Treatment of Multiple Myeloma: ASCO–Ontario Health (Cancer Care Ontario) Living Guideline

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ABSTRACT

ASCO Guidelines provide recommendations with comprehensive review and analyses of the relevant literature for each recommendation, following the guideline development process as outlined in the ASCO Guidelines Methodology Manual. ASCO Guidelines follow the ASCO Conflict of Interest Policy for Clinical Practice Guidelines.

Clinical Practice Guidelines and other guidance ("Guidance") provided by ASCO is not a comprehensive or definitive guide to treatment options. It is intended for voluntary use by clinicians and should be used in conjunction with independent professional judgment. Guidance may not be applicable to all patients, interventions, diseases or stages of diseases. Guidance is based on review and analysis of relevant literature, and is not intended as a statement of the standard of care. ASCO does not endorse third-party drugs, devices, services, or therapies and assumes no responsibility for any harm arising from or related to the use of this information. See complete disclaimer in Appendix 1 and Appendix 2 (online only) for more.

PURPOSE To provide updated guidance regarding the therapy for multiple myeloma.

METHODS ASCO and Ontario Health (Cancer Care Ontario) convened a joint Expert Panel and conducted an updated systematic review of the literature.

RESULTS The updated review identified a total of 161 relevant randomized trials.

UPDATED RECOMMENDATIONS Daratumumab therapy may be offered to patients with high-risk smoldering myeloma. Quadruplet therapy with daratumumab or isatuximab, combined with bortezomib, lenalidomide, and dexamethasone, should be offered as initial therapy for transplant eligible patients. They should also be offered at least lenalidomide maintenance, with or without daratumumab, carfilzomib, and/or dexamethasone. Quadruplet therapy with daratumumab or isatuximab, combined with bortezomib, lenalidomide, and dexamethasone, should be offered as therapy for suitable transplant-ineligible patients. Patients with relapsed or refractory multiple myeloma should be offered triplet therapy or T-cell redirecting therapies according to a set of recommended principles.

Additional information is available at www.asco.org/hematologic-malignancies-guidelines.

ACCOMPANYING CONTENT

Appendix

Data Supplement

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INTRODUCTION

The purpose of this guideline is to update the evidence-based recommendations on the treatment of multiple myeloma first published jointly by ASCO and Cancer Care Ontario in 2019.[1] Since the publication of that guideline, multiple randomized controlled trials (RCTs) have been published studying a large array of new therapies (eg, chimeric antigen receptor T-cell [CAR T-cell] therapy, bispecific antibody treatments) as well as new combinations of existing therapies demonstrating substantial improvements in progression-free survival (PFS). Also, changes in how active versus smoldering myeloma is defined and the publication of new trials in patients with smoldering myeloma mean there is a growing need for guidance in this space. Given these factors, the ASCO's Evidence-Based Medicine Committee (EBMC) and Ontario Health (Cancer Care Ontario; OH-CCO) agreed to jointly update the guideline.

TARGET POPULATION AND AUDIENCE

Target Population
Patients with multiple myeloma, including smoldering myeloma.

Target Audience
Clinicians and institutions providing care for patients with multiple myeloma.

GUIDELINE QUESTIONS

This clinical practice guideline update addresses four topic areas with these questions:

Smoldering Myeloma

- Should smoldering myeloma (asymptomatic) be treated?
- If smoldering myeloma is treated based on what criteria, and with what regimen(s)?

Transplant-Eligible Multiple Myeloma

- For whom should autologous stem cell transplantation (ASCT) be offered and based on what criteria?
- What is the recommended initial therapy before ASCT?
- What post-ASCT therapy (consolidation and/or maintenance) is recommended and for what duration?

Transplant-Ineligible Multiple Myeloma

- What is the recommended regimen for initial therapy(ies) in transplant-ineligible patients?
- What are the outcome goals following initial therapy for transplant-ineligible patients?

Relapsed Multiple Myeloma

- What are the recommended therapy(ies) at first relapse?
- What are the recommended therapy(ies) after subsequent relapses?
- How does previous treatment impact choice of therapy? What factors influence the choice of relapse therapy?

Note that the questions have been reorganized and reworded from the 2019 guideline and that smoldering myeloma has been added as a topic area.

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise (Appendix Table A1, online only).

The recommendations were informed by a systematic review of evidence identified through an online search of PubMed. To ensure that all relevant trials in patients with smoldering multiple myeloma were included, given that it was a new topic for this update, and because of changes in some search criteria from the 2019 guideline, this new search covered the period between January 1, 2005, and June 6, 2024. In addition, trial articles identified for the 2019 guideline were evaluated based on the updated criteria for inclusion. Articles were selected for inclusion in the systematic review based on the following criteria:

- Trial design and size: RCTs with at least 50 patients on each arm
- Population: patients with multiple myeloma or smoldering myeloma
- Interventions and comparators: any nonvaccine therapy regimen compared with any other nonvaccine therapy regimen
- Critical outcomes: overall survival (OS), PFS, deaths due to adverse events during treatment, serious adverse events, and treatment discontinuation rate from toxicity

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language.

Multiple full panel meetings were held, and members were asked to provide ongoing input on the updated guideline development protocol, quality and assessment of the evidence, generation of recommendations, draft content, as well as review and approve drafts during the entire development of the guideline. ASCO staff met regularly with the Expert Panel co-chairs and corresponded with the full panel via e-mail to coordinate the process to completion. Ratings for strength of the recommendation and evidence quality are provided with each recommendation; defined in Appendix Table A2. The quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process.[2,3] GRADE quality assessment labels (ie, high, moderate, low, very low) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel co-chairs and reviewed by the full Expert Panel. All funding for the administration of the project was provided by ASCO.

Guideline Review and Approval

The draft recommendations were released to the public for open comment from May 13, 2025, through May 27, 2025, and 14 responses were received. Response categories Agree as written, Agree with suggested modifications, and Disagree. See comments were captured for every proposed recommendation. Across all recommendations,

DISCUSSION POINTS BETWEEN PATIENTS AND CLINICIANS

- Shared decision making—There are many effective treatment options available for patients with both newly diagnosed and relapsed or refractory myeloma. With so many options available shared decision making is not just a buzzword, but a necessity. Patients should be actively participating in the decision-making process. This approach ensures that the treatment plan aligns with the patient's individual needs and circumstances, promoting better outcomes and satisfaction.
- Patients should receive clear and understandable information about their myeloma diagnosis—they should know the type of myeloma they have, their risk status (and what that means), and how their disease will be monitored. The discussion should include chromosomal abnormalities that were identified.
- Therapeutic options for patients with multiple myeloma depend greatly on transplant eligibility; discussion of what determines this eligibility and how it is assessed is crucial. Clinicians should discuss the benefits and risks associated with the therapy options offered, especially when the risks are different between the options.
- Therapy for multiple myeloma is a long-term process with multiple steps along the way. An outline of this overall journey may be useful. Long-term strategy should be discussed but also be flexible as new therapies are always becoming available. This discussion should include points to consider when sketching out a plan. Patients should be aware of their risk and frailty status. The discussion should include that risk and frailty may change as with treatment and disease progression.
- Clinicians should discuss with their patients the goals of care (depth of response and/or remission and duration of response). The discussion should include the fact that a cure (ie, elimination of cancer with no further therapy needed) may not be possible, but long (>5 years) survival is possible depending on the context. Goals of care should also include patient preference (ie, patient values, lifestyle, and quality-of-life concerns).
- All the therapeutic options involve toxicity concerns, but also wide differences in access, convenience, and ease of adherence. These important factors should be thoroughly discussed. Included in the discussion of side effects should be information on the success of side effect management strategies.
- There remain many open questions, so enrollment in clinical trials may provide not only high-quality care but also an opportunity for the patient to further the progress of science.

0-2 respondents (0%-14%) disagreed with the recommendation, and 8-13 (57%-93%) agreed as written, with the remainder agreeing with suggested modifications. Expert Panel members reviewed comments from all sources and determined whether to maintain the original draft recommendations, revise with minor language changes, or consider major revisions of a recommendation.

The draft was submitted to five clinicians with content expertise, as well as the members of the ASCO Hematological Malignancies Guideline Advisory Group, for external review. Seven reviews were received. It was rated as high quality, and it was agreed that it would be useful in practice. Reviewers provided comments that led to clarifications of the recommendations and text. In addition, the draft was submitted to OH-CCO's professional consultation process, yielding 15 responses, with all respondents rating the guideline's overall quality as 4 or 5 on a 5-point scale. These changes were reviewed by the Expert Panel co-chairs and integrated into the manuscript for approval by the panel. During development, four members gained new relationships that affected our panel majority. To mitigate this, four additional external reviewers who hold no relationships with affected companies reviewed the guideline before journal submission.

The guideline was submitted to OH-CCO Report Approval Panel for their review and approval. All changes were incorporated into the final manuscript before final ASCO EBMC approval. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO EBMC before submission to the *Journal of Clinical Oncology* for editorial review and consideration for publication.

Living Guideline

This guideline has been selected to become an ASCO living guideline. Living guidelines are developed for selected topic areas with rapidly evolving evidence that drives frequent change in recommended clinical practice. Living guidelines are updated on a regular schedule by a standing expert panel that systematically reviews the health literature on a continuous basis, as described in the ASCO Guidelines Methodology Manual. ASCO Living Guidelines follow the ASCO Conflict of Interest Policy Implementation for Clinical Practice Guidelines. Living Guidelines and updates are not intended to substitute for independent professional judgment of the treating clinician and do not account for individual variation among patients.

RESULTS

Characteristics of Studies Identified in the Updated Literature Search

A total of 2410 articles were identified and screened for inclusion. After applying the eligibility criteria, 400 remained. Of these, 183 articles were supplementary reports or analyses of trials that met the inclusion criteria but did not provide any other relevant information; these are listed in Data Supplement S1B (Table S6, online only).

Therefore, 217 articles were fully included describing 161 trials. The breakdown of these articles and trials is found in Table 1, and all are detailed in Data Supplement S1B (Tables S1-S5). Many of the trials had several random assignments and more than two arms per random assignment. Trials also often address several aspects of therapy and are therefore those trials, and the articles describing them are represented on multiple rows of Table 1. A PRISMA diagram for the search process can be found in Data Supplement S3.

Although all these trials are included in the systematic review because they met the selection criteria, not all were relevant to the development of the recommendations. Evidence Profiles (EPs) were created for key trials and found in the Data Supplement. The outcomes from these trials are reported here. The remaining trials have minimal outcome reporting in Data Supplement S1B (Tables S1-S5) and a reason as to why no EP was needed is provided for each.

Evidence Quality Assessment

The quality of evidence was assessed for each outcome and comparison within the EPs. This rating includes factors such as study design, consistency of results, directness of evidence, precision, publication bias, and magnitude of effect, assessed by one reviewer. Evidence quality ratings for the outcomes of interest are found within the EPs in the Data Supplement. Refer to Appendix Table A2 for definitions for the quality of the evidence and the Methodology Manual for more information. Throughout this guideline when outcome data are presented the certainty (also referred to as quality) of that outcome (High, Moderate, Low, Very Low) from the EP will also be listed if it is available. For example, PFS hazard ratio (HR) 0.28 (95% CI, 0.18 to 0.44); *Moderate*.

TABLE 1. Included Articles, Trials, and Research Arms

Topic	Articles, No.	Trials, No.	Arms, No.
Smoldering myeloma	5	3	10
Transplant eligible: Induction therapy	32	24	55
Transplant eligible: Conditioning	5	5	10
Transplant eligible: Transplant	12	11	24
Transplant eligible: Consolidation	5	5	8
Transplant eligible: Maintenance	25	23	48
Transplant ineligible	52	40	95
Both transplant eligible and transplant ineligible	5	5	10
Relapsed and/or refractory	81	57	119

Unchanged and Dropped Recommendations From the 2019 Guideline

Data Supplement S4 lists all recommendations from both the 2019 guideline and this update, comparing them so that the changes can be easily seen. Only cases where recommendations were substantially altered are discussed in detail here. Recommendations 2.1.1, 2.1.2, 2.5.1, and 3.2.1 to 3.2.3 are essentially unchanged from recommendations in the previous guideline. The 2019 Guideline contained recommendations (8.1-9.4) on risk assessment, response goals, and other topics. These recommendations were not considered by the panel, were not presented during open comment, and are not included in this update.

RECOMMENDATIONS

All recommendations are available in Table 2. Figures 1 and 2 present an algorithm depicting these recommendations.

SMOLDERING MULTIPLE MYELOMA

This section addresses Recommendations 1.1 to 1.3.

Literature Review Update and Analysis

Three RCTs were identified by the updated systematic review, Eastern Cooperative Oncology Group (ECOG) E3A06,[4] QuiRedex,[5,6] and AQUILA.[7] The ECOG E3A06 and QuiRedex trials both compared lenalidomide with observation (no treatment or active surveillance) but had important differences. In QuiRedex, lenalidomide was given with dexamethasone for the first nine cycles and then without dexamethasone until progression to active multiple myeloma initially, but after a protocol amendment the duration of lenalidomide was revised to a maximum of 2 years. In ECOG E3A06, lenalidomide was given until progression to active multiple myeloma without dexamethasone. In the AQUILA trial, daratumumab monotherapy for up to 3 years was compared with active monitoring. Outcome data from these trials are summarized in Table 3[4-7] with the full details presented in EPs 1.1, 1.2, and 1.3 and Data Supplement S1B (Table S1).

Clinical Interpretation

All three identified trials found a PFS benefit for the studied therapy compared with no therapy; QuiRedex[5,6] and AQUILA[7] found OS benefits as well. ECOG E3A06[4] and AQUILA found an increase in important adverse events. Given the important issues around patient inclusion criteria and monitoring for progression discussed later in this section, all outcomes from QuiRedex and ECOG E3A06 had their certainty

TABLE 2. Summary of All Recommendations

Topic	Recommendation
General Note. The following recommendations (strong or conditional/weak) and terminology (Data Supplement) represent reasonable options for patients depending on clinical circumstances and in the context of individual patient preferences. Recommended care should be accessible to patients whenever possible. Note on dose and schedule: see Discussion section for details on specific dose and schedule alternatives.	
Smoldering multiple myeloma	1.1. Patients with high-risk smoldering multiple myeloma may be offered active monitoring or daratumumab (for up to 36 months). Lenalidomide is not routinely recommended. See the Clinical Interpretation for details on shared decision making between these options. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	Qualifying Statements for Recommendation 1.1: In the AQUILA trial, high-risk smoldering multiple myeloma was defined as ≥10% clonal plasma cells in bone marrow and at least one of: (1) a serum M-protein level of at least 3 g per deciliter; (2) IgA smoldering multiple myeloma; (3) immunoparesis with reduced levels of two uninvolved immunoglobulin isotypes; (4) a ratio of involved FLCs to uninvolved FLCs (FLC ratio) in serum of 8 to <100; (5) a percentage of clonal plasma cells in bone marrow of more than 50% to <60%. It should be noted that this definition differs from other contemporary criteria for high-risk smoldering multiple myeloma and that using the AQUILA definition of high-risk may classify some patients as high-risk who would not meet high-risk criteria in other classification systems. Therefore, careful discussion and consideration of individual patient factors is essential when evaluating management options.
	1.2. Therapy for patients with smoldering multiple myeloma who are not at high risk is not recommended. (Evidence quality: Low; Strength of recommendation: Strong)
	1.3. Active multiple myeloma should be excluded using current diagnostic algorithms and procedures for smoldering multiple myeloma. See text for further considerations. (Good Practice Statement)
Transplant eligible—Evaluation of eligibility	2.1.1. Unless clearly ineligible, patients should be referred to a transplant center at time of diagnosis to determine transplant eligibility. (Good Practice Statement)
	2.1.2. Eligibility for autologous stem cell transplantation should not be based solely on a patient's chronological age or renal function. Instead, a comprehensive assessment of overall health, performance status, frailty, and comorbidities should guide the decision. (Evidence quality: Moderate; Strength of recommendation: Strong)
Transplant eligible—Initial therapy	2.2.1. Transplant-eligible patients should be offered 4 months of induction therapy with either daratumumab or isatuximab, each in combination with bortezomib, lenalidomide, and dexamethasone. (Evidence quality: Moderate; Strength of recommendation: Strong)
	Qualifying Statement for Recommendation 2.2.1: In areas where lenalidomide may be difficult to obtain, thalidomide is a reasonable substitute in daratumumab-containing regimens. At least four cycles of therapy should be considered the baseline, but patients can receive more cycles if they must wait for transplant.
	2.2.2. For patients who received daratumumab, bortezomib, lenalidomide, and dexamethasone and planned to receive post-transplant consolidation, two cycles of daratumumab, bortezomib, lenalidomide, and dexamethasone can be offered following induction therapy and stem cell transplantation. See Clinical Interpretation for details on decision making. (Evidence quality: Moderate; Strength of recommendation: Conditional)
	2.2.3. Carfilzomib can be used as a substitute for bortezomib in the recommended induction and consolidation regimens if toxicity is a concern. See Clinical Interpretation for details on decision making. (Evidence quality: Low; Strength of recommendation: Conditional)
Transplant eligible—Conditioning and transplant	2.3.1. Up-front transplantation should be offered to all transplant-eligible patients. (Evidence quality: High; Strength of recommendation: Strong)
	2.3.2. Agents associated with stem-cell toxicity such as melphalan should be avoided in patients who are potential candidates for ASCT. (Evidence quality: Moderate; Strength of recommendation: Strong)
	2.3.3. Regardless of transplant intent, ample stem cells (sufficient for at least two ASCT) should be collected following 4-6 months of induction therapy to allow for potential stem cell transplants later. (Good Practice Statement)
	2.3.4. High-dose melphalan is the recommended conditioning regimen for ASCT. (Evidence quality: High; Strength of recommendation: Strong)
Transplant eligible—Maintenance	2.4.1. Lenalidomide should be offered as maintenance therapy. See Clinical Interpretation regarding duration of therapy. (Evidence quality: High; Strength of recommendation: Strong)
	2.4.2. Carfilzomib or daratumumab may be added to lenalidomide with or without dexamethasone. See Clinical Interpretation for details on when these additions may be appropriate. (Evidence quality: Moderate; Strength of recommendation: Conditional)
Transplant eligible—Measurement of response	2.5.1. Depth of response should be assessed with each cycle using IMWG criteria as a guideline. Frequency of assessment once best response is attained or while receiving maintenance therapy may be less frequent but at minimum every 3 months. MRD status may be valuable in assessing depth of response but should not be relied on as the sole measure. Whole-body low-dose CT scan, fluorodeoxyglucose PET/CT and/or diffusion-weighted MRI are the recommended methods for assessing bone lesions at baseline and during surveillance. (Evidence quality: Low; Strength of recommendation: Conditional)

(continued on following page)

TABLE 2. Summary of All Recommendations (continued)

Topic	Recommendation
Transplant ineligible—Therapy	3.1.1. A CD38-targeted monoclonal antibody (daratumumab OR isatuximab) in combination with bortezomib, lenalidomide, and dexamethasone should be offered to transplant-ineligible patients who are not frail and can tolerate therapy. See Clinical Interpretation for details on shared decision making between clinicians and patients on choosing between these options and on geriatric assessment. (Evidence quality: High; Strength of recommendation: Strong)
	3.1.2. Daratumumab, lenalidomide, and dexamethasone OR bortezomib, lenalidomide, and dexamethasone are reasonable alternatives in transplant-ineligible patients who are not suitable candidates for quadruplet therapy. See Clinical Interpretation for details on shared decision making between clinicians and patients regarding who may not be able to receive quadruplet therapy. (Evidence quality: High; Strength of recommendation: Conditional)
Transplant ineligible—Goals of therapy and measurement of response	3.2.1. The goal of initial therapy for transplant-ineligible patients should be achievement of the best quality and depth of response. Depth of response for all patients should be assessed per Recommendation 2.5.1 regardless of transplant eligibility. (Evidence quality: Moderate; Strength of recommendation: Strong)
	3.2.2. Upon initiation of therapy, one should define patient-specific goals of therapy. Quality of life (including symptom management and tolerability of treatment) should be assessed at each visit to determine if the goals of therapy are being maintained/met, and this should influence the intensity and duration of treatment. The goals should be redefined periodically, based on response, symptoms, and quality of life. (Good Practice Statement)
	3.2.3. Patients should be monitored closely with consideration of dose modifications based on levels of toxicity, neutropenia, fever/infection, tolerability of adverse effects, performance status, liver and kidney function, and in keeping with the goals of treatment. (Good Practice Statement)
Relapsed/refractory—Therapy	4.1. Treatment of biochemically relapsed myeloma should be individualized. Factors to consider include patient's tolerance of prior treatment, rate of rise of myeloma markers, cytogenetic risk, presence of comorbid conditions (ie, renal insufficiency), frailty, and patient preference. (Good Practice Statement)
	4.2. All relapsed patients with disease-related symptoms due to myeloma should be treated immediately. (Evidence quality: High; Strength of recommendation: Strong)
	4.3. Triplet therapy or T-cell redirecting therapies should be offered to eligible patients with relapsed/refractory multiple myeloma based on the following principles: Whenever possible, patients should be offered treatment regimens that include agents that are different than those in their prior therapies. Triplets should be offered to eligible patients. See text for details on evidence-based triplet regimens. CAR T-cell therapy should be offered to eligible patients. A thorough patient-centered discussion regarding the risks, benefits, and timing of CAR T-cell therapy is advised. Patient preferences with respect to toxicity tolerance, dose and schedule convenience, and means of administration should be factored in with shared decision making when deciding between triplet or CAR T-cell therapy. CAR T-cell therapy may not be appropriate for patients with rapidly progressive relapsed myeloma given the time required for CAR T-cell manufacturing. In this setting, an agent that is immediately available may be favored over CAR T-cell therapy. If the patient is unable to receive triplet or CAR T-cell therapy (based on tolerability, frailty, access, etc), doublet therapy is reasonable. Bispecific antibodies should be offered to eligible patients (including older and frail patients). The optimal sequencing of therapy is an evolving consideration. In the context of a limited evidence base, sequencing decisions should be made based on patient factors, disease characteristics, mechanism of action, and prior treatment responses. Patients for whom existing options have been exhausted or for whom the risks are likely to outweigh the benefits should be offered best supportive care and hospice referral. See Clinical Interpretation for discussion on shared decision making among these options and the factors on which the decision should be based. (Evidence quality: High for primary recommendation in first sentence to offer triplet or T-cell redirecting therapies, individual bullet points vary in certainty; Strength of recommendation: Strong for first sentence; Conditional for principles.)
	4.4.1. ASCT, if not previously received, may be offered to transplant-eligible patients with relapsed multiple myeloma. (Evidence quality: Low; Strength of recommendation: Conditional)
	4.4.2. Repeat ASCT should not be offered in relapsed multiple myeloma unless the patient experienced a long remission (typically considered >4-5 years) from first transplant. (Evidence quality: Low; Strength of recommendation: Conditional)

NOTE. The strength of the recommendation is defined as follows: Strong: In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects. In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects. All or almost all informed people would make the recommended choice for or against an intervention. Conditional/Weak: In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists. In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists. Most informed people would choose the recommended course of action, but a substantial number would not.

Abbreviations: ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; CD38, cluster of differentiation 38; CT, computed tomography; FDA, US Food and Drug Administration; FLC, free light chain; IMWG, International Myeloma Working Group; MRD, minimal residual disease; MRI, magnetic resonance imaging; PET, positron emission tomography.

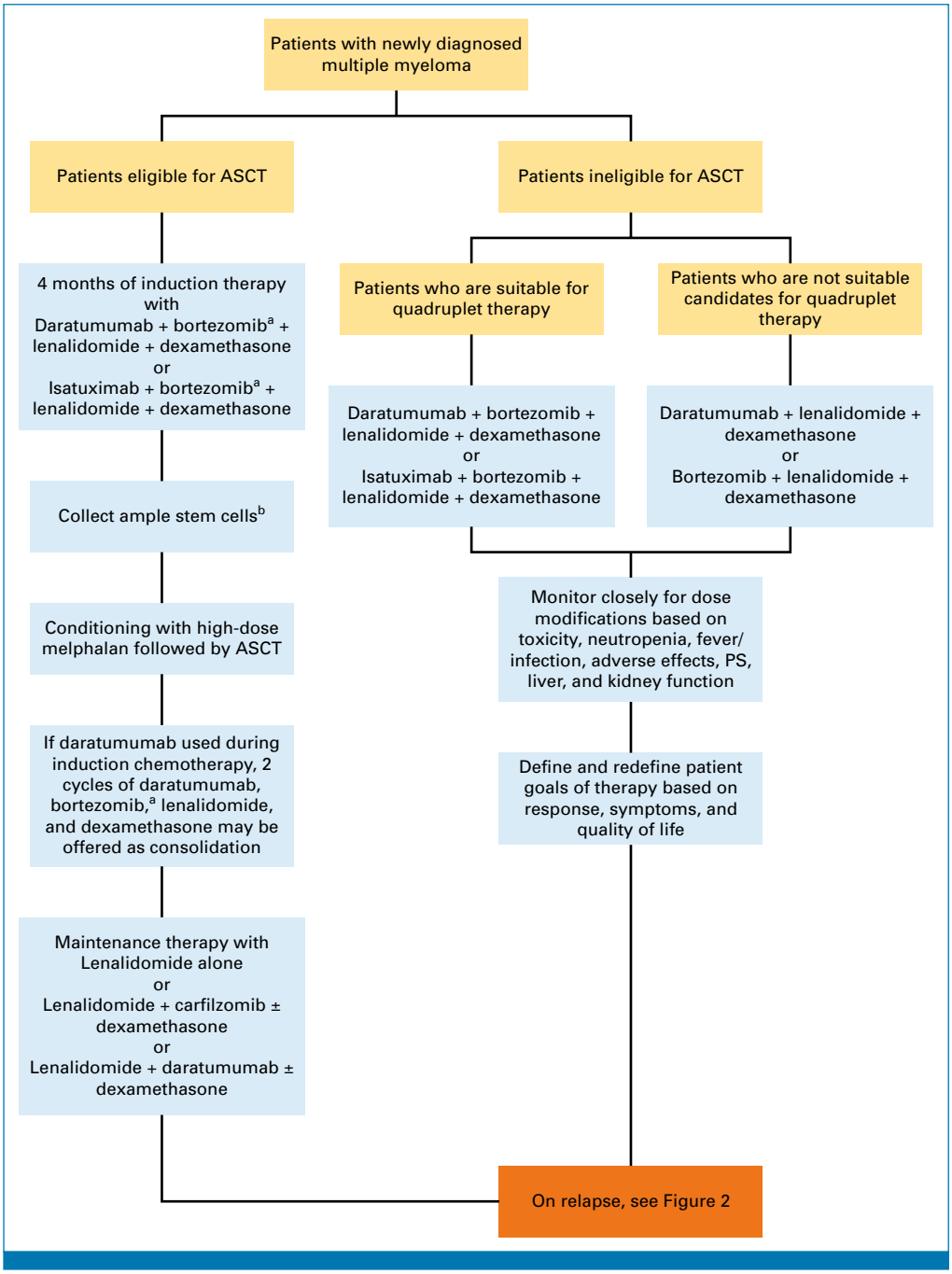

FIG 1. Treatment of newly diagnosed multiple myeloma. [a]Carfilzomib can be used as a substitute for bortezomib if toxicity is a concern. [b]Patients who choose to defer transplant should still have ample stem cells collected. ASCT, autologous stem cell transplantation; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; FDG, fluorodeoxyglucose; IMWG, International Myeloma Working Group; PET, positron emission tomography; PS, performance status; WBLDCT, whole-body low-dose CT.

downgraded for very serious indirectness and AQUILA for serious indirectness.

Smoldering multiple myeloma is not an active disease; rather, it reflects a statistical assessment of the likelihood of developing symptomatic multiple myeloma within a defined time frame. Older data indicated that patients meeting the criteria for smoldering multiple myeloma face a 10% annual risk of progressing to symptomatic multiple myeloma during the first 5 years, 3% annually between years 6 and 10, and 1% annually thereafter. Even after 20 years, 20% of individuals with smoldering multiple myeloma have not developed active multiple myeloma as defined by traditional Calcium elevation, Renal insufficiency, Anemia, and Bone lesions (CRAB) criteria.[8] Given that patients with smoldering multiple myeloma do not have active disease, the threshold

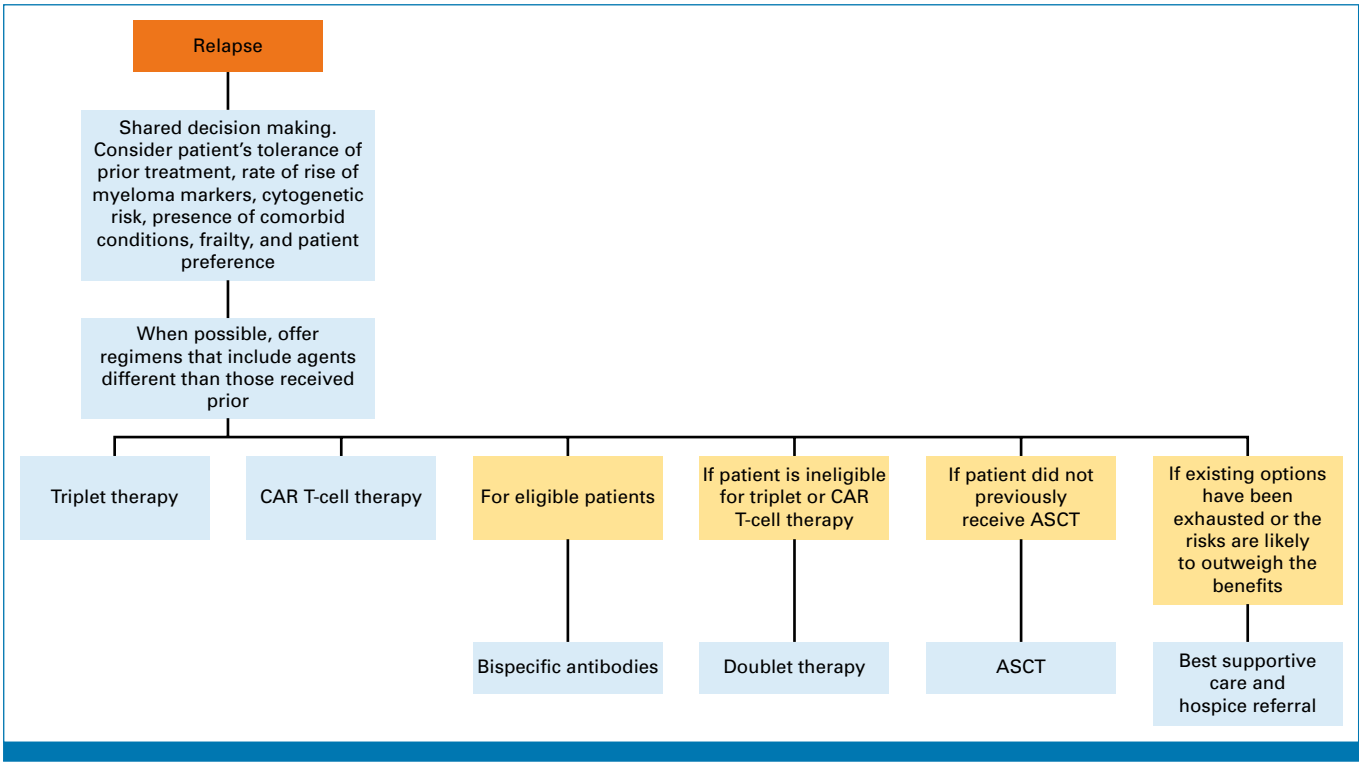

FIG 2. Treatment of relapsed or refractory multiple myeloma. ASCT, autologous stem cell transplantation; CAR, chimeric antigen receptor.

to recommend potentially long-term and toxic therapy is higher.

Various attempts have been made to predict a more specific risk of progression to multiple myeloma including the Programa Español de Tratamientos en Hematología (PETHEMA) model,[9] the Mayo 2018 2/20/20 model,[10] the International Myeloma Working Group (IMWG)[11] model, and the recent PANGEA model.[12] These models include different factors and are not easily comparable. One study[13] reported global agreement of only 16.6% when comparing PETHEMA, Mayo 2008 and Mayo 2018 models. Overall, the smoldering multiple myeloma models were created using large retrospective data sets, but they have not been prospectively validated for clinical use or to identify patients who are appropriate for participation in clinical trials.

In 2014, the IMWG updated the diagnostic criteria for multiple myeloma to include new myeloma-defining events.[14] The presence of biomarkers summarized by SLiM (Sixty, Light chain ratio, magnetic resonance imaging [MRI] lesions) is associated with a high risk of progression to end-organ damage. These include ≥60% clonal plasma cells in the bone marrow, an involved to uninvolved free light chain (FLC) ratio ≥100 (with the involved FLC level ≥100 mg/L) and/or MRI showing more than one focal lesion measuring at least 5 mm in bone or bone marrow was considered sufficient to initiate therapy. However, a recent analysis[15] reported that patients with a FLC ratio over 100 and urinary monoclonal protein excretion of <200 mg over 24 hours had only a 13.5% risk of symptomatic progression at 2 years, with a median time to symptomatic multiple myeloma development of 7.9 years. Even when urinary protein excretion exceeded 200 mg/24 hours, only 36.2% developed symptomatic myeloma within 2 years, with a median time of 3.4 years.[15] Likely due to the incorporation of advanced imaging techniques as part of the smoldering multiple myeloma, there are data suggesting that in the absence of other factors patients with FLC ratios over 100 or bone marrow plasma cell (BMPC) percentages of 60% or greater alone may transform to multiple myeloma less quickly than previously thought.[16] This evolving understanding of disease progression and the role of biomarkers highlights the ongoing learning and refinement of diagnostic and treatment strategies in multiple myeloma and the need for caution when making recommendations regarding the management of smoldering myeloma.

Another complicating factor is that all three randomized trials of smoldering myeloma included in the review use different definitions of active myeloma and/or different methods for assessing risk. Both ECOG E3A06 and QuiRedex recruited patients before the 2014 IMWG criteria and therefore included some patients that by SLiM CRAB criteria had active multiple myeloma. In QuiRedex[5,6] radiographic evaluations did not used advanced imaging such as positron emission tomography plus computed tomography (PET-CT) or whole-body MRI. Patients with BMPC burden over 60% were eligible for inclusion, and high FLC ratio was not identified as a myeloma-defining event. It is not possible to

TABLE 3. Outcomes From Key Randomized Trials of Patients With Smoldering Multiple Myeloma—See Evidence Profiles 1.1-1.3 for More Complete Accounting and Data

Trial	Intervention	Comparator	OS, HR (95% CI) [No. of participants]	OS Certainty	PFS, HR (95% CI) [No. of participants]	PFS Certainty	Important[a] AEs During Treatment, RR (95% CI) [No. of participants]	Important AEs Certainty
QuiRedex[5,6]	Lenalidomide plus dexamethasone	Observation	0.57 (0.34 to 0.95) [119]	Low	0.28 (0.18 to 0.44) [119]	Low	4.0 (0.84 to 19.0) [119]	Very low
ECOG E3A06[4]	Lenalidomide	Observation	0.46 (0.08 to 2.53) [182]	Very low	0.28 (0.12 to 0.62) [182]	Very low	1.73 (1.24 to 2.41) [174]	Very low
AQUILA[7]	Daratumumab	Active monitoring	0.52 (0.27 to 0.98) [390]	Low	0.49 (0.36 to 0.67) [390]	Moderate	1.49 (1.04 to 2.14) [389]	Low

Abbreviations: AEs, adverse events; ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.
[a]This column reports serious adverse events if they were reported but see evidence profile for the specific outcome.

measure what proportion of patients in the QuiRedEx trial were enrolled with active multiple myeloma as defined by contemporary IMWG diagnostic criteria as the necessary parameters were not measured. In ECOG E3A06,[4] 8.2% of patients had a FLC ratio >100 and 3.3% had BMPC ≥60% and thus would be considered to have active multiple myeloma by today's criteria. PET and MRI were not mandated in the trial, but 47.2% of patients had an abnormality on MRI, and it is unclear what proportion, if any, were focal lesions. By contrast, the AQUILA study used IMWG SLiM CRAB criteria to exclude patients and to determine the rate of progression. Also monitoring for progression was prespecified (laboratory screening at least once every 12 weeks, imaging at least once every 12 months) and centrally reviewed in the AQUILA study.

All three trials did not determine myeloma risk status based on contemporary risk models. For example, only 40.5% and 30.8% of patients in AQUILA[7] and ECOG EA306, respectively, met the Mayo 2018 definition of high risk after retrospective assessment. Therefore, all these trials suffer from indirectness given that the population we are interested in are patients who have high-risk smoldering multiple myeloma. This uncertainty is reflected in the EPs in the Data Supplement.

Interpretation of the smoldering myeloma trials is also complicated by the fact that therapy options have evolved for patients with active multiple myeloma and outcomes have improved. The therapies that were available for patients with disease progressing to active myeloma in all three smoldering trials are different than the initial treatments recommended in this updated guideline (Recommendations 2.2.1-2.2.3 for transplant eligible and Recommendations 3.1.1-3.1.2 for transplant ineligible). It is possible that the benefit of treating smoldering myeloma may be less in patients who are given contemporary first-line myeloma treatments at the time of progression to active myeloma.

Importantly, treating smoldering myeloma involves exposing a group of asymptomatic patients to the risks and side effects of systemic therapy. In this context, the Panel felt that a higher level of evidentiary certainty is required to recommend against active monitoring. As a result, the Panel recommended active monitoring as an option for all patients with smoldering myeloma. The Expert Panel believed that the potential, if moderately uncertain, OS and PFS benefits of daratumumab outweigh the likely increased adverse events for most patients and therefore made the conditional recommendation (1.1) in favor of daratumumab as an alternative to active monitoring with appropriate caveats in the qualifying statement around high-risk status assessment. Furthermore, the Panel made a clear statement in Recommendation 1.2 that therapy for patients who are low or intermediate risk is not recommended. The Panel did not believe the evidentiary threshold was met for lenalidomide given the increased uncertainty associated with the somewhat older trials and therefore recommended against routine use of lenalidomide therapy (Recommendation 1.1).

A critical aspect of managing smoldering multiple myeloma is ensuring that all necessary diagnostic tests are completed to accurately assess the patient's risk and rule out active multiple myeloma. The IMWG criteria[14] require several diagnostic and imaging tests and procedures which can be time consuming and resource intensive. However, it is imperative to exclude active multiple myeloma before initiating treatment for smoldering myeloma, so as not to undertreat. In cases where patients appear to be moving toward active multiple myeloma, but follow-up is incomplete, close monitoring over a short interval may help to clarify the diagnosis. For example, in a patient with new and worsening anemia but not yet meeting the diagnostic threshold of a hemoglobin of <10 or 2 g/dL decrease from baseline, it may be reasonable to follow very closely for transformation to active myeloma (in which case multiagent therapy for active multiple myeloma is recommended), rather than treating for smoldering myeloma. Prompt evaluation, including repeated assessments of biomarkers, imaging, and clinical parameters, can help guide timely and appropriate treatment decisions.

Ongoing Trials and Future Research

The Panel is aware of two ongoing trials of therapy in patients with high-risk smoldering multiple myeloma: the DETER-SMM/ECOG-EAA173 trial (ClinicalTrials.gov identifier: NCT03937635) of daratumumab plus lenalidomide and the ITHACA trial (ClinicalTrials.gov identifier: NCT04370409) of isatuximab, lenalidomide, and dexamethasone; both are compared with lenalidomide plus dexamethasone. See Data Supplement S1B (Table S7). The expected completion of these trials is 2029 and 2030, respectively.

NEWLY DIAGNOSED MULTIPLE MYELOMA—TRANSPLANT ELIGIBLE

Transplant Eligible—Initial Therapy

This section addresses Recommendations 2.2.1-2.2.3.

Literature Review Update and Analysis

The evidence on transplant eligible induction therapy and consolidation therapy is summarized in Table 1 and in Data Supplement S1B (Tables S2A and S2D).

Of the newly available evidence, the CASSIOPEIA (Part 1),[17] GRIFFIN,[18-20] PERSEUS,[21] and German-speaking Myeloma Multicenter Group (GMMG) HD7[22,23] warranted EPs. Outcome data from these trials are briefly summarized in Table 4[17-23] with the full details presented in EPs 2.1.1, 2.1.2, and 2.1.3.

Clinical Interpretation

In the panel's estimation, the PFS benefits identified in the PERSEUS,[21] GRIFFIN,[18,19] and GMMG-HD7 trials (EP 2.1.2 and

TABLE 4. Outcomes From Key Randomized Trials of Induction Therapy for Transplant Eligible Patients With Newly Diagnosed Multiple Myeloma—See Evidence Profiles 2.1.1-2.1.3 for More Complete Accounting and Data

Trial	Intervention	Comparator	OS, HR (95% CI) [No. of participants]	OS Certainty	PFS, HR (95% CI) [No. of participants]	PFS Certainty	Important[a] AEs During Treatment, RR (95% CI) [No. of participants]	Important AEs Certainty
CASSIOPEIA (part 1)[17]	Daratumumab, bortezomib, thalidomide, and dexamethasone	Bortezomib, thalidomide, and dexamethasone	0.43 (0.23 to 0.80) [1,085]	Moderate	0.47 (0.33 to 0.67) [1,085]	Moderate	0.99 (0.87 to 1.21) [1,074]	Moderate
GRIFFIN,[18-20] PERSEUS[21]	Daratumumab, bortezomib, lenalidomide, and dexamethasone	Bortezomib, lenalidomide, and dexamethasone	0.90 (0.31 to 2.56) [207]	Moderate	0.43 (0.31 to 0.58) [916]	High	1.05 (0.82 to 1.34) [899]	Very low
GMMG-HD7[22,23]	Isatuximab, bortezomib, lenalidomide, and dexamethasone	Bortezomib, lenalidomide, and dexamethasone	Not reported	Not reported	0.70 (0.52 to 0.95) [660]	Moderate	0.98 (0.77 to 1.26) [658]	Moderate

Abbreviations: AEs, adverse events; GMMG, German-speaking Myeloma Multicenter Group; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.
[a]This column reports serious adverse events if they were reported but see evidence profile for the specific outcome.

2.1.3) for the addition of daratumumab or isatuximab to bortezomib, lenalidomide, and dexamethasone are sufficient to recommend these regimens as the primary choices for induction therapy (Recommendation 2.2.1). There is a moderate or high certainty of PFS benefit in all patients for both options with little evidence of an important difference in any toxicity or tolerability harms (EP 2.1.2 and 2.1.3). As the previous guideline had already recommended three to four cycles of combination therapy with proteasome inhibitor, immunomodulatory drug, and dexamethasone the panel believes the comparison with bortezomib, lenalidomide and dexamethasone in these trials is relevant and supports the recommendation of these regimens. The evidence from the CASSIOPEIA trial[17] found similar benefits for the addition of daratumumab to bortezomib, thalidomide, and dexamethasone (EP 2.1.1) and in areas where lenalidomide may not be available it would be reasonable to replace lenalidomide with thalidomide in the daratumumab combination (Recommendation 2.2.1 qualifying statement).

At the time of this guideline, there have not been reported results of a trial of carfilzomib, lenalidomide, and dexamethasone, with or without daratumumab, for induction therapy in transplant-eligible patients. A random assignment in the Myeloma XI+ trial[24] compared carfilzomib, lenalidomide, cyclophosphamide, and dexamethasone with cyclophosphamide and dexamethasone with either lenalidomide or thalidomide. A PFS benefit was found for carfilzomib (HR, 0.63 [95% CI, 0.51 to 0.76]), but the interpretation of this result is complicated by the presence of cyclophosphamide on both arms. There were four trials comparing carfilzomib with bortezomib in multiple myeloma in nontransplant eligible patients identified. Two were in transplant-ineligible patients: CLARION[25] in combination with melphalan and prednisone and ENDURANCE[26] in combination with lenalidomide and dexamethasone also in transplant-ineligible or deferred patients; see Data Supplement S1B (Table S3). Two were in patients with relapsed or refractory disease: MUKFive[27] in combination with cyclophosphamide and dexamethasone and ENDEAVOR[28] in combination with dexamethasone alone; see Data Supplement S1B (Table S5). No significant difference in PFS was found in three of these superiority trials; ENDEAVOR found a PFS benefit (HR, 0.53 [95% CI, 0.44 to 0.65]) for carfilzomib. Serious adverse events were either similar or more frequent with carfilzomib. Treatment discontinuation rates were similar or more frequent with bortezomib. The frequency of grade 3 or higher peripheral neuropathy was greater with bortezomib than carfilzomib in all the studies. Taken together, these studies provide low-certainty indirect evidence that it is reasonable to use carfilzomib instead of bortezomib if treatment discontinuation and/or peripheral neuropathy toxicity is a concern (Recommendation 2.2.3).

With respect to the issue of consolidation therapy post-ASCT, both the GRIFFIN[18,19] and PERSEUS[21] trials are best described as trials of adding daratumumab to the strategy of bortezomib, lenalidomide, and dexamethasone induction (four cycles) and consolidation (two cycles) followed by lenalidomide maintenance until progression. Therefore, these trials provide no evidence regarding any independent value of two cycles of consolidation therapy added to four cycles of induction therapy. In keeping with the results of these trials, the panel made a conditional recommendation in favor of consolidation therapy in the context of daratumumab-based induction (Recommendation 2.2.2). The GMMG-HD7 trial involving isatuximab did not incorporate a consolidation strategy, although some patients received tandem ASCT before maintenance based on risk and/or response following the first ASCT. In the systematic review, the only trials that investigated the independent value of consolidation therapy were: European Myeloma Network (EMN) 02/Stichting Hemato-Oncologie voor Volwassenen Nederland (HOVON) 95,[29,30] Mellqvist 2012,[31] Sezer 2017,[32] and L'Intergroupe Francophone du myélome (IFM) 2005-01,[33] all of which are summarized in Data Supplement S1B (Tables S2A and S2D). In each of these trials, the interpretation is greatly complicated by the fact that the induction and/or transplant therapy used, and in some cases the consolidation therapy as well, would not have been recommended in the previous guideline. For example, the EMN02/HOVON 95 trial found a PFS benefit (HR, 0.77 [95% CI, 0.63 to 0.95]) for two cycles of bortezomib, lenalidomide, and dexamethasone consolidation therapy, but that was in a context of initial treatment with bortezomib, cyclophosphamide, and dexamethasone, and where only half of the patients received ASCT (the others received bortezomib, melphalan, and prednisone). Given the lack of interpretable evidence in other contexts, no general recommendation for or against consolidation therapy was made except for Recommendation 2.2.2.

Cyclophosphamide has historically been incorporated into induction regimens for patients with newly diagnosed myeloma with renal failure, largely due to concerns regarding lenalidomide use in this setting. However, randomized data from the MYRE trial[34] comparing bortezomib and dexamethasone with or without cyclophosphamide in patients with cast nephropathy and acute kidney injury demonstrated no improvement in renal or overall response with the addition of cyclophosphamide. The Panel emphasizes that lenalidomide is safe to use in patients with renal dysfunction, provided appropriate dose adjustments are made to account for renal clearance.

Ongoing Trials and Future Research

See Data Supplement S1B (Table S7) for a list of all known unpublished registered RCTs in multiple myeloma. For induction therapy in patients who are transplant eligible, three trials may have peer-reviewed publications in the next few years that warrant comment:

- ISKIA trial (ClinicalTrials.gov identifier: NCT04483739): Two conference abstracts[35,36] have reported superior rates of minimal residual disease (MRD) negativity with

isatuximab given with carfilzomib, lenalidomide, and dexamethasone compared with the triplet alone as induction and consolidation in transplant-eligible patients, meeting the primary end point. One challenge with interpretation of this study is that even if similar PFS benefits are found for this quadruplet strategy, the carfilzomib, lenalidomide, and dexamethasone comparator is not currently an approved regimen by regulatory agencies.

- COBRA trial (ClinicalTrials.gov identifier: NCT03729804): Compares a standard eight-cycle induction with bortezomib, lenalidomide, and dexamethasone, followed by lenalidomide and dexamethasone maintenance compared with 24 cycles of carfilzomib, lenalidomide, and dexamethasone without transplant intent.
- The ongoing ADVANCE trial (ClinicalTrials.gov identifier: NCT04268498) is comparing an induction strategy of carfilzomib, lenalidomide, and dexamethasone with and without daratumumab, although ASCT is not mandated in this study. A bortezomib, lenalidomide, and dexamethasone arm was originally also included, but was closed via protocol amendment. The panel is aware that results from this trial have been presented in abstract form.[37]

Transplant Eligible—Conditioning and Transplant

This section addresses Recommendations 2.3.1-2.3.4.

Literature Review Update and Analysis

The evidence on transplant eligible conditioning therapy and on transplant itself is summarized in Table 1 and in Data Supplement S1B (Tables S2B and S2C). Of these trials, only the Bashir 2019[38] trial has an EP (2.2) in the Data Supplement. In brief, Bashir 2019 found improved PFS (HR, 0.53 [95% CI, 0.3 to 0.91]; *Moderate*) and more frequent grade 3 or higher adverse events (relative risk, 2.53 [95% CI, 1.88 to 3.41]; *High*) for the combination of busulfan plus lower dose melphalan versus high-dose melphalan as conditioning therapy.

Clinical Interpretation

These recommendations are substantially altered and simplified from Recommendations 2.2 through 2.9 in the previous guideline. The primary recommendations in favor of offering up-front transplant and high-dose melphalan conditioning remain mostly unchanged. The wording has been altered to reflect current ASCO practice and the Strength of Recommendation and Evidence Quality categories have been updated to current ASCO definitions. The wording of Recommendation 2.3.1 (2.2 in the original guideline) was changed to delete reference to delayed ASCT; while some patients may need or choose to delay ASCT, all transplant-eligible patients should be offered the therapy up-front. Recommendation 2.5 in the original guideline was dropped as it was no longer considered necessary.

The previous guideline addressed the risks and benefits of up-front versus deferred ASCT in the context of triplet therapy. This has been further solidified by results of the DETERMINATION trial[39] comparing up-front bortezomib, lenalidomide, and dexamethasone with or without ASCT followed by indefinite lenalidomide maintenance therapy; delayed ASCT was associated with inferior PFS (HR, 1.53 [95% CI, 1.23 to 1.91]) with no difference in OS at a median follow-up of 76 months. Notably, only 35% of patients in the non-ASCT arm received ASCT as subsequent therapy.

Given the excellent outcomes for both transplant-eligible and transplant-ineligible patients with quadruplet therapy, there is some uncertainty as to whether upfront ASCT provides a similar benefit. However, the primary trials used to support Recommendation 2.2.1 in this updated guideline (PERSEUS, GRIFFIN, and GMMG HD7) all included ASCT in their protocol and thus it is not possible to tease out the relevant contributions of ASCT versus systemic therapy and these data do not support foregoing up-front ASCT. Regardless of transplant intent, the panel recommends that patients should have a sufficient quantity of stem cells collected within 4 months of commencing treatment, specifically enough for at least two stem cell rescues. This allows for future ASCT and also potentially for stem cell rescue post-CAR T if necessary.[40]

The Bashir 2019[38] trial provides some evidence that conditioning with busulfan plus melphalan may be associated with better PFS compared with melphalan alone, at the expense of additional toxicity. However, as none of the trials of initial and maintenance therapy that support these recommendations included busulfan, this trial is very difficult to interpret. No recommendation regarding busulfan plus melphalan is possible currently.

The previous guideline had a recommendation against routine allogenic transplantation, but allowing for its use in select high-risk patients or in clinical trials. The panel dropped this recommendation as they believe in the current context it was no longer necessary.

Ongoing Trials and Future Research

See Data Supplement S1B (Table S7) for a list of all known unpublished registered RCTs in multiple myeloma. For transplant therapy in patients who are transplant eligible, two trials may have peer-reviewed publications in the next few years that warrant comment: the MIDAS/IFM2020-20 trial (ClinicalTrials.gov identifier: NCT04934475) and the MASTER-2 trial (ClinicalTrials.gov identifier: NCT05231629). The panel is aware of one publication of the MIDAS/IFM2020-20 trial after the window of this guideline's systematic review that addresses MRD negativity.[41] Both trials measure MRD status after induction with isatuximab, carfilzomib, or daratumumab and bortezomib (both with lenalidomide and dexamethasone), respectively. MRD-negative patients are randomly assigned to further cycles of the induction regimen or to ASCT. All MRD-negative patients would also receive lenalidomide or daratumumab

plus lenalidomide maintenance, respectively. Both trials incorporate random assignment of MRD-positive patients to two different arms of more intense therapy; however, these strategies are more complicated and not fully outlined in the registry, see the trial registrations for details.

Transplant Eligible—Maintenance

This section addresses Recommendations 2.4.1 and 2.4.2.

Literature Review Update and Analysis

The evidence on transplant eligible maintenance therapy is summarized in Table 1 and in Data Supplement S1B (Table S2E). The ATLAS,[42] FORTE (Maintenance)[43] and AURIGA[44] trials were given EPs. Outcome data from these trials are briefly summarized in Table 5[42-44] with the full details presented in EPs 2.3.1, 2.3.2, and 2.3.3. The other trials were not given EPs as either they confirmed the recommendations made in the previous guideline or they had comparator arms that were considered irrelevant to current practice. See the Data Supplement for the reasoning in each case.

Clinical Interpretation

The previous guideline recommended (old Recommendation 3.2) at least 2 years of single-agent lenalidomide as maintenance therapy primarily based on data from randomized trials available at that time.[45-47] As there have been no trials published since then that contradict that recommendation, maintenance therapy with at least lenalidomide remains the primary choice. The benefits of increased PFS outweigh the harms of additional toxicity and long-term treatment, including a recognized risk of secondary malignancy estimated at approximately 6%.[48] Nonetheless, it is important that patients are advised of the risk of secondary malignancy when starting maintenance lenalidomide, and that informed consent is obtained. The impact of maintenance lenalidomide in patients who have had prior malignancy is unknown.

Four agents have been or are being investigated in maintenance therapy:

- Carfilzomib: The ATLAS[42] and FORTE[43] trials investigated the addition of carfilzomib (and in ATLAS, dexamethasone) to single-agent lenalidomide. Both trials provide moderate certainty evidence of a PFS benefit for the addition of carfilzomib and low certainty evidence that this addition has little effect on serious adverse events. The FORTE trial did not find a difference in OS. The panel is aware that an OS difference has been reported in a conference abstract for the ATLAS trial.[49] However, these trials are difficult to contextualize given the recommendations (2.2.1-2.2.3) for initial therapy in this updated guideline. Neither trial had patients who received an anti-CD38 monoclonal antibody as part of induction or consolidation; in FORTE, a third of patients did not receive ASCT and in ATLAS, only 11% received lenalidomide as part of induction (65% received bortezomib, thalidomide, and dexamethasone). Therefore, the value of carfilzomib added to lenalidomide is unclear in the current landscape.
- Daratumumab: The AURIGA trial[44] investigated the addition of daratumumab to lenalidomide maintenance in daratumumab-naïve patients with MRD positivity (10^{-5}) and at least a very good partial response (VGPR) following ASCT. The results of the AURIGA trial[44] are difficult to contextualize as patients with daratumumab exposure in induction were excluded, and because of the restriction of the study population to patients least VGPR, but still measurable residual disease after ASCT. As a result, the trial is low certainty evidence for a PFS benefit with low certainty that there is no difference in serious adverse events. No difference in OS was found. Complicating the picture are the GRIFFIN[18,19] and PERSEUS[21] trials as noted previously, whose investigational arms examined adding daratumumab to all phases of therapy, but with no second random assignment to ascertain the added effect of daratumumab as maintenance with lenalidomide. These trials provide indirect evidence in favor of adding daratumumab to lenalidomide as maintenance therapy, but the independent value of doing so separate from the value in induction or consolidation is unknown. The CASSIOPEIA (Part 2)[17,50] random assignment investigated single agent daratumumab versus no maintenance; daratumumab maintenance once every 8 weeks conferred a PFS benefit in patients who received daratumumab-containing quadruplet during induction and consolidation. However, because the comparator was observation rather than lenalidomide alone and because daratumumab was dosed less frequently than once every 4 weeks as it is typically dosed for maintenance today, this study does not address the question of adding daratumumab to lenalidomide or using it as a replacement.
- Ixazomib: The TOURMALINE-MM3[51] trial found a PFS benefit for ixazomib versus no maintenance, but the benefit compared with lenalidomide maintenance is unknown. The GEM2014MAIN trial[52] found no benefit to adding ixazomib to lenalidomide and dexamethasone maintenance. The MMRC-066 trial[53] found worse PFS with ixazomib versus lenalidomide maintenance.
- Isatuximab: The GMMG-HD7 (Part 2)[22] trial involves random assignment post-ASCT to isatuximab and lenalidomide *v* lenalidomide maintenance, but these results have not yet been reported.

Given this complicated situation, the panel believes that adding either daratumumab or carfilzomib, with or without dexamethasone, to lenalidomide maintenance is reasonable in some situations. For most patients with standard risk myeloma, maintenance with single-agent lenalidomide for at least 2 years is the recommended approach. However, as in the AURIGA trial in patients who did not receive an anti-CD38 antibody during induction and who achieve ≥VGPR with measurable residual disease after ASCT, it is reasonable to add daratumumab maintenance (maximum of 36 cycles) to lenalidomide. Patients with

TABLE 5. Outcomes From Key Randomized Trials of Maintenance Therapy for Transplant Eligible Patients With Newly Diagnosed Multiple Myeloma—See Evidence Profiles 2.3.1-2.3.3 for More Complete Accounting and Data

Trial	Intervention	Comparator	OS, HR (95% CI) [No. of participants]	OS Certainty	PFS, HR (95% CI) [No. of participants]	PFS Certainty	Important[a] AEs During Treatment, RR (95% CI) [No. of participants]	Important AEs Certainty
ATLAS[42]	Carfilzomib, lenalidomide, and dexamethasone	Lenalidomide	0.83 (0.35 to 2.0) [180]	Very low	0.51 (0.31 to 0.86) [180]	Moderate	1.38 (0.83 to 2.28) [178]	Low
FORTE (Maintenance)[43]	Carfilzomib and lenalidomide	Lenalidomide	0.54 (0.26 to 1.11) [356]	High	0.64 (0.44 to 0.94) [356]	Moderate	1.64 (0.89 to 3.01) [350]	Low
AURIGA[44]	Daratumumab and lenalidomide	Lenalidomide	0.5 (0.17 to 1.5) [200]	Low	0.53 (0.29 to 0.97) [200]	Low	1.35 (0.84 to 2.17) [194]	Low

Abbreviations: AEs, adverse events; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.
[a]This column reports serious adverse events if they were reported but see evidence profile for the specific outcome.

high-risk cytogenetic abnormalities (HRCAs), defined here as t(4;14), t(14;16), t(14;20), 17p deletion or TP53 mutation, and 1q amplification with 1p del, and especially those with two HRCAs, represent a special population. It is reasonable to offer this population multiagent maintenance therapy, but the evidence supporting this strategy is limited. The panel also notes that the International Myeloma Society and IMWG have very recently published updated consensus definitions of high-risk multiple myeloma.[54] Both the ATLAS and FORTE trials reported improved PFS with the addition of carfilzomib but both trials were underpowered to specifically assess the impact of carfilzomib in the subgroup of patients with high-risk disease. The PERSEUS and GRIFFIN trials both demonstrated improved PFS, including among high-risk patients; however, as previously outlined, it is not possible to determine the differential impact of the maintenance phase of these trials. Acknowledging the limitations of the existing literature, the panel felt that it was reasonable to add either carfilzomib or daratumumab to lenalidomide maintenance for patients with high-risk myeloma. An important consideration in these recommendations is the tolerability of lenalidomide over long periods of time. There is only one known trial, GMMG-MM5,[55] that has directly compared 2 years of lenalidomide versus lenalidomide until progression; this trial was a risk-adapted trial, whereby patients were randomly assigned to 2-year fixed duration lenalidomide maintenance versus lenalidomide until complete response or progression. The interpretation of this trial is complicated by the fact that none of the patients received lenalidomide during induction therapy; patients received bortezomib, dexamethasone, and either doxorubicin or cyclophosphamide. Also, while this trial found no difference in PFS, it was not designed as a noninferiority trial with respect to PFS.

It is important to note that all the randomized data for lenalidomide maintenance (compared with observation) were generated in the context of induction regimens that are no longer considered contemporary. In the era of quadruplet induction with high rates of deep response such as MRD negativity, the need for maintenance, the components of maintenance therapy, and the duration of maintenance all remain unanswered questions. The emerging paradigm suggests that time-limited therapy strategies guided by response biomarkers may represent the future of myeloma management, offering the potential to optimize treatment duration and minimize long-term toxicity while maintaining disease control. The panel is aware of MRD-guided strategies to discontinue treatment. The previously mentioned GEM2014MAIN trial[52] discontinued maintenance with lenalidomide and dexamethasone, plus or minus ixazomib, in patients with MRD negativity (10^{-6}) after 2 years. Nonrandomized trials such as the MASTER trial[56] and the MRD2STOP trial[57] involving quadruplet induction strategies have found 3-year PFS rates of 85% or higher in patients who discontinued therapy based on MRD negativity and suggest maintenance therapy may not need to be indefinite. However, larger prospective randomized trials with extended follow-up are critically needed to better define optimal maintenance duration and identify which patients can safely discontinue therapy early versus those who require extended treatment, thereby avoiding both undertreatment of high-risk patients and overtreatment of those achieving deep, sustained responses. Given that there is no randomized evidence regarding discontinuation, the panel did not make formal recommendations as to when lenalidomide therapy could or should be discontinued before progression. The trial evidence includes trials that used 2 years of lenalidomide and trials that used lenalidomide until progression. At present, it is likely that at least 2 years of lenalidomide should be offered to patients who are tolerating it, with a decision to continue therapy beyond that point based on patient preference, depth and duration of response, and whether uncertain disease control benefits outweigh the continued toxicity and inconveniences of therapy.

In the previous guideline, there was a weak recommendation (old Recommendation 3.3) that single-agent bortezomib maintenance was a reasonable alternative to lenalidomide. This was based primarily on the GEM05MENOS65 (Maintenance)[58] trial that studied the addition of bortezomib to thalidomide maintenance therapy and the HOVON 65/GMMG-HD4[59,60] trial which compared a strategy of bortezomib, doxorubicin, and dexamethasone, followed by bortezomib maintenance to vincristine, doxorubicin, and dexamethasone, followed by thalidomide maintenance. Both trials did find a PFS benefit for the bortezomib containing arms; data from the GMMG-HD4 trial[60] reported an OS benefit in patients with del(17p13). However, the comparator arms and other associated therapies mean that these trials are not relevant to current practice. The more recent VCAT trial[61] found no PFS benefit for the addition of bortezomib to thalidomide plus prednisolone maintenance but that is complicated by uncommon induction therapy and comparator arm. Given that there is no randomized evidence comparing bortezomib, either as single-agent maintenance or in combination, to single-agent lenalidomide maintenance this recommendation was dropped. As noted previously, single-agent daratumumab and single-agent ixazomib have been compared with no maintenance, but until or unless trials comparing them with lenalidomide maintenance are available, their role is unclear and they cannot be recommended. These agents may be of some value in patients who cannot receive lenalidomide, but as that was not the trial population studied in TOURMALINE-MM3 and CASSEIOPEIA, this value is highly uncertain.

Ongoing Trials and Future Research

See Data Supplement S1B (Table S7) for a list of all known unpublished registered RCTs in multiple myeloma. For maintenance therapy in patients who are transplant eligible, the *Daratumumab/rHuPh20 as Post-ASCT Maintenance for MM w/MRD to Direct Therapy Duration* (DRAMMATIC)

trial (ClinicalTrials.gov identifier: NCT04071457) warrants comment. This trial compares a strategy of daratumumab-lenalidomide versus lenalidomide maintenance, followed by a second randomization for patients with MRD negativity after 2 years to continue therapy versus discontinue all treatment. However, this trial is not estimated to be completed until 2029.

NEWLY DIAGNOSED MULTIPLE MYELOMA—TRANSPLANT INELIGIBLE

Transplant Ineligible—Therapy

This section addresses Recommendations 3.1.1 and 3.1.2.

Literature Review Update and Analysis

The evidence on transplant-ineligible maintenance therapy is summarized in Table 1 and in Data Supplement S1B (Table S3). Seven trials have associated EPs: ALCYONE,[62,63] CEPHEUS,[64] IMROZ,[65] MAIA,[66-68] OCTANS,[69,70] Palumbo 2010,[71,72] and SWOG S0777.[73,74] Outcome data from these trials are briefly summarized in Table 6[62-67,69-74] with the full details presented in EPs 3.1 to 3.6.

The SWOG S0777 and CEPHEUS trials stand out from ALCYONE, MAIA, IMROZ, and Palumbo 2010 in their approach to transplant eligibility criteria. While ALCYONE, MAIA, IMROZ, and Palumbo 2010 exclusively enrolled transplant-ineligible patients (typically age ≥65 years or with significant comorbidities), SWOG S0777 enrolled patients without intent for immediate autologous stem cell transplant with 229 patients (43.6%) confirmed in a later publication as never receiving transpant.[74] CEPHEUS specifically enrolled transplant-ineligible patients (≥70 years or <70 with limiting conditions) and transplant-deferred patients (<70 years not planning immediate transplant), while excluding up-front transplant-eligible patients. This variation in transplant eligibility criteria represents an important consideration when comparing outcomes.

Clinical Interpretation

Until 2024, the standard of care for most transplant-ineligible patients was a triplet regimen such as daratumumab, lenalidomide, and dexamethasone or bortezomib, lenalidomide, and dexamethasone. In the MAIA trial,[66,67] daratumumab, lenalidomide, and dexamethasone were shown to outperform lenalidomide-dexamethasone in terms of PFS, OS, and patient-reported outcomes including quality of life. In the SWOG S0777 trial,[73,74] bortezomib, lenalidomide, and dexamethasone similarly outperformed lenalidomide and dexamethasone in terms of PFS and OS, although this was in a context where 69% of patients did eventually receive ASCT. More recent phase III trials show that quadruplet regimens may be superior to these triplets in this patient population. The IMROZ[65] and CEPHEUS[64] trials have both demonstrated a PFS benefit with the addition of CD38-targeted monoclonal antibody (isatuximab and daratumumab, respectively) to bortezomib, lenalidomide, and dexamethasone in patients considered to be transplant ineligible or for whom upfront ASCT was not planned. OS data are immature for both trials. The IFM 2020-05/BENEFIT trial[75] investigated isatuximab plus bortezomib, lenalidomide, and dexamethasone versus isatuximab plus lenalidomide and dexamethasone in this patient population and is noted in the Data Supplement. It found approximately double the rates of MRD negativity with the addition of bortezomib, but PFS and OS data are immature.

Despite the slight differences in patient populations, these trials collectively suggest that quadruplet regimens containing a CD38-targeted monoclonal antibody should be considered as the starting point for all transplant-ineligible patients. These patients are at a particular risk of attrition after the failure of first-line therapy because of advancing age, comorbidities, and future frailty that may limit treatment options in the relapsed setting.[76] For some patients with symptomatic myeloma, more rapid disease debulking with a quadruplet regimen may mean improved pain control and thus better quality of life. Indeed, given the possibility of dynamic frailty whereby patients' fitness may improve with effective therapies,[77] starting with a quadruplet may allow some patients with disease-related frailty who were previously considered transplant ineligible to become transplant-eligible with the initiation of treatment. Although both IMROZ and CEPHEUS excluded patients age 81 years and older, the panel does not consider this age threshold as an absolute requirement. Older patients may sometimes benefit from quadruplet therapy in some cases. Geriatric assessment may be valuable in making these decisions and ASCO guidelines recommend all patients with cancer age 65 years and older receiving systemic therapy, including chemotherapy, targeted therapy, and/or immunotherapy with geriatric assessment-identified impairments should have geriatric assessment-guided management included in their care plan. Please refer to ASCO's guidelines on the topic.[78,79] As an important caveat, both the IMROZ and CEPHEUS trials used twice per week bortezomib based on the design of the SWOG S0777 trial. In modern practice, twice per week bortezomib should not be used outside of emergent situations given lower rates of neuropathy, less time toxicity, and equal efficacy with once per week dosing found in non-randomized data.[80-82]

As frailty remains an important consideration when selecting frontline therapy and may not be reversible with treatment, triplet regimens of either daratumumab or bortezomib combined with lenalidomide and dexamethasone may still be reasonable for some transplant-ineligible patients. No patients in the IMROZ,[65] CEPHEUS,[64] or BENEFIT[75] trials were age older than 80 years at registration, and frailty was not interrogated preregistration. The single-arm phase II REST study[83] of ASCT-ineligible patients (median age 77 years, 31% of patients older than 80 years,

TABLE 6. Outcomes From Key Randomized Trials in Transplant-Ineligible Patients—See Evidence Profiles 3.1-03.6 for More Complete Accounting and Data

Trial	Intervention	Comparator	OS, HR (95% CI) [No. of participants]	OS Certainty	PFS, HR (95% CI) [No. of participants]	PFS Certainty	Important[a] AEs During Treatment [No. of Participants]	Important AEs Certainty
ALCYONE[62,63] OCTANS[69,70]	Daratumumab, bortezomib, melphalan, and prednisone	Bortezomib, melphalan, and prednisone	0.6 (0.46 to 0.8) [706]	High	0.41 (0.34 to 0.49) [926]	High	1.17 (0.99 to 1.4) [915]	Moderate
CEPHEUS[64]	Daratumumab, bortezomib, lenalidomide, and dexamethasone	Bortezomib, lenalidomide, and dexamethasone	0.85 (0.58 to 1.24) [395]	Moderate	0.57 (0.41 to 0.79) [395]	High	1.07 (0.94 to 1.22) [392]	Low
IMROZ[65]	Isatuximab, bortezomib, lenalidomide, and dexamethasone	Bortezomib, lenalidomide, and dexamethasone	0.78 (0.65 to 0.93) [446]	Moderate	0.6 (0.51 to 0.7) [446]	High	1.05 (0.92 to 1.19) [444]	Low
MAIA[66,67]	Daratumumab, lenalidomide, and dexamethasone	Lenalidomide, and dexamethasone	0.68 (0.53 to 0.86) [737]	High	0.53 (0.43 to 0.66) [737]	High	1.1 (1.01 to 1.2) [729]	Moderate
Palumbo 2010[71,72]	Thalidomide, bortezomib, melphalan, and prednisone	Bortezomib, melphalan, and prednisone	0.7 (0.52 to 0.92) [511]	High	0.58 (0.47 to 0.71) [511]	Moderate	Not reported	Not applicable
SWOG S0777[73,74]	Bortezomib, lenalidomide, and dexamethasone	Lenalidomide, and dexamethasone	0.71 (0.54 to 0.93) [460]	High	0.74 (0.59 to 0.93) [460]	High	1.11 (0.92 to 1.33) [459]	Low

Abbreviations: AEs, adverse events; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.
[a]This column reports serious adverse events if they were reported but see evidence profile for the specific outcome.

45% frail by IMWG criteria) tested a dexamethasone-sparing version of bortezomib, lenalidomide, and dexamethasone in conjunction with isatuximab—in other words, a quadruplet regimen with dexamethasone discontinuation after 2 months. Even in this older and less fit patient population, relative dose intensities of medications were high (97% for isatuximab, 97% for bortezomib, 83% for lenalidomide) and over one third of patients achieved MRD negative-complete responses. Both the REST trial and the BENEFIT trial used once per week bortezomib, the former for eight cycles and the latter for 18 cycles. In the absence of randomized data, some patients beyond age 80 and/or IMWG-designated frail patients may reasonably opt for less aggressive treatment to avoid toxicities. There are significant toxicity concerns to consider when deciding on which regimen to use. In the BENEFIT trial,[75] higher rates of treatment-emergent grade 2 or higher peripheral neuropathy were reported with the addition of bortezomib (27% *v* 10%). This may be explained by the long duration of bortezomib therapy, even if at lower-frequency dosing.

Regardless of which quadruplet or triplet regimen is selected, another important consideration is how to tailor these regimens to individual patients. As mentioned previously, once per week bortezomib is recommended for all patients in this setting based on nonrandomized data[80-82] showing less toxicity. Similarly, a large secondary analysis of the S0777 and SWOG S1211 trials[84] (both of which enrolled largely transplant ineligible patients) has demonstrated that lowering dexamethasone doses during induction does not impact PFS or OS. This finding aligns with an earlier randomized trial, LaRocca 2012 in the Data Supplement,[85] of alternative lenalidomide and dexamethasone dosing strategies in this patient population. In this trial, stopping the dexamethasone after 9 months led to fewer toxicities and higher lenalidomide exposure, with no significant difference in PFS. Given the myriad of acute and long-term toxicities of dexamethasone including visually significant cataracts and impaired bone health,[86,87] these data collectively support the consideration of dexamethasone dose de-escalation after 6-9 months or earlier as toxicities develop.

While these trials all used triplets or quadruplets containing a lenalidomide and dexamethasone backbone, several other trials using bortezomib, melphalan, and prednisone as the backbone, also warrant discussion, particularly in settings where lenalidomide is not available in the frontline setting. In the previous guideline, the quadruplet of daratumumab, bortezomib, melphalan, and prednisone was recommended as a possible therapy based on preliminary results of the ALCYONE trial. Since that time full results of ALCYONE[62,63] and the very similar trial, OCTANS[69] have been published (EP 3.1) that show OS and PFS benefit for the addition of daratumumab to bortezomib, melphalan, and prednisone. In addition, the Palumbo 2010[71,72] trial (EP 3.4) found OS and PFS benefit for a bortezomib, thalidomide, melphalan, and prednisone regimen followed by bortezomib and thalidomide maintenance. The interpretation of these trials is contingent on whether one believes the bortezomib, melphalan, and prednisone comparator is reasonable. The consensus of the panel was that these regimens are infrequently used, and therefore, the ALYCONE/OCTANS and Palumbo 2010 regimens have not been recommended. However, in regions where lenalidomide is not available as frontline therapy and oral melphalan is, daratumumab, bortezomib, melphalan, and prednisone is a reasonable treatment option.

Ongoing Trials and Future Research

See Data Supplement S1B (Table S7) for a list of all known unpublished registered RCTs in multiple myeloma. In patients who are transplant ineligible, two trials warrant comment:

- IFM 2017-03 trial (ClinicalTrials.gov identifier: NCT03993912): In a conference abstract,[88] this trial has reported that daratumumab plus lenalidomide (with discontinuation of dexamethasone after two cycles) had significantly improved PFS (HR, 0.51 [95% CI, 0.37 to 0.71]) compared with lenalidomide and dexamethasone in frail patients; the full publication of these results is needed for confirmation.
- SWOG S2209 (ClinicalTrials.gov identifier: NCT05561387): This trial has three arms: daratumumab, lenalidomide, and dexamethasone followed by daratumumab plus lenalidomide maintenance; daratumumab, lenalidomide, and dexamethasone followed by single-agent lenalidomide maintenance; and bortezomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance. However, the trial has an estimated completion of 2030.

RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Relapsed or Refractory—Therapy

This section addresses Recommendations 4.1 to 4.4.2.

Literature Review Update and Analysis

The evidence on therapy for relapsed or refractory disease is summarized in Table 1 and in Data Supplement S1B (Table S5). Nineteen trials have associated EPs. Outcome data from these trials are briefly summarized in Table 7[28,89-105] with the full details presented in EPs 4.1-4.18.

Although an EP was created based on the OCEAN trial[6] of melphalan flufenamide (melflufen) plus dexamethasone for consistency (all trials that compared with a reasonable doublet and had a PFS benefit with no OS detriment had EPs created), melphalan flufenamide is not discussed further as it was withdrawn from the US market by the US Food and Drug Administration (FDA) owing to safety and efficacy concerns.

TABLE 7. Outcomes From Key Randomized Trials in Patients With Relapsed/Refractory Disease—See Evidence Profiles 4.1-4.18 for More Complete Accounting and Data

Trial	Population	Intervention	Comparator	OS, HR (95% CI) [No. of participants]	OS Certainty	PFS, HR (95% CI) [No. of participants]	PFS Certainty	Important[a] AEs During Treatment, RR (95% CI) [No. of participant]	Important AEs Certainty
CARTITUDE-4[89]	Refractory to lenalidomide; 1-3 prior treatments including a proteasome inhibitor and immunomodulatory agent	Ciltacabtagene autoleucel	Physician's choice of pomalidomide + bortezomib + dexamethasone or daratumumab + pomalidomide + dexamethasone	0.78 (0.5 to 1.2) [419]	Moderate	0.26 (0.18 to 0.38) [419]	Moderate	1.14 (0.9 to 1.43) [416]	Moderate
KarMMa-3[90]	2-4 prior treatments including immunomodulatory agent, proteasome inhibitor, daratumumab	Idecabtagene vicleucel	One of five standard regimens chosen by investigator	1.01 (0.73 to 1.4) [386]	Low	0.49 (0.38 to 0.63) [386]	Moderate	1.37 (1.06 to 1.76) [376]	Moderate
OPTIMISMM[91]	1-3 prior treatments	Pomalidomide, bortezomib, and dexamethasone	Bortezomib and dexamethasone	0.98 (0.73 to 1.32) [559]	Low	0.61 (0.49 to 0.77) [559]	High	1.35 (1.14 to 1.61) [548]	Moderate
CASTOR,[92] LEPUS[93]	1-3 prior treatments	Daratumumab, bortezomib, and dexamethasone followed by daratumumab	Bortezomib and dexamethasone	0.74 (0.59 to 0.92) [498]	Moderate	0.32 (0.26 to 0.39) [709]	Moderate	1.52 (1.26 to 1.82) [688]	Moderate
BOSTON[94]	1-3 prior treatments	Selinexor, bortezomib (once per week), and dexamethasone	Bortezomib (twice per week) and dexamethasone followed by bortezomib (once per week) and dexamethasone	0.84 (0.57 to 1.23) [402]	Moderate	0.7 (0.53 to 0.93) [402]	High	1.37 (1.1 to 1.71) [399]	Moderate
ENDEAVOR[28]	1-3 prior treatments; partial response to at least one treatment	Carfilzomib and dexamethasone	Bortezomib and dexamethasone	0.79 (0.65 to 0.96) [929]	High	0.53 (0.44 to 0.65) [929]	High	1.48 (1.29 to 1.69) [919]	Moderate
APOLLO[95]	At least 1 prior treatment with lenalidomide and proteasome inhibitor	Daratumumab, pomalidomide, and dexamethasone	Pomalidomide and dexamethasone	0.82 (0.61 to 1.11) [304]	Moderate	0.63 (0.47 to 0.85) [304]	High	1.34 (1.05 to 1.72) [299]	Moderate
ELOQUENT-3[96]	Two or more prior treatments including lenalidomide and proteasome inhibitor	Elotuzumab, pomalidomide, and dexamethasone	Pomalidomide and dexamethasone	0.59 (0.37 to 0.93) [117]	High	0.54 (0.34 to 0.86) [117]	Moderate	1.17 (0.89 to 1.53) [115]	Low
ICARIA-MM[97]	Two or more prior treatments; not responded to lenalidomide and a proteasome inhibitor	Isatuximab, pomalidomide, and dexamethasone	Pomalidomide and dexamethasone	0.78 (0.59 to 1.02) [307]	Moderate	0.6 (0.44 to 0.81) [307]	High	1.21 (1.03 to 1.42) [301]	Moderate

(continued on following page)

TABLE 7. Outcomes From Key Randomized Trials in Patients With Relapsed/Refractory Disease—See Evidence Profiles 4.1-4.18 for More Complete Accounting and Data (continued)

Trial	Population	Intervention	Comparator	OS, HR (95% CI) [No. of participants]	OS Certainty	PFS, HR (95% CI) [No. of participants]	PFS Certainty	Important[a] AEs During Treatment, RR (95% CI) [No. of participant]	Important AEs Certainty
CANDOR[98]	1-3 prior treatments; partial response to at least one treatment	Daratumumab, carfilzomib, and dexamethasone	Carfilzomib and dexamethasone	0.78 (0.6 to 1.03) [466]	Moderate	0.64 (0.49 to 0.83) [466]	High	1.31 (1.11 to 1.55) [461]	Moderate
IKEMA[99]	1-3 prior treatments	Isatuximab, carfilzomib, and dexamethasone	Carfilzomib and dexamethasone	0.78 (0.54 to 1.12) [302]	Low	0.58 (0.42 to 0.79) [302]	High	1.17 (0.98 to 1.39) [299]	Low
ASPIRE[100]	1-3 prior treatments	Carfilzomib, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	0.79 (0.67 to 0.95) [792]	High	0.69 (0.57 to 0.83) [792]	High	1.15 (1.03 to 1.29) [781]	Moderate
ELOQUENT-2[101]	1-3 prior treatments	Elotuzumab, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	0.82 (0.68 to 0.99) [646]	High	0.72 (0.6 to 0.87) [646]	High	1.23 (1.1 to 1.37) [635]	Moderate
POLLUX[102]	1-3 prior treatments, not lenalidomide refractory	Daratumumab, lenalidomide, and dexamethasone	Lenalidomide and dexamethasone	0.73 (0.58 to 0.91) [569]	High	0.37 (0.27 to 0.52) [569]	High	1.37 (1.2 to 1.57) [564]	Moderate
TOURMALINE-MM1[103]	1-3 prior treatments	Ixazomib, lenalidomide, and dexamethasone	Placebo, lenalidomide, and dexamethasone	0.94 (0.78 to 1.13) [722]	High	0.74 (0.59 to 0.94) [722]	High	1.01 (0.89 to 1.15) [720]	Moderate
DREAMM-7[104]	>1 prior treatments	Belantamab mafodotin, bortezomib, and dexamethasone	Daratumumab, bortezomib, and dexamethasone	Not reported	Not reported	0.41 (0.31 to 0.53) [494]	High	1.35 (1.1 to 1.66) [488]	Moderate
DREAMM-8[105]	>1 prior treatments	Belantamab mafodotin, pomalidomide, and dexamethasone	Bortezomib, pomalidomide, and dexamethasone	0.77 (0.53 to 1.14) [302]	Low	0.52 (0.37 to 0.73) [302]	High	1.4 (1.13 to 1.74) [295]	Moderate

Abbreviations: AEs, adverse events; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RR, relative risk.
[a]This column reports serious adverse events if they were reported but see evidence profile for the specific outcome.

Clinical Interpretation

Recommendations 4.1 and 4.2 are mostly unchanged from the previous guideline; 4.1 has been made a Good Practice Statement. The time frame and wording of Recommendation 4.4 were altered to clarify the distinction between patients who have never received ASCT and those that have, and to extend the duration of response after ASCT to 4-5 years. This time frame change was based on several factors. First, older retrospective data report that relapse more than 36 months after a first ASCT was associated with superior outcomes with a second ASCT.[106] Second, the panel acknowledges that with the introduction of triplet and now quadruplet induction therapy, the median PFS for patients receiving frontline ASCT was 67.5 months with bortezomib, lenalidomide, and dexamethasone and even longer with quadruplet therapies.[39] Finally, the availability of T-cell redirecting therapies has expanded the treatment options for patients with relapsed or refractory myeloma such that the threshold for a second ASCT should be higher. However, the panel recognizes that patients who are unable to receive maintenance therapy, especially as recommended in this guideline in the Transplant Eligible section, may not experience the long remission times experienced in the trials with maintenance, and that repeat ASCT sooner than 4-5 years may be reasonable in those patients when other options are not available. In the GMMG-ReLApsE study, patients with relapsed and/or refractory multiple myeloma, nearly all of whom received a prior ASCT, were randomly assigned to receive lenalidomide and dexamethasone alone or followed by a second ASCT. While time to progression following frontline ASCT was prognostic, it was not associated with benefit in the second ASCT arm. However, this study included over a third of patients who received a frontline tandem ASCT and excluded patients with lenalidomide-refractory disease, limiting applicability to current treatment paradigms. See the previous guideline for further justification of these recommendations and a discussion of the evidence that underlies them. Recommendation 4.3 is completely reworked in this updated guideline and is explained and justified in the remainder of this section. There have been many randomized trials of triplet therapy compared with doublet therapy. The general conclusion from these randomized trials is that triplet therapy should be offered to all eligible patients over doublet therapy. However, given the way these trials were conducted, there is great uncertainty as to how to best rank the many potential triplet therapies. Ten relevant agents have been tested in triplets including dexamethasone, bortezomib, carfilzomib, ixazomib, isatuximab, daratumumab, elotuzumab, belantamab mafodotin, selinexor, pomalidomide, and lenalidomide. Even if network meta-analysis could be relied upon to help rank these agents, there has never been a trial in relapsed or refractory patients comparing bortezomib plus dexamethasone to any of dexamethasone alone, pomalidomide plus dexamethasone, or lenalidomide plus dexamethasone. Therefore, the trials would not be connected within the network. Also, it is difficult to support a recommendation of any two drugs plus dexamethasone because not all possible combinations have been tested against reasonable doublets. In the absence of prospective studies, an adjusted real-world analysis of patients receiving daratumumab and dexamethasone-based triplet therapies in first or second relapse found no significant difference in time to next treatment between pomalidomide and carfilzomib as the third agent (HR, 1.1 [95% CI, 0.8 to 1.6]) and found both pomalidomide and carfilzomib superior to bortezomib (HR, 0.57 [95% CI, 0.43 to 0.77] and HR, 0.70 [95% CI, 0.49 to 0.99], respectively) as the third agent.[107]

The inclusion of anti-CD38 monoclonal antibodies (eg, daratumumab and isatuximab) into frontline therapy may render triplet combinations involving these agents potentially less useful at relapse. Thus, regimens without robust phase III evidence may be the only available options when other options have been exhausted.[108] In the GEM-KyCyDex trial,[109] the addition of cyclophosphamide to carfilzomib and dexamethasone was not associated with superior PFS overall but there was a significant PFS benefit (HR, 1.7 [95% CI, 1.1 to 2.7]) for patients with myeloma refractory to lenalidomide. To our knowledge, to date, there have been only two randomized triplet versus triplet trials (DREAMM-7[104] and DREAMM-8[105]); both found superior PFS with the belantamab mafodotin-based triplet.

The two pivotal phase III trials of CAR T-cell therapy versus standard-of-care doublets or triplets increase the complexity further. In the KarMMa-3 study, patients with 2-4 prior lines of therapy received either idecabtagene vicleucel (ide-cel) or investigator's choice of therapy; ide-cel was associated with a PFS benefit, meeting its primary end point. The randomized CARTITUDE-4 study found that ciltacabtagene autoleucel (cilta-cel) was associated with superior PFS and OS compared with standard-of-care triplet regimens in patients with lenalidomide-refractoriness and 1-3 prior lines of therapy. These trials did not include all potential triplets in the comparator arms, and only one, CARTITUDE 4,[89] was in patients at first relapse.

There is even less evidence that can be applied to determine the best choice on further relapse after the first. Most of the included randomized trials of triplet therapy included patients with one to three prior treatments, but the proportion of patients at each relapse was not consistent. Also, in many of these trials, patients may have received initial therapy that would not currently be recommended (Recommendations 1.1-3.2.3); for example, many transplant-eligible patients would have only received doublet or single-agent therapy and may not have received maintenance therapy. Patients treated according to this guideline will have received initial therapy with agents that were considered novel at the time the relapsed or refractory studies were initiated, for example, daratumumab. Finally, while CAR T-cell therapy has been shown to be superior to some triplets, one cannot conclude it would be superior to all triplet regimens.

Some novel therapies for myeloma involve unique toxicities which bear mentions.

- Belantamab ocular toxicity: Belantamab mafodotin therapy is associated with a substantially higher rate of ocular toxicity than comparator regimens. In the DREAMM-7 and DREAMM-8 trials, patients receiving belantamab mafodotin experienced more grade 3 or higher ocular adverse events than daratumumab and bortezomib, respectively (82/242 [34%] *v* 7/246 [3%], $P < .0001$ using Fisher exact test in DREAMM-7, 65/150 [43%] *v* 3/145 [2%], $P < .0001$ using Fisher exact test in DREAMM-8). Regular ocular examinations were mandated in both trials, and ocular toxicity was managed with dose reductions or interruptions. With this approach, ocular toxicity was usually temporary. Nonetheless, if belantamab mafodotin is used at relapse, regular ocular exams are required, and if they are not available belantamab mafodotin may not be an optimal choice.
- CAR-T therapy neurotoxicity: Neurotoxicity (immune effector cell-associated neurotoxicity syndrome [ICANS]) is a well-recognized, unique complication of CAR T-cell therapy. For instance, in the KarMMa-3 trial[90] of ide-cel, 7/225 (3%) versus 0/126 of patients experience grade 3 or four neuro-toxic events ($P = .0527$ using Fisher exact test). In the CARTITUDE-4 trial[89] of cilta-cel, 5/176 (3%) versus 0/208 of patients experienced grade 3 or four neuro-toxic events ($P = .0196$ using Fisher exact test). No grade 5 events were reported in either trial. Beyond traditional ICANS, B-cell maturation antigen (BCMA)-directed CAR T-cell therapies present unique non-ICANS neurotoxicities (NINTs), including movement and neurocognitive treatment-emergent adverse events that can manifest weeks to months after infusion.[110] These include parkinsonism-like symptoms, peripheral neuropathy, and cranial nerve palsies that are distinct from typical ICANS presentations. These complications are linked to high CAR T-cell expansion and prolonged persistence, with elevated peak absolute lymphocyte counts serving as a key risk factor.

There is very limited evidence regarding treatment at 4th or greater relapse. About half of the relevant trials excluded these patients, and of those that did they were included in limited numbers. There have been four therapies approved in the United States for patients at 4th or greater relapse, all stemming from nonrandomized trials. These include three BCMAxCD3-directed bispecific antibodies (elranatamab,[111] linvoseltamab,[112] and teclistamab[113]) and the GPRC5DxCD3-directed bispecific antibody talquetamab.[114] All four agents have led to impressive efficacy in heavily pretreated populations, but also at the expense of unique toxicities that must be taken into account. These outcomes are briefly summarized in Table 8.[111-114] In the absence of direct comparisons between these agents or with other treatment regimens, it is not possible to convey a recommendation for a preferred strategy, other than to say that these regimens may be offered to patients indicated by their regulatory approval.

Given this great uncertainty, the panel believed the best possible course of action at this time was to make more general recommendations (Recommendation 4.3) providing a list of principles that a clinician can use to guide decisions about the order in which to offer those therapies as the patient relapses over time. These principles include the following:

- Whenever possible, patients should be offered treatment regimens that include agents that are different than those in their prior therapies. This is based on the basic principle that if a person has cancer that relapsed on a particular agent, their myeloma is likely refractory to that agent.
- Triplets should be offered to eligible patients. The best data available indicate that triplet combinations have better PFS than doublets with similar toxicity or manageably increased toxicity. For anti-CD38 monoclonal antibodies, there is evidence supporting avoiding reintroduction for at least 6 months after last exposure.[115,116]
- CAR T-cell therapy should be offered to eligible patients. A thorough patient-centered discussion regarding the risks,

TABLE 8. Key Outcomes From Nonrandomized Studies of Bispecific Antibodies in Patients With Relapsed or Refractory Multiple Myeloma at Fourth or Greater Relapse

Agent; Study; No. of Patients	Key Efficacy Outcomes	Key Toxicity Outcomes
Elranatamab; MagnetisMM-3[111]; 123	ORR 61.0%, CR 35.0%, PFS at 15 months 50.9%	Grade 3 or 4 TEAEs 70.7%, grade 3 or 4 infection 39.8%, fatal infection 6.5%
Linvoseltamab: LINKER-MM1[112]; 117	ORR 71%, CR 50%, PFS at 12 months 70%	Grade 3 or 4 AEs 73.5%, including 6 treatment-related deaths (5 of which were due to fatal infections)
Teclistamab; MajesTEC-1[113]; 165	ORR 63.0%, CR 39.4%, median PFS 11.3 months	Grade 3 or 4 AEs 94.5%, 19 patients died of adverse events (12 from COVID-19 infection), 5 deaths considered by investigators to be related to teclistamab
Talquetamab[a]; MonumenTAL-1[114]; 232	ORR 64% to 72%, CR 23% to 28%	Grade 3 or 4 AEs 86%-90%, serious AEs in 34% to 43%, 3 fatal adverse events, none considered related to treatment by investigators

Abbreviations: AEs, adverse events; CR, complete response; ORR, overall or objective response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse events.

[a]MonumenTAL-1 studied two subcutaneous dose levels and one intravenous dose level of talquetamab. Outcomes are the range among these options.

TABLE 9. Key Ongoing Trials in Patients Relapsed and/or Refractory Multiple Myeloma

Primary Completion Date	Registry ID (name)	Arms	Setting
2025	NCT05020236 (MagnetisMM-5)	Elranatamab *v* elranatamab + DAR *v* DAR + POM + DEX	Relapsed/refractory, prior LEN and proteasome inhibitor
2025	NCT05083169 (MajesTEC-3)	Teclistamab + DAR *v* DAR + POM + DEX *v* DAR + BOR + DEX	Relapsed/refractory, 1-3 prior lines
2026	NCT05455320 (MonumenTAL-3)	Talquetamab + DAR + POM + DEX *v* talquetamab + DAR + DEX *v* DAR + POM + DEX	Relapsed/refractory, at least 1 prior line
2026	NCT05572515 (MajesTEC-9)	Teclistamab *v* investigator's choice of: BOR + POM + DEX or CAR + DEX	Relapsed/refractory, 1-3 prior lines
2026	NCT06152575 (MagnetisMM-32)	Elranatamab *v* investigator's choice of: ELO + POM + DEX, BOR + POM + EX, or CAR + DEX	Relapsed/refractory, 1-4 prior lines
2026	NCT06208150 (MonumenTAL-6)	Talquetamab + POM + DEX *v* talquetamab + teclistamab + DEX *v* investigator's choice of: ELO + POM + DEX or BOR + POM + DEX	Relapsed/refractory

Abbreviations: BOR, bortezomib; CAR, carfilzomib; DAR, daratumumab; DEX, dexamethasone; ELO, elotuzumab; POM, pomalidomide; SEL, selinexor.

benefits, and timing of CAR T-cell therapy is advised. CAR T-cell therapy has been shown to be a valuable option, but no guidance can be given as to exactly when it should be used, and not all patients may be able to access it. For example, patients who value a long treatment-free interval, higher efficacy, and accept a potential higher toxicity burden may prefer earlier administration of CAR T-cell therapy.

- Patient preferences with respect to toxicity tolerance, dose and schedule convenience, and means of administration should be factored in with shared decision making when deciding between triplet or CAR T-cell therapy. Given that there is little evidence upon which to base decisions about preferred therapy and sequencing, understanding patient preferences is crucial. For example, if a patient values a higher convenience option as their next therapy, there are no evidence-based reasons to suggest that option should not be chosen.
- CAR T-cell therapy may not be appropriate for patients with rapidly progressive relapsed myeloma given the time required for CAR T-cell manufacturing. In this setting, an agent that is immediately available with anticipated rapid efficacy may be favored over CAR T-cell therapy. CAR T-cell therapy may take between 3 and 6 weeks to manufacture engineered T cells.[117]
- If the patient is unable to receive triplet or CAR T-cell therapy (based on tolerability, frailty, access, etc), doublet therapy is reasonable. Doublet therapy has been demonstrated in earlier trials to be superior to single-agent dexamethasone and therefore remains an option in these patients. However, not all doublets are necessarily equally useful. For example, in the ENDEAVOR trial[28,118] (Table 7 and EP 4.6), carfilzomib plus dexamethasone was superior to bortezomib and dexamethasone in terms of PFS and OS, with an increase in toxicity.
- Bispecific antibodies should be offered to eligible patients (including older and frail patients). The four bispecific antibodies (elranatamab, linvoseltamab, teclistamab, talquetamab) with regulatory approval are reasonable options in patients where other options are not possible or exhausted.
- The optimal sequencing of therapy is an evolving consideration. Currently, there is limited evidence regarding optimal sequencing; in this context, sequencing decisions should be based on patient factors, disease characteristics, mechanism of action, and prior treatment responses. There is little evidence upon which a specific sequence of therapy can be justified. As noted previously, patients receiving care at diagnosis per the recommendations in this updated guideline may be considered refractory to many of the agents in the triplet regimens tested in relapsed or refractory RCTs. Unfortunately, the panel can provide little guidance on this matter until further data are available, and clinicians will need to exercise their best judgment among this uncertainty.
- For patients in whom existing options have been exhausted or for whom the risks are likely to outweigh the benefits, best supportive care and hospice referral should be offered. Given the very limited data available to inform therapy choices at increasing numbers of relapse some patients will exhaust all available options, especially as agents are moved earlier in the sequence of therapy.

Ongoing Trials and Future Research

See Data Supplement S1B (Table S7) for a list of all known unpublished registered RCTs in multiple myeloma. For patients with relapsed or refractory disease, Table 9 lists key trials with expected primary completion dates of 2026 or earlier that warrant mention here.

DISCUSSION

The 2019 guideline[1] contains discussion on patient access considerations, multiple chronic conditions, and cost implications. These sections are not reprinted here; please refer to the 2019 guideline for details.

PATIENT AND CLINICIAN COMMUNICATION

The 2019 guideline[1] contains discussion on patient and clinician communication that remains largely relevant; please refer to the 2019 guideline for details. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[119]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a community oncologist member on the panel. The additional role of this community oncologist member on the guideline panel is to assess the suitability of the recommendations for implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline recommendations table and accompanying tools (available at www.asco.org/hematologic-malignancies-guidelines) were designed to facilitate implementation of recommendations. This guideline will be distributed widely. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

INCLUSIVE LANGUAGE

ASCO is committed to promoting the health and well-being of all patients. ASCO guidelines are intended to apply to, and be discussed clearly and compassionately with, all patients. For this reason, guideline authors use appropriately inclusive language. In instances in which the guideline draws upon data based on research in a specified population (eg, studies regarding women with ovarian cancer), the guideline authors describe the characteristics and results of the research as reported.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

RELATED ASCO GUIDELINES

- Management of Immune-Related Adverse Events in Patients Treated With Chimeric Antigen Receptor T-cell Therapy: ASCO Guideline[120] (https://ascopubs.org/doi/10.1200/JCO.21.01992)
- Palliative Care for Patients With Cancer[119] (http://ascopubs.org/doi/10.1200/JCO.24.00542)
- Patient-Clinician Communication[121] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Practical Assessment and Management of Vulnerabilities in Older Patients Receiving Systemic Cancer Therapy[78] (https://ascopubs.org/doi/10.1200/JCO.23.00933)
- Geriatric Assessment: ASCO Global Guideline[79] (https://ascopubs.org/doi/10.1200/GO-25-00276)

ADDITIONAL RESOURCES

For current information, including selected updates, supplements, and clinical tools and resources, visit www.asco.org/hematologic-malignancies-guidelines. The Data Supplement for this guideline includes details of all included trials, EPs for selected trials, a listing of published trials, and details on the systematic review. Guideline recommendations and algorithms are also available in the free ASCO Guidelines app (available for download in the Apple App Store and Google Play Store). Listen to key recommendations and insights from panel members on the ASCO Guidelines podcast. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.org.

ASCO welcomes your comments on this guideline, including implementation challenges, new evidence, and how this guideline impacts you. To provide feedback, contact us at guidelines@asco.org. Comments may be incorporated into a future guideline update. To submit new evidence or suggest a topic for guideline development, complete the form available at www.asco.org/guidelines.

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EDITOR'S NOTE

This ASCO Clinical Practice Guideline Update provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, clinical tools and resources, and links to patient information at www.cancer.org, is available at www.asco.org/hematologic-malignancies-guidelines.

EQUAL CONTRIBUTION

L.H. and J.M. were Expert Panel Co-Chairs.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO-25-02587.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Treatment of Multiple Myeloma: ASCO–Ontario Health (Cancer Care Ontario) Living Guideline

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APPENDIX 1. GUIDELINE DISCLAIMER

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APPENDIX 2. GUIDELINE AND CONFLICTS OF INTEREST

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships.

TABLE A1. Treatment of Multiple Myeloma Guideline Expert Panel Membership

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Rahul Banerjee, MD	Fred Hutchinson Cancer Center, Seattle, WA	Hematologic Oncologist
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TABLE A2. Recommendation Rating Definitions

Term	Definition
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Conditional/Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

NOTE. GRADE Handbook.[122]