Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

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ASSOCIATED CONTENT

Appendix

Data Supplement

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Editor's note: This American Society of Clinical Oncology/Cancer Care Ontario joint Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/hematologic-malignancies-guidelines.

J.M. and T.M. were Expert Panel co-chairs.

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PURPOSE To provide evidence-based recommendations on the treatment of multiple myeloma to practicing physicians and others.

METHODS ASCO and Cancer Care Ontario convened an Expert Panel of medical oncology, surgery, radiation oncology, and advocacy experts to conduct a literature search, which included systematic reviews, meta-analyses, randomized controlled trials, and some phase II studies published from 2005 through 2018. Outcomes of interest included survival, progression-free survival, response rate, and quality of life. Expert Panel members used available evidence and informal consensus to develop evidence-based guideline recommendations.

RESULTS The literature search identified 124 relevant studies to inform the evidence base for this guideline.

RECOMMENDATIONS Evidence-based recommendations were developed for patients with multiple myeloma who are transplantation eligible and those who are ineligible and for patients with relapsed or refractory disease.

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

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INTRODUCTION

The purpose of this guideline is to provide evidence-based recommendations for the treatment of newly diagnosed and relapsed multiple myeloma. The treatment of multiple myeloma has changed significantly in the last 5 years. Since 2015, four new drugs have been approved, thus providing more options and adding to the complexity of treatment options (Table 1). Numerous large phase III trials have been performed in both the newly diagnosed and relapse/refractory disease settings in an attempt to prioritize various treatments. This guideline will put all the new drugs and randomized trials in context and provide guidance for incorporating the novel drugs.

Epidemiology

In 2018, an estimated 30,770 new cases of multiple myeloma were diagnosed in the United States, representing 1.8% of all new cancer cases. The estimated number of deaths as a result of multiple myeloma in 2018 was 12,770, representing 2.1% of all cancer deaths. Despite significant advances and improvements in overall survival (OS), multiple myeloma remains incurable, and additional treatments are needed. The median survival is just over 5 years, and most patients receive four or more different lines of therapy throughout their disease course. In 2015, there were an estimated 124,733 people living with myeloma, and this number continues to rise as drug therapy improves.[1]

Diagnosis

The majority of patients with myeloma present with symptoms related to organ involvement, including hypercalcemia, renal insufficiency, anemia, and bone lesions (known as calcium, renal failure, anemia, and bone lesions [CRAB] symptoms). A minority of patients are asymptomatic but are found to have abnormal blood and/or urine tests that lead to the diagnosis. The diagnosis requires the presence of clonal plasma cells in the bone marrow or in a biopsy-proven bone or extramedullary plasmacytoma. The specific diagnostic criteria for active multiple myeloma have recently been updated by the International Myeloma Working Group (IMWG) and include the presence of clonal plasma cells plus CRAB features or one of three new biomarkers (Table 2).[2,3]

The new diagnostic criteria are meant to define a population of patients with myeloma who are either symptomatic or will soon become symptomatic and thus require urgent therapy. With these new criteria, many patients who would have previously been defined as smoldering myeloma will now be more appropriately defined as active and in need of therapy. The intent is to facilitate earlier detection and earlier initiation of treatment, with the aim of improving survival.

Staging

The Durie-Salmon system has traditionally been used to define stage in patients with myeloma. According to

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Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

Guideline Questions

Transplant-Eligible Population

1. What criteria are used to assess eligibility for autologous stem-cell transplant (ASCT)?
2. What are the options for initial therapy before transplant?
3. What post-transplant therapy should be recommended?
4. What are the response goals for the transplant-eligible patient?

Transplant-Ineligible Population

5. What are the options for initial therapy in transplant-ineligible patients?
6. What are the response goals following initial therapy for transplant-ineligible patients?

Relapsed Disease

7. What factors influence choice of first relapse therapy?
8. How does risk status influence therapy in myeloma (newly diagnosed and relapse)?
9. When and how should response assessment be performed?

Please refer to the data supplement for the complete list of questions and subquestions.

Target Population

Patients with multiple myeloma

Target Audience

Medical oncologists, radiation oncologists, hematologists, surgeons, nurses, advanced practice providers, oncology pharmacists, and patients

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Transplant Eligible

Recommendation 1.1. Patients should be referred to a transplant center to determine transplant eligibility (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 1.2. Chronologic age and renal function should not be the sole criteria used to determine eligibility for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.1. The optimal regimen and number of cycles remain unproven. However, at least three to four cycles of induction therapy including an immunomodulatory drug, proteasome inhibitor (PI), and steroids is advised prior to stem-cell collection (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.2. Up-front transplant should be offered to all transplant-eligible patients. Delayed initial SCT may be considered in select patients (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 2.3. Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drug exposure (more than four cycles), should be avoided in patients who are potential candidates for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.4. Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

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Recommendation 2.5. The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy—patients should be referred for SCT independent of depth of response (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.6. High-dose melphalan is the recommended conditioning regimen for ASCT (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 2.7. Tandem ASCT should not be routinely recommended (Type: evidence based; Evidence quality: intermediate, benefit equals harm; Strength of recommendation: strong).

Recommendation 2.8. Salvage or delayed SCT may be used as consolidation at first relapse for those not choosing to proceed to transplant initially (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 2.9. Allogeneic transplant for multiple myeloma is not routinely recommended but may be considered in select high-risk patients or in the context of a clinical trial (Type: evidence based; Evidence quality: intermediate, harm outweighs benefit; Strength of recommendation: strong).

Recommendation 3.1. Consolidation therapy is not routinely recommended but may be considered in the context of a clinical trial. For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 3.2. Lenalidomide maintenance therapy should be routinely offered to standard-risk patients starting at approximately day 90 to 110 at 10 to 15 mg daily until progression. A minimum of 2 years of maintenance therapy is associated with improved survival, and efforts to maintain therapy for at least this duration are recommended (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 3.3. For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 3.4. For high-risk patients, maintenance therapy with a PI with or without lenalidomide may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 3.5. There is insufficient evidence to make modifications to maintenance therapy based on depth of response, including minimal residual disease (MRD) status (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 4.1. The quality and depth of response should be assessed by International Myeloma Working Group (IMWG) criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 4.2. The goal of initial therapy for transplant-eligible patients should be achievement of the best depth of remission. MRD-negative status has been associated with improved outcomes, but it should not be used to guide treatment goals outside the context of a clinical trial (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 4.3. It is recommended that depth of response be assessed with each cycle. Frequency of assessment once best response is attained or on maintenance therapy may be assessed less frequently but at minimum every 3 months (Type: evidence based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Recommendation 4.4. Whole-body low-dose computed tomography (CT) scan has been shown to be superior to skeletal survey done with plain x-rays and is the preferred method for baseline and routine bone surveillance. Fluorodeoxyglucose positron emission tomography/CT and/or magnetic resonance imaging may be used as alternatives at baseline. They may also be used in select situations (eg, risk-stratifying smoldering myeloma, for monitoring response of nonsecretory and oligosecretory myeloma, and if CT or skeletal survey is inconclusive) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

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Transplant Ineligible

Recommendation 5.1. Initial treatment recommendations for patients with multiple myeloma who are transplant ineligible should be individualized based on shared decision making between physicians and patients. Multiple factors should be considered; disease-specific factors such as stage and cytogenetic abnormalities, and patient-specific factors including age, comorbidities, functional status, frailty status, and patient preferences should also be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 5.2. Initial treatment of patients with multiple myeloma who are transplant ineligible should include at minimum a novel agent (immunomodulatory drug or PI) and a steroid if possible (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 5.3. Triplet therapies for patients with multiple myeloma who are transplant ineligible, including bortezomib, lenalidomide, dexamethasone, should be considered. Daratumumab plus bortezomib plus melphalan plus prednisone may also be considered (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 5.4. Physicians/patients should balance the potential improvement in response and disease control with a possible increase in toxicity. Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 5.5. Continuous therapy should be offered over fixed-duration therapy when initiating an immunomodulatory drug or PI-based regimen (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 6.1. The goal of initial therapy for transplant-ineligible patients should be achievement of the best quality and depth of remission (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.2. Depth of response for all patients should be assessed by IMWG criteria (Table 6) regardless of transplant eligibility (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.3. There is insufficient evidence to support change in type and length of therapy based on depth of response as measured by conventional IMWG approaches or MRD (Type: informal consensus; Evidence quality: low, harm outweighs benefit; Strength of recommendation: moderate).

Recommendations 6.4. Upon initiation of therapy, one should define patient-specific goals of therapy. Quality-of-life assessment (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. Redefining the goals prospectively, based on response, symptoms, and quality of life, is recommended (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.5. It is recommended that patients 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. (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Relapsed Disease

Recommendation 7.1. 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 comorbidities (ie, renal insufficiency), frailty, and patient preference. High-risk patients as defined by high-risk cytogenetics and early relapse post-transplant/initial therapy should be treated immediately. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse (Type: informal consensus/evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

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Recommendation 7.2. All clinically relapsed patients with symptoms due to myeloma should be treated immediately (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 7.3. Triplet therapy should be administered on first relapse, though the patient's tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PIs, immunomodulatory drugs, or monoclonal antibodies) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 7.4. Treatment of relapsed multiple myeloma may be continued until disease progression. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) (Type: evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 7.5. Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 7.6. ASCT, if not received after primary induction therapy, should be offered to transplant-eligible patients with relapsed multiple myeloma. Repeat SCT may be considered in relapsed multiple myeloma if progression-free survival after first transplant is 18 months or greater (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Recommendation 8.1. The risk status of the patients should be assessed using the Revised International Staging System for all patients at the time of diagnosis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.2. Repeat risk assessment at the time of relapse should be performed and should include bone marrow with fluorescence in situ hybridization for myeloma abnormalities seen with progression, including 17p and 1q abnormalities. Fluorescence in situ hybridization for primary abnormalities (translocations and trisomies), if seen in the initial diagnostic marrow, does not need to be repeated (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.3. Assessment of other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty, should also be considered/performed (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.4. In patients with genetic high-risk disease, a triplet combination of PI, immunomodulatory drug, and a steroid should be the initial treatment, followed by one or two ASCTs, followed by a PI-based maintenance until progression (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.5. In patients with renal insufficiency, drugs should be modified based on renal clearance (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 8.6. In patients with plasma cell leukemia or extramedullary disease, cytotoxic chemotherapy may have a role (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 9.1. The IMWG revised response criteria should be used for response assessment (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 9.2. All measurable parameters need to be followed, including light and heavy chain analysis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 9.3. All responses excluding marrow and imaging should be confirmed as per IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Recommendation 9.4. Response assessment should be performed after one cycle of therapy, and once a response trend is observed, it may be done every other cycle and less frequently once patient is in a plateau (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

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Additional Resources

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/hematologic-malignancies-guidelines. Patient information is available at https://www.cancer.net/

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.

this system, there are three stages (I, II, or III), and each stage is further classified into A or B, depending on whether there is evidence of renal dysfunction upon diagnosis (B). The system attempts to differentiate levels of disease burden and activity based on four factors: baseline hemoglobin, serum calcium, level of M-protein in blood and/or urine, and the presence and number of lytic bone lesions.

More recently, the International Staging System (ISS) and the Revised-ISS (R-ISS) have been more commonly used to define disease stage. The ISS system takes into account levels of serum albumin and serum β2-microglobulin (B2M), whereas the R-ISS also includes serum lactase dehydrogenase (LDH) and results from bone marrow fluorescence in situ hybridization (FISH) testing (Table 3).[4,5]

GUIDELINE QUESTIONS

This clinical practice guideline addresses several overarching clinical questions: In transplant-eligible patients:

1. What criteria are used to assess eligibility for autologous stem-cell transplant (ASCT)?
2. What are the options for initial therapy before transplant?
3. What post-transplant therapy should be recommended?
4. What are the response goals for the transplant-eligible patient? In transplant-ineligible patients:
5. What are the options for initial therapy in transplant-ineligible patients?
6. What are the response goals following initial therapy for transplant-ineligible patients, and in patients with relapsed disease?
7. What factors influence choice of first relapse therapy?
8. How does risk status influence therapy in myeloma (newly diagnosed and relapse)?
9. When and how should response assessment be performed?

Please refer to the Data Supplement for the complete list of questions and subquestions.

METHODS

Guideline Development Process

This systematic review-based guideline product was developed by a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The Expert Panel also included representatives from Cancer Care Ontario, in an effort to avoid duplication of guidelines on topics of mutual interest (Appendix Table A1, online only). The Expert Panel, co-chaired by T.M. and J.M., met via teleconference, a face-to-face meeting, webinars, and corresponded through e-mail. Based on the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of guideline, which was then circulated for external review and submitted to *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee prior to publication. All funding for the administration of the project was provided by ASCO.

The recommendations were developed by using a systematic review (2005 to 2018) of phase III randomized clinical trials (RCTs), phase II studies to address specific key questions, and clinical experience. Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: patients with active myeloma and relapsed or refractory myeloma
- Interventions that focused on pharmacologic interventions (induction, consolidation, maintenance chemotherapy), ASCT, and supportive care.
- Study designs included were systematic reviews, meta-analyses, RCTs, and larger phase II studies for questions with limited data, including issues addressing the older adult population.

Articles were excluded from the systematic review if they were meeting abstracts not subsequently published in peer-reviewed journals, editorials, commentaries, letters, news articles, case reports, narrative reviews, or observational studies, or published in a non-English language.

TABLE 1. Drugs Used in the Treatment of Patients With Multiple Myeloma

Agent	Route	Dose	Schedule
Immunomodulatory drugs			
Thalidomide	Oral	50-200 mg	Daily
Lenalidomide	Oral	5-25 mg	Daily for 21 of 28 days
Pomalidomide	Oral	1-4 mg	Daily for 21 of 28 days
Proteasome inhibitors			
Bortezomib	Subcutaneous/ intravenous	0.7-1.6 mg/m^2	Once or twice weekly
Carfilzomib	Intravenous	20-70 mg/m^2	Once or twice weekly for 3 or 4 weeks
Ixazomib	Oral	2.3-4 mg	Weekly for 3 or 4 weeks
Monoclonal antibodies			
Daratumumab	Intravenous	16 mg/kg	Weekly → every 2 weeks → monthly
Elotuzumab	Intravenous	10 mg/kg	Weekly → every 2 weeks → monthly
Alkylators			
Cyclophosphamide	Oral	50 mg	Daily
		300-500 mg/m^2	Weekly
Melphalan	Oral	9 mg/m^2	Daily × 4 days/cycle
Melphalan	Intravenous	140-200 mg/m^2	Once for transplant
HDAC inhibitors			
Panobinostat	Oral	10-20 mg	Three times weekly for 2 or 3 weeks
Steroids			
Dexamethasone	Oral	20-40 mg	Weekly
Prednisone	Oral	25-50 mg	Every other day
Anthracyclines			
Doxorubicin HCl liposomal	Intravenous	30 mg/m^2	Every 3 weeks

Abbreviation: HDAC, histone deacetylase.

The guideline recommendations are crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying BRIDGE-Wiz software.[6] In addition, a guideline implementability review is conducted. Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, evidence, and potential bias are provided with each recommendation. Please refer to the Methodology Supplement for further details.

TABLE 2. Diagnostic Criteria for Active Multiple Myeloma

Diagnostic Criteria
2014 IMWG criteria
Clonal bone marrow plasma cells ≥ 10% or biopsy-proven bone or extramedullary plasmacytoma
Any one or more of the following myeloma-defining events (attributed to the plasma cells)
Hypercalcemia (greater than upper limit of normal)
Renal insufficiency: serum creatinine > 2 g/dL or creatinine clearance < 40 mL/min
Anemia: hemoglobin < 10 g/dL or > 2 g/dL below lower limit of normal
Bone lesions: one or more osteolytic lesions (as demonstrated on imaging studies)
New criteria
Involved/uninvolved serum free light chains ratio ≥ 100, and the involved serum free light chain level > 100 mg/dL or greater
Clonal bone marrow plasma cells ≥ 60%
Two or more focal lesions based on MRI studies of the skeleton

NOTE. Adapted with permission from Rajkumar et al.[3]

Abbreviations: IMWG, International Myeloma Working Group; MRI, magnetic resonance imaging.

TABLE 3. Revised International Staging System

Stage	ISS Criteria
I	ISS stage I (β_2-M $<$ 3.5 mg/L and serum albumin $\geq$ 3.5 g/dL) and normal LDH, no abnormal FISH
II	Neither stage 1 or stage III
III	β_2-M $>$ 5.5 mg/L and elevated serum LDH, or abnormal FISH: presence of t(4;14), t(14;20), or 17p deletion

NOTE. Adapted with permission from Palumbo et al.[5]

Abbreviations: FISH, fluorescence in situ hybridization; ISS, International Staging System; LDH, lactate dehydrogenase.

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/hematologic-malignancies-guidelines, including an overview (eg, panel composition, development process, and revision dates), literature search and data extraction, the recommendation development process (GLIDES and BRIDGE-Wiz), and quality assessment.

The ASCO Expert Panel and guidelines staff will work with co-chairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, ASCO will determine the need to update. The updated search will be guided by the signals[7] approach, which is designed to identify only new, potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on targeted routine literature searching and the expertise of ASCO Expert Panel members to help identify potential signals. The Methodology Supplement (available at www.asco.org/hematologic-malignancies-guidelines) provides additional information about the signals approach. This is the most recent information as of the publication date.

Guideline Disclaimer

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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/rwc). 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. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

A total of 124 studies[8-131] met eligibility criteria and form the evidentiary basis for the guideline recommendations. These included 26 systematic reviews,[8-32,131] two pooled analyses,[33,34] 93 RCTs,[35-126,130] and three phase II studies.[127-129] The identified trials focused on transplant-eligible and -ineligible patients and patients with relapsed diseases. The primary outcomes reported included OS, progression-free survival (PFS), response rate, toxicity, and quality of life. Further details on the characteristics and outcomes of these studies can be found in the Data

Supplement. A systematic review Prisma flow diagram is also shown in Figure 1.

Study Quality Assessment

Study quality was formally assessed for all RCTs and systematic reviews identified. Design aspects related to the individual study quality were assessed by one reviewer, with factors such as randomization, blinding, allocation concealment, intention to treat, funding sources, etc., generally indicating a low to high potential risk of bias for most of the identified evidence. Follow-up times varied between studies, lowering the comparability of the results. Appendix Table A2 (online only) shows the risk of bias assessment for some of the major trials. Please refer to the Data Supplement for the assessment results of other studies identified. The Methodology Supplement also includes more information on definitions of ratings for overall potential risk of bias.

RECOMMENDATIONS

TRANSPLANT-ELIGIBLE POPULATION

Clinical Question 1

What criteria are used to assess eligibility for ASCT?

Recommendation 1.1. Patients should be referred to a transplant center to determine transplant eligibility (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Data from transplant registries and SEER data suggest that only a proportion of potentially transplant-eligible patients with multiple myeloma in the United States undergo SCT, influenced in part by several factors, including age, socioeconomic status, and comorbidities.[132] Therefore, the panel strongly recommends that patients with multiple myeloma should be referred to a transplant center early in the course of their care to determine eligibility for SCT. In addition, patients who present with significant disease-related debility can, with therapy, become transplant eligible and should then be referred for transplant evaluation.

Recommendation 1.2. Chronologic age and renal function should not be the sole criteria used to determine eligibility for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Chronologic age alone or a specific age cutoff is not optimal to determine transplant eligibility. In a phase II trial, there were no differences in transplant-related mortality (TRM) in patients 60 to 65 years of age versus 65 to 70 years of age, with low ($< 1\%$) TRM in both cohorts.[123] Retrospective registry data also demonstrate reduced TRM and improved OS with ASCT in older adults in recent years (in adults age 65 to 69 years and those age $\geq$ 70 years), possibly because of improved supportive care.[133]

There are no prospective data to evaluate the impact of organ function on eligibility for SCT. Data from transplant registries do not indicate an adverse impact of renal function on survival following SCT, and renal function alone should not be used to determine SCT eligibility.[134]

While several studies have used dose-reduced melphalan (70 to 140 mg/m^2) in older adults, low TRM has also been reported following full-dose melphalan.[135] A prospective trial comparing SCT with no SCT in the older adult (Intergroupe Francophone du Myelome [IFM] 99-06; ClinicalTrials.gov identifier: NCT00367185) demonstrated superior PFS and OS for nontransplant therapy.[63] It is relevant to note that supportive care strategies have improved since; the study used reduced-dose melphalan (tandem transplant with melphalan 100 mg/m^2), and TRM was highest in the transplant arm (toxic deaths = 5%).

Clinical Question 2

What are the options for initial therapy before transplant?

Recommendation 2.1. The optimal regimen and number of cycles remain unproven. However, at least three to four cycles of induction therapy including an immunomodulatory drug, proteasome inhibitor (PI), and steroids are advised prior to stem-cell collection (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are two randomized trials that have compared the use of PI plus immunomodulatory drug and dexamethasone versus PI plus cyclophosphamide and dexamethasone (bortezomib, thalidomide, dexamethasone *v* bortezomib, cyclophosphamide, dexamethasone and carfilzomib, lenalidomide, dexamethasone *v* carfilzomib, cyclophosphamide, dexamethasone) as induction therapy in transplant-eligible patients.[66,93] Both studies demonstrated statistically increased rates of achieving at least very good partial response (VGPR) in the PI plus immunomodulatory drug plus dexamethasone arm after four cycles of therapy. One study also showed improved minimal residual disease (MRD) negativity rates in the KRd arm.[66] Thus, the use of a PI with an immunomodulatory drug and dexamethasone is the preferred induction therapy in transplant-eligible patients. If an immunomodulatory drug is not immediately available, cyclophosphamide is an acceptable substitute until it becomes available. There are no randomized trials that have attempted to identify the optimal number of induction cycles prior to stem-cell collection. Historically, based upon the initial schema of vincristine, doxorubicin and dexamethasone chemotherapy, most clinical trials have arbitrarily included four cycles of induction therapy.[136] However, current data from trials incorporating triplet therapy show that the depth of response has improved

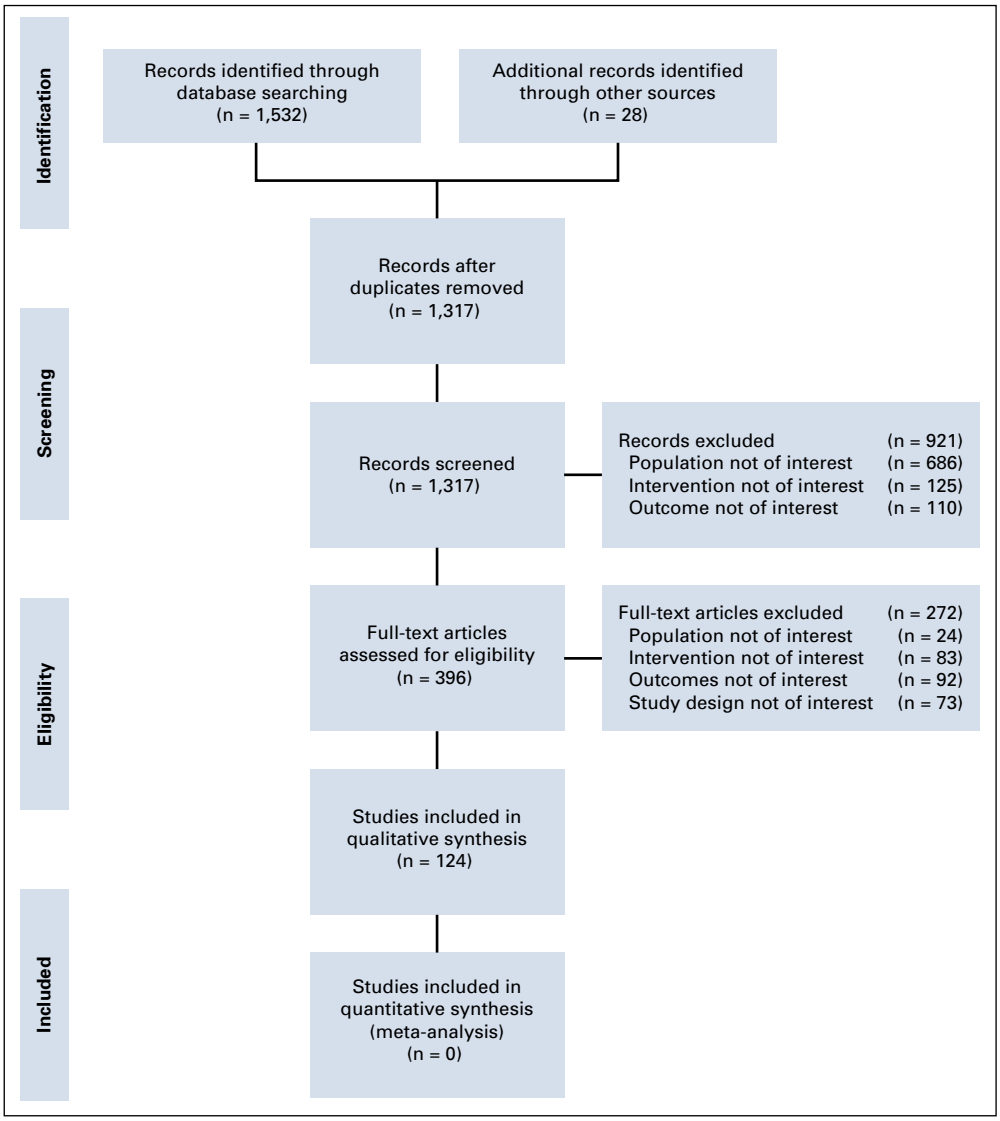

FIG 1. Prisma flow diagram.

significantly and the majority of patients achieve at least a very good partial remission within four cycles of therapy. In fact, the largest incremental decrease in paraprotein levels is observed following the first cycle of therapy and then, in general, a less steep decline is observed, with very small incremental decreases in paraprotein seen beyond three to four cycles of therapy. Therefore, it is recommended that three to four cycles of induction therapy be administered in those planned to proceed to autologous transplant.

Recommendation 2.2. Up-front transplant should be offered to all transplant-eligible patients. Delayed initial SCT may be considered in select patients (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Several contemporary RCTs have compared consolidative autologous transplant to conventional chemotherapy followed by delayed transplant as initial therapy for patients with newly diagnosed multiple myeloma.[35,68,106,137] All of these trials uniformly demonstrated improved PFS in patients who received up-front transplant therapy. One caveat is that these studies incorporated induction regimens containing either PIs or immunomodulatory drugs but not both together, suggesting a less potent induction and an unfair comparator to transplant. More recently, the IFM in France, in conjunction with the Dana-Farber Cancer Institute (DFCI) in the United States, IFM/DFCI 2009 (ClinicalTrials.gov identifier: NCT 01191060), performed a large randomized trial comparing induction therapy with lenalidomide, bortezomib, and dexamethasone (RVD) followed by autologous transplant and subsequent consolidation and maintenance versus RVD induction and stem-cell collection followed by consolidation and maintenance (with transplant reserved for first relapse).[35] The results showed a superior PFS in the early transplant group (50 months *v* 36 months; hazard ratio [HR], 0.65; $P < .001$) and improved rates of achieving MRD remission. The OS at 4 years

did not differ between the treatment arms; however, follow-up is still too short to reliably evaluate this endpoint. The majority of patients were able to undergo autologous transplant at disease relapse. Overall, the panel recommends up-front transplant as the standard of care, whereas delayed SCT may be considered in select patients (based on depth of response, risk status, and patient preference).

Recommendation 2.3. Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drugs exposure (more than four cycles), should be avoided in patients who are potential candidates for SCT (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. The use of ASCT requires procurement and storage of adequate hematopoietic stem cells. Prior to the incorporation of PIs/immunomodulatory drugs into front-line therapy, oral melphalan-based therapy was considered the standard of care for patients with newly diagnosed multiple myeloma. Emerging data at that time suggested that extended exposure to oral melphalan resulted in deleterious effects on stem-cell yield,[138,139] thus the transition to induction therapy with vincristine, doxorubicin and dexamethasone in SCT-eligible patients. More recently, with increasing use of immunomodulatory drugs, lenalidomide in particular, studies have shown that extensive exposure to lenalidomide (beyond four to six cycles) may also compromise stem-cell yield.[140,141] Although some of the deleterious effects from alkylator and lenalidomide exposure can be overcome by either combination of growth factor and chemotherapy or growth factor and CXCR4 antagonist (plerixafor), prolonged exposure (> cycles) to these agents should be avoided prior to stem-cell mobilization.

Recommendation 2.4. Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. A single ASCT is considered the standard of care based upon the randomized Blood and Marrow Transplant Clinical Trial Network (BMT CTN 0702; ClinicalTrials.gov identifier: NCT01109004) trial comparing single transplant versus single transplant with consolidation versus tandem transplant (all arms with lenalidomide maintenance) in which the PFS was not significantly different between the three arms.[61] Treatment with autologous transplantation followed by maintenance therapy is associated with a median PFS for standard-risk, low-ISS disease of approximately 5 years. During maintenance, most patients have extensive exposure to lenalidomide and upon relapse receive salvage therapy that may compromise future attempts at stem-cell collection. In addition, peripheral blood stem cells may be stored indefinitely without compromising their efficacy. Thus, in consideration for a future salvage transplant, collection of sufficient peripheral blood stem cells should be considered up front in appropriate transplant-eligible patients.

Recommendation 2.5. The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy; patients should be referred for SCT independent of depth of response (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are no randomized trials aimed at assessing the optimal number of induction cycles or identifying the ideal depth of response required prior to proceeding to SCT. It remains unclear if one should treat to maximal response or change induction regimen to achieve maximum response. Achievement of VGPR or better following induction was associated with superior PFS in the IFM-2005-01 trial (ClinicalTrials.gov identifier: NCT00200681); however, in the current paradigm of using an immunomodulatory drug plus PI-based triplet-induction regimen, such data are lacking.[92] Cohort-based studies suggest that post-transplant depth of response is more important than pre-SCT responses when using current triplet-based regimens.[142] Further, there are retrospective cohort-based data that do not support second-line induction therapy compared with immediate transplant.[143,144] Therefore, because autologous transplant is the single most efficacious treatment of multiple myeloma, patients should be referred to SCT independent of the depth of response, including stable disease, with the exception of those patients who demonstrate progressive disease.

Recommendation 2.6. High-dose melphalan is the recommended conditioning regimen for ASCT (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. High-dose melphalan is the standard conditioning regimen for ASCT in multiple myeloma. There have been randomized trials or cohort-based studies comparing high-dose melphalan to melphalan plus total body irradiation or melphalan with other chemotherapy (eg, busulfan, cyclophosphamide, bortezomib) without demonstrable superiority.[77,145] Melphalan doses may be attenuated at the discretion of the transplant physician for age, frailty, obesity, or renal function.[146,147]

Recommendation 2.7. Tandem ASCT should not be routinely recommended (Type: evidence based; Evidence quality: intermediate, benefit equals harm; Strength of recommendation: strong).

Literature review and clinical interpretation. A single ASCT is considered the standard of care based upon the randomized BMT CTN 0702 trial that compared single transplant versus single transplant with consolidation versus tandem transplant (all arms with lenalidomide maintenance), in which the PFS was not significantly different between the three arms.[61] In contrast to the BMT-CTN trial, data from the European Myeloma Network (EMN)-02 trial (ClinicalTrials.gov identifier: NCT01208766)—where patients did not receive immunomodulatory drug–PI induction as commonly used in the United States—demonstrated improved 3-year PFS and OS with tandem SCT in patients with high-risk cytogenetics.[89] In addition, an IFM trial[148] showed benefit for second SCT in patients who achieved less than VGPR following first SCT. Given these discordant findings, up-front tandem SCT may be considered in selected high-risk patients or those with a suboptimal response to first transplant.

Recommendation 2.8. Salvage or delayed SCT may be used as consolidation at first relapse for those not choosing to proceed to transplant initially (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Several retrospective studies and consensus guidelines suggest that salvage SCT can be a safe and potentially beneficial option, particularly in patients with remission duration of 18 months or more following first ASCT.[149] In general, PFS from second SCT is generally 12 to 18 months and shorter than that achieved following first SCT. A prospective trial comparing second salvage SCT to conventional chemotherapy with cyclophosphamide showed improved PFS but not OS.[47] Prospective data evaluating the efficacy or role of delayed SCT in the setting of immunomodulatory drug–PI (triplet) based induction therapy is limited, and mature data from ongoing studies are not yet available.[35,150]

Recommendation 2.9. Allogeneic transplant for multiple myeloma is not routinely recommended but may be considered in select high-risk patients or in the context of a clinical trial (Type: evidence based; Evidence quality: intermediate, harm outweighs benefit; Strength of recommendation: strong).

Literature review and clinical interpretation. Allogeneic transplant is based upon the immunologic potential of generating donor alloreactivity to produce a graft-versus-myeloma effect. In the relapse setting this alloreactivity appears modest, and outcomes of ASCT have been universally poor. More recently, in the up-front setting, efficacy has been demonstrated and the transplant-related morbidity and mortality have decreased substantially with better patient selection and use of reduced-intensity conditioning regimens. However, the long-term efficacy remains debatable: a large US trial, BMT CTN 0102 (ClincialTrials.gov identifier: NCT00075829), showed no PFS or OS benefit comparing tandem autologous transplant to autologous-allogeneic transplant.[74] There are several smaller European studies that suggest benefit for reduced-intensity ASCT.[67,151] However, given the inconsistent and contradictory results, the unclear potential of graft-versus-myeloma immune effects, and the advent of newer options, including monoclonal antibodies and other immune therapeutics, allogeneic transplant should be performed in the context of a clinical trial and in select patients, such as those with R-ISS high-risk disease.

Clinical Question 3

What post-transplant therapy should be recommended?

Recommendation 3.1. Consolidation therapy is not routinely recommended but may be considered in the context of a clinical trial. For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Consolidation therapy is defined as fixed-duration combination therapy post ASCT aimed at improving the depth of response. Although consolidation therapy may increase the depth of response and can improve PFS,[36,43,88] there are limited data to suggest that consolidation can improve OS. In fact, the BMT CTN 0702 trial, which compared single transplant plus lenalidomide maintenance versus single transplant plus RVD consolidation and lenalidomide maintenance, showed no difference in PFS or OS. Thus, there is little evidence to support the use of consolidation therapy following transplant in those receiving maintenance therapy. Although a randomized trial[118] demonstrated that 1 year of thalidomide consolidation given with indefinite prednisone maintenance improved PFS and OS compared with prednisone maintenance alone, the high incidence of thalidomide toxicity limits its current use.

Overall, lenalidomide maintenance has been shown to improve OS and is now a standard of care. There are no data to support using any consolidation approach when lenalidomide maintenance therapy is given.

Recommendation 3.2. Lenalidomide maintenance therapy should be routinely offered to standard-risk patients starting at approximately day 90 to 110 at 10 to 15 mg daily until progression. A minimum of 2 years of maintenance therapy is associated with improved survival, and efforts to maintain therapy for at least this duration are recommended (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Data from RCTs show a consistent PFS and OS benefit with a 25% reduction in the risk of death derived from lenalidomide

maintenance therapy. Treatment with lenalidomide as part of initial pretransplant therapy does not factor into the decision of whether to administer lenalidomide maintenance, and it appears that those who have been treated with lenalidomide as part of induction may derive additional benefit from lenalidomide maintenance. Data support the use of lenalidomide without dexamethasone as a preferred therapy in the maintenance setting.[18,68]

Recommendation 3.3. For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Bortezomib maintenance can be considered, but clinical trials have not been designed in a way to isolate the contribution of its effect as maintenance.[114,130] Evidence is emerging for the use of other agents as maintenance therapy, such as ixazomib[152], and future randomized trials will further define the use of novel agents for maintenance.

Recommendation 3.4. For high-risk patients, maintenance therapy with a PI with or without lenalidomide may be considered (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Although a PFS benefit appears to be gained, survival benefit has not been clearly shown for lenalidomide maintenance in patients with ISS stage III disease, those with adverse risk cytogenetics such as t(4;14) or deletion 17p, those with elevated lactate dehydrogenase, or those with low creatinine clearance. Due to the known short PFS on no maintenance therapy, consideration for bortezomib maintenance therapy should be made as part of the treatment plan in patients with adverse cytogenetic features, especially if bortezomib was part of the initial induction therapy, as this may be associated with improved survival.[130] OS benefit has been associated with bortezomib-based therapy in patients with deletion 17p13, and this strategy may be preferred in high-risk patients rather than lenalidomide maintenance alone, given the lack of OS data for high-risk patients on lenalidomide maintenance. Evidence is emerging for the use of ixazomib as maintenance therapy and may also be considered.[152]

Recommendation 3.5. There is insufficient evidence to make modifications to maintenance therapy based on depth of response, including MRD status (Type: informal consensus/evidence based; Evidence quality: low/intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. In a randomized trial assessing the use of fixed duration of lenalidomide maintenance versus maintenance until complete response (CR), patients receiving the fixed duration of 2 years of therapy had significantly improved PFS versus those stopping lenalidomide once CR was achieved.[36] The goal-directed group (until CR) received less lenalidomide and was associated with early relapse. Thus, current data suggest to continue maintenance for at least 2 years irrespective of response, and the optimal duration or depth of response has not been defined. Future clinical trials will address whether the MRD status of patients can be used to guide maintenance therapy.

Clinical Question 4

What are the response goals for the transplant-eligible patient?

Recommendation 4.1. The quality and depth of response should be assessed by IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Response evaluation in multiple myeloma was originally based on the assessment of bone marrow plasma cells as well as serum and urine monoclonal protein concentrations. The definition of a CR only required bone marrow with less than 5% plasma cells, regardless of whether they were clonally restricted. Revised criteria were introduced during the International Myeloma Workshop in 2011. The criteria were modified to include stringent CR, which requires normalization of the serum free light chains assay and absence of clonal plasma cells in the bone marrow by immunohistochemical testing. The revised IMWG criteria have been adopted as the international standard, allowing improved comparison of treatment combinations. Response assessments should be performed serially in individual patients to guide therapy and to assess sensitivity or resistance to therapy.

Recommendation 4.2. The goal of initial therapy for transplant-eligible patients should be achievement of the best depth of remission. MRD-negative status has been associated with improved outcomes, but it should not be used to guide treatment goals outside the context of a clinical trial (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. New technology allows the identification of residual tumor cells in the bone marrow of patients who meet criteria for stringent CR. MRD can be detected using several techniques. Next-generation flow cytometry relies on two eight-color antibody panels targeting cell surface antigens to identify phenotypically aberrant clonal plasma cells and includes detection of cytoplasmic κ and λ light-chain expression to confirm clonality. It has a sensitivity of 1 in 10^5 cells or higher. Next-generation sequencing uses sets of multiple

polymerase chain reaction primers for the amplification and sequencing of immunoglobulin gene segments. DNA sequencing of bone marrow aspirates using the LymphoSIGHT (Sequenta, South San Francisco, CA) platform (or validated equivalent method) has a minimum sensitivity of 1 in 10^5 nucleated cells or higher. MRD testing by sequencing requires a baseline sample, whereas Next Generation Flow does not. Multiple studies have shown improved outcomes in patients who have achieved MRD-negative status by one of these methods. However, there is no universal agreement as to which method is preferred, when the testing should be performed, and at what interval. None of these assays has been validated prospectively. The IMWG has published suggestions on how to incorporate MRD testing into new clinical trials.[153] Overall, MRD-negative status has been associated with improved outcomes;[13,19,28,33,102,110] however, until prospective trials have validated its use, this technology should not be used to guide treatment decisions.

Recommendation 4.3. It is recommended that depth of response be assessed with each cycle. Frequency of assessment once best response is attained or on maintenance therapy may be assessed less frequently but at minimum every 3 months (Type: evidence based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Literature review and clinical interpretation. There are no trials that compare the frequency of response assessment. The recommendation to assess response with each cycle during active treatment is based on the necessity of knowing whether the treatment is effective. This allows the clinician to change courses to a different treatment if the current regimen is proving to be ineffective. Quantification of serum and/or urine M-protein values and serum free light chain levels is considered standard.

Recommendation 4.4. Whole-body low-dose computed tomography (WBCT) scan has been shown to be superior to skeletal survey done with plain x-rays and is the preferred method for baseline and routine bone surveillance. Fluorodeoxyglucose positron emission tomography (FDG-PET)/CT and/or magnetic resonance imaging (MRI) may be used as alternatives at baseline. They may also be used in select situations (eg, risk stratifying smoldering myeloma, for monitoring response of nonsecretory and oligosecretory myeloma, and if CT or skeletal survey is inconclusive) (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Skeletal survey using plain x-rays including spine, pelvis, skull, humeri, and femurs has been the standard modality used to screen for bone lesions in multiple myeloma for many years. However, it is well recognized that this modality has limited sensitivity, as there must be 30% trabecular bone loss to identify lytic lesions on x-ray. As well, expert radiologic review of skeletal surveys already reported was able to detect additional abnormalities in 23% of the studied cases.[154] A systematic review of modern and conventional imaging techniques (MRI, WBCT, and FDG-PET/CT), showed that upwards of 80% more lesions were identified using the newer techniques.[131] A few studies compared WBCT to skeletal surveys, and up to 60% more relevant findings are identified on CT, leading to treatment changes in up to 20% of patients.[155] Thus, the IMWG recommends WBCT as the standard diagnostic tool for detecting bone disease in patients with myeloma. However, skull and rib lesions are not well detected by WBCT or MRI, as compared with skeletal surveys;[131] thus, focused x-rays may still be of value if these areas are of concern. Relatively few extra bone lesions were detected by MRI or FDG-PET/CT over WBCT. Studies comparing MRI to FDG-PET/CT have found them to be equivalent in rate of detection of bone lesions in patients with multiple myeloma. MRIs can be useful in screening patients with smoldering multiple myeloma for lesions, as 30% to 50% of such patients will have bone marrow abnormalities. However, MRI may show nonspecific lesions, and one can occasionally overestimate the extent of bony disease. PET/CTs are particularly useful in evaluating extramedullary disease, an equivocal lesion in a patient with smoldering multiple myeloma or solitary plasmacytoma or a patient with nonsecretory or oligosecretory multiple myeloma.

TRANSPLANT-INELIGIBLE POPULATION

Clinical Question 5

What are the options for initial therapy in transplant ineligible patients?

Recommendation 5.1. Initial treatment recommendations for patients with multiple myeloma who are transplant ineligible should be individualized based on shared decision making between physicians and patients. Multiple factors should be considered; disease-specific factors such as stage and cytogenetic abnormalities, and patient-specific factors including age, comorbidities, functional status, frailty status, and patient preferences should also be considered (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Initial therapeutic recommendations for older adults with myeloma will be informed by both disease-specific and patient-specific factors. Disease-specific considerations include stage and cytogenetics. The R-ISS was developed in a cohort that included about one-third older patients, and its prognostic utility is independent of age, confirming its relevance in the older subgroup.[34,156] In addition, the prognostic importance of high-risk cytogenetics is relevant across the age

spectrum. Older adults with deletion 17p, translocation 14; 16, or translocation 4;14 experience shorter PFS and OS.[62,156,157] Patient-specific considerations in older adults center on age-associated vulnerabilities and patient preferences. In a cohort of over 800 older adults, geriatric assessment factors, including functional status (independence in instrumental activities of daily living and activities of daily living) and comorbidities, were associated with OS. Using these factors, a frailty measure stratifying patients as fit, intermediate-fit, or frail was developed and shown to be predictive of nonhematologic toxicity of therapy, treatment discontinuation, and PFS and OS.[34] Other approaches to applying the concept of frailty to risk stratification in older adults with multiple myeloma have included the Revised Myeloma Comorbidity Index and the Geriatric Assessment in Hematology scale,[158-161] though neither has yet been shown to predict toxicity of therapy. See Table 4 for additional information.

Patient preferences are another importance consideration. Older patients often have multiple serious medical conditions and do not necessarily prioritize length of survival over other considerations. Maintaining functional independence, rather than OS, is prioritized by 60% to 75% of older adults with serious medical conditions or cancer.[162-164] Thus, toxicities that result in dependence, such as neuropathy or fatigue, would not be in line with the preferences of many older adults.

In summary, disease factors and patient factors can inform treatment options, which should be triangulated with patient preferences to inform shared decision making between providers and older adults with myeloma.

Recommendation 5.2. Initial treatment of patients with multiple myeloma who are transplant ineligible should include at minimum a novel agent (immunomodulatory drugs or PI) and a steroid if possible (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The introduction of immunomodulatory agents and PIs to the initial treatment of older adults with myeloma who are ineligible for transplant has significantly improved outcomes. The combination of thalidomide, melphalan, and prednisone,[165] as well as the combination of bortezomib, melphalan, and prednisone,[84,87,90,116] is superior to melphalan and prednisone alone. Continuous therapy with lenalidomide and dexamethasone prolongs survival compared with 18 months of thalidomide, melphalan, and prednisone.[40,62] In a randomized trial of melphalan, prednisone, and thalidomide compared with melphalan, prednisone, and lenalidomide, disease-focused outcomes were similar, though quality of life was better with the lenalidomide combination.[120] Table 5 presents a summary of available data on response rates and disease-free and OS as well as toxicities of combinations studies in older adults with myeloma.

Recommendation 5.3. Triplet therapies for patients with multiple myeloma who are transplant ineligible, including bortezomib, lenalidomide, and dexamethasone, should be considered. Daratumumab plus bortezomib plus melphalan plus prednisone may also be considered (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Triplet therapies (which include at least two novel agents) for patients with multiple myeloma who are transplant ineligible, including bortezomib plus lenalidomide plus dexamethasone (VRd) or daratumumab plus bortezomib plus melphalan plus prednisone (D-VMP), may be considered for select patients. VRd has been compared with Rd in a trial involving 472 patients.[60] At a median follow-up of 55 months, median PFS was significantly improved in the VRd group (43 months *v* 30 months in the Rd group; stratified HR, 0.712; 96% CI, 0.56 to 0.906; one-sided *P* value = .0018). The median OS was also significantly improved in the VRd group (75 months *v* 64 months in the Rd group; HR, 0.709; 95% CI, 0.524 to 0.959; two-sided *P* value = .025). Adverse events of grade 3 or higher were reported in 82% of patients in the VRd group and 75% in the Rd group; 23% and 10% of patients discontinued induction treatment because of adverse events, respectively. Subgroup and multivariate analysis revealed that all age groups benefitted in terms of PFS and OS, including those over 75 years, but the differences were statistically significant for PFS only in those younger than 65 years of age and for OS in those over 75 years.

D-VMP[166] has been compared with VMP in a trial involving 700 older patients. At a median follow-up of 16.5 months in a prespecified interim analysis, the 18-month PFS rate was 71.6% (95% CI, 65.5 to 76.8) in the daratumumab group and 50.2% (95% CI, 43.2 to 56.7) in the control group (HR for disease progression or death, 0.50; 95% CI, 0.38 to 0.65; $P < .001$). The overall response rate was 90.9% in the daratumumab group, as compared with 73.9% in the control group ($P < .001$), and the rate of CR or better (including stringent CR) was 42.6% versus 24.4% ($P < .001$). In the daratumumab group, 22.3% of the patients were negative for MRD (at a threshold of 1 tumor cell per 10^5 white cells), as compared with 6.2% of those in the control group ($P < .001$). All subgroups, other than minority groups of non–immunoglobulin G type, high-risk cytogenetics, and stage I, benefitted with improved PFS, including patients over 75 years of age. The most common adverse events of grade 3 or 4 were hematologic: neutropenia (in 39.9% of the patients in the daratumumab group and in 38.7% of those in the control group), thrombocytopenia (in 34.4% and 37.6%, respectively), and anemia (in 15.9% and 19.8%, respectively). The rate of grade 3 or 4 infections was 23.1% in the daratumumab group and 14.7% in the control group; the rate of treatment discontinuation due to infections was 0.9% and 1.4%, respectively.

TABLE 4. Comparison of Select Risk-Prediction Models Relevant to Older Adults With Multiple Myeloma

Factors Associated With Increased Risk	International Myeloma Working Group[180]		Revised Myeloma Comorbidity Index[161]		Geriatric Assessment in Hematology Scale[34,160]	
	Parameter	Points	Parameter	Points	Parameter	Points
Age, years	76-80	1	60-69	1		—
	> 80	2	≥ 70	2		—
Performance/functional status	Any ADL dependence	1	KPS 80-90	2	Gait speed ≤ 0.8 m/s	1
	Any IADL dependence	1	KPS < 70%	3	Any ADL dependence	1
Comorbidities	Charlson Comorbidity Index ≥ 2	1	Renal disease: eGFR < 60	1	Diabetes, BMI > 25 kg/m^2 or cancer, lung disease, heart failure, or smoking*	1
			Moderate/severe pulmonary disease	1		
Medications/ polypharmacy		—		—	≥ 5 medications	1
Nutrition		—		—	≤ 8 on MNA-SF	1
Cognition		—		—	≥ 3 errors on SPMSQ	1
Psychosocial		—		—	Felt depressed 3-7 days of past week	1
Other		—	Moderate/severe frailty phenotype	1	Self-reported health fair or poor	1
Cytogenetics		—	Unfavorable	1		—
Total score	Fit	0	Fit	0-3	Range	0-8
	Intermediate fit	1	Intermediate	4-6		
	Frail	2	Frail	7-9		

NOTE. Adapted with permission from Wildes.[203]

Abbreviations: ADL, activities of daily living; BMI, body mass index; eGFR, estimated glomerular filtration rate; IADL, instrumental activities of daily living; KPS, Karnofsky performance status; MMS, Mini Mental Status Exam; MNA-SF, Mini Nutritional Assessment–Short Form; SPMSQ, Short Portable Mental Status Questionnaire.

*See original publication for full details on scoring comorbidities.

Daratumumab-associated infusion-related reactions occurred in 27.7% of the patients. Median OS was not reached in either group at this early follow-up of 15.5 months.

Both VRd and D-VMP provide markedly improved PFS and, importantly, this benefit extends to those over 75 years. VRd provides, in addition, improved OS, again including for those over 75 years of age; D-VMP has not yet shown a survival advantage at the early follow-up period (16.5 months *v* 55 months for VRd). VRd does exhibit increased toxicities compared with Rd, with rates of discontinuation of therapy due to toxicity being 23% versus 10%. D-VMP has been extremely well tolerated up to 16.5 months, with only 0.9% of patients discontinuing therapy for toxicity. Important exclusion criteria in both trials included severe renal dysfunction (< 30 mL/min for D-VMP *v* VMP; < 40 mL/min for VRd *v* Rd).

Triplet therapies, therefore, provide improved response rates, longer PFS, and possibly improved OS. In general, the additional disease control attained with triplet therapies must be balanced with the potential increased toxicity in transplant-ineligible patients. Patients unsuitable for triplet therapy still have excellent options for therapy, including doublets such as lenalidomide-dexamethasone and bortezomib-based regimens such as bortezomib, dexamethasone and bortezomib, cyclophosphamide, dexamethasone.

Recommendation 5.4. Physicians/patients should balance the potential improvement in response and disease control with a possible increase in toxicity. Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Initial dosing of myeloma therapy in the transplant-ineligible population should be individualized. Factors to consider include patient age and comorbidities, renal function, functional status, and patient preferences. In particular, a frailty measure (that incorporates age, comorbidities, and functional status) can predict excessive toxicity and early treatment discontinuation.[34] When patient factors raise the concern for toxicity, as with very old adult patients (> 75 years) or those with multiple comorbidities, initiating treatment with lower doses of antimyeloma agents is reasonable. For example, the starting dose for

TABLE 5. Range of Reported Outcomes From Trials for Patients With Newly Diagnosed Multiple Myeloma Who Are Transplant Ineligible

Regimen	Overall Response Rate (%)	Complete Response Rate (%)	Median PFS (months)	Median OS (months)	Early Deaths/Death Due to Toxicity (%)	Treatment Discontinuation Due to Adverse Events (%)	≥ Grade 3 Fatigue (%)	≥ Grade 3 Neuropathy (%)
Proteasome inhibitor based								
VD	73	3	14.7	49.8	NR	29	11	22
VMP	70-89	4-32	17.3-25	53.1-not reached	2.3-6	9-34	2-8	7-17
CCyD	95	20	NR	87% 2-year OS	NR	14	2	0
Immunomodulatory agent based								
Rd	70-81	3-22	8.9-25.3	30.5-62.3	4.6	7-19	2-11	0-2
MPR	68	3-11	14-24	62% 3-year OS	0.7-2.3	4-18	2-3	0-3
MPR+R maintenance	70.4-84	11.2-16	18.7-31	69%-70% 3-year OS	2	16-41	5	0-2
CyPR	74	0.5	20	68% 4-year OS	3.6	15	2	3
Proteasome inhibitor plus immunomodulatory agent								
RVD lite	86	44	35.1	NR	NR	4	16	2
VMPT-VT	89	38	35.3	61% 5-year OS	4	23	6	16.8
VTD/VTP	80-81	4-28	15.4-34	43-51.5	5	17-38	12	9-27
PI + mAb								
VMP-dara	90.9	42.6	NR	NR	3.20	4.90	NR	1.4

Adapted with permission from Wildes.[203]

Abbreviations: C, carfilzomib; Cy, cyclophosphamide; D, dexamethasone; M, melphalan; NR, not reported; OS, overall survival; P, prednisone; PFS, progression-free survival; R, lenalidomide; T, thalidomide; V, bortezomib.

dexamethasone (when used with lenalidomide) is 20 mg once weekly for patients older than 75; however, further initial dose reduction (8 to 20 mg once weekly) can be considered for frail patients, with subsequent titration based on response and treatment tolerability.[40,70] Renal dysfunction is common in the elderly, and dose reductions for lenalidomide are warranted. These dose reductions do not appear to impact efficacy in the front-line setting, and dosing should be based on creatinine clearance as delineated by the pivotal FIRST trial.[50] Dose adjustment for frontline bortezomib-based regimens is not required for renal impairment.

Recommendation 5.5. Continuous therapy should be offered over fixed-duration therapy when initiating an immunomodulatory drugs or PI-based regimen (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The current era of novel therapies for myeloma has enabled the continuous use of these agents, in contrast to the fixed-duration dosing warranted by conventional chemotherapeutic options of the past. Continuous therapy in transplant-ineligible patients generally refers to treatment administered until progression or intolerance or treatment administered for a prolonged but finite time frame (eg, 2 to 3 years).[167] Lenalidomide and dexamethasone administered until progression was associated with improvement in PFS when compared with the same therapy given for only 18 months or to melphalan plus thalidomide plus prednisone (MPT) given for 18 months (phase III FIRST trial; ClinicalTrials.gov identifier: NCT00689936) in transplant-ineligible patients.[40] Continuous lenalidomide-dexamethasone was also associated with an improvement in OS compared with MPT. In an updated final analysis of the FIRST trial,[62] the majority of patients who required second-line treatment were given a bortezomib-based regimen; second-line outcomes were improved in the continuous lenalidomide-dexamethasone arm compared with MPT, suggesting that initial prolonged therapy did not compromise myeloma sensitivity to subsequent therapy. Palumbo et al[108] analyzed individual patient data from three randomized trials to establish the impact of continuous versus fixed-duration therapy; two of the trials were specific to transplant-ineligible populations. Although interpretation of this study is limited by the heterogeneity of the patient population (transplant eligible and ineligible) and treatment programs (including continuous therapy with lenalidomide- and bortezomib-based regimens), the pooled analysis does suggest an improvement in PFS and OS in patients receiving continuous therapy. As with the FIRST trial, there was again improvement in time from randomization to second progression or death, providing reassurance that ongoing drug exposure does not compromise future disease response. The decision around duration of therapy should be a joint decision between the physician and patient, with careful consideration of patient preferences and values, ongoing and future toxicities, quality of life, and treatment costs (including out-of-pocket expenses). Future studies are warranted to evaluate continuous therapy with less toxic agents, including monoclonal antibodies, and the role of MRD testing for selecting patients who might derive the most benefit from continuous therapy.

Clinical Question 6

What are the response goals following initial therapy for transplant-ineligible patients?

Recommendation 6.1. The goal of initial therapy for transplant-ineligible patients should be achievement of the best quality and depth of remission (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.2. Depth of response for all patients should be assessed by IMWG criteria (Table 6) regardless of transplant eligibility (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: moderate).

Recommendation 6.3. There is insufficient evidence to support change in type and length of therapy based on depth of response as measured by conventional IMWG approaches or MRD (Type: informal consensus; Evidence quality: low, harm outweighs benefit; Strength of recommendation: moderate).

Literature review and clinical interpretation. Response evaluation in multiple myeloma was originally based on the assessment of bone marrow plasma cells as well as serum and urine monoclonal protein concentrations. The definition of a CR only required bone marrow with less than 5% plasma cells, regardless of whether they were clonally restricted. Revised criteria were introduced during the International Myeloma Workshop in 2011. The criteria were modified to include stringent CR, which requires normalization of the serum free light chain assay and absence of clonal plasma cells in the bone marrow by immunohistochemical testing. The revised IMWG criteria have been adopted as the international standard, allowing improved comparison of treatment combinations. These criteria can be used whether the patient is transplant eligible or transplant ineligible. Response assessments should be followed serially to determine effectiveness of therapy. Although studies have identified prognostic implications of ongoing MRD positivity or FDG-PET/CT positivity in some populations, such as the transplant-eligible population, such data are still experimental and less explored in the transplant-ineligible group. As well, no studies have adapted therapy based on these results, and, as such, recommendations for changing therapy based on depth of response are not available.

TABLE 6. IMWG Response Criteria

Response	IMWG Criteria*
sCR	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow† by immunohistochemistry or immunofluorescence‡
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow†
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg/24 h
	If the serum and urine M-protein are unmeasurable,§ a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria
	If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%
	In addition to the above-listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
MR	NA
No change/stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Plateau	NA
Progressive disease§	Increase of ≥ 25% from lowest response value in any one or more of the following:
	Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)‖
	Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h)
	Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL
	Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%¶
	Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
	Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of:
	Direct indicators of increasing disease and/or end-organ dysfunction (CRAB features).‖ It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice
	Development of new soft tissue plasmacytomas or bone lesions
	Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
	Hypercalcemia (> 11.5 mg/dL [2.65 mmol/L])
	Decrease in hemoglobin of ≥ 2 g/dL (1.25 mmol/L)
	Rise in serum creatinine by 2 mg/dL or more (177 mmol/L or more)
Relapse from CR§ (to be used only if the end point studied is DFS)#	Any one or more of the following:
	Reappearance of serum or urine M-protein by immunofixation or electrophoresis
	Development of ≥ 5% plasma cells in the bone marrow¶
	Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)

NOTE. Adapted from the International Myeloma Working Group Web site[205] and Durie et al.[184]

Abbreviations: CR, complete response; CRAB, calcium, renal failure, anemia, and bone loss; DFS, disease-free survival; FLC, free light chain; IMWG, International Myeloma Working Group; MR, minimal response; PR, partial response; sCR, stringent clinical response; VGPR, very good partial response.

*A clarification to IMWG criteria for coding CR and VGPR in patients in whom the only measurable disease is by serum FLC levels: CR in such patients is defined as a normal FLC ratio of 0.26-1.65 in addition to CR criteria listed above. VGPR in such patients is defined as a > 90% decrease in the difference between involved and uninvolved FLC levels.

†Confirmation with repeat bone marrow biopsy not needed.

‡Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

§All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR patients must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse, and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

‖For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.

¶Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

#For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

Recommendation 6.4. Upon initiation of therapy, one should define patient-specific goals of therapy. Quality-of-life assessment (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. Redefining the goals prospectively, based on response, symptoms, and quality of life, is recommended (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are several different methods to measure quality of life, with a myeloma-specific quality-of-life scale recently published by Burckhardt and Anderson.[168] It facilitates the assignment of quantitative values to qualitative measurements, with the assessment consisting of 16 questions and resulting in a score of 16 to 112. The score can be used prospectively as patients are being treated. Defining specific goals of treatment is important (ie, is there an individual longevity goal) as these can help guide therapy. This quality-of-life scale can be used to assess quantitative and qualitative measurements in real time and can assist in determining the length and intensity of therapy. For example, if the score decreases by 30 points compared with prior assessment (ie, versus at initiation of treatment), then a re-evaluation of therapy should be initiated.

Recommendation 6.5. It is recommended that patients be monitored closely with consideration of dose modifications based on levels of toxicity, neutropenia, fever/infection, tolerability of adverse effects, performance status, and liver and kidney function, and in keeping with the goals of treatment (Type: informal consensus; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Standard toxicities are determined by the North Central Cancer Treatment Group and should be assessed regularly. The presence and severity of toxicity should be monitored and will strongly influence dose delays, reductions, and potential discontinuations. This should be done in conjunction with the patient's goals and quality of life as discussed in Recommendation 6.4.

RELAPSED DISEASE

Clinical Question 7

What factors influence choice of first relapse therapy?

Recommendation 7.1. 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 comorbidities (ie, neuropathy, renal insufficiency), frailty, and patient preference. High-risk patients as defined by high-risk cytogenetics and early relapse post-transplant/initial therapy should be treated immediately. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse (Type: informal consensus/evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. Biochemically relapsed myeloma is defined by IMWG criteria as a rise in serum or urine paraprotein in the absence of clinical signs or symptoms of myeloma.[153] Although the worsening myeloma markers define the clinical relapse, there is no set level of serum or urine paraproteins that consistently corresponds to the development of symptoms. Even in the same patient, paraprotein levels at different time points may produce variating symptoms, and, as such, the timing for initiation of treatment must be individualized.

Whether to start treatment or not requires a re-evaluation of the patient's disease, a discussion with the patient to understand the patient's preference, and a consideration of the patient's prior tolerance to chemotherapy. Repeat imaging should be performed to assess for active bone disease and should include assessment for new lytic lesions and extramedullary disease. For standard-risk patients, a bone-marrow biopsy should be considered to re-evaluate cytogenetic risk. Overall, treatment should be initiated at the time of biochemical relapse in those with high-risk cytogenetics, extramedullary disease, early relapse after transplant or initial therapy, and/or with evidence of rapid rise in myeloma markers. Close observation is appropriate for patients with slowly progressive and asymptomatic relapse. In these patients, close monitoring of symptoms and organ function and frequent assessment of myeloma paraprotein levels are required.

Recommendation 7.2. All clinically relapsed patients with symptoms due to myeloma should be treated immediately (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Patients with relapsed myeloma and evidence for active disease as defined by hypercalcemia, renal dysfunction, anemia, lytic bone lesions (CRAB) or other manifestations attributable to myeloma, such as extramedullary disease or central nervous system myeloma, should be initiated on treatment immediately. Most clinical trials have used the IMWG criteria for progressive disease, which includes criteria for both biochemical and clinical relapse for initiating therapy.[53,55,58,95,107,112]

Recommendation 7.3. Triplet therapy should be administered on first relapse, though the patient's tolerance for increased toxicity should be considered. A triplet is defined as a regimen with two novel agents (PI, immunomodulatory

drug, or monoclonal antibody) in combination with a steroid (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The treatment of relapsed multiple myeloma is complex and does not have a simple algorithm. When available, clinical trials are preferred and should be considered at every phase of treatment.

On first relapse, the choice of therapy should take into account patient-related, disease-related, as well as treatment-related factors. For patients who are fit, triplet is generally recommended over doublet therapy due to improved clinical outcomes. Triplet therapy is defined as containing two novel agents plus steroids. Novel agents include immunomodulatory drugs such as lenalidomide, pomalidomide, or thalidomide; PI such as ixazomib, bortezomib, or carfilzomib; and monoclonal antibodies such as daratumumab and elotuzumab. Doublet therapy is defined as one novel agent with steroids. Multiple randomized studies[53,55,58,95,107,112] as well as meta-analyses[10,17,21,26,31] have shown that triplets are more effective than doublet combinations in improving PFS, overall response rate, and/or OS, even in older adult patients.[58] In fact, the US Food and Drug Administration (FDA) approval of multiple recent drugs such as daratumumab,[55,107] elotuzumab,[53] carfilzomib,[58] ixazomib,[95] and panobinostat[112] have been based on the improved PFS of these drugs used in triplet combinations versus doublets in relapsed and/or refractory myeloma. Data suggest that even the use of alkylating agents as part of triplet therapy yields better outcomes than doublets.[75] Although triplet therapy offers better clinical outcomes, toxicity appears increased in triple versus doublet therapy,[17,21,26,31,58] and this must be considered when selecting therapy. For some patients, prior toxicity may result in the selection of doublet versus triplet therapy. The ENDEAVOR trial (ClinicalTrialos.gov identifier: NCT01568866) demonstrated the superiority of the doublet carfilzomib plus dexamethasone to bortezomib plus dexamethasone in both PFS and OS[52] in relapsed multiple myeloma. In subgroup analyses, carfilzomib, dexamethasone was superior to bortezomib, dexamethasone regardless of cytogenetic risk,[44] number of prior therapy lines,[94] or prior exposure to bortezomib or lenalidomide.[94] Overall, the selection of doublet versus triplet therapy should be individualized.

The best triplet or how to sequence triplet or doublet therapy in the relapse or refractory setting remains unclear. Published RCTs in relapsed myeloma comparing individual triplets or novel agents in triplet combination are lacking. Several network meta-analyses have been performed to ascertain which combination or type of novel agent was more efficacious, with variable results and no obvious conclusion.[9,10,24,31,60] Because the optimal sequence of therapies is unknown and most patients receive between two to more than 10 lines of therapy for relapsed disease, the general strategy has been to use all approved drugs in rational sequential combinations (ie, immunomodulatory drug plus PI plus steroid followed by second-generation immunomodulatory drug plus monoclonal antibody plus steroid followed by second-generation PI plus alkylator plus steroid, and so on).

Although clinical trials are preferred at all treatment time points, as patients become multiply relapsed and resistance develops to immunomodulatory dugs, PI, and antibodies, referral for a novel clinical trial can be considered. In addition, the use of chemotherapeutic agents such as cyclophosphamide, melphalan, or panobinostat[112] may also be considered.

Recommendation 7.4. Treatment of relapsed multiple myeloma may be continued until disease progression. There are not enough data to recommend risk-based versus response-based duration of treatment (such as MRD) (Type: evidence-based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. In clinical trials, an extended therapy duration has been associated with better outcomes in patients with newly diagnosed multiple myeloma. However, data on how therapy duration affects the outcomes for patients with relapsed/refractory multiple myeloma are limited, as many randomized trials had a reduction or discontinuation of therapy in the trial design. Subgroup analyses of large prospective trials in which treatment was given until progression have suggested that longer-term therapy is beneficial. In one study of 50 patients, those treated for more than 3 years had a longer median time to progression compared with those treated for 2 to 3 years, regardless of the response rate.[169] In another retrospective study of 67 patients, OS and overall response rates were significantly better for patients treated with lenalidomide and dexamethasone for more than 12 months compared with patients who stopped treatment at less than 12 months for reasons other than progression.[170]

A recent large, retrospective study was conducted in the United States to evaluate the effect of the duration of second-line therapy on OS. From January 2008 to June 2015, a total of 628 patients with newly diagnosed multiple myeloma were noted to have relapsed disease and were observed for response to second-line therapy. With a median duration of second-line therapy of 6.9 months, researchers noted that each additional month of second-line therapy was associated with a reduced adjusted risk of death at 1 year (odds ratio, 0.78; 95% CI, 0.77 to 0.83; $P < .001$). Thus, the authors concluded that there is clinical benefit for maintaining a longer duration of therapy at first relapse.[171]

Current standard practice is for patients who are responding to treatment to continue treatment until disease progression or until unacceptable toxicity. There are no data to guide duration of therapy based on risk assessment or response to treatment, such as achievement of MRD status.

Recommendation 7.5. Prior therapies should be taken into consideration when selecting the treatment at first relapse. A monoclonal antibody–based regimen in combination with an immunomodulatory drug and/or PI should be considered. Triplet regimens are preferred based on tolerability and comorbidities (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. In the past decade, there has been tremendous progress in the treatment of multiple myeloma, with a number of agents/combinations being approved by the FDA, including monoclonal antibodies (daratumumab, elotuzumab), histone deacetylase inhibitors (panobinostat), PIs (bortezomib, carfilzomib, ixazomib), and immunomodulatory drugs (lenalidomide, thalidomide, pomalidomide) along with historical alkylators and anthracyclines. This wealth of treatment options makes it challenging for the treating clinician to select which drugs to use, as well as when to use them and in what order.

In general, these regimens are tried sequentially based on many factors, including availability, prior therapy, and toxicity profile, as there are no randomized trials available to guide specific treatment sequences.

In the 2017 Journal of Clinical Oncology article by van Beurden-Tan et al,[9] they aimed to synthesize all efficacy evidence, enabling a comparison of all current treatments for relapsed multiple myeloma. They combined evidence from 17 phase III RCTs, including 16 treatments. Of 16 treatment options, the combination of daratumumab, lenalidomide, and dexamethasone was the best option in terms of both ranking and probability of being the best treatment. All three best-treatment options are triple-combination regimens, and all are in combination with lenalidomide and dexamethasone (with daratumumab, carfilzomib, or elotuzumab). This is in line with earlier observations that triplet combinations are better than doublets[9] and are preferred if tolerated as outlined above.

Prior treatments are important in deciding which regimen will be used. Patients who relapse more than 1 year after their treatment will likely respond to a repeat course of the previous therapy. If patients relapse during therapy or within 1 year of completing therapy, they are considered less sensitive to these agents and should be treated accordingly. For example, in patients progressing on lenalidomide maintenance therapy, salvage therapy with bortezomib and a monoclonal antibody can be considered. In bortezomib-refractory cases, lenalidomide with monoclonal antibody can be used. In double-refractory cases, pomalidomide combinations with monoclonal antibodies[172] or cyclophosphamide[173] are reasonable options.

This is particularly important in high-risk patients. Lui et al[209] performed a meta-analysis in relapsed multiple myeloma including patients with del(17p). Thirteen prospective studies were evaluated involving 3,187 patients with multiple myeloma and 685 with del (17p). The authors concluded that combined therapy (triplets and doublets) with second-generation PIs, monoclonal antibodies, and immunomodulatory drugs are associated with improved outcomes in patients with del (17p).

Recommendation 7.6. ASCT, if not received after primary induction therapy, should be offered to transplant-eligible patients with relapsed multiple myeloma. Repeat SCT may be considered in relapsed multiple myeloma if PFS after first transplant is 18 months or greater (Type: evidence-based; Evidence quality: low, benefit outweighs harm; Strength of recommendation: weak).

Literature review and clinical interpretation. There are many options for the treatment of relapsed or refractory multiple myeloma and for transplant-eligible patients; this includes the use of salvage hematopoietic cell transplantation. There are two general settings for which to consider salvage ASCT.

1. Relapse with no prior transplant. After initial chemotherapy and collection of stem cells, patients can either proceed to early (up-front) ASCT or can opt for delayed ASCT at the time of relapse.

There have been several randomized trials comparing early versus delayed transplant; only one[35] included patients receiving induction with an immunomodulatory agent and a PI. In this multicenter trial (IFM/DFCI 2009), 700 adults 65 years of age or younger with symptomatic newly diagnosed myeloma were randomly assigned to receive induction triplet regimen followed by either early or delayed transplant at relapse. Early transplant was associated with higher rates of CR (59% *v* 48%; $P = .03$) and achievement of MRD (79% *v* 65%; $P < .001$) and a longer median PFSPFS (50 *v* 36 months; $P < .001$). At the median follow-up of 44 months, OS at 4 years did not differ significantly (81% *v* 82%).[35] In the RVD-alone group, salvage transplantation was administered to 79% of patients with symptomatic relapse, and this likely contributed to the lack of OS difference. These results suggest that early transplant delays disease progression, that the majority of patients who defer transplant will be able to undergo transplant at relapse, and that this delay

does not appear to impact OS. Thus, for those patients who do not undergo SCT as part of their initial treatment, high-dose chemotherapy followed by ASCT at relapse is feasible.

2. Relapse in setting of prior SCT. Treatment options for relapsed multiple myeloma after an ASCT include a second ASCT, novel chemotherapy regimens, or in select cases a nonmyeloablative alloSCT, preferably as part of a clinical trial.

Alvares et al[174] found that patients with a PFS of less than 18 months after first ASCT had a median OS of less than 6 months, whereas those with a PFS of 18 months or more showed a median OS approaching 3 years.

A Mayo Clinic study that reviewed 345 patients who relapsed after ASCT found that the median OS was 10.8 months for patients in the early-relapse group (≤ 12 months from ASCT) as compared with 41.8 months in the late-relapse group (> 12 months from ASCT; $P < .001$). Hence, the authors recommended offering novel nontransplant therapies for patients in the early-relapse group due to poor outcomes with SCT.[175]

In the era of novel agents, the only RCT to evaluate the role of salvage ASCT in patients with myeloma at first relapse/progression after prior ASCT was the United Kingdom Myeloma X study (ClinicalTrials.gov identifier: NCT00747877). In this trial, 174 patients with first progression or relapsed disease at least 18 months after prior ASCT were treated with anthracycline-based chemotherapy and were randomly assigned to further treatment with ASCT or to oral cyclophosphamide. After a median follow-up of 31 months, second ASCT resulted in a longer median time to progression (19 *v* 11 months; HR, 0.36).[47]

In a large single-institution retrospective analysis of 200 patients undergoing second ASCT for relapsed multiple myeloma,[176] a partial or greater response was noted in 80% by day 100. At a median follow-up of 57 months, the median PFS and OS times following second ASCT were 15 and 42 months, respectively. Outcomes were worse among patients who had an initial remission duration less than 18 months and in those who had less than a partial response to re-induction therapy prior to SCT.

The IMWG has recommended consideration of a second SCT in those who tolerated the initial transplant well and had at minimum PFS of 12 to 18 months.[149]

Allogeneic hematopoietic cell transplantation has the potential of producing cure; however, its use is limited by high rate of treatment-related mortality and the risk of significant morbidity, especially from graft-versus-host disease. The treatment-related mortality associated with alloSCT is decreasing with the advent of nonmyeloablative preparative regimens, but this seems to reduce its efficacy in myeloma. The largest case series of nonmyeloablative allogeneic transplant in relapsed refractory disease is from the European Society for Blood and Marrow Transplantation. In a study involving 229 patients undergoing nonmyeloablative transplantation, the 3-year OS and PFS rates were 41% and 21%, respectively. Patients with prior transplant and primary progressive disease did worse, and those with graft-versus-host disease did better. This study demonstrated feasibility of nonmyeloablative transplants in carefully selected patients.[177]

At present, allogenic transplant is reserved for young patients with high-risk myeloma who have short durations of response and are willing to accept the high treatment-related morbidity and mortality risk. Clinical trials should be strongly considered.

Clinical Question 8

How does risk status influence therapy in myeloma (newly diagnosed and relapse)?

Recommendation 8.1. The risk status of the patients should be assessed using the R-ISS for all patients at the time of diagnosis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Every patient who is diagnosed with multiple myeloma should undergo risk stratification using R-ISS.[4,5] The R-ISS incorporates the original ISS (serum B2M and serum albumin), while adding prognostic information obtained from the serum LDH and chromosomal abnormalities (CAs) detected by plasma cell–specific interphase FISH. CAs are divided into high risk (del17p, t[4;14], t[14;16]) or standard risk. R-ISS stage I is ISS stage I with normal LDH and standard-risk CA. R-ISS stage II is neither stage I nor stage III. R-ISS stage III is stage III ISS (β_2M ≥ 5.5 mg/dL) with high LDH and/or high-risk CA.

Patients with R-ISS stage I, II, and III had 5-year OS rates of 82%, 62%, and 40%, respectively.

This risk stratification helps to determine prognosis and may impact treatment choice, with high-risk patients being treated more aggressively. The R-ISS can also be used for risk stratification of patients with relapsed multiple myeloma and should be performed at the time of disease relapse.[178]

Recommendation 8.2. Repeat risk assessment at the time of relapse should be performed and should include bone marrow with FISH for myeloma abnormalities seen with progression, including 17p and 1q abnormalities. FISH for primary abnormalities (translocations and trisomies), if seen in the initial diagnostic marrow, does not need to be repeated (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Nearly all patients with multiple myeloma have abnormalities

on FISH that can be broadly divided into translocations and trisomies.[179,180] These abnormalities are typically referred to as primary abnormalities and do not routinely change during the course of the disease. As myeloma evolves, patients may acquire new high-risk abnormalities such as 17p deletion and 1q amplification. Acquisition of these secondary abnormalities is typically associated with more aggressive disease behavior and shorter survival.[111,181] Therefore, a bone marrow examination with interphase FISH can reveal additional prognostic information in the setting of relapsed multiple myeloma. In patients with known abnormalities, a limited FISH panel to assess for new high-risk abnormalities is adequate.

Recommendation 8.3. Assessment of other risk factors such as renal insufficiency, age, presence of plasma cell leukemia/circulating plasma cells, extramedullary disease, and frailty should also be considered/performed (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Other disease-related factors that affect risk stratification include the development of extramedullary plasmacytomas or evolution into secondary plasma cell leukemia. These findings suggest more aggressive disease, place the patient in a high-risk category, and have an effect on prognosis.[37] Patient-related factors like age, performance status, renal dysfunction, as well as frailty score (IMWG score http://www.myelomafrailtyscorecalculator.net/) also play an important role in risk stratification at relapse.[34] Patients who progress while receiving therapy or within the first year of diagnosis also have a poor prognosis. Similarly, the duration of the interval between the last therapy and biochemical or clinical relapse is also critically important. Relapse soon after discontinuing therapy or within 18 months of ASCT or while receiving maintenance therapy suggests more aggressive disease. These patients should be considered to have high-risk disease regardless of their cytogenetic or FISH abnormalities.

Recommendation 8.4. In patients with genetic high-risk disease, a triplet combination of PI, immunomodulatory drug, and a steroid should be the initial treatment, followed by one or two ASCTs, followed by a PI-based maintenance until progression (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Patients with high-risk myeloma appear to have the best outcome when they achieved a deep response following initial therapy. One of the most effective approaches in inducing deep responses is to initiate therapy using a triplet combination of a PI, immunomodulatory drug, and steroid, and then to use consolidation including an ASCT and post-transplant maintenance therapy.[60] The use of a PI and immunomodulatory drug as initial therapy is associated with improved OS in myeloma. A recent phase III trial (IFM/DFCI 2009) confirms improved response and PFS when transplant is used as part of initial therapy.[35] A recent European phase III trial,EMN02, (ClinicalTrials.gov identifier: NCT01208766) and retrospective data demonstrate improved outcomes for high-risk disease when tandem autologous transplantation is used. However, data from the recent US phase III trial, STAMINA, (ClinicalTrials.gov identifier: NCT01863550) did not demonstrate an improvement for tandem SCT, and the role of tandem ASCT for high-risk disease remains unclear. Prospective, randomized data assessing the optimal maintenance therapy in high-risk disease are unavailable. However, in a meta-analysis of lenalidomide maintenance, the only group of patients with limited benefit was high-risk disease. In contrast, the HOVON-65 clinical trial (EudraCT No. 2004-000944-26) that incorporated bortezomib as maintenance as well as part of induction therapy had better outcomes for the high-risk patients.[97] Given these data, incorporation of a PI, immunomodulatory drug, and steroid as part of the induction therapy followed by ASCT followed by PI based maintenance (with or without immunomodulatory drug) appears to be the best approach for high-risk patients.

Recommendation 8.5. In patients with renal insufficiency, drugs should be modified based on renal clearance (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. Renal dysfunction is a common finding in patients with multiple myeloma at the time of diagnosis, with nearly 30% of the patients having some degree of renal dysfunction. As such, the Cockroft-Gault formula or similar creatinine clearance assessment tool should be routinely used to estimate clearance prior to initiating therapy. Many of the medications used to treat myeloma will need dosage modifications based on the degree of renal dysfunction. The treating physician should modify the doses of antimyeloma therapies accordingly, especially the immunomodulatory drugs such as lenalidomide and pomalidomide, and should follow the product insert guidelines. Monoclonal antibodies and most PIs do not need dose modifications in the setting of renal insufficiency, but ixazomib should be dose reduced in context of renal insufficiency as per the product insert.

Recommendation 8.6. In patients with plasma cell leukemia or extramedullary disease, cytotoxic chemotherapy may have a role (Type: evidence based; Evidence quality: intermediate, benefit outweighs harm; Strength of recommendation: moderate).

Literature review and clinical interpretation. There are very few prospective data to guide treatment of patients with extramedullary disease or plasma cell leukemia. Retrospective studies have examined the use of combination chemotherapy, such as dexamethasone, platinum, doxorubicin, cyclophosphamide, and etoposide, that includes cytotoxic agents such as anthracyclines and alkylating agents and have shown good response rates.[182] In general the durability of responses is short. However, given the aggressive nature of plasma cell leukemia or extramedullary disease, it is reasonable to consider using these combinations to debulk the disease as a bridge to more definitive therapy. Clinical trials are encouraged in this patient population.

Clinical Question 9

How and when should response assessment be performed?

Recommendation 9.1. The IMWG revised response criteria should be used for response assessment (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The IMWG response criteria for multiple myeloma have been used for assessment of disease response since they were introduced over a decade ago.[153,183-185] The uniform response criteria incorporated previously used European Bone Marrow Transplantation Registry criteria[183] and provided a consistent platform for disease response assessment in multiple myeloma. The original IMWG criteria have been revised over time to incorporate additional tests that have been introduced for measuring disease burden in multiple myeloma. Multiple studies over the years have validated the impact of various levels of response on survival outcomes in multiple myeloma.[27,99,142] These responses are currently used as measures of success for regulatory end points as well. The most recent revision of the response criteria further clarifies several points regarding the practical implementation of the response criteria.[153] Consistent application of these standard response criteria will allow for comparison of results from multiple clinical trials and also the degree of success with different therapies in a given patient.

Recommendation 9.2. All measurable parameters need to be followed, including light and heavy chain analysis (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. There are multiple disease measures that can be followed in patients with multiple myeloma. In general, disease response assessment in myeloma includes evaluation of the level of protein in the blood or urine, the proportion of plasma cells in the bone marrow (or in the peripheral blood in the case of plasma cell leukemia), and, if present, the size of plasmacytoma, assessed on imaging or clinical examination.[153] The level of monoclonal protein in the blood has traditionally been measured using serum protein electrophoresis. In the setting of certain immunoglobulins such as IgA, which can be difficult to quantify, the quantitation of the immunoglobulin by nephelometry can be used in place of serum protein electrophoresis. In patients with predominantly light chain monoclonal protein, the serum free light chain assay can be used for measurement of monoclonal kappa or lambda light chain levels. In patients with very low levels of monoclonal protein, immunofixation with isotype-specific antibodies can detect presence of the monoclonal protein. In the urine, the monoclonal protein can be measured using electrophoresis similar to what is done in the blood; however, formal quantitation requires a 24-hour urine sample with assessment of total protein and M-protein levels. The parameters that need to be followed in any individual patient depend greatly on the ability to measure the parameter in question at the time of initiating therapy. The IMWG guidelines provide the specific minimum thresholds for each of the measurable parameters used to assess response in multiple myeloma. In general, if there is measurable serum monoclonal protein then it should be followed, otherwise a measurable urine monoclonal protein should be followed. Over time, resistance to novel drug therapy can occur and the disease can evolve to becoming oligosecretory, nonsecretory, or even light chain disease only (light chain escape). Thus, serum free light chain levels should also be followed in addition to serum protein electrophoresis.

Recommendation 9.3. All responses excluding marrow and imaging should be confirmed as per IMWG criteria (Type: evidence based; Evidence quality: high, benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. The requirement of confirmatory testing was introduced into the IMWG criteria to ensure that laboratory variations are accounted for. While a minimum gap was previously prescribed between the initial testing and the confirmatory testing, the recent versions of the criteria have eliminated this requirement.[153,184] At this time, a repeat testing can be done on the same day from a separate blood draw, or the urine can be done a day apart to meet the requirement of confirmation. Given that the bone marrow findings and imaging findings are less likely to have variation in interpretation, and given the burden of repeat testing, these do not need to be confirmed.

Recommendation 9.4. Response assessment should be performed after one cycle of therapy, and once a response trend is observed, it may be done every other cycle and less frequently once patient is in a plateau (Type: evidence based; Evidence quality: high,

benefit outweighs harm; Strength of recommendation: strong).

Literature review and clinical interpretation. There are no prospective trials examining the appropriate timing of response assessment and any potential impact of altering therapy based on response status at any given time during the disease course. The recommendations are primarily based on the reported guidelines and practical implementation of the guidelines. Studies examining the impact of kinetics of response on outcomes in myeloma have demonstrated mixed results.[117,186,187] A rapid response has been associated with poorer outcomes in earlier studies with traditional treatment approaches but does not appear to be the case with newer therapies. Some of the observations may be the result of the high-risk patients, especially those with high-risk cytogenetics and high proliferative rates, being more sensitive to therapeutic interventions, especially with the traditional cytotoxic drugs. On the contrary, a slow and sustained deepening of response over time (time to plateau) has been recently reported to be a predictor of better survival. Given this heterogeneity in the impact of response kinetics, timing of response assessment cannot be based on the need for changing any treatment approaches and needs to be based more on the practical aspects. Assessment of the response using the paraprotein measurements and/or imaging should be evaluated in the context of the clinical picture. Assessment after one to two cycles will allow evaluation to ensure that the disease is not progressing based on the response criteria, in which case a change in therapy will be warranted. If the response after one to two cycles is stable disease, but there is evidence of clinical deterioration or lack of improvement, such as worsening end organ damage, a potential change in therapy should be addressed. Evidence of response at the end of the first cycle will be reassuring to the patient and provider. Once there is evidence of sustained disease response, then checking the response every other cycle will be adequate and can decrease the testing burden on the patient, especially as there is no evidence of improved outcomes by immediate intervention at the time of relapse, as discussed in section 7.0. However, if there is evidence of progression at any time, it should be repeated at the minimum during the next cycle, or sooner if there is evidence of clinical deterioration to confirm the progression. Once the patient is in plateau, the frequency can be altered to less-frequent testing that aligns best with the frequency of visits required for therapy and other logistical factors. Once there are results showing a trend toward increasing paraprotein, more frequent testing should be resumed, preferably every cycle until the patient meets criteria for progression or treatment is changed. Figure 2 provides a visual interpretation of these recommendations in the management algorithm.

PATIENT AND CLINICIAN COMMUNICATION

In the last 15 years, patients with multiple myeloma have enjoyed a plethora of new treatment options with significantly improved PFS and OS, especially for the more than 80% majority classified as standard risk. We have at least 10 new FDA-approved therapeutics for myeloma since 2003, with more coming. This dilemma of riches is a mixed blessing for both patients and clinicians as we must now choose the best therapeutic options at each stage of initial disease and multiple relapses.

There is no one-size-fits-all treatment for patients with myeloma, especially with autologous transplantation and other cellular therapy now part of our armamentarium. Clinical care pathways and patient-oriented care models have created an environment of additional complexity beyond transplantation (or not) and multiple drug and immunotherapy combination approaches. When recognized myeloma experts cannot always agree on best treatments, it is understandable that general oncologists and patients also find treatment decisions difficult.

Trust, ongoing education, and clear communication between physicians, patients, families, and oncology allied health personnel are essential. Patients with myeloma still die of their cancer, but most will live long enough to study and learn about their disease and their treatment options. A few become extremely educated and can help develop and promote myeloma clinical trials. Patients are empowered with factual information by support groups, national foundations, social media, and by each other. They expect greater roles in their own decision making and care, because patients understand that the final decision in their treatment is made by them, not by their physician.

It is vital that clinicians understand, accept, and encourage patient interest and education regarding their informed myeloma treatment decisions. Physicians should take the necessary time to orient their patients regarding their care but also make available recommended sources for information, including both print materials and trusted online sites. Encourage patients, family, and caregivers to keep good records, and especially to note changes in symptoms or health conditions after active treatment begins. Remind them that reporting an adverse effect will only improve their ability to receive optimal treatment and not immediately make them ineligible to continue receiving their current treatment.

Establish an atmosphere in which patients feel empowered to share what they have learned, such as a new potential clinical trial or a new therapeutic for which they might be eligible. Skillful physicians understand that the most satisfying clinician–patient relationships and best therapeutic decisions occur when those decisions are shared, not dictated.

For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician

Communication: American Society of Clinical Oncology Consensus Guideline.[188]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial/ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[189-191]

Based on the SEER database, African Americans are 26% more likely to receive no treatment of newly diagnosed multiple myeloma. Similarly, they are 37% less likely to undergo ASCT for myeloma.[192] Americans enrolled in Medicaid in addition to Medicare are 21% more likely not to be treated for a new diagnosis of myeloma.[132]

Age-related disparities are also prevalent in the treatment of multiple myeloma. While younger patients have greatly benefited from novel therapies, this benefit is less pronounced in patients older than 75 years of age, in part due to undertreatment.[132] Older age has been found to increase the odds of not having any treatment by 7% per every year of age.[132] It is important to consider that patients over the age of 75 with multiple myeloma are functionally heterogeneous and can be divided into fit, intermediate fit, and frail groups based on several easily available comprehensive geriatric assessment tools.[193]

Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

Increasing costs of novel antimyeloma treatment, particularly oral agents, have placed further financial barriers to timely and efficient myeloma treatment in the United States. It has been shown that beneficiaries of Medicare with low-income subsidy have higher use of immunomodulatory drugs compared with other Medicare recipients. Appropriate emphasis in policy making on novel oral agent coverage will be important to address this inequality in health care.[194]

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCC are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials whose study selection criteria may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups to make recommendations for care in this heterogeneous patient population.

As many patients for whom guideline recommendations apply present with MCC, any treatment plan needs to take into account the complexity and uncertainty created by the presence of MCC and highlights the importance of shared decision making regarding guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plan.

Cytopenias occur not infrequently with current myeloma therapies including alkylating agents and novel agents. Grade 3 to 4 anemia has been reported in 3% to 19% of cases with novel agents, and thus erythropoiesis-stimulating agents and optimal iron supplementation should be considered if myeloma-related anemia does not improve with chemotherapy. Thrombocytopenia is common with PIs such as bortezomib and carfilzomib as well as immunomodulatory drugs (thalidomide, lenalidomide, and pomalidomide), and thus dose reduction should be performed accordingly and treatment interrupted in the event of grade 4 thrombocytopenia. Neutropenia is a common adverse event with immunomodulatory drugs and the monoclonal antibody daratumumab, with incidence increasing in the relapsed setting and in combination therapy. Thus, in patients considered to be at high risk for febrile neutropenia, granulocyte colony-stimulating factor is recommended.[195]

It is crucial to select appropriate therapy in the case of renal impairment. Bortezomib and thalidomide may be administered without any dose adjustment, while adjustment of the starting dose of lenalidomide and pomalidomide should be made accordingly. Bortezomib has an additional advantage of rapid clearance of the free light chains, thus accelerating kidney response.[195]

Finally, as bone disease associated with myeloma is an important cause of morbidity and mortality, bisphosphonates are the backbone of supportive care for patients with osteoporosis and lytic lesions. For up-to-date recommendations of the use of bisphosphonate in myeloma,

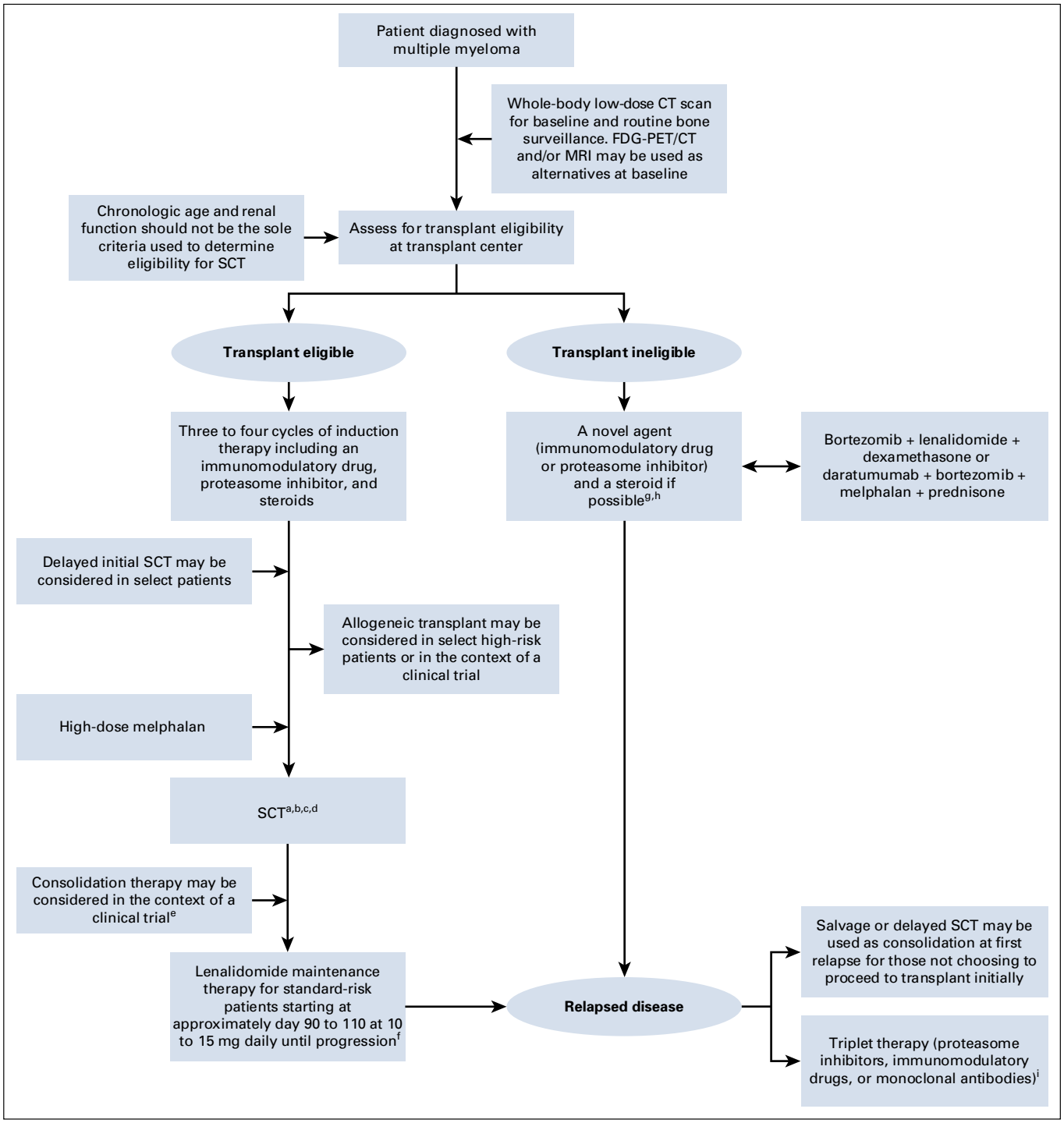

FIG 2. Algorithm on treatment of patients with multiple myeloma. (a) Agents associated with stem-cell toxicity, such as melphalan and/or prolonged immunomodulatory drug exposure (more than four cycles), should be avoided in patients who are potential candidates for stem-cell transplant (SCT). (b) Ample stem-cell collection (sufficient for more than one SCT) should be considered up front, due to concern for limited ability for future stem-cell collection after prolonged treatment exposure. (c) The level of minimal response required to proceed to SCT is not established for patients receiving induction therapy—patients should be referred for SCT independent of depth of response. (d) Tandem autologous SCT should not be routinely recommended. (e) For patients ineligible or unwilling to consider maintenance therapy, consolidation therapy for at least two cycles may be considered. (f) For patients intolerant of or unable to receive lenalidomide, bortezomib maintenance every 2 weeks may be considered. For high-risk patients, maintenance therapy with a proteasome inhibitor with or without lenalidomide may be considered. (g) Initial dosing should be individualized based on patient age, renal function, comorbidities, functional status, and frailty status. Subsequent dosing may be tailored based on initial response and tolerability. (h) Depth of response for all patients should be assessed by International Myeloma Working Group criteria. (i) Prior therapies should be taken into consideration when selecting the treatment at first relapse. CT, computed tomography; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging.

TABLE 7. Estimated Cost of Drugs for Multiple Myeloma

Drugs and Regimens	Approximate Drug Cost per Year (in US dollars)*	Comment
Drugs		
Thalidomide	60,000	
Lenalidomide	168,000	
Pomalidomide	192,000	
Bortezomib	50,000	
Ixazomib	111,000	
Carfilzomib	130,000	260,000 (at 56 mg/m^2)
Daratumumab	120,000	
Elotuzumab	120,000	
Panobinostat	96,000	
Cyclophosphamide	5,800	
Melphalan IV	10,000	Per transplant
Dexamethasone	3,400	
Regimens		
VRd	220,000	
KRd	300,000	
VCd	60,000	
DRd	290,000	
D-VRd	340,000	
D-KRd	590,000	

NOTE. Adapted with permission from Rajkumar.[203]

Abbreviations: DRd, daratumumab, lenalidomide, and dexamethasone; D-KRd, daratumumab, carfilzomib, lenalidomide, and dexamethasone; D-VRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; KRd, carfilzomib, lenalidomide, and dexamethasone; VCd, bortezomib, cyclophosphamide, and dexamethasone; VRd, bortezomib, lenalidomide, and dexamethasone.

*Source for calculating costs: parenteral drug prices: Centers for Medicare & Medicaid Services[206]; oral drug prices: GoodRx.com.[207]

practitioners are invited to familiarize themselves with recently published ASCO clinical practice guidelines on bone-modifying agents in multiple myeloma.[196]

In light of the above considerations, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.

COST IMPLICATIONS

Increasingly, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[197,198] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[199,200]

Discussion of cost can be an important part of shared decision making.[201] Clinicians should discuss with patients the use of less-expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[201]

Table 7 shows estimated prices for the available treatment options addressed in this guideline. Of note, medication prices may vary markedly, depending on negotiated discounts and rebates.

Patient out-of-pocket costs may vary depending on insurance coverage. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[201]

As part of the guideline development process, ASCO may opt to search the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. Excluded from consideration are cost-effective analyses that lack contemporary cost data and agents that are not currently available in either the United States or Canada and/or are industry sponsored.

The issue of cost is particularly important in multiple myeloma as many of the agents recently approved may carry a high burden of cost to the patient. These include both oral and parenteral medications. Furthermore, as more of these agents are being used in combination, it may further add to the financial burden of patients. Finally, there is a clear trend for longer treatment periods for patients with myeloma, both in maintenance therapy and at relapse—this may significantly increase costs and must be considered carefully. There is a potential in the future that MRD testing and status may be able to identify patients in whom treatment may be suspended. Incorporating this type of analysis in clinical trials is strongly recommended (and is being done internationally) with the possible effect of reducing duration of therapy, cost burden, and toxicity.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from August 15 through August 27, 2018. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for every proposed recommendation, with 13 written comments received. A total of 85% of the responses were either agreed or agreed with slight modifications to the recommendations, and 15% of the responses were disagreements. Expert Panel

members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated prior to Clinical Practice Guidelines Committee review and approval.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. 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 Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO Practice Guideline Implementation Network. ASCO guidelines are posted on the ASCO Web site and most often published in *Journal of Clinical Oncology* and *Journal of Oncology Practice*.

ADDITIONAL RESOURCES

More information, including a Data Supplement with additional evidence tables, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at asco.org/hematologic-malignancies-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[202] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[188] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Role of Bone-Modifying Agents in Multiple Myeloma[196] (http://ascopubs.org/doi/10.1200/JCO.2017.76.6402)

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Data analysis and intrepretation: All authors
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Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline

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APPENDIX

TABLE A1. Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline Expert Panel Membership

Name (designation)	Affiliation or Institution	Role or Area of Expertise
Joseph Mikhael, MD (co-chair)	City of Hope Cancer Center, Phoenix, AZ and International Myeloma Foundation, North Hollywood, CA	Hematology/oncology
Tom Martin, MD (co-chair)	University of California, San Francisco, CA	Hematology/oncology
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Brea Lipe, MD	University of Rochester Medical Center, Rochester, NY	Hematology/oncology
Caitlin Costello, MD	UC San Diego Moores Cancer Center, La Jolla, CA	Hematology/oncology
Martha Lacy, MD	Mayo Clinic, Rochester, MN	Hematology/oncology
Madhav V. Dhodapkar, MD	Winship Cancer Institute, Emory University, Atlanta, GA	Hematology/oncology
Sandy Wai Kuan Wong, MD	University of California, San Francisco, CA	Hematology/oncology
Richard F. Little, MD	National Cancer Institute, Bethesda, MD	Hematology/oncology
Alexander Whitley, MD	Central Alabama Radiation Oncology, Montgomery, AL	PGIN representative
Namrata Peswani, MD	Advocate Medical Group, Chicago, IL	PGIN representative
Rahul Seth, MD	Upstate Medical University, Syracuse, NY	PGIN representative
James Omel, MD	Education and Advocacy, Grand Island, NE	Patient representative
Matthew C. Cheung, MD	Sunnybrook Health Sciences Centre, Toronto, ON, Canada	Hematology/oncology (CCO representative)
Anca Prica, MD	Princess Margaret Cancer Centre, Toronto, ON, Canada	Hematology/oncology (CCO representative)
Anna Nikonova, MD	Juravinski Cancer Center, Hamilton, ON, Canada	Hematology/oncology (CCO representative)
Irwin Walker, MD	McMaster University, Hamilton, ON, Canada	Hematology/oncology (CCO representative)
Nofisat Ismaila, MD	American Society of Clinical Oncology, Alexandria, VA	Staff/health research methodologist

Abbreviations: CCO, Cancer Care Ontario; PGIN, Practice Guidelines Implementation Network.

TABLE A2. Study Quality

Trial Name (trial identifier)	Adequate Randomization	Allocation Concealment	Blinding	Blinding					Infrequent Loss to Follow-Up	Selective Outcome Reporting	Other Sources of Bias	Assessment of Bias
				Patients	Health Care Providers	Data Collectors	Outcome Assessors	Data Analysts				
FIRST (NCT00689936)	√	√	√	–	–	√	√	√	√	√	√	Low risk of bias for all key domains
ENDEAVOR (NCT01568866)	√	√	?	–	–	√	√	√	√	√	√	Unclear risk of bias for one or more key domains
CASTOR (NCT02136134)	?	?	?	–	–	–	–	–	√	√	?	Unclear risk of bias for one or more key domains
BSBMT/UKMF Myeloma X Relapse [Intensive] (NCT00747877)	√	√	√	√	√	√	√	√	√	√	√	Low risk of bias for all key domains
PETHEMA/ GEM2010MAS65 (NCT01237249)	?	?	?	?	?	?	?	?	?	√	?	Unclear risk of bias for one or more key domains
GMMG-HD2 (DRKS00008864)	√	√	?	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
IFM2013-04 (NCT01564537)	√	√	X	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
TOURMALINE-MM3 (NCT02181413)	√	?	√	√	√	?	√	?	√	√	√	Unclear risk of bias for one or more key domains
ECOG E1A06 (NCT00602641)	√	?	X	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
ELOQUENT-2 (NCT01239797)	√	√	X	X	X	X	√	√	√	√	√	High risk of bias for one or more key domains
GMMG-MM5 (ISRCTN 05622749)	√	?	X	X	X	X	X	?	√	√	?	High risk of bias for one or more key domains
PANORAMA 1 (NCT01023308)	√	√	√	√	√	√	√	√	√	√	√	Low risk of bias for all key domains
MM-003 (XXXX)	√	√	X	X	X	X	X	X	√	√	X	High risk of bias for one or more key domains

(continued on following page)

TABLE A2. Study Quality (continued)

Trial Name (trial identifier)	Adequate Randomization	Allocation Concealment	Blinding	Blinding					Infrequent Loss to Follow-Up	Selective Outcome Reporting	Other Sources of Bias	Assessment of Bias
				Patients	Health Care Providers	Data Collectors	Outcome Assessors	Data Analysts				
ASPIRE (NCT01080391)	√	√	√	–	–	√	√	√	√	√	√	Unclear risk of bias for one or more key domains
POLLUX (NCT02076009)	√	√	?	X	X	?	?	?	√	√	X	High risk of bias for one or more key domains
MRC Myeloma IX (ISRCTN68454111)	√	√	?	X	X	X	X	√	√	√	X	High risk of bias for one or more key domains
GEM2005 (NCT00443235)	√	√	X	X	X	X	X	X	√	√	√	High risk of bias for one or more key domains
MM-015 (NCT00405756)	√	√	√	√	√	√	√	√	√	√	√	Low risk of bias for all key domains
VISTA (NCT00111319)	√	?	?	–	–	–	–	–	√	√	√	Unclear risk of bias for one or more key domains
APEX (NCT00048230)	√	?	?	?	?	?	?	?	√	√	?	Unclear risk of bias for one or more key domains
IFM 99-06 (NCT00367185)	√	√	?	?	?	?	?	?	√	√	√	Unclear risk of bias for one or more key domains
PETHEMA (NCT00461747)	?	?	X	X	X	X	X	X	?	?	?	High risk of bias for one or more key domains

NOTE. √, indicates criteria were met; –, indicates criteria were likely not met; X, indicates criteria were definitely not met; ?, indicates insufficient detail, not reported, and/or uncertain if the criteria were met. Ratings are based on the estimation of whether the criterion was met and the extent of potential bias, not simply on reporting.

Abbreviations: BSBMT, British Society of Bone Marrow Transplantation; ECOG, Eastern Cooperative Oncology Group; GEM, Groupo Español de Mieloma; GMMG, German Myeloma Multicenter Group; IFM, Intergroupe Francophone du Myeloma; MRC, Medical Research Council; UKMF, UK Myeloma Forum.