) before high-dose therapy, this is not always necessary. We routinely do not change initial therapies unless there is genuine progressive disease or the therapy is not tolerated by the patient. Most patients then immediately go on to ASCT. Some patients, however, prefer to have their stem cells collected



and to delay ASCT while continuing prolonged induction therapy. This strategy has not recently been evaluated prospectively, but it remains an option for patients as delayed ASCT is feasible.⁵⁷

Most current strategies for initial therapy have been with 2 or 3 drug regimens. Most of them will combine at least 1 “novel” agent, including thalidomide, bortezomib, or lenalidomide. Three large (>400 patients each) recently published phase 3 trials (Table 6) that have heavily influenced up-front strategies include the following:

1. Lenalidomide—low-dose dexamethasone vs lenalidomide—high-dose dexamethasone.⁵⁸

This study was particularly remarkable not only in validating the use of lenalidomide in the frontline setting but also in setting a new standard for weekly low-dose dexamethasone therapy; it has also facilitated the use of delayed ASCT. The overall RR was 70% to 81%, with 3-year OS of 74% to 75%, and 80% of patients who underwent transplant were alive at 5 years.⁵⁸ Because transplant was not part of this trial, there was no plan for whether 1 or 2 ASCTs were to be performed and whether posttransplant maintenance therapy would be administered.

2. Vincristine-adriamycin-dexamethasone vs bortezomib-dexamethasone.⁵⁹ This was a

critical study in the up-front use of bortezomib and contributed to the “death” of vincristine-adriamycin-dexamethasone as a standard of care in transplant-eligible patients. The overall RR was 79% in bortezomib-dexamethasone, with 3-year OS of 81%. Transplant was also not part of this trial, although many patients were eventually enrolled in the Intergroupe Francophone du Myelome maintenance trial of lenalidomide vs placebo.

3. Thalidomide-dexamethasone vs bortezomib-thalidomide-dexamethasone.⁶⁰ This was one of the first trials to combine both classes of

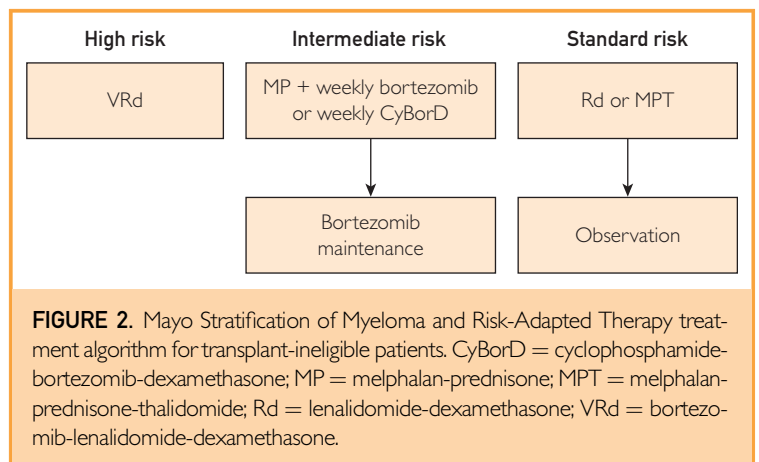


TABLE 6. Phase 3 Trials in Newly Diagnosed Myeloma

Reference, year	Regimen	No. of patients	Overall response rate (%)	CR plus VGPR (%)	PFS (mo), median	P value for PFS	3-y OS (%)	OS (mo), median	P value for OS
Rajkumar et al, ⁵⁸ 2010	RD	223	81	50	19.1	.026	75	NR	.47
	Rd	222	70	40	25.3		74	NR	
Harousseau et al, ⁵⁹ 2010	VAD	242	63	15	30	.06	77	NR	.46
	VD	240	79	38	36		81	NR	
Cavo et al, ⁶⁰ 2010	TD	238	79	28	40	.006	84	NR	.3
	VTD	236	93	62	NR		86	NR	

CR = complete response; NR = not reported; OS = overall survival; PFS = progression-free survival; Rd = lenalidomide–low-dose dexamethasone; RD = lenalidomide–high-dose dexamethasone; TD = thalidomide-dexamethasone; VAD = vincristine-adriamycin-dexamethasone; VD = bortezomib-dexamethasone; VGPR = very good partial response; VTD = bortezomib-thalidomide-dexamethasone.

novel agents, and despite great concerns about combining 2 agents with known potential for neuropathy, the combination was well tolerated. The overall RR was 79% for thalidomide-dexamethasone and 93% for bortezomib-thalidomide-dexamethasone, but with similar 3-year OS of 84% (thalidomide-dexamethasone) and 86% (bortezomib-thalidomide-dexamethasone). This trial included double transplant, followed by two 35-day cycles of their assigned regimen (bortezomib-thalidomide-dexamethasone or thalidomide-dexamethasone) as consolidation therapy. All the patients were subsequently maintained on dexamethasone, 40 mg on days 1 to 4 every 28 days.

A more recent trial by Moreau et al⁶¹ evaluated bortezomib-dexamethasone vs bortezomib-thalidomide-dexamethasone; the overall RR after 2 cycles favored bortezomib-thalidomide-dexamethasone (90% vs 77%), but PFS and OS rates are similar with less than 3 years of follow-up.

These trials provided a basis for using these combinations as frontline therapy and, indeed, the most commonly used regimens currently in the United States include bortezomib-dexamethasone and lenalidomide-dexamethasone. However, several other phase 2 trials have followed that have sought to improve outcomes with these agents and have further enhanced frontline options.

1. Cyclophosphamide-bortezomib-dexamethasone.⁶² Seeking to enhance the activity of bortezomib-dexamethasone by adding weekly oral cyclophosphamide, cyclophosphamide-bortezomib-dexamethasone use resulted in improved RRs. The conversion to weekly bortezomib therapy produced similar RRs, was more convenient, and resulted in fewer

toxic effects. Furthermore, it did not prevent the collection of stem cells for transplant. This combination has the added advantage of being less costly than bortezomib-thalidomide-dexamethasone or bortezomib-lenalidomide-dexamethasone and allows for the use of immunomodulatory drug (IMiD) therapy later in the disease course. Importantly, this trial was followed up by the EVOLUTION study,⁶³ which compared the addition of cyclophosphamide, lenalidomide, and cyclophosphamide plus lenalidomide to bortezomib-dexamethasone in a randomized trial (cyclophosphamide-bortezomib-dexamethasone vs bortezomib-lenalidomide-dexamethasone vs bortezomib-cyclophosphamide-lenalidomide-dexamethasone). Response rates were similar in all 3 arms; based on response, toxicity, and cost, therefore, cyclophosphamide-bortezomib-dexamethasone remains a very effective choice before ASCT.

2. Bortezomib-lenalidomide-dexamethasone.⁶⁴ A rational approach was to combine the 2 most active agents in MM with the addition of dexamethasone based on studies in the relapsed setting. An ongoing Southwest Oncology Group trial is evaluating this strategy in a large study cohort, but only preliminary results are currently available. Furthermore, a large phase 3 international trial evaluating the use of bortezomib-lenalidomide-dexamethasone alone vs early ASCT is ongoing.

As a result of these trials and clinical experience, many patients are now being treated with 3-drug regimens, often with cyclophosphamide-bortezomib-dexamethasone, bortezomib-thalidomide-dexamethasone, or bortezomib-lenalidomide-dexamethasone. Of these, bortezomib-thalidomide-dexamethasone has so

far not shown a survival benefit in phase 3 trials compared with either bortezomib-dexamethasone or thalidomide-dexamethasone. There are no phase 3 data with bortezomib-lenalidomide-dexamethasone. Bortezomib-lenalidomide-dexamethasone and bortezomib-thalidomide-dexamethasone contain both a proteasome inhibitor and an IMiD and are, therefore, significantly more expensive than cyclophosphamide-bortezomib-dexamethasone and carry the risk of more toxicity. There is also a concern that the use of bortezomib-lenalidomide-dexamethasone or bortezomib-thalidomide-dexamethasone may limit further options later in the disease course. Although cyclophosphamide-bortezomib-dexamethasone also lacks phase 3 data, in the EVOLUTION study there was no difference compared with bortezomib-lenalidomide-dexamethasone.⁶³ Moreover, in our opinion, cyclophosphamide-bortezomib-dexamethasone is a minor modification of the well-studied bortezomib-melphalan-prednisone regimen, in which cyclophosphamide is substituted for the more toxic melphalan. These considerations were taken into account when deciding on the risk-adapted approach outlined later herein. Our goal is to allow clinicians and patients to select the regimen best suited for their MM.

Standard Risk

As standard-risk patients tend to have a more indolent course, a “sequential” approach to their disease is more appropriate. This will reduce the toxic effects of certain combinations and even allow for treatment-free periods. We, therefore, recommend that patients be treated with either a lenalidomide- or bortezomib-based approach but that combining lenalidomide and bortezomib is not justified. Lenalidomide—low-dose dexamethasone is preferred when using lenalidomide, and cyclophosphamide-bortezomib-dexamethasone in a weekly regimen is preferred when using bortezomib. A weekly approach has been shown to be as efficacious as a twice-weekly approach but with reduced neuropathy and increased convenience.⁶⁵ The suggested dosing strategy consists of cyclophosphamide, 300 mg/m² orally; bortezomib, 1.5 mg/m² intravenously or subcutaneously; and dexamethasone, 40 mg orally.

Both strategies have excellent RRs, are well tolerated, and can be used in advance of stem cell collection. The selection of either regimen

depends on factors such as renal insufficiency (cyclophosphamide-bortezomib-dexamethasone is preferred at present until lenalidomide dosing is clarified), patient convenience (oral lenalidomide requires less frequent physician visits), and financial considerations. Indeed, in a comparison of 3 strategies at Mayo Clinic (lenalidomide-dexamethasone, cyclophosphamide-lenalidomide-dexamethasone, and cyclophosphamide-bortezomib-dexamethasone), cyclophosphamide-bortezomib-dexamethasone demonstrated superior RRs but more neuropathy; 80% of patients in all 3 groups were alive at 4 years.⁶⁶

Recommendation: Patients with standard-risk MM eligible for transplant should undergo induction therapy with lenalidomide—low-dose dexamethasone or cyclophosphamide-bortezomib-dexamethasone followed by ASCT.

Level of evidence: I-III

Grade: A

We recommend approximately 4 cycles of therapy followed by ASCT, assuming there has been a response to therapy, usually defined by at least a minor response, although most often a PR is achieved. If the patient is being treated with lenalidomide—low-dose dexamethasone, he or she may opt to delay transplant as discussed previously herein, but stem cell collection should be performed before prolonged exposure to lenalidomide (preferably ≤ 4 cycles).

Recommendation: Patients treated with lenalidomide—low-dose dexamethasone with at least a PR may have stem cells collected but delay ASCT.

Level of evidence: III

Grade: B

Intermediate Risk

One of the most common cytogenetic abnormalities in MM is t(4;14). Historically considered a high-risk feature, we now consider it intermediate risk by virtue of the longer-term outcomes of patients treated with modern agents. Similarly, deletion 13 has long been considered an adverse prognostic marker. When detected on conventional cytogenetic studies, it does, indeed, portend a poorer prognosis, but if seen on FISH, in the absence of hypodiploidy, it does not retain its significance.⁶⁷ Much work has been done to understand the significance of these cytogenetic findings, including discovery of

the *FGFR3* gene and its role in the cell cycle.⁶⁸ Importantly, repeated studies have found that this adverse marker may be mostly overcome with the use of bortezomib.⁶⁹⁻⁷¹ We, therefore, suggest a strategy that includes bortezomib in induction therapy, preferably cyclophosphamide-bortezomib-dexamethasone, followed by ASCT. As discussed later herein, owing to the known shortened PFS after ASCT,⁷² we recommend consolidation/maintenance therapy for a minimum of 1 year after ASCT.

Recommendation: In intermediate-risk patients, use a bortezomib-based regimen as induction therapy before ASCT.

Level of evidence: II

Grade: B

Recommendation: In intermediate-risk patients, use a bortezomib-based therapy for 1 year after ASCT.

Level of evidence: III

Grade: B

High Risk

Nearly 20% of patients with MM have high-risk disease as defined in Table 4. These patients have characteristically followed 2 major patterns: poorly responsive or resistant disease at first therapy or, in contrast, very responsive disease initially but with a very short disease-free period before relapse. Furthermore, these patients often have remitting, aggressive relapses with rapidly growing disease and features such as extramedullary disease and plasma cell leukemia. It is apparent, therefore, that a more aggressive approach to therapy, including more chemotherapy and for longer periods, is indicated in this group, with the intent of prolonging survival and enhancing quality of life. As a result, we recommend the combination of an IMiD and a proteasome inhibitor as initial therapy with bortezomib-lenalidomide-dexamethasone, followed by consolidation with ASCT, especially when a patient has not achieved a deep response with induction therapy. This method will also initially spare the patient exposure to the toxic effects of more traditional combination chemotherapy.

Recommendation: In high-risk patients, use bortezomib-lenalidomide-dexamethasone as induction therapy before ASCT.

Level of evidence: II

Grade: B/C

Owing to the known shortened PFS after transplant in patients with high-risk disease, we recommend the use of maintenance therapy. Furthermore, relapse may be rapid, hard to predict, and difficult to control if not treated immediately. Increasing evidence exists for bortezomib and lenalidomide in this population. When bortezomib was added to long-term therapy in patients with high-risk MM by virtue of the p53 deletion, PFS and OS rates were improved.⁷³ This has been the only study specifically reporting OS improvement in high-risk patients with a maintenance strategy. Furthermore, in the recently published trials of lenalidomide maintenance therapy reporting prolonged PFS^{74,75} and OS,⁷⁵ there seemed to be no less improvement in patients with high-risk disease. Indeed, in the Intergroupe Francophone du Myelome study, all the patients were given lenalidomide consolidation; perhaps this may have been a contributing factor to the lack of OS advantage, raising the question that perhaps enhanced consolidation therapy can be an option as opposed to prolonged maintenance therapy. This may also reduce the long-term toxic effects of long-term lenalidomide use. We, therefore, recommend that in this highest-risk population, the agents be combined as consolidation and longer-term therapy. With shortened OS in this group, the cost and risks of continuous therapy are likely outweighed by the PFS and OS benefits.

Recommendation: In high-risk patients, continue bortezomib-lenalidomide-dexamethasone maintenance therapy for a minimum of 1 year after ASCT.

Level of evidence: III

Grade: B

Important Trends in Transplant-Eligible Patients

In addition to the trials noted previously herein, certain trends are apparent in the care of MM that may influence therapeutic selection:

1. A CR is not necessarily the primary goal. It is generally accepted that depth of response is important and may generally predict duration of response. However, as noted previously herein, in higher-risk patients in particular, achievement of a CR is not sufficient. Indeed, the Arkansas experience has found that a shortened CR duration due to relapse may be one of the strongest prognostic factors for

poor long-term outcomes. Remember that response is as much a function of disease biology as it is a function of selected treatment and that patients who have a bad-prognosis disease and achieve a CR continue to relapse quickly and do not fare well.⁷⁶

2. Increasing use of consolidation strategies. With the introduction of less toxic and more convenient agents in MM, the total volume of therapy delivered to patients in general has increased. This has taken the form of longer induction, more consolidation, and prolonged maintenance therapy. As noted previously herein, with some of the toxicity concerns related to indefinite maintenance therapy, more attention has to be given to increasing consolidation therapy. Its exact effect on long-term outcomes and standard of care is not yet known.
3. Limited use of allogeneic stem cell transplant. Despite the reduction in treatment-related mortality with this modality, short- and long-term risks remain significant, and outcomes remain disappointing. With enhanced and increased numbers of novel agents available, allogeneic stem cell transplant will likely play a small role in myeloma therapy, likely only for younger patients who have high-risk disease and demonstrate rapidly relapsing disease. We do not routinely recommend allogeneic stem cell transplant in patients with MM unless they meet the previous criteria.
4. The role of ASCT in all eligible patients. Although ASCT remains the standard of care in MM, as noted previously herein, this has been questioned in light of newer, less toxic, and possibly less costly therapies with novel agents such as thalidomide, bortezomib, lenalidomide, and carfilzomib. A prospective, randomized, international trial is seeking to answer this question, comparing prolonged bortezomib-lenalidomide-dexamethasone therapy with ASCT. Until there is clear evidence to change practice, we continue to recommend ASCT.

MAINTENANCE THERAPY

Maintenance therapy is perhaps the most controversial topic in the care of patients with MM. Historically, this has been attempted with corticosteroids, interferon, and thalidomide.

The PFS, but not OS, was often prolonged and was frequently accompanied by significant morbidity and high discontinuation rates.⁷⁷⁻⁷⁹

The recently published Medical Research Council study reported differences in patients with favorable (prolonged PFS but not OS) and unfavorable (no prolongation of PFS and worse OS) cytogenetic characteristics.⁸⁰ A meta-analysis performed with this study reported a potential late OS benefit, but this has not been adopted into practice owing to toxic effects and the marginal benefit.

With the use of lenalidomide as a more tolerable IMiD, maintenance therapy with lenalidomide has been explored extensively. Three important studies evaluating the role of maintenance therapy were recently published.^{74,75,81}

Two studies evaluated the role of maintenance lenalidomide therapy in patients after ASCT compared with placebo, and the third evaluated extended-use lenalidomide in older patients initially treated with melphalan-based regimens. The 2 ASCT studies found, as expected, prolonged PFS after ASCT of approximately 20 months in favor of lenalidomide over placebo. The French trial, which provided 2 months of consolidation lenalidomide for all patients before randomization to receive lenalidomide vs placebo, did not report an OS advantage, but a modest OS rate was seen in the US trial. This has led to more widespread use of maintenance therapy, including a National Comprehensive Cancer Network recommendation for its use in certain patients after ASCT.⁸²

However, caution must be exerted in light of several considerations:

1. Increased risk of secondary primary malignancies (SPMs). Both posttransplant studies report an increased risk of SPMs in patients treated with lenalidomide. This is not an unknown phenomenon in MM, as it has been reported previously with thalidomide and after ASCT. Although the absolute risk remains low, SPMs remain a concern and should be considered when selecting maintenance therapy.
2. Patients who were not responding to lenalidomide therapy, or those who had not at least achieved stable disease after ASCT, would not have been eligible for the trial. There are few data on these patients regarding maintenance therapy.

3. Other toxic effects may be apparent, although lenalidomide is generally well tolerated and its use led to only a 16% discontinuation rate; myelosuppression, fatigue, and chronic diarrhea may occur with prolonged use.
4. Attention to cost will inevitably be a greater consideration in cancer care in the years to come. This is a rather expensive strategy, and the cost to the patient and the health care system should be considered.
5. Patients may have been undertreated in the placebo arm in the US study.⁷⁵ When there was a recommended unblinding and crossover at a median of 18 months of follow-up, patients were administered the maintenance dose of lenalidomide, which is half the normal dose. The fact that this dose did not maintain the status of these patients who were getting close to relapse (median time to relapse after ASCT is 18-22 months) would not be surprising.
6. Prolonged PFS is seen in many patients with MM; 50% of patients with myeloma stay free of progression for up to 2 years or more. Paradoxically, many of these patients have not even achieved a complete response (CR), albeit often a very good PR, and they may have been "restored to an MGUS state."⁸³ These patients may benefit most from a "watch-and-wait" strategy, with institution of therapy at the time of relapse, with a preserved quality of life without therapy.

With these and other caveats (such as selecting for a more resistant disease by prolonged exposure) in mind, we recommend that maintenance therapy be discussed as an option in standard-risk patients but not mandated for all. Future studies may further elucidate which groups may and may not benefit from lenalidomide maintenance therapy. Furthermore, with the risks of SPMs, it has been generally recommended that maintenance therapy be discontinued at 2 years.⁸⁴

Many studies are now evaluating the potential role of bortezomib maintenance therapy in patients after ASCT.⁸⁵ Early data seem to show some benefit, but it is too early to conclude whether bortezomib has a definitive role in standard-risk patients, and, therefore, it cannot yet be routinely recommended.

Although thalidomide maintenance therapy clearly results in worsening quality-of-life

variables, little work has been completed on the impact of lenalidomide and bortezomib on a patient's quality of life, but this kind of evaluation is more commonly being included in prospective clinical trials.

Recommendation: Consider lenalidomide maintenance therapy in patients after ASCT for a maximum of 2 years.

Level of evidence: I

Grade: A

TRANSPLANT-INELIGIBLE PATIENTS

Most patients older than 70 years or with significant comorbid illness will not be treated with high-dose therapy and stem cell support. Historically, patients in this category were treated for up to 1 year with melphalan-prednisone, with only a very small proportion achieving a CR or a prolonged disease-free state. With the introduction of new therapies, however, each has been sequentially added to melphalan-prednisone with increasing benefit:

1. Melphalan-prednisone-thalidomide. Six randomized trials have now compared melphalan-prednisone-thalidomide with melphalan-prednisone.⁸⁶⁻⁹¹ All the trials reported improved RRs, 4 found prolongation of PFS, and there was an OS advantage in 2. These trials have been summarized in 2 meta-analyses, both concluding the superiority of melphalan-prednisone-thalidomide over melphalan-prednisone.^{92,93} However, there are increased toxic effects with this regimen, especially in elderly patients, as evidenced by grade 3 or 4 adverse events occurring in 55% of patients compared with 22% with melphalan-prednisone. Despite these caveats, and with careful attention to adverse effects, melphalan-prednisone-thalidomide can be delivered to most transplant-ineligible patients and has become an international standard of care.
2. Melphalan-prednisone-bortezomib. A large phase 3 trial evaluated the efficacy of melphalan-prednisone-bortezomib over melphalan-prednisone and found an OS advantage in favor of the former.⁷⁰ This has also become an international standard of care, although less so in the United States, partly owing to a trend toward reduced use of melphalan in upfront therapy, resulting

- in greater use of bortezomib and corticosteroids, often in a weekly manner.
3. Bortezomib-thalidomide-prednisone. Compared with bortezomib-melphalan-prednisone, this regimen surprisingly did not show an advantage in RRs or outcomes.⁷¹ This combination may be more difficult to tolerate in the elderly, yet using a similar strategy of replacing prednisone with dexamethasone (bortezomib-thalidomide-dexamethasone) is highly effective in younger patients.⁹⁴ Neither regimen is recommended by our group as primary therapy except perhaps in the case of a presentation with renal failure.
 4. Melphalan-prednisone-lenalidomide. A recent 3-armed randomized trial of melphalan-prednisone vs melphalan-prednisone-lenalidomide vs melphalan-prednisone-lenalidomide with prolonged lenalidomide was conducted.⁸¹ There was no advantage to melphalan-prednisone-lenalidomide over melphalan-prednisone, with PFS of 14 and 13 months, respectively. This finding may be due to the dose reductions required with competing toxic effects, namely, myelosuppression, that lead to subtherapeutic dosing. However, there was prolonged PFS in patients in the melphalan-prednisone-lenalidomide with prolonged lenalidomide arm (23 months), suggesting that longer-term therapy with lenalidomide in elderly patients is feasible and effective.
 5. Lenalidomide—low-dose dexamethasone. As discussed in the transplant-eligible section, this is a commonly used, highly effective, and minimally toxic regimen as induction before ASCT; it has also been repeatedly validated in relapsed MM.^{95,96} It has now become more used in the elderly population as initial therapy also. An analysis of lenalidomide—low-dose dexamethasone vs lenalidomide—high-dose dexamethasone in patients older than 65 years validated its safety and efficacy, confirming its use in each age group.⁹⁷ A randomized trial of melphalan-prednisone-thalidomide vs lenalidomide—low-dose dexamethasone has been completed, but the results are pending.

As with transplant-eligible patients, our recommendations later herein are based on careful evaluation of the available data. In this patient population, one factor we took into account

was that in the United States (and many other countries), the upper age limit for transplant is flexible, often up to age 73 to 75 years. Thus, the type of patients studied in the melphalan-prednisone-bortezomib and melphalan-prednisone-thalidomide trials is not representative of the type of nontransplant patients seen in the United States. Second, when choosing a triple drug regimen, we are faced with having to choose between melphalan-prednisone-thalidomide and melphalan-prednisone-bortezomib for a given patient. In this regard, we considered the maturity of the data for melphalan-prednisone-thalidomide (6 randomized trials, including 3 reporting survival benefit, and 2 meta-analyses), and the data available in one of the trials were restricted to patients 75 years and older.^{92,93} Finally, for standard-risk elderly patients, we also factored in the convenience of oral administration and the safety of 2-drug combinations.

Standard Risk

Standard-risk patients represent most patients with MM, and selecting the appropriate therapy is critical. Owing to the risk of adverse events in elderly patients, combined with the prolonged survival now seen with newer therapies, balancing efficacy and toxicity is particularly important in this group. As with transplant-eligible standard-risk patients, we recommend a sequential approach, using sufficient therapy initially but recognizing that other options will be available later in the disease course. We, therefore, recommend lenalidomide—low-dose dexamethasone as the preferred treatment combination owing to its tolerability and efficacy in this population. If the regimen is tolerated well, it can be continued beyond a year, with either dose reduction or elimination of the dexamethasone. Extended use of lower-dose lenalidomide has been prospectively successful in the melphalan-prednisone-lenalidomide with prolonged lenalidomide strategy. However, awareness of and monitoring for SPMs is recommended.

The other recommended combination in this group is melphalan-prednisone-thalidomide. Neuropathy remains a concern but has been somewhat decreased with lower dosing of thalidomide to 100 mg daily. Thalidomide is also associated with thrombosis (as are the other IMiDs lenalidomide and pomalidomide). The risk of deep venous thrombosis (20% without prophylaxis) can be reduced with thromboprophylaxis,

usually with aspirin or full anticoagulation in higher-risk patients.

The exception to the previously mentioned recommendation is in patients with renal insufficiency, in whom bortezomib-containing regimens are recommended. The dosing of lenalidomide in patients with renal insufficiency remains unclear and may soon be available through the PrECOG prospective phase 1/2 trial. Although dose reductions are not necessary with thalidomide, the combination of melphalan-prednisone-thalidomide may be more difficult to tolerate in patients with renal insufficiency. However, bortezomib has proved its safety and efficacy in this population, including in patients undergoing dialysis.^{98,99}

Recommendation: In standard-risk patients ineligible for transplant, use lenalidomide—low-dose dexamethasone continuously as initial therapy.

Level of evidence: II

Grade: A

Recommendation: In standard-risk patients ineligible for transplant, use melphalan-prednisone-thalidomide as initial therapy for 1 year.

Level of evidence: I

Grade: A

Recommendation: In standard-risk patients ineligible for transplant with renal insufficiency, use a bortezomib-containing regimen as initial therapy.

Level of evidence: I

Grade: B

Intermediate Risk

As with transplant-eligible patients, the adverse prognostic markers of t(4;14) and hypodiploidy may be somewhat overcome with the use of bortezomib-containing regimens. We recommend, therefore, that bortezomib be used in this population in a combination that will reduce the risk of neuropathy, especially because we recommend extended use. The 2 most commonly used and validated regimens are melphalan-prednisone-bortezomib⁷⁰ and weekly cyclophosphamide-bortezomib-dexamethasone.⁶² The latter has the added feature of a less myelosuppressive alkylating agent that is well tolerated, especially when given orally.¹⁰⁰ We recommend weekly bortezomib use for both regimens owing to reduced neuropathy and increased convenience.

We also recommend that bortezomib maintenance therapy be continued indefinitely owing to the risk of shortened PFS. The exact strategy is not known, but continuing bortezomib use weekly or every other week has been feasible.⁸⁵

Recommendation: In intermediate-risk patients ineligible for transplant, treat with melphalan-prednisone-bortezomib as initial therapy.

Level of evidence: I

Grade: A

Recommendation: In intermediate-risk patients ineligible for transplant, treat with cyclophosphamide-bortezomib-dexamethasone as initial therapy.

Level of evidence: II

Grade: B

Recommendation: In intermediate-risk patients ineligible for transplant, treat with bortezomib as maintenance therapy.

Level of evidence: III

Grade: B

High Risk

This may be the most difficult group of patients with MM to treat by virtue of their aggressive disease and the proven limitations of combination therapies. However, we have seen an improvement in OS in patients in this group owing to continuous combination therapy. In the absence of long-term prospectively validated regimens, we recommend the most aggressive but feasible regimen of bortezomib-lenalidomide-dexamethasone. We recommend beginning at full-dose therapy, with dose modifications and reductions based on tolerability and the achievement of a CR. However, we recommend long-term indefinite therapy with this combination owing to known shortened PFS when any regimen is discontinued and patients are off all therapy.⁴⁴

Recommendation: In high-risk patients ineligible for transplant, treat initially with bortezomib-lenalidomide-dexamethasone until progression.

Level of evidence: III

Grade: B

Important Trends in Transplant-Ineligible Patients

1. Reduced use of melphalan as frontline therapy. With the prolongation of OS in MM, a

longer-term strategy must be used when treating patients. When limited options such as melphalan-prednisone existed, it was standard to use melphalan-prednisone initially, despite its known risk of leukemogenicity and myelosuppression. With several options available with increased efficacy and reduced toxicity, it is likely that fewer regimens will use melphalan early in the treatment course of MM.

2. Weekly instead of twice weekly bortezomib use. Several studies have now used this strategy to reduce neuropathy and retain efficacy.^{65,101} Indeed, in the Italian study using bortezomib-melphalan-prednisone vs bortezomib-melphalan-prednisone-thalidomide, the weekly regimen was as effective, resulted in similar dose delivery, but had significantly reduced neuropathy.¹⁰²
3. Subcutaneous vs intravenous delivery of bortezomib. A prospective trial of subcutaneous vs intravenous bortezomib administration reported similar efficacy but reduced neuropathy and thrombocytopenia when given subcutaneously.¹⁰³ This led to Food and Drug Administration approval of this approach. It has also reduced “chair time” in chemotherapy units by providing patients a more convenient modality of chemotherapy delivery.
4. Longer initial therapy. Historically, with limited efficacy of melphalan-prednisone and its known marrow effects, most patients received 6 to 8 months of therapy, and very rarely more than 1 year. With current agents, the length of initial therapy has been prolonged, with many patients being treated with IMiDs or proteasome inhibitors (possibly at a reduced dose or frequency) indefinitely.

THE FUTURE OF MM

The pace of progress in MM management is staggering, with an innumerable list of agents being tested in phase 1 and 2 trials. The novel irreversible proteasome antagonist carfilzomib was recently Food and Drug Administration approved for use in relapsed MM¹⁰⁴ and with increasing evidence will likely be used as upfront therapy in the near future.^{105,106} Other therapies being evaluated include the novel IMiD pomalidomide¹⁰⁷ and the oral proteasome inhibitor MLN 9708.¹⁰⁸ Other mechanisms of therapy are also being explored, such as monoclonal

antibodies, AKT inhibitors, aurora kinase inhibitors, vaccines, and many others. These are very much likely to further extend OS in MM and do so with fewer toxic effects.

CONCLUSION

The treatment of MM remains complex, with multiple conventional and novel therapies available to the clinician. However, this consensus statement provides a risk-stratified, evidence-based, and clinically practical approach to the treatment of patients with this as yet incurable disease.

Abbreviations and Acronyms: ASCT = autologous stem cell transplantation; CR = complete response; CRAB = elevated calcium, renal insufficiency, anemia, bone disease; FISH = fluorescence in situ hybridization; GEP = gene expression profiling; IMiD = immunomodulatory drug; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MRI = magnetic resonance imaging; mSMART = Mayo Stratification of Myeloma and Risk-Adapted Therapy; OS = overall survival; PET = positron emission tomography; PFS = progression-free survival; PR = partial response; RR = response rate; SPM = secondary primary malignancy

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