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Release date: January 10, 2022; Expiration date: January 10, 2023

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Multiple Myeloma
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Multiple Myeloma

Disclosure of Relevant Financial Relationships

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This activity is supported by educational grants from AstraZeneca; BeiGene; Exact Sciences; Gilead Sciences, Inc.; GlaxoSmithKline; Lantheus Medical Imaging Inc.; Novartis; Pharmacyclis LLC, an AbbVie Company and Janssen Biotech, Inc., administered by Janssen Scientific Affairs, LLC; and Taiho Oncology, Inc. This activity is supported by an independent educational grant from Astellas. This activity is supported by an education grant from Astellas and Seagen Inc. This activity is supported by a medical education grant from Karyopharm® Therapeutics. This activity is supported through an Independent Medical Education grant from Merck & Co., Inc.

Multiple Myeloma, Version 3.2022

Featured Updates to the NCCN Guidelines

Natalie S. Callander, MD^{1,*}; Muhamed Baljevic, MD^{2,*}; Kehinde Adekola, MD, MSCI³; Larry D. Anderson Jr, MD, PhD⁴; Erica Campagnaro, MD⁵; Jorge J. Castillo, MD⁶; Caitlin Costello, MD⁷; Srinivas Devarakonda, MD⁸; Noura Elsedawy, MD⁹; Matthew Faiman, MD, MBA¹⁰; Alfred Garfall, MD¹¹; Kelly Godby, MD¹²; Jens Hillengass, MD, PhD¹³; Leona Holmberg, MD, PhD¹⁴; Myo Htut, MD¹⁵; Carol Ann Huff, MD¹⁶; Malin Hultcrantz, MD, PhD¹⁷; Yubin Kang, MD¹⁸; Sarah Larson, MD¹⁹; Michaela Liedtke, MD²⁰; Thomas Martin, MD²¹; James Omel, MD²²; Douglas Sborov, MD, MSc²³; Kenneth Shain, MD, PhD²⁴; Keith Stockerl-Goldstein, MD²⁵; Donna Weber, MD²⁶; Ryan A. Berardi, MSc^{27,*}; Rashmi Kumar, PhD^{27,*}; and Shaji K. Kumar, MD^{28,*}

ABSTRACT

The NCCN Guidelines for Multiple Myeloma provide recommendations for diagnosis, initial workup, treatment, follow-up, and supportive care for patients with various plasma cell neoplasms, including multiple myeloma. These NCCN Guidelines Insights highlight some of the important updates/changes specific to the treatment of patients with multiple myeloma in the 2022 version of the guidelines.

J Natl Compr Canc Netw 2022;20(1):8–19
doi: 10.6004/jnccn.2022.0002

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

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

*Provided content development and/or authorship assistance.

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.

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MYEL-F

Overview

Multiple myeloma (MM) is a malignant neoplasm of the plasma cells that accumulate in bone marrow, leading to renal failure, hypercalcemia, bone destruction, and anemia due to marrow failure. MM accounts for approximately 1.8% of all cancers and 18.7% 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 34,920 new MM cases will be diagnosed in the United States in 2021, with an estimated 12,410 deaths.¹

The NCCN MM Panel has developed guidelines for managing patients with various plasma cell neoplasms, including monoclonal gammopathy of renal and neurologic significance, POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes), solitary plasmacytoma with and without minimal marrow involvement, smoldering myeloma, MM, systemic light-chain amyloidosis, and Waldenström macroglobulinemia. These guidelines are updated annually, or more often if new high-quality clinical data become available.

Significant updates have been made to the 2022 version of the NCCN Clinical Practice Guidelines in

Oncology (NCCN Guidelines) for MM. These NCCN Guidelines Insights focus only on those updates specific to recommendations for newly diagnosed transplant-eligible and transplant-ineligible candidates, maintenance, and previously treated MM, and principles of management of venous thromboembolism (VTE). For a complete list of updates to the 3.2022 version, visit NCCN.org.

General Considerations for MM Therapy

The panel has included a new page on general considerations for MM therapy. The content on this page was previously included in footnotes on the pages that include a list of options for myeloma therapy. This page contains general principles for consideration, screening and prophylaxis recommendations, important dosing and administration considerations, and a few noteworthy side effects and laboratory testing considerations. This year, the panel has noted that for elderly patients with MM, an assessment of frailty or calculation of frailty score is recommended using the tool developed by the International Myeloma Working Group (<http://www.myelomafrailtyscorecalculator.net/>) to predict mortality and the risk of toxicity³ (see MYEL-F, page 10).

PRIMARY THERAPY FOR TRANSPLANT CANDIDATES ^{a-d}	
Preferred Regimens	• Bortezomib/lenalidomide/dexamethasone (category 1)
Other Recommended Regimens	• Carfilzomib/lenalidomide/dexamethasone • Daratumumab/lenalidomide/bortezomib/dexamethasone • Ixazomib/lenalidomide/dexamethasone (category 2B)
Useful In Certain Circumstances	• 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	• Lenalidomide ^h (category 1)
Other Recommended Regimens	• Ixazomib (category 2B) • Bortezomib
Useful In Certain Circumstances	• Bortezomib/lenalidomide ± dexamethasone ⁱ

^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.

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[Continued](#)

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Updates to the Treatment Options for Newly Diagnosed MM

During the annual guidelines update this year, the panel reviewed the preference categories of all the regimens and reclassified a few based on updated data and/or panel consensus. The panel also added new regimens for both transplant-eligible as well as transplant-ineligible patients with newly diagnosed MM.

The bortezomib/cyclophosphamide/dexamethasone regimen was moved from the “preferred” category to “useful in certain circumstances” for transplant candidates. The rationale for this reclassification is that this regimen is used only in circumstances when patients do not have immediate access to bortezomib/lenalidomide/dexamethasone or if they have renal insufficiency. The regimen continues to be listed under “useful in certain circumstances” for nontransplant candidates (see MYEL-G 1 of 4, page 11).

The panel added the 4-drug regimen daratumumab/carfilzomib/lenalidomide/dexamethasone for transplant-eligible patients with newly diagnosed MM to the list of regimens in the “useful in certain circumstances” category (see MYEL-G 1 of 4, page 11). It was included as an option for nontransplant daratumumab/carfilzomib/lenalidomide/dexamethasone candidates in Version 1.2021.

The data for daratumumab/carfilzomib/lenalidomide/dexamethasone in the transplant setting come from 2 trials. In the first nonrandomized clinical trial in patients with newly diagnosed multiple myeloma (n=41),⁴ daratumumab/carfilzomib/lenalidomide/dexamethasone therapy was associated with high rates of minimal residual disease (MRD) negativity (29 of 41 evaluable patients were MRD-negative after 8 cycles of therapy).⁴ At 11 months of the median follow-up, the trial reported 1-year progression-free survival (PFS) and overall survival (OS) rates of 98% (95% CI, 93%–100%) and 100%, respectively.⁴

In the ongoing phase II MASTER trial, 123 patients received daratumumab/carfilzomib/lenalidomide/dexamethasone for 4 cycles as induction, followed by autologous stem cell transplant and then consolidation with the induction regimen according to MRD status. Patients who were MRD-positive at the end of consolidation received lenalidomide maintenance. Those were MRD-negative on 2 consecutive tests were moved to observation only. The percent of patients who were MRD-negative was 42% after induction, 73% after autologous hematopoietic cell transplant (HCT), and 82% during consolidation. MRD negativity rates were similar between the standard-risk and high-risk cytogenetic

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 	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Carfilzomib/cyclophosphamide/dexamethasone^f • Lenalidomide/low-dose dexamethasone (category 1)^k • Bortezomib/lenalidomide/dexamethasone (VRd-lite) for frail patients

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

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

^h 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.

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groups.⁵ Carfilzomib was given weekly in both trials to optimize tolerability.

This regimen is included under the category “useful in certain circumstances,” and the panel noted in a footnote that it is generally an option reserved for those with aggressive disease (see MYEL-G 1 of 4, page 11).

The panel also added the modified bortezomib/lenalidomide/dexamethasone (VRd-lite) for nontransplant patients. This is based on the following phase II study that evaluated modified dose and schedule of the triple combination of bortezomib/lenalidomide/dexamethasone (VRd-lite) in older transplant-ineligible patients with MM. The median age of patients in this trial was 73 years. VRd-lite administered in a 35-day cycle consisted of subcutaneous bortezomib at 1.3 mg/m² on days 1, 8, 15, and 22; dexamethasone at 20 mg orally on the day of and the day after bortezomib administration for those aged ≤75 years, and at 20 mg orally on the same days as bortezomib only for those aged ≥75 years; and lenalidomide at 15 mg on days 1 through 21. In 48 evaluable patients at a median follow-up of 17.2 months, the 1-year PFS was 95% and the 2-year PFS was 68%.⁶ At a follow-up of 61 months, continued improvement in PFS was seen. The median PFS was 41.9 months and

median OS was not reached. The 5-year OS was 61.3%⁷ (see MYEL-G 2 of 4, page 12).

Because VRd-lite is a well-tolerated regimen and provides an effective option of using a 3-drug regimen with modifications in dose and schedule without compromising efficacy in older, frail, transplant-ineligible patients, the panel has included this as an option for transplant-ineligible patients with MM.

Updates to Maintenance Therapy Recommendations

The TOURMALINE-MM3 trial studied 2 years of maintenance with ixazomib versus placebo in patients who had achieved at least a partial response after induction therapy and a single autologous HCT⁸ and the TOURMALINE-MM4 trial studied ixazomib maintenance in transplant-ineligible patients with newly diagnosed MM.⁹

Recently, the manufacturers of ixazomib released an information letter to healthcare providers stating that interim survival analyses of the TOURMALINE-MM3 and MM4 trials indicated slightly inferior 3- and 5-year OS in patients receiving ixazomib maintenance. These results are not published and the company has not released additional data. Considering this update, the panel changed

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 • Panobinostat/bortezomib/dexamethasone (category 1) • 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

^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.

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

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.

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the designation for ixazomib maintenance to a category 2B recommendation.

Extrapolating from the induction therapy, a single institution explored lenalidomide/bortezomib/dexamethasone as maintenance for up to 3 years followed by single-agent lenalidomide in patients with high-risk disease after autologous HCT (n=45). The results reported a median PFS of 32 months and a 3-year OS of 93% with the triple-drug regimen as maintenance/consolidation therapy.¹⁰

A retrospective study evaluated the efficacy of lenalidomide/bortezomib/dexamethasone in patients (n=1,000) with newly diagnosed MM with subsequent administration of maintenance therapy based on myeloma risk stratification. Maintenance therapy options included lenalidomide alone or lenalidomide/bortezomib. Overall, 753 patients in the trial received maintenance; 600 (60.7%) received lenalidomide alone as maintenance therapy based on standard-risk cytogenetics, and 107 (10.7%) received immunomodulatory drug (IMiD) and proteasome inhibitor (PI) maintenance therapy, predominantly with lenalidomide/bortezomib/dexamethasone. The median PFS of patients with high-risk disease who received maintenance with lenalidomide and bortezomib maintenance therapy was 40.3 months (95% CI, 33.5–47 months), with a median OS of 78.2 months. At a

median follow-up of 74 months, the median OS for this group was 78.2 months (95% CI, 62.2–94.2 months).¹¹

The NCCN MM Panel has now included lenalidomide/bortezomib with dexamethasone as a maintenance therapy option for transplant-eligible patients (see MYEL-G 1 of 4, page 11).

Updates to Treatment Options for Previously Treated MM

A variety of therapies are available for previously treated MM. The choice of appropriate therapy for a patient depends on the context of the clinical relapse, such as prior treatment, duration of response, the class of agents previously received, and residual or emerging side effects of previous treatment. Patient-specific factors also need to be considered, such as frailty, availability and accessibility to clinical trials, proximity to clinic, previous autologous stem cell collection, and patient preferences for specific treatment.

The panel received several requests to provide additional guidance in therapy selection for relapsed/refractory (R/R) MM. As a result, the panel segregated the therapies as used for early relapse (1–3 prior therapies) and late relapse (>3 therapies) in the 2022 version (see MYEL-G 3 of 4, page 13). The panel also clarified in a

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA ^{a-d,n,p}	
Useful in Certain Circumstances for Early Relapses (1–3 prior therapies) <i>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.</i>	
<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 	<ul style="list-style-type: none"> • After two prior therapies including bortezomib and an IMiD <ul style="list-style-type: none"> ▶ Panobinostat/carfilzomib ▶ Panobinostat/lenalidomide/dexamethasone • 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-bimf ▶ Idecabtagene vicleucel ▶ Melphalan flufenamide/dexamethasone • 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.

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footnote that “regimens included under 1–3 prior therapies can also be used later in the disease course. An attempt should be made to use drugs/drug classes that patients have not been exposed to or exposed to >1 line prior.” An example of this strategy would be to select a regimen that does not contain lenalidomide in a patient experiencing progression on that agent.

For the 2022 update, isatuximab-irfc/carfilzomib/dexamethasone and daratumumab/pomalidomide/dexamethasone were moved from the other recommended regimens to preferred regimens for early relapses (1–3 prior therapies) based on new data.

The multicenter, phase III, open-label IKEMA trial studied patients (n=302) with relapsed MM who had received 1 to 3 prior lines of therapy randomly assigned to receive carfilzomib/dexamethasone ± isatuximab-irfc until disease progression or unacceptable toxicity.¹² After a median follow-up of 21 months, the median PFS was not reached in the isatuximab-irfc group versus 19 months in the control group (hazard ratio [HR], 0.53; 95% CI, 0.32–0.89). Serious adverse reactions were seen in 59% versus 57% of patients in the isatuximab-irfc versus the control group, respectively. The most common adverse reactions with isatuximab-irfc were infusion-related

reactions, fatigue, hypertension, diarrhea, upper respiratory tract infection, pneumonia, dyspnea, and bronchitis. Based on the results of the IKEMA trial, the panel included isatuximab-irfc/carfilzomib/dexamethasone as a category 1, preferred regimen option for patients with R/R MM. Previously, this regimen was included under “other recommended regimens” as a category 2A recommendation.

The phase II MM-014 study investigated pomalidomide-containing therapies sequenced after a lenalidomide-based regimen in patients with R/R MM. The trial had 3 cohorts, one of which (cohort B) assessed triplet therapy with daratumumab/pomalidomide/dexamethasone in patients who had received 1 to 2 prior treatments with a lenalidomide-containing regimen in the immediate prior line. In cohort B, all patients had prior lenalidomide (75% had lenalidomide-refractory disease) and 77.7% had prior bortezomib. Most patients received 1 versus 2 prior lines of therapy (62.5% vs 37.5%). At a median follow-up of 28.4 months, the overall response rate (ORR) in cohort B (n=112) was 77.7%, and 52.7% achieved a very good partial response or better; median PFS was 30.8 months.¹³ In an updated analysis of MM-014, the ORR in patients with lenalidomide-relapsed (disease relapse >60 days of receiving lenalidomide-containing regimen) and lenalidomide-

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

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refractory disease was 82.1% and 76.2%, respectively. The most frequently occurring hematologic grade 3 or 4 treatment-related adverse events in the daratumumab/pomalidomide/dexamethasone arm were neutropenia (64.3%), anemia (17.9%), and thrombocytopenia (14.3%).¹⁴

An open-label, multicenter phase III study (APOLLO) investigated daratumumab/pomalidomide/dexamethasone versus pomalidomide/dexamethasone in patients who received ≥1 prior line of therapy, including lenalidomide and a PI.¹⁵ At a median follow-up of 16.9 months, the addition of daratumumab to pomalidomide/dexamethasone demonstrated an ORR of 69% versus 46% and improved median PFS of 12.4 versus 6.9 months (HR, 0.63; 95% CI, 0.47–0.85). The most common grade 3 or 4 adverse events seen in the daratumumab group included neutropenia, anemia, and thrombocytopenia.¹⁵

Based on these data, the panel has included daratumumab/pomalidomide/dexamethasone as a category 1, preferred treatment option for patients with R/R MM who have received at least 2 prior therapies, including an IMiD and a PI.

Earlier this year, the FDA granted accelerated approval for melphalan flufenamide, a peptide-drug conjugate with a unique delivery mechanism for melphalan and desethyl-

melphalen in combination with dexamethasone. This approval was based on the results of a multicenter, single-arm trial (HORIZON) of melphalan flufenamide/dexamethasone in patients (n=157) with R/R MM, the ORR was 29% and the estimated median PFS was 4.2 months.¹⁶

Based on these data, NCCN Guidelines included melphalan flufenamide/dexamethasone as a treatment option for patients with late relapses (≥4 prior therapies) and whose disease was refractory to at least one PI, one IMiD, and one CD38-directed monoclonal antibody. However, subsequently, concerns were raised about its efficacy and safety based on a preliminary analysis of a randomized trial (OCEAN) comparing melphalan flufenamide/dexamethasone with pomalidomide/dexamethasone that demonstrated a decrease in OS (data in abstract form only).¹⁷ Following the recent withdrawal of this drug from the market by the manufacturer,¹⁸ the panel voted unanimously to remove this regimen as an option for patients with late relapses (≥4 prior therapies).

The phase II KarMMa trial evaluated the efficacy and safety of idecabtagene vicleucel (ide-cel), an anti-B-cell maturation antigen (BCMA) CAR T-cell therapy, in

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 $<50,000/\mu\text{L}$; in patients with high risk for VTE, prophylactic anticoagulation may be appropriate even if platelet count is as low as $25,000/\mu\text{L}$.
- 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 $\pm$ 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

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 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.

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patients with R/R MM who received 3 prior lines of therapy.¹⁹ After a follow up of 13.3 months, 94 of 128 patients experienced a response. The ORR was 73%, and the estimated median PFS was 8.8 months (95% CI, 5.6–11.6 months).¹⁹ Common adverse effects included anemia (70%) and thrombocytopenia (63%); cytokine release syndrome was seen in 84% (5% were grade ≥ 3) and neurotoxic effects were seen in 23% (3% were grade ≥ 3).¹⁹

Based on the results of the KarMMa trial and FDA approval of this agent, the panel included this therapy as a treatment option for patients with relapsed MM who received at least 4 previous therapies (including a PI, an IMiD, and an anti-CD38 monoclonal antibody).

Management of VTE in Patients With MM

In the updated version of the guidelines for MM, the panel has included recommendations specific to VTE risk assessment and VTE prophylaxis for patients with MM (see MYEL-I, pages 15–17).

VTE Risk Stratification

Patients with MM have a 9-fold increase in VTE risk compared with the general population.²⁰ In MM, the use of IMiDs (thalidomide, lenalidomide, or pomalidomide)

with steroids or multiagent chemotherapy creates a significant risk for VTE,²¹ which is mostly seen within 6 months of treatment initiation, irrespective of the treatment regimen.^{22,23}

For patients with MM, risk scores may be obtained using 2 scoring systems. This risk score helps identify patients with high risk who would benefit from anticoagulation therapy versus those with low risk for whom treatment with anticoagulants may be avoided. Predictors of VTE, used to obtain the IMPEDE score,²⁴ include risk scoring based on immunomodulatory agent; body mass index $\geq 25 \text{ kg/m}^2$; pelvic, hip, or femur fracture; erythropoietin-stimulating agent; dexamethasone/doxorubicin; Asian ethnicity/race; VTE history; tunneled line/central venous catheter; and existing thromboprophylaxis. Predictors of VTE used to obtain the SAVED score²⁵ include previous surgery, Asian race, VTE history, age ≥ 80 years, and dexamethasone dose. The details on how many score points are associated with each of the predictors of VTE risk are included on MYEL-I 1 of 3, page 15.

VTE Prophylaxis

Administration of VTE prophylaxis is based on risk as long as there are no contraindications to anticoagulation

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)

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or antiplatelets agents. The NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease (available at NCCN.org) outline the contraindications for anticoagulation prophylaxis. All anticoagulants carry an increased risk of bleeding. Therefore, careful consideration is needed regarding risks and benefits for each patient.

The optimal choice of VTE prophylaxis agent depends on several patient-related factors, such as risk of bleeding (eg, concurrent coagulopathy, disseminated intravascular coagulation, hyperviscosity), cytopenia (eg, platelet count ± hemoglobin), concurrent medications (eg, strong cytochrome P inducers/inhibitors, single/dual antiplatelets), renal function (eg, creatinine clearance), extremes of body weight, and history of heparin-induced thrombocytopenia. It is also dependent on the availability of reversal agents in case of emergency bleeding, type of myeloma therapy received (eg, with carfilzomib, IMiD, dexamethasone), patient choice (eg, preference for mode of administration, dietary restrictions), and insurance coverage/restrictions (including cost of therapy).

Use of prophylactic anticoagulation agents may be considered if the risk of VTE is deemed high, particularly with IMiD-based induction therapy.^{21,26,27} One phase III trial has evaluated VTE prophylaxis specifically in patients

with newly diagnosed MM undergoing treatment with thalidomide-based regimens. In this study, low-dose low-molecular-weight heparin (LMWH) was compared with fixed-dose warfarin or aspirin. Of 659 analyzed patients, 43 had serious thromboembolic events (6.5%). No statistically significant differences were observed among the 3 arms.²⁸

Direct oral anticoagulants (DOACs) are effective for the treatment of cancer-associated thrombosis and have the advantage of oral administration without requiring intense laboratory monitoring. The AVERT and CASSINI studies evaluated their benefit for primary VTE prophylaxis in intermediate-risk to high-risk ambulatory patients with cancer.^{29,30}

Currently, apixaban and rivaroxaban are the only DOACs with evidence from randomized control trials for primary VTE prophylaxis in patients with cancer.^{29–31} However, generalizing their use in patients with MM is a challenge. The AVERT trial with apixaban included only 2.6% of patients with myeloma,²⁹ and patients with MM were excluded from the CASSINI trial with rivaroxaban altogether.³⁰ Nevertheless, based on these studies showing the efficacy and safety of DOACs for VTE prophylaxis in patients with cancer, recent smaller trials have

investigated prophylaxis with DOACs in patients with MM.^{32–35} The results of these trials are encouraging, but they need to be confirmed by larger studies.

The decision for VTE prophylaxis should be made after considering the risk of both VTE and bleeding, as well as patients' preference and values. Patients receiving VTE prophylaxis should be monitored for bleeding complications and any adverse effects impacting quality of life. A minority of patients may be deemed inappropriate for VTE prophylaxis, and such decisions should be reevaluated as the patients' clinical situation evolves.

In summary, the VTE prophylaxis recommendation for patients with ≤ 3 points by IMPEDE score or < 2 points by SAVED score is aspirin at 81 to 325 mg once daily.

For those with ≥ 4 points by IMPEDE score or ≥ 2 points by SAVED score, the recommendation is enoxaparin (40 mg/d subcutaneously), warfarin (target international normalized ratio, 2.0–3.0), fondaparinux (2.5 mg/d subcutaneously),³⁶ or a DOAC, such as rivaroxaban at 10 mg/d orally or apixaban at 2.5 mg orally twice daily.³⁷ A less common and less well-studied choice of LMWH includes dalteparin at 5,000 units daily subcutaneously (category 2B).

Duration of VTE prophylaxis

The duration of VTE prophylaxis is indefinite while on MM therapy, or 3 to 6 months followed by aspirin (longer periods of anticoagulation may be considered in the

presence of additional patient-specific, treatment-specific, or transient VTE risk factors). For any patients who develop VTE on IMiD-based therapy, the panel recommends continuing the therapeutic dose of anticoagulation for as long as IMiD-based therapy is indicated.

Conclusions

These NCCN Guidelines Insights highlight the important updates/changes specific to the treatment options for MM in the 2022 version of the NCCN Guidelines for MM. The NCCN Guidelines are in continuous evolution; they are updated annually, and sometimes more often if new high-quality clinical data become available in the interim. The recommendations in the NCCN Guidelines, with few exceptions, are based on evidence from clinical trials. Expert medical clinical judgment is required when applying these guidelines in the context of individual clinical circumstances to provide optimal care. The physician and the patient have the responsibility to jointly explore and select the most appropriate option from among the available alternatives. When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in prospective clinical trials.

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