Multiple Myeloma, Version 3.2021

Shaji K. Kumar, MD[1,*]; Natalie S. Callander, MD[2,*]; Kehinde Adekola, MD[3]; Larry Anderson, MD, PhD[4]; Muhamed Baljevic, MD[5]; Erica Campagnaro, MD[6]; Jorge J. Castillo, MD[7]; Jason C. Chandler, MD[8]; Caitlin Costello, MD[9]; Yvonne Efebera, MD, MPH[10]; Matthew Faiman, MD[11]; Alfred Garfall, MD[12]; Kelly Godby, MD[13]; Jens Hillengass, MD[14]; Leona Holmberg, MD, PhD[15]; Myo Htut, MD[16]; Carol Ann Huff, MD[17]; Yubin Kang, MD[18]; Malin Hultcrantz, MD, PhD[19]; Sarah Larson, MD[20]; Michaela Liedtke, MD[21]; Thomas Martin, MD[22]; James Omel, MD[23]; Kenneth Shain, MD, PhD[24]; Douglas Sborov, MD, MSc[25]; Keith Stockerl-Goldstein, MD[26]; Donna Weber, MD[27]; Jennifer Keller, MSS[28]; and Rashmi Kumar, PhD[28]

ABSTRACT

Multiple myeloma is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. This manuscript discusses the management of patients with solitary plasmacytoma, smoldering multiple myeloma, and newly diagnosed multiple myeloma.

J Natl Compr Canc Netw 2020;18(12):1685–1717
doi: 10.6004/jnccn.2020.0057

[1]Mayo Clinic Cancer Center; [2]University of Wisconsin Carbone Cancer Center; [3]Robert H. Lurie Comprehensive Cancer of Center Northwestern University; [4]UT Southwestern Simmons Comprehensive Cancer Center; [5]Fred & Pamela Buffett Cancer Center; [6]University of Michigan Rogel Cancer Center; [7]Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center; [8]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [9]UC San Diego Moores Cancer Center; [10]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [11]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [12]Abramson Cancer Center at the University of Pennsylvania; [13]O'Neal Comprehensive Cancer Center at UAB; [14]Roswell Park Comprehensive Cancer Center; [15]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [16]City of Hope National Medical Center; [17]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [18]Duke Cancer Institute; [19]Memorial Sloan Kettering Cancer Center; [20]UCLA Jonsson Comprehensive Cancer Center; [21]Stanford Cancer Institute; [22]UCSF Helen Diller Family Comprehensive Cancer Center; [23]Patient Advocate; [24]Moffitt Cancer Center; [25]Huntsman Cancer Institute at the University of Utah; [26]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [27]The University of Texas MD Anderson Cancer Center; and [28]National Comprehensive Cancer Network

*Discussion Writing Committee Member.

NCCN CATEGORIES OF EVIDENCE AND CONSENSUS

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

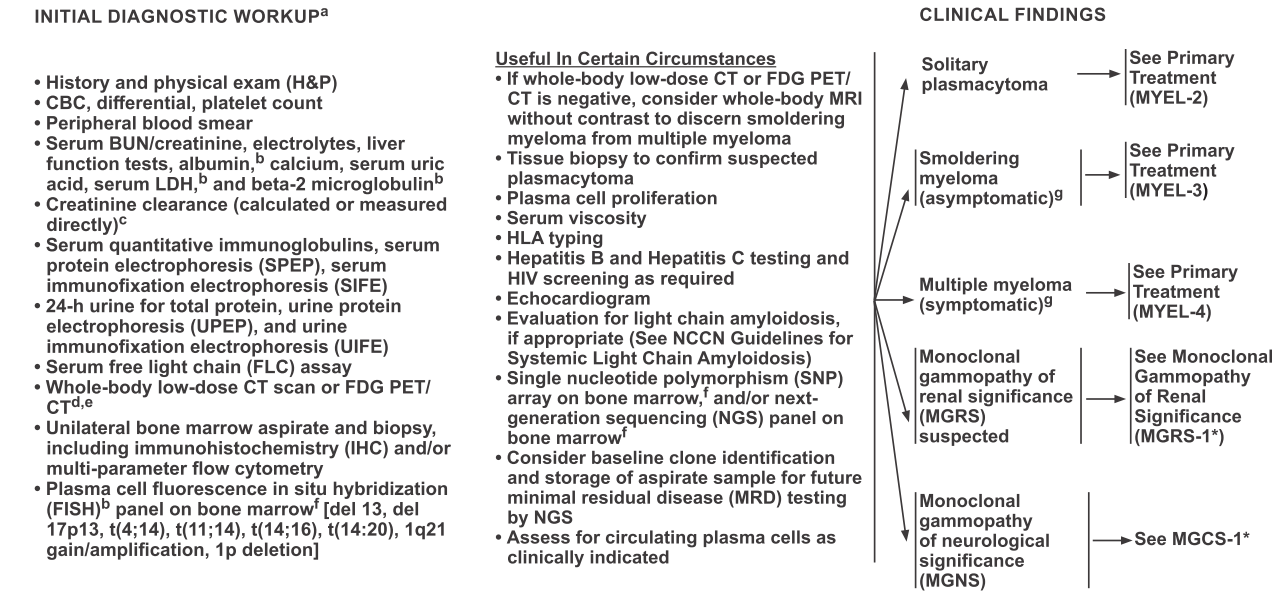
The complete NCCN Guidelines for Multiple Myeloma are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.

Disclosures for the NCCN Multiple Myeloma Panel

At the beginning of each NCCN Guidelines Panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Multiple Myeloma Panel members can be found on page 1717. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

The complete and most recent version of these guidelines is available free of charge at NCCN.org.



[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology†.
[b] These tests are essential for R-ISS staging. See Staging Systems for Multiple Myeloma (MYEL-A*).
[c] See Management of Renal Disease in Multiple Myeloma (MYEL-I*).
[d] Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG PET/CT. If whole-body FDG PET/CT or low-dose CT has been performed, then skeletal survey is not needed.
[e] See Principles of Imaging (MYEL-B*).
[f] CD138 positive selected sample is strongly recommended for optimized yield.
[g] See Definitions of Smoldering and Multiple Myeloma (MYEL-C*).

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

MYEL-1

Overview

Multiple myeloma (MM) accounts for about 1.8% of all cancers and 18% of hematologic malignancies in the United States.[1] MM is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.[2] The American Cancer Society has estimated 32,270 new MM cases in the United States in 2020, with an estimated 12,830 deaths.[1] The NCCN Multiple Myeloma Panel has developed guidelines for the management of patients with various plasma cell neoplasms, including monoclonal gammopathy of clinical significance, solitary plasmacytoma, smoldering myeloma, MM, POEMS syndrome, systemic light chain amyloidosis, and Waldenström macroglobulinemia. This manuscript focuses only diagnosis, workup and management solitary plasmacytoma, smoldering MM, and newly diagnosed MM. For the complete NCCN Guidelines for MM, visit NCCN.org.

Diagnosis and Workup

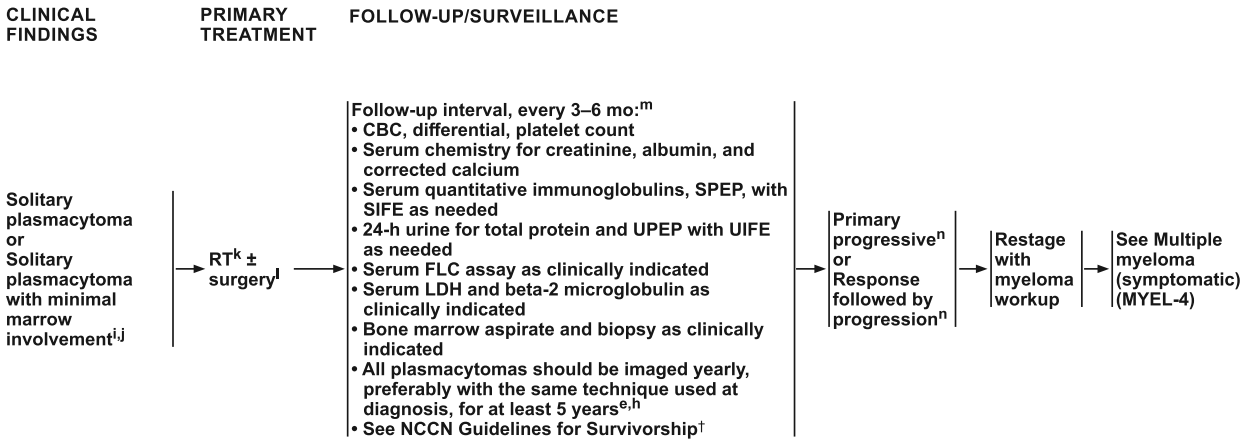
It is important to distinguish MM from other plasma cell neoplasms/dyscrasias to determine prognosis and provide appropriate treatment.

The initial diagnostic workup in all patients should include a history and physical examination. To differentiate symptomatic and asymptomatic MM, the following baseline laboratory studies are needed: a CBC with differential and platelet counts; examination of peripheral blood smear; blood urea nitrogen; serum creatinine; creatinine clearance (calculated or measured directly) and serum electrolytes; liver function tests, serum calcium; albumin; lactate dehydrogenase (LDH); and beta-2 microglobulin.

Peripheral smear may show abnormal distribution of red blood cells such as the Rouleaux formation (red cells taking on the appearance of a stack of coins) due to elevated serum proteins.[3] Increased blood urea nitrogen and creatinine indicate decreased kidney function, whereas LDH and beta-2 microglobulin levels reflect tumor cell characteristics.

Serum and Urine Analysis

Serum analysis includes quantitative immunoglobulin levels (IgG, IgA, and IgM), serum protein electrophoresis (SPEP) for quantitation of monoclonal protein, and serum immunofixation electrophoresis (SIFE) to obtain



[e] See Principles of Imaging (MYEL-B*).
[h] Whole-body MRI or PET/CT if MRI is not available is the first choice for initial evaluation of solitary osseous plasmacytoma (MRI of the spine and pelvis, whole-body PET/CT, or low-dose whole-body CT under certain circumstances). Whole-body PET/CT is the first choice for initial evaluation of solitary extraosseous plasmacytoma.
[i] All criteria must be present for the diagnosis. For diagnositic criteria, please refer to Rajkumar et al Lancet Oncol 2014;15(12):e538. Epub 2014 Oct 26.
[j] Solitary plasmacytoma with 10% or more clonal plasma cells is regarded as active (symptomatic) multiple myeloma and systemic therapy should be considered.
[k] See Principles of Radiation Therapy (MYEL-D*).
[l] Consider surgery if structurally unstable or if there is neurologic compromise due to mass effect.
[m] Patients with soft tissue and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up.
[n] See Response Criteria for Multiple Myeloma (MYEL-E*).

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

MYEL-2

more specific information about the type of M-protein present. Assessing changes in levels of various proteins, particularly the M-protein, helps track disease progression and response to treatment. Urine analysis as a part of the initial diagnostic workup includes evaluating 24-hour urine for total protein; urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE).

Free Light-Chain Assay

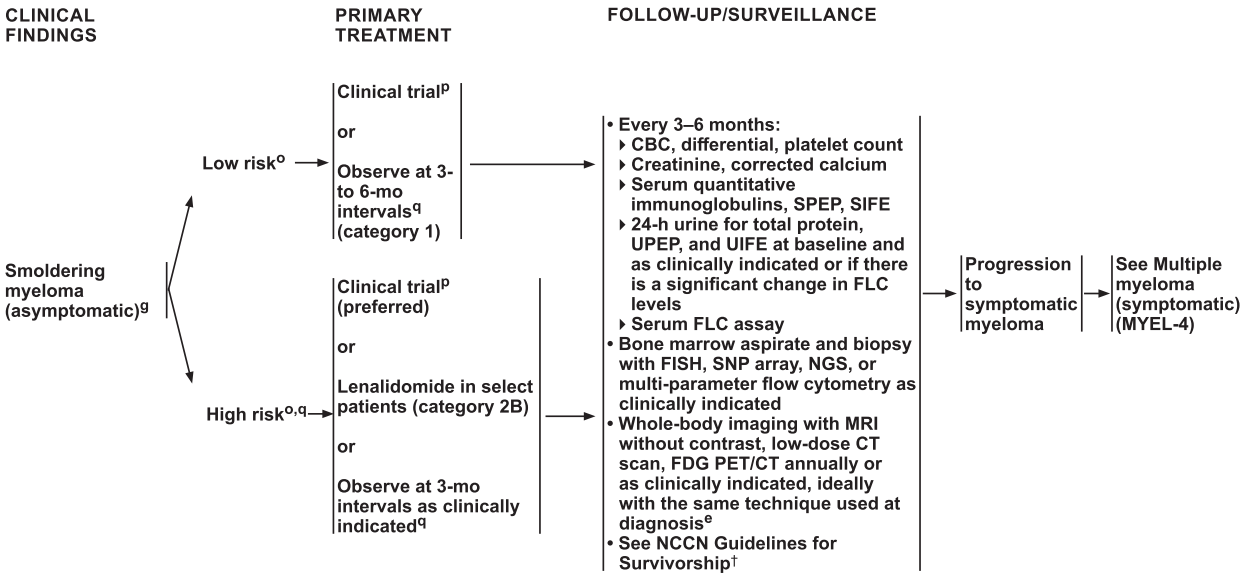
The serum free light-chain (FLC) assay along with serum analyses (SPEP and SIFE) yields high sensitivity while screening for MM and related plasma cell disorders.[4] It is also helpful in prognostication of monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, active MM, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.[4,5] The serum FLC assay also allows for quantitative monitoring of patients with light chain amyloidosis and light chain myeloma. In addition to all of the previously stated, the FLC ratio is required for documenting stringent complete response (CR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.[6] The serum FLC assay cannot replace the 24-hour UPEP for monitoring patients with measurable urinary M-protein and can also be affected by renal function. After the M-protein is quantified, it is important to use the same test for serial studies to ensure accurate relative quantification.

Bone Marrow Evaluation

The percentage of clonal bone marrow plasma cells (≥10%) is a major criterion for the diagnosis of MM. The percentage of plasma cells in bone marrow is estimated by unilateral bone marrow aspiration and biopsy. Immunohistochemistry and/or flow cytometry can be used to confirm the presence of monoclonal plasma cells and to more accurately quantify plasma cell involvement.[7] The cytoplasm of abnormal plasma cells contain either kappa or lambda light chains, and predominance of one or the other light chain–expressing plasma cells indicate clonality. Specific immunophenotypic profiles of the myeloma cells may have prognostic implications.[8]

Cytogenetic Studies

Although MM may be morphologically similar, several subtypes of the disease have been identified at the genetic and molecular level. Bone marrow studies at initial



g See Definitions of Smoldering and Multiple Myeloma (MYEL-C*).
º Bone marrow plasma cells (BMPC) % > 20%, M-protein > 2 g/dL, and serum free light chains (FLCr) > 20 are variables used to risk stratify patients at diagnosis. Patients with two or more of these risk factors are considered to have high risk of progression to MM. Lakshman A, Rajkumar SV, Buadi FK, et al. R Blood Cancer J 2018;8:59.
p The NCCN Panel strongly recommends enrolling eligible smoldering myeloma patients in clinical trials.
q Patients with rising parameters are considered high risk and should be closely monitored.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

MYEL-3

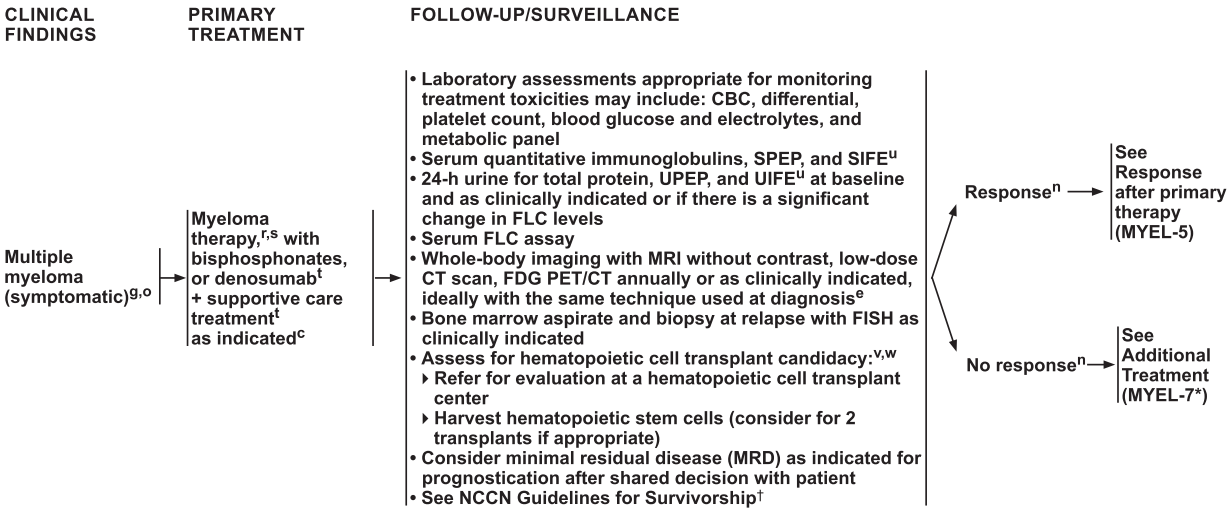
diagnosis should include chromosome analysis by fluorescence in situ hybridization (FISH) performed on the plasma cells obtained from bone marrow aspiration. Metaphase cytogenetics may provide additional information. Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications.

Deletion of 17p13 (the locus for the tumor-suppressor gene, *p53*) leads to loss of heterozygosity of *TP53* and is considered a high-risk feature in MM.[9–11] Higher proportion of myeloma cells with the abnormality as well as mutation of the remaining allele significantly enhances the risk. Other high-risk chromosomal aberrations in MM are characterized by structural changes that include specific rearrangements involving the *IGH* gene (encoding immunoglobulin heavy chain), located at 14q32. Several subgroups of patients are identified on the basis of 14q32 translocations. The main translocations are the t(11;14)(q13;q32), t(4;14)(p16;q32), t(14;16)(q32;q23), and t(14;20)(q32;q12). Several studies have confirmed that patients with MM with t(4;14), t(14;16), and t(14;20) have a poor prognosis, while t(11;14) is believed to impart less risk.[12–15] del(13q) is a common abnormality that is observed on FISH studies, but is a negative prognostic factor only when observed on metaphase cytogenetics. Abnormalities of chromosome 1 are also among the frequent chromosomal alterations in MM.[16] The short arm is most often associated with deletions and the long arm with amplifications.[17] Gains/amplification of 1q21 as well as 1p deletion increases the risk of MM progression, and incidence of the amplification is higher in relapsed than in newly diagnosed patients.[16,18]

Stratification of patients into various risk groups based on the chromosomal markers is being used by some centers for prognostic counseling, selection, and sequencing of therapy approaches.[19,20] According to the NCCN MM Panel, the FISH panel for prognostic estimation of plasma cells should examine for del 13, del 17p13, t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/amplification, and 1p deletion. The utility of this information is to determine biologic subtype and for prognostic recommendations as well as candidacy for clinical trials.

Imaging

A skeletal survey has been the standard for decades for assessing bone disease for any individual with suspected



[c] See Management of Renal Disease in Multiple Myeloma (MYEL-I*).
[e] See Principles of Imaging (MYEL-B*).
[g] See Definitions of Smoldering and Multiple Myeloma (MYEL-C*).
[n] See Response Criteria for Multiple Myeloma (MYEL-E*).
[o] See Staging Systems for Multiple Myeloma (MYEL-A*).
[r] See Myeloma Therapy (MYEL-G).
[s] See Principles of Myeloma Therapy (MYEL-F).
[t] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[u] Needed only if protein electrophoresis is negative during follow-up.
[v] Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and hematopoietic cell transplant. See Discussion.
[w] Renal dysfunction and advanced age are not contraindications to transplant.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

MYEL-4

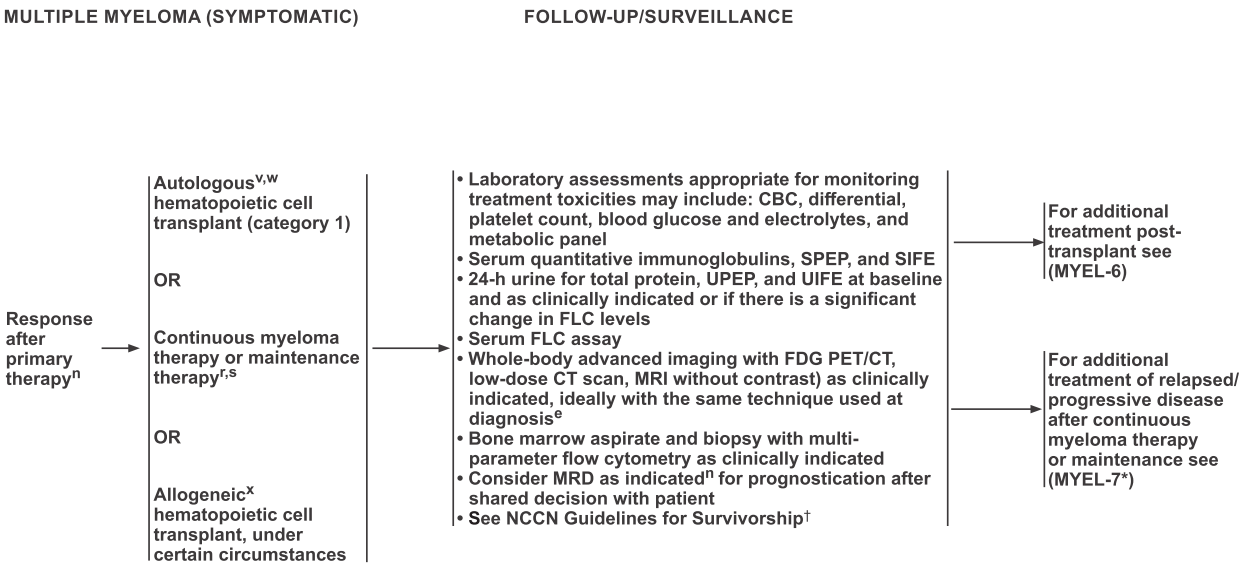
MM.[21] However, this technique has significant limitations related to lower sensitivity compared with advanced imaging. CT alone or in combination with FDG PET has been shown to be significantly superior regarding the sensitivity to detect osteolytic lesions in patients with monoclonal plasma cell disorders. In a multicenter analysis by the IMWG, conventional skeletal survey was compared with whole-body CT scans from 212 patients with monoclonal plasma cell disorders. Whole-body CT was positive in 25.5% of patients with negative skeletal survey. The sensitivity of the skeletal survey and whole-body low-dose CT in the long bones is not significantly different, the difference is mainly in detection of abnormalities in spine and pelvis.[22,23] In a study of 29 patients, 5 (17%) showed osteolytic lesions in CT while skeletal survey results were negative.[24] Furthermore, studies have shown whole-body low-dose CT is superior to skeletal survey radiographs in areas that are difficult to visualize with skeletal surveys such as skull and ribs.[25]

FDG PET/CT too has been shown to identify more lesions than plain X-rays and detect lesions in patients with negative skeletal surveys.[26–28] It is important to note that if PET/CT is chosen instead of whole-body low-dose CT, the imaging quality of the CT part of the PET/CT should be equivalent to a whole-body low-dose CT. Usually the CT part is used only for attenuation correction, which may not be sufficient to assess bone disease due to MM and stability of the spine. Whole body PET/CT is useful in detecting extramedullary disease outside of the spine.

For initial diagnostic workup of patients suspected of having MM, the NCCN Panel recommends either whole-body low-dose CT or FDG PET/CT. The panel has also noted that skeletal survey including long bones is acceptable where advanced imaging is not available (eg in low resource settings). CT contrast agents are not necessary for detection of myeloma bone disease and should be generally avoided in patients with myeloma whenever possible.

Additional Diagnostic Tests

The NCCN MM Panel recommends additional tests that may be useful in some circumstances. MRI is useful for discerning smoldering myeloma from MM. Because the disease burden in patients with smoldering myeloma is



[e] See Principles of Imaging (MYEL-B*).
[n] See Response Criteria for Multiple Myeloma (MYEL-E*).
[r] See Myeloma Therapy (MYEL-G).
[s] See Principles of Myeloma Therapy (MYEL-F).
[v] Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and hematopoietic cell transplant. See Discussion.
[w] Renal dysfunction and advanced age are not contraindications to transplant.
[x] Allogeneic hematopoietic cell transplant should preferentially be done in the context of a trial when possible.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

MYEL-5

lower than those with MM, imaging techniques with high sensitivity need to be used and MRI is a sensitive technique for detecting marrow infiltration by myeloma.[29,30] According to the panel, if whole-body low-dose CT or FDG PET/CT is negative, consider whole-body MRI without contrast to discern smoldering myeloma from MM.

A tissue biopsy may also be necessary to confirm the presence of plasmacytomas. Plasma cell proliferation assays may be helpful to identify the fraction of proliferating myeloma cell population.[31] Also, if amyloidosis is suspected, the diagnosis is established by following the recommendations outlined in the NCCN Guidelines for Systemic Light Chain Amyloidosis (available at NCCN.org).

Serum viscosity should be evaluated when clinical symptoms of hyperviscosity are suspected, particularly in those with high levels of M-protein. HLA type must be obtained if a patient is being considered for allogeneic transplant.

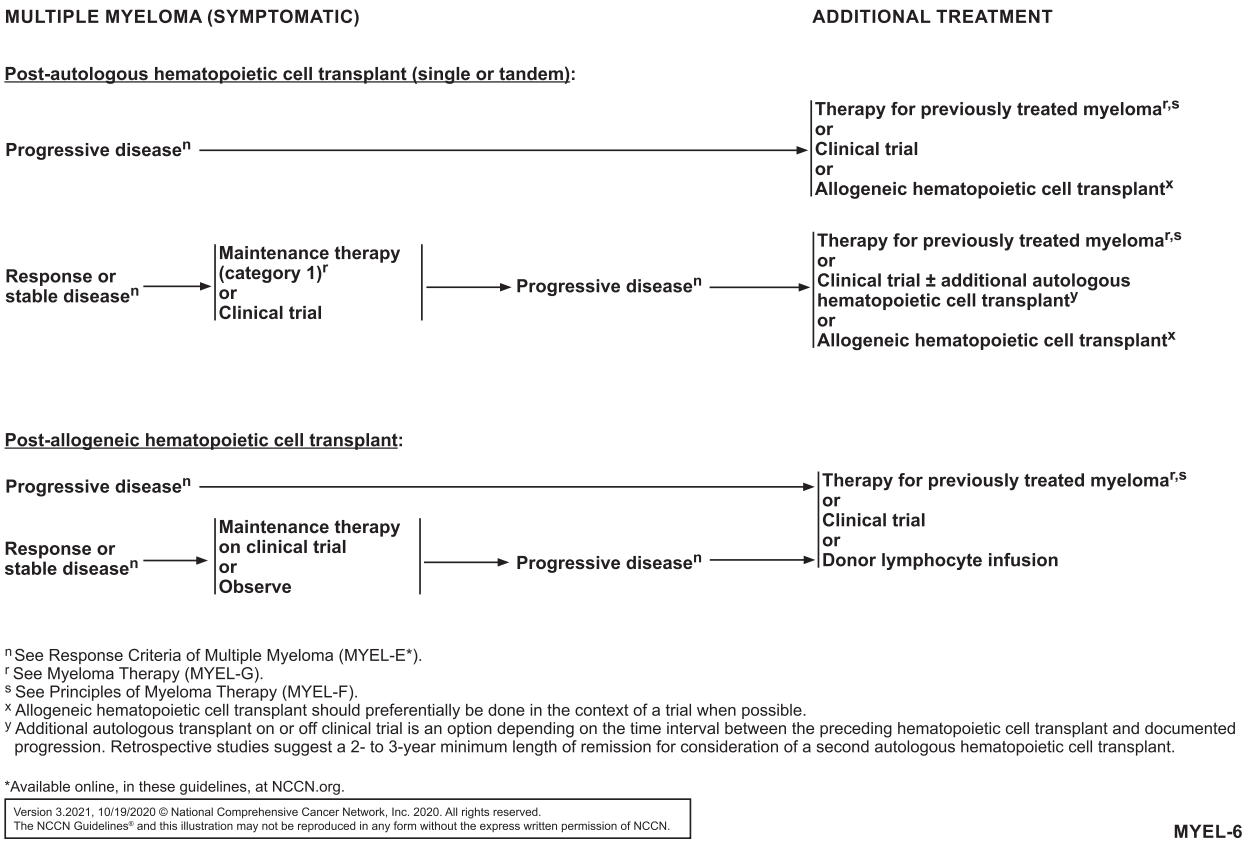
Single nucleotide polymorphism array and/or next generation sequencing (NGS) panel on bone marrow help provide a more detailed evaluation of MM genetics, allowing for further risk categorization through the identification of additional abnormalities that may be of prognostic and/or therapeutic value.[32] Therefore, the NCCN MM Panel has included these tests as useful adjunct in certain circumstances.

The panel also suggests baseline clone identification or storage of bone marrow aspirate sample for clone identification for future minimal residual disease (MRD) testing by NGS if required, and assessment for circulating plasma cells in peripheral blood, as clinically indicated.

Clinical Findings

Based on the results of the clinical and laboratory evaluation, patients are initially classified as having MGUS, solitary plasmacytoma, smoldering (asymptomatic) disease, or active (symptomatic) disease. More recently, patients with an MGUS who have systemic effect related to the monoclonal gammopathy have been variably classified as having monoclonal gammopathy of clinical significance or monoclonal gammopathy of renal significance, depending on the nature of organ involvement.

The IMWG recently updated the disease definition of MM to include biomarkers in addition to existing



[n] See Response Criteria of Multiple Myeloma (MYEL-E*).
[r] See Myeloma Therapy (MYEL-G).
[s] See Principles of Myeloma Therapy (MYEL-F).
[x] Allogeneic hematopoietic cell transplant should preferentially be done in the context of a trial when possible.
[y] Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding hematopoietic cell transplant and documented progression. Retrospective studies suggest a 2- to 3-year minimum length of remission for consideration of a second autologous hematopoietic cell transplant.

*Available online, in these guidelines, at NCCN.org.

MYEL-6

requirements of CRAB features.[33] The CRAB criteria that define MM include increased calcium levels (>11.5 mg/dL), renal insufficiency (creatinine >2 mg/dL or creatinine clearance <40 mL/min), anemia (hemoglobin <10 g/dL or 2 g/dL less than normal), and presence of bone lesions. The IMWG has also clarified that presence of one or more osteolytic lesions seen on skeletal radiography, whole-body MRI, or whole-body FDG PET/CT fulfills the criteria for bone disease.[33] The MM-defining biomarkers identified by the IMWG SLiM features (SLiM stands for sixty, light chain ratio, MRI) include one or more of the following: ≥60% clonal plasma cells in the bone marrow; involved/uninvolved free light chain ratio of ≥100 with the involved FLC being ≥100 mg/L; or MRI with more than one focal marrow (nonosteolytic) lesion[33] All of these myeloma-defining events are referred to as SLiM-CRAB.

The criteria by the IMWG for patients with smoldering (asymptomatic) MM include serum M-protein (IgG or IgA) ≥30 g/L and/or clonal bone marrow plasma cells 10%–59% and absence of CRAB features, myeloma-defining events, or amyloidosis.[33] The updated IMWG diagnostic criteria for MM allow initiation of therapy before end-organ damage on the basis of specific biomarkers, and also allow the use of sensitive imaging criteria to diagnose MM, including whole-body FDG PET/CT and MRI.[33] Recently, a study analyzed clinical and laboratory information from 421 patients with smoldering myeloma and identified monoclonal protein >2g/dL, FLC ratio of >20, and >20% plasma cells as important risk factors for progression. Patients with 2 or more of these features had a median time to progression (TTP) of 29 months.[34]

Those with active MM can be staged using the International Staging System (ISS).[35] The ISS is based on easily obtained laboratory measures (serum beta-2 microglobulin and serum albumin) and is easier to use than the Durie-Salmon Staging System for patients with previously untreated MM. The ISS has been revised (R-ISS) to include serum beta-2 microglobulin and serum albumin and prognostic information obtained from the LDH and high-risk chromosomal abnormalities [t(4;14), t(14;16), 17p13 deletion] detected by FISH and is the preferred staging approach.[36] Having del(17p) and/or translocation t(4;14) and/or translocation t(14;16) are considered as high-risk. Those with no high-risk chromosomal abnormality are considered standard-risk.

PRINICIPLES OF MYELOMA THERAPY

General Principles
- Triplet regimens should be used as the standard therapy for patients with multiple myeloma; however, patients who cannot be considered for initiation of treatment with a 3-drug regimen can be started with a 2-drug regimen, with a third drug added once performance status improves.
- Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology†.
- For additional supportive care while on myeloma therapy, see Supportive Care Treatment for Multiple Myeloma (MYEL-H).

Candidates for Hematopoietic Cell Transplants
- Exposure to myelotoxic agents (including alkylating agents and nitrosoureas) should be limited to avoid compromising stem cell reserve prior to stem cell harvest in patients who may be candidates for transplant.
- Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide and/or daratumumab in patients for whom transplant is being considered.

Screening Recommendations
- Test for hepatitis B before starting daratumumab or carfilzomib.
- Screen for HIV and hepatitis C, as clinically indicated.

Prophylaxis Recommendations
- Pneumocystis jiroveci pneumonia (PJP), herpes zoster, and antifungal prophylaxis should be given if receiving high-dose dexamethasone.
- Administer herpes zoster prophylaxis for all patients treated with proteasome inhibitors, daratumumab, isatuximab-irfc, or elotuzumab.

Side Effects and Lab Interference
- Daratumumab and isatuximab-irfc may interfere with serologic testing and cause false-positive indirect Coombs test.
- Type and screen should be performed before using daratumumab or isatuximab-irfc.
- Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.

Dosing and Administration of Proteasome Inhibitors
- Subcutaneous bortezomib is the preferred method of administration.
- Both weekly and twice-weekly dosing schemas of bortezomib may be appropriate; weekly preferred.
- Carfilzomib may be used once or twice weekly and at different doses.

†To view the most recent version of these guidelines, visit NCCN.org.

MYEL-F

Solitary Plasmacytoma

The diagnosis of solitary plasmacytoma requires a thorough evaluation with advanced imaging studies to rule out the presence of additional lesions or systemic disease, because many patients presumed to have solitary plasmacytomas are found to have additional sites[37,38]

Primary Therapy for Solitary Plasmacytoma

The treatment and follow-up options for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement (<10% plasma cells in bone marrow) are similar. Radiation therapy (RT) has been shown to provide excellent local control of solitary plasmacytomas.[39–45] The largest retrospective study (n=258) included patients with solitary plasmacytoma (n=206) or extramedullary plasmacytoma (n=52).[46] Treatments included RT alone (n=214), RT plus chemotherapy (n=34), and surgery alone (n=8). Five-year overall survival (OS) was 74%, disease-free survival was 50%, and local control was 85%. Patients who received localized RT had a lower rate of local relapse (12%) than those who did not (60%).[45]

The optimal radiation dose for treatment of solitary plasmacytomas is not known. The dose used in most published papers ranges from 30 to 60 Gy.[44,45,47] For those patients with osseous plasmacytoma, the NCCN Panel recommends primary RT (40–50 Gy in 1.8–2.0 Gy/fraction) to the involved field. Occasionally, surgery may be performed if a lesion causes structural instability or neurologic compromise. For extraosseous plasmacytomas, primary treatment is RT (40–50 Gy in 1.8–2.0 Gy/fraction)[42] to the involved field with surgery[48] if clinically necessary.

Surveillance/Follow-up Tests for Solitary Plasmacytoma

Follow-up and surveillance tests for solitary plasmacytoma consist of blood and urine tests and imaging. Serial measurements to check for re-emergence or appearance of M-protein are required to confirm disease sensitivity to radiation therapy. The recommended follow-up interval for these patients is every 3 to 6 months; however, patients with soft tissue and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up. According to the NCCN Panel, one should

MYELOMA THERAPY[a-d]

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1) • Bortezomib/cyclophosphamide/dexamethasone[e]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Daratumumab[f]/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[g] • Ixazomib/cyclophosphamide/dexamethasone[g] • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone • Daratumumab[f]/bortezomib/thalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib[h] (VTD-PACE)

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[i] (category 1)
Other Recommended Regimens • Ixazomib (category 1) • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See Principles of Myeloma Therapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-I*).
[e] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.
[f] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[g] Treatment option for patients with renal insufficiency and/or peripheral neuropathy.
[h] Generally reserved for the treatment of aggressive multiple myeloma.
[i] There appears to be an increased risk for secondary cancers, especially with lenalidomide maintenance following transplant. The benefits and risks of maintenance therapy vs. secondary cancers should be discussed with patients.

Continued

*Available online, in these guidelines, at NCCN.org.

consider using the same imaging modality used during the initial workup for the follow-up assessments. Bone surveys are inadequate for this type of surveillance.

The blood tests include CBC with differential and platelet count; serum chemistry for creatinine, albumin, and corrected calcium; serum quantitative immunoglobulins; and SPEP with SIFE as needed. Testing for serum FLC assay, LDH, and beta-2 microglobulin may be useful in some circumstances. Urine tests include 24-hour urine assay for total protein, UPEP, and UIFE.

Bone marrow aspirate and biopsy and imaging studies using whole-body MRI or low-dose CT or whole-body FDG PET/CT are recommended as clinically indicated. PET imaging may detect early bone marrow involvement in patients with solitary plasmacytoma.[49–51] Imaging studies are recommended yearly, preferably with the same technique used at diagnosis, for at least 5 years.

If progression to MM occurs, then the patient should be re-evaluated as described in "Diagnosis and Workup" (page 1686), and systemic therapy must be administered as clinically indicated.

Smoldering (Asymptomatic) Myeloma

Smoldering (asymptomatic) myeloma describes a stage of disease with no symptoms and no related organ or tissue impairment.[21] Patients with asymptomatic smoldering MM may have an indolent course for many years without therapy.

Primary Therapy for Smoldering (Asymptomatic) Myeloma

Smoldering myeloma is a precursor to MM. All patients with smoldering myeloma have a risk of progression to MM.[52] However, the rate of progression varies from months to several years based on certain risk features.[52]

The historic approach for management of smoldering myeloma has been close observation. However, recently there has been mounting evidence that those with high-risk features may benefit from early intervention.

A relatively small, randomized, prospective, phase III study by the PETHEMA group investigated whether early treatment with lenalidomide and dexamethasone in patients (n=119) with smoldering myeloma, at high risk of progression to active MM, prolongs the TTP.[53]

MYELOMA THERAPY[a-d]

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES
Preferred Regimens • Bortezomib/lenalidomide/dexamethasone (category 1)[j] • Daratumumab[f]/lenalidomide/dexamethasone (category 1) • Lenalidomide/low-dose dexamethasone (category 1)[k] • Bortezomib/cyclophosphamide/dexamethasone[e]
Other Recommended Regimens • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Daratumumab[f]/bortezomib/melphalan/prednisone (category 1) • Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone
Useful In Certain Circumstances • Bortezomib/dexamethasone • Cyclophosphamide/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone[g]

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide (category 1)
Other Recommended Regimens • Bortezomib
Useful In Certain Circumstances • Bortezomib/lenalidomide

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See Principles of MyelomaTherapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-I*).
[e] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to bortezomib/lenalidomide/dexamethasone. Consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

*Available online, in these guidelines, at NCCN.org.

[f] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[g] Treatment option for patients with renal insufficiency and/or peripheral neuropathy.
[j] This is the only regimen shown to have overall survival benefit.
[k] Continuously until progression. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.

Continued

The high-risk group in the study was defined using the following criteria: plasma cell bone marrow infiltration of at least 10% and/or a monoclonal component (defined as an IgG level of ≥3 g/dL, an IgA level of ≥2 g/dL, or a urinary Bence Jones protein level of >1 g per 24 hours); and at least 95% phenotypically aberrant plasma cells in the bone marrow infiltrate. The OS reported in the trial at 3 years was higher in the group treated with the lenalidomide and dexamethasone arm (94% vs 80%; hazard ratio [HR], 0.31; 95% CI, 0.10–0.91; P=.03).[53] At a median follow-up of 75 months (range, 27–57 months), treatment with lenalidomide and dexamethasone delayed median TTP to symptomatic disease compared with no treatment (TTP was not reached in the treatment arm compared with 23 months in the observation arm; HR, 0.24; 95% CI, 0.14–0.41).[54] The high OS rate seen after 3 years was also maintained (HR, 0.43; 95% CI, 0.20–0.90). According to the NCCN Panel, the flow cytometry–based high-risk criteria specified in the study is not uniformly available and participants did not receive advanced imaging. Based on the criteria used in the trial, some patients with active myeloma were classified as having high-risk smoldering myeloma.

In a larger multicenter phase III randomized trial, patients with smoldering myeloma (n=182) were either treated with lenalidomide until progression or observed. The lenalidomide group experienced improved progression-free survival (PFS) and decreased end organ damage (eg, renal failure, bone lesions) when compared with those who were observed.[55] Grade 3 or 4 adverse events were reported in 41% of patients treated with lenalidomide.[55] On subgroup analysis, the PFS benefit was seen in those with high-risk smoldering myeloma but was less clear in those with low- or intermediate-risk disease.[55]

The Mayo 2018 20/2/20 criteria stratify patients based on risk. The criteria take into consideration the following risk factors: percentage of bone marrow plasma cells >20%, M-protein >2 g/dL, and FLC ratio >20. Patients with 2 or more of the previously mentioned risk factors are considered to have high risk. These risk factors were developed from a retrospective study of patients with smoldering myeloma (n=417). In those with high risk (≥2 factors present), the estimated median TTP was 29 months, in those with intermediate risk (1 factor present), the estimated median TTP was 68 months, and for

MYELOMA THERAPY[a-d]

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[l,m]	
Preferred Regimens	
• Bortezomib/lenalidomide/dexamethasone	• Daratumumab[f]/lenalidomide/dexamethasone (category 1)
• Carfilzomib/lenalidomide/dexamethasone (category 1)[n]	• Isatuximab-irfc/pomalidomide/dexamethasone (category 1)[o]
• Daratumumab[f]/bortezomib/dexamethasone (category 1)	• Ixazomib/lenalidomide/dexamethasone (category 1)[n]
• Daratumumab[f]/carfilzomib/dexamethasone (category 1)	• Ixazomib/pomalidomide[p]/dexamethasone
	• Pomalidomide[p]/bortezomib/dexamethasone (category 1)
Other Recommended Regimens	
• Belantamab mafodotin-blmf[q]	• Daratumumab[f]/pomalidomide[r]/dexamethasone
• Bendamustine/bortezomib/dexamethasone	• Elotuzumab/bortezomib/dexamethasone
• Bendamustine/lenalidomide/dexamethasone	• Elotuzumab[s]/lenalidomide/dexamethasone (category 1)[n]
• Bortezomib/liposomal doxorubicin/dexamethasone (category 1)	• Elotuzumab/pomalidomide/dexamethasone[t]
• Bortezomib/cyclophosphamide/dexamethasone	• Ixazomib/cyclophosphamide/dexamethasone
• Carfilzomib/cyclophosphamide/dexamethasone	• Panobinostat[u]/bortezomib/dexamethasone (category 1)
• Carfilzomib (twice weekly)/dexamethasone (category 1)	• Pomalidomide[p]/cyclophosphamide/dexamethasone
• Cyclophosphamide/lenalidomide/dexamethasone	• Pomalidomide[p]/carfilzomib/dexamethasone
• Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone	
Useful In Certain Circumstances	
• Bendamustine	• High-dose cyclophosphamide
• Bortezomib/dexamethasone (category 1)	• Ixazomib/dexamethasone
• Carfilzomib/cyclophosphamide/thalidomide/dexamethasone	• Lenalidomide/dexamethasone[t] (category 1)
• Carfilzomib (weekly)/dexamethasone	• Panobinostat[u]/carfilzomib
• Daratumumab[f,v]	• Panobinostat[u]/lenalidomide/dexamethasone
• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[h]	• Pomalidomide[p]/dexamethasone[t] (category 1)
• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[h] ± bortezomib (VTD-PACE)[h]	• Selinexor/dexamethasone[w]
	• Venetoclax/dexamethasone only for t(11;14) patients

[a] Selected, but not inclusive of all regimens.
[b] See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] See Principles of Myeloma Therapy (MYEL-F).
[d] See Management of Renal Disease in Multiple Myeloma (MYEL-I*).
[f] Includes both daratumumab for intravenous infusion and daratumumab and hyaluronidase-fihj for subcutaneous injection. Daratumumab and hyaluronidase-fihj for subcutaneous injection has different dosing and administration instructions compared to daratumumab for intravenous infusion.
[h] Generally reserved for the treatment of aggressive multiple myeloma.
[l] Consideration for appropriate regimen is based on the context of clinical relapse.
[m] If a regimen listed on this page was used as a primary induction therapy and relapse is >6 mo, the same regimen may be repeated.
[n] Clinical trials with these regimens primarily included patients who were lenalidomide-naive or with lenalidomide-sensitive multiple myeloma.
[o] Indicated for patients who have received at least two prior therapies, including lenalidomide and a proteasome inhibitor.
[p] Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor and who have demonstrated disease progression on or within 60 days of completion of the last therapy.
[q] Indicated for patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.
[r] Indicated for the treatment of patients who have received at least two prior therapies including an immunomodulatory agent and a proteasome inhibitor.
[s] Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[t] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.
[u] Indicated for the treatment of patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent.
[v] Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[w] Indicated for patients who have received at least four prior therapies and whose disease is refractory to at least two proteasome inhibitors, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.

*Available online, in these guidelines, at NCCN.org.

MYEL-G
3 OF 3

those with low risk (none of the risk factors present), the estimated median TTP was 110 months.[34]

The Mayo 2018 20/2/20 criteria were validated in a large retrospective analysis of 2,004 patients with smoldering myeloma.[56] The estimated progression rates at 2 years among those with low-, intermediate-, and high-risk disease were 5%, 17%, and 46% respectively.[56]

The NCCN Panel suggests using the Mayo 2018/IMWG 20/2/20 criteria to stratify patients based on risk. According to the NCCN Panel, the low-risk group should be managed by enrolling in a clinical trial or observe at 3- to 6-month intervals (category 1). For the high-risk group, the panel prefers enrollment in an ongoing clinical trial or treatment with single-agent lenalidomide only in carefully selected patients (category 2B)[53,55] or observation at 3-month intervals, as clinically indicated. Those with rising markers or high-risk factors must be monitored closely.

Surveillance/Follow-up Tests for Smoldering (Asymptomatic) Myeloma

The surveillance/follow-up tests for smoldering myeloma include CBC with differential and platelet count; serum chemistry for creatinine, albumin, corrected calcium, serum quantitative immunoglobulins, SPEP, and SIFE; and serum FLC assay as clinically indicated. The urine tests include 24-hour urine assay for total protein, UPEP, and UIFE. Bone marrow aspirate and biopsy with FISH, single nucleotide polymorphism array, NGS, or multiparameter flow cytometry may be used as clinically indicated.

Imaging studies with MRI without contrast, whole-body low-dose CT and/or CT and/or whole-body FDG PET/CT are recommended annually or as clinically indicated. The NCCN Panel recommends considering using the same imaging modality used during the initial workup for the follow-up assessments. If the disease progresses to symptomatic myeloma, then patients should be treated according to the guidelines for symptomatic MM.

Active (Symptomatic) MM

Newly diagnosed MM is typically sensitive to a variety of classes of drugs: immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies.

SUPPORTIVE CARE FOR MULTIPLE MYELOMA

Bone Disease
- All patients receiving primary myeloma therapy should be given bisphosphonates (category 1)[a] or denosumab.[b]
  - A baseline dental exam is strongly recommended.
  - Monitor for renal dysfunction with use of bisphosphonate therapy.
  - Monitor for osteonecrosis of the jaw.
  - Continue bone-targeting treatment (bisphosphonates or denosumab) for up to 2 years. The frequency of dosing (monthly vs. every 3 months) would depend on the individual patient criteria and response to therapy. Continuing beyond 2 years should be based on clinical judgment.
- RT (See Principles of Radiation Therapy [MYEL-D*])
- Orthopedic consultation should be sought for impending or actual long-bone fractures or bony compression of spinal cord or vertebral column instability.
- Consider vertebroplasty or kyphoplasty for symptomatic vertebral compression fractures.

Hypercalcemia
- Hydration, bisphosphonates (zoledronic acid preferred), denosumab, steroids, and/or calcitonin are recommended.

Hyperviscosity
- Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.

Anemia
- See NCCN Guidelines for Hematopoietic Growth Factors†.
- Consider erythropoietin for anemic patients.

Infection
- See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections†.
- Intravenous immunoglobulin therapy should be considered in the setting of recurrent serious (<400 mg/dL) infection.
- The pneumococcal conjugate vaccine should be given followed by the pneumococcal polysaccharide vaccine one year later.
- Consider 3 months of antibiotic prophylaxis at diagnosis for patients at high risk for infection.
- See MYEL-F for myeloma therapy-specific prophylaxis

Renal Dysfunction
- See Management of Renal Disease in Multiple Myeloma (MYEL-I*)

Coagulation/Thrombosis
- Aspirin (81–325 mg) is recommended with immunomodulator-based therapy. Therapeutic anticoagulation is recommended for those at high risk for thrombosis.
- See NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease†

[a] Both pamidronate and zoledronic acid have shown equivalence in terms of reducing risk of skeletal-related events in randomized trials.
[b] Denosumab is preferred in patients with renal insufficiency.

*Available online, in these guidelines, at NCCN.org. †To view the most recent version of these guidelines, visit NCCN.org.

MYEL-H

Primary Therapy for Active (Symptomatic) MM

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and primary therapy is followed by high-dose chemotherapy with autologous hematopoietic cell transplant (HCT) in transplant-eligible patients.

Stem cell toxins, such as nitrosoureas or alkylating agents compromise stem cell reserve. Regimens with these agents (notably melphalan) should be avoided in patients who are potential candidates for HCT until stem cells are collected.

One of the first steps in evaluating newly diagnosed patients with MM is to determine whether they are candidates for high-dose therapy and transplant, based on age and comorbidities. However, it should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant. Therefore, referral to an HCT center to assess whether patient is eligible for HCT is important.

The page titled "Myeloma Therapy" in the algorithm (page 1693) has a list of primary therapy regimens recommended by the NCCN MM Panel for transplant eligible and nontransplant candidates and also lists drugs recommended for maintenance therapy in each setting. The list is selected and is not inclusive of all regimens.

The NCCN MM Panel has categorized all myeloma therapy regimens as "preferred," "other recommended," or "useful in certain circumstances." The purpose of classifying regimens as such is to convey the sense of the panel regarding the relative efficacy and toxicity of the regimens. Factors considered by the panel include evidence, efficacy, toxicity, preexisting comorbidities such as renal insufficiency, and in some cases access to certain agents.

The NCCN Panel prefers 3-drug regimens as the standard for primary treatment of all patients who are transplant eligible. This is based on improved response rates, depth of response, and rates of PFS or OS seen with 3-drug regimens in clinical trials. The doublet regimens are no longer recommended for transplant candidates with the rationale that doublets would be recommended for patients who would not be considered for initial treatment with a 3-drug regimen such as those not initially eligible for transplant. For nontransplant patients, the 2-drug regimens are still listed as options with a note that a triplet regimen is the standard therapy but patients

who cannot tolerate a 3-drug regimen due to poor performance status can be started with a 2-drug regimen, and the third drug can be added if the performance status improves.

It is also important to consider supportive care for all patients at diagnosis. For example, 80% of patients have bone disease and up to 33% have renal compromise. In all patients, careful attention to supportive care is critical to avoid early complications that may compromise therapeutic outcome.

Bone disease, renal dysfunction, and other complications such as infections, hypercalcemia, hyperviscosity, and coagulation/thrombosis should be treated with appropriate adjunctive measures (see "Supportive Care for MM", page 1710).

Although weekly and twice-weekly dosing schemas of bortezomib are considered appropriate, weekly dosing is preferred. Twice-weekly bortezomib can be associated with neuropathy that may limit efficacy due to treatment delays or discontinuation. Therefore, Reeder et al[57] modified the regimen to a once-weekly schedule of bortezomib. In the study, patients treated with weekly bortezomib experienced responses similar to the twice-weekly schedule (overall response rate [ORR], 93% vs 88%; very good partial response [VGPR], 60% vs 61%). In addition, they experienced less grade 3/4 adverse events (37%/3% vs 48%/12%). Fewer dose reductions of bortezomib/dexamethasone were required in the modified schedule, and neuropathy rates were the same in both cohorts, even though the total bortezomib dose per cycle was higher in the weekly versus the twice-weekly schedule (6.0 mg/m^2 vs 5.2 mg/m^2).[57]

The NCCN Panel has noted that subcutaneous administration is the preferred route for bortezomib. This is based on the results of the MMY-3021 trial. The trial randomized patients (n=222) to single-agent bortezomib administered either by the conventional intravenous route or by subcutaneous route.[58] The findings from the study demonstrate noninferior efficacy with subcutaneous versus intravenous bortezomib with regard to the primary endpoint (ORR after 4 cycles of single-agent bortezomib). The results showed no significant differences in terms of PFS or 1-year OS between groups.[58,59] However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy.

Carfilzomib can potentially cause cardiac, renal, and pulmonary toxicities.[60] Careful assessment before initiating treatment with carfilzomib and close monitoring during treatment is recommended.[60] Regarding dosing and administration, carfilzomib may be used once or twice weekly and at different doses.

A randomized trial has compared 2 formulations of daratumumab as monotherapy. The subcutaneous formulation of daratumumab and hyaluronidase-fihj resulted in a similar ORR, PFS, and safety profile and fewer infusion-related reactions compared with the intravenous daratumumab.[61] According to the NCCN Panel, daratumumab intravenous infusion or daratumumab and hyaluronidase-fihj, subcutaneous injection may be used in all daratumumab-containing regimens. Some patients may not be appropriate for subcutaneous treatment, for example those with significant thrombocytopenia.

Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

The preferred primary therapy options for patients who are HCT eligible include bortezomib/lenalidomide/dexamethasone and bortezomib/cyclophosphamide/dexamethasone.

Bortezomib/Lenalidomide/Dexamethasone

Phase II and III studies results have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is active and well tolerated in newly diagnosed patients with MM, transplant eligible as well as transplant ineligible.

In the first phase I/II prospective study of lenalidomide/bortezomib/dexamethasone in patients with newly diagnosed MM, the rate of partial response (PR) was 100%, with 74% VGPR or better and 52% complete response (CR)/near CR.[62]

The benefits of bortezomib/lenalidomide/dexamethasone as primary therapy were also seen in the results of the phase II IFM 2008 trial[63] and phase II EVOLUTION trial.[65] In the phase II IFM 2008 trial, patients received bortezomib, lenalidomide, and dexamethasone as induction therapy followed by HCT.[63] Patients subsequently received 2 cycles of bortezomib/lenalidomide/dexamethasone as consolidation cycles and 1-year lenalidomide maintenance. VGPR rate or better at the completion of induction was 58%.[63] After transplantation and consolidation therapy the rate of VGPR or better was 70% and 87%, respectively.[63]

The phase II EVOLUTION trial was designed to examine the tolerability and efficacy of combining bortezomib/cyclophosphamide/lenalidomide/dexamethasone versus bortezomib/lenalidomide/dexamethasone versus bortezomib/cyclophosphamide/dexamethasone in a randomized multicenter setting.[64] The ORR after primary treatment with bortezomib/lenalidomide/dexamethasone followed by maintenance with bortezomib was 85% (51% ≥ VGPR and 24% CR) and corresponding 1-year PFS was 83% in the bortezomib/lenalidomide/dexamethasone arm.[64]

Bortezomib/lenalidomide/dexamethasone was compared with lenalidomide/dexamethasone in the multicenter phase III SWOG S077 trial.[65] Patients (n=525) with

previously untreated MM were randomly assigned to receive 6 months of induction therapy with either bortezomib/lenalidomide/dexamethasone (n=264) or lenalidomide/dexamethasone (n=261), each followed by maintenance therapy with lenalidomide/dexamethasone until progression or unacceptable. The triple-drug regimen group had significantly longer PFS (43 months vs 30 months; HR, 0.712; 96% CI, 0.56–0.906) and improved median OS (75 vs 64 months; HR, 0.709; 95% CI, 0.524–0.959).[65] As expected, ≥ grade 3 neuropathy was more frequent in the bortezomib-containing arm (24% vs 5%; $P<.0001$) as bortezomib was administered intravenously in this study.[65]

With longer-term follow up (median 84 months), the benefits of adding bortezomib to lenalidomide and dexamethasone were seen to be maintained.[66] The PFS with bortezomib/lenalidomide/dexamethasone was 41 months versus 29 months for lenalidomide/dexamethasone.[66] The OS was not yet reached (>84 months) with the bortezomib regimen versus 69 months for lenalidomide/dexamethasone.[66]

A randomized multicenter phase 3 trial (ENDURANCE E1A11) studied newly diagnosed patients (n=1,053) with MM treated with either bortezomib/lenalidomide/dexamethasone or carfilzomib/lenalidomide/dexamethasone as induction therapy. Patients with high-risk features (with the exception of patients with t(4;14)) were not included in this trial. After a median follow-up of 9 months, median PFS was 34.4 months with the bortezomib-regimen versus 34.6 months with the carfilzomib regimen.[67] A response of VGPR or better was seen in 65% of patients treated with bortezomib/lenalidomide/dexamethasone and 74% of patients treated with carfilzomib/lenalidomide/dexamethasone ($P=.0015$). With respect to adverse events, the carfilzomib regimen was associated with less peripheral neuropathy but more cardiac, pulmonary and renal toxicities.[67]

To minimize the toxicities seen with the standard-dose of bortezomib/lenalidomide/dexamethasone, a phase II study evaluated the efficacy of dose-adjusted bortezomib/lenalidomide/dexamethasone (VRd-lite).[68] The VRd-lite regimen included subcutaneous bortezomib (1.3 mg/m2) on days 1, 8, 15 and 22, and oral dexamethasone (20 mg) on the day of and the day after bortezomib administration. Lenalidomide was omitted on days 1, 8 and 15, which are the days of bortezomib administration. The ORR after 4 cycles of VRd-lite was 83%, including a CR of 25%. The ORR and VGPR or better were further improved to 100% and 74%, in those who received autologous HCT.[68]

Based on with the above results, bortezomib/lenalidomide/dexamethasone, the NCCN Panel included this regimen as a category 1, preferred option for primary treatment of transplant-eligible patients with MM.

Bortezomib/Cyclophosphamide/Dexamethasone

Data from 3 phase II studies involving newly diagnosed patients with MM have demonstrated high response rates with cyclophosphamide, bortezomib, and dexamethasone (CyBorD) as primary treatment.[64,69,70] The trial by Reeder et al[69] performed in the United States and Canada demonstrated an ORR of 88% including a VGPR or greater of 61% and 39% CR/near CR with CyBorD as the primary regimen. The depth of response seen after primary treatment was maintained after transplant in those who underwent transplantation (70% rates of CR/near CR; rate of at least VGPR or better was 74%).[69] According to the long-term follow-up analysis, the 5-year PFS and OS rates were 42% (95% CI, 31–57) and 70% (95% CI, 59–82).[71]

Analysis of the German DSMM XIa study also demonstrated high responses with CyBorD as primary treatment (ORR was 84%, with 71.5% PR rate and 12.5% CR rate). High response rates were seen in patients with unfavorable cytogenetics.[70]

In the updated results of the phase II EVOLUTION study, primary treatment with CyBorD demonstrated an ORR of 75% (22% CR and 41% ≥ VGPR), and the 1-year PFS rate was 93%.[64]

Based on data from these and other phase II studies, the NCCN MM Panel has now included the combination of cyclophosphamide/bortezomib/dexamethasone to the list of primary treatment available for transplant candidates. This is a preferred option, especially in patients with acute renal insufficiency. According to the NCCN Panel, one can consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

Other Recommended Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

Carfilzomib/Lenalidomide/Dexamethasone

Carfilzomib is a second-generation PI that binds highly selectively and irreversibly to the proteasome. It is administered intravenously.

A multicenter phase I/II trial evaluated the combination of carfilzomib, lenalidomide, and dexamethasone in newly diagnosed patients with MM.[72] In this trial, patients (n=53) received carfilzomib with lenalidomide and low-dose dexamethasone. After 4 cycles, hematopoietic cells were collected from eligible patients.[72] Of 35 patients from whom hematopoietic cells were collected, 7 proceeded to transplantation, and the remainder continued with carfilzomib/lenalidomide/dexamethasone.[72] With median follow-up of 13 months, 24-month

PFS was estimated at 92%.The most common grade 3 and 4 toxicities in ≥10% of patients included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and neutropenia (17%). Peripheral neuropathy was limited to grade 1/2 (23%).[72]

Another phase II trial also evaluated the same regimen (carfilzomib in combination with lenalidomide and dexamethasone) in newly diagnosed patients (n=45) with MM. After 8 cycles of treatment, patients with stable disease received up to 24 cycles of lenalidomide 10 mg/day on days 1 to 21.[73] Thirty-eight patients were evaluable for response and toxicity. After a median follow-up of 10 months, PFS was 83.3%. Twenty-five patients completed 8 cycles of the carfilzomib, lenalidomide, and dexamethasone regimen, of which 24 continued to lenalidomide therapy and 1 patient opted to exit the study after initial therapy. The most common nonhematologic and hematologic toxicities (≥ grade 3) in >10% of patients included electrolyte disturbances (18%), liver function test elevation (13%), rash/pruritus (11%), fatigue (11%), lymphopenia (63%), anemia (16%), leukopenia (13%), and thrombocytopenia (11%).[74]

The results of another phase 2 trial multicenter study of carfilzomib/lenalidomide/dexamethasone in newly diagnosed transplant-eligible patients (n=76) showed that CR or better was seen in 86% of patients at the end of 18 cycles for carfilzomib/lenalidomide/dexamethasone + autologous HCT compared with 59% for carfilzomib/lenalidomide/dexamethasone and no autologous HCT. The 3-year PFS was 80% for carfilzomib/lenalidomide/dexamethasone alone and 86% for carfilzomib/lenalidomide/dexamethasone with autologous HCT. The 3-year OS was 96% for carfilzomib/lenalidomide/dexamethasone alone and 95% for carfilzomib/lenalidomide/dexamethasone with autologous HCT. The grade ≥3 adverse events, with autologous HCT versus autologous HCT, included lymphopenia (25% vs 45%), neutropenia (25% vs 30%), and infection (16% vs 8%). In the carfilzomib/lenalidomide/dexamethasone with autologous HCT, the cardiac adverse events were 4% for all grades (0% grade 3/4), hypertension was 16% (4% grade 3/4), and dyspnea was 32% (3% grade 3/4).[75]

The results of the phase III ENDURANCE trial[67] showed similar PFS with carfilzomib/lenalidomide/dexamethasone versus bortezomib/lenalidomide/dexamethasone. However, as mentioned previously, high-risk patients were not included. Carfilzomib/lenalidomide/dexamethasone was associated with less neuropathy but more dyspnea, hypertension, heart failure, and acute kidney injury compared with bortezomib/lenalidomide/dexamethasone.[67]

Based on the data from the previously discussed studies, the NCCN Panel has included the carfilzomib/lenalidomide/dexamethasone regimen as an option for primary treatment of transplant-eligible patients with MM.

Daratumumab/Lenalidomide/Bortezomib/Dexamethasone

The benefit of adding a fourth drug for the primary treatment transplant-eligible patients is emerging. In the GRIFFIN trial, transplant-eligible patients with MM (n=207) were randomized to daratumumab bortezomib/lenalidomide/dexamethasone or bortezomib/lenalidomide/dexamethasone followed by autologous HCT plus consolidation and maintenance.[76] The rate of stringent complete response rate after autologous HCT and consolidation with 4-drug regimen was 42% versus 32% with the 3-drug regimen.[76] Follow-up after median of 22 months showed further improved stringent CR rates for the daratumumab-containing 4 drug regimen (62.6% vs 45.4%; P=.0177).[76] Although the hematologic toxicities were higher with the 4-drug regimen, no major safety concerns were reported in the study.[76]

The NCCN Panel has included daratumumab/lenalidomide/bortezomib/dexamethasone as an option for primary treatment of transplant-eligible patients with MM.

Ixazomib/Lenalidomide/Dexamethasone

Ixazomib is an oral PI that was approved by the FDA in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received at least one prior therapy. In a phase I/II trial, Kumar et al[77] studied an all-oral combination of ixazomib/lenalidomide/dexamethasone in patients with newly diagnosed MM. The results of this trial show that the regimen was well tolerated and active in the study population. Of the 64 patients in whom the response could be evaluated, 37 (58%; 95% CI, 45–70) had a VGPR or better. Grade 3 or higher adverse events related to any drug in the combination were reported in 41 (63%) patients. These included skin and subcutaneous tissue disorders (11 patients, 17%), neutropenia (8 patients, 12%), and thrombocytopenia (5 patients, 8%); drug-related peripheral neuropathy of grade 3 or higher occurred in 4 (6%) patients.

A phase III trial (TOURMALINE-MM2) evaluated the addition of ixazomib to lenalidomide and dexamethasone versus lenalidomide/dexamethasone plus placebo in patients with newly diagnosed MM not eligible for autologous stem cell transplant.[78] The results presented at the Eighth SOHO Annual Meeting reported higher CR with the addition of ixazomib (26% vs 14%). The median TTP was longer in the ixazomib arm (45.8 vs 26.8 months; HR, 0.738).[78] The median PFS was increased by 13.5 months with the addition of ixazomib (35.3 months vs 21.8 months; HR, 0.830; P=.073).[78] This trial did not meet its prespecified primary endpoint of improved PFS as the data failed to meet the threshold for statistical significance.

Based on the previously noted data and pending publication of the phase III TOURMALINE trial, the NCCN Panel has included ixazomib/lenalidomide/dexamethasone as an option (category 2B) for treatment of patients with newly diagnosed MM.

Regimens Useful In Certain Circumstances for Newly Diagnosed Transplant Candidates

Bortezomib/Doxorubicin/Dexamethasone

The updated results from the HOVON-65/GMMG-HD4 group phase III trial of newly diagnosed patients with stage II/III MM demonstrated high response rates after primary therapy with bortezomib/doxorubicin/dexamethasone versus vincristine/doxorubicin/dexamethasone (VAD), and this superior response rate (CR + near CR was 31% vs 15%; $P<.001$) was maintained even after HCT with significantly higher ORR.[79] No unexpected toxicities occurred, and del(13q) did not have a significant impact on response. Response rates improved with bortezomib maintenance (34% vs 49%; $P<.001$).[79] After a median follow-up of 41 months, PFS in patients treated with bortezomib/doxorubicin/dexamethasone as primary therapy followed by HCT and bortezomib maintenance was 35 months versus 28 months in patients treated with VAD followed by HCT and maintenance with thalidomide. Patients treated with bortezomib/doxorubicin/dexamethasone had a significantly better PFS (HR, 0.75; 95% CI, 0.62–0.90; $P=.002$).[79] The OS was also found to be better in the bortezomib, doxorubicin, and dexamethasone arm (HR, 0.77; 95% CI, 0.60–1.00; $P=.049$). In high-risk patients presenting with increased creatinine more than 2 mg/dL, bortezomib significantly improved PFS from a median of 13 months to 30 months (HR, 0.45; 95% CI, 0.26–0.78; $P=.004$) and OS from a median of 21 months to 54 months (HR, 0.33; 95% CI, 0.16–0.65; $P<.001$). A benefit in terms of increased PFS was also observed in patients with deletion of 17p13.[79] The rate of grade 2 to 4 peripheral neuropathy was higher in those treated with the bortezomib-containing regimen versus VAD (40% vs 18%). In addition, newly developed grade 3 to 4 peripheral neuropathy occurred in 8% of patients during thalidomide maintenance and 5% of patients during bortezomib maintenance.[79]

Based on data from the HOVON-65/GMMG-HD4 trial and the uniform consensus among the NCCN Multiple Myeloma Panel, bortezomib/doxorubicin/dexamethasone is a category 1 option for primary therapy for transplant-eligible patients with MM.

Carfilzomib/Cyclophosphamide/Dexamethasone

The carfilzomib/cyclophosphamide/dexamethasone regimen has been studied in phase I/II trials of transplant-ineligible newly diagnosed patients with MM. Trials have investigated both once-weekly and twice weekly carfilzomib dosing combined with fixed dose cyclophosphamide and dexamethasone.[80,81] A pooled analysis of 2 phase I and II studies comparing 2 alternative schedules of carfilzomib, transplant-ineligible newly diagnosed patients with MM showed similar response rates in those treated with once-weekly carfilzomib at a dose of 70 mg/m^2 compared with those treated with twice weekly carfilzomib at a dose of 36 mg/m^2. The PFS and OS were also similar. The median PFS was 35.7 months in the once-weekly group and 35.5 months in the twice-weekly group (HR=1.39; $P=.26$). The 3-year OS was 70% and 72%, respectively (HR=1.27; $P=.5$).[82]

Consistent with the previously noted results, a phase 1b study, CHAMPION-2 evaluated the safety and tolerability of twice-weekly carfilzomib (3 different doses) in combination with cyclophosphamide and dexamethasone for the treatment of patients with newly diagnosed MM. This study found that 56 mg/m^2 carfilzomib combined with weekly cyclophosphamide and dexamethasone was effective and with manageable toxicity.[83]

The NCCN Panel has included carfilzomib/cyclophosphamide/dexamethasone for both transplant and nontransplant settings as an option useful in certain circumstances such as those with renal insufficiency and/or peripheral neuropathy.

Ixazomib/Cyclophosphamide/Dexamethasone

In a phase I trial, this regimen was shown to be a convenient, all oral combination that is well tolerated and effective in newly diagnosed patients with MM.[84] Subsequently, a multicenter, phase 2 trial investigated the efficacy and toxicity of ixazomib, cyclophosphamide and low-dose dexamethasone as induction, followed by single-agent ixazomib maintenance, in elderly, transplant-ineligible newly diagnosed patients.[85] The ORR after initial therapy with ixazomib/cyclophosphamide/dexamethasone was 73%. After a median follow-up of 26.1 months, the PFS was 23.5 months.

NCCN Panel has included ixazomib/cyclophosphamide/dexamethasone for both transplant and nontransplant settings as options useful in certain circumstances such as those with renal insufficiency and/or peripheral neuropathy.

Bortezomib/Thalidomide/Dexamethasone

The GIMEMA Italian Multiple Myeloma Network reported results of a phase III trial investigating bortezomib/thalidomide/dexamethasone (n=241) versus thalidomide/dexamethasone (n=239) as primary therapy, followed by tandem autologous HCT with high-dose melphalan and then consolidation therapy with the same primary regimen.[86] The addition of bortezomib to thalidomide and dexamethasone significantly improved

ORR after primary treatment. After primary therapy, CR/near CR was achieved in 73 patients (31%; 95% CI, 25.0–36.8) receiving bortezomib/thalidomide/dexamethasone, and 27 patients (11%; 95% CI, 7.3–15.4) receiving thalidomide/dexamethasone.[86] Rates of CR/near CR and VGPR or better continued to be significantly higher in the bortezomib/thalidomide/dexamethasone group than in the thalidomide/dexamethasone group after the first and second autologous HCT and subsequent consolidation therapy.[86] Patients receiving the bortezomib-containing regimen experienced grade 3/4 peripheral neuropathy.

Data from a single-institution retrospective study are similar to the interim data from the GIMEMA trial.[87] The findings of this analysis demonstrate that ORR after primary therapy with bortezomib/thalidomide/dexamethasone was 94% of the patients (32 of 34 patients showed some response, including a VGPR rate ≥56%).[87]

The results of the randomized phase III trial by the Spanish Myeloma Group (PETHEMA/GEM) also demonstrated a significantly higher CR rate with bortezomib/thalidomide/dexamethasone as primary therapy overall (35% vs 14%, P=.001) and in patients with high-risk cytogenetics (35% vs 0%, P=.002).[88] The CR rate continued to be significantly higher after autologous HCT (46% vs 24%) in patients treated with bortezomib/thalidomide/dexamethasone versus thalidomide/dexamethasone as primary therapy.[88]

The phase III IFM 2013-04 trial is evaluating 4 cycles of CyBorD versus 4 cycles of bortezomib/thalidomide/dexamethasone as induction therapy before autologous HCT in patients (n=340) with newly diagnosed MM.[89] The results reported during the 2015 ASH meeting show that patients who received bortezomib/thalidomide/dexamethasone as induction therapy achieved higher ORR (92.3%) compared with those who received CyBorD (84%). Those who received bortezomib/thalidomide/dexamethasone had significantly greater VGPR (P=.04) and PR (P=.02) rates.[89] The hematologic toxicity was greater in the CyBorD arm; however, higher rates of peripheral neuropathy were reported in the bortezomib/thalidomide/dexamethasone arm.[89] No significant difference in OS was observed in any of the trials with bortezomib/thalidomide/dexamethasone. A longer follow-up period is required.

Bortezomib/thalidomide/dexamethasone is listed as a primary treatment option (category 1) under the category "useful in certain circumstances." Thalidomide is not widely used in the United States; however, it is more easily available and affordable in other resource-constrained parts of the world.

Cyclophosphamide/Lenalidomide/Dexamethasone

The efficacy and tolerability of cyclophosphamide/lenalidomide/dexamethasone in newly diagnosed patients was demonstrated in a phase II study. Of the 53 patients enrolled in the trial, 85% had a PR or better including VGPR in 47%. The median PFS was 28 months (95% CI, 22.7–32.6) and at 2 years the OS was 87% (95% CI, 78–96).[90]

The Myeloma XI trial compared responses to cyclophosphamide/lenalidomide/dexamethasone with cyclophosphamide/thalidomide/dexamethasone.[91] The preliminary results reported that the combination of lenalidomide/cyclophosphamide/dexamethasone is effective and has a good safety profile in patients of all ages.[91]

The NCCN Panel included cyclophosphamide/lenalidomide/dexamethasone as a primary therapy option for transplant-eligible patients with MM under the category "useful in certain circumstances" (category 2A).

Daratumumab/Bortezomib/Thalidomide/Dexamethasone

In the CASSIOPEIA trial, patients with newly diagnosed MM (n=1,085) were first randomly assigned to receive induction with 4 cycles of bortezomib/thalidomide/dexamethasone with or without daratumumab, followed by autologous HCT plus 2 cycles of consolidation with the induction regimen.[92] The primary endpoint of the first part of this trial was assessment of response 100 days after transplantation. The second randomization of this trial (randomization to maintenance with daratumumab) is ongoing.

At day 100 after transplantation, the daratumumab arm reported deeper response rates (CR or better of 39% vs 26%). Addition of daratumumab increased neutropenia (28% vs 15%), lymphopenia (17% vs 10%). Infusion reactions to daratumumab (mostly mild) were reported in 35%.

The NCCN Panel has included daratumumab/bortezomib/thalidomide/dexamethasone as a primary therapy option for transplant-eligible patients with MM under the category "useful in certain circumstances" (category 2A) based on the results of CASSIOPEIA trial and FDA approval for this indication.

Daratumumab/Cyclophosphamide/Bortezomib/Dexamethasone

Patients with MM (n=101) including newly diagnosed patients (n=87) and patients with relapsed MM (n=14) received daratumumab,/bortezomib/cyclophosphamide/dexamethasone.[93] In newly diagnosed patients, after 4 cycles of induction therapy, VGPR or better was seen in 44.2% and the ORR was observed was 79.1%.[93] The median PFS was not reached and the 12-month PFS rate was 87%. At the time of clinical cut-off, the 12-month OS rate was 98.8% (95% CI, 92.0–99.8%).[93] Efficacy was also observed in patients with relapsed MM.

Based on the previously discussed results, NCCN Panel has included daratumumab/bortezomib/thalidomide/dexamethasone for patients with newly diagnosed MM (transplant eligible and ineligible patients) as an option useful in certain circumstances.

Bortezomib, Dexamethasone, Thalidomide, Cisplatin, Doxorubicin, Cyclophosphamide, and Etoposide (VTD-PACE)

The total therapy 3 (TT3) trial evaluated induction therapy with the multiagent regimen, VTD-PACE (bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide) prior to high-dose melphalan-based tandem auto-transplants and later as consolidation therapy.[94] This regimen is a potent combination of newer agents as well as traditional chemotherapy agents.

This regimen is listed under the category "useful in certain circumstances." According to the NCCN Panel, VTD-PACE could be an option for newly diagnosed patients presenting with high-risk and aggressive extramedullary disease or plasma cell leukemia.

Preferred Primary Therapy Regimens for Newly Diagnosed Non-Transplant Candidates

Many of the regimens described above for transplant candidates are also options for nontransplant candidates. As in transplant-eligible patients, 3-drug regimens are preferred by the NCCN Panel as these regimens have been shown to induce higher response rates and depth of response in clinical trials. The 2-drug regimens are reserved for elderly and/or frail patients. The list of preferred options for nontransplant candidates includes: bortezomib/cyclophosphamide/dexamethasone, bortezomib/lenalidomide/dexamethasone, and lenalidomide/low-dose dexamethasone.

Bortezomib/Lenalidomide/Dexamethasone

Phase II study results (discussed in the transplant setting) have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is active and well tolerated in all newly diagnosed patients with MM regardless of autologous HCT status.[62]

The randomized phase III SWOG S0777 trial, comparing bortezomib/lenalidomide/dexamethasone to lenalidomide/dexamethasone as induction therapy without an intent of immediate transplantation, reported superior results with the 3-drug regimen.[65,66]

In transplant-ineligible newly diagnosed patients with MM, a phase II study with the dose-adjusted VRd-lite regimen, showed that the dose-adjusted regimen had comparable efficacy and better tolerability than the standard dose regimen. The VRd-lite dosage included lenalidomide 15 mg days orally on 1–21; bortezomib 1.3 mg/m2 subcutaneously days 1, 8, 15, and 22 and dexamethasone 20 mg orally on the day of and the day after bortezomib for 9 cycles followed by 6 cycles of consolidation with lenalidomide and bortezomib. The ORR after 4 cycles of VRd-lite was 86%, with 66% achieving a VGPR or better.[95]

The NCCN Panel included the bortezomib/lenalidomide/dexamethasone regimen as a category 1, preferred option for patients with MM not eligible for HCT.

Daratumumab/Lenalidomide/Dexamethasone

In transplant-ineligible patients with newly diagnosed MM, results of a recently reported phase III trial (MAIA) showed that daratumumab/lenalidomide/dexamethasone significantly reduced the risk of disease progression or death by 44% (HR, 0.56 (95% CI = 0.43–0.73; $P<.001$).[96] The addition of daratumumab to lenalidomide/dexamethasone resulted in deeper responses compared with lenalidomide/dexamethasone, including increased rates of complete response (CR) or better (48% vs 25%), VGPR or better (79% vs 53%), and ORR (93% vs 81%).[96] The rates of pneumonia, neutropenia, and leukopenia were higher in those receiving daratumumab.[96] Based on the results of this study, the FDA has approved the use of daratumumab/lenalidomide/dexamethasone in this setting.

The NCCN Panel has also included daratumumab/lenalidomide/dexamethasone as a category 1, preferred option for newly diagnosed patients who are transplant ineligible.

Bortezomib/Cyclophosphamide/Dexamethasone

The role of bortezomib/cyclophosphamide/dexamethasone as initial therapy for patients with MM ineligible for HCT was studied in a small phase II trial (n=20).[97] The median age of patients in this study was 76 years (range 66–90 years). After a median of 5 cycles, the ORR was 95% with 70% of patients achieving VGPR or better response. With respect to toxicity, 6 patients experienced nonhematologic grade 3/4 adverse events (20%), including muscle weakness, sepsis, and pneumonia. Neutropenia and thrombocytopenia were seen in 2 patients (10%).[97]

Based on this and the results from the EVOLUTION trial[64] (described earlier) that had included transplant-ineligible patients and the phase II trial results,[97] the NCCN Panel has included bortezomib/cyclophosphamide/dexamethasone as a preferred option for nontransplant candidates. This is a preferred option, especially in patients with acute renal insufficiency. According to the NCCN Panel, one can consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

Lenalidomide/Low-Dose Dexamethasone

The results of the SWOG SO232 trial[98] that included transplant-ineligible patients and the ECOG E4A03 trial[99]

that included elderly patients with MM demonstrate that lenalidomide in combination with low-dose dexamethasone is a well-tolerated and effective regimen for these groups of patients. In the ECOG E4A03 trial the OS rate was significantly higher in the lenalidomide plus low-dose dexamethasone arm compared with the lenalidomide plus high-dose dexamethasone arm (also discussed under "Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates," page 1697).[99] The inferior survival outcome seen with high-dose dexamethasone was greatest in patients aged 65 years and older. At 2 years, patients who did not proceed to transplant had an OS rate of 91% with lenalidomide and low-dose dexamethasone.[99]

The international, multicenter trial (FIRST trial) evaluated efficacy and safety of lenalidomide/dexamethasone given continuously or for 72 weeks with melphalan/prednisone/thalidomide (MPT) in elderly (n=1623) transplantation-ineligible patients with newly diagnosed MM.[100] The primary endpoint of this trial was PFS, and secondary endpoints were OS and adverse events, including the incidence of secondary malignancies. After a median of 37 months of follow-up, the risk of progression or death was reduced by 28% in patients receiving continuous lenalidomide/dexamethasone versus MPT (HR, 0.72; 95% CI, 0.61–0.85; $P<.001$).[100] Continuous lenalidomide/dexamethasone also reduced the risk of progression or death compared with 18 cycles of lenalidomide/dexamethasone (HR, 0.70; 95% CI, 0.89–1.20; $P=.70$). In the interim analysis, an OS benefit was seen in the lenalidomide/dexamethasone arm versus MPT (HR, 0.78; CI, 0.64–0.96; $P=.02$).[100]

There are several reports showing higher incidences of secondary malignancies when lenalidomide is used as a maintenance therapy posttransplantation or in a melphalan-containing regimen.[101–104] In the FIRST trial, the overall incidence of secondary malignancies, including hematologic malignancies, was lower in the continuous lenalidomide/dexamethasone arm. The overall rates of second primary cancers were 3.0% in the continuous lenalidomide/dexamethasone arm, 6.0% in the arm receiving 18 cycles of lenalidomide/dexamethasone, and 5.0% in the MPT arm.[100] In an analysis based on renal function of patients enrolled in the FIRST trial, continuous lenalidomide/low-dose dexamethasone compared with MPT reduced the risk of progression or death in patients with normal, mild, and moderate renal impairment by 33%, 30%, and 35%, respectively.[105]

Lenalidomide/low-dose dexamethasone is considered a category 1, preferred option by the NCCN MM Panel for transplant-ineligible patients with MM. The Panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Based on the results of the FIRST trial,[100,106] the NCCN Panel recommends considering treatment with continuous lenalidomide/dexamethasone until disease progression for patients who are not eligible for transplant.

Other Recommended Primary Therapy Regimens for Newly Diagnosed Non-Transplant Candidates

Carfilzomib/Lenalidomide/Dexamethasone

The results of a phase I/II trial demonstrated that the combination of carfilzomib/lenalidomide/dexamethasone is well-tolerated and is also effective in all newly diagnosed patients.[72] An updated follow-up analysis of the subset of 23 elderly patients (aged ≥65 years) showed that use of the carfilzomib, lenalidomide, and low-dose dexamethasone regimen for an extended period of time resulted in deep and durable responses. All patients achieved at least a PR. With a median follow-up of 30.5 months, the reported PFS rate was 79.6% (95% CI, 53.5–92.0) and OS was 100%.[107]

The phase II trial by Korde et al[74] also showed that treatment with the carfilzomib/lenalidomide/dexamethasone regimen results in high rates of deep remission. The results were very similar across age groups, with the oldest patient on the trial being 88 years of age,[74] and the regimen was found to be effective in individuals with high-risk disease.[108]

Based on the above phase II studies that did not exclude transplant-ineligible patients, the NCCN Panel has included carfilzomib/lenalidomide/dexamethasone as an option for treatment of all patients with newly diagnosed MM, including those who are not eligible for HCT.

Ixazomib/Lenalidomide/Dexamethasone

A phase I/II study (discussed in the previous section for HCT-eligible candidates) evaluated the safety and efficacy of the all-oral combination of ixazomib with lenalidomide and dexamethasone in patients with newly diagnosed MM treated with combination lenalidomide and dexamethasone.[77] Both tolerability and activity of this regimen in older patients (those ≥65 years of age) was similar to that in younger patients in this study.

Based on the previously discussed phase II study, the NCCN Panel has included ixazomib in combination with lenalidomide and dexamethasone as a primary treatment option for all patients with newly diagnosed MM, including those not eligible for HCT.

Daratumumab/Bortezomib/Melphalan/Prednisone

In the randomized phase III trial (ALCYONE), randomized patients (n=706) with newly diagnosed MM ineligible for transplant were to receive bortezomib/melphalan/prednisone with or without daratumumab until disease progression.[109] The addition of daratumumab increased the ORR (90.9% vs 73.9%) and PFS at 18 months

was 72% versus 50%. With respect to toxicity, there was an increased rate of grade 3 or 4 infections (23% vs 15%), and daratumumab-related infusion reactions were seen in 27.7% of patients.

Based on the results of the ALCYCLONE trial, the NCCN Panel has included daratumumab/bortezomib/melphalan/prednisone as a category 1 option for treatment of patients with newly diagnosed MM not eligible for HCT. Because regimens containing melphalan are rarely used in North America, the regimen daratumumab in combination with bortezomib/lenalidomide/dexamethasone has now been listed under "Other Recommended Regimens" in this setting.

Daratumumab/Cyclophosphamide/Bortezomib/Dexamethasone

Based on the results of the LYRA study (described previously),[93] the NCCN Panel has included daratumumab/bortezomib/thalidomide/dexamethasone as a treatment option for both transplant and nontransplant settings as options useful in certain circumstances.

Regimens Useful In Certain Circumstances for Newly Diagnosed Non-Transplant Candidates

Bortezomib/Dexamethasone

A U.S. community-based, randomized, open-label, multicenter, phase IIIb UPFRONT trial compared the safety and efficacy of 3 highly active bortezomib-based regimens in previously untreated elderly patients with MM ineligible for HCT.[110] The patients with symptomatic, measurable MM were randomized (1:1:1) to one of the following regimens: bortezomib/dexamethasone (n=168); bortezomib/thalidomide/dexamethasone (n=167); or melphalan/prednisone/bortezomib (n=167) followed by maintenance therapy with bortezomib. The primary endpoint was PFS; secondary endpoints included ORR, CR/near CR and VGPR rates, OS, and safety. All 3 induction regimens exhibited substantial activity, with an ORR of 73% (bortezomib/dexamethasone), 80% (bortezomib/thalidomide/dexamethasone), and 70% (melphalan/prednisone/bortezomib) during the treatment period.[111] After a median follow-up of 42.7 months, the median PFS and OS were not significantly different between the 3 treatment arms.[110] Response rates, including CR and VGPR or better, improved after bortezomib maintenance, with no concomitant increase in the incidence of peripheral neuropathy.

Although the triple regimen with bortezomib/lenalidomide/dexamethasone is the preferred therapy for patients with newly diagnosed MM, elderly or frail patients may be treated with doublet regimens. The NCCN MM Panel has included bortezomib/dexamethasone as a primary therapy as an option that is useful in certain circumstances for patients with MM who are ineligible for HCT.

Cyclophosphamide/Lenalidomide/Dexamethasone

Based on results of the phase II trial by Kumar et al,[90] and the Myeloma ×1,[91] the NCCN Panel has included cyclophosphamide/lenalidomide/dexamethasone as an option for treatment of all patients with newly diagnosed MM, including those who are not eligible for HCT.

Carfilzomib/Cyclophosphamide/Dexamethasone

A phase II study examined the safety and efficacy of carfilzomib/cyclophosphamide/dexamethasone in patients ≥65 years of age with newly diagnosed MM and ineligible for autologous HCT.[80] Of 55 patients, 52 (95%) had at least a PR, 39 of 55 (71%) patients had at least a VGPR, 27 of 55 (49%) patients had a near CR or CR, and 11 of 55 (20%) patients had a stringent CR. After a median follow-up of 18 months, the 2-year PFS and OS rates were 76% and 87%, respectively.[80] Frequently reported grade 3 to 5 toxicities were neutropenia (20%), anemia (11%), and cardiopulmonary events (7%). Peripheral neuropathy was limited to grades 1 and 2 (9%).

The NCCN Panel has included carfilzomib/cyclophosphamide/dexamethasone as an option for treatment of patients with newly diagnosed MM not eligible for HCT.

Monitoring After Primary Myeloma Therapy of Both Transplant and Non-Transplant Candidates

Response Criteria

Assessing the response to treatment is a key determinant of MM treatment. Patients on treatment should be monitored for response to therapy and for symptoms related to disease and/or treatment.

The updated IMWG response criteria definitions[6,112,113] for CR, stringent CR, immunophenotypic CR, molecular CR, VGPR, PR, minimal response for relapsed/refractory MM, stable disease, and progressive disease are outlined in "Response Criteria for Multiple Myeloma" in the algorithm (MYEL-E, online). This was recently updated to include measures of MRD assessments. It is recommended that the IMWG uniform response criteria should be used in all clinical trials.[114] According to the NCCN Panel, response should be assessed using the IMWG criteria.[6]

The same imaging modality used during the initial workup should ideally be used for the follow-up assessments. Follow-up tests after primary MM therapy include those used for initial diagnosis: a CBC with differential and platelet counts; serum creatinine and corrected serum calcium; and quantification of M-protein. The serum immunoglobulins and FLC

(especially in patients with oligo- or nonsecretory MM) may be assessed as clinically indicated.

The NCCN Panel recommends considering harvesting peripheral blood hematopoietic stem cells prior to prolonged exposure to lenalidomide and/or daratumumab in patients for whom transplant is being considered. Collecting enough hematopoietic stem cells for 2 transplants (depending on the intended number of transplants and age) in anticipation of a tandem transplant or a second transplant as subsequent therapy is recommended. Alternatively, all patients may consider continuation of primary therapy until the best response is reached. The optimal duration of primary therapy after achieving maximal response is unknown; hence, maintenance therapy (see section on "Maintenance Therapy," page 1708) or observation can be considered beyond maximal response.

Hematopoietic Cell Transplantation

Transplant Eligibility

All patients are assessed to determine eligibility for HCT. The NCCN Panel recommends that all patients eligible for HCT should be referred for evaluation by HCT center and hematopoietic stem cells (for at least 2 transplants, in younger patients) should be harvested.

High-dose therapy with hematopoietic stem cell support is a critical component in the treatment plan of eligible patients newly diagnosed with MM. The types of HCT may be single autologous HCT, a tandem HCT (a planned second course of high-dose therapy and HCT within 6 months of the first course), or an allogeneic HCT.

The NCCN Guidelines for MM indicate that all types of HCT are appropriate in different clinical settings; these indications are discussed further below. In general, all candidates for high-dose chemotherapy must have sufficient hepatic, renal, pulmonary, and cardiac function. However, renal dysfunction is not an absolute contraindication to transplant.

Autologous Hematopoietic Cell Transplantation

Autologous HCT results in high response rates and remains the standard of care after primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous HCT is associated with statistically significantly higher response rates and increased OS and event-free survival (EFS) when compared with the response of similar patients treated with conventional therapy.[115] In 2003, results of a second trial comparing high-dose therapy to standard therapy showed an increase in the CR rate and an improvement in OS (54 months in the high-dose group compared with 42 months for standard therapy).[116] Barlogie et al[117] reported on the results of an American trial that randomized 510 patients to receive high-dose therapy with autologous hematopoietic cell transplant or standard therapy. With a median follow-up of 76 months, there were no differences in response rates, PFS, or OS between the 2 groups. The reason for the discrepant results is not clear, but may be related to differences in the specific high-dose and conventional regimens between the American and French study. For example, the American study included total body irradiation (TBI) as part of the high-dose regimen; TBI has subsequently been found to be inferior to high-dose melphalan.[118]

Another trial included 190 patients 55 to 65 years of age randomized to standard or high-dose therapy.[119] This study was specifically designed to include older patients, since the median age of the participants in other trials ranged from 54 to 57 years and the median age in this trial was 61 years. After 120 months of follow-up, there was no significant difference in OS, although there was a trend toward improved EFS in the high-dose group (P=.7). Additionally, the period of time without symptoms, treatment, or treatment toxicity was significantly longer in the high-dose group. The study concluded that the equivalent survival suggests that the treatment choice between high-dose and conventional-dose chemotherapy should be based on personal choice in older patients. For example, an early transplant may be favored because patients can enjoy a longer interval of symptom-free time.

A phase III study compared high-dose melphalan followed by autologous HCT with MPR (melphalan, prednisone, and lenalidomide) consolidation after induction. Patients (n=402) were randomly assigned (in a 1:1:1:1 ratio) to one of the 4 groups: high-dose therapy and autologous HCT followed by maintenance with lenalidomide; high-dose therapy and HCT alone; primary therapy with MPR followed by lenalidomide; and primary therapy with lenalidomide alone.[120] At a median follow-up of 51 months, HCT resulted in longer median PFS (43 vs 22 months; HR 0.44; 95% CI, 0.32–0.61) and OS (82% vs 65% at 4 years; HR 0.55; 95% CI, 0.32–0.93).[120]

Results from the IFM 2005/01 study of patients with symptomatic MM receiving primary therapy with bortezomib and dexamethasone versus VAD showed a marked improvement in ORR with bortezomib and dexamethasone over VAD (see "Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates," page 1697).[121] Responses were evaluated after primary treatment and postautologous HCT. After the first autologous HCT, CR/near-CR rates were 35.0% in the bortezomib plus dexamethasone arm, compared with 18.4% in the VAD arm.[121] The VGPR rates were 54.3% versus 37.2%. Median PFS was 36.0 months versus

29.7 months (P=.064) with bortezomib plus dexamethasone versus VAD after a median follow-up of 32.2 months.[121] Also, PFS was also significantly longer in the patients achieving greater than or equal to a VGPR after primary treatment than in patients achieving a less than VGPR (median 36 vs 29.7 months).[121]

In another study, 474 patients were randomized to primary therapy with bortezomib/dexamethasone/thalidomide (n=236) or thalidomide/dexamethasone (n=238) before double autologous HCT and as consolidation therapy after HCT.[122] The 3-drug regimen yielded high response rates compared with the 2-drug regimen, with a CR rate of 19% (vs. 5%) and greater than or equal to a VGPR of 62% (vs. 31%). After HCT, improved incremental responses were still seen with bortezomib/dexamethasone/thalidomide compared with thalidomide plus dexamethasone.[123]The IFM 2009 phase III trial compared the efficacy and safety of bortezomib/lenalidomide/dexamethasone alone versus bortezomib/lenalidomide/dexamethasone plus autologous HCT for the treatment of newly diagnosed MM in patients 65 years or younger.[123] The reported CR rate was 48% in the group that received induction therapy alone versus 59% in the transplantation group (P=.03). No MRD was detected in 65% of the patients who received bortezomib/lenalidomide/dexamethasone alone versus no MRD in 79% of the patients who received induction therapy plus autologous HCT (P<.001).[123] There was a clear improvement in PFS with HCT (50 months vs 36 months). These results clearly show the benefit of autologous HCT, with higher rates of durable responses in those with no MRD after initial therapy.[123] Taken together, the studies suggest that improved responses with the primary regimen result in improved outcomes after transplantation even for patients receiving an IMiD and PI-based triplet regimen.

The OS of patients in the IFM 2009 phase III trial was high in both groups, the one that received autologous HCT and the one that did not.[123] Although autologous HCT improved PFS it did not improve OS, suggesting that delaying HCT is an option and is not associated with negative effects on OS.

According to the NCCN Guidelines, for transplant-eligible patients, autologous HCT is the preferred option after primary induction therapy and a delayed HCT after early stem cell collection and storage is appropriate as well (category 1). Repeat HCT can be considered for treatment of progressive/refractory disease after primary treatment in patients with prolonged response to initial HCT.

Tandem Hematopoietic Cell Transplantation

Tandem HCT refers to a planned second course of high-dose therapy and HCT within 6 months of the first course. Planned tandem transplants have been studied in several randomized trials. The IFM94 trial reported by Attal et al randomized newly diagnosed patients with MM to single or tandem autologous transplants.[124] A total of 78% of patients assigned to the tandem transplant group received the second transplant at a median time of 2.5 months after the first. A variety of options for therapy of relapsed disease were provided. For example, relapsing patients in either group underwent either no therapy, additional conventional therapy, or another HCT. The probability of EFS for 7 years after the diagnosis was 10% in the single transplant group compared with 20% in the double transplant group. In a subset analysis, those patients who did not achieve a complete CR or VGPR within 3 months after the first transplant appeared to benefit the most from a second transplant. The investigators of the IFM94 study have suggested that the improvement in projected survival associated with tandem transplant is related not to improved response rates, but to longer durations of response. Four other randomized trials have compared single versus tandem transplant.[119,125–127] None of these trials showed a significant improvement in OS. However, since the median follow-up in these trials ranged from 42 to 53 months, the lack of significant improvement is not surprising. The trial by Cavo et al[125] found that patients not in CR or near CR after the first transplant benefited the most from a second transplant. This confirms the observations of the IFM94 trial using non-TBI–based high-dose regimens. In both the French and Italian trials, the benefit of a second autologous HCT was seen in patients who do not achieve a CR or VGPR (>90% reduction in M-protein level) with the first procedure. These 2 studies were not adequately powered to evaluate the equivalence of one versus 2 transplants in patients achieving a CR or VGPR after the first transplantation.

A review of long-term outcomes of several trials of autologous transplantation by Barlogie et al[128] found that tandem transplantations were superior to both single transplantations and standard therapies. Also, post-relapse survival was longer when EFS was sustained for at least 3.5 years after tandem transplantation.[128,129] Results of the multicenter, phase III study (EMN02/HO95 MM trial) suggested that tandem autologous HCT for newly diagnosed MM may be superior in extending PFS compared with single autologous HCT after induction therapy with a bortezomib-based regimen.[130] In another more recent study, after initial HCT patients were randomly assigned to receive a second HCT followed by lenalidomide maintenance; or 4 cycles of bortezomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance; or lenalidomide maintenance alone.[131] At 38 months, all 3 arms showed similar PFS and OS.[131]

The NCCN MM Panel recommends collecting enough hematopoietic stem cells for at least one HCT in *all* eligible patients, and for 2 transplants in the younger patients if tandem transplant or salvage transplant would be considered. According to the NCCN Panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for HCT and is an option for patients who do not achieve at least a VGPR after the first autologous HCT and those with high-risk features. The support for use of maintenance therapy after tandem transplant comes from the study by Palumbo et al,[120] which addressed the role of maintenance therapy with lenalidomide after autologous transplantation.[120] Although associated with more frequent grade 3 or 4 neutropenia and infections, maintenance therapy with lenalidomide was found to significantly reduce risk of disease progression or death (HR, 0.47) after both single and tandem transplantation compared with no maintenance.[120]

A second autologous HCT can be considered at the time of disease relapse. A retrospective case-matched control analysis was performed comparing patients who underwent a second autologous HCT to those treated with conventional chemotherapy for relapsed MM.[132] Similar to previously published smaller studies,[133–135] this retrospective analysis demonstrated that a second autologous HCT is associated with superior relapse-associated mortality compared with conventional chemotherapy (68% vs 78%), along with improved OS (32% vs 22%) at 4 years. In this analysis, factors associated with improved OS and PFS included younger age (<55 years), beta-2 microglobulin <2.5 mg/L at diagnosis, a remission duration of >9 months, and a greater than PR to their first autologous HCT. This analysis indicates that a second autologous transplant, for relapsed or progressive MM, may be an option for carefully selected patients. Some of these patients can achieve durable complete or partial remission.[135,136]

A multicenter, randomized phase III trial compared treatment with high-dose melphalan plus second autologous HCT with cyclophosphamide in patients with relapsed MM who had received autologous HCT as primary treatment.[137] The patients included in the study were greater than 18 years of age and needed treatment of progressive or relapsed disease at least 18 months after a previous autologous HCT. All patients first received bortezomib/doxorubicin/dexamethasone induction therapy. Patients with adequately harvested hematopoietic stem cells were then randomized to high-dose melphalan plus second autologous HCT (n=89) or oral cyclophosphamide (n=85). The primary endpoint was time to disease progression.[137] After a median follow-up of 31 months, median TTP in patients who underwent second autologous HCT after induction therapy was 19 months versus 11 months for those treated with cyclophosphamide (HR, 0.36; 95% CI, 0.25–0.53; $P<.0001$). Grade 3-4 neutropenia (76% vs 13%) and thrombocytopenia (51% vs 5%) were higher in the group that underwent autologous HCT versus cyclophosphamide.[137] Median OS in the HCT group was 67 months versus 52 months in the cyclophosphamide maintenance group.[138]

According to the NCCN MM Panel, repeat autologous HCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding HCT and documented progression.

The prognosis of patients who relapse after autologous HCT appears to differ depending on the timing of the relapse.[139–143] Data from retrospective studies[144–147] suggest 2 to 3 years as the minimum length of remission for consideration of second autologous HCT for relapsed disease.

Allogeneic Hematopoietic Cell Transplantation

Allogeneic HCT includes either myeloablative or non-myeloablative (ie, "mini" transplant) transplants. Allogeneic HCT has been investigated as an alternative to autologous HCT to avoid the contamination of reinfused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population. Non-myeloablative transplants are designed to decrease the morbidity of the high-dose chemotherapy but preserve the beneficial graft-versus-tumor effect. Therefore, the principal difference between myeloablative and non-myeloablative transplants relates to the chemotherapy regimen used. Specific preparatory regimens have not been a focus of the NCCN Guidelines, and therefore these guidelines do not make a distinction between these approaches.

Given the small candidate pool, it is not surprising that there have been no randomized clinical trials comparing myeloablative allogeneic to autologous HCT, but multiple case series have been published describing allogeneic HCT as an initial therapy or as therapy for relapsed/refractory MM. In a 1999 review, Kyle[148] reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured. Other reviews have also reported increased morbidity without convincing proof of improved survival.[149,150] However, there are intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.[117] The original trial had an ablative, allogeneic transplant group consisting of patients with HLA identical siblings. Thirty-six patients received allografts, and due to the

high 6-month mortality of 45%, the allogeneic arm was closed. After 7 years of follow-up the OS of the conventional chemotherapy, autologous, and allogeneic arms were all identical at 39%. The autologous and conventional chemotherapy arms do not demonstrate a plateau, whereas the allogenic curve was flat at 39%. This suggests that a proportion of these patients are long-term survivors. Thus, there is ongoing interest in myeloablative allogeneic HCT, particularly given the lack of a significant cure rate for single or tandem autologous HCT.

Patients whose disease either does not respond to or relapses after allogeneic hematopoietic cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft-versus-myeloma effect[151–158] or other myeloma therapies on or off a clinical trial.

Follow-Up After Hematopoietic Cell Transplantation

Follow-up tests after HCT are similar to those done after primary myeloma therapy. In addition, MRD assessment is increasingly being incorporated into posttreatment assessments. MRD has been identified as an important prognostic factor. A prospective study of patients with newly diagnosed MM evaluated MRD in bone marrow samples and showed that at a median follow-up of 57 months, MRD negativity after autologous HCT translated to significantly improved PFS and OS rates.[159] Similarly, in another study, MRD negativity after autologous HCT was predictive of favorable PFS and OS.[160] Similar results have also been reported in the allogeneic HCT setting where the presence of MRD after allogeneic HCT has been associated with a significantly adverse PFS and OS.[161] The NCCN Panel recommends assessing for MRD during follow-up as indicated prognostication after shared decision with patient.[114]

Maintenance Therapy

The NCCN Panel has clarified in the algorithm section the maintenance regimens appropriate for those who received autologous HCT versus those who did not and classified them as either preferred"; "other recommended"; or "useful in certain circumstances"

Lenalidomide as Maintenance Therapy

Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in 2 independent randomized phase III studies.[101,102]

In the CALGB 100104 trial, patients were randomized to maintenance therapy with lenalidomide (n=231) versus placebo (n=229) after autologous HCT.[102] At a median follow-up of 34 months, 37% of the patients who received lenalidomide versus 58% who received placebo had disease progression or died. The median TTP in the lenalidomide group was 46 months versus 27 months in the placebo group ($P<.001$). Second primary cancers occurred in 18 patients who received lenalidomide (8%) and in 6 patients who received placebo (3%).[102]

Data from the international, randomized, double-blind phase III IFM 2005-02 trial (n=614) show that patients treated with lenalidomide as consolidation therapy after an autologous HCT followed by lenalidomide as maintenance therapy had upgraded responses. Of the 614 patients enrolled in the trial, 307 were randomly assigned to lenalidomide maintenance therapy and 307 to placebo. Maintenance treatment was continued until the patient withdrew consent, the disease progressed, or unacceptable toxic effects occurred. The final analysis of the IFM 2005-02 trial was performed after a median follow-up of 30 months and 264 patients had disease progression (104 in the lenalidomide group and 160 in the placebo group). The median PFS was 41 months in the lenalidomide group, compared with 23 months in the placebo group (HR, 0.50; $P<.001$; median follow-up period was 30 months). The probability of surviving without progression for 3 years after randomization was 59% in those treated with lenalidomide and 35% in those who received the placebo. The benefit of lenalidomide maintenance therapy, evidenced by rate of PFS at 3 years after randomization, was higher in all patients who received lenalidomide maintenance therapy compared with those who received placebo. This benefit was observed in patients who had a VGPR at randomization (64% vs 49%, $P=.006$) and those who did not (51% vs 18%, $P<.001$).[101] An increased incidence of second primary cancers was observed in the lenalidomide group (32 had second primary cancers in the lenalidomide group and 12 in the placebo group).[101] The updated survival analysis of the same study after 91 months for follow-up reported median TTP of 57.3 months (95% CI, 44.2–73.3) with lenalidomide and 28.9 months (23.0–36.3) with placebo (HR, 0.57; 95% CI, 0.46–0.71; $P<.0001$).[162] The most common grade 3-4 adverse events in the lenalidomide group compared with placebo were neutropenia (50% vs 18%) and thrombocytopenia (15% vs 5%). An increased rate of second primary malignancies (hematologic plus solid tumor) were diagnosed in the lenalidomide group compared with placebo (14% vs 4%).[162]

The study by Palumbo et al[120] (discussed in "Autologous Hematopoietic Cell Transplantation," page 1705) showed that although maintenance therapy with lenalidomide is associated with more frequent grade 3 or 4 neutropenia and infections, it significantly reduced risk of disease progression or death (HR, 0.47) compared with no maintenance.[120]

The benefit of lenalidomide maintenance was studied in a meta-analysis of data from 1209 patients

enrolled in the trials discussed above randomized to maintenance with lenalidomide or placebo.[163] The study showed improved median PFS with lenalidomide maintenance (52.8 vs 23.5 months; HR 0.48; 95% CI, 0.42–0.55). At 7 years, the OS was 62% in the group receiving lenalidomide maintenance versus 50% in the group receiving placebo. In those with high-risk cytogenetics, a PFS benefit, but not an OS benefit was seen with lenalidomide maintenance versus placebo.

The lenalidomide group had higher rates of second primary malignancy occurring before progression, and the rates of progressive disease were higher in the group receiving placebo.

A report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option after mini-allogeneic HCT.[164] However, another recently reported study has shown the feasibility of maintenance therapy with low-dose lenalidomide after allogeneic HCT in patients with high-risk MM.[165]

Data from the phase III MM-015 study show that lenalidomide maintenance after primary therapy with melphalan/prednisone/lenalidomide (MPL) significantly reduced the risk of disease progression and also increased PFS.[166] In this study, newly diagnosed patients with MM (n=459) aged ≥65 years were randomized to receive MP followed by placebo, MPL, or MPL followed by lenalidomide until progression. Maintenance with lenalidomide significantly prolonged PFS. The PFS of patients treated with MPL followed by maintenance lenalidomide was significantly prolonged (n=152; median, 31 months) compared with the other 2 arms: MPL (n=153; median, 14 months; HR, 0.49; $P<.001$) or MP (n=154; median, 13 months; HR, 0.40; $P<.001$). Lenalidomide maintenance therapy improved PFS by 66% compared with placebo, regardless of age.[166] In the FIRST trial, use of lenalidomide indefinitely until progression was associated with a superior PFS compared with a fixed duration of 18 months.

Based on the evidence from the phase III trials,[101,102,166] the NCCN MM Panel lists single-agent lenalidomide as one of the preferred maintenance regimens (category 1) for transplant -eligible as well ineligible patients. Lenalidomide lacks the neurologic toxicity seen with thalidomide. However, there seems to be an increased risk for secondary cancers, especially posttransplantation,[101–103] or after a melphalan-containing regimen.[104] According to the results of the FIRST trial, in the continuous lenalidomide/dexamethasone arm, the absence of the alkylator melphalan seems to be more effective in terms of improving PFS and lowering incidence of second malignancies.[100]

A meta-analysis of 4 randomized controlled trials examined patients treated with lenalidomide maintenance versus patients with no maintenance or placebo in both the transplant and nontransplant settings.[167] The analysis showed that patients treated with lenalidomide maintenance had significantly improved PFS (HR, 0.49; $P<.001$) and a trend toward OS (HR, 0.77; $P=.071$) versus no maintenance or placebo.[167] There was significantly more grade 3/4 neutropenia with the use of lenalidomide and a 2-fold increased risk of secondary malignancies.

The benefits of improved PFS with lenalidomide maintenance must be weighed against the increased rate of severe (grade 3 and 4) neutropenia, risk of second cancers, and other toxicities.[168] The NCCN Panel notes that the benefits and risks of maintenance therapy with lenalidomide versus secondary cancers should be discussed with patients.

Bortezomib as Maintenance Therapy

The results from the HOVON study show that maintenance with single-agent bortezomib after autologous HCT is well tolerated and is associated with improvement of ORR.[79] Patients in the HOVON trial were randomly assigned to 1 of the 2 arms consisting of either primary treatment with VAD followed by autologous HCT and maintenance with thalidomide or with bortezomib/doxorubicin/dexamethasone followed by autologous HCT and bortezomib as maintenance therapy for 2 years. The study reported high near-CR/CR rates after primary treatment with the bortezomib-based regimen. Bortezomib as maintenance therapy was well tolerated and associated with additional improvement of response rates[79] (see "Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates," page 1697*)*.

A multicenter phase III trial in newly diagnosed patients with MM showed that consolidation with bortezomib after autologous HCT improved PFS only in patients not achieving at least VGPR after autologous HCT.[169] There was no difference in PFS in patients with VGPR or better after autologous HCT.[169]

The results of the phase III UPFRONT study showed that maintenance with single-agent bortezomib is well-tolerated when administered after treatment with bortezomib-based primary therapy.[110] Newly diagnosed patients with MM, ineligible for high-dose therapy and HCT enrolled in the UPFRONT trial were randomized (1:1:1) and treated with one of the following bortezomib-based primary regimens: bortezomib and dexamethasone; bortezomib in combination with thalidomide and dexamethasone; or bortezomib with melphalan and prednisone followed by maintenance treatment with bortezomib. The response rates, including CR and ≥VGPR, improved after bortezomib maintenance in all arms, with no concomitant increase in the incidence of peripheral neuropathy.[110] The NCCN MM Panel has added

bortezomib as a maintenance therapy option for both transplant eligible as well ineligible patients.

Ixazomib as Maintenance Therapy After Autologous HCT

The TOURMALINE-MM3 trial studied 2 years of maintenance with ixazomib versus placebo in patients who had achieved at least a partial response (PR) following induction therapy and a single autologous HCT. Ixazomib improved PFS (median 26.5 [95% CI 23·7-33·8] vs 21.3 months; HR 0.72, 95% CI 0.58-0.89).[170] The risk of developing secondary malignancies was similar in control arm and with maintenance ixazomib. Based on the positive results of the phase III TOURMALINE-MM3 trial, designed specifically to study benefit maintenance ixazomib, the NCCN Panel has included ixazomib as a category 1 "other recommended" maintenance option for transplant-eligible patients.

Supportive Care for MM

Important advances have been made in adjunctive treatment/supportive care of patients with MM. This involves careful patient education about the probable side effects of each drug, the drug combinations being used, and the supportive care measures required. Supportive care can be categorized into those measures required for all patients and those that address specific drugs.

Bony manifestations in the form of diffuse osteopenia and/or osteolytic lesions, develop in 85% of patients with MM. Related complications are the major cause of limitations in quality of life and performance status in patients with MM. A large, double-blind, randomized trial has shown that monthly use of IV pamidronate (a bisphosphonate) can decrease pain and bone-related complications, improve performance status, and, importantly, preserve quality of life in patients with Durie-Salmon stage III MM and at least one lytic lesion.[171,172] Zoledronic acid has equivalent benefits.[173] Results from the study conducted by Zervas et al[174] show a 9.5-fold greater risk for the development of osteonecrosis of the jaw (ONJ) with zoledronic acid compared with pamidronate. Patients who are on bisphosphonates should have their renal function monitored. They should have a dental exam prior to the start of bisphosphonate therapy and should be monitored for ONJ.

The Medical Research Council (MRC) Myeloma IX study examined effects of zoledronic acid versus clodronate (a bisphosphonate not currently FDA approved) in patients with MM initiating chemotherapy regardless of bone disease. The patients were randomized to receive zoledronic acid (n=981) or clodronic acid (n=979). Zoledronic acid was reported to reduce mortality and significantly improve PFS.[175] Patients on clodronate and zoledronic acid had similar occurrence of acute renal failure and treatment-related serious adverse events. Zoledronic acid was associated with higher rates of ONJ than was clodronic acid.[176] An extended follow-up (median, 5.9 years) of the MRC Myeloma IX showed significant improvement in OS (52 vs 46 months; HR, 0.86; P=.01) compared with clodronic acid.[177] The long-term rates of ONJ were also observed to be higher with zoledronic acid compared with clodronate (3.7% vs 0.5%; P=.0001).[177]

A recent meta-analysis of 20 randomized controlled trials comparing bisphosphonates with either placebo or a different bisphosphonate as a comparator concluded that adding bisphosphonates to the treatment of MM reduces vertebral fractures and probably reduces pain.[178] It did not find a particular bisphosphonate to be superior to another.[178] In a multicenter trial (CALGB 70604), patients with MM or bone metastases from a solid malignancy were randomly assigned to zoledronic acid either monthly or every 3 months for 2 years.[179] The rates of skeletal-related events were similar in both arms. Among the 278 patients with MM, rates of skeletal-related events were 26% in those receiving monthly versus 21% in those receiving treatment every 3 months.[179]

A large, placebo-controlled, randomized trial compared denosumab with zoledronic acid in patients (n=1718) with newly diagnosed MM with bone lesions. Time to first skeletal-related events and OS was similar in both arms. The denosumab arm had lower rates of renal toxicity and higher rates of hypocalcemia. ONJ was slightly higher in the denosumab arm (3% vs 2%) but not statistically significant.[180]

The NCCN Guidelines for MM recommend bisphosphonates (category 1) or denosumab for all patients receiving therapy for symptomatic MM regardless of documented bone disease. Denosumab is preferred by the NCCN Panel in patients with renal disease. The panel recommends a baseline dental exam and monitoring for ONJ in all patients receiving a bone-modifying agent and monitoring for renal dysfunction with use of bisphosphonate therapy.

With respect to duration of therapy, the panel also recommends continuing bone-targeting treatment (bisphosphonates or denosumab) for up to 2 years and continuing beyond 2 years would be based on clinical judgement. The frequency of dosing (monthly vs every 3 months) would depend on the individual patient criteria and response to therapy.

Low-dose (10–30 Gy) or single fraction (8 Gy) are used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.[40,181] Limited involved fields should be used to limit the effect of irradiation on hematopoietic stem cell harvest or its effect on potential future treatments;

the radiation doses administered should not preclude hematopoietic stem cell collection in potential candidates for high-dose therapy and HCT. Orthopedic consultation should be obtained for impending or actual fractures in weight-bearing bones, bony compression of the spinal cord, or vertebral column instability. Either vertebroplasty or kyphoplasty should be considered for symptomatic vertebral compression fractures.

Excess bone resorption from bone disease can lead to excessive release of calcium into the blood, contributing to hypercalcemia. Symptoms include polyuria and gastrointestinal disturbances, with progressive dehydration and decreases in glomerular filtration rate. Hypercalcemia should be treated with hydration, bisphosphonates, denosumab,[180] steroids, and/or calcitonin. Among the bisphosphonates (zoledronic acid, pamidronate, and ibandronate), the NCCN MM Panel members prefer zoledronic acid for treatment of hypercalcemia.[173,182,183]

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.[184] Institutions differ in their use of plasmapheresis for adjunctive treatment of renal dysfunction.

Erythropoietin therapy may be considered for anemic patients, especially those with renal failure. Measuring endogenous erythropoietin levels may also be helpful in treatment planning[185,186] (see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections, at NCCN.org). Daratumumab can interfere with cross-matching and red blood cell antibody screening. The NCCN Panel recommends performing type and screen prior to receiving daratumumab to inform future matching.

Thrombosis is relatively common with the use of IMiDs (thalidomide, lenalidomide, or pomalidomide) with steroids, and is particularly frequent when treating newly diagnosed patients. Use of prophylactic anticoagulation agents (see NCCN Guidelines for Venous Thromboembolic Disease, available at NCCN.org) is recommended when IMiDs are used in combination therapy during induction.[187–189] For those receiving an IMiD-based therapy, prophylaxis with aspirin (81–325 mg) is recommended. An anticoagulation agent is recommended for patients receiving an IMiD-based therapy and who are at high risk for thrombosis.

To prevent infections, intravenous immunoglobulin therapy should be considered for recurrent, life-threatening infections; pneumococcal conjugate vaccine should be given followed by the pneumococcal polysaccharide vaccine 1 year later. Reactivation of hepatitis B virus is a complication in patients receiving carfilzomib or daratumumab. Therefore, testing for hepatitis B in these patients is recommended.

Pneumocystis jiroveci pneumonia, herpes zoster, and antifungal prophylaxis is recommended if high-dose dexamethasone is used. Prophylactic antiviral therapy is recommended for all patients receiving PI-based and antibody based therapies.[190,191] This is because impaired lymphocyte function that results from MM and/or its treatment-related myelosuppression may lead to reactivation of herpes simplex infection or herpes zoster.[191–194] Herpes zoster prophylaxis is recommended all patients treated with PIs, daratumumab, isatuximab-irfc, or elotuzumab. According to the NCCN Panel, 3 months of antibiotic prophylaxis should be considered at diagnosis for patients at high risk for infection (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections, available at NCCN.org).

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7–30.
2. Stat Fact Sheets SEER. Myeloma. http://seer.cancer.gov/statfacts/html/mulmy.html. Accessed on October 20th, 2020.
3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21–33.
4. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 2009;23:215–224.
5. Kühnemund A, Liebisch P, Bauchmüller K, et al. 'Light-chain escape-multiple myeloma'-an escape phenomenon from plateau phase: report of the largest patient series using LC-monitoring. J Cancer Res Clin Oncol 2009;135:477–484.
6. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467–1473.
7. Craig FE, Foon KA. Flow cytometric immunophenotyping for hematologic neoplasms. Blood 2008;111:3941–3967.
8. Paiva B, Vidriales MB, Pérez JJ, et al. Multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides more prognostic information than morphological assessment in myeloma patients. Haematologica 2009;94:1599–1602.
9. Xiong W, Wu X, Starnes S, et al. An analysis of the clinical and biologic significance of TP53 loss and the identification of potential novel transcriptional targets of TP53 in multiple myeloma. Blood 2008;112:4235–4246.
10. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. Blood 1998;92:802–809.
11. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myélome. Blood 2007;109:3489–3495.
12. Gertz MA, Lacy MQ, Dispenzieri A, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. Blood 2005;106:2837–2840.
13. Gutiérrez NC, Castellanos MV, Martín ML, et al. Prognostic and biological implications of genetic abnormalities in multiple myeloma undergoing autologous stem cell transplantation: t(4;14) is the most relevant adverse prognostic factor, whereas RB deletion as a unique abnormality is not associated with adverse prognosis. Leukemia 2007;21:143–150.
14. Ross FM, Chiecchio L, Dagrada G, et al. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. Haematologica 2010;95:1221–1225.

15. Ross FM, Avet-Loiseau H, Ameye G, et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica 2012;97:1272–1277.
16. Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. Blood 2006;108:1724–1732.
17. Carrasco DR, Tonon G, Huang Y, et al. High-resolution genomic profiles define distinct clinico-pathogenetic subgroups of multiple myeloma patients. Cancer Cell 2006;9:313–325.
18. Rosiñol L, Carrió A, Bladé J, et al. Comparative genomic hybridisation identifies two variants of smoldering multiple myeloma. Br J Haematol 2005;130:729–732.
19. Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. Mayo Clin Proc 2007;82:323–341.
20. Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. Mayo Clin Proc 2009;84:1095–1110.
21. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003;121:749–757.
22. Hillengass J, Moulopoulos LA, Delorme S, et al. Findings of whole body computed tomography compared with conventional skeletal survey in patients with monoclonal plasma cell disorders - a Study of the International Myeloma Working Group. Blood 2016;128:4468.
23. Hinge M, Andersen KT, Lund T, et al. Baseline bone involvement in multiple myeloma - a prospective comparison of conventional X-ray, low-dose computed tomography, and 18flourodeoxyglucose positron emission tomography in previously untreated patients. Haematologica 2016;101:e415–e418.
24. Kröpil P, Fenk R, Fritz LB, et al. Comparison of whole-body 64-slice multidetector computed tomography and conventional radiography in staging of multiple myeloma. Eur Radiol 2008;18:51–58.
25. Princewill K, Kyere S, Awan O, et al. Multiple myeloma lesion detection with whole body CT versus radiographic skeletal survey. Cancer Invest 2013;31:206–211.
26. Nanni C, Zamagni E, Farsad M, et al. Role of 18F-FDG PET/CT in the assessment of bone involvement in newly diagnosed multiple myeloma: preliminary results. Eur J Nucl Med Mol Imaging 2006;33:525–531.
27. Siontis B, Kumar S, Dispenzieri A, et al. Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: identification of patients needing therapy. Blood Cancer J 2015;5:e364.
28. Zamagni E, Nanni C, Gay F, et al. 18F-FDG PET/CT focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease. Leukemia 2016;30:417–422.
29. Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol 2010;28:1606–1610.
30. Merz M, Hielscher T, Wagner B, et al. Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma. Leukemia 2014;28:1902–1908.
31. Greipp PR, Lust JA, O'Fallon WM, et al. Plasma cell labeling index and beta 2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. Blood 1993;81:3382–3387.
32. Kumar SK, Rajkumar SV. The multiple myelomas - current concepts in cytogenetic classification and therapy. Nat Rev Clin Oncol 2018;15:409–421.
33. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;15:e538–e548.
34. Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J 2018;8:59.
35. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. J Clin Oncol 2005;23:3412–3420.
36. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol 2015;33:2863–2869.
37. Knowling MA, Harwood AR, Bergsagel DE. Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. J Clin Oncol 1983;1:255–262.
38. Dores GM, Landgren O, McGlynn KA, et al. Plasmacytoma of bone, extramedullary plasmacytoma, and multiple myeloma: incidence and survival in the United States, 1992-2004. Br J Haematol 2009;144:86–94.
39. Dimopoulos MA, Goldstein J, Fuller L, et al. Curability of solitary bone plasmacytoma. J Clin Oncol 1992;10:587–590.
40. Hu K, Yahalom J. Radiotherapy in the management of plasma cell tumors. Oncology (Williston Park) 2000;14:101-108, 111; discussion 111-102, 115.
41. Creach KM, Foote RL, Neben-Wittich MA, et al. Radiotherapy for extramedullary plasmacytoma of the head and neck. Int J Radiat Oncol Biol Phys 2009;73:789–794.
42. Tournier-Rangeard L, Lapeyre M, Graff-Caillaud P, et al. Radiotherapy for solitary extramedullary plasmacytoma in the head-and-neck region: A dose greater than 45 Gy to the target volume improves the local control. Int J Radiat Oncol Biol Phys 2006;64:1013–1017.
43. Reed V, Shah J, Medeiros LJ, et al. Solitary plasmacytomas: outcome and prognostic factors after definitive radiation therapy. Cancer 2011;117:4468–4474.
44. Frassica DA, Frassica FJ, Schray MF, et al. Solitary plasmacytoma of bone: Mayo Clinic experience. Int J Radiat Oncol Biol Phys 1989;16:43–48.
45. Ozsahin M, Tsang RW, Poortmans P, et al. Outcomes and patterns of failure in solitary plasmacytoma: a multicenter Rare Cancer Network study of 258 patients. Int J Radiat Oncol Biol Phys 2006;64:210–217.
46. Knobel D, Zouhair A, Tsang RW, et al. Prognostic factors in solitary plasmacytoma of the bone: a multicenter Rare Cancer Network study. BMC Cancer 2006;6:118.
47. Sasaki R, Yasuda K, Abe E, et al. Multi-institutional analysis of solitary extramedullary plasmacytoma of the head and neck treated with curative radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:626–634.
48. Gerry D, Lentsch EJ. Epidemiologic evidence of superior outcomes for extramedullary plasmacytoma of the head and neck. Otolaryngol Head Neck Surg 2013;148:974–981.
49. Kato T, Tsukamoto E, Nishioka T, et al. Early detection of bone marrow involvement in extramedullary plasmacytoma by whole-body F-18 FDG positron emission tomography. Clin Nucl Med 2000;25:870–873.
50. Schirrmeister H, Bommer M, Buck AK, et al. Initial results in the assessment of multiple myeloma using 18F-FDG PET. Eur J Nucl Med Mol Imaging 2002;29:361–366.
51. Nanni C, Rubello D, Zamagni E, et al. 18F-FDG PET/CT in myeloma with presumed solitary plasmocytoma of bone. In Vivo 2008;22:513–517.
52. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med 2007;356:2582–2590.
53. Mateos MV, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438–447.
54. Mateos MV, Hernández MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. Lancet Oncol 2016;17:1127–1136.
55. Lonial S, Jacobus S, Fonseca R, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. J Clin Oncol 2020;38:1126–1137.
56. San Miguel J, Mateos M-V, Gonzalez V, et al. Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria. J Clin Oncol 2019;37(15_suppl):8000–8000.
57. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood 2010;115:3416–3417.
58. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 2011;12:431–440.
59. Arnulf B, Pylypenko H, Grosicki S, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. Haematologica 2012;97:1925–1928.
60. FDA Safety Information. Accessed November 4, 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/202714s025lbl.pdf

61. Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol 2020;7:e370–e380.
62. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. Blood 2010;116:679–686.
63. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myélome. J Clin Oncol 2014;32:2712–2717.
64. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012;119:4375–4382.
65. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. Lancet 2017;389:519–527.
66. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). Blood Cancer J 2020;10:53.
67. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. Lancet Oncol 2020;21:1317–1330.
68. Okazuka K, Ishida T, Nashimoto J, et al. The efficacy and safety of modified bortezomib-lenalidomide-dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma. Eur J Haematol 2020;104:110–115.
69. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. Leukemia 2009;23:1337–1341.
70. Knop S, Liebisch P, Wandt H, et al. Bortezomib, IV cyclophosphamide, and dexamethasone (VelCD) as induction therapy in newly diagnosed multiple myeloma: Results of an interim analysis of the German DSMM Xia trial. J Clin Oncol 2009;27:8516–8516.
71. Reeder CB, Reece DE, Kukreti V, et al. Long-term survival with cyclophosphamide, bortezomib and dexamethasone induction therapy in patients with newly diagnosed multiple myeloma. Br J Haematol 2014;167:563–565.
72. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. Blood 2012;120:1801–1809.
73. Korde N, Zingone A, Kwok M, et al. Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone (CRd) in newly diagnosed multiple myeloma (MM) patients. [abstract] Blood 2012;120:732. (Abstract 732)
74. Korde N, Zingone A, Kwok M, et al. Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide extended dosing (CRD-R) induces high rates of MRD negativity in newly diagnosed multiple myeloma (MM) patients. [Abstract] Blood 2013;122:538–538.
75. Zimmerman T, Raje NS, Vij R, et al. Final results of a phase 2 trial of extended treatment (tx) with carfilzomib (CFZ), lenalidomide (LEN), and dexamethasone (KRd) plus autologous stem cell transplantation (ASCT) in newly diagnosed multiple myeloma (NDMM). Blood 2016;128:675–675.
76. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood 2020;136:936–945.
77. Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol 2014;15:1503–1512.
78. Facon T, Venner CP, Bahlis NJ, et al. Ixazomib Plus LenalidomideDexamethasone (IRd) vs PlaceboRd for Newly Diagnosed Multiple Myeloma (NDMM) Patients Not Eligible for Autologous Stem Cell Transplant: The Double-Blind, Placebo-Controlled, Phase 3 TOURMALINE-MM2 Trial [Abstract]. Abstract MM-347 presented at Society of Hematologic Oncology (SOHO) Eighth Annual Meeting 2020.
79. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol 2012;30:2946–2955.
80. Bringhen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood 2014;124:63–69.
81. Bringhen S, D'Agostino M, De Paoli L, et al. Phase 1/2 study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma. Leukemia 2018;32:979–985.
82. Bringhen S, Mina R, Petrucci MT, et al. Once-weekly versus twice-weekly carfilzomib in patients with newly diagnosed multiple myeloma: a pooled analysis of two phase I/II studies. Haematologica 2019;104:1640–1647.
83. Boccia RV, Bessudo A, Agajanian R, et al. A multicenter, open-label, phase 1b study of carfilzomib, cyclophosphamide, and dexamethasone in newly diagnosed multiple myeloma patients (CHAMPION-2). Clin Lymphoma Myeloma Leuk 2017;17:433–437.
84. Kumar SK, Buadi FK, LaPlant B, et al. Phase 1/2 trial of ixazomib, cyclophosphamide and dexamethasone in patients with previously untreated symptomatic multiple myeloma. Blood Cancer J 2018;8:70.
85. Dimopoulos MA, Grosicki S, Jędrzejczak WW, et al. All-oral ixazomib, cyclophosphamide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. Eur J Cancer 2019;106:89–98.
86. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. Lancet 2010;376:2075–2085.
87. Kaufman JL, Nooka A, Vrana M, et al. Bortezomib, thalidomide, and dexamethasone as induction therapy for patients with symptomatic multiple myeloma: a retrospective study. Cancer 2010;116:3143–3151.
88. Rosiñol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. Blood 2012;120:1589–1596.
89. Moreau P, Hulin C. Bortezomib, thalidomide and dexamethasone (VTD) is superior to bortezomib, cyclophosphamide and dexamethasone (VCD) prior to autologous stem cell transplantation for patients with de novo multiple myeloma. Results of the prospective IFM 2013-04 trial. Blood 2015;126:393–393.
90. Kumar SK, Lacy MQ, Hayman SR, et al. Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial. Am J Hematol 2011;86:640–645.
91. Pawlyn C, Brioli A, Gregory W, et al. Lenalidomide combined with cyclophosphamide and dexamethasone is effective and well tolerated induction treatment of newly diagnosed myeloma patients of all ages. Blood 2013;122:540–540.
92. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet 2019;394:29–38.
93. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. Br J Haematol 2019;185:492–502.
94. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol 2007;138:176–185.
95. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. Br J Haematol 2018;182:222–230.
96. Facon T, Kumar S, Plesner T, et al. Daratumumab plus lenalidomide and dexamethasone for untreated myeloma. N Engl J Med 2019;380:2104–2115.

97. Zepeda JHV, Duggan P, et al. Cyclophosphamide, bortezomib and dexamethasone (CyBORD) is a feasible and active regimen for non-transplant eligible multiple myeloma patients [Abstract}. Blood 2014; 124:5751–5751.
98. Zonder JA, Crowley J, Hussein MA, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared with HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): Results of the randomized, double-blinded, placebo-controlled SWOG Trial S0232. [abstract] Blood 2007;110:77. (Abstract 77)
99. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. Lancet Oncol 2010;11:29–37.
100. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906–917.
101. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med 2012; 366:1782–1791.
102. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366: 1770–1781.
103. Usmani SZ, Sexton R, Hoering A, et al. Second malignancies in total therapy 2 and 3 for newly diagnosed multiple myeloma: influence of thalidomide and lenalidomide during maintenance. Blood 2012;120: 1597–1600.
104. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. Lancet Oncol 2014;15:333–342.
105. Dimopoulos MA, Cheung MC, Roussel M, et al. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. Haematologica 2016;101: 363–370.
106. Hulin C, Belch A, Shustik C, et al. Updated outcomes and impact of age with lenalidomide and low-dose dexamethasone or melphalan, prednisone, and thalidomide in the randomized, phase III FIRST trial. J Clin Oncol 2016;34:3609–3617.
107. Dytfeld D, Jasielec J, Griffith KA, et al. Carfilzomib, lenalidomide, and low-dose dexamethasone in elderly patients with newly diagnosed multiple myeloma. Haematologica 2014;99:e162–e164.
108. Korde N, Roschewski M, Zingone A, et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. JAMA Oncol 2015;1:746–754.
109. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. N Engl J Med 2018;378:518–528.
110. Niesvizky R, Flinn IW, Rifkin R, et al. Community-based phase IIIB trial of three UPFRONT bortezomib-based myeloma regimens. J Clin Oncol 2015;33:3921–3929.
111. Niesvizky R, Flinn IW, Rifkin R, et al. Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: Results from all randomized patients in the community-based, phase 3b UPFRONT study. [abstract] Blood 2011;•••:118. (Abstract 478)
112. Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol 2011;86:57–65.
113. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. J Clin Oncol 2014;32:587–600.
114. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016;17:e328–e346.
115. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med 1996;335:91–97.
116. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003;348:1875–1883.
117. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. J Clin Oncol 2006;24: 929–936.
118. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myélome 9502 randomized trial. Blood 2002;99:731–735.
119. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005;23:9227–9233.
120. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 2014;371: 895–905.
121. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. J Clin Oncol 2010;28:4621–4629.
122. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell transplantation in patients with newly diagnosed multiple myeloma. Blood 2012;120:9–19.
123. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, bortezomib, and dexamethasone with transplantation for myeloma. N Engl J Med 2017;376:1311–1320.
124. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med 2003;349: 2495–2502.
125. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. J Clin Oncol 2007;25:2434–2441.
126. Sonneveld P, van der Holt B, Segeren C, et al. Intensive versus double intensive therapy in untreated multiple myeloma: Updated analysis of the randomized phase III study HOVON 24 MM. [abstract] Blood 2004; 104:948. (Abstract 948)
127. Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. Br J Haematol 2016;173:731–741.
128. Barlogie B, Attal M, Crowley J, et al. Long-term follow-up of auto-transplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. J Clin Oncol 2010;28:1209–1214.
129. Stadtmauer A, Pasquini M, Blackwell B, et al. Comparison of autologous hematopoietic cell transplant (autoHCT), bortezomib, lenalidomide (Len) and dexamethasone (RVD) consolidation with Len maintenance (ACM), tandem auto-HCT with Len maintenance (TAM) and AutoHCT with Len maintenance (AM) for up-front treatment of patients with Multiple Myeloma (MM): Primary results from the randomized phase III trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 – StaMINA Trial). Presented at the 2016 ASH Annual Meeting; December 3–6, 2016; San Diego, California.
130. Petrucci T, Raimondo FD, Zamagni E, et al. Upfront single versus double autologous stem cell transplantation for newly diagnosed multiple myeloma: An intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM Trial. Presented at the 2016 ASH Annual Meeting; December 3–6, 2016; San Diego, California.
131. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous transplantation, consolidation, and maintenance therapy in multiple myeloma: results of the BMT CTN 0702 Trial. J Clin Oncol 2019;37: 589–597.
132. Cook G, Liakopoulou E, Pearce R, et al. Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British Society of Blood and Marrow Transplantation Registry. Biol Blood Marrow Transplant 2011;17: 1638–1645.
133. Olin RL, Vogl DT, Porter DL, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplant 2009;43:417–422.
134. Burzynski JA, Toro JJ, Patel RC, et al. Toxicity of a second autologous peripheral blood stem cell transplant in patients with relapsed or recurrent multiple myeloma. Leuk Lymphoma 2009;50:1442–1447.

135. Alvares CL, Davies FE, Horton C, et al. The role of second autografts in the management of myeloma at first relapse. Haematologica 2006;91:141–142.
136. Fenk R, Liese V, Neubauer F, et al. Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. Leuk Lymphoma 2011;52:1455–1462.
137. Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:874–885.
138. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. Lancet Haematol 2016;3:e340–e351.
139. Kumar S, Mahmood ST, Lacy MQ, et al. Impact of early relapse after auto-SCT for multiple myeloma. Bone Marrow Transplant 2008;42:413–420.
140. Vangsted AJ, Klausen TW, Andersen NF, et al. Improved survival of multiple myeloma patients with late relapse after high-dose treatment and stem cell support, a population-based study of 348 patients in Denmark in 1994-2004. Eur J Haematol 2010;85:209–216.
141. Kumar SK, Dispenzieri A, Fraser R, et al. Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time. Leukemia 2018;32:986–995.
142. Kastritis E, Roussou M, Eleutherakis-Papaiakovou E, et al. Early relapse after autologous transplant is associated with very poor survival and identifies an ultra-high-risk group of patients with myeloma. Clin Lymphoma Myeloma Leuk 2020;20:445–452.
143. Bygrave C, Pawlyn C, Davies F, et al. Early relapse after high-dose melphalan autologous stem cell transplant predicts inferior survival and is associated with high disease burden and genetically high-risk disease in multiple myeloma. Br J Haematol 2020;bjh.16793.
144. Auner HW, Szydlo R, Rone A, et al. Salvage autologous stem cell transplantation for multiple myeloma relapsing or progressing after upfront autologous transplantation. Leuk Lymphoma 2013;54:2200–2204.
145. Jimenez-Zepeda VH, Mikhael J, Winter A, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: impact on progression-free and overall survival. Biol Blood Marrow Transplant 2012;18:773–779.
146. Sellner L, Heiss C, Benner A, et al. Autologous retransplantation for patients with recurrent multiple myeloma: a single-center experience with 200 patients. Cancer 2013;119:2438–2446.
147. Shah N, Ahmed F, Bashir Q, et al. Durable remission with salvage second autotransplants in patients with multiple myeloma. Cancer 2012;118:3549–3555.
148. Kyle RA. High-dose therapy in multiple myeloma and primary amyloidosis: an overview. Semin Oncol 1999;26:74–83.
149. Kumar A, Loughran T, Alsina M, et al. Management of multiple myeloma: a systematic review and critical appraisal of published studies. Lancet Oncol 2003;4:293–304.
150. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. Biol Blood Marrow Transplant 2003;9:4–37.
151. Zeiser R, Bertz H, Spyridonidis A, et al. Donor lymphocyte infusions for multiple myeloma: clinical results and novel perspectives. Bone Marrow Transplant 2004;34:923–928.
152. van de Donk NW, Kröger N, Hegenbart U, et al. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. Bone Marrow Transplant 2006;37:1135–1141.
153. Lokhorst HM, Wu K, Verdonck LF, et al. The occurrence of graft-versus-host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. Blood 2004;103:4362–4364.
154. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor lymphocyte infusions for relapsed multiple myeloma after allogeneic stem-cell transplantation: predictive factors for response and long-term outcome. J Clin Oncol 2000;18:3031–3037.
155. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor leukocyte infusions are effective in relapsed multiple myeloma after allogeneic bone marrow transplantation. Blood 1997;90:4206–4211.
156. Salama M, Nevill T, Marcellus D, et al. Donor leukocyte infusions for multiple myeloma. Bone Marrow Transplant 2000;26:1179–1184.
157. Tricot G, Vesole DH, Jagannath S, et al. Graft-versus-myeloma effect: proof of principle. Blood 1996;87:1196–1198.
158. Ayuk F, Shimoni A, Nagler A, et al. Efficacy and toxicity of low-dose escalating donor lymphocyte infusion given after reduced intensity conditioning allograft for multiple myeloma. Leukemia 2004;18:659–662.
159. Paiva B, Vidriales MB, Cerveró J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood 2008;112:4017–4023.
160. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol 2013;31:2540–2547.
161. Putkonen M, Kairisto V, Juvonen V, et al. Depth of response assessed by quantitative ASO-PCR predicts the outcome after stem cell transplantation in multiple myeloma. Eur J Haematol 2010;85:416–423.
162. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol 2017;4:e431–e442.
163. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide maintenance after autologous stem-cell transplantation in newly diagnosed multiple myeloma: a meta-analysis. J Clin Oncol 2017;35:3279–3289.
164. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. Blood 2011;118:2413–2419.
165. Alsina M, Becker PS, Zhong X, et al. Lenalidomide maintenance for high-risk multiple myeloma after allogeneic hematopoietic cell transplantation. Biol Blood Marrow Transplant 2014;20:1183–1189.
166. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 2012;366:1759–1769.
167. Singh P, Kumar SK, LaPlant BR, et al. Lenalidomide maintenance therapy in multiple myeloma: a meta-analysis of randomized trials. Blood 2013;122:407–407.
168. Musto P, Anderson KC, Attal M, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. Ann Oncol 2017;28:228–245.
169. Mellqvist UH, Gimsing P, Hjertner O, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. Blood 2013;121:4647–4654.
170. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2019;393:253–264.
171. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. J Clin Oncol 1998;16:593–602.
172. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. N Engl J Med 1996;334:488–493.
173. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. J Clin Oncol 2001;19:558–567.
174. Zervas K, Verrou E, Teleioudis Z, et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. Br J Haematol 2006;134:620–623.
175. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. Lancet 2010;376:1989–1999.
176. Jackson GH, Morgan GJ, Davies FE, et al. Osteonecrosis of the jaw and renal safety in patients with newly diagnosed multiple myeloma: Medical Research Council Myeloma IX Study results. Br J Haematol 2014;166:109–117.

177. Morgan GJ, Davies FE, Gregory WM, et al. Long-term follow-up of MRC Myeloma IX trial: survival outcomes with bisphosphonate and thalidomide treatment. Clin Cancer Res 2013;19:6030–6038.
178. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma: a network meta-analysis. Cochrane Database Syst Rev 2012;5: CD003188.
179. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of longer-interval vs standard dosing of zoledronic acid on skeletal events in patients with bone metastases: a randomized clinical trial. JAMA 2017;317: 48–58.
180. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol 2018;19:370–381.
181. Resende Salgado L, Chang S, Ru M, et al. Utilization patterns of single fraction radiation therapy for multiple myeloma. Clin Lymphoma Myeloma Leuk 2019;19:e238–e246.
182. Major PP, Coleman RE. Zoledronic acid in the treatment of hypercalcemia of malignancy: results of the international clinical development program. Semin Oncol 2001; 28(2, Suppl 6)17–24.
183. Pecherstorfer M, Steinhauer EU, Rizzoli R, et al. Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. Support Care Cancer 2003;11:539–547.
184. Lindsley H, Teller D, Noonan B, et al. Hyperviscosity syndrome in multiple myeloma. A reversible, concentration-dependent aggregation of the myeloma protein. Am J Med 1973;54:682–688.
185. Ludwig H, Fritz E, Kotzmann H, et al. Erythropoietin treatment of anemia associated with multiple myeloma. N Engl J Med 1990;322: 1693–1699.
186. Osterborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma–a randomized multicenter study. Blood 1996;87:2675–2682.
187. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia 2008;22:414–423.
188. Ikhlaque N, Seshadri V, Kathula S, et al. Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. Am J Hematol 2006;81:420–422.
189. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. Mayo Clin Proc 2005;80: 1568–1574.
190. Mateos MV. Management of treatment-related adverse events in patients with multiple myeloma. Cancer Treat Rev 2010;36(Suppl 2): S24–S32.
191. Siegel D, Martin T, Nooka A, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4 phase II clinical studies. Haematologica 2013;98:1753–1761.
192. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. J Clin Oncol 2008;26:4784–4790.
193. Mateos MV, Hernández JM, Hernández MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. Blood 2006;108: 2165–2172.
194. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. N Engl J Med 2005;352:2487–2498.

Individual Disclosures for the NCCN Multiple Myeloma Panel

Panel Member	Clinical Research Support/Data Safety Monitoring Board	Scientific Advisory Boards, Consultant, or Expert Witness	Promotional Advisory Boards, Consultant, or Speakers Bureau	Specialties
Kehinde Adekola, MD	Blood and Marrow Transplant Clinical Trials Network - BMT CTN	None	None	Medical Oncology; Hematology; and Internal Medicine
Larry Anderson, MD, PhD	Amgen Inc.; Bristol-Myers Squibb Company; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; and Karyopharm Therapeutics	Celgene Corporation; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; and Karyopharm Therapeutics	Celgene Corporation; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; and Karyopharm Therapeutics	Hematology, and Internal Medicine
Muhamed Baljevic, MD	None	Celgene Corporation	AlphaSights; Amgen Inc.; Bristol-Myers Squibb Company; Exelixis Inc.; GlaxoSmithKline; GLG; Guidepoint Global; Karyopharm Therapeutics; and Putnam Associates	Medical Oncology; Hematology; Internal Medicine; and Bone Marrow Transplantation
Natalie S. Callander, MD	None	None	None	Hematology, and Bone Marrow Transplantation
Erica Campagnaro, MD	None	None	None	Hematology
Jorge J. Castillo, MD	AbbVie, Inc.; BeiGene; Janssen Pharmaceutica Products, LP; Pharmacyclics, Inc.; and TG Therapeutics, Inc.	BeiGene; Janssen Pharmaceutica Products, LP; Pharmacyclics, Inc.; and Roche Laboratories, Inc.	None	Hematology
Jason C. Chandler, MD	None	AbbVie, Inc.; George Clinical; and Janssen Pharmaceutica Products, LP	None	Medical Oncology
Caitlin Costello, MD	Multiple Myeloma Research Foundation	Celgene Corporation; Karyopharm Therapeutics; Oncopeptides; and Takeda Pharmaceuticals North America, Inc.	None	Medical Oncology; Hematology; and Bone Marrow Transplantation
Yvonne Efebera, MD, MPH	None	None	Akcea Pharmaceutical; Janssen Pharmaceutica Products, LP; and Takeda Pharmaceuticals North America, Inc.	Hematology
Matthew Faiman, MD	None	None	None	Internal Medicine
Alfred Garfall, MD[a]	Janssen Pharmaceutica Products, LP; Novartis Pharmaceuticals Corporation; and Tmunity Therapeutics, Inc.	GlaxoSmithKline; Janssen Pharmaceutica Products, LP; and Surface Oncology	None	Hematology
Kelly Godby, MD	None	None	None	Medical Oncology
Jens Hillengass, MD	None	Adaptive; Bristol-Myers Squibb Company; GlaxoSmithKline; and Myeloma 360	Curio Science; Rapid Payer Response; and Research to Practice	Hematology
Leona Holmberg, MD, PhD[a]	Bristol-Myers Squibb Company; Janssen Pharmaceutica Products, LP; Merck & Co., Inc.; sanofi-aventis U.S.; Seattle Genetics, Inc.; and Takeda Pharmaceuticals North America, Inc.	None	None	Bone Marrow Transplantation, and Hematology
Myo Htut, MD	Celgene Corporation	None	None	Hematology, and Internal Medicine
Carol Ann Huff, MD	GlaxoSmithKline; Glenmark / Ichnos; Karyopharm Therapeutics; and sanofi-aventis U.S.	GlaxoSmithKline, and sanofi-aventis U.S.	None	Medical Oncology, and Hematology
Malin Hultcrantz, MD, PhD	Amgen Inc.; Daiichi-Sankyo Co.; and GlaxoSmithKline	None	None	Medical Oncology, and Hematology
Yubin Kang, MD	Apogee Biotechnology Corporation, and RedHill Pharmaceutical Co.	None	sanofi-aventis U.S.	Hematology; Medical Oncology; and Bone Marrow Transplantation
Shaji K. Kumar, MD	AbbVie, Inc.; Allogene Therapeutics; Bristol-Myers Squibb Company; Carsgen Therapeutics; Celgene Corporation; GlaxoSmithKline; MedImmune Inc.; Oncogene; Roche Laboratories, Inc.; Takeda Pharmaceuticals North America, Inc.; and Teneobio	AbbVie, Inc.; BeiGene; Celgene Corporation; Cellectar Biosciences, Inc.; Oncopeptides; Roche Laboratories, Inc.; and Takeda Pharmaceuticals North America, Inc.	None	Hematology, and Bone Marrow Transplantation
Sarah Larson, MD	AbbVie, Inc.; Bristol-Myers Squibb Company; Celgene Corporation; Janssen Pharmaceutica Products, LP; and Juno Therapeutics, Inc.	None	None	Medical Oncology
Michaela Liedtke, MD	Agios, Inc.; Allogene; Caelum Biosciences; Celator Pharmaceuticals, Inc.; Celgene Corporation; Genentech, Inc.; Janssen Pharmaceutica Products, LP; and Seattle Genetics, Inc.	Caelum Biosciences; Celgene Corporation; GlaxoSmithKline; and Tanabe	Amgen Inc., and Pfizer Inc.	Hematology
Thomas Martin, MD	Amgen Inc.; Janssen Pharmaceutica Products, LP; sanofi-aventis U.S.; and Seattle Genetics, Inc.	GlaxoSmithKline	None	Hematology
James Omel, MD	None	None	None	Patient Advocacy
Douglas Sborov, MD, MSc	Amgen Inc.; Bristol-Myers Squibb Company; Celgene Corporation; GlaxoSmithKline; and Janssen Pharmaceutica Products, LP	GlaxoSmithKline; Janssen Pharmaceutica Products, LP; and SkylineDX	None	Medical Oncology; Hematology; Internal Medicine; and Bone Marrow Transplantation
Kenneth Shain, MD, PhD	AbbVie, Inc., and Karyopharm Therapeutics	Bristol-Myers Squibb Company, and GlaxoSmithKline	Amgen Inc.; Bristol-Myers Squibb Company; GlaxoSmithKline; Janssen Pharmaceutica Products, LP; sanofi-aventis U.S.; and Takeda Pharmaceuticals North America, Inc.	Medical Oncology, and Hematology
Keith Stockerl-Goldstein, MD[a]	Cellerant Therapeutics, Inc.	None	None	Medical Oncology, and Bone Marrow Transplantation
Donna Weber, MD	None	None	None	Medical Oncology; Hematology; and Internal Medicine

The NCCN Guidelines Staff have no conflicts to disclose.
[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty:
Alfred Garfall, MD: University of Pennsylvania, royalties on licensed IP in the field of CAR T cell therapy
Leona Holmberg, MD, PhD: Up-To-Date
Keith Stockerl-Goldstein, MD: Abbott Laboratories; AbbVie, Inc.; and Novartis Pharmaceuticals Corporation