National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Multiple Myeloma

Version 2.2021 — September 9, 2020

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Discussion

***Shaji K. Kumar, MD/Chair ‡ ξ**
Mayo Clinic Cancer Center

***Natalie S. Callander, MD/Vice Chair ‡ ξ**
University of Wisconsin
Carbone Cancer Center

Muhamed Baljevic, MD † ‡ Þ ξ
Fred & Pamela Buffett Cancer Center

Erica Campagnaro, MD ‡
University of Michigan Rogel Cancer Center

Jorge J. Castillo, MD ‡
Dana-Farber/Brigham and Women's Cancer Center | Massachusetts General Hospital Cancer Center

Jason C. Chandler, MD †
St. Jude Children's Research Hospital/ The University of Tennessee Health Science Center

Caitlin Costello, MD † ‡ ξ
UC San Diego Moores Cancer Center

Yvonne Efebera, MD, MPH ‡
The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute

Matthew Faiman, MD Þ
Case Comprehensive Cancer Center/ University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute

Alfred Garfall, MD ‡
Abramson Cancer Center at the University of Pennsylvania

Kelly Godby, MD †
O'Neal Comprehensive Cancer Center at UAB

Jens Hillengass, MD ‡
Roswell Park Comprehensive Cancer Center

Leona Holmberg, MD, PhD ξ ‡
Fred Hutchinson Cancer Research Center/ Seattle Cancer Care Alliance

Myo Htut, MD ‡ Þ
City of Hope National Medical Center

Carol Ann Huff, MD † ‡
The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Yubin Kang, MD ‡ † ξ
Duke Cancer Institute

Ola Landgren, MD, PhD † ‡
Memorial Sloan Kettering Cancer Center

Sarah Larson, MD †
UCLA Jonsson Comprehensive Cancer Center

Michaela Liedtke, MD ‡
Stanford Cancer Institute

Thomas Martin, MD ‡
UCSF Helen Diller Family Comprehensive Cancer Center

James Omel, MD ¥
Patient Advocate

Douglas Sborov, MD, MSc † ‡ Þ ξ
Huntsman Cancer Institute at the University of Utah

Keith Stockerl-Goldstein, MD † ξ
Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine

Donna Weber, MD † ‡ Þ
The University of Texas MD Anderson Cancer Center

NCCN
Rashmi Kumar, PhD
Jennifer Keller, MSS

NCCN Guidelines Panel Disclosures

Continue

ξ Bone marrow transplantation
‡ Hematology
Þ Internal medicine
† Medical oncology
¥ Patient advocacy
* Discussion section writing committee

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/member_institutions.aspx.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference:
All recommendations are considered appropriate.

See NCCN Categories of Preference.

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Updates in Version 2.2021 of the NCCN Guidelines for Multiple Myeloma from Version 1.2021 include:

MYEL-G 3 of 3
- **Category 1 designation was added to daratumumab/carfilzomib/dexamethasone under Preferred Regimens**

Updates in Version 1.2021 of the NCCN Guidelines for Multiple Myeloma from Version 4.2020 include:

New pages added to the Guidelines:
- **Principles of Myeloma Therapy (MYEL-F) contains footnotes moved from the Therapy pages (MYEL-G 1, MYEL-G 2, and MYEL-G 3)**
- **Monoclonal Gammopathy of Clinical Significance (MGCS-1)**
- **Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, Skin Changes (POEMS-1, POEMS-2, POEMS-3, and POEMS-4)**

MYEL-1
- **Initial Diagnostic Workup**
  - **Bullet 4 revised to add: liver function tests**
  - **Last bullet revised to add: *gain/*amplification**
- **Useful in Certain Circumstances**
  - **Bullet 6 added: Hepatitis B testing and HIV screening as required**
  - **Bullet 10 added: Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS**
  - **Bullet 11 revised: Assess *for* circulating plasma cells ~~on bone marrow~~ as clinically indicated**

MYEL-3
- **Smoldering myeloma was divided into "Low risk" and "High risk"**
- **High-risk options were added: Clinical trial (preferred) or Lenalidomide in select patients (category 2B) or Observe at 3-mo intervals as clinically indicated**
- **Follow-Up Surveillance, bullet 3 revised: *Whole-body examination with* ~~Advanced imaging (ie, whole-body~~ MRI without contrast, low-dose CT scan, FDG PET/CT~~)~~ annually or as clinically indicated, ideally with the same technique used at diagnosis (also for MYEL-4)**
- **Footnote removed: See Staging Systems for Multiple Myeloma (MYEL-A).**
- **Footnote o added: 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.**
- **Footnote p revised: The NCCN Panel strongly recommends enrolling eligible smoldering myeloma patients ~~with high-risk criteria~~ in clinical trials.**

MYEL-4
- **Follow Up/Surveillance, bullet added: Consider minimal residual disease (MRD) as indicated for prognostication after shared decision with patient**
- **Footnote added: See Principles of Myeloma Therapy (MYEL-F).**

MYEL-5
- **Follow-Up/Surveillance, bullet 7 revised: ~~Assess~~ *Consider* MRD as indicated for ~~prognosis~~ *prognostication* after shared decision with patient**
- **Footnote x revised: ~~Allogeneic stem cell transplant in multiple myeloma preferentially should only be used in the setting of a clinical trial. Current data do not support miniallografting alone.~~ *Allogeneic stem cell transplant should preferentially be done in the context of a trial when possible. (*Also for MYEL-6 and MYEL-7)**

MYEL-B
- **Imaging for Initial Diagnostic Workup and Imaging of Solitary Plasmacytoma, bullet 1 revised: Whole-body *examination with*..."**

CONTINUED

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Updates in Version 1.2021 of the NCCN Guidelines for Multiple Myeloma from Version 4.2020 include:

- **Imaging for Follow-up of Smoldering Myeloma and Imaging for Follow-up of Multiple Myeloma: bullet 1 revised: Advanced *whole-body examination* with imaging (ie, ~~whole-body~~..."**

MYEL-D

- **Treatment Information/Dosing: bullets combined and remamed as "Solitary Plasmacytoma"**

MYEL-G 1 of 3

- **Other Recommended Regimens, regimen added: Daratumumab/lenalidomide/bortezomib/dexamethasone**
- **Useful in Certain Circumstances, regimen added: Daratumumab/cyclophosphamide/bortezomib/dexamethasone**
- **Footnote c added: See Principles of Myeloma Therapy (MYEL-F).**

MYEL-G 2 of 3

- **Other Recommended Regimens, regimen added: Daratumumab/cyclophosphamide/bortezomib/dexamethasone**

MYEL-G 3 of 3

- **The following regimens were moved from Preferred to Other Recommended Regimens:**
  - **Carfilzomib (twice weekly)/dexamethasone (category 1)**
  - **Elotuzumabx/lenalidomide/dexamethasone (category 1)**
- **The following regimen was moved from Preferred to Useful in Certain Circumstances**
  - **Carfilzomib (weekly)/dexamethasone**
- **The following were added as Other Recommended Regimens:**
  - **Belantamab mafodotin-blmf**
  - **Daratumumab/cyclophosphamide/bortezomib/dexamethasone**
- **The following regimens were moved from Other Recommended to Preferred Regimens**
  - **Daratumumab/carfilzomib/dexamethasone**
  - **Isatuximab-irfc/pomalidomide/dexamethasone (category 1)**
  - **Ixazomib/pomalidomide/dexamethasone**
  - **Pomalidomide/bortezomib/dexamethasone (category 1)**
- **The following regimens were moved from Other Recommended Regimens to Useful in Certain Circumstances**
  - **Bortezomib/dexamethasone (category 1)**
  - **Daratumumab**
  - **Ixazomib/dexamethasone**
  - **Lenalidomide/dexamethasone (category 1)**
  - **Panobinostat/carfilzomib**
  - **Panobinostat/lenalidomide/dexamethasone**
  - **Pomalidomide/dexamethasone (category 1)**
- **The following regimen was added as Useful in Certain Circumstances**
  - **Venetoclax/dexamethasone only for t(11;14) patients**

MYEL-H

- **Infection**
  - **Bullet 2 revised: Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening serious (<400 mg/dL) infection.**
  - **Bullet 4 revised by adding "herpes *zoster*"**
  - **Bullet 7 revised: Consider short-term 3 months of antibiotic prophylaxis at diagnosis for patients at high risk for infection.**

CONTINUED

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Updates in Version 1.2021 of the NCCN Guidelines for Multiple Myeloma from Version 4.2020 include:

MYEL-I

- **Bottom table name revised: ~~Pamidronate and Zoledronic Acid~~ *Bone-Modifying Agent* Dosing in Patients with Multiple Myeloma Who Have Renal Impairment**
  - **Denosumab section added to table**
- **Footnote added: Patients with creatinine clearance <30 cc/min can experience severe hypocalcemia and should be monitored.**

MGRS-1

- **Initial Workup**
  - **Defer renal biopsy if, bullet 2 revised: ~~Bland~~ *Normal* urinalysis**
- **Additional Workup**
  - **To confirm diagnosis of MGRS, bullet moved from Additional Workup as Clinically Indicated section below: Bone marrow biopsy, if suspected to have WM or MM**
  - **Bullet removed: Biopsy of suspected lesion**
- **Sub-heading revised: ~~Useful in certain circumstances~~ *Additional Workup as Clinically Indicated***

MGRS-2

- **Treatment, note below bullet 2 removed, "Note: Avoid neurotoxic agents such as vincristine and bortezomib" and footnote a added, "Systemic agents associated with neurotoxicity should be used with caution."**

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INITIAL DIAGNOSTIC WORKUP[a]

- History and physical exam (H&P)
- CBC, differential, platelet count
- Peripheral blood smear
- Serum BUN/creatinine, electrolytes, liver function tests, albumin,[b] calcium, serum uric acid, serum LDH,[b] and beta-2 microglobulin[b]
- Creatinine clearance (calculated or measured directly)[c]
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Serum free light chain (FLC) assay
- Whole-body low-dose CT scan or FDG PET/CT[d,e]
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multi-parameter flow cytometry
- Plasma cell fluorescence in situ hybridization (FISH)[b] panel on bone marrow[f] [del 13, del 17p13, t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/amplification, 1p deletion]

Useful In Certain Circumstances

- If whole-body low-dose CT or FDG PET/CT is negative, consider whole-body MRI without contrast to discern smoldering myeloma from multiple myeloma
- Tissue biopsy to confirm suspected plasmacytoma
- Plasma cell proliferation
- Serum viscosity
- HLA typing
- Hepatitis B and Hepatitis C testing and HIV screening as required
- Echocardiogram
- Evaluation for light chain amyloidosis, if appropriate (See NCCN Guidelines for Systemic Light Chain Amyloidosis)
- Single nucleotide polymorphism (SNP) array on bone marrow,[f] and/or next-generation sequencing (NGS) panel on bone marrow[f]
- Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS
- Assess for circulating plasma cells as clinically indicated

CLINICAL FINDINGS

- Solitary plasmacytoma → See Primary Treatment (MYEL-2)
- Smoldering myeloma (asymptomatic)[g] → See Primary Treatment (MYEL-3)
- Multiple myeloma (symptomatic)[g] → See Primary Treatment (MYEL-4)
- Monoclonal gammopathy of renal significance (MGRS) suspected → See Monoclonal Gammopathy of Renal Significance (MGRS-1)

[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).

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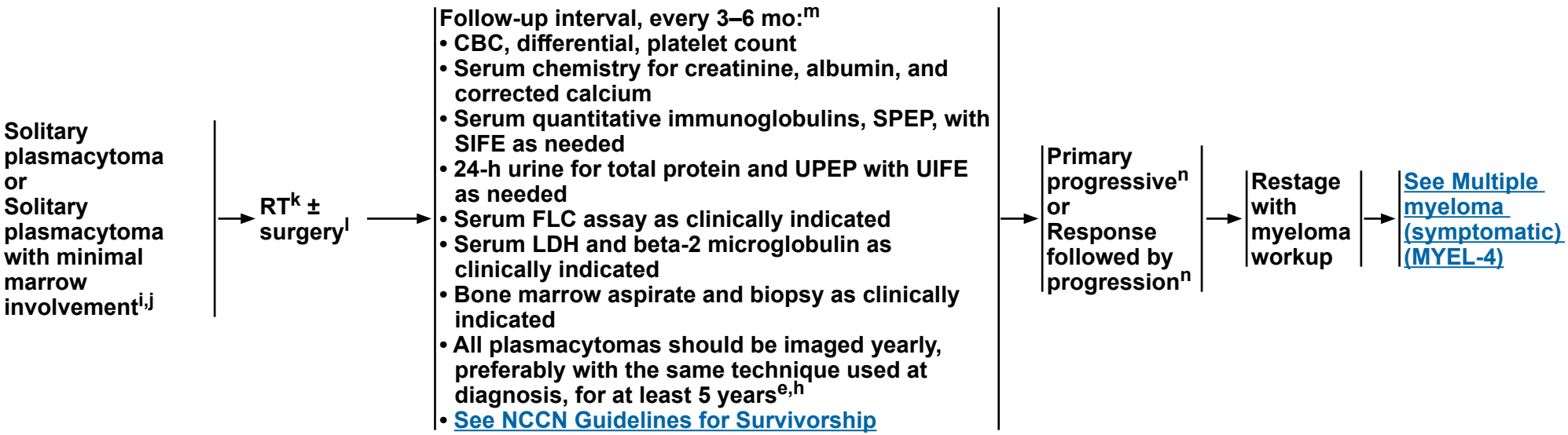

[e] See Principles of Imaging (MYEL-B).
[h] Whole-body MRI or PET/CT if MRI is not available is the first choice for initial evaluation of solitary osseous plasmacytoma (MRI of the spine and pelvis, whole-body PET/CT, or low-dose whole-body CT under certain circumstances). Whole-body PET/CT is the first 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).

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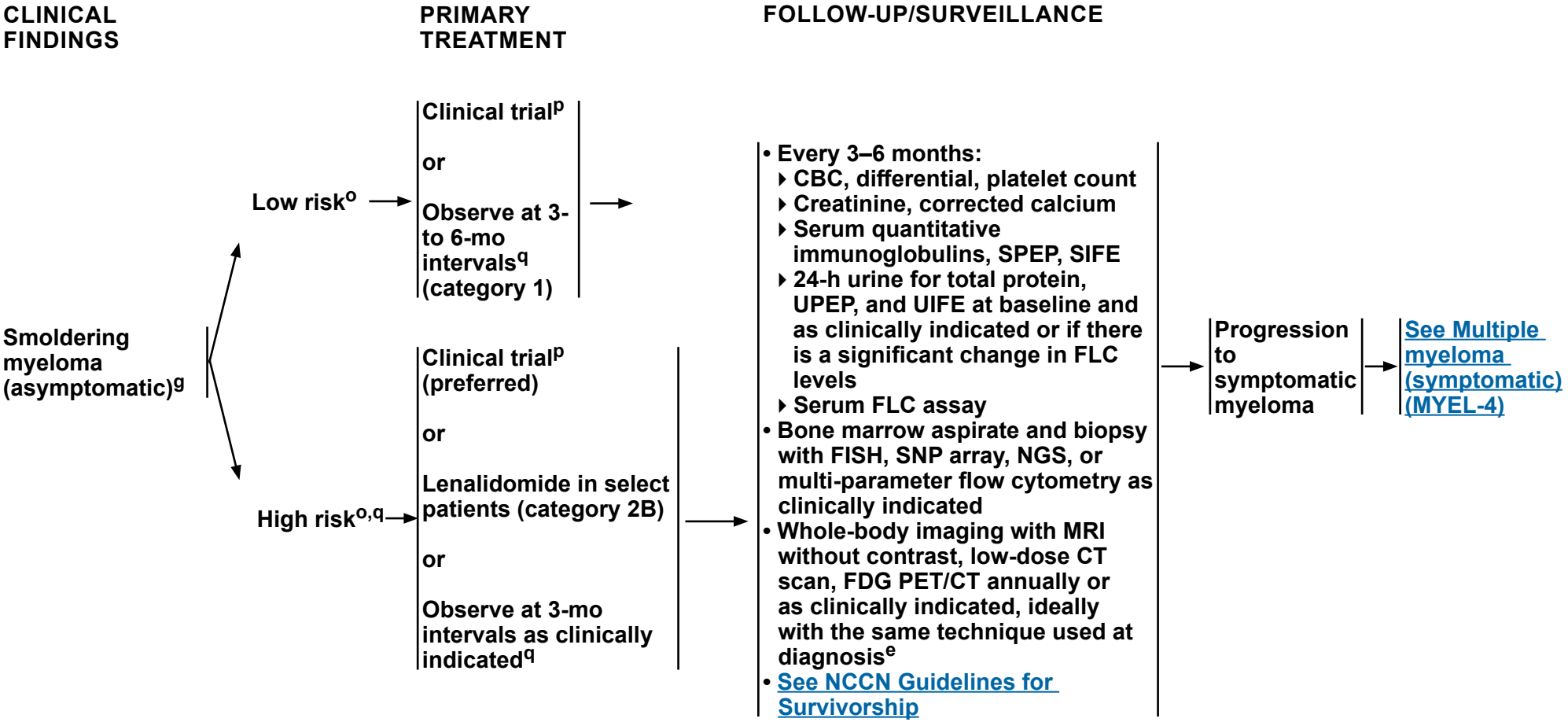

g See Definitions of Smoldering and Multiple Myeloma (MYEL-C).
º Bone marrow plasma cells (BMPC) % > 20%, M-protein > 2 g/dL, and serum free light chains (FLCr) > 20 are variables used to risk stratify patients at diagnosis. Patients with two or more of these risk factors are considered to have high 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.

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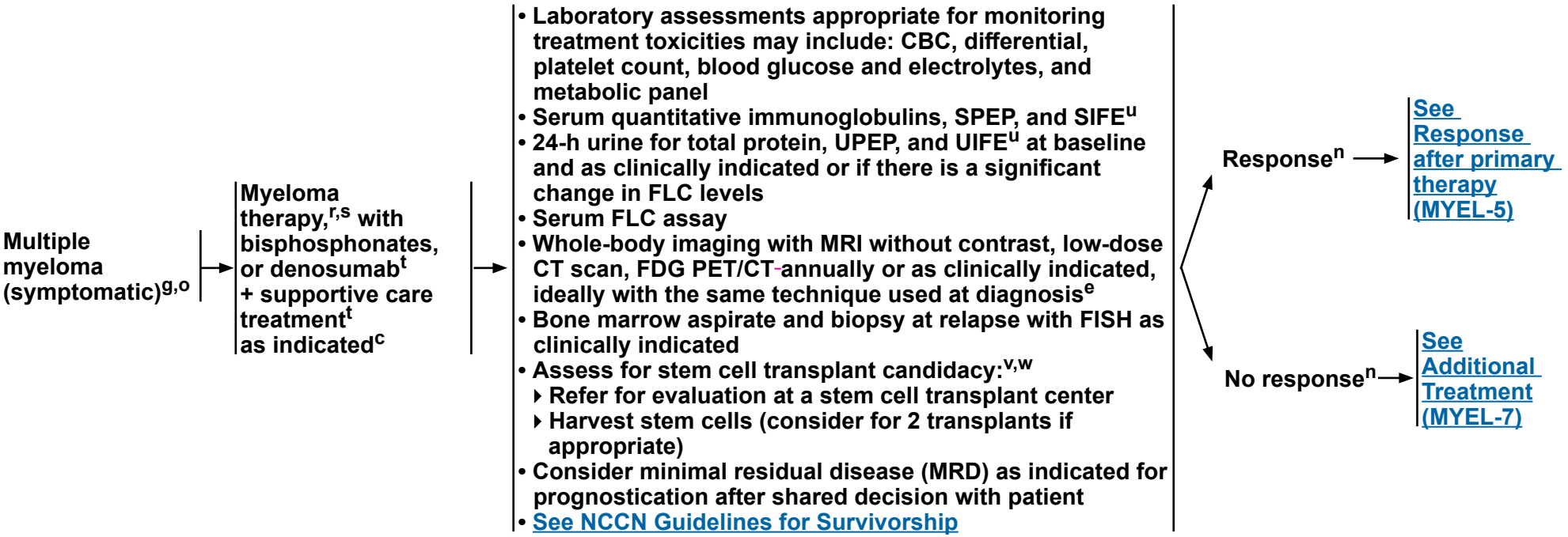

c See Management of Renal Disease in Multiple Myeloma (MYEL-I).
e See Principles of Imaging (MYEL-B).
g See Definitions of Smoldering and Multiple Myeloma (MYEL-C).
n See Response Criteria for Multiple Myeloma (MYEL-E).
o See Staging Systems for Multiple Myeloma (MYEL-A).
r See Myeloma Therapy (MYEL-G).
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 stem cell transplant. See Discussion.
w Renal dysfunction and advanced age are not contraindications to transplant.

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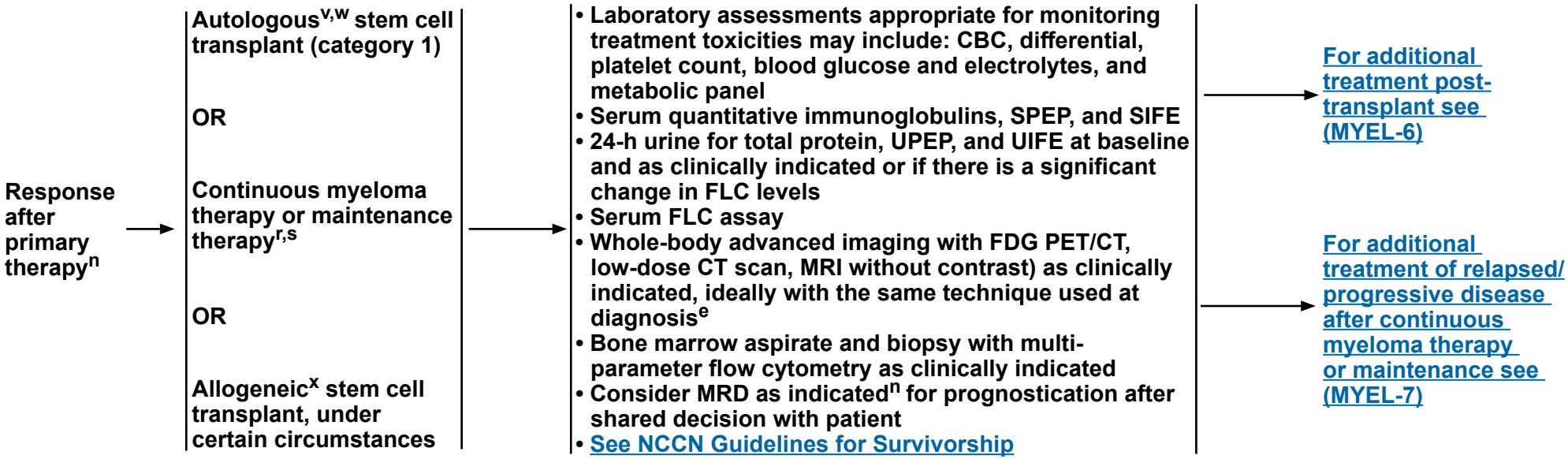
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MULTIPLE MYELOMA (SYMPTOMATIC)



FOLLOW-UP/SURVEILLANCE

[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 stem cell transplant. See Discussion.
[w] Renal dysfunction and advanced age are not contraindications to transplant.
[x] Allogeneic stem cell transplant should preferentially be done in the context of a trial when possible.

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MULTIPLE MYELOMA (SYMPTOMATIC)

ADDITIONAL TREATMENT

Post-autologous stem cell transplant (single or tandem):

Progressive disease[n] → **Therapy for previously treated myeloma[r,s]** or **Clinical trial** or **Allogeneic stem cell transplant[x]**

Response or stable disease[n] → **Maintenance therapy (category 1)[r]** or **Clinical trial** → **Progressive disease[n]** → **Therapy for previously treated myeloma[r,s]** or **Clinical trial ± additional autologous stem cell transplant[y]** or **Allogeneic stem cell transplant[x]**

Post-allogeneic stem cell transplant:

Progressive disease[n] → **Therapy for previously treated myeloma[r,s]** or **Clinical trial** or **Donor lymphocyte infusion**

Response or stable disease[n] → **Maintenance therapy on clinical trial** or **Observe** → **Progressive disease[n]** → **Therapy for previously treated myeloma[r,s]** or **Clinical trial** or **Donor lymphocyte infusion**

[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 stem 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 stem cell transplant and documented progression. Retrospective studies suggest a 2- to 3-year minimum length of remission for consideration of a second autologous stem cell transplant.

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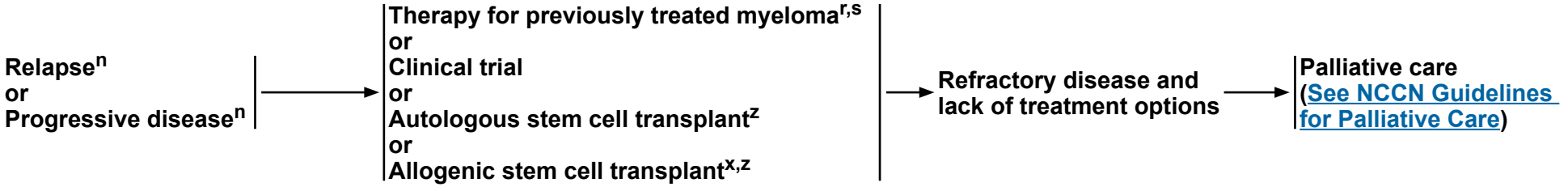
MULTIPLE MYELOMA (SYMPTOMATIC)

ADDITIONAL TREATMENT (FOR PATIENTS TREATED WITH OR WITHOUT A PRIOR TRANSPLANT)



[n] See Response Criteria for Multiple Myeloma (MYEL-E).
[r] See Myeloma Therapy (MYEL-G).
[s] See Principles of Myeloma Therapy (MYEL-F).
[x] Allogeneic stem cell transplant should preferentially be done in the context of a trial when possible.
[z] Assess for stem cell transplant candidacy.

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STAGING SYSTEMS FOR MULTIPLE MYELOMA[a]

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)
I	Serum beta-2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromosomal abnormalities by FISH[b] and Serum LDH ≤ the upper limit of normal
II	Not ISS stage I or III	Not R-ISS stage I or III
III	Serum beta-2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH[b] or Serum LDH > the upper limit of normal

[a] 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.
[b] Standard-risk: No high-risk chromosomal abnormality. High-risk: Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).

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PRINCIPLES OF IMAGING

Imaging for Initial Diagnostic Workup (for patients suspected of myeloma/solitary plasmacytoma)

- Whole-body imaging with low-dose CT or FDG PET/CT is recommended for initial diagnostic workup of patients suspected to have multiple myeloma or solitary plasmacytoma. Skeletal survey is acceptable in certain circumstances. However, skeletal survey is significantly less sensitive than whole-body low-dose CT and FDG PET/CT in detecting osteolytic lesions in patients with monoclonal plasma cell disorders.[a-e]
- If whole-body low-dose CT or FDG PET/CT is negative, whole-body MRI without contrast may be considered to discern smoldering myeloma from multiple myeloma.

Imaging of Solitary Plasmacytoma

- Whole-body imaging with MRI (or PET/CT if MRI is not available) is the first choice for initial evaluation of solitary osseous plasmacytoma, and whole-body FDG PET/CT is the first choice for initial evaluation of solitary extraosseous plasmacytoma. The sensitivity of FDG PET/CT for areas of increased metabolism and the high soft-tissue resolution of MRI enable both techniques to provide information on the presence or absence of solitary plasmacytomas. While the sensitivity of both techniques for the detection of focal lesions is similar, MRI provides a higher sensitivity for a diffuse infiltration.[f,g] No data exist on the comparison of FDG PET/CT and MRI in solitary plasmacytoma. In retrospective analyses, the risk of progression to multiple myeloma within 2 years of diagnosis has been shown to be higher with osseous plasmacytoma (35%) compared with extramedullary lesions (7%).[h] This might, at least in part, be due to undetected diffuse infiltration reflecting systemic disease, which makes the superior sensitivity of MRI significant in this regard.
- Since the risk of progression of solitary plasmacytoma into multiple myeloma or relapse is relatively high (14%–38% within the first 3 years of diagnosis), yearly follow-up with the same imaging technique used at first diagnosis should be performed for the first 5 years and subsequently only in case of clinical or laboratory signs or symptoms.[i]

Imaging for Follow-up of Smoldering Myeloma

- Advanced whole-body imaging (ie, MRI without contrast, low-dose CT scan, FDG PET/CT) is recommended annually or as clinically indicated. A retrospective analysis of 63 patients with smoldering myeloma with sequential whole-body MRI revealed that only 49% progressed over a follow-up period of 5.4 years. Patients with disease progression seen on MRI had a 16.5-time higher risk of clinical progression compared to those with no change on MRI.[j] Therefore, if imaging findings are the only parameters indicating initiation of treatment and if findings are doubtful, the same imaging technique should be repeated after 3–6 months. If only an MRI had been performed, whole-body low-dose CT should be done to exclude lytic lesions.

Imaging for Follow-up of Multiple Myeloma

- Advanced whole-body imaging (ie, FDG PET/CT, low-dose CT scan, whole-body MRI without contrast) is recommended as clinically indicated. Residual focal lesions detected by either FDG PET/CT or MRI have been shown to be of adverse prognostic significance.[k-n] Zamagni et al reported progression-free survival (PFS) of 44 months in patients with residual focal lesions on PET/CT versus 84 months for those without residual focal lesions on PET/CT after systemic treatment (P = .0009).[m] In the IMAJEM trial, both PFS and OS were significantly better in patients with negative PET/CT results before initiation of maintenance therapy (P = .011 and P = .033, respectively).[n] An analysis by Walker et al showed that conventional MRI normalizes over a prolonged period of time making PET/CT superior in this regard.[k] However, in small cohorts, functional imaging sequence for MRI called diffusion-weighted imaging was shown to have superior sensitivity to detect residual disease compared with FDG PET/CT.[o-q] Furthermore, unlike FDG PET/CT, MRI does not expose the patient to radiation.

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PRINCIPLES OF IMAGING
References

[a] Hillengass J, Moulopoulos LA, Delorme S, et al. Findings of whole body computed tomography compared to conventional skeletal survey in patients with monoclonal plasma cell disorders - a study of the International Myeloma Working Group [Abstract]. Blood 2016;128:4468.
[b] 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.
[c] Kropil 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.
[d] Wolf MB, Murray F, Kilk K, et al. Sensitivity of whole-body CT and MRI versus projection radiography in the detection of osteolyses in patients with monoclonal plasma cell disease. Eur J Radiol 2014;83:1222-1230.
[e] 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.
[f] Zamagni E, Nanni C, Patriarca F, et al. A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. Haematologica 2007;92:50-55.
[g] Fonti R, Salvatore B, Quarantelli M, et al. 18F-FDG PET/CT, 99mTc-MIBI, and MRI in evaluation of patients with multiple myeloma. J Nucl Med 2008;49:195-200.
[h] Nahi H, Genell A, Walinder G, et al. Incidence, characteristics, and outcome of solitary plasmacytoma and plasma cell leukemia. Population-based data from the Swedish Myeloma Register. Eur J Haematol 2017;99:216-222.
[i] Paiva B, Chandia M, Vidriales MB, et al. Multiparameter flow cytometry for staging of solitary bone plasmacytoma: new criteria for risk of progression to myeloma. Blood 2014;124:1300-1303.
[j] 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.
[k] Walker R, Barlogie B, Haessler J, et al. Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. J Clin Oncol 2007;25:1121-1128.
[l] Bartel TB, Haessler J, Brown TL, et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009;114:2068-2076.
[m] Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. Clin Cancer Res 2015;21:4384-4390.
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[p] Rasche L, Angtuaco E, McDonald JE, et al. Low expression of hexokinase-2 is associated with false-negative FDG-positron emission tomography in multiple myeloma. Blood 2017;130:30-34.
[q] Rasche L, Alapat D, Kumar M, et al. Combination of flow cytometry and functional imaging for monitoring of residual disease in myeloma. Leukemia 2019;33:1713-1722.

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DEFINITIONS OF SMOLDERING AND MULTIPLE MYELOMA

Smoldering Myeloma (Asymptomatic)[a]

- **Serum monoclonal protein ≥3 g/dL**

or

- **Bence-Jones protein ≥500 mg/24 h**

and/or

- **Clonal bone marrow plasma cells 10%–59%**

and

- **Absence of myeloma-defining events or amyloidosis**
  - **If skeletal survey negative, assess for bone disease with whole-body MRI, FDG PET/CT, or low-dose CT scan**

Multiple Myeloma (Symptomatic)[a,b]

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma

and

Any one or more of the following myeloma-defining events:

- **Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)**
- **Renal insufficiency (creatinine >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min**
- **Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)**
- **One or more osteolytic bone lesions on skeletal radiography, CT, or FDG PET/CT**
- **Clonal bone marrow plasma cells ≥60%**
- **Involved:uninvolved serum FLC ratio ≥100 and involved FLC concentration 10 mg/dL or higher**
- **>1 focal lesions on MRI studies ≥5 mm**

[a] 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.

[b] Other examples of active disease include: repeated infections, amyloidosis, light chain deposition disease, or hyperviscosity.

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PRINCIPLES OF RADIATION THERAPY

Solitary Plasmacytoma

General Principle:
- **Radiation therapy (RT) is the intervention of choice for solitary plasmacytoma.**

Treatment Information/Dosing:
- **Solitary Plasmacytoma (MYEL-2)**
  - **RT (40–50 Gy in 1.8–2.0 Gy/fraction) to involved field**

Multiple Myeloma

General Principles:
- **RT is primarily used for palliation in patients with multiple myeloma.**
- **RT should be used judiciously in patients with multiple myeloma who are undergoing or being considered for systemic therapy.**
- **Systemic therapy should not be delayed for RT.**
- **When systemic therapy and palliative RT are used concurrently, patients must be carefully monitored for toxicities.**

Palliative RT Dosing for MM:
- **Low-dose RT (8 Gy x 1 fraction or 10–30 Gy in 2.0–3.0 Gy fractions) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or for impending cord compression.**
- **Limited involved fields should be used to limit the impact of irradiation on stem cell harvest or impact on potential future treatments.**

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA
(Revised based on the new criteria by International Myeloma Working Group [IMWG])

IMWG criteria for response assessment including criteria for minimal residual disease (MRD)	
Response Category[a]	**Response Criteria**
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (next-generation flow [NGF], next-generation sequencing [NGS], or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years).[b]
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF[c] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher.
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using a validated equivalent method with a minimum sensitivity of 1 in 10^5 nucleated cells[d] or higher.
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding FDG PET/CT or decrease to less mediastinal blood pool standardized uptake value (SUV) or decrease to less than that of surrounding normal tissue.[e]
Standard IMWG response criteria[f]	
Stringent complete response	Complete response as defined below plus normal FLC ratio[g] and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells).[h]
Complete response[i]	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates.
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h.
Partial response	≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions)[j] of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a 25%–49% reduction in SPD[j] of soft tissue plasmacytomas is also required.

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Continued
Footnotes

RESPONSE CRITERIA FOR MULTIPLE MYELOMA
(Revised based on the new criteria by International Myeloma Working Group [IMWG])

Response Category[a]	Response Criteria
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease.
Progressive disease[k,l]	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0.5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD[j] of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease.
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD[j] of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non–myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein.
Relapse from complete response (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis[i]; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia) (see above).
Relapse from MRD negative (to be used only if the endpoint is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA
Footnotes

[a]All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

[b]Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

[c]Bone marrow MFC should follow NGF guidelines. The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilised mixture of antibodies, which reduces errors, time, and costs. Five million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells. Paiva B, Gutierrez NC, Rosinol L, et al, for the GEM (Grupo Españolde MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood 2012; 119: 687–91.

[d]DNA sequencing assay on bone marrow aspirate should use a validated assay.

[e]Criteria used by Zamagni and colleagues, and expert panel (IMPetUs; Italian Myeloma Criteria for PET Use). Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUVmax = 2.5 within osteolytic CT areas >1 cm in size, or SUVmax = 1.5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS. Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma.Clin Cancer Res 2015; 21: 4384–90.

[f]Derived from international uniform response criteria for multiple myeloma. Minor response definition and clarifications derived from Rajkumar and colleagues. When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response. Durie BG, Harousseau JL, Miguel JS, et al, for the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia 2006; 20: 1467–73.

[g]All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated serum FLC assay.

[h]Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

[i]Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

[j]Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

[k]Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

[l]In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

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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 Stem 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.

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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/cyclosphosphamide/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

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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.
[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

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MYELOMA THERAPY[a-d]

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[l,m]

Preferred Regimens

- Bortezomib/lenalidomide/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)[n]
- Daratumumab[f]/bortezomib/dexamethasone (category 1)
- Daratumumab[f]/carfilzomib/dexamethasone (category 1)
- Daratumumab[f]/lenalidomide/dexamethasone (category 1)
- Isatuximab-irfc/pomalidomide/dexamethasone (category 1)[o]
- Ixazomib/lenalidomide/dexamethasone (category 1)[n]
- Ixazomib/pomalidomide[p]/dexamethasone
- Pomalidomide[p]/bortezomib/dexamethasone (category 1)

Other Recommended Regimens

- Belantamab mafodotin-blmf[q]
- Bendamustine/bortezomib/dexamethasone
- Bendamustine/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone
- Carfilzomib/cyclophosphamide/dexamethasone
- Carfilzomib (twice weekly)/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[f]/cyclophosphamide/bortezomib/dexamethasone
- Daratumumab[f]/pomalidomide[r]/dexamethasone
- Elotuzumab/bortezomib/dexamethasone
- Elotuzumab[s]/lenalidomide/dexamethasone (category 1)[n]
- Elotuzumab/pomalidomide/dexamethasone[r]
- Ixazomib/cyclophosphamide/dexamethasone
- Panobinostat[u]/bortezomib/dexamethasone (category 1)
- Pomalidomide[p]/cyclophosphamide/dexamethasone
- Pomalidomide[p]/carfilzomib/dexamethasone

Useful In Certain Circumstances

- Bendamustine
- Bortezomib/dexamethasone (category 1)
- Carfilzomib/cyclophosphamide/thalidomide/dexamethasone
- Carfilzomib (weekly)/dexamethasone
- Daratumumab[f,v]
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)[h]
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)[h] ± bortezomib (VTD-PACE)[h]
- High-dose cyclophosphamide
- Ixazomib/dexamethasone
- Lenalidomide/dexamethasone[t] (category 1)
- Panobinostat[u]/carfilzomib
- Panobinostat[u]/lenalidomide/dexamethasone
- Pomalidomide[p]/dexamethasone[t] (category 1)
- 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 steroid-intolerant individuals.
[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.

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SUPPORTIVE CARE TREATMENT FOR MULTIPLE MYELOMA

Bone Disease
- All patients receiving primary myeloma therapy should be given bisphosphonates (category 1)[a] or denosumab.[b,c]
  - A baseline dental exam is strongly recommended.
  - Monitor for renal dysfunction with use of bisphosphonate therapy.
  - Monitor for osteonecrosis of the jaw.
- 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.
- *Pneumocystis jiroveci pneumonia* (PJP), herpes zoster, and antifungal prophylaxis should be given if receiving high-dose dexamethasone regimen.
- Test for hepatitis B before starting daratumumab.
- Herpes zoster prophylaxis for all patients treated with proteasome inhibitors, daratumumab, or elotuzumab.
- Consider 3 months of antibiotic prophylaxis at diagnosis for patients at high risk for infection.

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.
[c] 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.

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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.

MANAGEMENT OF RENAL DISEASE IN MULTIPLE MYELOMA[a]

Tests
- Serum creatinine, electrolytes, and uric acid
- Urinalysis, electrolytes, and sediment
- 24-h urine collection for protein and UPEP/UIFE
- SPEP/SIFE and serum FLCs
- Consider renal ultrasound, renal biopsy

Treatment Options
- Pulse dexamethasone
- Bortezomib-based regimen
- Consider third drug: cyclophosphamide, thalidomide, anthracycline, or daratumumab
- Can switch to other regimen once renal function has improved
- Use other plasma cell-directed therapy with caution
- See Response Criteria for Multiple Myeloma (MYEL-E)
- See Myeloma Therapy (MYEL-G)

Supportive Care
- Provide hydration to dilute tubular light chains; goal urine output is 100–150 cc/h
- Monitor fluid status
- Treat hypercalcemia, hyperuricemia, and other metabolic abnormalities
- Discontinue nephrotoxic medications
- Dialysis
  - Refractory electrolyte disturbances, uremia, and fluid overload
- Mechanical removal of serum FLCs; goal removal of 50%
  - High cutoff dialysis filters
  - Plasmapheresis
- Renal dosing of all medications

Recommendations for Lenalidomide Dosing in Patients with Multiple Myeloma Who Have Renal Impairment

Category	Renal Function (Cockcroft-Gault CL_{Cr})	Lenalidomide Dosing in Multiple Myeloma
Moderate renal impairment	CL_{Cr} ≥30 mL/min to <60 mL/min	10 mg every 24 h
Severe renal impairment	CL_{Cr} <30 mL/min (not requiring dialysis)	15 mg every 48 h
End-stage renal disease	CL_{Cr} <30 mL/min (requiring dialysis)	5 mg once daily; on dialysis days, dose should be administered after dialysis

CL_{Cr} = creatinine clearance

Bone-Modifying Agent Dosing in Patients with Multiple Myeloma Who Have Renal Impairment

Degree of Renal Impairment	Pamidronate (focal segmental glomerulosclerosis)	Zoledronic Acid (tubular cell toxicity)	Denosumab
None	90 mg IV over >2 h every 3–4 wks	4 mg IV over >5 min every 3–4 wks	120 mg SQ Q 4 weeks
Mild/moderate renal impairment	Use standard dose	Reduce dose	120 mg SQ Q 4 weeks
Severe renal impairment	60–90 mg over 4–6 h	Not recommended	120 mg SQ Q 4 weeks[b]

[a] Defined as serum creatinine >2 mg/dL or established glomerular filtration rate (eGFR) <60 mL/min/1.73 sqm.
[b] Patients with creatinine clearance <30 cc/min can experience severe hypocalcemia and should be monitored.

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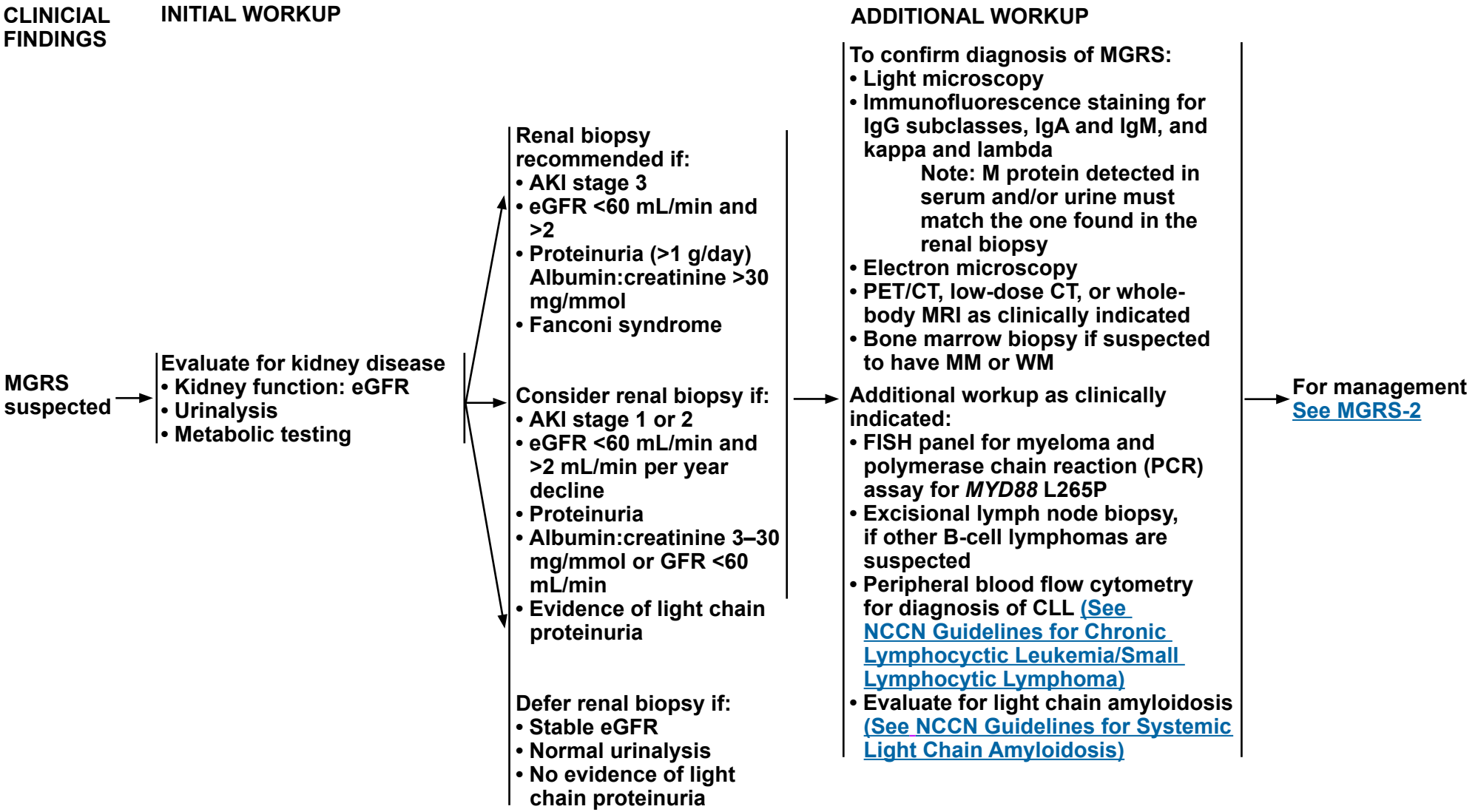
MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE



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MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

TREATMENT

- For IgG, IgA, or FLC MGRS, use the management algorithm for MM (See MYEL-4)
- For IgM MGRS, See NCCN Guidelines for Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma[a]
- For any MGRS with monoclonal B-cell lymphocytosis (MBL) features, See NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

→

RESPONSE ASSESSMENT

- For IgG- or IgA-associated MGRS, use the response criteria for MM[b]
- For IgM-associated MGRS, use the response criteria for WM (See NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma)
- For FLC-associated MGRS, use the response criteria for amyloidosis (See NCCN Guidelines for Systemic Light Chain Amyloidosis)
- For cases in which the causal monoclonal paraprotein is not detectable or is difficult to measure:
  - evaluate renal function
  - bone marrow involvement or radiologic findings

→ Relapse →

Individualize treatment based on response and toxicity of prior therapy, patient's performance status, and renal function at the time of relapse

[a] Systemic agents associated with neurotoxicity should be used with caution.
[b] See Response Criteria for Multiple Myeloma (MYEL-E).

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MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE (FOR MGRS SEE MGRS-1)

INITIAL WORKUP

IgM[a] MGNS suspected →

- Rule out other causes of neuropathy
  - Diabetes
  - Cobalamin deficiency
  - Thyroid dysfunction
  - Lyme disease
  - HIV infection
  - Syphilis
  - Autoimmune disease
  - Cryoglobulinemia
  - Evaluation for light chain amyloidosis, if appropriate (See NCCN Guidelines for Systemic Light Chain Amyloidosis)
- Anti-MAG antibodies[a]
- Ganglioside Antibody Panel
- Nerve conduction study (NCS)/ electromyogram (EMG)[a]
- Neurology consult
- *MYD88*,[b] L265P allele-specific PCR (AS-PCR) testing of bone marrow
- Chest/abdominal/pelvic CT with contrast when possible

Useful in certain circumstances
- Sural nerve biopsy
- *CXCR4* gene mutation testing

CLINICAL FINDINGS

→

High suspicion
- Sensory predominant
- Length dependent
- Slow progression (years)
- Bilateral and symmetrical
- Antibodies present
- Demyelination by EMG/NCS OR intermediate suspicion (not high or low suspicion) AND affecting activities of daily living (ADLs)

→ See NCCN Guidelines for Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Low suspicion
- Motor/pain predominant
- Non-length dependent
- Rapid progression (weeks to months)
- Unilateral/asymmetrical
- Antibodies not present
- No demyelination by EMG/NCS OR intermediate/high suspicion AND not affecting ADLs

→ Observation

[a] In patients presenting with suspected disease related to peripheral neuropathy, rule out amyloidosis in patients presenting with nephrotic syndrome or unexplained cardiac problems.
[b] *MYD88* wild-type occurs in <10% of patients and should not be used to exclude diagnosis of WM if other criteria are met.

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POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)

CLINICAL FINDINGS	INITIAL WORKUP	RECOMMENDED INITIAL TESTING	ADDITIONAL TESTING AS INDICATED	DIAGNOSIS
POEMS suspected	• Complete H&P examination • Evaluate for organomegaly • Fundoscopic exam • Hyperhidrosis • Diarrhea • Weight loss • Menstrual and sexual function • Skin examination for hyperpigmentation, hypertrichosis, acrocyanosis, glomeruloid hemangiomata, plethora, flushing, clubbing, etc. • Detailed neurologic history (numbness, pain, weakness, balance, orthostasis) and exam (sensation and motor function)	• Electrophysiologic (nerve conduction) studies • CT chest/abdomen/pelvis to document lymphadenopathy, organomegaly, ascites, pleural effusion, edema • Testosterone, estradiol, fasting glucose, thyroid-stimulating hormone, parathyroid hormone, prolactin, serum cortisol, luteinizing hormone • CBC, complete metabolic panel, serum immunoglobulins (IgG, IgA, IgM), electrophoresis and immunofixation, serum free light chain, 24-h urine total protein, vascular endothelial growth factor (VEGF), interleukin 6 (IL-6) • Bone marrow aspirate and biopsy, FISH panel for myeloma, and PCR • Echocardiography to assess right ventricular systolic and pulmonary artery pressures • CT body bone windows and or PET/CT for sclerotic bone lesions	• For criteria for diagnosis, see POEMS-3 • Sural nerve biopsy • Follicle-stimulating hormone, adrenocorticotropin hormone, cortrosyn stimulation test • Biopsy of bone lesion if needed	For management of POEMS syndrome, see POEM-2
			• Excisional lymph node biopsy, if Castleman's or other B-cell lymphomas are suspected • FISH panel for myeloma • Evaluate for light chain amyloidosis, if appropriate (See NCCN Guidelines for Systemic Light Chain Amyloidosis)	If diagnosis is MM, follow MM algorithm If diagnosis is WM, see NCCN Guidelines for WM/LPL If diagnosis is Castleman's disease, See NCCN Guidelines for B-Cell Lymphomas If diagnosis is AL amyloidosis, see NCCN Guidelines for Systemic Light Chain Amyloidosis

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POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)

TREATMENT

- Radiation therapy alone to isolated bone lesion (<3 sites) in patients without clonal bone marrow plasma cell
- Autologous stem cell transplant in patients who are eligible as sole therapy or as consolidation after induction therapy
  - Induction therapy options include:
    - ◊ Lenalidomide/dexamethasone
    - ◊ Bortezomib[a]/dexamethasone
    - ◊ Melphalan/dexamethasone
    - ◊ Cyclophosphamide/dexamethasone
    - ◊ Pomalidomide/dexamethasone
- In patients who are transplant ineligible, options include:
  - Lenalidomide/dexamethasone
  - Bortezomiba/dexamethasone
  - Melphalan/dexamethasone
  - Cyclophosphamide/dexamethasone
  - Pomalidomide/dexamethasone

→ See POEMS-4 for Response Criteria → Progression → Individualize treatment based on response and toxicity of prior therapy and patient's performance status at the time of progression

[a] Bortezomib may cause exacerbation of neuropathy.

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POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)

Table 1 Criteria for the Diagnosis of POEMS Syndrome[a]

Mandatory major criteria	**1. Polyneuropathy (typical demyelinating)**
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	**3. Castleman's disease[b]**
	4. Sclerotic bone lesions
	5. Vascular endothelial growth factor elevation
Minor criteria	**6. Organomegaly (splenomegaly, hepatomegaly, lymphadenopathy)**
	7. Extravascular volume overload (edema, pleural effusion, or ascites)
	8. Endocrinopathy (adrenal, thyroid,c pituitary, gonadal, parathyroid, pancreatic)
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[d]
Other signs and symptoms	**Clubbing, weight loss, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} levels**

[a] The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the other three major criteria, and one of the six minor criteria are present.
[b] There is a Castleman's disease variant of POEMS that occurs **without** evidence of a clonal plasma cell disorder that is not accounted for in this table. This entity should be considered separately.
[c] Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.
[d] Approximately 50% of patients will have bone marrow changes that distinguish it from a typical MGUS or myeloma bone marrow. Anemia and/or thrombocytopenia are distinctively unusual in this syndrome unless Castleman's disease is present.

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POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)

Table 2 Response Criteria for POEMS Syndrome

Parameter	Evaluable	Complete Response	Improvement	Progression[a]
Plasma VEGF	2x ULN	Normal[b]	50% reduction from baseline[b]	50% increase from lowest level
Hematologic	M-spike 0.5 g/dl,[c] 1.0 g/dL[d,e]	Negative serum and urine IFE and bone marrow[b]	50% reduction of M-spike from baseline[f]	25% increase from lowest level, which must be >0.5 g/DL
PET/CT	At least one lesion with FDG SUV_{max}[g]	No FDG uptake	50% reduction in sum of SUV_{max}[g]	30% increase in sum of SUV_{max}[g] from lowest level which must be at least 4 SUV_{max}[g] OR appearance of new FDG avid lesion
mNIS $+7_{POEMS}$	All patients	...	15% decrease from baseline (a minimum of 10 points)	15% increase from lowest value (a minimum of 10 points)
Ascites/effusion/edema	Present	Absent	Improved by 1 CTCAE grade from baseline	Worsened by 1 CTCAE grade from lowest grade
ECHO RVSP	≥40 mm Hg	...	<40 mm Hg	
Papilledema	Present		Absent	Worsening by 1 CTCAE grade
DLCO	<70% predicted	≥70% predicted	...	Worsening by 1 CTCAE grade

Abbreviations: IFE, immunofixation, ECHO, RVSP, echocardiogram right ventricular systolic pressure, DLCO, diffusing capacity of carbon monoxide.

[a] Any progression event (VEGF, hematologic, or clinical will be considered progression, assuming change is attributable to disease and not an adverse event. To document progression, option exists for repeating value. If confirmed, progression date is first date of suspected progression.
[b] For VEGF, M-spike, and IFE response documentation, blood values need to be repeated for verification.
[c] For VGPR evaluable.
[d] For PR evaluable.
[e] Quantitative IgA is acceptable surrogate for M-spike for proteins migrating in the beta region.
[f] VGPR is defined as no measurable monoclonal protein on serum or urine electrophoresis, but positive IFE.
[g] By body weight.

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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 indicated.

NCCN Categories of Preference	
Preferred intervention	Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability.
Other recommended intervention	Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes.
Useful in certain circumstances	Other interventions that may be used for selected patient populations (defined with recommendation).

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2021
Multiple Myeloma

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 06/19/19

Table of Contents

Overview

Multiple myeloma (MM) is a malignant neoplasm of plasma cells that accumulate in bone marrow, leading to bone destruction and marrow failure. MM accounts for about 1.8% of all cancers and slightly over 17% of hematologic malignancies in the United States.[1] Myeloma is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.[2] Myeloma 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 32,110 new myeloma cases in the United States in 2019, with an estimated 12,960 deaths.[1]

Newly diagnosed MM is typically sensitive to a variety of cytotoxic drugs. Although responses are typically durable, relapse is an expected part of the disease course and MM is not considered curable with current approaches. Treatment of MM has been rapidly evolving with the introduction of new classes and newer generation of drugs: immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies, and histone deacetylase (HDAC) inhibitors.[3,4] Other emerging immunotherapy approaches such as chimeric antigen receptor (CAR) T-cell therapy and bi-specific T-cell engagers (BiTEs) appear quite promising and will further change the treatment landscape.

The NCCN Guidelines for Multiple Myeloma address diagnosis, treatment, and follow-up for patients with MM.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Multiple Myeloma, an electronic search of the PubMed database was performed to obtain key literature in MM published since the last update of this Discussion section, using the following search terms: Smoldering Myeloma OR Multiple Myeloma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[5]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The results of the PubMed search were examined for their potential relevance. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available at www.NCCN.org.

Diagnosis and Workup

The initial diagnostic workup in all patients should include a history and physical examination and the following baseline blood studies and biological assessments to differentiate symptomatic and asymptomatic MM: a complete blood count (CBC) with differential and platelet counts; examination of peripheral blood smear; blood urea nitrogen (BUN); serum creatinine; creatinine clearance (calculated or measured directly) and serum electrolytes; 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.[6] Increased BUN and creatinine indicate decreased kidney function, whereas LDH and beta-2 microglobulin levels reflect tumor cell characteristics. These tests are essential for R-ISS staging.

Serum and Urine Analysis: The monoclonal protein (M-protein) components in serum and urine are evaluated by the following urine and serum analyses.

Serum analysis includes quantitative immunoglobulin levels (IgG, IgA, and IgM); serum protein electrophoresis (SPEP); and serum immunofixation electrophoresis (SIFE) to obtain 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: Use of serum free light-chain (FLC) assay along with SPEP and SIFE yields high sensitivity while screening for MM and related plasma cell disorders.[7] Therefore, this assay is now included as a part of the initial diagnostic workup in the NCCN Guidelines for Multiple Myeloma. The serum FLC assay also has prognostic value in plasma cell disorders, including monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, active myeloma, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.[7,8] The serum FLC assay also allows for quantitative monitoring of patients with light chain amyloidosis and oligosecretory myeloma. In addition to all of the above, the FLC ratio is required for documenting stringent complete response (sCR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.[9] The FLC assay cannot replace the 24-hour UPEP for monitoring patients with measurable urinary M-protein. Once the myeloma or M-protein is quantified, it is important to use the same test for serial studies to ensure accurate relative quantification.

Bone Marrow Evaluation: To evaluate bone marrow plasma cell infiltration, bone marrow aspiration and biopsy is recommended to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells.

Radiographic Evaluation: To evaluate for lytic bone lesions, full skeleton radiographic survey or whole body low-dose CT is recommended.[10-12] The latter is more sensitive in identifying bone lesions and is the preferred method.

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 diagnosis should include chromosome analysis by fluorescence in situ hybridization (FISH) performed with 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.[13-15] 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 MM patients 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.[16-19] 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.[20] The short arm is most often associated with deletions and the long arm with amplifications.[21] 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.[20,22]

Stratification of patients into various risk groups based on the chromosomal markers is being utilized by some centers for prognostic counseling, selection, and sequencing of therapy approaches.[23,24]

According to the NCCN Multiple Myeloma Panel members, the FISH panel for prognostic estimation of plasma cells should, at minimum, examine for t(4;14), t(14;16), 17p13 deletions, and chromosome 1 amplification. The utility of this information is to determine biological subtype and for prognostic recommendations as well as candidacy for clinical trials.

Gene Expression Profiling: In addition to cytogenetic markers of prognosis, gene expression signatures may be capable of discerning prognosis and helping rational therapeutic decisions.[25,26] Further understanding of the molecular subtypes of MM is emerging from the application of high-throughput genomic tools such as gene expression profiling (GEP).[27] With the currently available novel treatment approaches, a majority of patients with MM can now anticipate long-term disease control. However, patients with cytogenetically and molecularly defined high-risk disease do not receive the same benefit from certain approaches as the low-risk patients and need alternative therapies. GEP can provide additional prognostic information and further refine risk stratification, help therapeutic decisions, and inform novel drug design and development. Several groups have identified and developed 15-gene, 70-gene, and 92-gene models based on GEP signatures of MM cells.[28-30] Studies show that patients in the high-risk group based on the 15-gene,[28] 70-gene,[29] or 92-gene[30] models had shorter survival compared with the low-risk group. The NCCN Panel unanimously agreed that although GEP is not currently *routinely* used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment.

Bone Marrow Immunohistochemistry and Flow Cytometry: Immunohistochemistry and/or flow cytometry may be used to confirm presence of monoclonal plasma cells, and to more accurately quantify plasma cell involvement.[31] 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 indicateclonality. Specific immunophenotypic profiles of the myeloma cells may have prognostic implications.[32]

Additional Diagnostic Tests

The NCCN Multiple Myeloma Panel recommends additional tests that may be useful under some circumstances. These include whole body MRI[33] or whole body FDG PET/CT scan.[12] The majority of patients with active myeloma will have positive results on PET scan.[34,35] Whole body FDG PET/CT and MRI scans are more sensitive than plain radiographs and are

indicated when symptomatic areas show no abnormality on routine radiographs. Whole body FDG PET/CT results after induction therapy and stem cell transplant (SCT) help in predicting prognosis of patients with symptomatic MM.[36-38]

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.[39] Also, if amyloidosis is suspected, the diagnosis is established by following the recommendations outlined in the NCCN Guidelines for Systemic Light Chain Amyloidosis.

Serum viscosity should be evaluated when clinical symptoms of hyperviscosity are suspected, particularly in those with high levels of M-protein.

In selected patients with MM, allogeneic transplantation may be considered. In this approach, myeloablative or non-myeloablative/reduced-intensity therapy is administered with infusion of stem cells (ie, peripheral blood or bone marrow) obtained from a donor, preferably a human leukocyte antigen (HLA)-identical sibling. In such cases, the patient will need to be HLA-typed.

Based on the results of the clinical and laboratory evaluation discussed in previous sections, patients are initially classified as either having smoldering (asymptomatic) disease or active (symptomatic) disease. For definitions refer to *Definition of Multiple Myeloma (Smoldering and Active)* in the algorithm.

The IMWG recently updated the disease definition of MM to include biomarkers in addition to existing requirements of CRAB features.[40] The CRAB criteria that define MM include: hypercalcemia (>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 < 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.[40] The MM-defining biomarkers identified by the IMWG include one or more of the following: ≥60% clonal plasma cells in the bone marrow; involved/uninvolved FLC ratio of 100 or more with the involved FLC being ≥100 mg/L; or MRI with more than one focal lesion (involving bone or bone marrow).[40]

The criteria by the IMWG for smoldering (asymptomatic) patients include serum M-protein (IgG or IgA) ≥30 g/L and/or clonal bone marrow plasma cells 10% to 59% ***and*** absence of CRAB features, myeloma-defining events, or amyloidosis.[40] 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.[40] 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 of 29 months.[41]

Those with active myeloma can be staged using the International Staging System (ISS) or Durie-Salmon Staging System.[42] 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 recently revised to incorporate the serum LDH and high-risk FISH

abnormalities [t(4;14), t(14;16), 17p13 deletion] and is the preferred staging approach.[43]

Solitary Plasmacytoma

The diagnosis of solitary plasmacytoma requires a thorough evaluation to rule out the presence of additional lesions or systemic disease, because many patients presumed to have solitary plasmacytomas are found to have occult disease. Solitary plasmacytomas are further categorized as osseous or extraosseous. Osseous plasmacytoma is defined as a plasmacytoma emanating from bone without other evidence of disease. Solitary plasmacytomas derived from soft tissue are termed extraosseous.[44] An analysis of the SEER database between 1992 and 2004 found that incidence of osseous plasmacytoma was 40% higher than extraosseous plasmacytoma ($P < .0001$).[45]

Primary Therapy for Solitary Plasmacytoma

The treatment and follow-up options for osseous and extraosseous plasmacytomas are similar. Radiation therapy has been shown to provide excellent local control of solitary plasmacytomas.[46-52] The largest retrospective study (N = 258) included patients with solitary plasmacytoma (n = 206) or extramedullary plasmacytoma (n = 52).[53] 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%).[52]

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.[51,52,54]

For those patients with osseous plasmacytoma, the NCCN Panel recommends primary radiation therapy (40–50 Gy in 1.8–2.0 Gy/fraction) to the involved field followed by surgery if structurally unstable or if there are any issues related to neurologic compromise due to mass effect. For extraosseous plasmacytomas primary treatment is radiation therapy (40–50 Gy in 1.8–2.0 Gy/fraction)[49] to the involved field followed by surgery,[55] if necessary.

Surveillance/Follow-up Tests for Solitary Plasmacytoma

Follow-up and surveillance tests for both solitary plasmacytoma and extraosseous plasmacytoma consist of blood and urine tests. Serial and frequent measurements of M-protein are required to confirm disease sensitivity. 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 consider using the same imaging modality used during the initial workup for the follow-up assessments.

The blood tests include CBC; 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 under some circumstances.

The 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.[35,56,57] Imaging studies are recommended as clinically indicated.

If progression to myeloma occurs, then the patient should be re-evaluated as described in *Diagnosis and Workup*, 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.[58] Patients with Durie-Salmon stage I myeloma with low amounts of M-protein without significant anemia, hypercalcemia, or bone disease would be included in this category. Patients with asymptomatic smoldering MM may have an indolent course for many years without therapy.

Primary Therapy for Smoldering (Asymptomatic) Myeloma

Patients with smoldering myeloma do not need primary therapy, as it may take many months to years before the disease progresses. The risk of transformation to symptomatic myeloma[59] in these patients is life-long and therefore should be followed closely.

A relatively small, randomized, prospective, phase III study by the PETHEMA group investigated whether early treatment with lenalidomide and dexamethasone in patients (n = 125) with smoldering myeloma, at high risk of progression to active MM, prolongs the time to progression.[60] 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%; HR, 0.31; 95% CI, 0.10–0.91; *P* = .03).[60] At a median follow-up of 75 months (range, 27–57 months), treatment with lenalidomide and dexamethasone delayed median time to progression to symptomatic disease compared to no treatment (time to progression was not reached in the treatment arm compared to 23 months in the observation arm; HR, 0.24; 95% CI, 0.14–0.41).[61] The high OS rate seen after 3 years was also maintained (HR, 0.43; 95% CI, 0.20–0.90). Recently, the data from the randomized ECOG E3A06 trial was presented at the 2019 ASCO Annual Meeting. Lenalidomide given until progression or toxicity versus observation for patients with smoldering myeloma showed a progression-free advantage. The median 3-year PFS was 91% with lenalidomide treatment versus 66% for those under observation. The NCCN Panel strongly recommends that smoldering patients with high-risk features should be encouraged to join a clinical trial.[62]

According to the NCCN Panel, the flow cytometry-based high-risk criteria specified in the study is not uniformly available. Based on the criteria used in the trial, some patients with active myeloma were classified as having high-risk smoldering myeloma. The NCCN Panel strongly believes there is need to re-evaluate the definition of high-risk smoldering myeloma.[41] The panel believes that it is too early to begin treating *all* patients with smoldering myeloma at high risk (as defined in the trial) of progression to active MM with any anti-myeloma therapy. The NCCN Multiple Myeloma Panel recommends that patients with smoldering myeloma should initially be observed at 3- to 6-month intervals (category 1 recommendation) or strongly recommends enrolling eligible patients with smoldering myeloma in clinical trials.

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

The surveillance/follow-up tests include CBC; 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 and multiparameter flow cytometry may be used as clinically indicated

Skeletal survey or whole body low-dose CT is recommended as clinically indicated. Bone marrow aspiration and biopsy and imaging studies with MRI and/or CT and/or whole body FDG PET/CT are recommended as clinically indicated.[63] PET imaging seems to reliably predict active myeloma; by virtue of FDG uptake, low-level smoldering myeloma is typically negative on the PET scan.[34] It can also assess the extent of active disease, detect extramedullary involvement, or evaluate treatment response.[35,64-66] The NCCN Panel recommends considering using the same imaging modality used during the initial workup for the follow-up assessments.

Multiparameter flow cytometry is a newly available tool that can help individualize the follow-up/surveillance strategy for patients with smoldering myeloma. It measures abnormal cells in the bone marrow and provides information regarding the risk of progression to active myeloma. A high proportion of abnormal plasma cells within the bone marrow plasma cell compartment (>95%) has been shown to predict the risk of progression in patients with smoldering myeloma or MGUS, as has quantity and type of M-protein (non-IgG) and abnormal serum FLC assay.[67,68] According to the NCCN Multiple Myeloma Panel members, multiple parameter flow cytometry information may be a useful consideration in the follow-up/surveillance plan of patients with smoldering myeloma. Since this test is not standardized or widely available, they recommend that it should only be performed in laboratories with experience.

If the disease progresses to symptomatic myeloma, then patients should be treated according to the guidelines for symptomatic MM.

Active (Symptomatic) Multiple Myeloma

Primary Therapy for Active (Symptomatic) Multiple Myeloma

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and in selected patients, primary therapy is followed by high-dose chemotherapy with autologous SCT. Research into various primary regimens has focused on improving the response rates and depth of response in both transplant and non-transplant candidates. The NCCN Panel Members have noted that it is important to assess for response to primary therapy after every cycle of therapy.

Stem cell toxins, such as nitrosoureas or alkylating agents, may compromise stem cell reserve, and regimens with these agents (notably melphalan) should be avoided in patients who are potential candidates for SCT. Therefore, one of the first steps in evaluating patients with advanced 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 a stem cell center to assess stem cell candidacy is important.

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. PI-based regimens may be of value in patients with renal failure, and in those with certain adverse cytogenetic features.[69]

Bone disease, renal dysfunction, and other complications such as hypercalcemia, hyperviscosity, and coagulation/thrombosis should be treated with appropriate adjunctive measures (see *Supportive Care Treatment for Multiple Myeloma* in this Discussion). In all patients, careful

attention to supportive care is critical to avoid early complications that may compromise therapeutic outcome.

The page titled *Myeloma Therapy* in the algorithm has a list of primary therapy regimens recommended by the NCCN Multiple Myeloma Panel members for transplant and non-transplant candidates and also lists drugs recommended for maintenance therapy. The list is selected and is not inclusive of all regimens. The NCCN Multiple Myeloma Panel has categorized all myeloma therapy regimens as: "preferred," "other recommended," or "useful under 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, pre-existing comorbidities such as renal insufficiency, and in some cases access to certain agents.

The NCCN Panel prefers 3-drug regimens over 2-drug regimens as the standard of care for primary treatment of myeloma. This is based on improved response rates, depth of response, and rates of progression-free survival (PFS) or OS seen with 3-drug regimens in clinical trials. However, the panel notes that doublets could be used if a patient is elderly and/or frail and unable to tolerate a 3-drug regimen.

Prophylaxis with aspirin (81–325 mg) is recommended for those receiving an IMiD-based therapy. An anticoagulation agent is recommended for patients receiving an IMiD-based therapy and who are at high risk for thrombosis.

Prophylactic antiviral therapy is recommended for all patients receiving PI-based therapies.[70,71] 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.[71-74]

Carfilzomib can potentially cause cardiac and pulmonary toxicities.[75] Careful assessment before initiating treatment with carfilzomib and close monitoring during treatment is recommended.[75]

Preferred Primary Therapy Regimens for Transplant Candidates

Bortezomib-based 3-drug regimens have been listed as preferred primary therapy options for patients who are SCT eligible. These include bortezomib/lenalidomide/dexamethasone, bortezomib/doxorubicin/dexamethasone, and bortezomib/cyclophosphamide/dexamethasone.

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 222 patients to single-agent bortezomib administered either by the conventional intravenous (IV) route or by subcutaneous route.[76] The findings from the study demonstrate non-inferior efficacy with subcutaneous versus IV bortezomib with regard to the primary endpoint (overall response rate [ORR] after 4 cycles of single-agent bortezomib). Consistent results were shown with regard to secondary endpoints.[76] The results showed no significant differences in terms of time to progression or in one-year OS between groups.[76,77] However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy. The panel recommends herpes prophylaxis in patients receiving bortezomib therapy.

The NCCN Multiple Myeloma Panel recommends harvesting peripheral blood stem cells early in the course of primary treatment, preferably after 3 to 4 cycles of initial therapy.

Bortezomib/Lenalidomide/Dexamethasone

Phase II and III studies results have shown that primary therapy with bortezomib/lenalidomide/dexamethasone is active and well tolerated in all newly diagnosed patients with MM, transplant eligible as well as transplant ineligible.[78-80]

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% very good partial response (VGPR) or better and 52% complete response (CR)/near CR.[78] The benefits of bortezomib/lenalidomide/dexamethasone as primary therapy were also seen in the results of the phase II IFM 2008 trial[80] and phase II EVOLUTION trial.[79] In the phase II IFM 2008 trial, patients received bortezomib, lenalidomide, and dexamethasone as induction therapy followed by SCT.[80] Patients subsequently received two cycles of bortezomib/lenalidomide/dexamethasone as consolidation cycles and 1-year lenalidomide maintenance. VGPR rate or better at the completion of induction was 58%.[80] After transplantation and consolidation therapy the rate of VGPR or better was 70% and 87%, respectively.[80] 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.[79] The ORR after primary treatment with bortezomib/lenalidomide/dexamethasone followed by maintenance with bortezomib was 85% (51% ≥ VGPR and 24% CR) and corresponding one-year PFS was 83% in the bortezomib/lenalidomide/dexamethasone arm.[79]

This triplet was compared to lenalidomide/dexamethasone in the multicenter phase III SWOG S077 trial.[81] 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 months vs. 64 months; HR, 0.709; 95% CI, 0.524–0.959).[81] 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.[81]

Based on the significant improvement in PFS and OS seen with 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.[79,82,83] The trial by Reeder et al carried out 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.[82] 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%).[82] 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).[84]

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.[83]

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 one-year PFS rate was 93%.[79]

Based on data from these and other phase II studies, the NCCN Multiple Myeloma 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.

Twice-weekly bortezomib can be associated with toxicities that may limit efficacy caused by treatment delays or discontinuation. Therefore, Reeder et al modified the regimen to a once-weekly schedule of bortezomib.[85] In the study, patients treated with weekly bortezomib achieved responses similar to the twice-weekly schedule (ORR, 93% vs. 88%; 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).[85]

Other Recommended Primary Therapy Regimens for 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 SCT with significantly higher ORR.[86] No unexpected toxicities occurred, and del(13q) did not have a significant impact on response. Response rates improved with bortezomib maintenance (34% vs. 49%; $P < .001$).[86] After a median follow-up of 41 months, PFS in patients treated with bortezomib/doxorubicin/dexamethasone as primary therapy followed by SCT and bortezomib maintenance was 35 months versus 28 months in patients treated with VAD followed by SCT and maintenance with thalidomide. Patients treated with bortezomib/doxorubicin/dexamethasone had a significantly better PFS (HR, 0.75; 95% CI, 0.62–0.90; $P = .002$).[86] 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.[86] 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.[86]

Based on data from the HOVON-65/GMMG-HD4 trial and the uniform consensus among the NCCN Multiple Myeloma Panel members,

bortezomib/doxorubicin/dexamethasone is a category 1 option for primary therapy for transplant-eligible patients with MM.

Carfilzomib/Lenalidomide/Dexamethasone

Carfilzomib is a second-generation PI that binds highly selectively and irreversibly to the proteasome. It is administered intravenously. Carfilzomib has demonstrated anti-myeloma activity in patients with relapsed and/or refractory MM with an acceptable tolerability profile, including limited neuropathy after prolonged treatment.[87,88]

The safety and efficacy of carfilzomib in combination with lenalidomide and dexamethasone, as *primary* therapy for patients with MM, were evaluated in two single-arm trials.

First, a multicenter phase I/II trial evaluated the combination of carfilzomib, lenalidomide, and dexamethasone in newly diagnosed patients with MM.[89] In this trial, patients (n = 53) received carfilzomib with lenalidomide and low-dose dexamethasone. After 4 cycles, stem cells were collected from eligible patients.[89] Out of 35 patients from whom stem cells were collected, 7 proceeded to transplantation, and the remainder continued with carfilzomib/lenalidomide/dexamethasone.[89] 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%).[89]

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 SD received up to 24 cycles of lenalidomide 10 mg/d on days 1 to 21.[90] 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 non-hematologic 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%).[91]

The results of a 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 plus autologous SCT compared to 59% for carfilzomib/lenalidomide/dexamethasone and no autologous SCT. The 3-year PFS was 80% for carfilzomib/lenalidomide/dexamethasone alone and 86% for carfilzomib/lenalidomide/dexamethasone with autologous SCT patients. The 3-year OS was 96% for carfilzomib/lenalidomide/dexamethasone alone and 95% for carfilzomib/lenalidomide/dexamethasone with autologous SCT. The grade ≥3 adverse events, with autologous SCT versus autologous SCT, included lymphopenia (25% vs. 45%), neutropenia (25% vs. 30%), and infection (16% vs. 8%). In the carfilzomib/lenalidomide/dexamethasone with autologous SCT, 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).[92]

Based on the data from the above phase II studies, the NCCN Panel has included the carfilzomib, lenalidomide, and dexamethasone regimen as an option for primary treatment of transplant-eligible patients with MM. A phase III trial by the ECOG-ACRIN Cancer Research Group comparing

carfilzomib/lenalidomide/dexamethasone to bortezomib/lenalidomide/dexamethasone is currently recruiting patients (Clinical Trial ID: NCT01863550). The NCCN Panel strongly encourages participation in clinical trial.

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 studied an all-oral combination of ixazomib/lenalidomide/dexamethasone in patients with newly diagnosed MM.[93] The results of this trial show that the regimen was well tolerated and active in the study population. Out 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.

Based on these phase II results and the fact that the combination of other PIs (bortezomib or carfilzomib) in combination with lenalidomide/dexamethasone have been shown to be as effective as primary therapy in newly diagnosed MM,[81,89-91,94] the NCCN Panel has included ixazomib/lenalidomide/dexamethasone as an option (category 2B) for treatment of patients with newly diagnosed MM. An ongoing phase III trial is evaluating ixazomib/lenalidomide/dexamethasone versus lenalidomide/dexamethasone (Clinical trial ID: NCT01850524).

Regimens Useful Under Certain Circumstances for Transplant Candidates

While triple-drug regimens remain the preferred primary therapy option for patients with MM, selected patients such as those who are elderly or frail may be initially treated with regimens containing two drugs such as bortezomib/dexamethasone or lenalidomide/dexamethasone; a third drug could be added when the patient's condition improves.

Bortezomib/Dexamethasone

In the IFM cooperative group trial, 482 patients eligible for transplant were randomized to one of the following 4 primary therapy arms: VAD (n = 121) alone; VAD plus consolidation therapy with dexamethasone/cyclophosphamide, etoposide/cisplatin (DCEP; n = 121); bortezomib/dexamethasone (n = 121); or bortezomib/dexamethasone plus consolidation with DCEP (n = 119).[95] The primary endpoint was assessing response rate after primary therapy. The investigators evaluated the response according to modified European Group for Blood and Marrow Transplantation (EBMT) criteria,[96] including additional categories of near CR (CR but immunofixation-positive)[97] and VGPR (serum M-protein reduction ≥90%; urine light chain <100 mg/24 hours).[9] After primary therapy, the ORR (78.5% vs. 62.8%) and the rates of CR/near CR (14.8% vs. 6.4%) and VGPR (37.7% vs. 15.1%) were significantly higher with bortezomib/dexamethasone versus VAD.[95] At a median follow-up of 32.2 months, median PFS was modestly but not statistically significantly prolonged compared to VAD (36.0 months vs. 29.7 months).[95] Use of DCEP as consolidation therapy after primary therapy did not have a significant impact on the rates of response.[95] The bortezomib/dexamethasone regimen was equally effective in patients with high-risk MM, including those with ISS stage III disease and poor-risk cytogenetic abnormalities. The incidence of severe adverse events

reported was similar between the two groups. Hematologic toxicity and deaths related to toxicity were more frequent with VAD versus bortezomib/dexamethasone. The rates of grade 2 (20.5% vs. 10.5%) and grades 3 to 4 (9.2% vs. 2.5%) peripheral neuropathy during induction through first transplantation were significantly higher with bortezomib/dexamethasone compared to VAD.[95]

The IFM conducted a phase III randomized trial comparing bortezomib/dexamethasone with a combination of reduced doses of bortezomib and thalidomide plus dexamethasone.[98] The response rates achieved in the comparing bortezomib/dexamethasone arm seen in this study match those described in previous trials comparing VAD with bortezomib and dexamethasone.[95]

Patients with either t(4;14) or del(17p) are known to have a short event-free survival (EFS) and OS. A study analyzed a large series of patients (<65 years) with newly diagnosed transplant-eligible MM treated and t(4;14) or del(17p) treated with bortezomib/dexamethasone versus VAD as primary therapy before treatment.[69] The analysis demonstrated that bortezomib improves the prognosis (in terms of both EFS and OS; $P <$ .001 and $P <$ .001, respectively) of patients with t(4;14) compared with patients treated with VAD primary therapy.[69]

Based on these data and the uniform consensus among the NCCN Multiple Myeloma Panel members, bortezomib/dexamethasone is listed as a category 1 primary therapy option for transplant-eligible patients with MM under the category “useful under certain circumstances” because, as mentioned above, triple-drug regimens are preferred as primary therapy for transplant-eligible patients with MM. However, those with comorbid conditions such as with renal insufficiency may be treated with the bortezomib/dexamethasone doublet initially and a third drug could be added when renal insufficiency or overall condition improves.

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).[99]

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

Lenalidomide/Dexamethasone

Lenalidomide is a potent analogue of thalidomide. Like thalidomide, it is believed to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis and inhibition of angiogenesis and cytokine circuits, among others. Lenalidomide received approval from the U.S. Food and Drug Administration (FDA) for the treatment of relapsed/refractory MM in combination with dexamethasone. Lenalidomide and dexamethasone have also been investigated as primary therapy. The phase III randomized controlled study, S0232, by Southwest Oncology Group (SWOG) compared dexamethasone single agent with lenalidomide and dexamethasone for patients newly diagnosed with MM.[100] There were 198 patients enrolled; upon disease progression, patients on the dexamethasone arm were allowed to cross over to the open-label lenalidomide and dexamethasone arm. Participants with progressive disease (PD) on lenalidomide and dexamethasone (initially or after crossover) were removed from the protocol. Due to inferior efficacy of

dexamethasone alone and concern of combining high-dose dexamethasone with lenalidomide, the data safety monitoring committee permanently closed enrollment in this trial.[101] At the time the trial was closed, at the end of one year, the lenalidomide plus dexamethasone arm showed improved CR rate compared to dexamethasone alone (22.1% vs. 3.8%).[100] At 3 years, PFS remained superior for lenalidomide and dexamethasone: 52% versus 32%.[102] The OS was not different between the two arms. The 1-, 2-, and 3-year OS for lenalidomide and dexamethasone were 94%, 87%, and 79% versus 88%, 78%, and 73% for dexamethasone.

E4A03 was an open-label trial, with 445 newly diagnosed patients with MM randomly assigned to high-dose or low-dose dexamethasone regimens. The response was superior with high-dose dexamethasone. One hundred sixty-nine (79%) of 214 patients receiving high-dose therapy and 142 (68%) of 205 patients receiving low-dose therapy had CR or PR within 4 cycles.[103] At 1-year interim analysis, OS was 96% in the low-dose dexamethasone group compared with 87% in the high-dose group (P = .0002); 2-year OS was 87% versus 75%, respectively.

Fifty-two percent of patients on the high-dose regimen compared with 35% on the low-dose regimen had grade 3 or worse toxic effects in the first 4 months, including deep vein thrombosis (DVT) (26% vs. 12%); infections including pneumonia (16 vs. 9%); and fatigue (15% vs. 9%).

The effect of SCT and outcome of patients who continued the primary therapy in either group was analyzed at the end of 3 years.[103] The 3-year OS of patients who received 4 cycles of primary treatment with either dose followed by autologous SCT was 92%, suggesting that lenalidomide and dexamethasone is a reasonable choice for primary therapy before SCT. However, it should be noted that the choice to proceed to SCT was not randomized but based on physician and patient preference.[103]

The incidence of DVT is low with single-agent lenalidomide or lenalidomide plus low-dose dexamethasone, but risk rises when combined with high-dose dexamethasone. According to a recent report, patients treated with lenalidomide and high-dose dexamethasone that developed a venous thromboembolism (VTE) did not experience shorter OS or time to progression.[104] Prophylactic anticoagulation is recommended in patients receiving this therapy.[70,105]

A decrease in CD34-positive cells collected after prolonged lenalidomide treatment has been reported.[106,107] Guidelines by the IMWG suggest that patients treated with lenalidomide and dexamethasone should have stem cells collected within the first 4 cycles of therapy.[108] This inability to collect stem cells may be overcome by chemo-mobilization.[109] Addition of plerixafor can also allow stem cell mobilization when conventional mobilization methods fail.[110,111]

Lenalidomide/dexamethasone is listed as a category 1 primary treatment option in the NCCN Guidelines under the category “useful under certain circumstances,” noting that triple-drug regimens are preferred as primary therapy for transplant-eligible patients with MM. However, elderly or frail patients may be treated with doublet regimens. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Bortezomib/Thalidomide/Dexamethasone

Thalidomide attacks multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others. 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 SCT with high-dose melphalan and then consolidation therapy with the same primary regimen.[112] 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.[112] 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 SCT and subsequent consolidation therapy.[112] 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.[113] 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%).[113]

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%, $P = .002$).[114] The CR rate continued to be significantly higher after autologous SCT (46% vs. 24%) in patients treated with bortezomib/thalidomide/dexamethasone versus thalidomide/dexamethasone as primary therapy.[114]

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 SCT in patients (N = 340) with newly diagnosed MM.[115] 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.[115] The hematologic toxicity was greater in the CyBorD arm; however, higher rates of peripheral neuropathy were reported in the bortezomib/thalidomide/dexamethasone arm.[115]

No significant difference in OS was observed in any of the trials with bortezomib/thalidomide/dexamethasone. A longer follow-up period is required. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Bortezomib/thalidomide/dexamethasone is listed as a primary treatment option (category 1) under the category "useful under 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.

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

The total therapy 3 (TT3) trial evaluated induction therapy with the multi-agent 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.[116] This regimen is a potent combination of new agents as well as traditional chemotherapy agents.

This regimen is listed under the category "useful under 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 Non-Transplant Candidates

Many of the regimens described above for transplant candidates are also options for non-transplant candidates. As in transplant-eligible patients, 3-drug regimens are preferred by the NCCN Panel as these regimens have 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 non-transplant 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 SCT status.[78]

The randomized phase III SWOG S0777 trial (discussed in the transplant setting), comparing bortezomib/lenalidomide/dexamethasone to lenalidomide/dexamethasone as induction therapy without an intent of immediate transplantation, reported superior results with the 3-drug regimen.[81] The NCCN Panel included the bortezomib/lenalidomide/dexamethasone regimen as a category 1, preferred option for patients with MM not eligible for SCT.

Lenalidomide/Low-dose Dexamethasone

The results of the SWOG SO232 trial[100] that included transplant-ineligible patients and the ECOG E4A03 trial[103] 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 Transplant Candidates*).[103] 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.[103]

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.[117] 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; $P < .001$).[117] 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).[117]

There are several reports showing higher incidences of secondary malignancies when lenalidomide is used as a maintenance therapy post-transplantation or in a melphalan-containing regimen.[118-121] 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.[117] 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.[122]

Lenalidomide/low-dose dexamethasone is considered a category 1, preferred option by the NCCN Multiple Myeloma Panel for transplant-ineligible patients with MM, especially the frail or elderly patients with standard-risk features. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Based on the results of the FIRST trial,[117,123] the NCCN Panel recommends considering treatment with continuous lenalidomide/dexamethasone until disease progression for patients who are not eligible for transplant.

Bortezomib/Cyclophosphamide/Dexamethasone

The role of bortezomib/cyclophosphamide/dexamethasone as initial therapy for patients with MM ineligible for SCT was studied in a small phase II trial (n = 20).[124] 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 non-hematologic grade 3/4 adverse events (20%), including muscle weakness, sepsis, and pneumonia. Neutropenia and thrombocytopenia were seen in 2 patients (10%).[124]

Based on the above *and* the results from the EVOLUTION trial[79] (described earlier) that had included transplant-ineligible patients and the above phase II trial results,[124] the NCCN Panel has included bortezomib/cyclophosphamide/dexamethasone as a preferred option for non-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.

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.[125] 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 SCT.

Other Recommended Primary Therapy Regimens for 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.[89] 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 and with a median follow-up of 30.5 months. PFS rate reported was 79.6% (95% CI, 53.5–92.0) and OS was 100%.[94]

The phase II trial by Korde et al[97] 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,[97] and the regimen was found to be effective in individuals with high-risk disease.[126]

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 SCT.

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 SCT.[127] Out 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 an sCR. After a median follow-up of 18 months, the 2-year PFS and OS rates were 76% and 87%, respectively.[127] 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 SCT.

Ixazomib/Lenalidomide/Dexamethasone

A phase I/II study (discussed in the previous section for SCT-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.[93] 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 above 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 SCT.

Regimens Useful Under Certain Circumstances for Non-Transplant Candidates

Bortezomib/Dexamethasone

A U.S. community-based, randomized, open-label, multicenter, phase IIIb UPFRONT trial compared safety and efficacy of 3 highly active bortezomib-based regimens in previously untreated elderly patients with MM ineligible for SCT.[128] 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.[129] After a median follow-up of 42.7 months, the median PFS and OS were not significantly different between the 3 treatment arms.[128] Response rates, including CR and ≥VGPR, improved after bortezomib maintenance, with no concomitant increase in the incidence of peripheral neuropathy.

While 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 Multiple Myeloma Panel has included bortezomib/dexamethasone as a primary therapy as an option that is useful under certain circumstances for patients with MM who are ineligible for SCT.

Response Criteria

Assessing the response to treatment is a key determinant of myeloma treatment.

The updated IMWG response criteria definitions[9,130,131] for CR, sCR, immunophenotypic CR, molecular CR, VGPR, PR, minimal response (MR) for relapsed/refractory myeloma, stable disease (SD), and PD are outlined in *Response Criteria for Multiple Myeloma* in the algorithm. This has been recently updated to include measures of minimal residual disease (MRD) assessments. It is recommended that the IMWG uniform response criteria should be used in all clinical trials.[132]

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

Patients on treatment should be monitored for response to therapy and for symptoms related to disease and/or treatment. It is recommended to re-evaluate (after 1–2 cycles) with the laboratory tests for M-protein (with imaging and bone marrow examination if indicated) to determine treatment response or whether the primary disease is progressive. Potential transplant candidates should undergo a stem cell harvest after 4 to 6 cycles of therapy, collecting enough stem cells for two transplants (depending on the intended number of transplants and age) in anticipation of a tandem transplant or a second transplant as subsequent therapy. 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*) or observation can be considered beyond maximal response.

Consider using the same imaging modality used during the initial workup for the follow-up assessments. Follow-up tests after primary myeloma 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 and immunoglobulins. The serum FLC may be assessed as clinically indicated (especially in patients with oligo- or non-secretory MM). According to the NCCN Panel, response should be assessed using the IMWG criteria.[9]

Other tests such as skeletal survey, whole body low-dose CT, bone marrow aspiration and biopsy, skeletal MRI, and whole body FDG PET/CT

scan may be performed as indicated by symptoms to detect disease progression.

Transplant Eligibility

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

Stem Cell Transplants

High-dose therapy with stem cell support is a critical component in the treatment plan of eligible patients newly diagnosed with MM. The types of SCT may be single autologous SCT, a tandem SCT (a planned second course of high-dose therapy and SCT within 6 months of the first course), or an allogeneic SCT. An allogeneic SCT can be performed after prior myeloablative therapy or after nonmyeloablative therapy. Nonmyeloablative therapy, also referred to as “mini transplant,” has been investigated as a technique to decrease toxicity of the allotransplant while preserving the alloimmune graft-versus-myeloma effect.[133,134] It is important to note that nonmyeloablative allogeneic transplant by itself is not adequate therapy and is usually done following maximal tumor control through adequate induction therapy or an autologous SCT. An allogeneic SCT may also follow an autologous SCT.

The NCCN Guidelines for Multiple Myeloma indicate that all types of SCT are appropriate in different clinical settings; these indications are discussed further below. In general, all candidates for high-dose chemotherapy must have sufficient liver, renal, pulmonary, and cardiac function. However, renal dysfunction is not an absolute contraindication to transplant. Earlier studies of autologous transplant included total body irradiation (TBI) as a component of the preparative regimen. Regimens with chemotherapy have been shown to have equivalent efficacy and less toxicity than TBI. TBI regimens have now been abandoned,[135] but newer, potentially less toxic radiation techniques aimed to deliver total marrow irradiation while reducing toxicities to non-target organs are currently undergoing evaluation in clinical trials.[136]

Autologous Stem Cell Transplants

Autologous SCT 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 SCT is associated with statistically significantly higher response rates and increased OS and EFS when compared with the response of similar patients treated with conventional therapy.[137] 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 to 42 months for standard therapy).[138] Barlogie and colleagues reported on the results of an American trial that randomized 510 patients to receive high-dose therapy with autologous stem cell support or standard therapy.[139] With a median follow-up of 76 months, there were no differences in response rates, PFS, or OS between the two groups. The reason for the discrepant results are 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 TBI as part of the high-dose regimen; TBI has subsequently been found to be inferior to high-dose melphalan.[135]

Another trial included 190 patients 55 to 65 years of age randomized to standard or high-dose therapy.[140] 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.

The choice of early versus late transplant was examined in a randomized French trial, and the results in both arms are comparable with respect to OS.[141] However, early SCT was superior in terms of quality of life, assessed as time without symptoms and side effects from therapy.[141] However, these early randomized studies of autologous SCT after primary therapy were designed and implemented before the availability of newer drugs.

A phase III study compared high-dose melphalan followed by autologous SCT 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 four groups: high-dose therapy and autologous SCT followed by maintenance with lenalidomide; high-dose therapy and SCT alone; primary therapy with MPR followed by lenalidomide; and primary therapy with lenalidomide alone.[142] At a median follow-up of 51 months, SCT resulted in longer median PFS (43 vs. 22 months; HR 0.44; 95% CI, 0.32–0.61) and OS (82% vs. 65% at four years; HR 0.55; 95% CI, 0.32–0.93).[142]

Results from the IFM 2005/01 study of patients with symptomatic myeloma 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 Transplant Candidates*).[95] Responses were evaluated after primary treatment and post-autologous SCT. After the first autologous SCT, CR/near-CR rates were 35.0% in the bortezomib plus dexamethasone arm, compared with 18.4% in the VAD arm.[95] 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.[95] 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).[95]

In another study, 474 patients were randomized to primary therapy with bortezomib/dexamethasone/thalidomide (n = 236) or thalidomide/dexamethasone (n = 238) before double autologous SCT and as consolidation therapy after SCT.[143] 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 SCT, improved incremental responses were still seen with bortezomib/dexamethasone/thalidomide compared with thalidomide plus dexamethasone.[143]The IFM 2009 phase III trial compared the efficacy and safety of bortezomib/lenalidomide/dexamethasone alone versus bortezomib/lenalidomide/dexamethasone plus autologous SCT for the treatment of newly diagnosed MM in patients 65 years or younger.[144] 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 SCT (P < .001).[144] There was a clear improvement in PFS with SCT (50 months vs. 36 months). These results clearly show the benefit of autologous SCT, with higher rates of durable responses in those with no MRD after initial therapy.[144] 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 SCT and the one that did not. [144]

Although autologous SCT improved PFS it did not improve OS, suggesting that delaying SCT is an option and is not associated with negative effects on OS. According to the NCCN Guidelines, for transplant-eligible patients autologous SCT is an option after primary induction therapy (category 1) and for treatment of progressive/refractory disease after primary treatment.

Tandem Stem Cell Transplants

Tandem SCT refers to a planned second course of high-dose therapy and SCT 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.[145] 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 SCT. The probability of EFS for 7 years after the diagnosis was 10% in the single transplant group compared to 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.[140,146-148] 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[146] 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 SCT was seen in patients who do not achieve a CR or VGPR (>90% reduction in M-protein level) with the first procedure. These two studies were not adequately powered to evaluate the equivalence of one versus two 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 found that tandem transplantations were superior to both single transplantations and standard therapies.[149] Also, post-relapse survival was longer when EFS was sustained for at least 3.5 years after tandem transplantation.[149-150] A recently reported result of an intergroup, multicenter, phase III study (EMN02/HO95 MM trial) suggests that tandem autologous SCT for newly diagnosed MM appears to be superior in extending PFS compared with single autologous SCT after induction therapy with a bortezomib-based regimen.[151] However, in a recently published study, patients were randomly assigned after initial SCT to receive a second SCT followed by lenalidomide maintenance; four cycles of bortezomib, lenalidomide, and dexamethasone followed by

lenalidomide maintenance; or lenalidomide maintenance alone.[152] At 38 months, all three arms showed similar PFS and OS.

The NCCN Multiple Myeloma Panel recommends collecting enough stem cells for 2 transplants in *all* eligible patients. According to the NCCN Multiple Myeloma Panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT. The support for use of maintenance therapy after tandem transplant comes from the study by Palumbo et al[142] (discussed in the previous section, page MS-22), which addressed the role of maintenance therapy with lenalidomide after autologous transplantation.[142] 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.[142]

A second autologous SCT can be considered at the time of disease relapse. A retrospective case-matched control analysis was performed comparing patients who underwent a second autologous SCT to those treated with conventional chemotherapy for relapsed MM.[153] Similar to previously published smaller studies,[154-156] this retrospective analysis demonstrated that a second autologous SCT 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 SCT. 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.[156,157]

A multicenter, randomized phase III trial compared treatment with high-dose melphalan plus second autologous SCT with cyclophosphamide in patients with relapsed MM who had received autologous SCT as primary treatment.[158] The patients included in the study were greater than 18 years of age and needed treatment for progressive or relapsed disease at least 18 months after a previous autologous SCT. All patients first received bortezomib/doxorubicin/dexamethasone induction therapy. Patients with adequately harvested stem cells then were randomized to high-dose melphalan plus second autologous SCT (n = 89) or oral cyclophosphamide (n = 85). The primary endpoint was time to disease progression.[158] After a median follow-up of 31 months, median time to progression in patients who underwent second autologous SCT 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 SCT versus cyclophosphamide.[158] Median OS in the SCT group was 67 months versus 52 months in the cyclophosphamide maintenance group.[159]

According to the NCCN Multiple Myeloma Panel, repeat autologous SCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding SCT and documented progression. Data from retrospective studies[160-163] suggest 2 to 3 years as the minimum length of remission for consideration of second autologous SCT for relapsed disease.

Allogeneic Stem Cell Transplant

Allogeneic SCT includes either myeloablative or nonmyeloablative (ie, "mini" transplant) transplants. Allogeneic SCT has been investigated as an alternative to autologous SCT 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 nonmyeloablative 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 SCT, but multiple case series have been published describing allogeneic SCT as an initial therapy or as therapy for relapsed/refractory MM. In a 1999 review, Kyle reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured.[164] Other reviews have also reported increased morbidity without convincing proof of improved survival.[165,166] However, there are intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.[139] 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 SCT, particularly given the lack of a significant cure rate for single or tandem autologous SCT.

The NCCN Guidelines consider myeloablative allogeneic SCT an accepted option, preferably in a clinical trial in: 1) patients whose disease responds to primary therapy; 2) patients with primary PD; or 3) patients with PD after an initial autologous SCT.

Another strategy that has been investigated is initial autologous SCT followed by a mini-allogeneic transplant. A prospective trial by Bruno et al[167] showed that, among patients (<65 years) with HLA-matched siblings who received an autograft-allograft regimen, CR rate after allografting was 55%, compared with 26% after double autograft in patients without HLA-matched siblings. Median OS was higher (80 vs. 54 months). In the prospective PETHEMA trial in patients who did not achieve at least near-CR with a first autologous SCT, there was no significant difference in OS after double autologous SCT versus autologous SCT followed by mini-allogeneic transplant. However, a trend toward a longer PFS was observed in the group treated with autologous SCT followed by mini-allogeneic transplant.[168] In contrast, the IFM trial (99-03) by Garban et al[169] and the BMT-CTN 0102 trial[170] reported no OS or PFS advantage with autologous transplant followed by allogeneic transplant in any subgroup, even after 10 years of follow-up.

In a prospective study of patients with previously untreated MM, patients were selected for treatment with autologous SCT followed by reduced-intensity conditioning allogeneic SCT or autologous SCT based on the availability of an HLA-identical sibling.[171] The induction chemotherapy in

this study consisted of the chemotherapy that was standard at the time—the VAD or VAD-like regimen. After 60 months, the incidence of relapse/disease progression was 49% in the group treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT versus 78% in the autologous SCT group. At 60 months, the OS and CR rates were 65% and 51%, respectively, for patients treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT compared with 58% and 41% for those treated with autologous SCT. Based on these study results, patients who have an HLA-identical sibling may be considered candidates for reduced-intensity allogeneic SCT as part of their first-line treatment.

Mini-allogeneic transplants have also been investigated as therapy for relapsed/refractory disease by virtue of their graft-versus-myeloma effect. Responsive disease to prior transplantation and younger age are associated with better response and OS rates.[172-175] In a case series report, 54 patients with previously treated relapsed disease or PD were treated with an autologous SCT followed by a mini-allogeneic transplant.[173] There was a 78% OS at a median 552 days after the mini-allogeneic transplant, with a 57% CR rate and an ORR of 83%. This study concluded that this approach reduced the acute toxicities of a myeloablative allogeneic SCT while preserving anti-tumor activity. The largest case series was reported by the EBMT.[174] In this heterogeneous population of 229 patients, the 3-year OS and PFS were 41% and 21%, respectively. Adverse OS was associated with chemoresistant disease and more than 1 prior transplant, whereas improved[176] OS was associated with graft-versus-host disease (GVHD), confirming the importance of a graft-versus-leukemia effect. This study concluded that mini-allogeneic transplantation is feasible, but heavily pretreated disease and patients with PD are unlikely to benefit.

Patients whose disease either does not respond to or relapses after allogeneic stem cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft-versus-myeloma effect[177-184] or other myeloma therapies on or off a clinical trial.

Follow-Up After Stem Cell Transplantation

Follow-up tests after SCT are similar to those done after primary myeloma therapy (see page MS-20).

In addition, MRD assessment is increasingly being incorporated into post-treatment 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 SCT translated to significantly improved PFS and OS rates.[185] Similarly, in another study, MRD negativity after autologous SCT was predictive of favorable PFS and OS.[186]

Similar results have also been reported in the allogeneic SCT setting where the presence of MRD after allogeneic SCT has been associated with a significantly adverse PFS and OS.[176] The NCCN Panel recommends assessing for MRD during follow-up as indicated.[132]

Maintenance Therapy

Lenalidomide as Maintenance Therapy After Autologous SCT

Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in two independent randomized phase III studies.[118,119]

In the CALGB 100104 trial, patients were randomized to maintenance therapy with lenalidomide (n = 231) versus placebo (n = 229) after

autologous SCT.[119] 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 time to progression 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%).[119]

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 SCT 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%, $P < .001$).[118] 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).[118] The updated survival analysis of the same study after 91 months for follow-up reported median time to progression 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; $P < .0001$).[187] The most common grade 3-4 adverse events in the lenalidomide group compared to 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%).[187]

The study by Palumbo et al[142] (discussed in *Autologous Stem Cell Transplants*) 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.[142]

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.[188] 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 those 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 PD were higher in the group receiving placebo.

Maintenance therapy after allogeneic transplant: A report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option after mini-allogeneic SCT.[189] However, another recently

reported study has shown the feasibility of maintenance therapy with low-dose lenalidomide after allogeneic SCT in patients with high-risk MM.[190]

Lenalidomide as Maintenance Therapy After Non-Transplant Primary Treatment

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.[191] 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 two 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.[191] 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,[118,119,191] the NCCN Multiple Myeloma Panel lists single-agent lenalidomide as one of the preferred maintenance regimens (category 1). Lenalidomide lacks the neurologic toxicity seen with thalidomide. However, there seems to be an increased risk for secondary cancers, especially post-transplantation,[118-120] or after a melphalan-containing regimen.[121] 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.[117]

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 non-transplant settings.[192] 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.[193] 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.[194] The NCCN Panel notes that the benefits and risks of maintenance therapy with lenalidomide versus secondary cancers should be discussed with patients.

Other Recommended Maintenance Regimens

Bortezomib as Maintenance Therapy After Autologous SCT

The results from the HOVON study show that maintenance with single-agent bortezomib after autologous SCT is well tolerated and is associated with improvement of ORR.[86] Patients in the HOVON trial were randomly assigned to one of the two arms consisting of either primary treatment with VAD followed by autologous SCT and maintenance with thalidomide or with bortezomib/doxorubicin/dexamethasone followed by autologous SCT 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[86] (see *Preferred Primary Therapy Regimens for Transplant Candidates).*

A multicenter phase III trial in newly diagnosed patients with MM showed that consolidation with bortezomib after autologous SCT improved PFS only in patients not achieving at least VGPR after autologous SCT.[195]

There was no difference in PFS in patients with ≥VGPR after autologous SCT.

Bortezomib as Maintenance Therapy After Non-Transplant Active Primary Treatment

The results of the phase III UPFRONT study also show that maintenance with single-agent bortezomib is well-tolerated when administered after treatment with bortezomib-based primary therapy.[128] Newly diagnosed patients with MM ineligible for high-dose therapy and SCT 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 results show that the response rates, including CR and ≥VGPR, improved after bortezomib maintenance in all arms, with no concomitant increase in the incidence of peripheral neuropathy.[128]

The NCCN Multiple Myeloma Panel members have added bortezomib as a maintenance therapy option.

Treatment of Progressive or Relapsed Myeloma

Therapy for previously treated relapsed/refractory MM is considered in the following clinical situations: patients with relapsed disease after allogeneic or autologous SCT; patients with primary PD after initial autologous or allogeneic SCT; and patients ineligible for SCT with progressive or relapsing disease after initial primary therapy.

A variety of therapies are available as options for previously treated MM depending on the prior therapy and duration of response. The options include systemic therapy; SCT (for eligible patients who did not receive SCT as part of their initial treatment); or clinical trial. For those who had autologous SCT as part of initial treatment and had a durable response or had SD, consideration must be given to a second transplantation on or off clinical trial at the time of relapse/disease progression.

If the relapse occurs at greater than 6 months after completion of the initial primary therapy, patients may be retreated with the same primary regimen.

Preferred Regimens for Previously Treated Multiple Myeloma

Bortezomib/Lenalidomide/Dexamethasone

Data from preclinical studies showed lenalidomide sensitizes myeloma cells to bortezomib and dexamethasone. The results of phase I and phase II studies show that bortezomib/lenalidomide/dexamethasoneis well tolerated and active, with durable responses in heavily pretreated patients with relapsed and/or refractory MM, including patients who have had prior lenalidomide, bortezomib, thalidomide, and SCT.[196,197] After a median follow-up of 44 months, the median PFS was 9.5 months and median OS was 30 months (95% CI, 24–37).[197] The NCCN Multiple Myeloma Panel members have included bortezomib/lenalidomide/dexamethasone as a preferred option for relapsed/refractory MM.

Carfilzomib/Lenalidomide/Dexamethasone

A randomized, multicenter, phase III trial of 792 patients (ASPIRE) studied the combination of lenalidomide and dexamethasone with or without carfilzomib in patients with relapsed/refractory myeloma who had received one to three prior lines of therapy. The primary endpoint of the study was PFS. The results showed that addition of carfilzomib to lenalidomide and

dexamethasone significantly improved PFS by 8.7 months (26.3 months for the carfilzomib arm vs. 17.6 months for lenalidomide and low-dose dexamethasone; HR for progression or death, 0.69; 95% CI, 0.57–0.83; *P* = .0001). The median duration of treatment was longer in the carfilzomib group (88.0 weeks vs. 57 weeks). The incidence of peripheral neuropathy was nearly identical in both arms (17.1% in the carfilzomib group vs. 17.0%). Non-hematologic adverse effects (≥ grade 3) that were higher in the carfilzomib group compared with lenalidomide and dexamethasone included dyspnea (2.8% vs. 1.8%), cardiac failure (3.8% vs. 1.8%), and hypertension (4.3% and 1.8%). There were fewer discontinuations due to side effects in the carfilzomib arm (15.3% vs. 17.7%). Patients in the carfilzomib arm reported superior health-related quality of life than those who received lenalidomide and dexamethasone.[198]

Based on the above data, the NCCN Multiple Myeloma Panel has included the combination of carfilzomib with lenalidomide and dexamethasone as a preferred option for patients with relapsed/refractory myeloma (category 1).

Carfilzomib (twice weekly)/Dexamethasone

The results of the phase III ENDEAVOR trial in patients with relapsed/refractory MM treated with multiple prior lines of therapy showed a 2-fold improvement in median PFS with carfilzomib/dexamethasone compared to bortezomib/dexamethasone (18.7 months vs. 9.4 months; HR, 0.53; *P* < .0001).[199] ORR was 77% in the carfilzomib group versus 63% in the bortezomib group; rates of CR or better were 13% and 6% and rates of VGPR were 42% and 22%, respectively. Median duration of response was 21.3 months in the carfilzomib group and 10.4 months in the bortezomib group. Adverse events (grade 3 or higher) in the carfilzomib arm compared to the bortezomib arm included hypertension (6% vs. 3%), anemia (12% vs. 9%), thrombocytopenia (10% vs. 14%), and dyspnea (5% vs. 2%). Rate of grade ≥2 peripheral neuropathy was 6% in the carfilzomib group and 32% in the bortezomib group.[199]

The OS analysis showed that those treated with carfilzomib/dexamethasone lived 7.6 months longer (median OS was 47.6 months in the carfilzomib group vs. 40 months in the bortezomib group; HR, 0.791 [95% CI, 0.648–0.964]; *P* = .010).[200] The most frequent grade 3 or worse adverse events in the carfilzomib arm compared to the bortezomib arm included hypertension (15% vs. 3%), anemia (16 % vs. 10%), dyspnea (6% vs. 2%), decreased lymphocyte count (6% vs. 2%), diarrhea (4% vs. 9%), and peripheral neuropathy (1% vs. 6%).[200] Rates of thrombocytopenia, pneumonia, and fatigue were similar in both groups.[200]

Based on the above phase III data, the NCCN Multiple Myeloma Panel has included the combination of carfilzomib (twice weekly) and dexamethasone as a preferred option for patients with relapsed/refractory myeloma (category 1).

Carfilzomib (weekly)/Dexamethasone

The data from a phase 1 study (CHAMPION-1) determined the maximum tolerated dose of carfilzomib (in combination with dexamethasone) to be 70 mg/m^2, once weekly.[201] Subsequently, a phase II study was conducted in patients with relapsed/refractory MM (n = 104) to evaluate safety and efficacy of weekly dosing of carfilzomib with dexamethasone. The ORR observed in this study was 77% (95% CI, 68–85). At 13.6 months, the median PFS was 16.2 months (95% CI, 10.2–21.0).[202] The most common grade 3 or higher adverse events occurring in at least 3% of all patients were fatigue (11%), pneumonia (6%), acute kidney injury (7%), and hypertension (8%).

The NCCN Multiple Myeloma Panel has included the carfilzomib (weekly)/dexamethasone regimen as an option for patients with relapsed/refractory myeloma.

Daratumumab/Bortezomib/Dexamethasone

A phase III trial showed that adding daratumumab to bortezomib and dexamethasone markedly improved outcomes for patients with recurrent/refractory MM.[203] Patients (n = 498) were randomized to receive daratumumab/bortezomib/dexamethasone or bortezomib/dexamethasone. The ORR in the daratumumab arm was 82.9% compared to 63.2% in the control arm ($P < .001$).[203] The rates of VGPR and CR were double in the daratumumab arm compared to the control arm (59.2% vs. 29.1%, $P < .001$ and 19.2% vs. 9.0%, $P = .001$, respectively). The 12-month estimated rate of PFS was significantly higher in the daratumumab arm compared to the control arm (60.7% vs. 26.9%).[203] The most common grade 3 or 4 adverse events reported in the daratumumab and control groups were thrombocytopenia (45.3% and 32.9%, respectively), anemia (14.4% and 16.0%, respectively), and neutropenia (12.8% and 4.2%, respectively).[203] Grade 1 or 2 infusion-related reactions associated with daratumumab were reported in 45.3% of the patients in the daratumumab group and grade 3 in 8.6% of the patients. These infusion-related reaction rates are consistent with findings from previous trials of daratumumab.[204,205]

Based on the above phase III data, the NCCN Panel has added daratumumab/bortezomib/dexamethasone as a preferred option (category 1) for the treatment of patients with relapsed/refractory MM.

Daratumumab/Lenalidomide/Dexamethasone

A phase III trial randomized patients (n = 569) 1:1 to receive daratumumab/lenalidomide/dexamethasone or lenalidomide/dexamethasone.[206]

According to the reported results, the ORR (in patients with an evaluable response) was higher in the daratumumab group (92.9% vs. 76.4%; $P < .001$) as was the CR (43.1% vs. 19.2%, $P < .001$). In the group that received daratumumab, the estimated rate of PFS at 12 months was 83.2% (95% CI, 78.3–87.2) compared with 60.1% (95% CI, 54.0–65.7) in the lenalidomide/dexamethasone group. Since deeper responses are known to result in longer PFS, a subgroup analysis showed that in those having a PR or better, the rate of PFS at 12 months was 87.8% (95% CI, 83.1–91.3) with daratumumab versus 73.6% (95% CI, 67.0–79.1) with lenalidomide/dexamethasone. Among patients with a VGPR or better, the rate of PFS was further improved: 91.7% (95% CI, 87.1–94.8) in the daratumumab group versus 85.8% (95% CI, 78.1–90.9) in the lenalidomide/dexamethasone group. The estimated rate of OS at 12 months in the daratumumab group was also significantly higher: 92.1% (95% CI, 88.2–94.7) compared with 86.8% (95% CI, 82.2–90.3) in the lenalidomide/dexamethasone group.

The most common adverse events of grade 3 or 4 in patients treated with the daratumumab regimen versus lenalidomide/dexamethasone were neutropenia (51.9 vs. 37.0%), thrombocytopenia (12.7% vs. 13.5%), and anemia (12.4% vs. 19.6%). Daratumumab-associated infusion-related reactions (mostly grade 1 or 2) were reported in 47.7% of the patients.

Based on the above phase III data, the NCCN Panel has added daratumumab/lenalidomide/dexamethasone as a preferred option (category 1) for the treatment of patients with relapsed/refractory MM.

Elotuzumab/Lenalidomide/Dexamethasone

Elotuzumab is a humanized monoclonal antibody targeted against signaling lymphocytic activation molecule F7 (SLAMF7). SLAMF7, also called CS1 (cell-surface glycoprotein CD2 subset 1) is a glycoprotein expressed on myeloma and natural killer cells but not on normal tissues.[207] The FDA has approved elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received one to three prior therapies. This is based on the results of the phase III trial, ELOQUENT-2. The trial randomized 646 patients (1:1) to receive either elotuzumab in combination with lenalidomide and dexamethasone or lenalidomide and dexamethasone alone.[208]

The rates of PFS at the end of 1 and 2 years were higher for those receiving the elotuzumab-containing regimen (68% at 1 year and 41% at 2 years) compared with those receiving lenalidomide and dexamethasone alone (57% at 1 year and 27% at 2 years).[208] Median PFS in the group receiving the elotuzumab-containing regimen was 19.4 months versus 14.9 months in those receiving lenalidomide and dexamethasone alone (HR for progression or death in the elotuzumab group, 0.70; 95% CI, 0.57–0.85; $P < .001$) indicating a relative reduction of 30% in the risk of disease progression or death.[208] Common grade 3 or 4 adverse events in both arms of the trial were lymphocytopenia, neutropenia, fatigue, and pneumonia. Infusion reactions occurred in 33 patients (10%) in the elotuzumab group and were grade 1 or 2 in 29 patients.[208]

Consistent with the above findings, a subset analysis of 3-year follow-up reported a reduced risk of progression by 27% with elotuzumab/lenalidomide/dexamethasone combination compared with lenalidomide/dexamethasone.[209]

Based on the above data and FDA approval the NCCN Panel has included elotuzumab in combination with lenalidomide and dexamethasone as a preferred regimen option (category 1) for previously treated MM.

Ixazomib/Lenalidomide/Dexamethasone

A double-blind, randomized, placebo-controlled, phase III TOURMALINE MM1 trial randomized 722 patients with relapsed and/or refractory MM to a combination of ixazomib plus lenalidomide and dexamethasone or lenalidomide and dexamethasone alone (control group). This trial was designed based on the promising results of a phase I/II study (discussed under *Other Recommended Primary Therapy Regimens for Transplant Candidates*).[93]

The results of the TOURMALINE MM1 trial show a significant improvement in PFS with the ixazomib-containing regimen. After a median follow-up of almost 15 months, a 35% improvement in PFS was seen in the group treated with the ixazomib regimen compared with the control group (HR, 0.74; $P = .01$).[210] Median PFS was 20.6 months in the ixazomib-treated group versus 14.7 months in the group receiving lenalidomide and dexamethasone alone. In the ixazomib-treated group versus the control group, the ORR (78% vs. 72%, $P = .035$) and CR (11.7% vs. 6.6%, $P = .019$) were also improved. Of note, patients with high-risk cytogenetics enrolled in the trial receiving ixazomib had a similar HR for PFS as the entire study population (HR, 0.596 and 0.543, respectively).[210] Grade ≥3 adverse events were reported in 74% and 69% of patients in the ixazomib-treated and control groups, respectively. These included anemia (9% with ixazomib/lenalidomide/dexamethasone vs. 13% with lenalidomide/dexamethasone), thrombocytopenia (19% vs. 9%), and neutropenia (23% vs. 24%).[210] The addition of the ixazomib/lenalidomide/dexamethasone group had a slightly higher rate of

peripheral neuropathy compared to lenalidomide/dexamethasone (27% vs. 22%).

Based on the results of the phase III TOURMALINE MM1 trial[210] the NCCN Panel has included ixazomib/lenalidomide/dexamethasone as a preferred regimen option for previously treated MM.

Other Recommended Regimens for Previously Treated MM

Bendamustine/Lenalidomide/Dexamethasone
A multicenter phase I/II trial investigated the combination of bendamustine, lenalidomide, and dexamethasone as treatment for patients (n = 29) with relapsed/refractory MM.[211] PR rate was seen in 52% (n = 13) of patients, with VGPR in 24% (n = 6) of patients. The median PFS in the trial was 6.1 months (95% CI, 3.7–9.4 months), and the one-year PFS rate was 20% (95% CI, 6%–41%).[211] The NCCN Panel has included lenalidomide in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM.

Bendamustine/Bortezomib/Dexamethasone
A phase II study evaluated bendamustine/bortezomib/dexamethasone administered over six 28-day cycles and then every 56 days for six more cycles in patients (n = 75; median age 68 years) with relapsed/refractory MM treated with multiple prior therapies and *not* refractory to bortezomib. The PR rate was 71.5% (16% CR, 18.5% VGPR, 37% partial remission). At 12-month follow-up, median time to progression was 16.5 months and 1-year OS was 78%.[212]

Bortezomib/Liposomal Doxorubicin/Dexamethasone
Bortezomib with liposomal doxorubicin (PLD) was approved by the FDA as a treatment option for patients with MM who have not previously received bortezomib and have received at least one prior therapy. The approval was based on a priority review of data from an international phase III trial (n = 646) showing that use of the combination significantly extended the median time to disease progression compared with bortezomib alone (9.3 vs. 6.5 months).[213] Median duration of response was increased from 7.0 months to 10.2 months with the combination therapy. Based on these results, the NCCN Multiple Myeloma Panel considers bortezomib with the PLD regimen as a category 1 option for patients with relapsed/refractory MM.

Bortezomib/Cyclophosphamide/Dexamethasone
The effects of adding of an alkylating agent (such as cyclophosphamide) and a novel agent (such as lenalidomide or bortezomib) to dexamethasone have been investigated for patients with relapsed/refractory MM. The combination of bortezomib, dexamethasone, and cyclophosphamide was found to be effective in patients with relapsed/refractory myeloma with an acceptable toxicity profile.[214,215] The NCCN Multiple Myeloma Panel members have included bortezomib/cyclophosphamide/dexamethasone to the list of options for relapsed/refractory MM.

Bortezomib/Dexamethasone
Addition of dexamethasone to bortezomib in patients with relapsed/refractory myeloma who had PD during bortezomib monotherapy resulted in improvement of response in 18% to 34% of patients.[216-218] The NCCN Multiple Myeloma Panel members have included the bortezomib and dexamethasone regimen as an option for patients with relapsed/refractory myeloma (category 1).

Carfilzomib/Cyclophosphamide/Dexamethasone

A phase II trial compared the safety and toxicity of carfilzomib/cyclophosphamide/dexamethasone with bortezomib/cyclophosphamide/dexamethasone in patients who had received one prior regimen for relapsed/refractory MM.[219] The study reported carfilzomib/cyclophosphamide/dexamethasone as well tolerated with toxicity profile of carfilzomib being similar to that seen in other trials.[219]

This regimen is included in the NCCN Guidelines for Multiple Myeloma as an option for patients with relapsed/refractory myeloma.

Lenalidomide/Dexamethasone

Lenalidomide combined with dexamethasone received approval from the FDA as a treatment option for patients with MM who had received at least one prior treatment. This was based on the results of two studies of a total of 692 patients randomized to receive dexamethasone either with or without lenalidomide. The primary efficacy endpoint in both studies was time to progression. A pre-planned interim analysis of both studies reported that the median time to progression was significantly longer in the lenalidomide arm compared to the control group.[220,221] The updated clinical data from the pivotal North American phase III trial (MM-009) in 353 previously treated patients with MM reported increased OS and median time to disease progression in patients receiving lenalidomide plus dexamethasone compared to patients receiving dexamethasone plus placebo.[221] Similar results were seen in the international trial MM-010.[220] Patients in both of these trials had been heavily treated before enrollment. Many had 3 or more prior lines of therapies with other agents and more than 50% of patients having undergone SCT.[220,221] Most adverse events and grade 3/4 adverse events were more frequent in patients with MM who received the combination of lenalidomide/dexamethasone compared to placebo and dexamethasone. Thrombocytopenia (61.5%) and neutropenia (58.8%) were the most frequently reported adverse events observed. The NCCN Multiple Myeloma Panel now considers this regimen as a category 1 option as therapy for patients with relapsed/refractory MM. Lenalidomide monotherapy has also been investigated and found effective in patients with relapsed/refractory MM.[222] The NCCN Multiple Myeloma Panel suggests considering lenalidomide monotherapy for steroid-intolerant individuals.

Lenalidomide/Cyclophosphamide/Dexamethasone

A retrospective analysis to assess the efficacy of lenalidomide in combination with cyclophosphamide and dexamethasone showed that this regimen is effective in heavily pre-treated patients with manageable adverse effects.[223]

Pomalidomide/Dexamethasone

Pomalidomide, like lenalidomide, is an analogue of thalidomide. It possesses potent immunomodulatory and significant anti-myeloma properties.[224]

A phase III, multicenter, randomized, open-label study (MM-003) conducted in Europe compared the efficacy and safety of pomalidomide and low-dose dexamethasone (n = 302) versus high-dose dexamethasone (n = 153) in patients with relapsed MM who were refractory to both lenalidomide and bortezomib.[225] After a median follow-up of 10 months, PFS, the primary endpoint of the study, was significantly longer in patients who received pomalidomide and low-dose dexamethasone compared with those who received high-dose dexamethasone (4.0 vs. 1.9 months; HR, 0.45; $P < .0001$).[225] The median OS was significantly longer in the patients who received pomalidomide and low-dose dexamethasone as well (12.7 months vs. 8.1 months; HR, 0.74; $P = .0285$).[225] The most common

hematologic grade 3 and 4 adverse effects found to be higher with the low-dose dexamethasone compared with the high-dose dexamethasone were neutropenia and pneumonia.[225] Other phase III studies of pomalidomide plus low-dose dexamethasone in combination with other agents (eg, bortezomib) are currently ongoing (Clinical Trial ID: NCT01734928). A European multicenter, single-arm, open-label, phase IIIb trial evaluated the safety and efficacy of pomalidomide and low-dose dexamethasone in a large patient population (N = 604).[226] The median PFS reported was 4.2 months and OS was 11.9 months. Whether the patients received prior lenalidomide or bortezomib, the PFS, OS, and ORR reported were similar.[226] The results of this trial are consistent with those observed in the pivotal MM-003 trial.[225]

In addition, several complementary phase II studies have been published evaluating the use of pomalidomide and dexamethasone in patients with MM relapsed/refractory to lenalidomide and/or bortezomib. A phase II study investigated two different dose regimens of pomalidomide and dexamethasone in 84 patients with advanced MM. Pomalidomide (4 mg) was given orally on days 1 to 21 or continuously over a 28-day cycle, and dexamethasone (40 mg) was given orally once weekly.[227] ORR was 35% and 34% for patients in the 21-day and 28-day groups, respectively. With median follow-up of 23 months, median duration of response, PFS, and OS were 7.3, 4.6, and 14.9 months across both groups, respectively. All patients experienced similar adverse events in both groups. The adverse events were primarily due to myelosuppression.[227] Another phase II trial evaluated two doses of pomalidomide 2 or 4 mg/day with dexamethasone 40 mg weekly in heavily pre-treated patients (n = 35).[228] The ORR in the 2-mg cohort was 49% versus 43% in the 4-mg cohort. OS at 6 months was 78% and 67% in the 2- and 4-mg cohort, respectively. Myelosuppression was the most common toxicity.[228]

The FDA has approved pomalidomide for patients with MM who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. The FDA-recommended dose and schedule of pomalidomide is 4 mg orally on days 1 to 21 of repeated 28-day cycles with cycles repeated until disease progression along with the recommendation to monitor patients for hematologic toxicities, especially neutropenia.

Based on the above data, the NCCN Panel has included pomalidomide plus dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy (category 1). For steroid-intolerant individuals, the NCCN Multiple Myeloma Panel suggests considering pomalidomide monotherapy.

Pomalidomide/Bortezomib/Dexamethasone

A phase 3 trial studied pomalidomide/bortezomib/dexamethasone versus bortezomib/dexamethasone in patients (n= 559) with relapsed or refractory multiple myeloma who previously received lenalidomide.[229] After a median follow-up of 15.9 months, a significantly improved PFS was seen in the pomalidomide arm (median 11.20 months vs. 7.10 months; HR, 0.61; 95% CI, 0.49–0.77; $P < .0001$). The most common grade 3/4 treatment-related adverse events in the pomalidomide arm reported in this trial were neutropenia, infections, and thrombocytopenia.[229]

The NCCN Panel has included pomalidomide/bortezomib/dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Pomalidomide/Carfilzomib/Dexamethasone

Based on the encouraging results of the phase I study,[230] a phase II study was carried out to evaluate the safety and efficacy of pomalidomide, carfilzomib, and dexamethasone in lenalidomide-refractory and proteasome-naïve/sensitive patients with relapsed/refractory MM. After a median of 7.2 cycles (range = 0.6–27.1 cycles), PR was 84%, MR was 91%, VGPR was 26%, and CR/near CR was 12%.[231] After a median follow-up of 18 months (range = 1–39 months), the median PFS for all 55 patients was 12.9 months and the estimated 18-month OS was 86.5%.[231]

The NCCN Panel has included this regimen pomalidomide/carfilzomib/dexamethasone as a therapeutic option in patients who have received at least two prior therapies, including an IMiD and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Pomalidomide/Cyclophosphamide/Dexamethasone

A phase II study compared the combination of pomalidomide/cyclophosphamide/dexamethasone to pomalidomide/dexamethasone in patients (n = 70) with relapsed/refractory MM who had received more than 2 prior therapies.[232]

The triple-drug combination significantly improved the ORR (≥PR, 64.7% vs. 38.9%; *P* = .0355). The median PFS reported was 9.5 months versus 4.4 months. There were no significant differences in adverse event reports between the treatment arms; grade 3 and 4 anemia, neutropenia, and thrombocytopenia, respectively, were reported in 11%, 31%, and 6% of patients treated with pomalidomide/dexamethasone and 24%, 52%, and 15% of patients treated with the triplet regimen.[232] Similar results were reported by a single-center retrospective study[233] of patients (n = 20) with relapsed/refractory MM who received pomalidomide/cyclophosphamide/dexamethasone until transplant or disease progression was reported.[232] Response to the triple-drug regimen was 63%, with nearly half of patients (42%) responding after 1 cycle with a median time to response of 3 cycles. One-year median PFS was 80.7% and 65% of patients were relapse-free.[233]

Based on the above phase II trial data, the NCCN Panel has included pomalidomide/cyclophosphamide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least one prior therapy.

Daratumumab

Daratumumab is a human IgG kappa monoclonal antibody that targets the CD38 surface protein on myeloma cells.[204] In a phase I/II study, patients who had received more than 3 lines of therapy including an IMiD and a PI or were double refractory to PI and IMiD were randomized to 2 different doses of daratumumab (8 mg/kg vs. 16 mg/kg). ORR was 29.2% (3 sCR, 10 VGPR, and 18 PR). Median duration of response was 7.4 months and median time to progression was 3.7 months. The estimated 1-year OS rate was 65%.[205] Adverse events reported were fatigue (39.6%), anemia (33.0%), nausea (29.2%), and thrombocytopenia (25.5%). Grade 1 and 2 infusion-related reactions were seen in 42.5% of patients, mainly during first infusion. No patients discontinued the study due to infusion-related reactions.[205]

Based on the above phase II results and FDA approval, the panel has added daratumumab as an option for the treatment of patients with MM who have received at least 3 prior lines of therapy including a PI and an IMiD or who are double refractory to a PI and IMiD.

Daratumumab/Pomalidomide/Dexamethasone

The combination of daratumumab/pomalidomide/dexamethasone was evaluated in an open-label, multicenter, phase 1b study (MMY1001). This study included patients (n = 103 patients) who had received at least two prior lines of therapy (excluding daratumumab or pomalidomide).[234] At a median follow-up of 13.1 months, the ORR was 60%. The median PFS and median OS were 8.8 and 17.5 months, respectively, and estimated survival at 1 year was 66%.[234] Toxicities reported were similar to those seen in other trials of pomalidomide and daratumumab, except for increase in neutropenia.[234]

Based on the above data, the NCCN Panel has included daratumumab/pomalidomide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least 2 prior therapies including an IMiD and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Elotuzumab/Pomalidomide/Dexamethasone

In a phase II study, patients (n= 117) with refractory/relapsed MM and refractory to lenalidomide and a PI were randomized to receive pomalidomide/dexamethasone or pomalidomide/dexamethasone/elotuzumab.[235] After a follow-up of 9.1 months, the median PFS and ORR were both more than double with elotuzumab (PFS, 10.3 months vs. 4.7; ORR, 53% vs. 26%).

The NCCN Panel has included the combination of pomalidomide/dexamethasone/elotuzumab as an option for patients who have received at least two prior therapies including an iMID and a PI.

Ixazomib/Dexamethasone

Data from two phase I studies of single-agent ixazomib in patients with relapsed/refractory MM established the maximum tolerated dose of ixazomib to be 2.0 mg/m^2 on a twice-weekly schedule and 2.97 mg/m^2 on a weekly schedule.[236,237] The patients in these studies had multiple prior lines of therapy (median of 4 prior lines of therapy in both studies). In the study with the weekly schedule,[236] out of 30 evaluable patients the rate of PR or better (≥PR) was 27%. In the twice-weekly schedule, out of 55 evaluable patients ≥PR rate was 15%.[237] Adverse events, grade ≥3, were reported in 78% (drug-related in 62%) of patients on the twice-weekly schedule[237] and 65% (53%) of patients on the weekly schedule.[236] These included thrombocytopenia (37%), neutropenia (17%), and skin and subcutaneous tissue disorders (8%) on the twice-weekly schedule, and thrombocytopenia (33%), neutropenia (18%), and diarrhea (17%) on the weekly schedule. Peripheral neuropathy was reported in 17% (drug-related in 12%) of patients, with no grade 3 events, on the twice-weekly schedule.[237] On the weekly schedule drug-related peripheral neuropathy was reported in 20% of patients (2% grade 3). [236]

Subsequently, phase II trials were designed to evaluate ixazomib with or without dexamethasone in patients with myeloma who have limited prior exposure to bortezomib.[238,239] In one trial, patients (n = 33) with relapsed MM received weekly ixazomib 5.5 mg and had dexamethasone added for suboptimal response or disease progression (in 67% of patients). Six additional patients achieved a PR after the addition of dexamethasone.[238]

The ORR (≥PR) with or without the addition of dexamethasone reported was 34%.[238] Adverse events, grade ≥3, were reported in 78%. The most common adverse events observed included thrombocytopenia, fatigue, nausea, and diarrhea.[238]

Another phase II study evaluated two doses of weekly ixazomib (arm A, 4 mg and arm B, 5.5 mg) plus weekly dexamethasone (40 mg) in patients (n = 70) with relapsed MM. The patients enrolled in the trial had not been previously treated with a PI (including bortezomib) or had received less than 6 cycles of therapy with bortezomib and had a PR or better and no progression at the time of discontinuation.[239] The ORRs were 31% in arm A (95% CI, 17–49) and 51% (95% CI, 34–69) in arm B. Among the patients with no prior bortezomib exposure the response rates were 38% for arm A and 52% for arm B.[239] The most common toxicities reported in this trial were fatigue, thrombocytopenia, diarrhea, and nausea with more grade 3 toxicities among arm B. Peripheral neuropathy, possibly related to ixazomib, was seen in 55% (only grade 1 or 2) in arm A and 43% (2 patients with grade 3) in arm B.[239]

Based on the above phase I/II trial data, the NCCN Panel has included ixazomib/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least one prior therapy.

Ixazomib/Pomalidomide/Dexamethasone

In phase I Alliance A061202 study (n= 22), 32% of patients were refractory to a lenalidomide/PI combination and 68% were refractory to the sequential use of these drugs. The majority of patients (65%) had high-risk cytogenetics. More than half the patients experienced grade 3 and 4 neutropenia, lymphopenia, and reductions in white blood cell count. Peripheral neuropathy, rash, diarrhea, and other side effects were limited to grades 1 and 2. The ORR was 55% in those with PI- or lenalidomide-refractory disease and responses were found to be durable over time.[240]

Another phase I/II study studied the safety and efficacy of ixazomib/pomalidomide/dexamethasone in patients who had multiple prior therapies, were refractory to lenalidomide alone, or were refractory to lenalidomide and bortezomib, or lenalidomide, bortezomib, and carfilzomib.[241] The ORR was 33% and 40% with 2 different doses of ixazomib.[241]

Considering promising preliminary response rates, especially in patients refractory to both lenalidomide and a PI, the NCCN Panel has included ixazomib/pomalidomide/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least 2 prior therapies including an IMiD and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Elotuzumab/Bortezomib/Dexamethasone

Numerous randomized trials have shown that 3-drug combinations have been shown to be consistently more effective than 2-drug combinations for the treatment of MM. A phase II trial studied the effect of addition of elotuzumab to bortezomib/dexamethasone in patients with relapsed/refractory MM.[242]

Interim analysis results demonstrated a 28% reduction in risk of disease progression or death for patients in the elotuzumab-containing triple-drug arm compared to patients treated with bortezomib/dexamethasone (HR, 0.72; 70% CI, 0.59–0.88). Median PFS was significantly higher in the elotuzumab-containing arm (9.7 months vs. 6.9 months). After 2 years the addition of elotuzumab continued to show an efficacy benefit compared to

bortezomib/dexamethasone alone with a 24% relative risk reduction in PFS (HR, 0.76; 70% CI, 0.63–0.91).[242]

Based on the above phase II trial data, the NCCN Panel has included elotuzumab/bortezomib/dexamethasone as a treatment option for patients with relapsed/refractory MM who have received at least one prior therapy.

Panobinostat/Carfilzomib

A multicenter phase I/II study assessed the safety and efficacy of the combination of panobinostat/carfilzomib in patients with relapsed/refractory MM who had relapsed after at least one prior treatment.[243] Phase I of the study was to determine the maximum tolerable dose of panobinostat and carfilzomib. The primary endpoint of the phase II was ORR.

No dose-limiting toxicities were observed at any of the planned dose levels in the phase I study. Of the 42 evaluable patients in phase II, the ORR was 67% and the clinical benefit rate was 79%.[243] The ORR was 67% for patients refractory to prior PI treatment and 75% for patients refractory to prior immune-modulating drug treatment. At a median follow-up of 17 months, median PFS was 7.7 months.[243] Grade 3/4 treatment-related adverse events included thrombocytopenia (38%), neutropenia (21%), fatigue (11%), anemia (9%), hypertension (9%), and diarrhea (7%).[243]

The maximum tolerated dose of carfilzomib and panobinostat was not reached with the 4 dosing schedules in the first phase I study;[243] two additional dosing schedules were evaluated. The maximum planned dose from the first study was 30 mg panobinostat plus 20/45 mg/m^2 of carfilzomib. In this study,[243] the dose of carfilzomib was escalated to 20/56 mg/m^2 in one cohort. Due to dose reductions of panobinostat in the first study, the second cohort in this study explored 20 mg of panobinostat and carfilzomib 20/56 mg/m^2. The most common adverse events grade ≥3 were thrombocytopenia (31%), fatigue (4%), and diarrhea (4%). The ORR was 82% (34% ≥VGPR and 48% PR). The clinical benefit rate was 91%.

Based on promising phase I/II data, the NCCN Panel has added panobinostat in combination with carfilzomib as a treatment option for patients with previously treated MM.

Panobinostat/Bortezomib/Dexamethasone

Panobinostat is a pan-deacetylase inhibitor that epigenetically modulates class I and II HDAC enzymes.[244] Recently, the FDA approved the use of panobinostat in combination with bortezomib and dexamethasone for patients with relapsed/refractory MM who have had at least two prior therapies with regimens containing an IMiD and bortezomib.

The approval was based on the results of a randomized, placebo-controlled, phase III study, PANORAMA-1. The study randomized 768 patients with MM who had received prior treatment with an IMiD and bortezomib to receive bortezomib and dexamethasone along with either panobinostat or placebo. The results showed an improved median PFS with the panobinostat-containing regimen compared with the control arm (11.99 months [95% CI; 10.33–12.94 months] vs. 8.08 months [95% CI; 7.56–9.23 months]; HR, 0.63; 95% CI, 0.52–0.76; $P < .0001$) along an increased depth of response.[245] The final OS data from this study are not yet available.

The regimen containing panobinostat is associated with significant toxicity. Serious adverse events were reported in 228 (60%) of 381 patients in the panobinostat group and 157 (42%) of 377 patients in the placebo group. Common grade 3–4 laboratory abnormalities and adverse events were greater in the panobinostat group versus the control group, including

thrombocytopenia (67% vs. 31%), lymphopenia (53% vs. 40%), diarrhea (26% vs. 8%), fatigue (4% vs. 2%), and peripheral neuropathy (18% vs. 5%).[245]

The PANORAMA-2 is a phase II, single-arm, multicenter trial that evaluated the combination of panobinostat with bortezomib and dexamethasone in patients who had relapsed disease, refractory to bortezomib (N = 55).[246] Patients in this study achieved an ORR of 34.5% with the panobinostat-containing regimen.[246] The median PFS was 5.4 months and OS had not been reached at a median follow-up of 8.3 months.[246] Common grade 3/4 adverse events included thrombocytopenia (63.6%), diarrhea (20.0%), and fatigue (20.0%).[246]

The NCCN Multiple Myeloma Panel has included panobinostat in combination with bortezomib and dexamethasone as a category 1 option for patients who have received at least two prior therapies, including an immunomodulator and bortezomib.

Panobinostat/Lenalidomide/Dexamethasone

A single-center, phase II study evaluated the safety and efficacy of the oral regimen containing panobinostat with lenalidomide and dexamethasone in patients (n = 27) with relapsed or relapsed/refractory MM (including those refractory to IMID and PIs).[247] ORR was 41% and median PFS was 7.1 months. In lenalidomide-refractory patients (n = 22), the ORR was 36% and median PFS was 6.5 months.[247] The expected hematologic toxicities seen and GI toxicities seen with the combination of HDAC inhibitors and bortezomib was not seen in this trial.[247]

Based on the encouraging ORR and PFS in iMID–refractory patients, the NCCN Multiple Myeloma Panel has included panobinostat with lenalidomide and dexamethasone for patients who have received at least two prior therapies, including an immunomodulator and bortezomib.

Regimens Useful Under Certain Circumstances for Previously Treated MM

In a trial by Knop and colleagues, 31 patients who had experienced relapse after autologous transplantation were enrolled to receive increasing doses of bendamustine.[248] The ORR was 55%, with a median PFS of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90–100 mg/m^2). Toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients has reported that bendamustine is effective and tolerable in patients with advanced progressive MM, with an ORR of 36%.[249]

The ECOG studied treatment with high-dose cyclophosphamide in poor-risk myeloma patients who had disease refractory to prior chemotherapy.[250] The overall objective response rate reported was 43% (29% response rate in patients refractory to prior therapy with cyclophosphamide).[250]

Patients with an aggressive relapse may need multi-drug combinations such as DCEP,[251-253] TD-PACE (thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide),[254,255] and VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide)[256-258] for effective disease control.

Bendamustine is currently a treatment option for relapsed/refractory MM. High-dose cyclophosphamide is included as an option in the NCCN Guidelines for patients with relapsed/refractory MM.

The NCCN Guidelines include bendamustine, high-dose cyclophosphamide, DCEP, DT-PACE, and VTD-PACE as therapeutic

options that are useful under certain circumstances for patients with previously treated MM.

Supportive Care Treatment for Multiple Myeloma

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 of myeloma, in the form of diffuse osteopenia and/or osteolytic lesions, develop in 85% of patients. 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.[259,260] Zoledronic acid has equivalent benefits.[261]

Results from the study conducted by Zervas et al[262] show a 9.5-fold greater risk for the development of osteonecrosis of the jaw (ONJ) with zoledronic acid compared to pamidronate. Patients who are on bisphosphonates should have their renal function monitored. They should have a dental exam prior to 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.[263] 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.[264] 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.[265] 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).[265]

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.[266] It did not find a particular bisphosphonate to be superior to another.[266]

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 (SREs) 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.[267]

The NCCN Guidelines for Multiple Myeloma recommend bisphosphonates (category 1) or denosumab for all patients receiving myeloma therapy for symptomatic disease 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.

In patients with smoldering or stage I MM, according to the NCCN Panel, bisphosphonates may be considered but preferably in a clinical trial. Skeletal survey annually or as clinically indicated is recommended for these patients. Bone densitometry or other metabolic studies should be reserved for clinical trials.

Low-dose radiation therapy (10–30 Gy) is used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.[47] Limited involved fields should be used to limit the effect of irradiation on stem cell harvest or its effect on potential future treatments; the radiation doses administered should not preclude stem cell collection in potential candidates for high-dose therapy and hematopoietic SCT. 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 myeloma 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,[268] steroids, and/or calcitonin. Among the bisphosphonates (zoledronic acid, pamidronate, and ibandronate), the NCCN Multiple Myeloma Panel members prefer zoledronic acid for treatment of hypercalcemia.[261,269,270]

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.[271] 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[272,273] (see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections). 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.

To prevent infection: 1) IV immunoglobulin therapy should be considered for recurrent, life-threatening infections; 2) pneumococcal and influenza vaccine should also be considered; and 3) *Pneumocystis carinii* pneumonia (PCP), herpes, and antifungal prophylaxis is recommended if a high-dose regimen is used. PIs (bortezomib, carfilzomib, and ixazomib) and daratumumab treatment have been associated with an incidence of herpes zoster.[73,74] Herpes prophylaxis is recommended in patients receiving PI or daratumumab therapy.[72] (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections).

Thrombosis is relatively common when thalidomide or lenalidomide is used with steroids, and is particularly frequent when treating newly diagnosed patients. Use of prophylactic anticoagulation agents (see NCCN Guidelines for Venous Thromboembolic Disease) is recommended when IMiDs are used in combination therapy during induction.[105,274,275]

Hydration should be maintained and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided to decrease the chances of renal dysfunction. According to the NCCN Multiple Myeloma Panel members, the use of plasmapheresis to improve renal function is a category 2B recommendation. The use of IV contrast media should also be avoided in patients with renal impairment. Renal function should be monitored with chronic use of bisphosphonates.

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