



National Comprehensive
Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Multiple Myeloma

Version 4.2022 — December 14, 2021

NCCN.org

NCCN Guidelines for Patients® available at www.nccn.org/patients

Continue



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 4.2022

Multiple Myeloma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

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

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

Kehinde Adekola, MD, MSCI ‡ †
Robert H. Lurie Comprehensive
Cancer Center of Northwestern University

Larry D. Anderson, Jr., MD, PhD ‡ †
UT Southwestern Simmons
Comprehensive Cancer Center

Muhammed Baljevic, MD † ‡ † §
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

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

Srinivas Devarakonda, MD ‡ †
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Noura Elsedawy, MD †
St. Jude Children's Research Hospital/
The University of Tennessee
Health Science Center

Matthew Faiman, MD, MBA †
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, PhD ‡
Roswell Park Comprehensive Cancer Center

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

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

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

Malin Hultcrantz, MD, PhD ‡ †
Memorial Sloan Kettering Cancer Center

Yubin Kang, MD ‡ † §
Duke Cancer Institute

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 † ‡ † §
Huntsman Cancer Institute
at the University of Utah

Kenneth Shain, MD, PhD †
Moffitt Cancer Center

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

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

NCCN
Rashmi Kumar, PhD
Ryan Berardi, MSc

[NCCN Guidelines Panel Disclosures](#)

Continue

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



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 4.2022

Multiple Myeloma

[NCCN Guidelines Index](#)
[Table of Contents](#)
[Discussion](#)

[NCCN Multiple Myeloma Panel Members](#)
[Summary of Guidelines Updates](#)

[Initial Diagnostic Workup and Clinical Findings \(MYEL-1\)](#)

[Solitary Plasmacytoma or Solitary Plasmacytoma with Minimal Marrow Involvement:](#)

[Primary Treatment and Follow-up/Surveillance \(MYEL-2\)](#)

[Smoldering Myeloma \(Asymptomatic\): Primary Treatment and Follow-Up/Surveillance \(MYEL-3\)](#)

[Multiple Myeloma \(Symptomatic\): Primary Treatment and Follow-Up/Surveillance \(MYEL-4\)](#)

[Multiple Myeloma \(Symptomatic\): Response After Primary Therapy and Follow-Up Surveillance \(MYEL-5\)](#)

[Additional Treatment Post-Autologous Hematopoietic Cell Transplant \(MYEL-6\)](#)

[Multiple Myeloma \(Symptomatic\): Additional Treatment for Relapse or Progressive Disease \(MYEL-7\)](#)

[Staging Systems for Multiple Myeloma \(MYEL-A\)](#)

[Principles of Imaging \(MYEL-B\)](#)

[Definitions of Smoldering and Multiple Myeloma \(MYEL-C\)](#)

[Principles of Radiation Therapy \(MYEL-D\)](#)

[Response Criteria for Multiple Myeloma \(MYEL-E\)](#)

[General Considerations for Myeloma Therapy \(MYEL-F\)](#)

[Myeloma Therapy \(MYEL-G\)](#)

[Supportive Care for Multiple Myeloma \(MYEL-H\)](#)

[Management of Venous Thromboembolism \(VTE\) in Multiple Myeloma \(MYEL-I\)](#)

[Management of Renal Disease in Multiple Myeloma \(MYEL-J\)](#)

[Monoclonal Gammopathy of Clinical Significance](#)

- [Monoclonal Gammopathy of Renal Significance \(MGRS-1\)](#)
- [Monoclonal Gammopathy of Neurological Significance \(MGNS-1\)](#)

[POEMS \(Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, Skin Changes\) \(POEMS-1\)](#)

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.

Find an NCCN Member Institution: <https://www.nccn.org/home/member-institutions>

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](#).

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2021.



Updates in Version 4.2022 of the NCCN Guidelines for Multiple Myeloma from Version 3.2022 include:

[MYEL-G 3 of 4](#)

- **Therapy for Previously Treated Multiple Myeloma:**

- ▶ **The following regimen was removed from Other Recommended Regimens for Early Relapse (1-3 prior therapies):**

- ◊ **Panobinostat /bortezomib/dexamethasone (category 1)**

[MYEL-G 4 of 4](#)

- **Therapy for Previously Treated Multiple Myeloma**

- ▶ **Useful in Certain Circumstances for Early Relapses (1-3 prior therapies):**

- ◊ **The following new regimen was added: Selinexor/carfilzomib/dexamethasone**

- ◊ **The following were removed:**

- **After two prior therapies including bortezomib and an IMiD:**

- **Panobinostat/carfilzomib**

- **Panobinostat/lenalidomide/dexamethasone**

Note: All recommendations are category 2A unless otherwise indicated.

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.

[CONTINUED](#)

UPDATES



Updates in Version 3.2022 of the NCCN Guidelines for Multiple Myeloma from Version 2.2022 include:

[MYEL-G 4 of 4](#)

- Therapies for Late Relapses (>3 prior therapies)
 - The regimen melphalan flufenamide/dexamethasone was removed.

Updates in Version 2.2022 of the NCCN Guidelines for Multiple Myeloma from Version 1.2022 include:

[MYEL-G 1 of 4 and 2 of 4](#)

- Maintenance Therapy
 - Other Recommended Regimens
 - ◊ Ixazomib was modified to: Ixazomib (~~category 4~~ **category 2B**)
- Footnote i added: Results from interim analyses of TOURMALINE MM3 and MM4 trials of ixazomib in the maintenance setting suggests a potential decrease in overall survival.

[MYEL-G 2 of 4](#)

- Primary Therapy for Non-Transplant Candidates
 - Preferred Regimens
 - ◊ Footnote j removed from regimen Bortezomib/lenalidomide/dexamethasone: This is the only regimen shown to have overall survival benefit.

Updates in Version 1.2022 of the NCCN Guidelines for Multiple Myeloma from Version 7.2021 include:

[MYEL-2](#)

- Primary Treatment
 - Revised: RT ± surgery *or Consider clinical trial*
- Follow-Up Surveillance
 - Second bullet added: Tests as needed:
 - ◊ First sub-bullet revised: Serum quantitative immunoglobulins, SPEP, with SIFE ~~as needed~~
 - ◊ Third sub-bullet revised: Serum FLC assay ~~as clinically indicated~~
 - ◊ Fourth sub-bullet revised: Serum LDH and beta-2 microglobulin ~~as clinically indicated~~
 - ◊ Fifth sub-bullet revised: Bone marrow aspirate and biopsy ~~as clinically indicated~~
 - ◊ Sixth sub-bullet added: All plasmacytomas should be imaged yearly, preferably with the same technique used at diagnosis, for at least 5 years.

[MYEL-3](#)

- Follow-Up/Surveillance
 - Second bullet revised: Bone marrow aspirate and biopsy with FISH, SNP array, NGS, or multi-parameter flow cytometry as ~~clinically indicated~~ **needed**.
 - Third bullet revised: Whole-body imaging with MRI without contrast, low-dose CT scan, FDG PET/CT annually or as ~~clinically indicated~~ **needed**, ideally with the same technique used at diagnosis.

[MYEL-4](#)

- Footnote d added from MYEL-1: 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.

Note: All recommendations are category 2A unless otherwise indicated.

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.

[CONTINUED](#)



NCCN Guidelines Version 4.2022

Multiple Myeloma

Updates in Version 1.2022 of the NCCN Guidelines for Multiple Myeloma from Version 7.2021 include:

MYEL-5

- Multiple Myeloma (Symptomatic)
 - Revised: *Tandem autologous* or allogeneic hematopoietic cell transplant, under certain circumstances.
- Follow-Up/Surveillance
 - Third bullet revised: 24-h urine for total protein, UPEP, and UIFE at baseline and as ~~clinically indicated~~ *needed* or if there is a significant change in FLC levels
 - Fifth bullet revised: Whole-body advanced imaging with FDG PET/CT, low-dose CT scan, MRI without contrast as ~~clinically indicated~~ *needed*, ideally with the same technique used at diagnosis
 - Sixth bullet revised: Bone marrow aspirate and biopsy with multiparameter flow cytometry as ~~clinically indicated~~ *needed*

MYEL-B 1 of 2

- Imaging for Initial Diagnostic Workup (for patients suspected of myeloma/solitary plasmacytoma)
 - First bullet revised by adding sentence: A small percentage of patients may have a negative PET/CT with active MM.
- Imaging for Follow-up of MM
 - First bullet revised: Advanced whole-body imaging (ie, FDG PET/CT, low-dose CT scan, whole-body MRI without contrast) is recommended as ~~clinically indicated~~ *needed*.

MYEL-C

- Footnote b added: (BMPCs) >20%, M-protein >2 g/dL, and (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, et al. Blood Cancer J 2018;8:59.

MYEL-D

- Solitary Plasmacytoma
 - Treatment Information/Dosing:
 - ◊ First bullet, first sub-bullet revised: RT (40–50 Gy in 1.8–2.0 Gy fractions [*20–25 total fractions*]) to involved field.
- Multiple Myeloma
 - Palliative RT Dosing for MM
 - ◊ First bullet revised: Low-dose RT (8 Gy x 1 fraction or 10–30 Gy in 2.0–3.0 Gy fractions [*5–10 total fractions*]) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or for impending cord compression.

MYEL-F

- Heading has been revised: ~~Principles of General Considerations for Myeloma Therapy~~
- General Principles
 - Fourth bullet added: For the Myeloma Frailty Score Calculator developed by International Myeloma Working Group for the prognosis of elderly myeloma patients, see <http://www.myelomafrailtyscorecalculator.net/>
 - Fifth bullet added: Consider dose modifications based on functional status and age.
- Dosing and Administration
 - Fourth bullet was moved from MYEL-G: For any regimen that includes daratumumab, this could be daratumumab for intravenous infusion or 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.
- Reference added: Palumbo A, Bringhen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. Blood 2015;125:2068-2074.

Note: All recommendations are category 2A unless otherwise indicated.

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.

[CONTINUED](#)



NCCN Guidelines Version 4.2022

Multiple Myeloma

Updates in Version 1.2022 of the NCCN Guidelines for Multiple Myeloma from Version 7.2021 include:

[MYEL-G 1 of 4](#)

- **Primary Therapy for Transplant Candidates**
 - The following regimens were moved from Preferred Regimens to Useful in Certain Circumstances
 - ◊ Bortezomib/cyclophosphamide/dexamethasone
 - The following new regimen was added to Useful in Certain Circumstances
 - ◊ Daratumumab/carfilzomib/lenalidomide/dexamethasone
- **Maintenance Therapy**
 - Useful in Certain Circumstances
 - ◊ The regimen Bortezomib/lenalidomide was revised to Bortezomib/lenalidomide±dexamethasone
- Footnote f was moved to General Considerations for Myeloma Therapy. (Also for MYEL-G 2 of 4)
- Footnote i added: Dual maintenance recommended for high-risk MM.

[MYEL-G 2 of 4](#)

- **Primary Therapy for Non-Transplant Candidates**
 - The following regimens were moved from Preferred Regimens to Useful in Certain Circumstances:
 - ◊ Lenalidomide/low-dose dexamethasone (category 1)
 - ◊ Bortezomib/cyclophosphamide/dexamethasone
 - The following new regimen was added to Useful in Certain Circumstances:
 - ◊ Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail Patients
- **Maintenance Therapy**
 - The following regimen was added to Other Recommended Regimens:
 - ◊ Ixazomib (category 1)

[MYEL-G 3 of 4](#)

- Regimens were reorganized by early (1-3 prior therapies) and late relapses (> 3 prior therapies).
- **Early Relapses:**
 - The following regimens were moved from Other Recommended to Preferred:
 - ◊ Isatuximab-irfc/carfilzomib/dexamethasone (category 1)
 - ◊ Daratumumab/pomalidomide/dexamethasone (category 1)

- Footnote added: Regimens included under 1-3 prior therapies can also be used later in the disease course/ Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.
- Footnote added: Autologous stem cell transplant should be considered in an eligible patient who had not previously received transplant or had a prolonged response to initial transplant.

[MYEL-G 4 of 4](#)

- Useful in Certain Circumstances:
 - ◊ Fifth bullet revised: High-dose *or fractionated* cyclophosphamide

[MYEL-I 1 of 3](#)

- New section added: Management of Venous Thromboembolism (VTE) in Multiple Myeloma

[MGRS-1](#)

- **Initial Workup**
 - Renal Biopsy recommended if:
 - ◊ Second bullet revised: eGFR <60 mL/min and >2ml/min per year decline
 - Consider renal biopsy if:
 - ◊ Second bullet revised: eGFR <60mL/min and ≥<2 mL/min per year decline
 - ◊ Third bullet removed: Proteinuria
 - ◊ Fourth Bullet revised: Albumin: creatinine 3-30 mg/mmol or and GFR <60 mL/min

[MGNS-1](#)

- **Initial Workup**
 - First bullet, ninth sub-bullet revised: Evaluation for light chain amyloidosis, if appropriate ([See NCCN Guidelines for Systemic Light Chain Amyloidosis](#)), WM ([See NCCN Guidelines for WM](#)), or POEMS ([See POEMS-1](#)), if appropriate.

Note: All recommendations are category 2A unless otherwise indicated.

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.

[CONTINUED](#)

UPDATES



NCCN Guidelines Version 4.2022

Multiple Myeloma

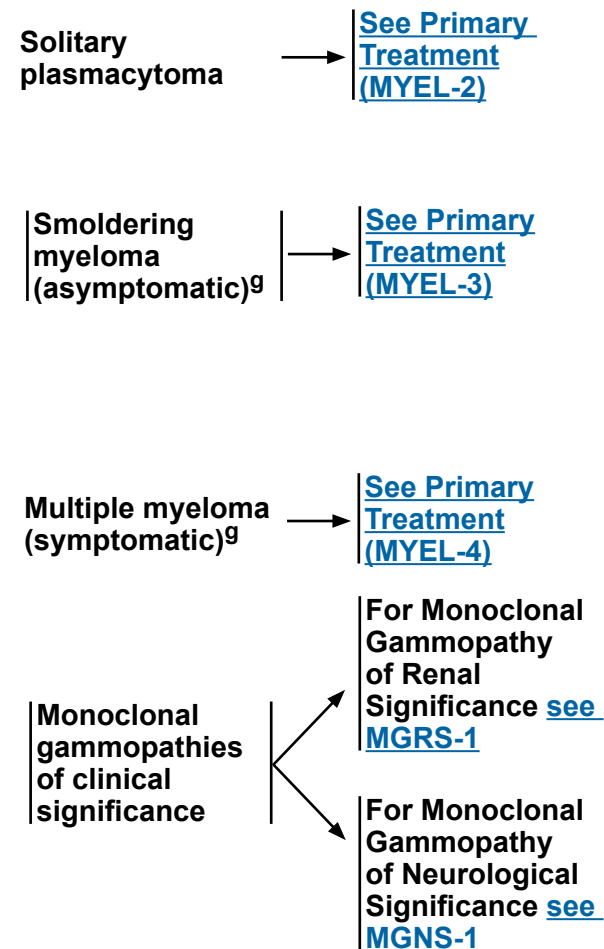
INITIAL DIAGNOSTIC WORKUP^a

- 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 MM
- 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



^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 \(MYEL-J\)](#).

^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 \(MYEL-C\)](#).

Note: All recommendations are category 2A unless otherwise indicated.

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.



NCCN Guidelines Version 4.2022

Multiple Myeloma

CLINICAL FINDINGS

PRIMARY TREATMENT

FOLLOW-UP/SURVEILLANCE

Solitary plasmacytoma or Solitary plasmacytoma with minimal marrow involvement^{i,j}

RT^k ± surgery^l or Consider clinical trial

- Follow-up interval, every 3–6 mo:^m
 - ▶ CBC, differential, platelet count
 - ▶ Serum chemistry for creatinine, albumin, and corrected calcium
- Tests as needed:
 - ▶ Serum quantitative immunoglobulins, SPEP, with SIFE
 - ▶ 24-h urine for total protein and UPEP with UIFE
 - ▶ Serum FLC assay
 - ▶ Serum LDH and beta-2 microglobulin
 - ▶ Bone marrow aspirate and biopsy
 - ▶ All plasmacytomas should be imaged yearly, preferably with the same technique used at diagnosis, for at least 5 years^{e,h}
- [See NCCN Guidelines for Survivorship](#)

Primary progressiveⁿ or Response followed by progressionⁿ

Restage with myeloma workup

[See Multiple myeloma \(symptomatic\) \(MYEL-4\)](#)

^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 diagnostic criteria, please refer to Rajkumar SV, et al. Lancet Oncol 2014;15:e538-e548.

^j Solitary plasmacytoma with 10% or more clonal plasma cells is regarded as active (symptomatic) MM 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 \(MYEL-E\)](#).

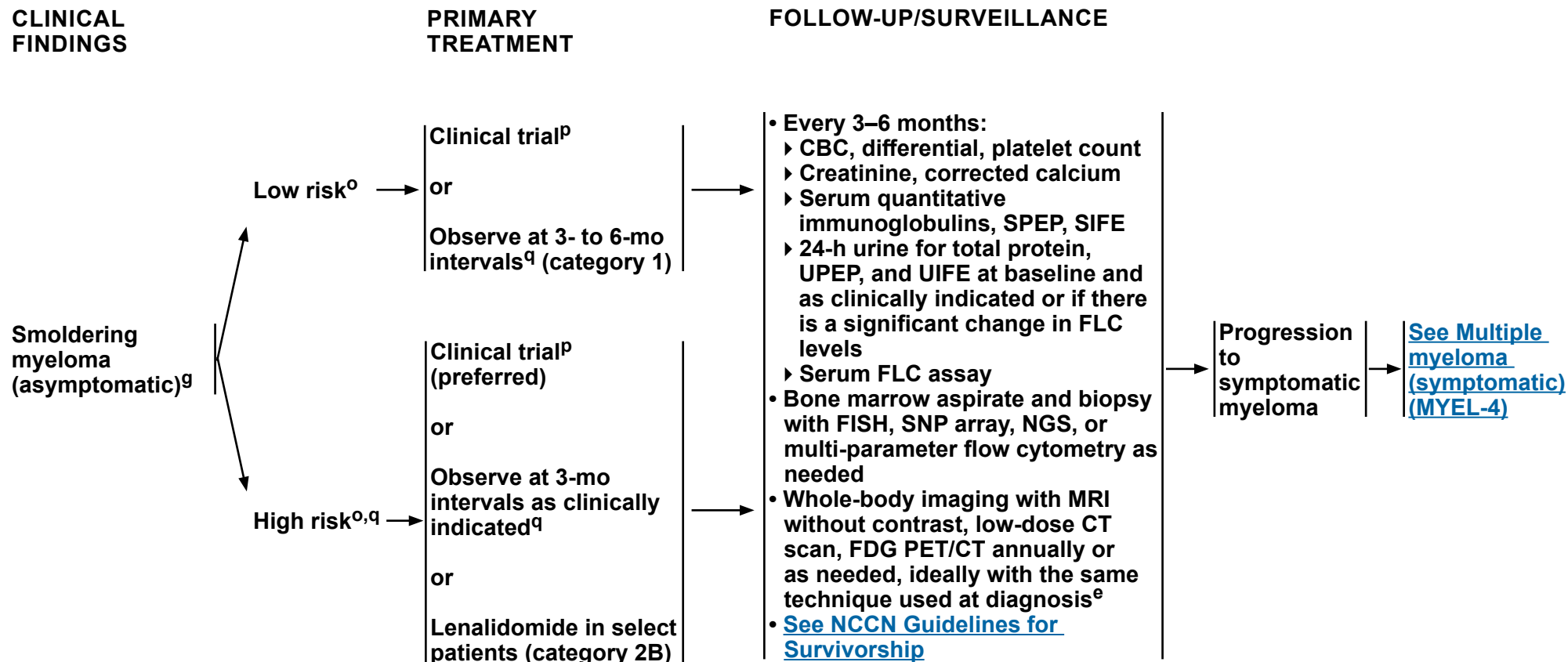
Note: All recommendations are category 2A unless otherwise indicated.

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.



NCCN Guidelines Version 4.2022

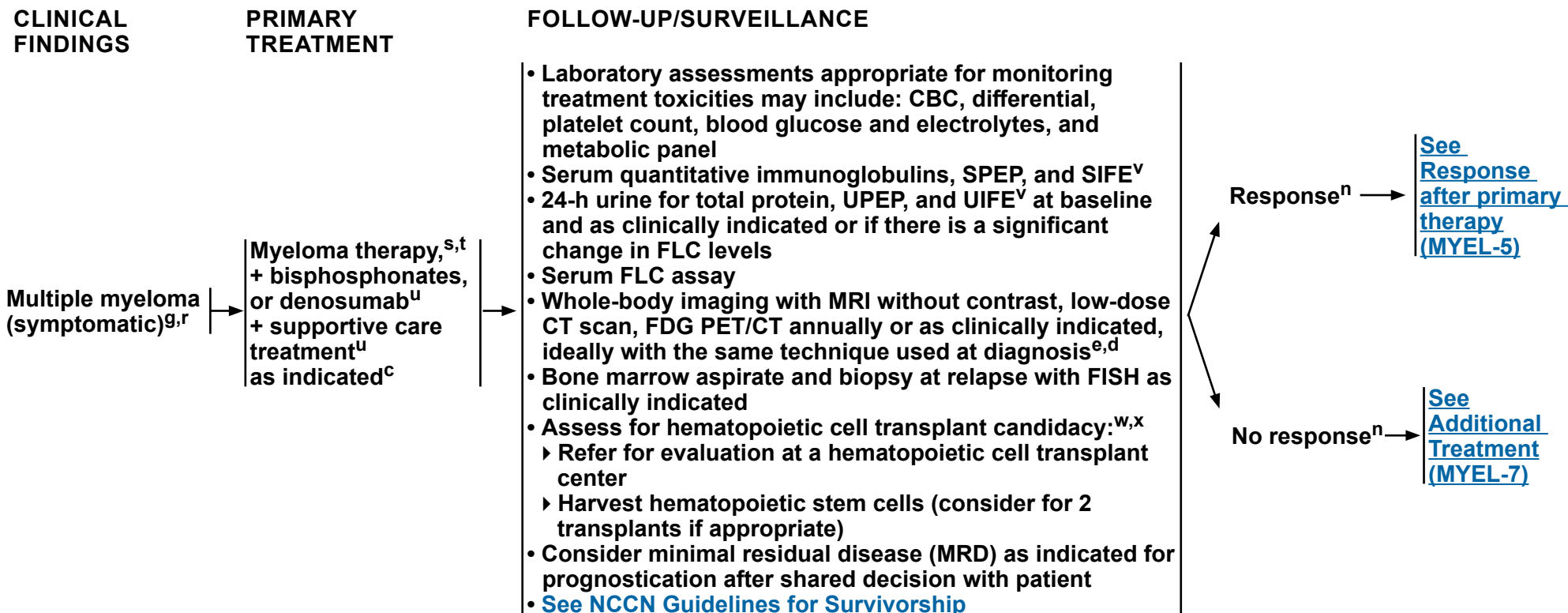
Multiple Myeloma

^e See Principles of Imaging (MYEL-B).^g See Definitions of Smoldering and Multiple Myeloma (MYEL-C).^o Bone marrow plasma cells (BMPCs) > 20%, M-protein > 2 g/dL, and serum free light chain ratio (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, et al. 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.**Note: All recommendations are category 2A unless otherwise indicated.****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.**



NCCN Guidelines Version 4.2022

Multiple Myeloma



^c See [Management of Renal Disease in Multiple Myeloma \(MYEL-J\)](#).

^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 \(MYEL-B\)](#).

^g See [Definitions of Smoldering and Multiple Myeloma \(MYEL-C\)](#).

ⁿ See [Response Criteria for Multiple Myeloma \(MYEL-E\)](#).

^r See [Staging Systems for Multiple Myeloma \(MYEL-A\)](#).

^s See [Myeloma Therapy \(MYEL-G\)](#).

^t See [General Considerations for Myeloma Therapy \(MYEL-F\)](#).

^u See [Supportive Care Treatment for Multiple Myeloma \(MYEL-H\)](#).

^v Needed only if protein electrophoresis is negative during follow-up.

^w Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and hematopoietic cell transplant. [See Discussion](#).

^x Renal dysfunction and advanced age are not contraindications to transplant.

Note: All recommendations are category 2A unless otherwise indicated.

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.

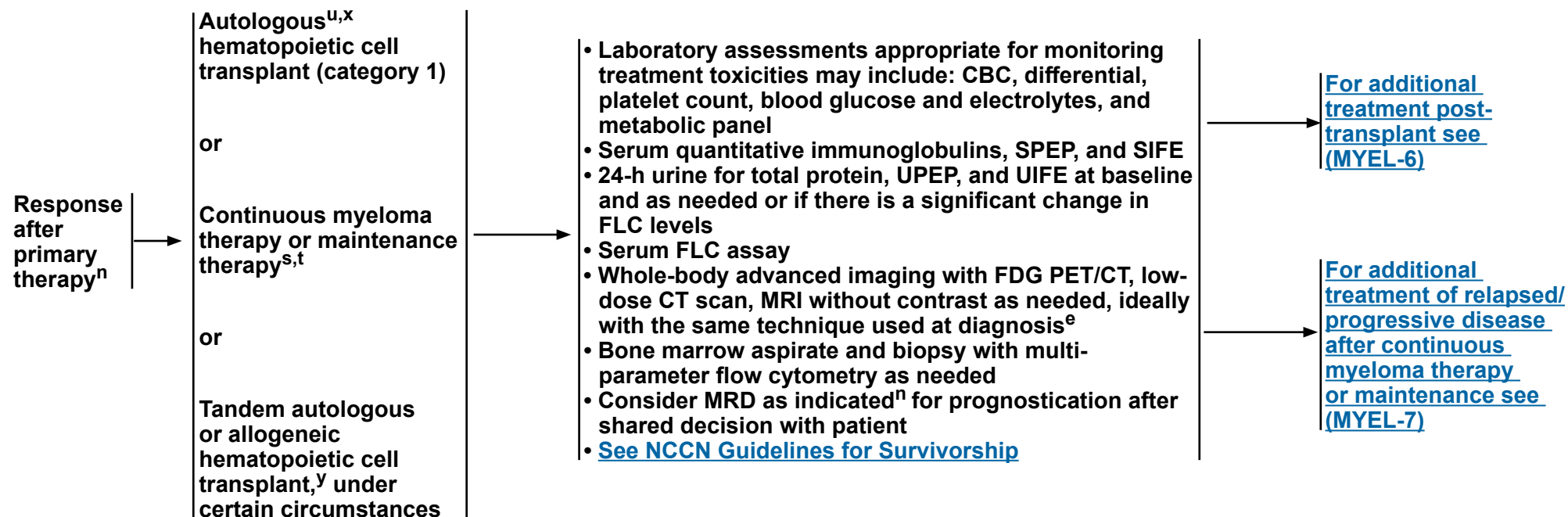


NCCN Guidelines Version 4.2022

Multiple Myeloma

MULTIPLE MYELOMA (SYMPTOMATIC)

FOLLOW-UP/SURVEILLANCE



^e [See Principles of Imaging \(MYEL-B\).](#)

ⁿ [See Response Criteria for Multiple Myeloma \(MYEL-E\).](#)

^s [See Myeloma Therapy \(MYEL-G\).](#)

^t [See General Considerations for Myeloma Therapy \(MYEL-F\).](#)

^u Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and hematopoietic cell transplant. [See Discussion.](#)

^x Renal dysfunction and advanced age are not contraindications to transplant.

^y Allogeneic hematopoietic cell transplant should preferentially be done in the context of a trial when possible.

Note: All recommendations are category 2A unless otherwise indicated.

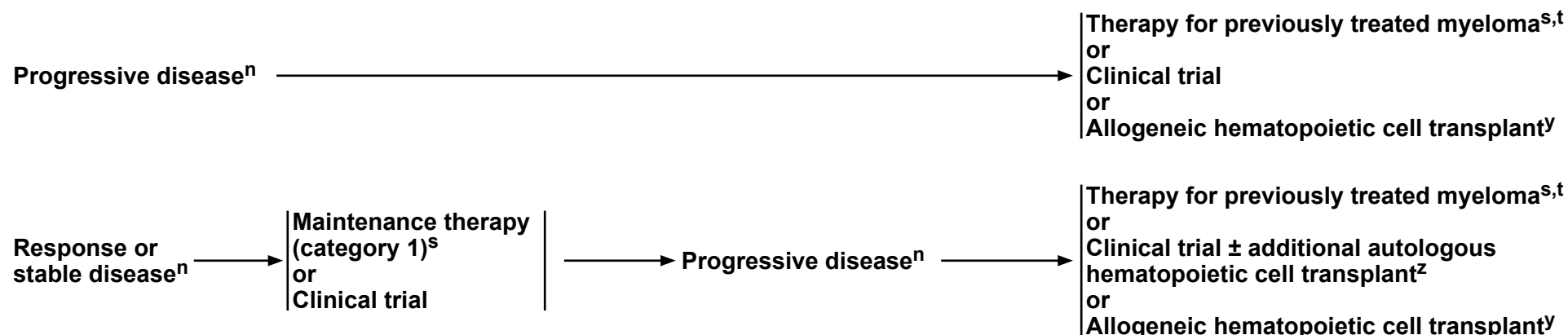
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



MULTIPLE MYELOMA (SYMPTOMATIC)

ADDITIONAL TREATMENT

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



Post-allogeneic hematopoietic cell transplant:


ⁿ See Response Criteria of Multiple Myeloma (MYEL-E).

^s See Myeloma Therapy (MYEL-G).

^t See General Considerations for Myeloma Therapy (MYEL-F).

^y Allogeneic hematopoietic cell transplant should preferentially be done in the context of a trial when possible.

^z Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding hematopoietic cell transplant and documented progression. Retrospective studies suggest a 2- to 3-year minimum length of remission for consideration of a second autologous hematopoietic cell transplant.

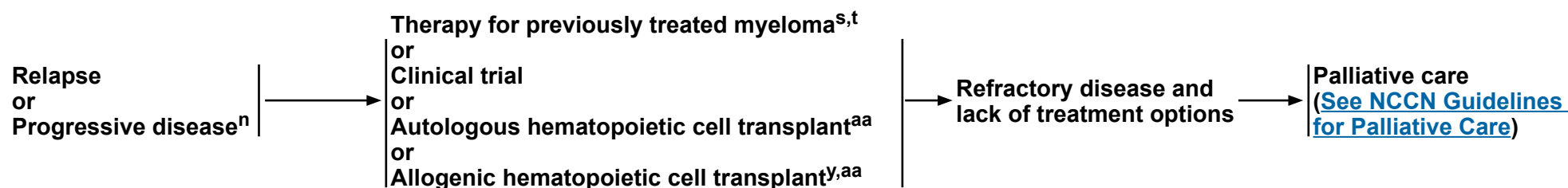
Note: All recommendations are category 2A unless otherwise indicated.

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)

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



ⁿ See [Response Criteria for Multiple Myeloma \(MYEL-E\)](#).

^s See [Myeloma Therapy \(MYEL-G\)](#).

^t See [General Considerations for Myeloma Therapy \(MYEL-F\)](#).

^y Allogeneic hematopoietic cell transplant should preferentially be done in the context of a trial when possible.

^{aa} Assess for hematopoietic cell transplant candidacy.

Note: All recommendations are category 2A unless otherwise indicated.

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.



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).

Note: All recommendations are category 2A unless otherwise indicated.

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.

**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 MM 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 small percentage of patients may have a negative PET/CT with active multiple myeloma MM.^{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 MM.

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 MM 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 MM 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 MM

- Advanced whole-body imaging (ie, FDG PET/CT, low-dose CT scan, whole-body MRI without contrast) is recommended as needed. 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 overall survival (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.

Note: All recommendations are category 2A unless otherwise indicated.

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.

**PRINCIPLES OF IMAGING**
References

- ^a Hillengass J, Mouloupoulos 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 18fluorodeoxyglucose 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.
- ⁿ Moreau P, Attal M, Caillot D, et al. Prospective evaluation of magnetic resonance imaging and [(18)F]fluorodeoxyglucose positron emission tomography-computed tomography at diagnosis and before maintenance therapy in symptomatic patients with multiple myeloma included in the IFM/DFCI 2009 trial: Results of the IMAJEM study. *J Clin Oncol* 2017;35:2911-2918.
- ^o Pawlyn C, Fowkes L, Otero S, et al. Whole-body diffusion-weighted MRI: a new gold standard for assessing disease burden in patients with multiple myeloma? *Leukemia* 2016;30:1446-1448.
- ^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.

Note: All recommendations are category 2A unless otherwise indicated.**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.**



DEFINITIONS OF SMOLDERING AND MULTIPLE MYELOMA

Smoldering Myeloma (Asymptomatic)^{a,b}

- 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,c}

- Clonal bone marrow plasma cells $\geq 10\%$ 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 μ mol/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 $\geq 60\%$
 - 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 (BMPCs) $>20\%$, M-protein >2 g/dL, and (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, et al. *Blood Cancer J* 2018;8:59.

^c Other examples of active disease include: repeated infections, amyloidosis, light chain deposition disease, or hyperviscosity.

Note: All recommendations are category 2A unless otherwise indicated.

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.



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 fractions [20–25 total fractions]) 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 [5–10 total 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 hematopoietic stem cell harvest or impact on potential future treatments.

Note: All recommendations are category 2A unless otherwise indicated.

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.



NCCN Guidelines Version 4.2022

Multiple Myeloma

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.

Reprinted from The Lancet Oncology, 17: Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328-e346, Copyright (2016), with permission from Elsevier.

Note: All recommendations are category 2A unless otherwise indicated.

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.

[Continued](#)
[Footnotes](#)

MYEL-E
1 OF 3



NCCN Guidelines Version 4.2022

Multiple Myeloma

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 $\geq 10\%$); Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD ^j of >1 lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion >1 cm in short axis; $\geq 50\%$ increase in circulating plasma cells (minimum of 200 cells per μ L) 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 $\geq 5\%$ 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 $\geq 5\%$ clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia).

Reprinted from The Lancet Oncology, 17: Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328-e346, Copyright (2016), with permission from Elsevier.

Note: All recommendations are category 2A unless otherwise indicated.

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.

Footnotes

**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 10⁵ plasma cells. Paiva B, Gutierrez NC, Rosinol L, et al, for the GEM (Grupo Español de 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.

Reprinted from The Lancet Oncology, 17: Kumar S, Paiva B, Anderson K, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma, e328-e346, Copyright (2016), with permission from Elsevier.

Note: All recommendations are category 2A unless otherwise indicated.

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.

**GENERAL CONSIDERATIONS FOR MYELOMA THERAPY****General Principles**

- Triplet regimens (2 drug classes and steroids) should be used as the standard therapy for patients with MM; however, patients with poor performance status or who are frail can be started on a 2-drug regimen, with a third drug added once performance status improves.
- A new triplet should preferably include drugs or drug classes patients have not been exposed to, or not exposed to at least 6 months.
- Frailty assessment should be considered in older adults. [See NCCN Guidelines for Older Adult Oncology.](#)
- For the Myeloma Frailty Score Calculator developed by International Myeloma Working Group for the prognosis of elderly myeloma patients, see <http://www.myelomafrailtyscorecalculator.net/>^a
- Consider dose modifications based on functional status and age.
- For additional supportive care while on myeloma therapy, [see Supportive Care Treatment for Multiple Myeloma \(MYEL-H\).](#)

Candidates for Hematopoietic Cell Transplant

- 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.

Dosing and Administration

- 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.
- For any regimen that includes daratumumab, this could be daratumumab for intravenous infusion or 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.

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.

^a Palumbo A, Brinchen S, Mateos MV, et al. Geriatric assessment predicts survival and toxicities in elderly myeloma patients: An International Myeloma Working Group report. Blood 2015;125:2068-2074.

Note: All recommendations are category 2A unless otherwise indicated.

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.



NCCN Guidelines Version 4.2022

Multiple Myeloma

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES ^{a-d}
Preferred Regimens <ul style="list-style-type: none"> • Bortezomib/lenalidomide/dexamethasone (category 1)
Other Recommended Regimens <ul style="list-style-type: none"> • Carfilzomib/lenalidomide/dexamethasone • Daratumumab/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances <ul style="list-style-type: none"> • Bortezomib/cyclophosphamide/dexamethasone^e • Bortezomib/doxorubicin/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone^f • Ixazomib/cyclophosphamide/dexamethasone^f • Bortezomib/thalidomide/dexamethasone (category 1) • Cyclophosphamide/lenalidomide/dexamethasone • Daratumumab/carfilzomib/lenalidomide/dexamethasone^g • Daratumumab/cyclophosphamide/bortezomib/dexamethasone • Daratumumab/bortezomib/thalidomide/dexamethasone • Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib^g (VTD-PACE)

MAINTENANCE THERAPY
Preferred Regimens <ul style="list-style-type: none"> • Lenalidomide^h (category 1)
Other Recommended Regimens <ul style="list-style-type: none"> • Ixazomib (category 2B)ⁱ • Bortezomib
Useful In Certain Circumstances <ul style="list-style-type: none"> • Bortezomib/lenalidomide ± dexamethasone^j

^a Selected, but not inclusive of all regimens.

^b [See Supportive Care Treatment for Multiple Myeloma \(MYEL-H\).](#)

^c [See General Considerations for Myeloma Therapy \(MYEL-F\).](#)

^d [See Management of Renal Disease in Multiple Myeloma \(MYEL-J\).](#)

^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 Treatment option for patients with renal insufficiency and/or peripheral neuropathy.

^g Generally reserved for the treatment of aggressive MM.

^h 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.

ⁱ Results from interim analyses of TOURMALINE MM3 and MM4 trials of ixazomib in the maintenance setting suggests a potential decrease in overall survival.

^j Dual maintenance recommended for high-risk MM.

Note: All recommendations are category 2A unless otherwise indicated.

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.

[Continued](#)

MYEL-G
1 OF 4



NCCN Guidelines Version 4.2022

Multiple Myeloma

PRIMARY THERAPY FOR NON-TRANSPLANT CANDIDATES ^{a-d}	
Preferred Regimens <ul style="list-style-type: none"> • Bortezomib/lenalidomide/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) 	
Other Recommended Regimens <ul style="list-style-type: none"> • Carfilzomib/lenalidomide/dexamethasone • Ixazomib/lenalidomide/dexamethasone • Daratumumab/bortezomib/melphalan/prednisone (category 1) • Daratumumab/cyclophosphamide/bortezomib/dexamethasone 	
Useful In Certain Circumstances <ul style="list-style-type: none"> • Bortezomib/dexamethasone • Bortezomib/cyclophosphamide/dexamethasone^e • Cyclophosphamide/lenalidomide/dexamethasone • Carfilzomib/cyclophosphamide/dexamethasone^f • Lenalidomide/low-dose dexamethasone (category 1)^k • Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients 	

MAINTENANCE THERAPY
Preferred Regimens <ul style="list-style-type: none"> • Lenalidomide (category 1)
Other Recommended Regimens <ul style="list-style-type: none"> • Ixazomib (category 2B)ⁱ • Bortezomib
Useful In Certain Circumstances <ul style="list-style-type: none"> • Bortezomib/lenalidomide^j

^a Selected, but not inclusive of all regimens.

^b [See Supportive Care Treatment for Multiple Myeloma \(MYEL-H\).](#)

^c [See General Considerations for Myeloma Therapy \(MYEL-F\).](#)

^d [See Management of Renal Disease in Multiple Myeloma \(MYEL-J\).](#)

^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 Treatment option for patients with renal insufficiency and/or peripheral neuropathy.

ⁱ Results from interim analyses of TOURMALINE MM3 and MM4 trials of ixazomib in the maintenance setting suggests a potential decrease in overall survival.

^j Dual maintenance recommended for high-risk MM.

^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.

Note: All recommendations are category 2A unless otherwise indicated.

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.

[Continued](#)

MYEL-G
2 OF 4



NCCN Guidelines Version 4.2022

Multiple Myeloma

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA^{a-d,l-n}

Note: If a regimen listed for previously treated multiple myeloma was used as a primary induction therapy and relapse is >6 months, the same regimen may be repeated.

Preferred Regimens for Early Relapses (1–3 prior therapies)

Order of regimens do not indicate comparative efficacy

- | | |
|--|---|
| <ul style="list-style-type: none"> • Bortezomib/lenalidomide/dexamethasone • Carfilzomib/lenalidomide/dexamethasone (category 1)^o • Daratumumab/bortezomib/dexamethasone (category 1) • Daratumumab/carfilzomib/dexamethasone (category 1) • Daratumumab/lenalidomide/dexamethasone (category 1) • Ixazomib/lenalidomide/dexamethasone (category 1)^m • Isatuximab-irfc/carfilzomib/dexamethasone (category 1) | <ul style="list-style-type: none"> • After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy <ul style="list-style-type: none"> ▶ Ixazomib/pomalidomide/dexamethasone ▶ Pomalidomide/bortezomib/dexamethasone (category 1) • After two prior therapies including lenalidomide and a PI <ul style="list-style-type: none"> ▶ Isatuximab-irfc/pomalidomide/dexamethasone (category 1) ▶ Daratumumab/pomalidomide/dexamethasone (category 1) |
|--|---|

Other Recommended Regimens for Early Relapses (1–3 prior therapies)

- | | |
|--|---|
| <ul style="list-style-type: none"> • 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/cyclophosphamide/bortezomib/dexamethasone • Elotuzumab/bortezomib/dexamethasone • Elotuzumab/lenalidomide/dexamethasone (category 1) • Ixazomib/cyclophosphamide/dexamethasone • Selinexor/bortezomib/dexamethasone (once weekly) (category 1) | <ul style="list-style-type: none"> • After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy <ul style="list-style-type: none"> ▶ Pomalidomide/carfilzomib/dexamethasone ▶ Pomalidomide/cyclophosphamide/dexamethasone • After two prior therapies including lenalidomide and a PI <ul style="list-style-type: none"> ▶ Elotuzumab/pomalidomide/dexamethasone |
|--|---|

For Useful in Certain Circumstances for Early Relapses (1–3 prior therapies), [see MYEL-G 4 of 4](#)

^a Selected, but not inclusive of all regimens.

^b [See Supportive Care Treatment for Multiple Myeloma \(MYEL-H\).](#)

^c [See General Considerations for Myeloma Therapy \(MYEL-F\).](#)

^d [See Management of Renal Disease in Multiple Myeloma \(MYEL-J\).](#)

^l Consideration for appropriate regimen in previously treated myeloma should be based on the context of clinical relapse.

^m Regimens included under 1–3 prior therapies can also be used later in the disease course/ Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.

ⁿ Autologous stem cell transplant should be considered in an eligible patient who had not previously received transplant or had a prolonged response to initial transplant

^o Clinical trials with these regimens primarily included patients who were lenalidomide-naïve or with lenalidomide-sensitive MM. Patients with lenalidomide refractory disease should be considered for a lenalidomide free triplet regimen.

Note: All recommendations are category 2A unless otherwise indicated.

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.

[Continued](#)

MYEL-G
3 OF 4



NCCN Guidelines Version 4.2022

Multiple Myeloma

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA^{a-d,n,p}

Useful in Certain Circumstances for Early Relapses (1–3 prior therapies)

If a regimen listed for previously treated multiple myeloma was used as a primary induction therapy and relapse is >6 months, the same regimen may be repeated.

- | | |
|---|---|
| <ul style="list-style-type: none"> • Bendamustine • Bortezomib/dexamethasone (category 1) • Carfilzomib/cyclophosphamide/thalidomide/dexamethasone • Carfilzomib (weekly)/dexamethasone • High-dose or fractionated cyclophosphamide • Ixazomib/dexamethasone • Lenalidomide/dexamethasone (category 1)^q • Selinexor/daratumumab/dexamethasone • Venetoclax/dexamethasone only for t(11;14) patients • Selinexor/carfilzomib/dexamethasone | <ul style="list-style-type: none"> • After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy <ul style="list-style-type: none"> ▶ Pomalidomide/dexamethasone (category 1)^q ▶ Selinexor/pomalidomide/dexamethasone • For treatment of aggressive MM <ul style="list-style-type: none"> ▶ Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP) ▶ Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE) • After at least three prior therapies including a PI and an IMiD or are double-refractory to a PI and an IMiD <ul style="list-style-type: none"> ▶ Daratumumab |
|---|---|

Therapies for patients with Late Relapses (>3 prior therapies)^{a-c,m,n}

- | |
|---|
| <ul style="list-style-type: none"> • After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD <ul style="list-style-type: none"> ▶ Belantamab mafodotin-blmf ▶ Idecabtagene vicleucel |
| <ul style="list-style-type: none"> • After 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 <ul style="list-style-type: none"> ▶ Selinexor/dexamethasone |

^a Selected, but not inclusive of all regimens.

^b See [Supportive Care Treatment for Multiple Myeloma \(MYEL-H\)](#).

^c See [General Considerations for Multiple Myeloma Therapy \(MYEL-F\)](#).

^d See [Management of Renal Disease in Multiple Myeloma \(MYEL-J\)](#).

^m Regimens included under 1–3 prior therapies can also be used later in the disease course/ Attempt should be made to use drugs/drug classes the patients have not been exposed to or exposed to >1 line prior.

ⁿ Autologous stem cell transplant should be considered in an eligible patient who had not previously received transplant or had a prolonged response to initial transplant

^p Consideration for appropriate regimen in previously treated myeloma should be based on the context of clinical relapse.

^q Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

Note: All recommendations are category 2A unless otherwise indicated.

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.

**SUPPORTIVE CARE FOR MULTIPLE MYELOMA****Bone Disease**

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

Hypercalcemia

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

Hyperviscosity

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

Anemia

- [See NCCN Guidelines for Hematopoietic Growth Factors.](#)
- Consider erythropoietin for anemic patients.

Infection

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

Renal Dysfunction

- [See Management of Renal Disease in Multiple Myeloma \(MYEL-J\)](#)

Venous Thromboembolism (VTE)

- For management of VTE, risk stratification, and VTE prophylaxis, [See MYEL-I](#)

^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.**Note:** All recommendations are category 2A unless otherwise indicated.**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.



NCCN Guidelines Version 4.2022

Multiple Myeloma

MANAGEMENT OF VENOUS THROMBOEMBOLISM (VTE) IN MULTIPLE MYELOMA

VTE RISK STRATIFICATION USING IMPEDE OR SAVED SCORING SYSTEM

IMPEDE Score ^a for Risk Stratification (points assigned)			
Individual Risk Factors	Points	Myeloma Risk Factors	Points
Positive Factors			
Central venous catheter/Tunneled central line	+2	Immunomodulatory drug (IMiD)	+4
Pelvic, hip, or femur fracture	+4	Erythropoiesis-stimulating agent	+1
Obesity (BMI ≥25)	+1	Low-dose dexamethasone	+2
Previous VTE	+5	High-dose dexamethasone	+4
		Doxorubicin or multiagent chemotherapy	+3
Negative Factors			
Ethnicity/Race = Asian/Pacific Islander	-3		
Existing thromboprophylaxis: prophylactic LMWH (low-molecular-weight heparin) or aspirin	-3		
Existing thromboprophylaxis: therapeutic LMWH or warfarin	-4		

SAVED Score ^b for Risk Stratification	
Variable	Points
Surgery within 90 days	+2
Asian Race	-3
VTE history	+3
Age ≥ 80 years	+1
Dexamethasone (regimen dose)	
• Standard dose (120-160 mg/cycle)	+1
• High dose (>160 mg/cycle)	+2

^a Adapted from Sanfilippo KM. Am J Hematol 2019;94:1176-1184.

^b Adapted from: Li A, Wu Q, Luo S, et al.. J Natl Compr Canc Netw 2019;17:840-847

Note: All recommendations are category 2A unless otherwise indicated.

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 VENOUS THROMBOEMBOLISM (VTE) IN MULTIPLE MYELOMA****General Principles:**

- Highest risk for VTE is in the first 6 months following new diagnosis of MM.
- VTE prophylaxis is administered assuming there are no contraindications to anticoagulation agents or anti-platelets (Please see page VTE-A of the [NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease](#).)
- All anticoagulants carry increased risk of bleeding; careful consideration needs to be made regarding risks and benefits for each patient.
- Warfarin at INR 2–3 is not directly comparable to the other agents listed at prophylactic doses with respect to bleeding and thrombotic risks.
- Patients already on therapeutic anticoagulants for other reasons (eg, atrial fibrillation) should continue anticoagulation therapy.
- If no other coagulopathy, full-dose anticoagulation is contraindicated with thrombocytopenia <50,000/μL; in patients with high risk for VTE, prophylactic anticoagulation may be appropriate even if platelet count is as low as 25,000/μL.
- Indications for long-term anticoagulation include unprovoked VTE or provoked VTE in the presence of a risk factor that is still present.
- For any patients who develop VTE on IMiD-based therapy, continue using therapeutic dose AC for as long as IMiD-based therapy is indicated.

Factors Impacting the Choice of Optimal VTE Prophylaxis Agent:

- Bleeding risk (eg, concurrent coagulopathy, disseminated intravascular coagulation, hyperviscosity)
- Cytopenias (eg, platelet count ± hemoglobin)
- Concurrent medications (eg, strong cytochrome P inducers/inhibitors, single/dual anti-platelets)
- Current renal function (eg, creatinine clearance)
- Patient choice (eg, preference for mode of administration, dietary restrictions)
- Insurance coverage/restrictions (including cost of therapy)
- Availability of reversal agents in case of emergency bleeding
- History of heparin-induced thrombocytopenia
- Extremes of body weight
- Carfilzomib + IMiD therapy

References:

Palumbo A. Leukemia 2008;22:414-423.
 Kristinsson SY. Hematology Am Soc Hematol Educ Program 2010;2010:437-444.
 Carrier M. N Engl J Med 2019;380:711-719.
 Khorana AA. N Engl J Med 2019;380:720-728.
 Wang T-F. J Thromb Haemost 2019;17:1772-1778. Note: The AVERT apixaban trial had only 2.6% myeloma patients, and myeloma patients were excluded from the CASSINI rivaroxaban trial.

Note: All recommendations are category 2A unless otherwise indicated.

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 VENOUS THROMBOEMBOLISM (VTE) IN MULTIPLE MYELOMA

RECOMMENDATIONS FOR VTE PROPHYLAXIS

VTE Prophylaxis Recommendations	
≤3 Points by IMPEDE Score or <2 Points by SAVED Score	≥4 Points by IMPEDE Score or ≥2 SAVED Score ^c
<ul style="list-style-type: none"> Aspirin 81–325 mg once daily 	<ul style="list-style-type: none"> LMWH (equivalent to enoxaparin 40 mg daily) OR Rivaroxaban 10 mg daily OR Apixaban 2.5 mg twice daily OR Fondaparinux 2.5 mg daily OR Warfarin (target INR 2.0–3.0)

Duration of VTE Prophylaxis
<ul style="list-style-type: none"> Indefinite while on myeloma therapy 3–6 months followed by aspirin (longer periods of anticoagulation may be considered in the presence of additional patient, treatment-specific, or transient VTE risk factors)

^c A less common choice of agent includes Dalteparin 5,000 units SC daily (category 2B)

Note: All recommendations are category 2A unless otherwise indicated.

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.

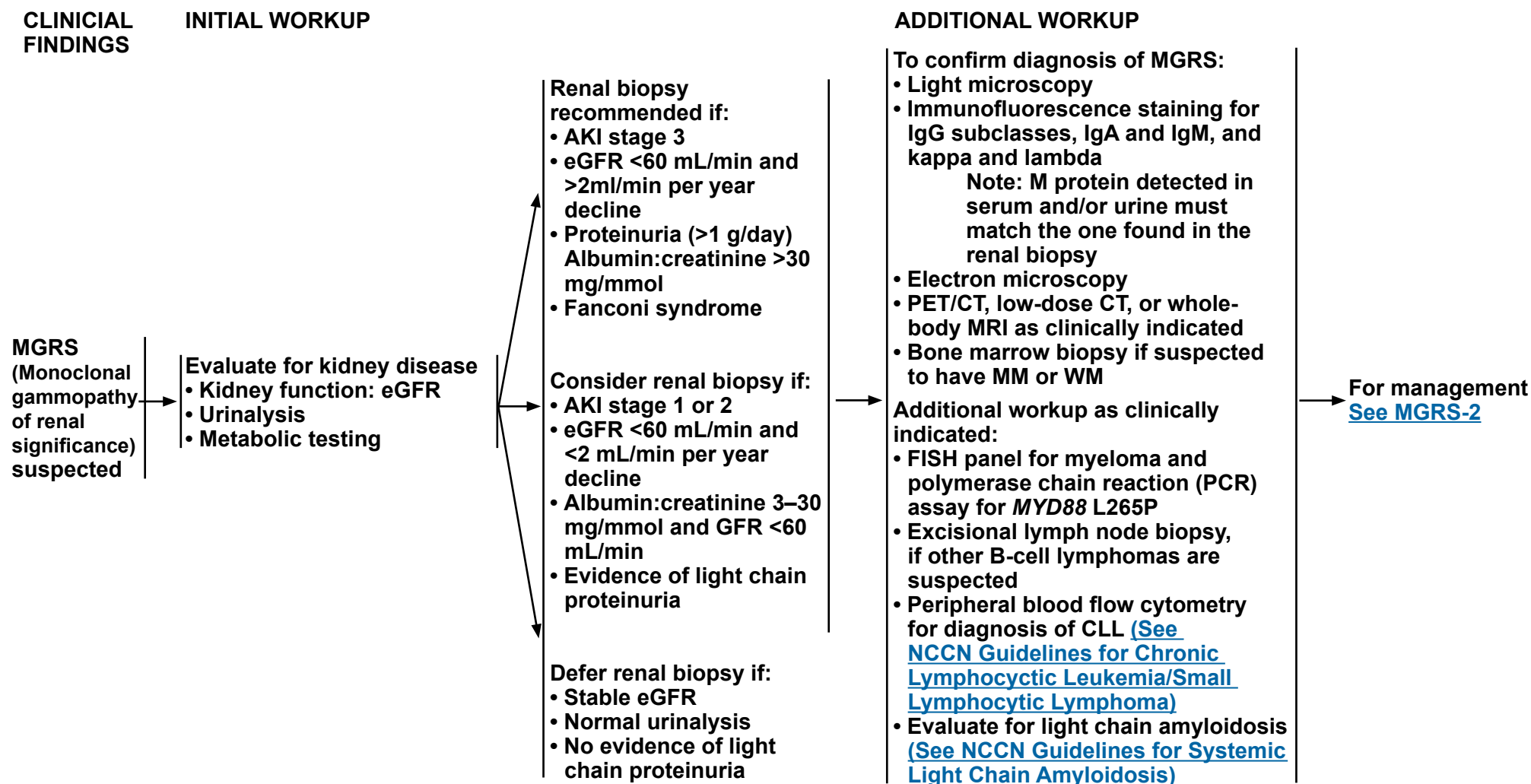
Note: All recommendations are category 2A unless otherwise indicated.

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.



MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE



Note: All recommendations are category 2A unless otherwise indicated.

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.



MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

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 \(MYEL-E\)](#).

Note: All recommendations are category 2A unless otherwise indicated.

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.



NCCN Guidelines Version 4.2022

Multiple Myeloma

MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE (FOR MGRS, [SEE MGRS-1](#))

MONOCLONAL GAMMOPATHY OF NEUROLOGICAL SIGNIFICANCE

INITIAL WORKUP

CLINICAL FINDINGS

IgM^a MGNS
(Monoclonal
gammopathy
of neurological
significance)
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, ([See NCCN Guidelines for Systemic Light Chain Amyloidosis](#)), WM ([See NCCN Guidelines for WM/LPL](#)), or POEMS ([See POEMS-1](#)), if appropriate.
 - 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

- 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)

- 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

[See NCCN Guidelines for Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma](#)

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.

Note: All recommendations are category 2A unless otherwise indicated.

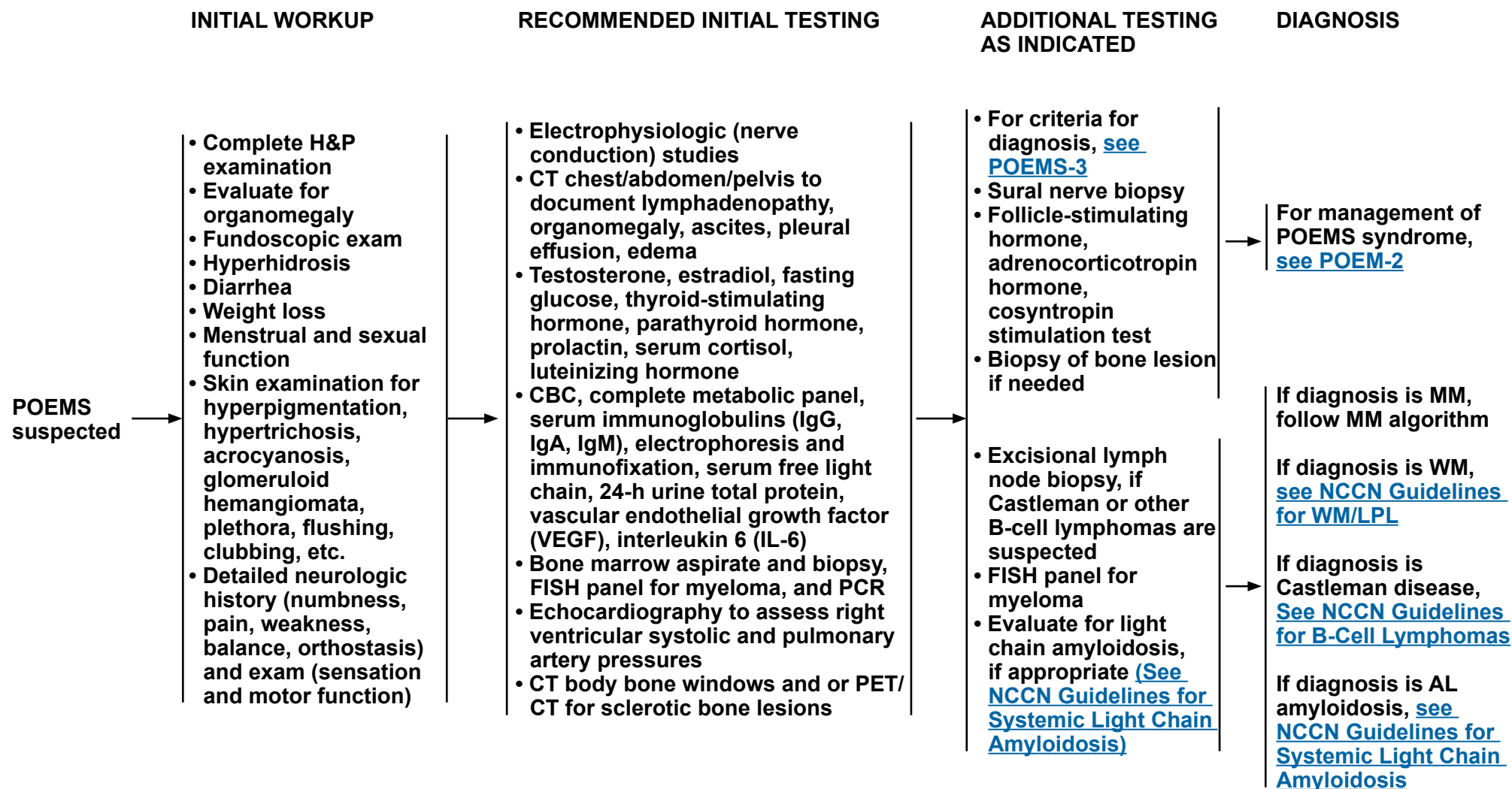
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.



NCCN Guidelines Version 4.2022

Multiple Myeloma

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



Adapted with permission: Dispenzieri A. Am J Hematol 2019;94:812-827.

Note: All recommendations are category 2A unless otherwise indicated.

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.



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 hematopoietic 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
 - ▶ Bortezomib^a/dexamethasone
 - ▶ Melphalan/dexamethasone
 - ▶ Cyclophosphamide/dexamethasone
 - ▶ Pomalidomide/dexamethasone

RESPONSE ASSESSMENT

→ [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.

Note: All recommendations are category 2A unless otherwise indicated.

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.



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 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, pituitary, gonadal, parathyroid, pancreatic)
	9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomas, 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 B₁₂ levels

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.

^a There is a Castleman 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.

^b Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion.

^c 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 disease is present.

Reprinted with permission: Dispenzieri A. Am J Hematol 2019;94:812-827.

Note: All recommendations are category 2A unless otherwise indicated.

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.



NCCN Guidelines Version 4.2022

Multiple Myeloma

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.

Reprinted with permission: Dispenzieri A. Am J Hematol 2019;94:812-827.

Note: All recommendations are category 2A unless otherwise indicated.

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.



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.



NCCN Guidelines Version 4.2022

Multiple Myeloma

Discussion

This discussion corresponds to the NCCN Guidelines for Multiple Myeloma. Last updated: October 19th, 2020.
Note: Regimens containing panobinostat were removed due to market withdrawal of the agent (Dec 14th, 2021).

Table of Contents

Overview	2
Literature Search Criteria and Guidelines Update Methodology	2
Diagnosis and Workup	2
Solitary Plasmacytoma	5
Primary Therapy for Solitary Plasmacytoma	6
Surveillance/Follow-up Tests for Solitary Plasmacytoma	6
Smoldering (Asymptomatic) Myeloma	6
Primary Therapy for Smoldering (Asymptomatic) Myeloma	7
Surveillance/Follow-up Tests for Smoldering (Asymptomatic) Myeloma	8
Active (Symptomatic) Multiple Myeloma	8
Primary Therapy for Active (Symptomatic) Multiple Myeloma	8
Monitoring After Primary Myeloma Therapy of Both Transplant and Non-Transplant Candidates	20
Hematopoietic Cell Transplantation	20
Follow-Up After Hematopoietic Cell Transplantation	25
Maintenance Therapy	25
Therapy for previously treated Multiple Myeloma	27

Supportive Care for Multiple Myeloma	39
Management of Renal Disease in Multiple Myeloma	42
Monoclonal gammopathy of Clinical significance (MGCS)	44
Monoclonal Gammopathy of Renal Significance (MGRS)	44
Initial Workup	44
Treatment	44
Monoclonal Gammopathy of Neurological Significance (MGNS)	46
POEMS Syndrome	47
References	48



NCCN Guidelines Version 4.2022

Multiple Myeloma

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 18% of hematologic malignancies in the United States.¹ MM is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.² The American Cancer Society has estimated 32,270 new MM cases in the United States in 2020, with an estimated 12,830 deaths.¹

Literature Search Criteria and Guidelines Update Methodology

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 Multiple Myeloma, Solitary Plasmacytoma, Multiple Myeloma, Monoclonal Gammopathy of Undetermined Significance, POEMS syndrome. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes biomedical literature.³

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

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

The initial diagnostic workup in all patients should include a history and physical examination. To differentiate symptomatic and asymptomatic MM the following baseline laboratory studies are needed: a 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; liver function tests, serum calcium; albumin; lactate dehydrogenase (LDH); and beta-2 microglobulin.

Peripheral smear may show abnormal distribution of red blood cells such as the Rouleaux formation (red cells taking on the appearance of a stack of coins) due to elevated serum proteins.⁴ Increased BUN and creatinine indicate decreased kidney function, whereas LDH and beta-2 microglobulin levels reflect tumor cell characteristics.

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



NCCN Guidelines Version 4.2022

Multiple Myeloma

Free Light-chain Assay: The serum FLC assay along with serum analyses (SPEP and SIFE) yields high sensitivity while screening for MM and related plasma cell disorders.⁵ It is also helpful in prognostication of monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, active MM, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.^{5,6} The serum FLC assay also allows for quantitative monitoring of patients with light chain amyloidosis and light chain myeloma. In addition to all of the above, the FLC ratio (FLCr) is required for documenting stringent complete response (sCR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.⁷ The serum FLC assay cannot replace the 24-hour UPEP for monitoring patients with measurable urinary M-protein and can also be affected by renal function. Once the M-protein is quantified, it is important to use the same test for serial studies to ensure accurate relative quantification.

Bone Marrow Evaluation: The percentage of clonal bone marrow plasma cells (≥10%) is a major criterion for the diagnosis of MM. The percentage of plasma cells in bone marrow is estimated by unilateral bone marrow aspiration and biopsy. Immunohistochemistry and/or flow cytometry can be used to confirm presence of monoclonal plasma cells, and to more accurately quantify plasma cell involvement.⁸ The cytoplasm of abnormal plasma cells contain either kappa or lambda light chains, and predominance of one or the other light chain expressing plasma cells indicate clonality. Specific immunophenotypic profiles of the myeloma cells may have prognostic implications.⁹

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 on the plasma cells obtained from bone marrow aspiration.

Metaphase cytogenetics may provide additional information. Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications.

Deletion of 17p13 (the locus for the tumor-suppressor gene, *p53*) leads to loss of heterozygosity of *TP53* and is considered a high-risk feature in MM.¹⁰⁻¹² 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.¹³⁻¹⁶ 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.¹⁷ The short arm is most often associated with deletions and the long arm with amplifications.¹⁸ 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.^{17,19}

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.^{20,21}

According to the NCCN Multiple Myeloma Panel members, the FISH panel for prognostic estimation of plasma cells should examine for del 13, del 17p13, t(4;14), t(11;14), t(14;16), t(14;20), 1q21 gain/amplification, and 1p deletion. The utility of this information is to determine biological subtype



NCCN Guidelines Version 4.2022

Multiple Myeloma

and for prognostic recommendations as well as candidacy for clinical trials.

Imaging: A skeletal survey has been the standard for decades for assessing bone disease for any individual with suspected MM.²² However, this technique has significant limitations related to lower sensitivity compared to advanced imaging. CT alone or in combination with FDG PET has been shown to be significantly superior regarding the sensitivity to detect osteolytic lesions in patients with monoclonal plasma cell disorders. In a multi-center analysis by the IMWG conventional skeletal survey was compared with whole-body CT scans from 212 patients with monoclonal plasma cell disorders. Whole-body CT was positive in 25.5% of patients with negative skeletal survey. The sensitivity of the skeletal survey and whole-body low-dose CT in the long bones is not significantly different, the difference is mainly in detection of abnormalities in spine and pelvis.^{23,24} In a study of 29 patients, 5 (17%) showed osteolytic lesions in CT while skeletal survey results were negative.²⁵ Furthermore, studies have shown whole-body low-dose CT is superior to skeletal survey radiographs in areas that are difficult to visualize with skeletal surveys such as skull and ribs.²⁶

FDG PET/CT too has been shown to identify more lesions than plain x-rays and detect lesions in patients with negative skeletal surveys.²⁷⁻²⁹ It is important to note that if PET/CT is chosen instead of whole-body low-dose CT, the imaging quality of the CT part of the PET/CT should be equivalent to a whole-body low-dose CT. Usually the CT part is used only for attenuation correction, which may not be sufficient to assess bone disease due to MM and stability of the spine. Whole body PET/CT is useful in detecting extramedullary disease outside of the spine.

For initial diagnostic workup of patients suspected of having MM, the NCCN Panel recommends, either whole-body low-dose CT or FDG PET/CT. The Panel has also noted that skeletal survey including long

bones is acceptable where advanced imaging is not available (eg. in low resource settings). CT contrast agents are not necessary for detection of myeloma bone disease and should be generally avoided in myeloma patients whenever possible.

Additional Diagnostic Tests

The NCCN Multiple Myeloma Panel recommends additional tests that may be useful in some circumstances. MRI is useful for discerning smoldering myeloma from MM. Since the disease burden in patients with smoldering myeloma is lower than those with MM, imaging techniques with high sensitivity need to be used and MRI is a sensitive technique for detecting marrow infiltration by myeloma.^{30,31} According to the NCCN Panel, if whole-body low-dose CT or FDG PET/ CT is negative, consider whole-body MRI without contrast to discern smoldering myeloma from MM.

A tissue biopsy may also be necessary to confirm the presence of plasmacytomas. Plasma cell proliferation assays may be helpful to identify the fraction of proliferating myeloma cell population.³² 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.

Human leukocyte antigen (HLA)-type must be obtained, if a patient is being considered for allogeneic transplant.

Single nucleotide polymorphism (SNP) array and/or next generation sequencing (NGS) panel on bone marrow help provide a more detailed evaluation of MM genetics allows for further risk categorization through the identification of additional abnormalities that may be of prognostic and/or



NCCN Guidelines Version 4.2022

Multiple Myeloma

therapeutic value.³³ Therefore, the NCCN Multiple Myeloma Panel has included these tests as useful adjunct in certain circumstances.

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

Clinical Findings

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

The IMWG recently updated the disease definition of MM to include biomarkers in addition to existing requirements of CRAB features.³⁴ The CRAB criteria that define MM include: increased calcium levels (greater than 11.5 mg/dL), renal insufficiency (creatinine greater than 2 mg/dL or creatinine clearance less than 40 mL/min), anemia (hemoglobin less than 10 g/dL or 2 g/dL less than normal), and presence of bone lesions. The IMWG has also clarified that presence of one or more osteolytic lesions seen on skeletal radiography, whole-body MRI, or whole-body FDG PET/CT fulfills the criteria for bone disease.³⁴ The MM-defining biomarkers identified by the IMWG SLiM features (SLiM- stands for **S**ixty, **L**ight chain ratio, **M**RI) features include one or more of the following: greater than or equal to sixty percent clonal plasma cells in the bone marrow; involved/uninvolved free light chain ratio of 100 or more with the involved FLC being greater than or equal 100 mg/L; or MRI with more than one

focal marrow (non-osteolytic) lesion³⁴ All of these myeloma defining events are referred to as SLiM-CRAB.

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.³⁴ 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.³⁴ Recently, a study analyzed clinical and laboratory information from 421 patients with smoldering myeloma and identified monoclonal protein greater than 2g/dL, FLCr of greater than 20, and greater than 20% plasma cells as important risk factors for progression. Patients with 2 or more of these features had a median time to progression (TTP) of 29 months.³⁵

Those with active MM can be staged using the International Staging System (ISS).³⁶ The ISS is based on easily obtained laboratory measures (serum beta-2 microglobulin and serum albumin) and is easier to use than the Durie-Salmon Staging System for patients with previously untreated MM. The ISS has been revised (R-ISS) to include serum beta-2 microglobulin and serum albumin and prognostic information obtained from the LDH and high-risk chromosomal abnormalities [t(4;14), t(14;16), 17p13 deletion] detected by FISH and is the preferred staging approach.³⁷ Having del(17p) and/or translocation t(4;14) and/or translocation t(14;16) are considered as high-risk. Those with no high-risk chromosomal abnormality are considered standard-risk.

Solitary Plasmacytoma

The diagnosis of solitary plasmacytoma requires a thorough evaluation with advanced imaging studies to rule out the presence of additional



NCCN Guidelines Version 4.2022

Multiple Myeloma

lesions or systemic disease, because many patients presumed to have solitary plasmacytomas are found to have additional sites^{38,39}

Primary Therapy for Solitary Plasmacytoma

The treatment and follow-up options for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement (less than 10% plasma cells in bone marrow) are similar. Radiation therapy has been shown to provide excellent local control of solitary plasmacytomas.⁴⁰⁻⁴⁶ The largest retrospective study (N = 258) included patients with solitary plasmacytoma (n = 206) or extramedullary plasmacytoma (n = 52).⁴⁷ 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%).⁴⁶

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.^{45,46,48}

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. Occasionally, surgery may be performed if a lesion causes structural instability or neurologic compromise. For extraosseous plasmacytomas primary treatment is radiation therapy (40–50 Gy in 1.8–2.0 Gy/fraction)⁴³ to the involved field with surgery,⁴⁹ if clinically necessary.

Surveillance/Follow-up Tests for Solitary Plasmacytoma

Follow-up and surveillance tests for solitary plasmacytoma consist of blood and urine tests and imaging. Serial measurements to check for re-emergence or appearance of M-protein are required to confirm disease sensitivity to radiation therapy. The recommended follow-up interval for these patients is every 3 to 6 months; however, patients with soft tissue

and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up. According to the NCCN Panel, one should consider using the same imaging modality used during the initial workup for the follow-up assessments. Bone surveys are inadequate for this type of surveillance.

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

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.⁵⁰⁻⁵² Imaging studies are recommended yearly, preferably with the same technique used at diagnosis, for at least 5 years.

If progression to MM occurs, then the patient should be re-evaluated as described in *Diagnosis and Workup*, 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.⁵³ Patients with asymptomatic smoldering MM may have an indolent course for many years without therapy.



NCCN Guidelines Version 4.2022

Multiple Myeloma

Primary Therapy for Smoldering (Asymptomatic) Myeloma

Smoldering myeloma is a precursor to MM. All patients with smoldering myeloma have a risk of progression to MM.⁵⁴ However, the rate of progression varies from months to several years based on certain risk features.⁵⁴

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

A relatively small, randomized, prospective, phase III study by the PETHEMA group investigated whether early treatment with lenalidomide and dexamethasone in patients (n = 119) with smoldering myeloma, at high risk of progression to active MM, prolongs the TTP.⁵⁵ 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 greater than or equal to 3 g/dL, an IgA level of greater than or equal to 2 g/dL, or a urinary Bence Jones protein level of greater than 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).⁵⁵ At a median follow-up of 75 months (range, 27–57 months), treatment with lenalidomide and dexamethasone delayed median TTP to symptomatic disease compared to no treatment (TTP was not reached in the treatment arm compared to 23 months in the observation arm; HR, 0.24; 95% CI, 0.14–0.41).⁵⁶ The high OS rate seen after 3 years was also maintained (HR, 0.43; 95% CI, 0.20–0.90). According to the NCCN Panel, the flow cytometry-based high-risk criteria specified in the study is not uniformly available and participants did not receive advanced imaging. Based on the criteria used in the trial, some patients with active myeloma were classified as having high-risk smoldering myeloma.

In a larger multicenter phase III randomized trial, patients with smoldering myeloma (n= 182) were either treated with lenalidomide until progression or observed. The lenalidomide group experienced improved progression-free survival (PFS) and decreased end organ damage (eg, renal failure, bone lesions) when compared with those who were observed.⁵⁷ Grade 3 or 4 adverse events were reported in 41% of patients treated with lenalidomide.⁵⁷ On subgroup analysis, the PFS benefit was seen in those with high-risk smoldering myeloma but was less clear in those with low- or intermediate-risk disease.⁵⁷

The Mayo 2018 20/20 criteria stratify patients based on risk. The criteria take into consideration the following risk factors: percentage of bone marrow plasma cells (BMPC) greater than 20%, M-protein greater than 2 g/dL, and FLCr greater than 20. Patients with two or more of the above risk factors are considered to have high risk. These risk factors were developed from a retrospective study of patients with smoldering myeloma (n= 417). In those with high risk (≥ 2 factors present), the estimated median TTP was 29 months, in those with intermediate risk (1 factor present), the estimated median TTP was 68 months, and for those with low risk (none of the risk factors present), the estimated median TTP was 110 months.³⁵

The Mayo 2018 20/20 criteria were validated in a large retrospective analysis of 2004 patients with smoldering myeloma.⁵⁸ The estimated progression rates at 2 years among those with low-, intermediate-, and high-risk disease were 5%, 17%, and 46% respectively.⁵⁸

The NCCN Panel suggests using the Mayo 2018/IMWG 20/20 criteria to stratify patients based on risk. According to the NCCN Panel, the low risk group should be managed by enrolling in a clinical trial or observe at 3- to 6-month intervals (category 1). For the high-risk group, the NCCN Panel prefers enrollment in an ongoing clinical trial or treatment with single-agent lenalidomide only in carefully selected patients (category 2B)^{55,57} or



NCCN Guidelines Version 4.2022

Multiple Myeloma

observation at 3-month intervals, as clinically indicated. Those with rising markers or high-risk factors must be monitored closely.

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

The surveillance/follow-up tests for smoldering myeloma include CBC with differential and platelet count; serum chemistry for creatinine, albumin, corrected calcium, serum quantitative immunoglobulins, SPEP, and SIFE; and serum FLC assay as clinically indicated. The urine tests include 24-hour urine assay for total protein, UPEP, and UIFE.

Bone marrow aspirate and biopsy with FISH, SNP array, NGS, or multiparameter flow cytometry may be used as clinically indicated.

Imaging studies with MRI without contrast, whole-body low-dose CT and/or CT and/or whole-body FDG PET/CT are recommended annually or as clinically indicated. The NCCN Panel recommends considering using the same imaging modality used during the initial workup for the follow-up assessments.

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

Active (Symptomatic) Multiple Myeloma

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

Primary Therapy for Active (Symptomatic) Multiple Myeloma

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

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

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

The page titled *Myeloma Therapy* in the algorithm has a list of primary therapy regimens recommended by the NCCN Multiple Myeloma Panel members for transplant eligible and non-transplant candidates and also lists drugs recommended for maintenance therapy in each setting. The list is selected and is not inclusive of all regimens.

The NCCN Multiple Myeloma Panel has categorized all myeloma therapy regimens as: “preferred,” “other recommended,” or “useful in certain circumstances.” The purpose of classifying regimens as such is to convey the sense of the Panel regarding the relative efficacy and toxicity of the regimens. Factors considered by the Panel include evidence, efficacy, toxicity, pre-existing comorbidities such as renal insufficiency, and in some cases access to certain agents.

The NCCN Panel prefers 3-drug regimens as the standard for primary treatment of all patients who are transplant eligible. This is based on improved response rates, depth of response, and rates of progression-free survival (PFS) or OS seen with 3-drug regimens in clinical trials. The doublet regimens are no longer recommended for transplant candidates with the rationale that doublets would be recommended for patients who would not be considered for initial treatment with a three-drug regimen.



NCCN Guidelines Version 4.2022

Multiple Myeloma

such as those not initially eligible for transplant. For non-transplant patients, the 2- drug regimens are still listed as options with a note that a triplet regimen is the standard therapy but patients who cannot tolerate a 3-drug regimen due to poor performance status, can be started with a 2-drug regimen, and the third drug can be added if the performance status improves.

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

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

While weekly and twice-weekly dosing schemas of bortezomib are considered appropriate, weekly dosing is preferred. Twice-weekly bortezomib can be associated with neuropathy that may limit efficacy due to treatment delays or discontinuation. Therefore, Reeder et al modified the regimen to a once-weekly schedule of bortezomib.⁵⁹ In the study, patients treated with weekly bortezomib achieved responses similar to the twice-weekly schedule (ORR, 93% vs. 88%; very good partial response (VGPR), 60% vs. 61%). In addition, they experienced less grade 3/4 adverse events (37%/3% vs. 48%/12%). Fewer dose reductions of bortezomib/dexamethasone were required in the modified schedule and neuropathy rates were the same in both cohorts, even though the total bortezomib dose per cycle was higher in the weekly versus the twice-weekly schedule (6.0 mg/m² vs. 5.2 mg/m²).⁵⁹

The NCCN Panel has noted that subcutaneous administration is the preferred route for bortezomib. This is based on the results of the MMY-3021 trial. The trial randomized patients (n=222) to single-agent bortezomib administered either by the conventional intravenous (IV) route or by subcutaneous route.⁶⁰ 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). The results showed no significant differences in terms of PFS or 1-year OS between groups.^{60,61} However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy.

Carfilzomib can potentially cause cardiac, renal, and pulmonary toxicities.⁶² Careful assessment before initiating treatment with carfilzomib and close monitoring during treatment is recommended.⁶² Regarding dosing and administration, carfilzomib may be used once or twice weekly and at different doses.

A randomized trial has compared two formulations of daratumumab as monotherapy. The subcutaneous formulation of daratumumab and hyaluronidase-fihj resulted in a similar ORR, PFS, and safety profile and fewer infusion-related reactions compared with the IV daratumumab⁶³. According to the NCCN Panel, daratumumab IV infusion or daratumumab and hyaluronidase-fihj, subcutaneous injection may be used in all daratumumab-containing regimens. Some patients may not be appropriate for subcutaneous treatment, for example those with significant thrombocytopenia.

Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

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



NCCN Guidelines Version 4.2022

Multiple Myeloma

Bortezomib/Lenalidomide/Dexamethasone

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

In the first phase I/II prospective study of lenalidomide/bortezomib/dexamethasone in patients with newly diagnosed MM, the rate of partial response (PR) was 100%, with 74% very good partial response (VGPR) or better and 52% complete response (CR)/near CR.⁶⁴

The benefits of bortezomib/lenalidomide/dexamethasone as primary therapy were also seen in the results of the phase II IFM 2008 trial⁶⁵ and phase II EVOLUTION trial.⁶⁶ In the phase II IFM 2008 trial, patients received bortezomib, lenalidomide, and dexamethasone as induction therapy followed by HCT.⁶⁵ 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%.⁶⁵ After transplantation and consolidation therapy the rate of VGPR or better was 70% and 87%, respectively.⁶⁵

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.⁶⁶ 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.⁶⁶

Bortezomib/lenalidomide/dexamethasone was compared to lenalidomide/dexamethasone in the multicenter phase III SWOG S077 trial.⁶⁷ 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).⁶⁷ 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.⁶⁷

With longer-term follow up (median 84 months), the benefits of adding bortezomib to lenalidomide and dexamethasone were seen to be maintained.⁶⁸ The PFS with Bortezomib/lenalidomide/dexamethasone was 41 months versus 29 months for lenalidomide/dexamethasone.⁶⁸ The OS was not yet reached (>84 months) with the bortezomib regimen versus 69 months for lenalidomide/dexamethasone.⁶⁸

A randomized multicenter phase 3 trial (ENDURANCE E1A11) studied newly diagnosed patients (n=1053) with MM treated with either bortezomib/lenalidomide/dexamethasone or carfilzomib/lenalidomide/dexamethasone as induction therapy. Patients with high-risk features (with the exception of patients with t(4;14)) were not included in this trial. After a median follow-up of 9 months, median PFS was 34.4 months with the bortezomib-regimen versus 34.6 months with the carfilzomib regimen.⁶⁹ A response of VGPR or better was seen in 65% of patients treated with bortezomib/lenalidomide/dexamethasone and 74% of patients treated with carfilzomib/lenalidomide/dexamethasone (*P* = .0015). With respect to



NCCN Guidelines Version 4.2022

Multiple Myeloma

adverse events, the carfilzomib regimen was associated with less peripheral neuropathy but more cardiac, pulmonary and renal toxicities.⁶⁹

In order to minimize the toxicities seen with the standard-dose of bortezomib/lenalidomide/dexamethasone, a phase II study evaluated the efficacy of dose-adjusted bortezomib/lenalidomide/dexamethasone (VRd-lite).⁷⁰ The VRd-lite regimen included subcutaneous bortezomib (1.3 mg/m²) on days 1, 8, 15 and 22, and oral dexamethasone (20 mg) on the day of and the day after bortezomib administration. Lenalidomide was omitted on days 1, 8 and 15, which are the days of bortezomib administration. The ORR after four cycles of VRd-lite was 83%, including a CR of 25%. The ORR and VGPR or better were further improved to 100% and 74%, in those who received autologous HCT.⁷⁰

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

Bortezomib/Cyclophosphamide/Dexamethasone

Data from three phase II studies involving newly diagnosed patients with MM have demonstrated high response rates with cyclophosphamide, bortezomib, and dexamethasone (CyBORd) as primary treatment.^{66,71,72} 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.⁷¹ 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%).⁷¹ 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).⁷³

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.⁷²

In the updated results of the phase II EVOLUTION study, primary treatment with CyBORd demonstrated an ORR of 75% (22% CR and 41% ≥ VGPR), and the 1-year PFS rate was 93%.⁶⁶

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.

Other Recommended Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

Carfilzomib/Lenalidomide/Dexamethasone

Carfilzomib is a second-generation PI that binds highly selectively and irreversibly to the proteasome. It is administered intravenously. A multicenter phase I/II trial evaluated the combination of carfilzomib, lenalidomide, and dexamethasone in newly diagnosed patients with MM.⁷⁴ In this trial, patients (n = 53) received carfilzomib with lenalidomide and low-dose dexamethasone. After 4 cycles, Hematopoietic cells were collected from eligible patients.⁷⁴ Out of 35 patients from whom hematopoietic cells were collected, 7 proceeded to transplantation, and the remainder continued with carfilzomib/lenalidomide/dexamethasone.⁷⁴ 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%),



NCCN Guidelines Version 4.2022

Multiple Myeloma

thrombocytopenia (17%), and neutropenia (17%). Peripheral neuropathy was limited to grade 1/2 (23%).⁷⁴

Another phase II trial also evaluated the same regimen (carfilzomib in combination with lenalidomide and dexamethasone) in newly diagnosed patients (n = 45) with MM. After 8 cycles of treatment, patients with stable disease (SD) received up to 24 cycles of lenalidomide 10 mg/day on days 1 to 21.⁷⁵ 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%).⁷⁶

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

cardiac adverse events were 4% for all grades (0% grade 3/4), hypertension was 16% (4% grade 3/4), and dyspnea was 32% (3% grade 3/4).⁷⁷

The results of the phase III ENDURANCE trial⁶⁹ showed similar PFS with carfilzomib/lenalidomide/dexamethasone versus bortezomib/lenalidomide/dexamethasone. However, as mentioned previously, high risk patients were not included.

Carfilzomib/lenalidomide/dexamethasone was associated with less neuropathy but more dyspnea, hypertension, heart failure, and acute kidney injury compared with bortezomib/lenalidomide/dexamethasone.⁶⁹

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

Daratumumab/Lenalidomide/Bortezomib/Dexamethasone

The benefit of adding a fourth drug for the primary treatment transplant-eligible patients is emerging. In the GRIFFIN trial, transplant-eligible patients with MM (n= 207) were randomized to daratumumab bortezomib/lenalidomide/dexamethasone or bortezomib/lenalidomide/dexamethasone followed by autologous HCT plus consolidation and maintenance.⁷⁸ The rate of stringent complete response rate after autologous HCT and consolidation with 4-drug regimen was 42% versus 32% with the 3-drug regimen.⁷⁸ Follow-up after median of 22 months showed further improved sCR rates for the daratumumab-containing 4 drug regimen (62.6% vs 45.4%; *P* = .0177).⁷⁸ Although the hematological toxicities were higher with the 4-drug regimen, no major safety concerns were reported in the study.⁷⁸

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



NCCN Guidelines Version 4.2022

Multiple Myeloma

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.⁷⁹ 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.

A phase III trial (TOURMALINE-MM2) evaluated the addition of ixazomib to lenalidomide and dexamethasone versus lenalidomide/dexamethasone plus placebo in newly diagnosed MM patients not eligible for autologous stem cell transplant.⁸⁰ The results presented at the Eighth SOHO Annual Meeting reported higher CR with the addition of ixazomib (26% vs. 14%). The median TTP was longer in the ixazomib arm (45.8 months vs. 26.8 months; HR, 0.738).⁸⁰ The median PFS was increased by 13.5 months with the addition of ixazomib (35.3 months vs. 21.8 months; HR, 0.830; $P = .073$).⁸⁰ This trial did not meet its pre-specified primary endpoint of improved PFS as the data failed to meet the threshold for statistical significance.

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

Regimens Useful In Certain Circumstances for Newly Diagnosed Transplant Candidates

Bortezomib/Doxorubicin/Dexamethasone

The updated results from the HOVON-65/GMMG-HD4 group phase III trial of newly diagnosed patients with stage II/III MM demonstrated high response rates after primary therapy with bortezomib/doxorubicin/dexamethasone versus vincristine/doxorubicin/dexamethasone (VAD), and this superior response rate (CR + near CR was 31% vs. 15%; $P < .001$) was maintained even after HCT with significantly higher ORR.⁸¹ No unexpected toxicities occurred, and del(13q) did not have a significant impact on response. Response rates improved with bortezomib maintenance (34% vs. 49%; $P < .001$).⁸¹ After a median follow-up of 41 months, PFS in patients treated with bortezomib/doxorubicin/dexamethasone as primary therapy followed by HCT and bortezomib maintenance was 35 months versus 28 months in patients treated with VAD followed by HCT and maintenance with thalidomide. Patients treated with bortezomib/doxorubicin/dexamethasone had a significantly better PFS (HR, 0.75; 95% CI, 0.62–0.90; $P = .002$).⁸¹ 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 17p13.⁸¹ 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.⁸¹



NCCN Guidelines Version 4.2022

Multiple Myeloma

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/Cyclophosphamide/Dexamethasone

The carfilzomib/cyclophosphamide/dexamethasone regimen has been studied in phase I/II trials of transplant-ineligible newly diagnosed patients with MM. Trials have investigated both once-weekly and twice weekly carfilzomib dosing combined with fixed dose cyclophosphamide and dexamethasone.^{82,83} A pooled analysis of two phase I and II studies comparing two alternative schedules of carfilzomib, transplant-ineligible newly diagnosed patients with MM showed similar response rates in those treated with once-weekly carfilzomib at a dose of 70 mg/m² compared to those treated with twice weekly carfilzomib at a dose of 36 mg/m². The PFS and OS were also similar. The median PFS was 35.7 months in the once-weekly group and 35.5 months in the twice-weekly group (HR = 1.39; P = .26). The 3-year OS was 70% and 72%, respectively (HR = 1.27; P = .5).⁸⁴

Consistent with the above results, a phase 1b study, CHAMPION-2 evaluated the safety and tolerability of twice-weekly carfilzomib (3 different doses) in combination with cyclophosphamide and dexamethasone for the treatment of newly diagnosed MM patients. This study found that 56 mg/m² carfilzomib combined with weekly cyclophosphamide and dexamethasone was effective and with manageable toxicity.⁸⁵

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

Ixazomib/cyclophosphamide/dexamethasone: In a phase I trial, this regimen was shown to be a convenient, all oral combination that is well

tolerated and effective in newly diagnosed patients with MM.⁸⁶

Subsequently, a multicenter, phase 2 trial investigated the efficacy and toxicity of ixazomib, cyclophosphamide and low-dose dexamethasone as induction, followed by single-agent ixazomib maintenance, in elderly, transplant-ineligible newly diagnosed patients.⁸⁷ The ORR after initial therapy with ixazomib/cyclophosphamide/dexamethasone was 73%. After a median follow-up of 26.1 months, the PFS was 23.5 months.

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

Bortezomib/Thalidomide/Dexamethasone

The GIMEMA Italian Multiple Myeloma Network reported results of a phase III trial investigating bortezomib/thalidomide/dexamethasone (N = 241) versus thalidomide/dexamethasone (N = 239) as primary therapy, followed by tandem autologous HCT with high-dose melphalan and then consolidation therapy with the same primary regimen.⁸⁸ 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.⁸⁸ Rates of CR/near CR and VGPR or better continued to be significantly higher in the bortezomib/thalidomide/dexamethasone group than in the thalidomide/dexamethasone group after the first and second autologous HCT and subsequent consolidation therapy.⁸⁸ Patients receiving the bortezomib-containing regimen experienced grade 3/4 peripheral neuropathy.



NCCN Guidelines Version 4.2022

Multiple Myeloma

Data from a single-institution retrospective study are similar to the interim data from the GIMEMA trial.⁸⁹ 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 $\geq 56\%$).⁸⁹

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%, $P = .002$).⁹⁰ The CR rate continued to be significantly higher after autologous HCT (46% vs. 24%) in patients treated with bortezomib/thalidomide/dexamethasone versus thalidomide/dexamethasone as primary therapy.⁹⁰

The phase III IFM 2013-04 trial is evaluating 4 cycles of CyBorD versus 4 cycles of bortezomib/thalidomide/dexamethasone as induction therapy before autologous HCT in patients ($N = 340$) with newly diagnosed MM.⁹¹ 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.⁹¹ The hematologic toxicity was greater in the CyBorD arm; however, higher rates of peripheral neuropathy were reported in the bortezomib/thalidomide/dexamethasone arm.⁹¹ No significant difference in OS was observed in any of the trials with bortezomib/thalidomide/dexamethasone. A longer follow-up period is required.

Bortezomib/thalidomide/dexamethasone is listed as a primary treatment option (category 1) under the category “useful in certain circumstances.”

Thalidomide is not widely used in the United States; however, it is more easily available and affordable in other resource-constrained parts of the world.

Cyclophosphamide/Lenalidomide/Dexamethasone

The efficacy and tolerability of cyclophosphamide/lenalidomide/dexamethasone in newly diagnosed patients was demonstrated in a phase II study. Of the 53 patients enrolled in the trial, 85% had a PR or better including VGPR in 47%. The median PFS was 28 months (95% CI, 22.7–32.6) and at 2 years the OS was 87% (95% CI, 78–96).⁹²

The Myeloma XI trial compared responses to cyclophosphamide/lenalidomide/dexamethasone with cyclophosphamide/thalidomide/dexamethasone.⁹³ The preliminary results reported that the combination of lenalidomide/cyclophosphamide/dexamethasone is effective and has a good safety profile in patients of all ages.⁹³

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

Daratumumab/Bortezomib/Thalidomide/Dexamethasone

In the CASSIOPEIA trial, patients with newly diagnosed MM ($n=1085$) were first randomly assigned to receive induction with four cycles of bortezomib/thalidomide/dexamethasone with or without daratumumab, followed by autologous HCT plus two cycles of consolidation with the induction regimen.⁹⁴ The primary endpoint of the first part of this trial was assessment of response 100 days after transplantation. The second randomization of this trial (randomization to maintenance with daratumumab) is ongoing.



NCCN Guidelines Version 4.2022

Multiple Myeloma

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

The NCCN Panel has included

Daratumumab/bortezomib/thalidomide/dexamethasone as a primary therapy option for transplant-eligible patients with MM under the category “useful in certain circumstances” (category 2A) based on the results of CASSIOPEIA trial and FDA approval for this indication.

Daratumumab/Cyclophosphamide/Bortezomib/Dexamethasone

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

Based on the above results, NCCN Panel has included

Daratumumab/bortezomib/thalidomide/dexamethasone for newly diagnosed patients with MM (transplant eligible and ineligible patients) as an option useful in certain circumstances.

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

The total therapy 3 (TT3) trial evaluated induction therapy with the 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.⁹⁶ This regimen is a potent combination of newer agents as well as traditional chemotherapy agents.

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

Preferred Primary Therapy Regimens for Newly Diagnosed Non-Transplant Candidates

Many of the regimens described above for transplant candidates are also options for non-transplant candidates. As in transplant-eligible patients, three-drug regimens are preferred by the NCCN Panel as these regimens have been shown to induce higher response rates and depth of response in clinical trials. The 2-drug regimens are reserved for elderly and/or frail patients. The list of preferred options for 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 HCT status.⁶⁴

The randomized phase III SWOG S0777 trial, comparing bortezomib/lenalidomide/dexamethasone to lenalidomide/dexamethasone as induction therapy without an intent of immediate transplantation, reported superior results with the 3-drug regimen.^{67,68}

In transplant-ineligible newly diagnosed patients with MM, a phase II study with the dose-adjusted VRd-lite regimen, showed that the dose-adjusted



NCCN Guidelines Version 4.2022

Multiple Myeloma

regimen had comparable efficacy and better tolerability than the standard dose regimen. The VRd-lite dosage included lenalidomide 15 mg days orally on 1–21; bortezomib 1.3 mg/m² subcutaneously days 1, 8, 15, and 22 and dexamethasone 20 mg orally on the day of and the day after bortezomib for 9 cycles followed by 6 cycles of consolidation with lenalidomide and bortezomib. The ORR after 4 cycles of VRd-lite was 86%, with 66% achieving a VGPR or better.⁹⁷

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

Daratumumab/lenalidomide/dexamethasone: In transplant-ineligible patients with newly diagnosed MM, results of a recently reported phase III trial (MAIA) showed that daratumumab/lenalidomide/dexamethasone significantly reduced the risk of disease progression or death by 44% (HR, 0.56 (95% CI = 0.43–0.73; $P < .001$)).⁹⁸ The addition of daratumumab to lenalidomide/dexamethasone resulted in deeper responses compared with lenalidomide/dexamethasone, including increased rates of complete response (CR) or better (48% vs 25%), VGPR or better (VGPR) (79% vs 53%), and ORR (93% vs 81%).⁹⁸ The rates of pneumonia, neutropenia, and leukopenia were higher in those receiving daratumumab.⁹⁸ Based on the results of this study, the FDA has approved the use of daratumumab/lenalidomide/dexamethasone in this setting.

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

Bortezomib/Cyclophosphamide/Dexamethasone

The role of bortezomib/cyclophosphamide/dexamethasone as initial therapy for patients with MM ineligible for HCT was studied in a small phase II trial (n = 20).⁹⁹ 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%).⁹⁹

Based on the above *and* the results from the EVOLUTION trial⁶⁶ (described earlier) that had included transplant-ineligible patients and the above phase II trial results,⁹⁹ 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.

Lenalidomide/Low-dose Dexamethasone

The results of the SWOG SO232 trial¹⁰⁰ that included transplant-ineligible patients and the ECOG E4A03 trial¹⁰¹ that included elderly patients with MM demonstrate that lenalidomide in combination with low-dose dexamethasone is a well-tolerated and effective regimen for these groups of patients. In the ECOG E4A03 trial the OS rate was significantly higher in the lenalidomide plus low-dose dexamethasone arm compared with the lenalidomide plus high-dose dexamethasone arm (also discussed under *Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates*).¹⁰¹ 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.¹⁰¹

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.¹⁰² The



NCCN Guidelines Version 4.2022

Multiple Myeloma

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; $P < .001$).¹⁰² 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; $P = .02$).¹⁰²

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.^{103–106} 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.¹⁰² 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.¹⁰⁷

Lenalidomide/low-dose dexamethasone is considered a category 1, preferred option by the NCCN Multiple Myeloma Panel for transplant-ineligible patients with MM. The Panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Based on the results of the FIRST trial,^{102,108} the NCCN Panel recommends considering

treatment with continuous lenalidomide/dexamethasone until disease progression for patients who are not eligible for transplant.

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

Carfilzomib/Lenalidomide/Dexamethasone

The results of a phase I/II trial demonstrated that the combination of carfilzomib/lenalidomide/dexamethasone is well-tolerated and is also effective in all newly diagnosed patients.⁷⁴ An updated follow-up analysis of the subset of 23 elderly patients (aged ≥ 65 years) showed that use of the carfilzomib, lenalidomide, and low-dose dexamethasone regimen for an extended period of time resulted in deep and durable responses. All patients achieved at least a PR. With a median follow-up of 30.5 months, the reported PFS rate was 79.6% (95% CI, 53.5–92.0) and OS was 100%.¹⁰⁹

The phase II trial by Korde et al⁷⁶ 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,⁷⁶ and the regimen was found to be effective in individuals with high-risk disease.¹¹⁰

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

Ixazomib/Lenalidomide/Dexamethasone

A phase I/II study (discussed in the previous section for HCT-eligible candidates) evaluated the safety and efficacy of the all-oral combination of ixazomib with lenalidomide and dexamethasone in patients with newly diagnosed MM treated with combination lenalidomide and dexamethasone.⁷⁹ Both tolerability and activity of this regimen in older



NCCN Guidelines Version 4.2022

Multiple Myeloma

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 HCT.

Daratumumab/Bortezomib/Melphalan/Prednisone

In the randomized phase III trial (ALCYONE), randomized patients (n = 706) with newly diagnosed MM ineligible for transplant were to receive bortezomib/melphalan/prednisone with or without daratumumab until disease progression.¹¹¹ The addition of daratumumab increased the ORR (90.9% vs. 73.9%) and PFS at 18 months was 72% versus 50%. With respect to toxicity, there was an increased rate of grade 3 or 4 infections (23% vs. 15%) and daratumumab-related infusion reactions were seen in 27.7% of patients.

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

Daratumumab/cyclophosphamide/bortezomib/dexamethasone

Based on the results of the LYRA study (described above),⁹⁵ the NCCN Panel has included

Daratumumab/bortezomib/thalidomide/dexamethasone as a treatment option for both transplant and non-transplant settings as options useful in certain circumstances.

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

Bortezomib/Dexamethasone

A U.S. community-based, randomized, open-label, multicenter, phase IIIb UPFRONT trial compared the safety and efficacy of three highly active bortezomib-based regimens in previously untreated elderly patients with MM ineligible for HCT.¹¹² 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 three 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.¹¹³ After a median follow-up of 42.7 months, the median PFS and OS were not significantly different between the three treatment arms.¹¹² Response rates, including CR and \geq 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 in certain circumstances for patients with MM who are ineligible for HCT.

Cyclophosphamide/lenalidomide/dexamethasone

Based on results of the phase II trial by Kumar et al,⁹² and the Myeloma X1,⁹³ the NCCN Panel has included cyclophosphamide/



NCCN Guidelines Version 4.2022

Multiple Myeloma

lenalidomide/dexamethasone as an option for treatment of all patients with newly diagnosed MM, including those who are not eligible for HCT.

Carfilzomib/Cyclophosphamide/Dexamethasone

A phase II study examined the safety and efficacy of carfilzomib/cyclophosphamide/dexamethasone in patients ≥65 years of age with newly diagnosed MM and ineligible for autologous HCT.⁸² 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 a stringent CR. After a median follow-up of 18 months, the 2-year PFS and OS rates were 76% and 87%, respectively.⁸²

Frequently reported grade 3 to 5 toxicities were neutropenia (20%), anemia (11%), and cardiopulmonary events (7%). Peripheral neuropathy was limited to grades 1 and 2 (9%).

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

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

Response Criteria

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

The updated IMWG response criteria definitions^{7,114,115} for CR, stringent CR, immunophenotypic CR, molecular CR, VGPR, PR, minimal response (MR) for relapsed/refractory MM, SD, and progressive disease (PD) are outlined in *Response Criteria for Multiple Myeloma* in the algorithm. This has been recently updated to include measures of MRD assessments. It is recommended that the IMWG uniform response criteria should be used in

all clinical trials.¹¹⁶ According to the NCCN Panel, response should be assessed using the IMWG criteria.⁷

The same imaging modality used during the initial workup should ideally be used for the follow-up assessments. Follow-up tests after primary MM therapy include those used for initial diagnosis: a CBC with differential and platelet counts; serum creatinine and corrected serum calcium; and quantification of M-protein. The serum immunoglobulins and FLC (especially in patients with oligo- or non-secretory MM) may be assessed as clinically indicated.

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

Hematopoietic Cell Transplantation

Transplant Eligibility

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

High-dose therapy with hematopoietic stem cell support is a critical component in the treatment plan of eligible patients newly diagnosed with



NCCN Guidelines Version 4.2022

Multiple Myeloma

MM. The types of HCT may be single autologous HCT, a tandem HCT (a planned second course of high-dose therapy and HCT within 6 months of the first course), or an allogeneic HCT.

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

Autologous Hematopoietic Cell Transplantation

Autologous HCT results in high response rates and remains the standard of care after primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous HCT is associated with statistically significantly higher response rates and increased OS and event-free survival (EFS) when compared with the response of similar patients treated with conventional therapy.¹¹⁷ 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).¹¹⁸ Barlogie and colleagues reported on the results of an American trial that randomized 510 patients to receive high-dose therapy with autologous hematopoietic cell transplant or standard therapy.¹¹⁹ 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 is not clear, but may be related to differences in the specific high-dose and conventional regimens between the American and French study. For example, the American study included total body irradiation (TBI) as part of the high-dose regimen; TBI has subsequently been found to be inferior to high-dose melphalan.¹²⁰

Another trial included 190 patients 55 to 65 years of age randomized to standard or high-dose therapy.¹²¹ This study was specifically designed to include older patients, since the median age of the participants in other trials ranged from 54 to 57 years and the median age in this trial was 61 years. After 120 months of follow-up, there was no significant difference in OS, although there was a trend toward improved EFS in the high-dose group ($P = .7$). Additionally, the period of time without symptoms, treatment, or treatment toxicity was significantly longer in the high-dose group. The study concluded that the equivalent survival suggests that the treatment choice between high-dose and conventional-dose chemotherapy should be based on personal choice in older patients. For example, an early transplant may be favored because patients can enjoy a longer interval of symptom-free time.

A phase III study compared high-dose melphalan followed by autologous HCT with MPR (melphalan, prednisone, and lenalidomide) consolidation after induction. Patients ($n = 402$) were randomly assigned (in a 1:1:1:1 ratio) to one of the four groups: high-dose therapy and autologous HCT followed by maintenance with lenalidomide; high-dose therapy and HCT alone; primary therapy with MPR followed by lenalidomide; and primary therapy with lenalidomide alone.¹²² At a median follow-up of 51 months, HCT resulted in longer median PFS (43 vs. 22 months; HR 0.44; 95% CI, 0.32–0.61) and OS (82% vs. 65% at 4 years; HR 0.55; 95% CI, 0.32–0.93).¹²²

Results from the IFM 2005/01 study of patients with symptomatic MM receiving primary therapy with bortezomib and dexamethasone versus VAD showed a marked improvement in ORR with bortezomib and dexamethasone over VAD (see *Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates*).¹²³ Responses were evaluated after primary treatment and post-autologous HCT. After the first autologous HCT, CR/near-CR rates were 35.0% in the bortezomib plus



NCCN Guidelines Version 4.2022

Multiple Myeloma

dexamethasone arm, compared with 18.4% in the VAD arm.¹²³ 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.¹²³ 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).¹²³

In another study, 474 patients were randomized to primary therapy with bortezomib/dexamethasone/thalidomide ($n = 236$) or thalidomide/dexamethasone ($n = 238$) before double autologous HCT and as consolidation therapy after HCT.¹²⁴ The 3-drug regimen yielded high response rates compared with the 2-drug regimen, with a CR rate of 19% (vs. 5%) and greater than or equal to a VGPR of 62% (vs. 31%). After HCT, improved incremental responses were still seen with bortezomib/dexamethasone/thalidomide compared with thalidomide plus dexamethasone.¹²⁴ The IFM 2009 phase III trial compared the efficacy and safety of bortezomib/lenalidomide/dexamethasone alone versus bortezomib/lenalidomide/dexamethasone plus autologous HCT for the treatment of newly diagnosed MM in patients 65 years or younger.¹²⁵ The reported CR rate was 48% in the group that received induction therapy alone versus 59% in the transplantation group ($P = .03$). No MRD was detected in 65% of the patients who received bortezomib/lenalidomide/dexamethasone alone versus no MRD in 79% of the patients who received induction therapy plus autologous HCT ($P < .001$).¹²⁵ There was a clear improvement in PFS with HCT (50 months vs. 36 months). These results clearly show the benefit of autologous HCT, with higher rates of durable responses in those with no MRD after initial therapy.¹²⁵ Taken together, the studies suggest that improved responses with the primary regimen result in improved outcomes after transplantation even for patients receiving an IMiD and PI-based triplet regimen.

The OS of patients in the IFM 2009 phase III trial was high in both groups, the one that received autologous HCT and the one that did not.¹²⁵ Although autologous HCT improved PFS it did not improve OS, suggesting that delaying HCT is an option and is not associated with negative effects on OS.

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

Tandem Hematopoietic Cell Transplantation

Tandem HCT refers to a planned second course of high-dose therapy and HCT within 6 months of the first course. Planned tandem transplants have been studied in several randomized trials. The IFM94 trial reported by Attal et al randomized newly diagnosed patients with MM to single or tandem autologous transplants.¹²⁶ A total of 78% of patients assigned to the tandem transplant group received the second transplant at a median time of 2.5 months after the first. A variety of options for therapy of relapsed disease were provided. For example, relapsing patients in either group underwent either no therapy, additional conventional therapy, or another HCT. The probability of EFS for 7 years after the diagnosis was 10% in the single transplant group compared 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.^{121,127-129}



NCCN Guidelines Version 4.2022

Multiple Myeloma

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 al¹²⁷ found that patients not in CR or near CR after the first transplant benefited the most from a second transplant. This confirms the observations of the IFM94 trial using non-TBI-based high-dose regimens. In both the French and Italian trials, the benefit of a second autologous HCT was seen in patients who do not achieve a CR or VGPR (>90% reduction in M-protein level) with the first procedure. These 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.¹³⁰ Also, post-relapse survival was longer when EFS was sustained for at least 3.5 years after tandem transplantation.¹³⁰⁻¹³¹ Results of the multicenter, phase III study (EMN02/HO95 MM trial) suggested that tandem autologous HCT for newly diagnosed MM may be superior in extending PFS compared with single autologous HCT after induction therapy with a bortezomib-based regimen.¹³² In another more recent study, after initial HCT patients were randomly assigned to receive a second HCT followed by lenalidomide maintenance; or four cycles of bortezomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance; or lenalidomide maintenance alone.¹³³ At 38 months, all three arms showed similar PFS and OS.¹³³

The NCCN Multiple Myeloma Panel recommends collecting enough hematopoietic stem cells for at least one HCT in *all* eligible patients, and for 2 transplants in the younger patients if tandem transplant or salvage transplant would be considered. According to the NCCN Multiple Myeloma

Panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for HCT and is an option for patients who do not achieve at least a VGPR after the first autologous HCT and those with high-risk features. The support for use of maintenance therapy after tandem transplant comes from the study by Palumbo et al,¹²² which addressed the role of maintenance therapy with lenalidomide after autologous transplantation.¹²² 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.¹²²

A second autologous HCT can be considered at the time of disease relapse. A retrospective case-matched control analysis was performed comparing patients who underwent a second autologous HCT to those treated with conventional chemotherapy for relapsed MM.¹³⁴ Similar to previously published smaller studies,¹³⁵⁻¹³⁷ this retrospective analysis demonstrated that a second autologous HCT is associated with superior relapse-associated mortality compared with conventional chemotherapy (68% vs. 78%), along with improved OS (32% vs. 22%) at 4 years. In this analysis, factors associated with improved OS and PFS included younger age (<55 years), beta-2 microglobulin <2.5 mg/L at diagnosis, a remission duration of >9 months, and a greater than PR to their first autologous HCT. This analysis indicates that a second autologous transplant, for relapsed or progressive MM, may be an option for carefully selected patients. Some of these patients can achieve durable complete or partial remission.^{137,138}

A multicenter, randomized phase III trial compared treatment with high-dose melphalan plus second autologous HCT with cyclophosphamide in patients with relapsed MM who had received autologous HCT as primary treatment.¹³⁹ The patients included in the study were greater than 18 years



NCCN Guidelines Version 4.2022

Multiple Myeloma

of age and needed treatment for progressive or relapsed disease at least 18 months after a previous autologous HCT. All patients first received bortezomib/doxorubicin/dexamethasone induction therapy. Patients with adequately harvested hematopoietic stem cells were then randomized to high-dose melphalan plus second autologous HCT (n = 89) or oral cyclophosphamide (n = 85). The primary endpoint was time to disease progression.¹³⁹ After a median follow-up of 31 months, median TTP in patients who underwent second autologous HCT after induction therapy was 19 months versus 11 months for those treated with cyclophosphamide (HR, 0.36; 95% CI, 0.25–0.53; $P < .0001$). Grade 3-4 neutropenia (76% vs. 13%) and thrombocytopenia (51% vs. 5%) were higher in the group that underwent autologous HCT versus cyclophosphamide.¹³⁹ Median OS in the HCT group was 67 months versus 52 months in the cyclophosphamide maintenance group.¹⁴⁰

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

The prognosis of patients who relapse after autologous HCT appears to differ depending on the timing of the relapse.¹⁴¹⁻¹⁴⁵ Data from retrospective studies¹⁴⁶⁻¹⁴⁹ suggest 2 to 3 years as the minimum length of remission for consideration of second autologous HCT for relapsed disease.

Allogeneic Hematopoietic Cell Transplantation

Allogeneic HCT includes either myeloablative or nonmyeloablative (ie, “mini” transplant) transplants. Allogeneic HCT has been investigated as an alternative to autologous HCT to avoid the contamination of reinfused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population. Non-myeloablative

transplants are designed to decrease the morbidity of the high-dose chemotherapy but preserve the beneficial graft-versus-tumor effect. Therefore, the principal difference between myeloablative and 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 HCT, but multiple case series have been published describing allogeneic HCT as an initial therapy or as therapy for relapsed/refractory MM. In a 1999 review, Kyle reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured.¹⁵⁰ Other reviews have also reported increased morbidity without convincing proof of improved survival.^{151,152} However, there are intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.¹¹⁹ 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 allogeneic curve was flat at 39%. This suggests that a proportion of these patients are long-term survivors. Thus, there is ongoing interest in myeloablative allogeneic HCT, particularly given the lack of a significant cure rate for single or tandem autologous HCT.

Patients whose disease either does not respond to or relapses after allogeneic hematopoietic cell grafting may receive donor lymphocyte



NCCN Guidelines Version 4.2022

Multiple Myeloma

infusions to stimulate a beneficial graft-versus-myeloma effect¹⁵³⁻¹⁶⁰ or other myeloma therapies on or off a clinical trial.

Follow-Up After Hematopoietic Cell Transplantation

Follow-up tests after HCT are similar to those done after primary myeloma therapy. In addition, MRD assessment is increasingly being incorporated into 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 HCT translated to significantly improved PFS and OS rates.¹⁶¹ Similarly, in another study, MRD negativity after autologous HCT was predictive of favorable PFS and OS.¹⁶² Similar results have also been reported in the allogeneic HCT setting where the presence of MRD after allogeneic HCT has been associated with a significantly adverse PFS and OS.¹⁶³ The NCCN Panel recommends assessing for MRD during follow-up as indicated prognostication after shared decision with patient.¹¹⁶

Maintenance Therapy

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

Lenalidomide as Maintenance

Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in two independent randomized phase III studies.^{103,104}

In the CALGB 100104 trial, patients were randomized to maintenance therapy with lenalidomide (n = 231) versus placebo (n = 229) after autologous HCT.¹⁰⁴ At a median follow-up of 34 months, 37% of the

patients who received lenalidomide versus 58% who received placebo had disease progression or died. The median TTP in the lenalidomide group was 46 months versus 27 months in the placebo group ($P < .001$). Second primary cancers occurred in 18 patients who received lenalidomide (8%) and in 6 patients who received placebo (3%).¹⁰⁴

Data from the international, randomized, double-blind phase III IFM 2005-02 trial (n = 614) show that patients treated with lenalidomide as consolidation therapy after an autologous HCT followed by lenalidomide as maintenance therapy had upgraded responses. Of the 614 patients enrolled in the trial, 307 were randomly assigned to lenalidomide maintenance therapy and 307 to placebo. Maintenance treatment was continued until the patient withdrew consent, the disease progressed, or unacceptable toxic effects occurred. The final analysis of the IFM 2005-02 trial was performed after a median follow-up of 30 months and 264 patients had disease progression (104 in the lenalidomide group and 160 in the placebo group). The median PFS was 41 months in the lenalidomide group, compared with 23 months in the placebo group (HR, 0.50; $P < .001$; median follow-up period was 30 months). The probability of surviving without progression for 3 years after randomization was 59% in those treated with lenalidomide and 35% in those who received the placebo. The benefit of lenalidomide maintenance therapy, evidenced by rate of PFS at 3 years after randomization, was higher in all patients who received lenalidomide maintenance therapy compared with those who received placebo. This benefit was observed in patients who had a VGPR at randomization (64% vs. 49%, $P = .006$) and those who did not (51% vs. 18%, $P < .001$).¹⁰³ 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).¹⁰³ The updated survival analysis of the same study after 91 months for follow-up reported median TTP of 57.3 months (95% CI, 44.2–73.3) with lenalidomide and 28.9 months (23.0–36.3) with placebo (HR, 0.57; 95% CI, 0.46–0.71; $P <$



NCCN Guidelines Version 4.2022

Multiple Myeloma

.0001).¹⁶⁴ 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%).¹⁶⁴

The study by Palumbo et al¹²² (discussed in *Autologous Hematopoietic Cell Transplantation*) 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.¹²²

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.¹⁶⁵ The study showed improved median PFS with lenalidomide maintenance (52.8 vs. 23.5 months; HR 0.48; 95% CI, 0.42–0.55). At 7 years, the OS was 62% in the group receiving lenalidomide maintenance versus 50% in the group receiving placebo. In those with high-risk cytogenetics, a PFS benefit, but not an OS benefit was seen with lenalidomide maintenance versus placebo.

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

A report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option after mini-allogeneic HCT.¹⁶⁶ However, another recently reported study has shown the feasibility of maintenance therapy with low-dose lenalidomide after allogeneic HCT in patients with high-risk MM.¹⁶⁷

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.¹⁶⁸ 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.¹⁶⁸ 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,^{103,104,168} 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,¹⁰³⁻¹⁰⁵ or after a melphalan-containing regimen.¹⁰⁶ 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.¹⁰²

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.¹⁶⁹ 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



NCCN Guidelines Version 4.2022

Multiple Myeloma

placebo.¹⁶⁹ 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.¹⁷⁰ The NCCN Panel notes that the benefits and risks of maintenance therapy with lenalidomide versus secondary cancers should be discussed with patients.

Bortezomib as Maintenance Therapy

The results from the HOVON study show that maintenance with single-agent bortezomib after autologous HCT is well tolerated and is associated with improvement of ORR.⁸¹ Patients in the HOVON trial were randomly assigned to one of the two arms consisting of either primary treatment with VAD followed by autologous HCT and maintenance with thalidomide or with bortezomib/doxorubicin/dexamethasone followed by autologous HCT and bortezomib as maintenance therapy for 2 years. The study reported high near-CR/CR rates after primary treatment with the bortezomib-based regimen. Bortezomib as maintenance therapy was well tolerated and associated with additional improvement of response rates⁸¹ (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 HCT improved PFS only in patients not achieving at least VGPR after autologous HCT.¹⁷¹ There was no difference in PFS in patients with ≥VGPR after autologous HCT.

Bortezomib as Maintenance Therapy

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.¹¹² Newly diagnosed patients with MM ineligible for high-dose therapy and HCT enrolled in the

UPFRONT trial were randomized (1:1:1) and treated with one of the following bortezomib-based primary regimens: bortezomib and dexamethasone; bortezomib in combination with thalidomide and dexamethasone; or bortezomib with melphalan and prednisone followed by maintenance treatment with bortezomib. The 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.¹¹²

The NCCN Multiple Myeloma Panel members have added bortezomib as a maintenance therapy option for transplant eligible as well as ineligible patients.

Ixazomib as Maintenance Therapy After Autologous HCT

The TOURMALINE-MM3 trial studied two years of maintenance with ixazomib versus placebo in patients who had achieved at least a partial response (PR) following induction therapy and a single autologous HCT. Ixazomib improved PFS (median 26.5 [95% CI 23.7-33.8] vs. 21.3 months; HR 0.72, 95% CI 0.58-0.89).¹⁷² The risk of developing secondary malignancies was similar in control arm and with maintenance ixazomib. Based on the results of the phase III TOURMALINE-MM3 trial, the NCCN Panel has included ixazomib as “other recommended” maintenance option for transplant-eligible patients.

Therapy for previously treated Multiple Myeloma

A variety of therapies are available for previously treated MM. The choice of appropriate therapy for a patient would depend on the context of clinical relapse such as prior treatment and duration of response.

Therapy for previously treated relapsed/refractory MM is considered in the following clinical situations: patients with relapsed disease after allogeneic or autologous HCT; patients with primary PD after initial autologous or



NCCN Guidelines Version 4.2022

Multiple Myeloma

allogeneic HCT; and patients ineligible for HCT 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; HCT (for eligible patients who did not receive HCT as part of their initial treatment); or clinical trial. For those who had autologous HCT 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/dexamethasone is 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 HCT.^{173,174} 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).¹⁷⁴ The NCCN Multiple Myeloma Panel members have included bortezomib/lenalidomide/dexamethasone as a preferred option for relapsed/refractory MM.

Daratumumab/Lenalidomide/Dexamethasone

In a multicenter, open-label phase 3 trial (POLLUX), patients (n= 569) with relapsed/refractory MM were randomized to

lenalidomide/dexamethasone with or without daratumumab until disease progression or unacceptable toxicity.¹⁷⁵

After a median follow-up of 13.5 months, daratumumab in combination with lenalidomide and dexamethasone was associated with better PFS and ORR compared with lenalidomide/dexamethasone alone. After a median follow-up of 25.4 months, a subsequent analysis reported that the higher ORR (92.9% versus 76.4%, $P < .001$), and PFS (83% vs. 60% at 12 months; 68% vs. 41% at 24 months; HR 0.41, 95% CI 0.31-0.53) was maintained in those who received daratumumab.¹⁷⁵

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.

With an extended follow-up of 3.5 years, the improvements in PFS and ORR continued to be maintained in patients treated with the daratumumab regimen (16.7 vs. 7.1 months; HR, 0.31; 95% CI, 0.25-0.40; $P < .0001$). In subgroup of patients with one prior line of therapy, the median PFS was 27.0 months with daratumumab versus 7.9 months with bortezomib and lenalidomide (HR, 0.22; 95% CI, 0.15-0.32; $P < .0001$). The ORR rates for patients with one prior line of therapy for those receiving daratumumab-regimen was 92% compared with 74% in those receiving bortezomib/dexamethasone.¹⁷⁶

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

Carfilzomib/Lenalidomide/Dexamethasone



NCCN Guidelines Version 4.2022

Multiple Myeloma

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 MM 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%). Non-hematologic adverse effects (\geq 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.¹⁷⁷

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

Daratumumab/Bortezomib/Dexamethasone

A phase III trial showed that adding daratumumab to bortezomib and dexamethasone markedly improved outcomes for patients with recurrent/refractory MM.¹⁷⁸ 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 ($P < .001$).¹⁷⁸ 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%).¹⁷⁸ 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).¹⁷⁸ 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.^{179,180}

After a median follow-up of 40 months, patients receiving the daratumumab containing regimen demonstrated a 69% reduction in the risk of disease progression or death (median PFS, 16.7 months vs 7.1 months; HR, 0.31; 95% CI, 0.25–0.40; $P < .0001$); showed significantly better ORR (85% vs 63%; $P < .0001$).¹⁸¹ Patients who received a prior line of therapy demonstrated the greatest benefit with daratumumab (median PFS, 27.0 months vs 7.9 months; HR, 0.22; 95% CI, 0.15–0.32; $P < .0001$).

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

Daratumumab/carfilzomib/dexamethasone

A phase 1b, open-label, non-randomized, multicenter trial first studied this regimen in patients ($n = 82$) with relapsed or refractory MM. At a median follow-up of 16 months, the ORR was 84%. In the overall treatment population, while the median PFS was not reached, the 12-month and 18-month PFS rates were 74% and 66%, respectively.¹⁸² In a multicenter, open-label phase 3 trial (CANDOR), the addition of daratumumab to carfilzomib plus dexamethasone showed deeper responses and improved PFS. Based on the above data and the FDA approval, the NCCN Panel



NCCN Guidelines Version 4.2022

Multiple Myeloma

has included this regimen as a category 1, preferred regimen option for relapsed/refractory MM, for patients with relapsed or refractory MM.

Isatuximab-irfc/pomalidomide/dexamethasone

In an open-label, multicenter, phase 3 trial (ICARIA-MM), patients (n= 307) with MM who had received at least two lines of prior therapy, including lenalidomide and a PI were randomized to receive pomalidomide/dexamethasone with or without isatuximab-irfc.¹⁸³ After a median follow-up of 12 months, a higher ORR (60% vs. 35%) and improved PFS (median 11.5 months vs. 6.5 months; HR 0.6, 95% CI 0.44-0.81) was reported in the isatuximab-irfc/pomalidomide/dexamethasone arm. In a prespecified subgroup analysis of this study, the addition of isatuximab-irfc showed improved ORR and PFS in patients with renal impairment.¹⁸⁴

The NCCN Panel has included Isatuximab-irfc/pomalidomide/dexamethasone as a category 1, preferred option for the treatment of patients with relapsed/refractory 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*).⁷⁹

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; $P = .01$).¹⁸⁵ 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).¹⁸⁵ 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%).¹⁸⁵ 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 trial¹⁸⁵ the NCCN Panel has included ixazomib/lenalidomide/dexamethasone as a category 1, preferred regimen option for previously treated MM.

Ixazomib/Pomalidomide/Dexamethasone

In the 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 of 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.¹⁸⁶

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



NCCN Guidelines Version 4.2022

Multiple Myeloma

carfilzomib.¹⁸⁷ The ORR was 33% and 40% with two different doses of ixazomib.¹⁸⁷

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 two prior therapies including an IMiD and a PI and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Based on the above results the NCCN Panel has included ixazomib/pomalidomide/dexamethasone as a preferred regimen option for previously treated MM.

Pomalidomide/Bortezomib/Dexamethasone

A phase 3 open-label, multicenter, randomized, trial (OPTIMISMM) evaluated pomalidomide/bortezomib/dexamethasone (n=281) versus bortezomib/dexamethasone in patients (n= 278) with relapsed or refractory MM who previously received lenalidomide.¹⁸⁸ 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.¹⁸⁸

Based on the above data, NCCN Panel had included pomalidomide/bortezomib/dexamethasone as a category 1, preferred option in patients who have received at least two prior therapies, including an immunomodulator (IMiD) and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Other Recommended Regimens for Previously Treated MM

Belantamab mafodotin-blmf

Belantamab mafodotin-blmf is an anti-B cell maturation antigen (BCMA) antibody, conjugated to a microtubule disrupting agent— monomethyl auristatin—via a stable, protease resistant linker. It is the first in its class. In the open-label phase II trial (DREAMM-2), belantamab mafodotin was evaluated in patients whose MM was refractory to multiple agents. Responses were seen in approximately one-third of patients.¹⁸⁹ The most common grade 3/4 adverse events in the safety population were keratopathy, thrombocytopenia, and anemia.¹⁸⁹

Based on the results of the DREAMM-2 trial and FDA approval, the NCCN Panel has included this as a treatment option for patients with relapsed MM who received at least four previous therapies (including a PI, an IMiD, and an anti-CD38 monoclonal antibody).

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 TTP was 16.5 months and 1-year OS was 78%.¹⁹⁰

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.¹⁹¹ 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%).¹⁹¹ The NCCN Panel has included lenalidomide in



NCCN Guidelines Version 4.2022

Multiple Myeloma

combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM.

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).¹⁹² 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 MM with an acceptable toxicity profile.^{193,194} The NCCN Multiple Myeloma Panel members have included bortezomib/cyclophosphamide/dexamethasone to the list of options for relapsed/refractory MM.

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.¹⁹⁵ The study

reported carfilzomib/cyclophosphamide/dexamethasone as well tolerated with the toxicity profile of carfilzomib being similar to that seen in other trials.¹⁹⁵ This regimen is included in the NCCN Guidelines for Multiple Myeloma as an option for patients with relapsed/refractory MM.

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 two-fold improvement in median PFS with carfilzomib/dexamethasone compared to bortezomib/dexamethasone (18.7 months vs. 9.4 months; HR, 0.53; $P < .0001$).¹⁹⁶ 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.¹⁹⁶

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]; $P = .010$).¹⁹⁷ 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%).¹⁹⁷ Rates of thrombocytopenia, pneumonia, and fatigue were similar in both groups.¹⁹⁷

Based on the above phase III data, the NCCN Multiple Myeloma Panel has included the combination of carfilzomib (twice weekly) and



NCCN Guidelines Version 4.2022

Multiple Myeloma

dexamethasone as a category 1, preferred option for patients with relapsed/refractory MM.

Cyclophosphamide/Lenalidomide/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.¹⁹⁸

Daratumumab/Cyclophosphamide/Bortezomib/Dexamethasone

In the LYRA study,⁹⁵ among the small cohort of patients with relapsed MM ($n = 14$), after 4 cycles of induction therapy ORR was 12.3% and VGPR or better was seen in 57.1% of patients.⁹⁵ The ORR after 4 induction cycles was 71.4%. The median PFS was 13.3 months (95% CI, 6.8–13.3). At 12-months, the OS rate was 54.5% (95% CI, 8.6%–86.1%).⁹⁵

Based on this, the NCCN Panel has included Daratumumab/bortezomib/thalidomide/dexamethasone as treatment option for relapsed/refractory MM.

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).¹⁹⁹ 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%.¹⁹⁹ Toxicities reported were similar to those seen in other trials of pomalidomide and daratumumab, except for increase in neutropenia.¹⁹⁹

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/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.²⁰⁰

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).²⁰⁰

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.

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.²⁰¹ The FDA has approved elotuzumab in combination with lenalidomide and dexamethasone for the treatment of patients with MM who have received



NCCN Guidelines Version 4.2022

Multiple Myeloma

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.²⁰²

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).²⁰² 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.²⁰² 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.²⁰²

Consistent with the above findings, a subset analysis of 3-year follow-up reported a reduced risk of progression by 27% with the elotuzumab/lenalidomide/dexamethasone combination compared with lenalidomide/dexamethasone.²⁰³

The final results of the ELOQUENT-2 study have demonstrated that the addition of elotuzumab to lenalidomide/dexamethasone improved OS in patients with MM who received 1–3 prior lines of therapy (48.3 months vs 39.6 months).²⁰⁴

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

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.²⁰⁵ 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/cyclophosphamide/dexamethasone

This regimen has been shown to be tolerable and efficacious in newly diagnosed patients.^{86, 87} A phase II study evaluated this regimen in the relapsed/refractory setting in patients with a median age of 63.5 years and found that it is well tolerated. At a median follow-up of 15.2 months in the phase II study, median PFS was 14.2 months. The PFS trend with this regimen was better in patients aged 65 and older compared with those less than 65 years (median 18.7 months vs. 12.0 months; HR 0.62, $P = .14$).²⁰⁶ The NCCN Panel has included this all oral regimen under the list of “other recommended regimens” for relapsed/refractory MM.

Pomalidomide/Carfilzomib/Dexamethasone

Based on the encouraging results of the phase I study,²⁰⁷ 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%.²⁰⁸ 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%.²⁰⁸



NCCN Guidelines Version 4.2022

Multiple Myeloma

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 two prior therapies.²⁰⁹

The triple-drug combination significantly improved the ORR (\geq 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.²⁰⁹ Similar results were reported by a single-center retrospective study of patients (n = 20) with relapsed/refractory MM who received pomalidomide/cyclophosphamide/dexamethasone until transplant or disease progression was reported.²¹⁰ 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.²¹⁰

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.

Regimens Useful In Certain Circumstances for Previously Treated MM

Bendamustine: In a trial by Knop and colleagues, 31 patients who had experienced relapse after autologous transplantation were enrolled to receive increasing doses of bendamustine.²¹¹ 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/m²). 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%.²¹²

The ECOG studied treatment with high-dose cyclophosphamide in patients with poor-risk features who had disease that was refractory to prior chemotherapy.²¹³ The ORR reported was 43% (29% response rate in patients refractory to prior therapy with cyclophosphamide).²¹³ Bendamustine is currently a treatment option for relapsed/refractory MM.

Carfilzomib/cyclophosphamide/thalidomide/dexamethasone: The results of the phase I/II trial (CYCLONE) showed that this 4-drug regimen is efficacious with an ORR of 91%, with 76% achieving VGPR or greater after 4 cycles in patients with MM.²¹⁴ This regimen has now been included under the list of regimens “useful in certain circumstances” for relapsed/refractory MM.

Bortezomib/Dexamethasone

The addition of dexamethasone to bortezomib in patients with relapsed/refractory MM who had PD during bortezomib monotherapy resulted in improvement of response in 18% to 34% of patients.^{215–217} The NCCN Multiple Myeloma Panel members have included the bortezomib and dexamethasone regimen as an option for patients with relapsed/refractory MM (category 1).



NCCN Guidelines Version 4.2022

Multiple 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 TTP. A pre-planned interim analysis of both studies reported that the median TTP was significantly longer in the lenalidomide arm compared to the control group.^{218,219} 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.²¹⁹ Similar results were seen in the international trial MM-010.²¹⁸ Patients in both of these trials had been heavily treated before enrollment. Many had three or more prior lines of therapies with other agents and more than 50% of patients having undergone HCT.^{218,219} 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.²²⁰ The NCCN Multiple Myeloma Panel suggests considering lenalidomide monotherapy for steroid-intolerant individuals.

Pomalidomide/Dexamethasone

Pomalidomide, like lenalidomide, is an analogue of thalidomide. It possesses potent immunomodulatory and significant anti-myeloma properties.²²¹

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.²²² 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 months vs. 1.9 months; HR, 0.45; $P < .0001$).²²² 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; $P = .0285$).²²² 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.²²² 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).²²³ 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.²²³ The results of this trial are consistent with those observed in the pivotal MM-003 trial.²²²

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.²²⁴ ORR was 35% and 34% for patients in the 21-day and 28-day groups, respectively. With



NCCN Guidelines Version 4.2022

Multiple Myeloma

a 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.²²⁴ 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).²²⁵ 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.²²⁵

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.

Daratumumab

Daratumumab is a human IgG kappa monoclonal antibody that targets the CD38 surface protein on myeloma cells.¹⁷⁹ In a phase I/II study, patients who had received more than three lines of therapy including an IMiD and a PI or were double refractory to PI and IMiD were randomized to two 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 TTP was 3.7 months. The estimated 1-year OS rate was 65%.¹⁸⁰ 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.¹⁸⁰

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 three prior lines of therapy including a PI and an IMiD or who are double refractory to a PI and IMiD.

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/m² on a twice-weekly schedule and 2.97 mg/m² on a weekly schedule.^{226,227} The patients in these studies had multiple prior lines of therapy (median of four prior lines of therapy in both studies). In the study with the weekly schedule,²²⁶ 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%.²²⁷ Adverse events, grade ≥3, were reported in 78% (drug-related in 62%) of patients on the twice-weekly schedule²²⁷ and 65% (53%) of patients on the weekly schedule.²²⁶ 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.²²⁷ On the weekly schedule drug-related peripheral neuropathy was reported in 20% of patients (2% grade 3).²²⁶



NCCN Guidelines Version 4.2022

Multiple Myeloma

Subsequently, phase II trials were designed to evaluate ixazomib with or without dexamethasone in patients with MM who have limited prior exposure to bortezomib.^{228,229} 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.²²⁸ The ORR (≥PR) with or without the addition of dexamethasone reported was 34%.²²⁸ Adverse events, grade ≥3, were reported in 78%. The most common adverse events observed included thrombocytopenia, fatigue, nausea, and diarrhea.²²⁸

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.²²⁹ 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.²²⁹ 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.²²⁹

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.

Selinexor/dexamethasone: Selinexor was recently approved for treatment of MM. Selinexor induces apoptosis of MM cells by selectively inhibiting the nuclear export compound that blocks exportin 1 (XPO1), forcing nuclear accumulation and activation of tumor suppressor proteins, and

inhibiting nuclear factor κB and the translation of oncoprotein mRNAs such as c-Myc and cyclin-D. Selinexor in combination with dexamethasone was studied in a phase IIb trial (STORM) in patients with relapsed/refractory MM.²³⁰ The patients in the trial had multiple prior therapies and were refractory to IMiDs (lenalidomide and pomalidomide), PIs (bortezomib and carfilzomib), and the CD38 antibody (daratumumab). A total of 122 patients were included in the intent-to-treat population. PR or better was observed in 26% of patients (95% confidence interval [CI], 19 to 35) with stringent CR in 2%, VGPR in 5%, and PR in 20% of the patients.

The most common adverse events reported during treatment were thrombocytopenia in 73% of the patients, fatigue in 73%, nausea in 72%, and anemia in 67%.

Based on the above results, the NCCN Panel has included selinexor/dexamethasone under the list of regimens “Useful in Certain Circumstances” as an option for patients with relapsed/refractory MM 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.

Venetoclax/dexamethasone only for t(11;14) patients

A phase I study of patients (n=66) with relapsed/refractory MM who received a median of five prior lines of therapy reported an ORR in 21% of patients with the response rate being higher in patients (n=30) with t(11;14) compared with those without the t(11;14) (40% versus 6%).²³¹ Similar higher response rates have been in patients with t(11;14) in real-world experience as well.²³² The NCCN Panel had included venetoclax in combination with dexamethasone as an option for patients with t(11;14) translocation.

Patients with an aggressive relapse may need multi-drug combinations such as DCEP,²³³⁻²³⁵ TD-PACE (thalidomide, dexamethasone, cisplatin,



NCCN Guidelines Version 4.2022

Multiple Myeloma

doxorubicin, high-dose cyclophosphamide, and etoposide),^{236,237} and VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide)²³⁸⁻²⁴⁰ for effective disease control.

Supportive Care 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 in the form of diffuse osteopenia and/or osteolytic lesions, develop in 85% of patients with MM. Related complications are the major cause of limitations in quality of life and performance status in patients with MM. A large, double-blind, randomized trial has shown that monthly use of IV pamidronate (a bisphosphonate) can decrease pain and bone-related complications, improve performance status, and, importantly, preserve quality of life in patients with Durie-Salmon stage III MM and at least one lytic lesion.^{241,242} Zoledronic acid has equivalent benefits.²⁴³ Results from the study conducted by Zervas et al²⁴⁴ 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 the start of bisphosphonate therapy and should be monitored for ONJ.

The Medical Research Council (MRC) Myeloma IX study examined effects of zoledronic acid versus clodronate (a bisphosphonate not currently FDA approved) in patients with MM initiating chemotherapy regardless of bone disease. The patients were randomized to receive zoledronic acid (n =

981) or clodronic acid (n = 979). Zoledronic acid was reported to reduce mortality and significantly improve PFS.²⁴⁵ 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.²⁴⁶ 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.²⁴⁷ The long-term rates of ONJ were also observed to be higher with zoledronic acid compared with clodronate (3.7% vs. 0.5%; $P = .0001$).²⁴⁷

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.²⁴⁸ It did not find a particular bisphosphonate to be superior to another.²⁴⁸ In a multicenter trial (CALGB 70604), patients with MM or bone metastases from a solid malignancy were randomly assigned to zoledronic acid either monthly or every three months for two years.²⁴⁹ The rates of skeletal-related events were similar in both arms. Among the 278 patients with MM, rates of SRE were 26% in those receiving monthly versus 21% in those receiving treatment every three months.²⁴⁹

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.²⁵⁰

The NCCN Guidelines for Multiple Myeloma recommend bisphosphonates (category 1) or denosumab for all patients receiving therapy for symptomatic MM regardless of documented bone disease. Denosumab is



NCCN Guidelines Version 4.2022

Multiple Myeloma

preferred by the NCCN Panel in patients with renal disease. The NCCN Panel recommends a baseline dental exam and monitoring for ONJ in all patients receiving a bone-modifying agent and monitoring for renal dysfunction with use of bisphosphonate therapy.

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

Low-dose (10–30 Gy) or single fraction (8 Gy) are used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.^{41,251} Limited involved fields should be used to limit the effect of irradiation on hematopoietic stem cell harvest or its effect on potential future treatments; the radiation doses administered should not preclude hematopoietic stem cell collection in potential candidates for high-dose therapy and HCT. Orthopedic consultation should be obtained for impending or actual fractures in weight-bearing bones, bony compression of the spinal cord, or vertebral column instability. Either vertebroplasty or kyphoplasty should be considered for symptomatic vertebral compression fractures.

Excess bone resorption from bone disease can lead to excessive release of calcium into the blood, contributing to hypercalcemia. Symptoms include polyuria and gastrointestinal disturbances, with progressive dehydration and decreases in glomerular filtration rate. Hypercalcemia should be treated with hydration, bisphosphonates, denosumab,²⁵⁰ 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.^{243,252,253}

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.²⁵⁴ 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^{255,256} (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.

Thrombosis is relatively common with the use of IMiDs (thalidomide, lenalidomide, or pomalidomide) with steroids, and is particularly frequent when treating newly diagnosed patients. Use of prophylactic anticoagulation agents (see [NCCN Guidelines for Venous Thromboembolic Disease](#)) is recommended when IMiDs are used in combination therapy during induction.²⁵⁷⁻²⁵⁹ For those receiving an IMiD-based therapy, prophylaxis with aspirin (81–325 mg) is recommended. An anticoagulation agent is recommended for patients receiving an IMiD-based therapy and who are at high risk for thrombosis.

To prevent infections, IV immunoglobulin therapy should be considered for recurrent, life-threatening infections; pneumococcal conjugate vaccine should be given followed by the pneumococcal polysaccharide vaccine one year later.

Reactivation of hepatitis B virus (HBV) is a complication in patients receiving carfilzomib or daratumumab. Therefore, testing for hepatitis B in these patients is recommended.

Pneumocystis jiroveci pneumonia (PJP), herpes zoster, and antifungal prophylaxis is recommended if high-dose dexamethasone is used.



NCCN Guidelines Version 4.2022 Multiple Myeloma

Prophylactic antiviral therapy is recommended for all patients receiving PI-based and antibody based therapies.^{260,261} 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.²⁶¹⁻²⁶⁴ Herpes zoster prophylaxis is recommended all patients treated with PIs, daratumumab, isatuximab-irfc, or elotuzumab. According to the NCCN Panel, three months of antibiotic prophylaxis should be considered at diagnosis for patients at high risk for infection (See [NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections](#)).

Discussion
update in
progress



NCCN Guidelines Version 4.2022

Multiple Myeloma

Management of Renal Disease in Multiple Myeloma

In patients with MM and monoclonal gammopathies, renal disease usually results from the production of monoclonal immunoglobulin or light/heavy chains by a clonal proliferation of plasma cells or B cells. Renal disease is seen in 20-50% of patients with MM and has been observed to negatively affect outcomes.²⁶⁵⁻²⁶⁷ The NCCN Panel has added a new page outlining management of renal disease in MM.

Renal insufficiency defined as elevated serum creatinine greater than 2 mg/dL or established glomerular filtration rate (eGFR) <60 mL/min/1.73 m² in patients with MM is usually due to light chain cast nephropathy, but other etiologies need to be considered including hypercalcemia, volume depletion, and hyperuricemia as well as nephrotoxic medications or IV contrast. In addition, concomitant amyloidosis and monoclonal immunoglobulin deposition should be suspected when renal insufficiency or albuminuria is present without high levels of light chains.

Diagnostic tests

According to the NCCN Panel, diagnostic workup of patients with symptomatic MM should include serum creatinine, electrolytes measurements, eGFR, electrophoresis of a sample from a 24-hour urine collection, serum electrophoresis, and serum free light chain measurement. If proteinuria predominantly consists of light chains with high serum levels of free light chain, and the cause of renal insufficiency can be attributed to MM, a renal biopsy may not be necessary. However, in patients without a clear and complete explanation for their renal insufficiency should undergo renal biopsy to look for other pathophysiology such as monoclonal immunoglobulin deposition disease (MIDD) or membranoproliferative glomerulonephritis (MPGN).

Treatment Options

The initial treatment of cast nephropathy includes initiating appropriate MM therapy and providing adequate supportive care.

Myeloma therapy: Myeloma therapy using bortezomib-containing regimens should be initiated as soon as possible to decrease the production of nephrotoxic clonal immunoglobulin.²⁶⁸

Bortezomib/dexamethasone-based regimens can be administered in patients with severe renal impairment and also those on dialysis and does not require renal dose adjustment.²⁶⁸ If two-drug regimen, bortezomib and dexamethasone is used as initial treatment, a third drug that does not require dose adjustment can be added including cyclophosphamide, thalidomide, an anthracycline or daratumumab. Other agents used in myeloma therapy should be used with caution and with dose adjustments based on the degree of renal function impairment as recommended by the IMWG.²⁶⁹ A retrospective study evaluated lenalidomide and dexamethasone based on two phase III trials of lenalidomide/low-dose dexamethasone in patients with relapsed/refractory MM with a serum creatinine of <2.5 mg/dL. Patients grouped by creatinine clearance >60 mL/min (n=243), 30-60 mL/min (n=82), and <30 mL/min (n=16) showed no difference in response rates to lenalidomide/low-dose dexamethasone.²⁷⁰ Patients with renal insufficiency had higher rates of thrombocytopenia and lenalidomide discontinuation than seen in patients without renal insufficiency. The NCCN Panel had outlined recommendations for lenalidomide dosing based on the degree of renal function in patients with MM and renal impairment. While prospective data to define optimal dosing are often lacking, pomalidomide has been studied in patients with relapsed MM in three different categories of renal insufficiency (eGFR 30-40 mL/min/1.73 sqm, eGFR <30 mL/min/1.73 sqm, and those requiring dialysis) and full dose pomalidomide of 4 mg daily was found to be safe in all three groups.²⁷¹



NCCN Guidelines Version 4.2022 Multiple Myeloma

Supportive Care: Intravenous fluids should be started promptly to decrease the renal tubular light chain concentration with a goal urine output of 100 to 150 cc per hour. Careful assessment of the fluid status is critical to avoid hypervolemia especially in patients with oliguria renal failure.

In addition, nephrotoxic medications should be discontinued and other metabolic abnormalities such as hypercalcemia and hyperuricemia should be corrected. Hydration, bisphosphonates or denosumab, and calcitonin are recommended to reduce calcium levels in the case of hypercalcemia. In patients with renal disease, pamidronate and zoledronic acid should be used with caution. The NCCN Panel has provided the recommended dosing of these agents in those who have renal impairment.

Dialysis may be required in selected patients in addition to prompt institution of anti-myeloma therapy. Mechanical removal of light chains may be considered on a case by case basis. While the benefit of mechanical removal of free light chains has not been established, there is limited evidence for the use of plasmapheresis or high-cutoff dialysis to reduce pathogenic light chains.



NCCN Guidelines Version 4.2022

Multiple Myeloma

Monoclonal gammopathy of Clinical significance (MGCS)

Monoclonal gammopathy of undetermined significance (MGUS) is defined by the absence of MM defining events, presence of monoclonal gammopathy of <3 g/dL, and clonal population of bone marrow plasma cells less than 10%. The prevalence of MGUS in the general population is about 0.7%, and it increases with age.

Monoclonal gammopathy of clinical significance (MGCS) refers to the potentially organ-toxic properties of M-protein. Typically, the M-protein in MGCS does not meet the diagnostic criteria MM and Waldenström macroglobulinemia (WM). Previously MGCS were all grouped under MGUS. Monoclonal gammopathy affects the renal function, it is referred to as monoclonal gammopathy of renal significance (MGRS). Peripheral neuropathy mediated by a monoclonal protein in the serum and urine without any evidence of MM or WM is now defined as monoclonal gammopathy of neurological significance (MGNS).

Monoclonal Gammopathy of Renal Significance (MGRS)

The term MGRS was proposed by the International Kidney and Monoclonal Gammopathy Research Group to collectively describe patients who meet the criteria MGUS but demonstrate renal injury attributable to the underlying monoclonal protein.²⁷²

When the presence of monoclonal gammopathy affects the renal function, it is referred to as MGRS. Renal damage in the setting of symptomatic MM is not considered MGRS.

Initial Workup

In patients suspected of having MGRS, kidney biopsy is performed. A kidney biopsy is essential in demonstrating the nephrotoxicity of the monoclonal protein. The biopsy may be deferred if the eGFR is stable, the

urinalysis is normal or there is no evidence of proteinuria. (it's not always light chain proteinuria).

The presence of monoclonal immunoglobulin deposits in the kidney indicates the existence of a plasma cell, B cell, or lymphoplasmacytic clone that is responsible for the production of the monoclonal protein.

M-protein must be detected by electrophoresis and immunofixation in the urine and serum and must be correlated with the one found in biopsy. Immunofluorescence staining should be performed with the biopsy sample for IgG subclasses, IgA and IgM, and kappa and lambda.

Imaging by PET/CT, low-dose CT, or whole-body MRI should be performed as clinically indicated. Bone marrow biopsy is carried out if suspected to have MM or WM.

Additional workup for appropriate diagnosis of suspected WM, CLL/SLL, or systemic light chain amyloidosis maybe carried out as outlined in the respective NCCN Guidelines (see [NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma](#), [NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma](#), and [NCCN Guidelines for Systemic Light Chain Amyloidosis](#)).

Treatment

The treatment of MGRS is directed at the underlying plasma cell or B-cell clones to improve or prevent further kidney damage in these patients. For IgG, IgA and FLC MGRS, use the management algorithms for MM; For IgM MGRS, see [NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma](#). For any MGRS with monoclonal B-cell lymphocytosis (MBL) features, see [NCCN Guidelines for Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma](#).



NCCN Guidelines Version 4.2022 Multiple Myeloma

The response assessment in patients with MGRS who are being actively treated is as per the NCCN Guidelines listed above and includes SPEP and immunofixation; 24-hour urine collection for total protein, protein electrophoresis, and immunofixation; serum free light chain assay; and serum creatinine.

A large, light gray circular graphic with a double-line border. Inside the circle, the text "Discussion update in progress" is written in a large, bold, sans-serif font, centered vertically and horizontally.

**Discussion
update in
progress**



National
Comprehensive
Cancer
Network®

NCCN Guidelines Version 4.2022

Multiple Myeloma

Monoclonal Gammopathy of Neurological Significance (MGNS)



**Discussion
update in
progress**



POEMS Syndrome

POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) syndrome is characterized by the presence of a monoclonal plasma cell disorder, peripheral neuropathy, and one or more of the following features: osteosclerotic myeloma, Castleman disease (angiofollicular lymph node hyperplasia), increased levels of serum vascular endothelial growth factor (VEGF), organomegaly, endocrinopathy, edema, typical skin changes, and papilledema.

Discussion
update in
progress



References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. *CA Cancer J Clin* 2020;70:7-30. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31912902>.
2. SEER Stat Fact Sheets: Myeloma. Available at: <http://seer.cancer.gov/statfacts/html/mulmy.html>.
3. U.S. National Library of Medicine-Key MEDLINE® Indicators. Available at: http://www.nlm.nih.gov/bsd/bsd_key.html.
4. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. *Mayo Clin Proc* 2003;78:21-33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12528874>.
5. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. *Leukemia* 2009;23:215-224. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/19020545>.
6. Kuhnemund A, Liebisch P, Bauchmuller K, et al. 'Light-chain escape-multiple myeloma'-an escape phenomenon from plateau phase: report of the largest patient series using LC-monitoring. *J Cancer Res Clin Oncol* 2009;135:477-484. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18802723>.
7. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. *Leukemia* 2006;20:1467-1473. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16855634>.
8. Craig FE, Foon KA. Flow cytometric immunophenotyping for hematologic neoplasms. *Blood* 2008;111:3941-3967. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18198345>.
9. Paiva B, Vidriales MB, Perez JJ, et al. Multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides more prognostic information than morphological assessment in myeloma patients. *Haematologica* 2009;94:1599-1602. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19880781>.
10. Xiong W, Wu X, Starnes S, et al. An analysis of the clinical and biologic significance of TP53 loss and the identification of potential novel transcriptional targets of TP53 in multiple myeloma. *Blood* 2008;112:4235-4246. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18337559>.
11. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. *Blood* 1998;92:802-809. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9680348>.
12. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. *Blood* 2007;109:3489-3495. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17209057>.
13. Gertz MA, Lacy MQ, Dispenzieri A, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. *Blood* 2005;106:2837-2840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15976175>.
14. Gutierrez NC, Castellanos MV, Martin ML, et al. Prognostic and biological implications of genetic abnormalities in multiple myeloma undergoing autologous stem cell transplantation: t(4;14) is the most relevant adverse prognostic factor, whereas RB deletion as a unique abnormality is not associated with adverse prognosis. *Leukemia* 2007;21:143-150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17024116>.
15. Ross FM, Chiecchio L, Dagrada G, et al. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. *Haematologica* 2010;95:1221-1225. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20410185>.
16. Ross FM, Avet-Loiseau H, Ameye G, et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. *Haematologica* 2012;97:1272-1277. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22371180>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

17. Hanamura I, Stewart JP, Huang Y, et al. Frequent gain of chromosome band 1q21 in plasma-cell dyscrasias detected by fluorescence in situ hybridization: incidence increases from MGUS to relapsed myeloma and is related to prognosis and disease progression following tandem stem-cell transplantation. *Blood* 2006;108:1724-1732. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16705089>.

18. Carrasco DR, Tonon G, Huang Y, et al. High-resolution genomic profiles define distinct clinico-pathogenetic subgroups of multiple myeloma patients. *Cancer Cell* 2006;9:313-325. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16616336>.

19. Rosinol L, Carrio A, Blade J, et al. Comparative genomic hybridisation identifies two variants of smoldering multiple myeloma. *Br J Haematol* 2005;130:729-732. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16115129>.

20. Dispenzieri A, Rajkumar SV, Gertz MA, et al. Treatment of newly diagnosed multiple myeloma based on Mayo Stratification of Myeloma and Risk-adapted Therapy (mSMART): consensus statement. *Mayo Clin Proc* 2007;82:323-341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17352369>.

21. Kumar SK, Mikhael JR, Buadi FK, et al. Management of newly diagnosed symptomatic multiple myeloma: updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) consensus guidelines. *Mayo Clin Proc* 2009;84:1095-1110. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19955246>.

22. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003;121:749-757. Available at:

23. 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. *Blood* 2016;128:4468-4468. Available at:

24. 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. Available at:

25. 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. Available at:

26. Princewill K, Kyere S, Awan O, Mulligan M. Multiple myeloma lesion detection with whole body CT versus radiographic skeletal survey. *Cancer Invest* 2013;31:206-211. Available at:

27. Nanni C, Zamagni E, Farsad M, et al. Role of 18F-FDG PET/CT in the assessment of bone involvement in newly diagnosed multiple myeloma: preliminary results. *Eur J Nucl Med Mol Imaging* 2006;33:525-531. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16453155>.

28. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26495861>.

29. Zamagni E, Nanni C, Gay F, et al. 18F-FDG PET/CT focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease. *Leukemia* 2016;30:417-422. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26490489>.

30. Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. *J Clin Oncol* 2010;28:1606-1610. Available at:

31. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24535407>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

32. Greipp PR, Lust JA, O'Fallon WM, et al. Plasma cell labeling index and beta 2-microglobulin predict survival independent of thymidine kinase and C-reactive protein in multiple myeloma. *Blood* 1993;81:3382-3387. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8507875>.

33. Kumar SK, Rajkumar SV. The multiple myelomas - current concepts in cytogenetic classification and therapy. *Nat Rev Clin Oncol* 2018;15:409-421. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29686421>.

34. Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *Lancet Oncol* 2014;15:e538-548. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25439696>.

35. Lakshman A, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. *Blood Cancer J* 2018;8:59. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29895887>.

36. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol* 2005;23:3412-3420. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15809451>.

37. 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. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26240224>.

38. Knowling MA, Harwood AR, Bergsagel DE. Comparison of extramedullary plasmacytomas with solitary and multiple plasma cell tumors of bone. *J Clin Oncol* 1983;1:255-262. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/6668499>.

39. Does GM, Landgren O, McGlynn KA, et al. Plasmacytoma of bone, extramedullary plasmacytoma, and multiple myeloma: incidence and survival in the United States, 1992-2004. *Br J Haematol* 2009;144:86-94. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19016727>.

40. Dimopoulos MA, Goldstein J, Fuller L, et al. Curability of solitary bone plasmacytoma. *J Clin Oncol* 1992;10:587-590. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/1548521>.

41. Hu K, Yahalom J. Radiotherapy in the management of plasma cell tumors. *Oncology (Williston Park)* 2000;14:101-108, 111; discussion 111-102, 115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10680152>.

42. Creach KM, Foote RL, Neben-Wittich MA, Kyle RA. Radiotherapy for extramedullary plasmacytoma of the head and neck. *Int J Radiat Oncol Biol Phys* 2009;73:789-794. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18707826>.

43. Tournier-Rangear L, Lapeyre M, Graff-Caillaud P, et al. Radiotherapy for solitary extramedullary plasmacytoma in the head-and-neck region: A dose greater than 45 Gy to the target volume improves the local control. *Int J Radiat Oncol Biol Phys* 2006;64:1013-1017. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/16343803>.

44. Reed V, Shah J, Medeiros LJ, et al. Solitary plasmacytomas: outcome and prognostic factors after definitive radiation therapy. *Cancer* 2011;117:4468-4474. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21437886>.

45. Frassica DA, Frassica FJ, Schray MF, et al. Solitary plasmacytoma of bone: Mayo Clinic experience. *Int J Radiat Oncol Biol Phys* 1989;16:43-48. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/2912957>.

46. Ozsahin M, Tsang RW, Poortmans P, et al. Outcomes and patterns of failure in solitary plasmacytoma: a multicenter Rare Cancer Network study of 258 patients. *Int J Radiat Oncol Biol Phys* 2006;64:210-217. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16229966>.

47. Knobel D, Zouhair A, Tsang RW, et al. Prognostic factors in solitary plasmacytoma of the bone: a multicenter Rare Cancer Network study. *BMC Cancer* 2006;6:118. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16677383>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

48. Sasaki R, Yasuda K, Abe E, et al. Multi-institutional analysis of solitary extramedullary plasmacytoma of the head and neck treated with curative radiotherapy. *Int J Radiat Oncol Biol Phys* 2012;82:626-634. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21277117>.
49. Gerry D, Lentsch EJ. Epidemiologic evidence of superior outcomes for extramedullary plasmacytoma of the head and neck. *Otolaryngol Head Neck Surg* 2013;148:974-981. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23482476>.
50. Kato T, Tsukamoto E, Nishioka T, et al. Early detection of bone marrow involvement in extramedullary plasmacytoma by whole-body F-18 FDG positron emission tomography. *Clin Nucl Med* 2000;25:870-873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11079582>.
51. Schirrmeister H, Bommer M, Buck AK, et al. Initial results in the assessment of multiple myeloma using 18F-FDG PET. *Eur J Nucl Med Mol Imaging* 2002;29:361-366. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12002711>.
52. Nanni C, Rubello D, Zamagni E, et al. 18F-FDG PET/CT in myeloma with presumed solitary plasmacytoma of bone. *In Vivo* 2008;22:513-517. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18712181>.
53. Group TIMW. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *British Journal of Haematology* 2003;121:749-757. Available at: <http://dx.doi.org/10.1046/j.1365-2141.2003.04355.x>.
54. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med* 2007;356:2582-2590. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17582068>.
55. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. *N Engl J Med* 2013;369:438-447. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23902483>.
56. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smoldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. *Lancet Oncol* 2016;17:1127-1136. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27402145>.
57. Lonial S, Jacobus S, Fonseca R, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. *J Clin Oncol* 2020;38:1126-1137. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31652094>.
58. San Miguel J, Mateos M-V, Gonzalez V, et al. Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria. *Journal of Clinical Oncology* 2019;37:8000-8000. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.8000.
59. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. *Blood* 2010;115:3416-3417. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20413666>.
60. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. *Lancet Oncol* 2011;12:431-440. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21507715>.
61. Arnulf B, Pylypenko H, Grosicki S, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. *Haematologica* 2012;97:1925-1928. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22689676>.
62. FDA Safety Information. Available at: <http://www.fda.gov/safety/medwatch/safetyinformation/ucm441458.htm>.
63. Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple



NCCN Guidelines Version 4.2022

Multiple Myeloma

myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. *Lancet Haematol* 2020;7:e370-e380. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32213342>.

64. Richardson PG, Weller E, Lonial S, et al. Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma. *Blood* 2010;116:679-686. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20385792>.

65. Roussel M, Lauwers-Cances V, Robillard N, et al. Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome. *J Clin Oncol* 2014;32:2712-2717. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/25024076>.

66. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. *Blood* 2012;119:4375-4382. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22422823>.

67. Durie BGM, Hoering A, Abidi MH, et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial. *Lancet* 2017;389:519-527. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28017406>.

68. Durie BGM, Hoering A, Sexton R, et al. Longer term follow-up of the randomized phase III trial SWOG S0777: bortezomib, lenalidomide and dexamethasone vs. lenalidomide and dexamethasone in patients (Pts) with previously untreated multiple myeloma without an intent for immediate autologous stem cell transplant (ASCT). *Blood Cancer J* 2020;10:53. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32393732>.

69. Kumar SK, Jacobus SJ, Cohen AD, et al. Carfilzomib or bortezomib in combination with lenalidomide and dexamethasone for patients with newly diagnosed multiple myeloma without intention for immediate autologous stem-cell transplantation (ENDURANCE): a multicentre, open-label, phase 3, randomised, controlled trial. *Lancet Oncol* 2020;21:1317-1330. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32866432>.

70. Okazuka K, Ishida T, Nashimoto J, et al. The efficacy and safety of modified bortezomib-lenalidomide-dexamethasone in transplant-eligible patients with newly diagnosed multiple myeloma. *Eur J Haematol* 2020;104:110-115. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31733155>.

71. Reeder CB, Reece DE, Kukreti V, et al. Cyclophosphamide, bortezomib and dexamethasone induction for newly diagnosed multiple myeloma: high response rates in a phase II clinical trial. *Leukemia* 2009;23:1337-1341. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19225538>.

72. Knop S, Liebisch P, Wandt H, et al. Bortezomib, IV cyclophosphamide, and dexamethasone (VelCD) as induction therapy in newly diagnosed multiple myeloma: Results of an interim analysis of the German DSMM Xia trial. 2009;27:8516-8516. Available at: <https://ascopubs.org/doi/abs/10.1200/jco.2009.27.15s.8516>.

73. Reeder CB, Reece DE, Kukreti V, et al. Long-term survival with cyclophosphamide, bortezomib and dexamethasone induction therapy in patients with newly diagnosed multiple myeloma. *Br J Haematol* 2014;167:563-565. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24974945>.

74. Jakubowiak AJ, Dytfeld D, Griffith KA, et al. A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma. *Blood* 2012;120:1801-1809. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22665938>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

75. Korde N, Zingone A, Kwok M, et al. Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone (CRd) in newly diagnosed Multiple Myeloma (MM) patients [abstract]. Blood 2012;120:Abstract 732. Available at: <http://abstracts.hematologylibrary.org/cgi/content/abstract/ashmtg;120/21/732>.

76. Korde N, Zingone A, Kwok M, et al. Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone followed by lenalidomide extended dosing (CRD-R) induces high rates of MRD negativity in newly diagnosed multiple myeloma (MM) patients [Abstract]. Blood 2013 Vol. 122; 538-538.

77. Zimmerman T, Raje NS, Vij R, et al. Final Results of a Phase 2 Trial of Extended Treatment (tx) with Carfilzomib (CFZ), Lenalidomide (LEN), and Dexamethasone (KRd) Plus Autologous Stem Cell Transplantation (ASCT) in Newly Diagnosed Multiple Myeloma (NDMM). Blood 2016;128:675-675. Available at: <https://doi.org/10.1182/blood.V128.22.675.675>.

78. Voorhees PM, Kaufman JL, Laubach J, et al. Daratumumab, lenalidomide, bortezomib, and dexamethasone for transplant-eligible newly diagnosed multiple myeloma: the GRIFFIN trial. Blood 2020;136:936-945. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32325490>.

79. Kumar SK, Berdeja JG, Niesvizky R, et al. Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study. Lancet Oncol 2014;15:1503-1512. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25456369>.

80. Facon T, Venner, CP, Bahlis, NJ, et al. Ixazomib Plus Lenalidomide/Dexamethasone (IRd) vs. PlaceboRd for Newly Diagnosed Multiple Myeloma (NDMM) Patients Not Eligible for Autologous Stem Cell Transplant: The Double-Blind, Placebo-Controlled, Phase 3 TOURMALINE-MM2 Trial [Abstract]. Abstract MM-347 presented at Society of Hema-to-logic Oncology (SOHO) Eighth Annual Meeting 2020.

Available at: <https://clml-soho2020.elsevierdigitaledition.com/306/index.html#zoom=z>.

81. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/GMMG-HD4 trial. J Clin Oncol 2012;30:2946-2955. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22802322>.

82. Bringhen S, Petrucci MT, Larocca A, et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood 2014;124:63-69. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24855212>.

83. Bringhen S, D'Agostino M, De Paoli L, et al. Phase 1/2 study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma. Leukemia 2018;32:979-985. Available at:

84. Bringhen S, Mina R, Petrucci MT, et al. Once-weekly versus twice-weekly carfilzomib in patients with newly diagnosed multiple myeloma: a pooled analysis of two phase I/II studies. Haematologica 2019;104:1640-1647. Available at:

85. Boccia RV, Bessudo A, Agajanian R, et al. A Multicenter, Open-Label, Phase 1b Study of Carfilzomib, Cyclophosphamide, and Dexamethasone in Newly Diagnosed Multiple Myeloma Patients (CHAMPION-2). Clin Lymphoma Myeloma Leuk 2017;17:433-437. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28576443>.

86. Kumar SK, Buadi FK, LaPlant B, et al. Phase 1/2 trial of ixazomib, cyclophosphamide and dexamethasone in patients with previously untreated symptomatic multiple myeloma. Blood Cancer J 2018;8:70. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30061664>.

87. Dimopoulos MA, Grosicki S, Jedrzejczak WW, et al. All-oral ixazomib, cyclophosphamide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. Eur J Cancer



NCCN Guidelines Version 4.2022

Multiple Myeloma

2019;106:89-98. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30471652>.

88. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 2010;376:2075-2085.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21146205>.

89. Kaufman JL, Nooka A, Vrana M, et al. Bortezomib, thalidomide, and dexamethasone as induction therapy for patients with symptomatic multiple myeloma: a retrospective study. *Cancer* 2010;116:3143-3151.

Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20564642>.

90. Rosinol L, Oriol A, Teruel AI, et al. Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study. *Blood* 2012;120:1589-1596. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/22791289>.

91. Moreau P, Hulin C, MACRO M, et al. Bortezomib, thalidomide and dexamethasone (VTD) is superior to bortezomib, cyclophosphamide and dexamethasone (VCD) prior to autologous stem cell transplantation for patients with de novo multiple myeloma. Results of the prospective IFM 2013-04 trial. *Blood* 2015;126:393-393. Available at:

<http://www.bloodjournal.org/content/126/23/393>.

92. Kumar SK, Lacy MQ, Hayman SR, et al. Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial. *Am J Hematol* 2011;86:640-645. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/21630308>.

93. Pawlyn C, Brioli A, Gregory W, et al. Lenalidomide Combined With Cyclophosphamide and Dexamethasone Is Effective and Well Tolerated Induction Treatment For Newly Diagnosed Myeloma Patients Of All Ages. *Blood* 2013;122:540-540. Available at:

<https://doi.org/10.1182/blood.V122.21.540.540>.

94. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. *Lancet* 2019;394:29-38. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/31171419>.

95. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and relapsed multiple myeloma: LYRA study. *Br J Haematol* 2019;185:492-502. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30828799>.

96. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. *Br J Haematol* 2007;138:176-185. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/17593024>.

97. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. *Br J Haematol* 2018;182:222-230. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/29740809>.

98. Facon T, Kumar S, Plesner T, et al. Daratumumab plus Lenalidomide and Dexamethasone for Untreated Myeloma. *N Engl J Med* 2019;380:2104-2115. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/31141632>.

99. Zepeda J, H. V, Duggan P, et al. Cyclophosphamide, bortezomib and dexamethasone (CyBORD) is a feasible and active regimen for non-transplant eligible multiple myeloma patients [Abstract]. *Blood* 2014;124:5751-5751. Available at:

<http://www.bloodjournal.org/content/124/21/5751>.

100. Zonder JA, Crowley J, Hussein MA, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): Results of the randomized, double-blinded, placebo-controlled SWOG Trial S0232 [abstract]. *Blood* 2007;110:Abstract 77. Available at:

<http://abstracts.hematologylibrary.org/cgi/content/abstract/110/11/77>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

101. Rajkumar SV, Jacobus S, Callander NS, et al. Lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol* 2010;11:29-37. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19853510>.

102. 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. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25184863>.

103. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012;366:1782-1791. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22571202>.

104. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. *N Engl J Med* 2012;366:1770-1781. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22571201>.

105. Usmani SZ, Sexton R, Hoering A, et al. Second malignancies in total therapy 2 and 3 for newly diagnosed multiple myeloma: influence of thalidomide and lenalidomide during maintenance. *Blood* 2012;120:1597-1600. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22674807>.

106. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a meta-analysis of individual patient data. *Lancet Oncol* 2014;15:333-342. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24525202>.

107. Dimopoulos MA, Cheung MC, Roussel M, et al. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. *Haematologica* 2016;101:363-370. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26659916>.

108. Hulin C, Belch A, Shustik C, et al. Updated Outcomes and Impact of Age With Lenalidomide and Low-Dose Dexamethasone or Melphalan, Prednisone, and Thalidomide in the Randomized, Phase III FIRST Trial. *J Clin Oncol* 2016;34:3609-3617. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27325857>.

109. Dytfeld D, Jasieles J, Griffith KA, et al. Carfilzomib, lenalidomide, and low-dose dexamethasone in elderly patients with newly diagnosed multiple myeloma. *Haematologica* 2014;99:e162-164. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/24972772>.

110. Korde N, Roschewski M, Zingone A, et al. Treatment with carfilzomib-lenalidomide-dexamethasone with lenalidomide extension in patients with smoldering or newly diagnosed multiple myeloma. *JAMA Oncol* 2015. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26181891>.

111. Mateos MV, Dimopoulos MA, Cavo M, et al. Daratumumab plus Bortezomib, Melphalan, and Prednisone for Untreated Myeloma. *N Engl J Med* 2018;378:518-528. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29231133>.

112. Niesvizky R, Flinn IW, Rifkin R, et al. Community-Based Phase IIIB Trial of Three UPFRONT Bortezomib-Based Myeloma Regimens. *J Clin Oncol* 2015;33:3921-3929. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26056177>.

113. Niesvizky R, Flinn IW, Rifkin R, et al. Efficacy and safety of three bortezomib-based combinations in elderly, newly diagnosed multiple myeloma patients: Results from all randomized patients in the community-based, phase 3b UPFRONT study [abstract]. *Blood* 2011;118:Abstract 478. Available at: <http://abstracts.hematologylibrary.org/cgi/content/abstract/118/21/478>.

114. Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, risk-stratification, and management. *Am J Hematol* 2011;86:57-65. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/21181954>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

115. Palumbo A, Rajkumar SV, San Miguel JF, et al. International Myeloma Working Group consensus statement for the management, treatment, and supportive care of patients with myeloma not eligible for standard autologous stem-cell transplantation. *J Clin Oncol* 2014;32:587-600. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24419113>.

116. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol* 2016;17:e328-e346. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27511158>.

117. Attal M, Harousseau JL, Stoppa AM, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* 1996;335:91-97. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8649495>.

118. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. *N Engl J Med* 2003;348:1875-1883. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12736280>.

119. Barlogie B, Kyle RA, Anderson KC, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *J Clin Oncol* 2006;24:929-936. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16432076>.

120. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m² melphalan and 8 Gy total body irradiation plus 140 mg/m² melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. *Blood* 2002;99:731-735. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11806971>.

121. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. *J Clin*

Oncol 2005;23:9227-9233. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16275936>.

122. Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. *N Engl J Med* 2014;371:895-905. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25184862>.

123. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM 2005-01 phase III trial. *J Clin Oncol* 2010;28:4621-4629. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/20823406>.

124. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy following autologous hematopoietic stem-cell transplantation in patients with newly diagnosed multiple myeloma. *Blood* 2012. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22498745>.

125. Attal M, Lauwers-Cances V, Hulin C, et al. Lenalidomide, Bortezomib, and Dexamethasone with Transplantation for Myeloma. *N Engl J Med* 2017;376:1311-1320. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28379796>.

126. Attal M, Harousseau JL, Facon T, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. *N Engl J Med* 2003;349:2495-2502. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14695409>.

127. Cavo M, Tosi P, Zamagni E, et al. Prospective, randomized study of single compared with double autologous stem-cell transplantation for multiple myeloma: Bologna 96 clinical study. *J Clin Oncol* 2007;25:2434-2441. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17485707>.

128. Sonneveld P, van der Holt B, Segeren C, et al. Intensive versus double intensive therapy in untreated multiple myeloma: Updated analysis of the randomized phase III study HOVON 24 MM [abstract].



NCCN Guidelines Version 4.2022

Multiple Myeloma

Blood 2004;104:Abstract 948. Available at:
<http://abstracts.hematologylibrary.org/cgi/content/abstract/104/11/948>.

129. Mai EK, Benner A, Bertsch U, et al. Single versus tandem high-dose melphalan followed by autologous blood stem cell transplantation in multiple myeloma: long-term results from the phase III GMMG-HD2 trial. Br J Haematol 2016;173:731-741. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/26990892>.

130. Barlogie B, Attal M, Crowley J, et al. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. J Clin Oncol 2010;28:1209-1214. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/20085933>.

131. Stadtmauer A, Pasquini M, Blackwell B, et al. Comparison of autologous hematopoietic cell transplant (autoHCT), bortezomib, lenalidomide (Len) and dexamethasone (RVD) consolidation with Len maintenance (ACM), tandem auto-HCT with Len maintenance (TAM) and AutoHCT with Len maintenance (AM) for up-front treatment of patients with Multiple Myeloma (MM): Primary results from the randomized phase III trial of the Blood and Marrow Transplant Clinical Trials Network (BMT CTN 0702 – StaMINA Trial). ASH annual meeting 2016 ; Late breaking Abstract. Available at:
<https://ash.confex.com/ash/2016/webprogram/Paper98809.html>.

132. Petrucci T, Raimondo FD, Zamagni E, et al. Upfront single versus double autologous stem cell transplantation for newly diagnosed multiple myeloma: An intergroup, multicenter, phase III study of the European Myeloma Network (EMN02/HO95 MM Trial (Oral Presentation). 2016 ASH annual meeting. Available at:
<https://ash.confex.com/ash/2016/webprogram/Paper93518.html>.

133. Stadtmauer EA, Pasquini MC, Blackwell B, et al. Autologous Transplantation, Consolidation, and Maintenance Therapy in Multiple Myeloma: Results of the BMT CTN 0702 Trial. J Clin Oncol 2019;37:589-597. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30653422>.

134. Cook G, Liakopoulou E, Pearce R, et al. Factors influencing the outcome of a second autologous stem cell transplant (ASCT) in relapsed multiple myeloma: a study from the British Society of Blood and Marrow Transplantation Registry. Biol Blood Marrow Transplant 2011;17:1638-1645. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21565277>.

135. Olin RL, Vogl DT, Porter DL, et al. Second auto-SCT is safe and effective salvage therapy for relapsed multiple myeloma. Bone Marrow Transplant 2009;43:417-422. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18850013>.

136. Burzynski JA, Toro JJ, Patel RC, et al. Toxicity of a second autologous peripheral blood stem cell transplant in patients with relapsed or recurrent multiple myeloma. Leuk Lymphoma 2009;50:1442-1447. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19637091>.

137. Alvares CL, Davies FE, Horton C, et al. The role of second autografts in the management of myeloma at first relapse. Haematologica 2006;91:141-142. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/16434386>.

138. Fenk R, Liese V, Neubauer F, et al. Predictive factors for successful salvage high-dose therapy in patients with multiple myeloma relapsing after autologous blood stem cell transplantation. Leuk Lymphoma 2011;52:1455-1462. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/21657961>.

139. Cook G, Williams C, Brown JM, et al. High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. Lancet Oncol 2014;15:874-885. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24948586>.

140. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. The Lancet



NCCN Guidelines Version 4.2022

Multiple Myeloma

Haematology 2016;3:e340-e351. Available at:
[http://dx.doi.org/10.1016/S2352-3026\(16\)30049-7](http://dx.doi.org/10.1016/S2352-3026(16)30049-7).

141. Kumar S, Mahmood ST, Lacy MQ, et al. Impact of early relapse after auto-SCT for multiple myeloma. Bone Marrow Transplant 2008;42:413-420. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18587435>.

142. Vangsted AJ, Klausen TW, Andersen NF, et al. Improved survival of multiple myeloma patients with late relapse after high-dose treatment and stem cell support, a population-based study of 348 patients in Denmark in 1994-2004. Eur J Haematol 2010;85:209-216. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/20477864>.

143. Kumar SK, Dispenzieri A, Fraser R, et al. Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time. Leukemia 2018;32:986-995. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29263438>.

144. Kastritis E, Roussou M, Eleutherakis-Papaiakovou E, et al. Early Relapse After Autologous Transplant Is Associated With Very Poor Survival and Identifies an Ultra-High-Risk Group of Patients With Myeloma. Clin Lymphoma Myeloma Leuk 2020;20:445-452. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/32284296>.

145. Bygrave C, Pawlyn C, Davies F, et al. Early relapse after high-dose melphalan autologous stem cell transplant predicts inferior survival and is associated with high disease burden and genetically high-risk disease in multiple myeloma. Br J Haematol 2020. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/32524584>.

146. Auner HW, Szydlo R, Rone A, et al. Salvage autologous stem cell transplantation for multiple myeloma relapsing or progressing after up-front autologous transplantation. Leuk Lymphoma 2013;54:2200-2204. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23387937>.

147. Jimenez-Zepeda VH, Mikhael J, Winter A, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma:

Impact on progression-free and overall survival. Biol Blood Marrow Transplant 2012;18:773-779. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/22062804>.

148. Sellner L, Heiss C, Benner A, et al. Autologous retransplantation for patients with recurrent multiple myeloma: a single-center experience with 200 patients. Cancer 2013;119:2438-2446. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/23576287>.

149. Shah N, Ahmed F, Bashir Q, et al. Durable remission with salvage second autotransplants in patients with multiple myeloma. Cancer 2012;118:3549-3555. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/22086552>.

150. Kyle RA. High-dose therapy in multiple myeloma and primary amyloidosis: an overview. Semin Oncol 1999;26:74-83. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/10073564>.

151. Kumar A, Loughran T, Alsina M, et al. Management of multiple myeloma: a systematic review and critical appraisal of published studies. Lancet Oncol 2003;4:293-304. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/12732167>.

152. Hahn T, Wingard JR, Anderson KC, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of multiple myeloma: an evidence-based review. Biol Blood Marrow Transplant 2003;9:4-37. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/12533739>.

153. Zeiser R, Bertz H, Spyridonidis A, et al. Donor lymphocyte infusions for multiple myeloma: clinical results and novel perspectives. Bone Marrow Transplant 2004;34:923-928. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/15361911>.

154. van de Donk NW, Kroger N, Hegenbart U, et al. Prognostic factors for donor lymphocyte infusions following non-myeloablative allogeneic stem cell transplantation in multiple myeloma. Bone Marrow Transplant 2006;37:1135-1141. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/16757975>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

155. Lokhorst HM, Wu K, Verdonck LF, et al. The occurrence of graft-versus-host disease is the major predictive factor for response to donor lymphocyte infusions in multiple myeloma. *Blood* 2004;103:4362-4364. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14976044>.

156. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor lymphocyte infusions for relapsed multiple myeloma after allogeneic stem-cell transplantation: predictive factors for response and long-term outcome. *J Clin Oncol* 2000;18:3031-3037. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10944138>.

157. Lokhorst HM, Schattenberg A, Cornelissen JJ, et al. Donor leukocyte infusions are effective in relapsed multiple myeloma after allogeneic bone marrow transplantation. *Blood* 1997;90:4206-4211. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9354693>.

158. Salama M, Nevill T, Marcellus D, et al. Donor leukocyte infusions for multiple myeloma. *Bone Marrow Transplant* 2000;26:1179-1184. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11149728>.

159. Tricot G, Vesole DH, Jagannath S, et al. Graft-versus-myeloma effect: proof of principle. *Blood* 1996;87:1196-1198. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8562947>.

160. Ayuk F, Shimoni A, Nagler A, et al. Efficacy and toxicity of low-dose escalating donor lymphocyte infusion given after reduced intensity conditioning allograft for multiple myeloma. *Leukemia* 2004;18:659-662. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14671630>.

161. Paiva B, Vidriales MB, Cervero J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. *Blood* 2008;112:4017-4023. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18669875>.

162. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. *J Clin*

Oncol 2013;31:2540-2547. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23733781>.

163. Putkonen M, Kairisto V, Juvonen V, et al. Depth of response assessed by quantitative ASO-PCR predicts the outcome after stem cell transplantation in multiple myeloma. *Eur J Haematol* 2010;85:416-423. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20722702>.

164. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple myeloma: a randomised, double-blind, phase 3 trial. *Lancet Haematol* 2017;4:e431-e442. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28826616>.

165. McCarthy PL, Holstein SA, Petrucci MT, et al. Lenalidomide Maintenance After Autologous Stem-Cell Transplantation in Newly Diagnosed Multiple Myeloma: A Meta-Analysis. *J Clin Oncol* 2017;35:3279-3289. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28742454>.

166. Kneppers E, van der Holt B, Kersten MJ, et al. Lenalidomide maintenance after nonmyeloablative allogeneic stem cell transplantation in multiple myeloma is not feasible: results of the HOVON 76 Trial. *Blood* 2011;118:2413-2419. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21690556>.

167. Alsina M, Becker PS, Zhong X, et al. Lenalidomide maintenance for high-risk multiple myeloma after allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant* 2014;20:1183-1189. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24769014>.

168. Palumbo A, Hajek R, Delforge M, et al. Continuous lenalidomide treatment for newly diagnosed multiple myeloma. *N Engl J Med* 2012;366:1759-1769. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22571200>.

169. Kumar SK, LaPlant BR, Gertz MA, et al. Lenalidomide Maintenance Therapy In Multiple Myeloma: A Meta-Analysis Of Randomized Trials.



NCCN Guidelines Version 4.2022

Multiple Myeloma

2013;122:407-407. Available at:

<http://www.bloodjournal.org/content/122/21/407?sso-checked=true>.

170. Musto P, Anderson KC, Attal M, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. *Ann Oncol* 2017;28:228-245. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27864218>.

171. Mellqvist UH, Gimsing P, Hjertner O, et al. Bortezomib consolidation after autologous stem cell transplantation in multiple myeloma: a Nordic Myeloma Study Group randomized phase 3 trial. *Blood* 2013;121:4647-4654. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23616624>.

172. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet* 2019;393:253-264. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/30545780>.

173. Richardson PG, Weller E, Jagannath S, et al. Multicenter, phase I, dose-escalation trial of lenalidomide plus bortezomib for relapsed and relapsed/refractory multiple myeloma. *J Clin Oncol* 2009;27:5713-5719. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19786667>.

174. Richardson PG, Xie W, Jagannath S, et al. A phase 2 trial of lenalidomide, bortezomib, and dexamethasone in patients with relapsed and relapsed/refractory myeloma. *Blood* 2014;123:1461-1469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24429336>.

175. Dimopoulos MA, Oriol A, Nahi H, et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2016;375:1319-1331. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27705267>.

176. Bahlis NJ, Dimopoulos MA, White DJ, et al. Daratumumab plus lenalidomide and dexamethasone in relapsed/refractory multiple myeloma: extended follow-up of POLLUX, a randomized, open-label, phase 3 study. *Leukemia* 2020;34:1875-1884. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32001798>.

177. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2015;372:142-152. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/25482145>.

178. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2016;375:754-766. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/27557302>.

179. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with daratumumab monotherapy in multiple myeloma. *N Engl J Med* 2015;373:1207-1219. Available at:

<http://www.ncbi.nlm.nih.gov/pubmed/26308596>.

180. Lonial S, Weiss BM, Usmani SZ, et al. Daratumumab monotherapy in patients with treatment-refractory multiple myeloma (SIRIUS): an open-label, randomised, phase 2 trial. *Lancet* 2016;387:1551-1560. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26778538>.

181. Mateos MV, Sonneveld P, Hungria V, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. *Clin Lymphoma Myeloma Leuk* 2020;20:509-518. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/32482541>.

182. Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. *Blood* 2019;134:421-431. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/31113777>.

183. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet* 2019;394:2096-2107. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/31735560>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

184. Dimopoulos MA, Leleu X, Moreau P, et al. Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis. *Leukemia* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32444867>.

185. Moreau P, Masszi T, Grzasko N, et al. Oral Ixazomib, Lenalidomide, and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2016;374:1621-1634. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27119237>.

186. Voorhees PM, Mulkey F, Hassoun H, et al. Alliance A061202. a Phase I/II Study of Pomalidomide, Dexamethasone and Ixazomib Versus Pomalidomide and Dexamethasone for Patients with Multiple Myeloma Refractory to Lenalidomide and Proteasome Inhibitor Based Therapy: Phase I Results. *Blood* 2015;126:375-375. Available at: <https://doi.org/10.1182/blood.V126.23.375.375>.

187. Krishnan AY, Kapoor P, Palmer J, et al. A phase I/II study of ixazomib (Ix) pomalidomide (POM) dexamethasone (DEX) in relapsed refractory (R/R) multiple myeloma: Initial results. *Journal of Clinical Oncology* 2016;34:8008-8008. Available at: http://ascopubs.org/doi/abs/10.1200/JCO.2016.34.15_suppl.8008.

188. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISM): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2019. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31097405>.

189. Lonial S, Lee HC, Badros A, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. *Lancet Oncol* 2020;21:207-221. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31859245>.

190. Offidani M, Corvatta L, Maracci L, et al. Efficacy and tolerability of bendamustine, bortezomib and dexamethasone in patients with relapsed-refractory multiple myeloma: a phase II study. *Blood Cancer J*

2013;3:e162. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24270324>.

191. Lentzsch S, O'Sullivan A, Kennedy RC, et al. Combination of bendamustine, lenalidomide, and dexamethasone (BLD) in patients with relapsed or refractory multiple myeloma is feasible and highly effective: results of phase 1/2 open-label, dose escalation study. *Blood* 2012;119:4608-4613. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22451423>.

192. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. *J Clin Oncol* 2007;25:3892-3901. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17679727>.

193. Davies FE, Wu P, Jenner M, et al. The combination of cyclophosphamide, velcade and dexamethasone induces high response rates with comparable toxicity to velcade alone and velcade plus dexamethasone. *Haematologica* 2007;92:1149-1150. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17650451>.

194. Kropff M, Bisping G, Schuck E, et al. Bortezomib in combination with intermediate-dose dexamethasone and continuous low-dose oral cyclophosphamide for relapsed multiple myeloma. *Br J Haematol* 2007;138:330-337. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17614819>.

195. Yong K, Brown S, Hinsley S, et al. Carfilzomib, cyclophosphamide and dexamethasone is well tolerated in patients with relapsed/refractory multiple myeloma who have received one prior regimen. 2015;126:1840. Available at: <https://ash.confex.com/ash/2015/webprogramscheduler/Paper82080.html>.

196. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised,



NCCN Guidelines Version 4.2022

Multiple Myeloma

phase 3, open-label, multicentre study. *Lancet Oncol* 2016;17:27-38. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26671818>.

197. Dimopoulos MA, Goldschmidt H, Niesvizky R, et al. Carfilzomib or bortezomib in relapsed or refractory multiple myeloma (ENDEAVOR): an interim overall survival analysis of an open-label, randomised, phase 3 trial. *Lancet Oncol* 2017;18:1327-1337. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28843768>.

198. Morgan GJ, Schey SA, Wu P, et al. Lenalidomide (Revlimid), in combination with cyclophosphamide and dexamethasone (RCD), is an effective and tolerated regimen for myeloma patients. *Br J Haematol* 2007;137:268-269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17408469>.

199. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood* 2017;130:974-981. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28637662>.

200. Jakubowiak A, Offidani M, Pegourie B, et al. Randomized phase 2 study: elotuzumab plus bortezomib/dexamethasone vs bortezomib/dexamethasone for relapsed/refractory MM. *Blood* 2016;127:2833-2840. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27091875>.

201. Hsi ED, Steinle R, Balasa B, et al. CS1, a potential new therapeutic antibody target for the treatment of multiple myeloma. *Clin Cancer Res* 2008;14:2775-2784. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18451245>.

202. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab therapy for relapsed or refractory multiple myeloma. *N Engl J Med* 2015;373:621-631. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26035255>.

203. Dimopoulos MA, Lonial S, White D, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. *Br J Haematol*

2017;178:896-905. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28677826>.

204. Dimopoulos MA, Lonial S, White D, et al. Elotuzumab, lenalidomide, and dexamethasone in RRMM: final overall survival results from the phase 3 randomized ELOQUENT-2 study. *Blood Cancer J* 2020;10:91. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32887873>.

205. Dimopoulos MA, Dytfield D, Grosicki S, et al. Elotuzumab plus Pomalidomide and Dexamethasone for Multiple Myeloma. *N Engl J Med* 2018;379:1811-1822. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30403938>.

206. Kumar SK, Grzasko N, Delimpasi S, et al. Phase 2 study of all-oral ixazomib, cyclophosphamide and low-dose dexamethasone for relapsed/refractory multiple myeloma. *Br J Haematol* 2019;184:536-546. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30460684>.

207. Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. *Blood* 2015;126:2284-2290. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26384354>.

208. Rosenbaum CA, Stephens LA, Kukreti V, et al. Phase 1/2 study of carfilzomib, pomalidomide, and dexamethasone (KPd) in patients (Pts) with relapsed/refractory multiple myeloma (RRMM): A Multiple Myeloma Research Consortium multicenter study. *ASCO Meeting Abstracts* 2016;34:8007. Available at: http://meeting.ascopubs.org/cgi/content/abstract/34/15_suppl/8007.

209. Baz RC, Martin TG, 3rd, Lin HY, et al. Randomized multicenter phase 2 study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma. *Blood* 2016;127:2561-2568. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26932802>.

210. Garderet L, Polge E, Gueye mS, et al. Pomalidomide, Cyclophosphamide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: A Retrospective Single Center Experience. *Blood*



NCCN Guidelines Version 4.2022

Multiple Myeloma

2015;126:1858-1858. Available at:
<https://doi.org/10.1182/blood.V126.23.1858.1858>.

211. Knop S, Straka C, Haen M, et al. The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy. *Haematologica* 2005;90:1287-1288. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/16154860>.

212. Michael M, Bruns I, Bolke E, et al. Bendamustine in patients with relapsed or refractory multiple myeloma. *Eur J Med Res* 2010;15:13-19. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20159666>.

213. Lenhard RE, Jr., Oken MM, Barnes JM, et al. High-dose cyclophosphamide. An effective treatment for advanced refractory multiple myeloma. *Cancer* 1984;53:1456-1460. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/6697291>.

214. Mikhael JR, Reeder CB, Libby EN, et al. A Phase I/II Trial Of Cyclophosphamide, Carfilzomib, Thalidomide and Dexamethasone (CYCLONE) In Patients With Newly Diagnosed Multiple Myeloma: Final Results Of MTD Expansion Cohort. *Blood* 2013;122:3179-3179. Available at:

215. Mikhael JR, Belch AR, Prince HM, et al. High response rate to bortezomib with or without dexamethasone in patients with relapsed or refractory multiple myeloma: results of a global phase 3b expanded access program. *Br J Haematol* 2009;144:169-175. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/19036114>.

216. Jagannath S, Barlogie B, Berenson J, et al. A phase 2 study of two doses of bortezomib in relapsed or refractory myeloma. *Br J Haematol* 2004;127:165-172. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/15461622>.

217. Jagannath S, Richardson PG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. *Haematologica* 2006;91:929-934. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16818280>.

218. Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med* 2007;357:2123-2132. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18032762>.

219. Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* 2007;357:2133-2142. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/18032763>.

220. Richardson P, Jagannath S, Hussein M, et al. Safety and efficacy of single-agent lenalidomide in patients with relapsed and refractory multiple myeloma. *Blood* 2009;114:772-778. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/19471019>.

221. Gorgun G, Calabrese E, Soydan E, et al. Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma. *Blood* 2010;116:3227-3237. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20651070>.

222. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol* 2013;14:1055-1066. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/24007748>.

223. Dimopoulos MA, Palumbo A, Weisel K, et al. Safety and efficacy in the stratus (MM-010) trial, a single-arm phase 3b study evaluating pomalidomide + low-dose dexamethasone in patients with refractory or relapsed and refractory multiple myeloma. *Vol. 124; 2014:80-80*. Available at: <http://www.bloodjournal.org/content/124/21/80>.

224. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low dose dexamethasone is active and well tolerated in bortezomib and lenalidomide refractory multiple myeloma: IFM 2009-02. *Blood* 2013;121:1968-1975. Available at:
<http://www.ncbi.nlm.nih.gov/pubmed/23319574>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

225. Lacy MQ, Allred JB, Gertz MA, et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease. *Blood* 2011;118:2970-2975. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21690557>.

226. Kumar SK, Bensinger WI, Zimmerman TM, et al. Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma. *Blood* 2014;124:1047-1055. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24904120>.

227. Richardson PG, Baz R, Wang M, et al. Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. *Blood* 2014;124:1038-1046. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24920586>.

228. Kumar SK, LaPlant B, Roy V, et al. Phase 2 trial of ixazomib in patients with relapsed multiple myeloma not refractory to bortezomib. *Blood Cancer J* 2015;5:e338. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/26275080>.

229. Kumar SK, Laplant BR, Reeder CB, et al. Randomized phase 2 trial of two different doses of ixazomib in patients with relapsed multiple myeloma not refractory to bortezomib. *Blood* 2015;126:3050-3050. Available at: <http://www.bloodjournal.org/content/126/23/3050>.

230. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor–Dexamethasone for Triple-Class Refractory Multiple Myeloma. *New England Journal of Medicine* 2019;381:727-738. Available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa1903455>.

231. Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. *Blood* 2017. Available at: <https://ashpublications.org/blood/article/130/22/2401/36573>.

232. Basali D, Chakraborty R, Rybicki L, et al. Real-world data on safety and efficacy of venetoclax-based regimens in relapsed/refractory t(11;14)

multiple myeloma. *Br J Haematol* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32012228>.

233. Lazzarino M, Corso A, Barbarano L, et al. DCEP (dexamethasone, cyclophosphamide, etoposide, and cisplatin) is an effective regimen for peripheral blood stem cell collection in multiple myeloma. *Bone Marrow Transplant* 2001;28:835-839. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11781643>.

234. Dadacaridou M, Papanicolaou X, Maltesas D, et al. Dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) for relapsed or refractory multiple myeloma patients. *J BUON* 2007;12:41-44. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17436400>.

235. Griffin PT, Ho VQ, Fulp W, et al. A comparison of salvage infusional chemotherapy regimens for recurrent/refractory multiple myeloma. *Cancer* 2015;121:3622-3630. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26149422>.

236. Lee CK, Barlogie B, Munshi N, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. *J Clin Oncol* 2003;21:2732-2739. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12860952>.

237. Srikanth M, Davies FE, Wu P, et al. Survival and outcome of blastoid variant myeloma following treatment with the novel thalidomide containing regime DT-PACE. *Eur J Haematol* 2008;81:432-436. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18691254>.

238. Buda G, Orciuolo E, Galimberti S, et al. VDT-PACE As Salvage Therapy For Heavily Pretreated MM Patients. *Blood* 2013;122:5377-5377. Available at:

239. Andoh S, Togano T, Itoi S, et al. Efficacy and Safety of VTD-PACE Regimen in Relapsed or Refractory Multiple Myeloma. *Clinical Lymphoma Myeloma and Leukemia* 2017;17:e57. Available at: <http://dx.doi.org/10.1016/j.clml.2017.03.104>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

240. Lakshman A, Singh PP, Rajkumar SV, et al. Efficacy of VDT PACE-like regimens in treatment of relapsed/refractory multiple myeloma. *Am J Hematol* 2018;93:179-186. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29067723>.

241. Berenson JR, Lichtenstein A, Porter L, et al. Long-term pamidronate treatment of advanced multiple myeloma patients reduces skeletal events. Myeloma Aredia Study Group. *J Clin Oncol* 1998;16:593-602. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9469347>.

242. Berenson JR, Lichtenstein A, Porter L, et al. Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. *N Engl J Med* 1996;334:488-493. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8559201>.

243. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol* 2001;19:558-567. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11208851>.

244. Zervas K, Verrou E, Teleioudis Z, et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. *Br J Haematol* 2006;134:620-623. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16889620>.

245. Morgan GJ, Davies FE, Gregory WM, et al. First-line treatment with zoledronic acid as compared with clodronic acid in multiple myeloma (MRC Myeloma IX): a randomised controlled trial. *Lancet* 2010;376:1989-1999. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21131037>.

246. Jackson GH, Morgan GJ, Davies FE, et al. Osteonecrosis of the jaw and renal safety in patients with newly diagnosed multiple myeloma: Medical Research Council Myeloma IX Study results. *Br J Haematol* 2014;166:109-117. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24673708>.

247. Morgan GJ, Davies FE, Gregory WM, et al. Long-term follow-up of MRC Myeloma IX trial: Survival outcomes with bisphosphonate and thalidomide treatment. *Clin Cancer Res* 2013;19:6030-6038. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23995858>.

248. Mhaskar R, Redzepovic J, Wheatley K, et al. Bisphosphonates in multiple myeloma: a network meta-analysis. *Cochrane Database Syst Rev* 2012;5:CD003188. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/22592688>.

249. Himelstein AL, Foster JC, Khatcheressian JL, et al. Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone Metastases: A Randomized Clinical Trial. *JAMA* 2017;317:48-58. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28030702>.

250. Raje N, Terpos E, Willenbacher W, et al. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *Lancet Oncol* 2018;19:370-381. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29429912>.

251. Resende Salgado L, Chang S, Ru M, et al. Utilization Patterns of Single Fraction Radiation Therapy for Multiple Myeloma. *Clin Lymphoma Myeloma Leuk* 2019;19:e238-e246. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30904388>.

252. Major PP, Coleman RE. Zoledronic acid in the treatment of hypercalcemia of malignancy: results of the international clinical development program. *Semin Oncol* 2001;28:17-24. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11346861>.

253. Pecherstorfer M, Steinhauer EU, Rizzoli R, et al. Efficacy and safety of ibandronate in the treatment of hypercalcemia of malignancy: a randomized multicentric comparison to pamidronate. *Support Care Cancer* 2003;11:539-547. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12783289>.



NCCN Guidelines Version 4.2022

Multiple Myeloma

254. Lindsley H, Teller D, Noonan B, et al. Hyperviscosity syndrome in multiple myeloma. A reversible, concentration-dependent aggregation of the myeloma protein. *Am J Med* 1973;54:682-688. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/4701949>.

255. Ludwig H, Fritz E, Kotzmann H, et al. Erythropoietin treatment of anemia associated with multiple myeloma. *N Engl J Med* 1990;322:1693-1699. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/2342535>.

256. Osterborg A, Boogaerts MA, Cimino R, et al. Recombinant human erythropoietin in transfusion-dependent anemic patients with multiple myeloma and non-Hodgkin's lymphoma--a randomized multicenter study. The European Study Group of Erythropoietin (Epoetin Beta) Treatment in Multiple Myeloma and Non-Hodgkin's Lymphoma. *Blood* 1996;87:2675-2682. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/8639883>.

257. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia* 2008;22:414-423. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18094721>.

258. Ikhlague N, Seshadri V, Kathula S, Baumann MA. Efficacy of prophylactic warfarin for prevention of thalidomide-related deep venous thrombosis. *Am J Hematol* 2006;81:420-422. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16680743>.

259. Baz R, Li L, Kottke-Marchant K, et al. The role of aspirin in the prevention of thrombotic complications of thalidomide and anthracycline-based chemotherapy for multiple myeloma. *Mayo Clin Proc* 2005;80:1568-1574. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16342649>.

260. Mateos MV. Management of treatment-related adverse events in patients with multiple myeloma. *Cancer Treat Rev* 2010;36 Suppl 2:S24-32. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20472185>.

261. Siegel D, Martin T, Nooka A, et al. Integrated safety profile of single-agent carfilzomib: experience from 526 patients enrolled in 4

phase II clinical studies. *Haematologica* 2013;98:1753-1761. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23935022>.

262. Chanan-Khan A, Sonneveld P, Schuster MW, et al. Analysis of herpes zoster events among bortezomib-treated patients in the phase III APEX study. *J Clin Oncol* 2008;26:4784-4790. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18711175>.

263. Mateos MV, Hernandez JM, Hernandez MT, et al. Bortezomib plus melphalan and prednisone in elderly untreated patients with multiple myeloma: results of a multicenter phase 1/2 study. *Blood* 2006;108:2165-2172. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/16772605>.

264. Richardson PG, Sonneveld P, Schuster MW, et al. Bortezomib or high-dose dexamethasone for relapsed multiple myeloma. *N Engl J Med* 2005;352:2487-2498. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15958804>.

265. Blade J, Fernandez-Llama P, Bosch F, et al. Renal failure in multiple myeloma: presenting features and predictors of outcome in 94 patients from a single institution. *Arch Intern Med* 1998;158:1889-1893. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/9759684>.

266. Knudsen LM, Hippe E, Hjorth M, et al. Renal function in newly diagnosed multiple myeloma--a demographic study of 1353 patients. The Nordic Myeloma Study Group. *Eur J Haematol* 1994;53:207-212. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/7957804>.

267. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. *Eur J Haematol* 2000;65:175-181. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11007053>.

268. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. *Am J*



Hematol 2016;91:499-502. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/26890495>.

269. Dimopoulos MA, Sonneveld P, Leung N, et al. International Myeloma Working Group Recommendations for the Diagnosis and Management of Myeloma-Related Renal Impairment. J Clin Oncol 2016;34:1544-1557. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/26976420>.

270. Dimopoulos MA, Christoulas D, Roussou M, et al. Lenalidomide and dexamethasone for the treatment of refractory/relapsed multiple myeloma: dosing of lenalidomide according to renal function and effect on renal impairment. Eur J Haematol 2010;85:1-5. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/20192988>.

271. Dimopoulos M, Weisel K, van de Donk N, et al. Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial. J Clin Oncol 2018;36:2035-2043. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/29394124>.

272. Leung N, Bridoux F, Hutchison CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood 2012;120:4292-4295. Available at:
<https://www.ncbi.nlm.nih.gov/pubmed/23047823>.

Discussion
update in
progress