National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Multiple Myeloma

Version 3.2023 — December 8, 2022

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NCCN Multiple Myeloma Panel Members
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POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, Skin Changes) (POEMS-1)

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

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.

Updates in Version 3.2023 of the NCCN Guidelines for Multiple Myeloma from Version 2.2023 include:

MYEL-G 5 of 5

- Therapy for Previously Treated Multiple Myeloma
  - Therapies for patients with Late Relapses (>3 prior therapies)
    - ◊ After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD:
      - – Fourth bullet added: Useful in certain circumstances
        - ▪ Belantamab mafodotin-blmf has been moved to useful in certain circumstances: *Belantamab mafodotin-blmf (if available through compassionate use program)*

Updates in Version 2.2023 of the NCCN Guidelines for Multiple Myeloma from Version 1.2023 include:

MYEL-G 5 of 5

- Therapy for Previously Treated Multiple Myeloma
  - Therapies for patients with Late Relapses (>3 prior therapies):
    - ◊ Teclistamab-cqyv was added as an option after at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.

Updates in Version 1.2023 of the NCCN Guidelines for Multiple Myeloma from Version 5.2022 include:

MYEL-1

- Initial Diagnostic Workup:
  - 11th bullet modified: Plasma cell fluorescence in situ hybridization (FISH) panel on bone marrow [del(13), del(17p13), t(4;14), t(11;14), t(14;16), t(14:20), 1q21 gain/*1q21* amplification, 1p deletion]
  - 12th bullet added: NT-proBNP/BNP
- Footnote d modified: 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. *FDG PET should always be performed with CT.* (Also on MYEL-4)
- Footnote g added: 1q21 amplification is defined as ≥4 copies detected by FISH, and a gain is defined as 3 copies of 1q21.
- Footnote h added: If NT-proBNP is not available, BNP can be performed.

MYEL-2

- Follow-up/Surveillance, 2nd bullet, 5th sub-bullet modified: Bone marrow aspirate and biopsy *as indicated*
- Footnote j modified: 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 *FDG* PET/CT, or low-dose whole-body CT under certain circumstances). Whole-body *FDG* PET/CT is the first choice for initial evaluation of solitary extraosseous plasmacytoma.
- Footnote o added: Systemic therapy may be considered in patients with high risk of progression based on the clinical context.
- Footnote p modified: *Reassess after at least 3 months following radiation as the assessment of response with imaging may not be accurate if the scans are performed sooner.* Patients with soft tissue and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up.

Note: All recommendations are category 2A unless otherwise indicated.
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Updates in Version 1.2023 of the NCCN Guidelines for Multiple Myeloma from Version 5.2022 include:

MYEL-4
- Primary Treatment:
  - Modified*: Initiate* Myeloma therapy *and bone-targeting therapy* ~~+ bisphosphonates, or denosumab~~ + Supportive treatment as indicated *for symptom management*
  - Added: Assess for candidacy for transplant after starting therapy and reassess for transplant as performance status improves
  - The following bullets have been moved from Follow-Up/Surveillance to Primary Treatment:
    - ◊ Refer to HCT center
    - ◊ Harvest hematopoietic stem cells (consider for 2 transplants if appropriate)
- Follow-Up/Surveillance, modified: ~~No response~~ Progression
- Footnote bb added: Patients with stable disease can be considered for autologous HCT.

MYEL-5
- This page has been extensively revised.

MYEL-6
- The former page has been removed. The content from this page has been incorporated into other pages of the algorithm.
- Multiple Myeloma (Symptomatic), Additional Treatment, Relapse or Progressive disease, added:
  - Clinical trial, if eligible
  - Consider referral to CAR T-cell therapy specialist for consideration for CAR T-cell therapies.
  - Consider referral to palliative care specialist for symptom management (See NCCN Guidelines for Palliative Care)
  - Discuss patient preferences and goals of care through a shared decision-making process
- Multiple Myeloma (Symptomatic), Additional Treatment, Refractory disease and lack of treatment options, modified:
  - Continue palliative care; consider re-evaluation of goals of care and hospice initiation
- Footnote cc added: Folllow up with the tests listed on MYEL-4 under follow-up/surveillance.
- Footnote gg added: Donor lymphocyte infusion can be considered in patients relapsing after allogeneic HCT.

MYEL-A
- Page heading modified: *Disease* Staging and Risk Stratification ~~Systems~~ for Multiple Myeloma
- New table added: Factors Considered High Risk for MM
- Footnote c added: Presence of ≥5% of plasma cells in circulation is defined as plasma cell leukemia.

MYEL-B
- Imaging of Solitary Plasmacytoma, 1st bullet modified: Whole-body imaging with MRI (or *FDG* PET/CT if MRI is not available)...

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Updates in Version 1.2023 of the NCCN Guidelines for Multiple Myeloma from Version 5.2022 include:

MYEL-D

- Solitary Plasmacytoma, Treatment Information/Dosing, 1st bullet, 1st sub-bullet modified: RT (40–50 Gy in 1.8–2.0 Gy fractions [20–25 total fractions]) to involved ~~field~~ *site*.
- Palliative RT Dosing for MM, 1st bullet modified: 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. *Consider RT postoperatively if urgent surgical intervention is indicated.*
- Palliative RT Dosing for MM, 2nd bullet modified: Limited involved ~~fields~~ *sites* should be used to limit the impact of irradiation on hematopoietic stem cell harvest or impact on potential future treatments.

MYEL-F

- General Principles, 1st bullet modified: *Patients should receive at least a triplet regimen (2 drug classes and steroids) if they can tolerate it.* ~~Triplet regimens (2 drug classes and steroids) should be used as the standard therapy for patients with MM; however,~~
- General Principles, 3rd bullet added: Clinical trials with these triplet regimens primarily included patients who were naïve or sensitive to the novel drug in the doublet comparator arm. Patients with disease refractory to the novel drug in the doublet backbone should be considered for triplet therapy that does not contain the drug they are progressing on.
- Candidates for Hematopoietic Cell Transplant, 2nd bullet modified: Consider harvesting peripheral blood stem cells *after several cycles of therapy* prior to prolonged exposure to lenalidomide and/or daratumumab in patients for whom transplant is being considered.
- Screening Recommendations, 1st bullet modified: Test for hepatitis B ~~before starting daratumumab or carfilzomib~~ *as clinically indicated.*
- Prophylaxis Recommendations, 1st bullet modified: Pneumocystis jiroveci pneumonia (PJP)~~, herpes zoster, and antifungal prophylaxis~~ should be given if receiving ~~high-dose dexamethasone~~ *steroids*.
- Side Effects and Lab Interference, 4th bullet added: In patients intended to receive CAR T-cell therapy, bendamustine should be used with caution unless after leukapheresis prior to CAR T-cell therapy, since it could impact the success of the patient's T-cell collection.

MYEL-G 1 of 5

- Primary Therapy for Transplant Candidates:
  - The following regimen was moved from Other Recommended Regimens to Preferred Regimens:
    - ◊ Carfilzomib/lenalidomide/dexamethasone
  - The following regimen was moved from Other Recommended Regimens to Useful in Certain Circumstances:
    - ◊ Ixazomib/lenalidomide/dexamethasone (category 2B)
- Maintenance Therapy:
  - The following regimen was added to Other Recommended Regimens:
    - ◊ Daratumumab
  - The following regimen was added to Useful in Certain Circumstances as an option for high risk MM:
    - ◊ Carfilzomib/lenalidomide
- Footnote a has been modified: Selected, but not inclusive of all regimens. *The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.* (Also on MYEL-G 2 of 5, MYEL-G 3 of 5, MYEL-G 4 of 5, MYEL-G 5 of 5)

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Updates in Version 1.2023 of the NCCN Guidelines for Multiple Myeloma from Version 5.2022 include:

MYEL-G 3 of 5

- This page has been reformatted.
- Therapy for Previously Treated Multiple Myeloma:
  - The following regimens have been added for Bortezomib-Inhibitor Refractory, and Lenalidomide-Refractory:
    - ◊ Carfilzomib/pomalidomide/dexamethasone (previously this regimen was listed under: Other Recommended Regimens for Early Relapse (1–3 prior therapies)
    - ◊ After one prior therapy including lenalidomide and a PI
      - – Daratumumab/pomalidomide/dexamethasone (category 1)
- Footnote removed: Clinical trials with these regimens primarily included patients who were naïve or sensitive to the novel drug in the doublet comparator arm. Patients with disease refractory to the novel drug in the doublet backbone should be considered for triplet therapy that does not contain the drug they are progressing on. lenalidomide-naive or with lenalidomide-sensitive MM. Patients with lenalidomide refractory disease should be considered for a lenalidomide free triplet regimen.

MYEL-G 4 of 5

- The following regimens have been moved from Other Recommended Regimens for Early Relapse (1–3 prior therapies) to Therapies for Patients with Late Relapses (>3 prior therapies) on MYEL-G 5 of 5:
  - Bendamustine/bortezomib/dexamethasone
  - Bendamustine/lenalidomide/dexamethasone
- The following regimens have been moved from Useful in Certain Circumstances (1-3 prior therapies) to Therapies for Patients with Late Relapses (>3 prior therapies) on MYEL-G 5 of 5:
  - Bendamustine
  - High-dose or fractionated cyclophosphamide
- The following regimen has been removed from Useful in Certain Circumstances for Early Relapse (1–3 prior therapies):
  - Ixazomib/dexamethasone

MYEL-G 5 of 5

- The following regimen has been added to Therapies for Patients with Late Relapses (>3 prior therapies):
  - Bendamustine/carfilzomib/dexamethasone

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Updates in Version 1.2023 of the NCCN Guidelines for Multiple Myeloma from Version 5.2022 include:

MYEL-H

- Bone Disease
  - 1st bullet, 5th sub-bullet added: Patients receiving denosumab for bone disease who ~~and~~ subsequently discontinue therapy should be given maintenance denosumab every 6 months or a single dose of bisphosphonate to mitigate risk of rebound osteoporosis.
  - 1st bullet, 2nd sub-bullet added: Assess Vitamin D status
- Infection:
  - 2nd bullet modified: Intravenous immunoglobulin therapy should be considered in the setting of recurrent serious ~~(<400 mg/dL)~~ infection *and/or hypogammaglobulinemia (IgG ≤400 mg/dL).*
  - 4th bullet added: Influenza vaccination recommended. Consider two doses of the high-dose inactivated quadrivalent influenza vaccine.
  - 5th bullet added: Consider 12 weeks of levofloxacin 500 mg daily at the time of initial diagnosis for MM.
  - 6th bullet added: See NCCN Guidance on Cancer and COVID-19 Vaccination
  - Bullet added: Assess Vitamin D status
  - Bullet removed: Consider 3 months of antibiotic prophylaxis at diagnosis for patients at high risk for infection.
- Footnote c added: This is based on observations with denosumab discontinuation in non-myeloma settings. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res 2018;33:190-198.

MYEL-I 1 of 3

- IMPEDE Score for Risk Stratification (points assigned), Myeloma Risk Factors:
  - Modified: ~~Low-dose~~ Dexamethasone *<160 mg/cycle)*
  - Modified: ~~High dose~~ Dexamethasone *>160 mg/cycle*

MYEL-J

- Treatment Options:
  - 2nd bullet modified: *Regimens containing* bortezomib *and/or daratumumab*~~-based regimen~~
  - 3rd bullet added: Can switch to other regimen once renal function has improved *or stabilized*
  - Bullet removed: Consider third drug: cyclophosphamide, thalidomide, anthracycline, or daratumumab
- Supportive Care:
  - 6th bullet modified: Mechanical removal of serum FLCs ~~; goal removal of 50%~~ *with high cutoff dialysis filters or plasmapheresis may have a limited role. Systemic therapy should not be delayed if performing this procedure.*
    - ◊ 6th bullet, 1st and 2nd sub-bullets removed:
      - High cutoff dialysis filters
      - Plasmapheresis
- Footnote b added: Consider other diagnosis such as amyloid and light chain disease for patients with significant proteinuria.

MGRS-2

- Treatment, 1st bullet modified: For ~~IgG, IgA, or FLC~~ *plasma cell-related* MGRS, use the management algorithm for MM...
- Treatment, 2nd bullet modified: For ~~IgM~~ *lymphoplasmacytic-related* MGRS...

ABBR-1

- New page added: Abbreviations

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INITIAL DIAGNOSTIC WORKUP[a]

- History and physical (H&P) exam
- CBC, differential, and 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), and 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/1q21 amplification, 1p deletion][g]
- NT-proBNP/BNP[h]

Useful In Certain Circumstances

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

CLINICAL FINDINGS

- Solitary plasmacytoma → See Primary Treatment (MYEL-2)
- Smoldering myeloma (asymptomatic)[i] → See Primary Treatment (MYEL-3)
- MM (symptomatic)[i] → See Primary Treatment (MYEL-4)
- Monoclonal gammopathies of clinical significance
  - For Monoclonal Gammopathy of Renal Significance see MGRS-1
  - For Monoclonal Gammopathy of Neurological Significance see MGNS-1

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] These tests are essential for R-ISS staging. See Disease Staging and Risk Stratification 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. FDG PET should always be performed with CT.
[e] See Principles of Imaging (MYEL-B).
[f] CD138-positive selected sample is strongly recommended for optimized yield.
[g] 1q21 amplification is defined as ≥4 copies detected by FISH, and a gain is defined as 3 copies of 1q21.
[h] If NT-proBNP is not available, BNP can be performed.
[i] See Definitions of Smoldering and Multiple Myeloma (MYEL-C).

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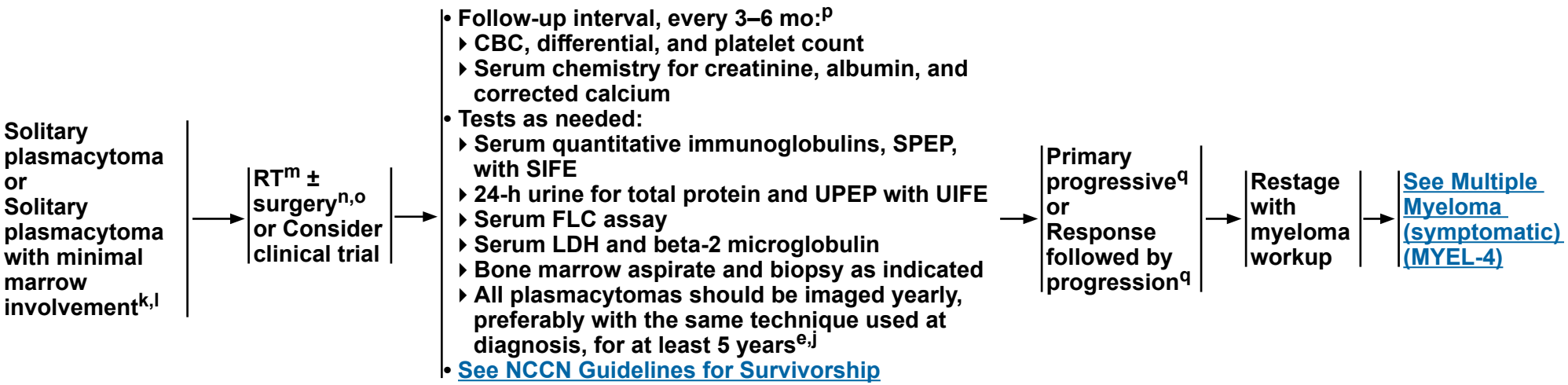

[e] See Principles of Imaging (MYEL-B).
[j] Whole-body MRI (or PET/CT if MRI is not available) is the first choice for initial evaluation of solitary osseous plasmacytoma (MRI of the spine and pelvis, whole-body FDG PET/CT, or low-dose whole-body CT under certain circumstances). Whole-body FDG PET/CT is the first choice for initial evaluation of solitary extraosseous plasmacytoma.
[k] All criteria must be present for the diagnosis. For diagnostic criteria, please refer to Rajkumar SV, et al. Lancet Oncol 2014;15:e538-e548.
[l] Solitary plasmacytoma with 10% or more clonal plasma cells is regarded as active (symptomatic) MM and systemic therapy should be considered.
[m] See Principles of Radiation Therapy (MYEL-D).
[n] Consider surgery if structurally unstable or if there is neurologic compromise due to mass effect.
[o] Systemic therapy may be considered in patients with high risk of progression based on the clinical context.
[p] Reassess after at least 3 months following radiation as the assessment of response with imaging may not be accurate if the scans are performed sooner. Patients with soft tissue and head/neck plasmacytoma could be followed less frequently after initial 3-month follow-up.
[q] See Response Criteria for Multiple Myeloma (MYEL-E).

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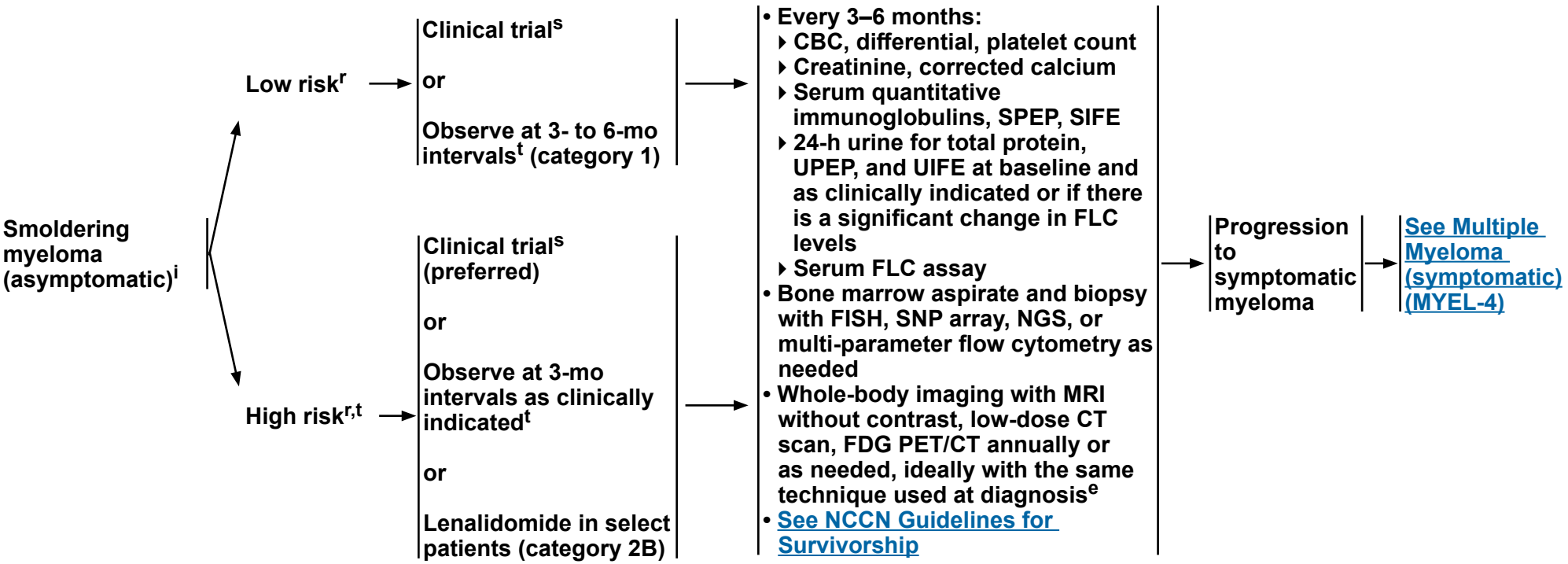

[e] See Principles of Imaging (MYEL-B).
[i] See Definitions of Smoldering and Multiple Myeloma (MYEL-C).
[r] Bone marrow plasma cells (BMPCs) >20%, M-protein >2 g/dL, and serum FLC ratio (FLCr) >20 are variables used to risk stratify patients at diagnosis. Patients with two or more of these risk factors are considered to have high risk of progression to MM. Lakshman A, et al. Blood Cancer J 2018;8:59.
[s] The NCCN Panel strongly recommends enrolling eligible patients with smoldering myeloma in clinical trials.
[t] Patients with rising parameters are considered high risk and should be closely monitored.

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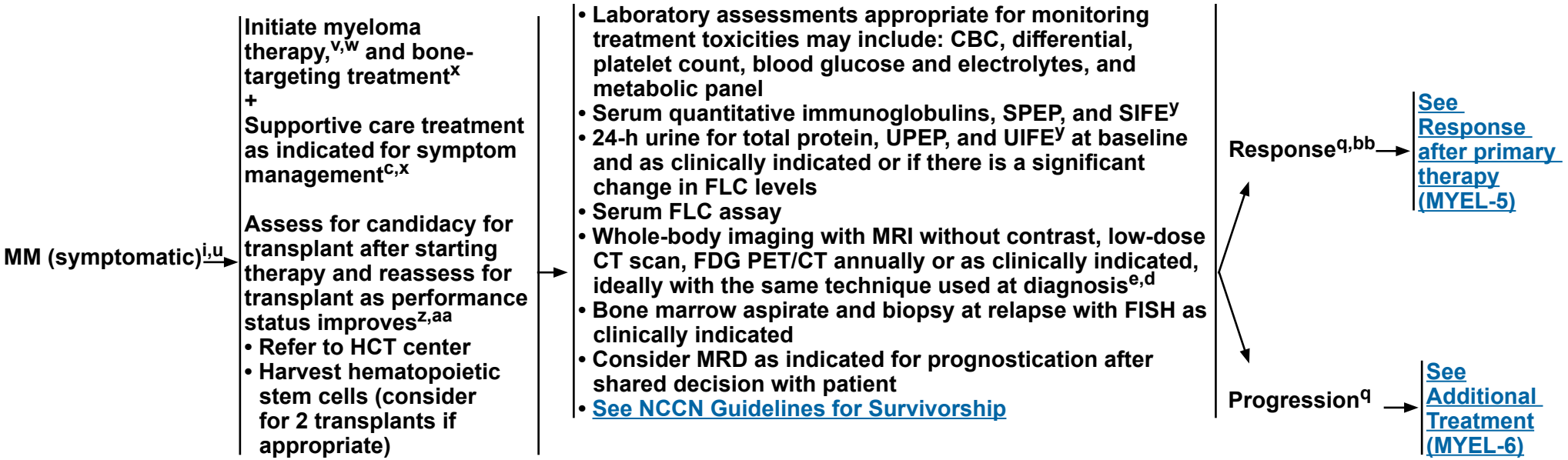

c See Management of Renal Disease in Multiple Myeloma (MYEL-J).
d Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG PET/CT. If whole-body FDG PET/CT or low-dose CT has been performed, then skeletal survey is not needed. FDG PET should always be performed with CT.
e See Principles of Imaging (MYEL-B).
i See Definitions of Smoldering and Multiple Myeloma (MYEL-C).
q See Response Criteria for Multiple Myeloma (MYEL-E).
u See Disease Staging and Risk Stratification for Multiple Myeloma (MYEL-A).
v See Myeloma Therapy (MYEL-G).
w See General Considerations for Myeloma Therapy (MYEL-F).
x See Supportive Care Treatment for Multiple Myeloma (MYEL-H).
y Needed only if protein electrophoresis is negative during follow-up.
z Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and HCT. See Discussion.
aa Renal dysfunction and advanced age are not contraindications to transplant.
bb Patients with stable disease can be considered for autologous HCT.

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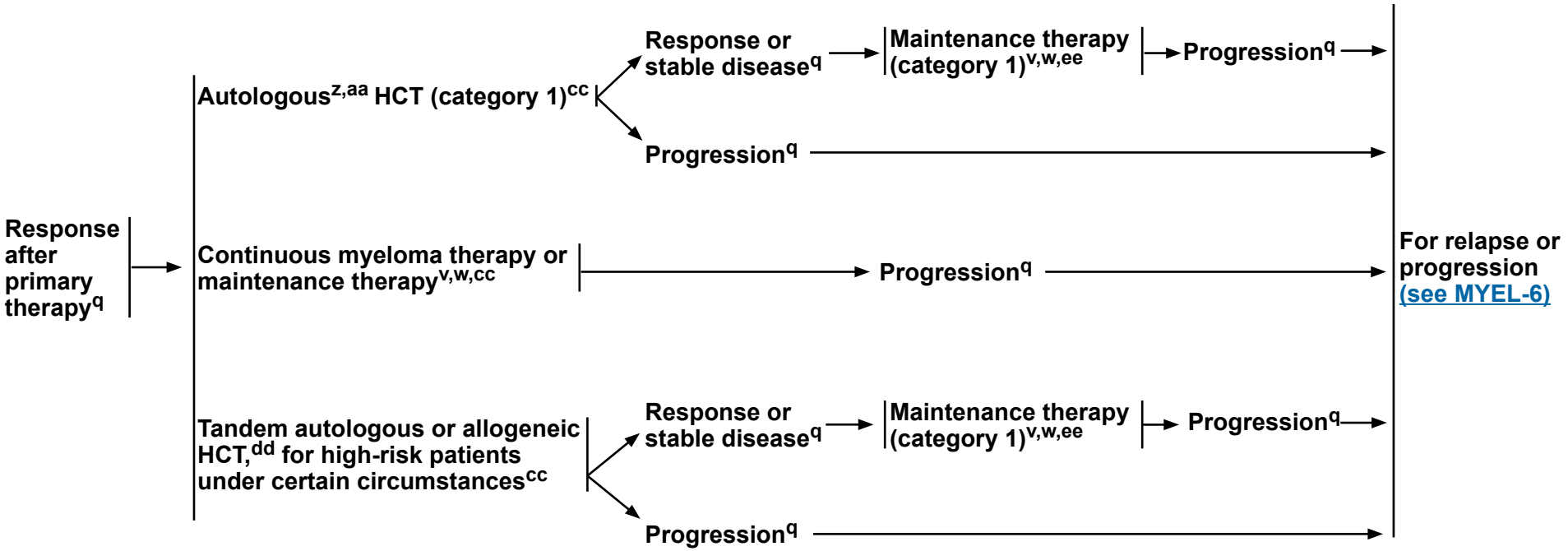
MULTIPLE MYELOMA (SYMPTOMATIC)

FOLLOW-UP/SURVEILLANCE



[q] See Response Criteria for Multiple Myeloma (MYEL-E).
[v] See Myeloma Therapy (MYEL-G).
[w] See General Considerations for Myeloma Therapy (MYEL-F).
[z] Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and HCT. See Discussion.
[aa] Renal dysfunction and advanced age are not contraindications to transplant.
[cc] Follow up with the tests listed on MYEL-4 under Follow-up/Surveillance.
[dd] Allogeneic HCT should preferentially be done in the context of a trial when possible.
[ee] The length of therapy should be balanced with toxicity and depth of response and disease status.

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MULTIPLE MYELOMA (SYMPTOMATIC)

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

Relapse or Progressive disease[q,cc] →

Clinical trial, if eligible
or
Therapy for previously treated myeloma[v,w]
or
Autologous HCT[ff]
or
Allogeneic HCT[dd,ff,gg]
and
- **Consider referral to CAR T-cell therapy specialist for consideration for CAR T-cell therapies**
- **Consider referral to palliative care specialist for symptom management (See NCCN Guidelines for Palliative Care)**
- **Discuss patient preferences and goals of care through a shared decision-making process**

→ **Refractory disease[cc] and lack of treatment options** → **Continue palliative care; consider re-evaluation of goals of care and hospice initiation (See NCCN Guidelines for Palliative Care)**

[q] See Response Criteria for Multiple Myeloma (MYEL-E).
[v] See Myeloma Therapy (MYEL-G).
[w] See General Considerations for Myeloma Therapy (MYEL-F).
[cc] Folllow up with the tests listed on MYEL-4 under Follow-up/Surveillance.
[dd] Allogeneic HCT should preferentially be done in the context of a trial when possible.
[ff] Assess for HCT candidacy.
[gg] Donor lymphocyte infusion can be considered in patients relapsing after allogeneic HCT.

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DISEASE STAGING AND RISK STRATIFICATION 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

Factors Considered High Risk for MM		
Cytogenetic abnormalities	▸ t(4;14) ▸ t(14;16) ▸ Del(17p)/monosomy 17 ▸ 1q21 gain/1q21 amplification	▸ *MYC* translocation ▸ *TP53* mutation [with del(17p)] ▸ Tetrasomies ▸ Complex karyotype (when done) or karyotypic del(13)
Other risk factors	▸ High-risk gene expression signature ▸ Extramedullary disease ▸ Circulating plasma cellsc ▸ High plasma cell proliferation ▸ Frailty	▸ Renal failure ▸ Thrombocytopenia ▸ High serum FLC ▸ Lymphopenia ▸ Immunoparesis ▸ Elevated LDH

[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).
[c] Presence of ≥5% of plasma cells in circulation is defined as plasma cell leukemia.

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PRINCIPLES OF IMAGING

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

- Whole-body imaging with low-dose CT or FDG PET/CT is recommended for initial diagnostic workup of patients suspected of having 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 MM.[1-5]
- 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 FDG 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.[6,7] 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%).[8] 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.[9]

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.[10] 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.[11-14] 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).[13] 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).[14] An analysis by Walker et al showed that conventional MRI normalizes over a prolonged period of time making PET/CT superior in this regard.[11] 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.[15-17]Furthermore, unlike FDG PET/CT, MRI does not expose the patient to radiation.

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PRINCIPLES OF IMAGING
References

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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 (BMPCs) 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 BMPCs ≥10% or biopsy-proven bony or extramedullary plasmacytoma

and

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

- **Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)**
- **Renal insufficiency (creatinine >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min**
- **Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)**
- **One or more osteolytic bone lesions on skeletal radiography, CT, or FDG PET/CT**
- **Clonal BMPCs ≥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 a 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.

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PRINCIPLES OF RADIATION THERAPY

Solitary Plasmacytoma

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

Treatment Information/Dosing:
- **Solitary plasmacytoma (MYEL-2)**
  - **RT (40–50 Gy in 1.8–2.0 Gy fractions [20–25 total fractions]) to involved site.**

MM

General Principles:
- **RT is primarily used for palliation in patients with MM.**
- **RT should be used judiciously in patients with MM 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. Consider RT postoperatively if urgent surgical intervention is indicated.**
- **Limited involved sites should be used to limit the impact of irradiation on hematopoietic stem cell harvest or impact on potential future treatments.**

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

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

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Continued
Footnotes

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

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

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA

Footnotes

[a] All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ Autologous stem cell transplants (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 Flow Cytometry Method (FCM) method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells. Paiva B, Gutierrez NC, Rosinol L, et al, for the GEM (Grupo Españolde MM)/PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood 2012;119: 687-91.

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

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

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

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

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

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

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

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

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

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GENERAL CONSIDERATIONS FOR MYELOMA THERAPY

General Principles

- Patients should receive at least a triplet regimen (2 drug classes and steroids) if they can tolerate it. 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 regimen should preferably include drugs or drug classes patients have not been exposed to, or not exposed to for at least 6 months.
- Clinical trials with these triplet regimens primarily included patients who were naïve or sensitive to the novel drug in the doublet comparator arm. Patients with disease refractory to the novel drug in the doublet backbone should be considered for triplet therapy that does not contain the drug they are progressing on.
- 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 HCT

- 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 after several cycles of therapy prior to prolonged exposure to lenalidomide and/or daratumumab in patients for whom transplant is being considered.

Screening Recommendations

- Test for hepatitis B as clinically indicated.
- Screen for HIV and hepatitis C as clinically indicated.

Prophylaxis Recommendations

- Pneumocystis jiroveci pneumonia (PJP) should be given if receiving steroids.
- Administer herpes zoster prophylaxis for all patients treated with proteasome inhibitors (PIs), 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.
- Agents such as bendamustine can impact the ability to collect T cells for CAR T-cell therapy.

[a] 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.

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

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide[h] (category 1)
Other Recommended Regimens • Bortezomib • Daratumumab • Ixazomib (category 2B)[i]
Useful In Certain Circumstances • Bortezomib/lenalidomide ± dexamethasone[j] • Carfilzomib/lenalidomide[j]

a Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
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 suggest a potential decrease in overall survival (OS).
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

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

MAINTENANCE THERAPY
Preferred Regimens • Lenalidomide (category 1)
Other Recommended Regimens • Bortezomib • Ixazomib (category 2B)[i]
Useful In Certain Circumstances • Bortezomib/lenalidomide[j]

a Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
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 suggest a potential decrease in OS.
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.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
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THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-m]

Preferred Regimens for Early Relapses (1–3 prior therapies)
Order of regimens does not indicate comparative efficacy

- **If relapse is >6 months, the regimen used for primary therapy may be repeated.**
- **For patients still sensitive to bortezomib and/or lenalidomide, any of the regimens listed on this page may be appropriate.**
- **Ixazomib/lenalidomide/dexamethasone (category 1)**
- **Bortezomib/lenalidomide/dexamethasone**

Bortezomib-Refractory	Lenalidomide-Refractory
• **Daratumumab/lenalidomide/dexamethasone (category 1)** • **Daratumumab/carfilzomib/dexamethasone (category 1)** • **Carfilzomib/lenalidomide/dexamethasone (category 1)** • **Isatuximab-irfc/carfilzomib/dexamethasone (category 1)** • **Carfilzomib/pomalidomide/dexamethasone**	• **Daratumumab/carfilzomib/dexamethasone (category 1)** • **Daratumumab/bortezomib/dexamethasone (category 1)** • **Isatuximab-irfc/carfilzomib/dexamethasone (category 1)** • **Carfilzomib/pomalidomide/dexamethasone**
After one prior therapy including lenalidomide and a PI ▸ **Daratumumab/pomalidomide/dexamethasone (category 1)**	*After one prior therapy including lenalidomide and a PI* ▸ **Daratumumab/pomalidomide/dexamethasone (category 1)**
After two prior therapies including lenalidomide and a PI ▸ **Isatuximab-irfc/pomalidomide/dexamethasone (category 1)**	*After two prior therapies including lenalidomide and a PI* ▸ **Isatuximab-irfc/pomalidomide/dexamethasone (category 1)**
After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy ▸ **Ixazomib/pomalidomide/dexamethasone**	*After two prior therapies including an IMiD and a PI and with disease progression on/within 60 days of completion of last therapy* ▸ **Pomalidomide/bortezomib/dexamethasone (category 1)** ▸ **Ixazomib/pomalidomide/dexamethasone**

For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Early Relapses (1–3 prior therapies), see MYEL-G 4 of 5

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
[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 HCT should be considered in an eligible patient who had not previously received transplant or had a prolonged response to initial transplant.

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

Continued

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-o]

- **If relapse is >6 months, the regimen used for primary therapy may be repeated.**
- **For patients still sensitive to bortezomib and/or lenalidomide, any of the regimens listed on this page may be appropriate.**

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

- **Bortezomib/liposomal doxorubicin/dexamethasone (category 1)**
- **Carfilzomib (twice weekly)/dexamethasone (category 1)**
- **Elotuzumab/lenalidomide/dexamethasone (category 1)**
- **Selinexor/bortezomib/dexamethasone (once weekly) (category 1)**
- **Bortezomib/cyclophosphamide/dexamethasone**
- **Carfilzomib/cyclophosphamide/dexamethasone**
- **Cyclophosphamide/lenalidomide/dexamethasone**
- **Daratumumab/cyclophosphamide/bortezomib/dexamethasone**
- **Elotuzumab/bortezomib/dexamethasone**
- **Ixazomib/cyclophosphamide/dexamethasone**

After two prior therapies including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy

- **Pomalidomide/cyclophosphamide/dexamethasone**

After two prior therapies including lenalidomide and a PI

- **Elotuzumab/pomalidomide/dexamethasone**

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

- **Bortezomib/dexamethasone (category 1)**
- **Lenalidomide/dexamethasone (category 1)**
- **Carfilzomib/cyclophosphamide/thalidomide/dexamethasone**
- **Carfilzomib (weekly)/dexamethasone**
- **Selinexor/daratumumab/dexamethasone**
- **Selinexor/carfilzomib/dexamethasone**
- **Venetoclax/dexamethasone only for t(11;14) patients**

After two prior therapies including IMiD and a PI and with disease progression on/within 60 days of completion of last therapy

- **Pomalidomide/dexamethasone (category 1)**
- **Selinexor/pomalidomide/dexamethasone**

For treatment of aggressive MM

- **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

- **Daratumumab**

a Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
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 HCT should be considered in an eligible patient who had not previously received transplant or had a prolonged response to initial transplant.
o Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

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

Continued

THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,l-n]
Therapies for Patients with Late Relapses (>3 prior therapies)
• Bendamustine **• Bendamustine/bortezomib/dexamethasone** **• Bendamustine/carfilzomib/dexamethasone** **• Bendamustine/lenalidomide/dexamethasone** **• High-dose or fractionated cyclophosphamide** *After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD* **▸ Idecabtagene vicleucel** **▸ Ciltacabtagene autoleucel** **▸ Teclistamab-cqyv** **▸ Useful in certain circumstances:** ◊ **Belantamab mafodotin-blmf (if available through compassionate use program)** *After at least four prior therapies and whose disease is refractory to at least two PIs, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody* **▸ Selinexor/dexamethasone**

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order NCCN Category of Evidence and Consensus alphabetically.
[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 HCT should be considered in an eligible patient who had not previously received transplant or had a prolonged response to initial transplant.

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SUPPORTIVE CARE FOR MULTIPLE MYELOMA

Bone Disease

- All patients receiving primary myeloma therapy should be given bone-targeting treatment (bisphosphonates (category 1)[a] or denosumab.[b])
  - A baseline dental exam is strongly recommended.
  - Assess Vitamin D status
  - 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.
  - Patients receiving denosumab for bone disease who subsequently discontinue therapy should be given maintenance denosumab every 6 months or a single dose of bisphosphonate to mitigate risk of rebound osteoporosis.[c]
- 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 infection and/or hypogammaglobulinemia (IgG ≤400 mg/dL).
- The pneumococcal conjugate vaccine should be given followed by the pneumococcal polysaccharide vaccine one year later.
- Influenza vaccination recommended. Consider two doses of the high-dose inactivated quadrivalent influenza vaccine.
- Consider 12 weeks of levofloxacin 500 mg daily at the time of initial diagnosis for MM.
- See NCCN Guidance on Cancer and COVID-19 Vaccination
- 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.
[c] This is based on observations with denosumab discontinuation in non-myeloma settings. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. J Bone Miner Res 2018;33:190-198.

Note: All recommendations are category 2A unless otherwise indicated.
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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 (Body Mass Index ≥25)	+1	Dexamethasone <160 mg/month	+2
Previous VTE	+5	Dexamethasone >160 mg/month	+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) • High dose (>160 mg/cycle)	 +1 +2

[a] Adapted from Sanfilippo KM, et al. Am J Hematol 2019;94:1176-1184.
[b] Adapted from: Li A, et al. J Natl Compr Canc Netw 2019;17:840-847.

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

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 international normalized ratio (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 anticoagulants 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.
Piedra K. Br J Haematol. 2022;196:105-109.
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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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

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]**
• Aspirin 81–325 mg once daily	• 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
• 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 subcutaneously (SC) daily (category 2B).

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MANAGEMENT OF RENAL DISEASE IN MULTIPLE MYELOMA[a]

Tests[b]
- 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 and renal biopsy

Treatment Options
- Pulse dexamethasone
- Regimens containing bortezomib and/or daratumumab
- Can switch to other regimen once renal function has improved or stabilized
- 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 with high cutoff dialysis filters or plasmapheresis may have a limited role. Systemic therapy should not be delayed if performing this procedure.
- 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[c]

[a] Defined as serum creatinine >2 mg/dL or established glomerular filtration rate (eGFR) <60 mL/min/1.73 sqm.
[b] Consider other diagnosis such as amyloid and light chain disease for patients with significant proteinuria.
[c] Patients with creatinine clearance <30 cc/min can experience severe hypocalcemia and should be monitored.

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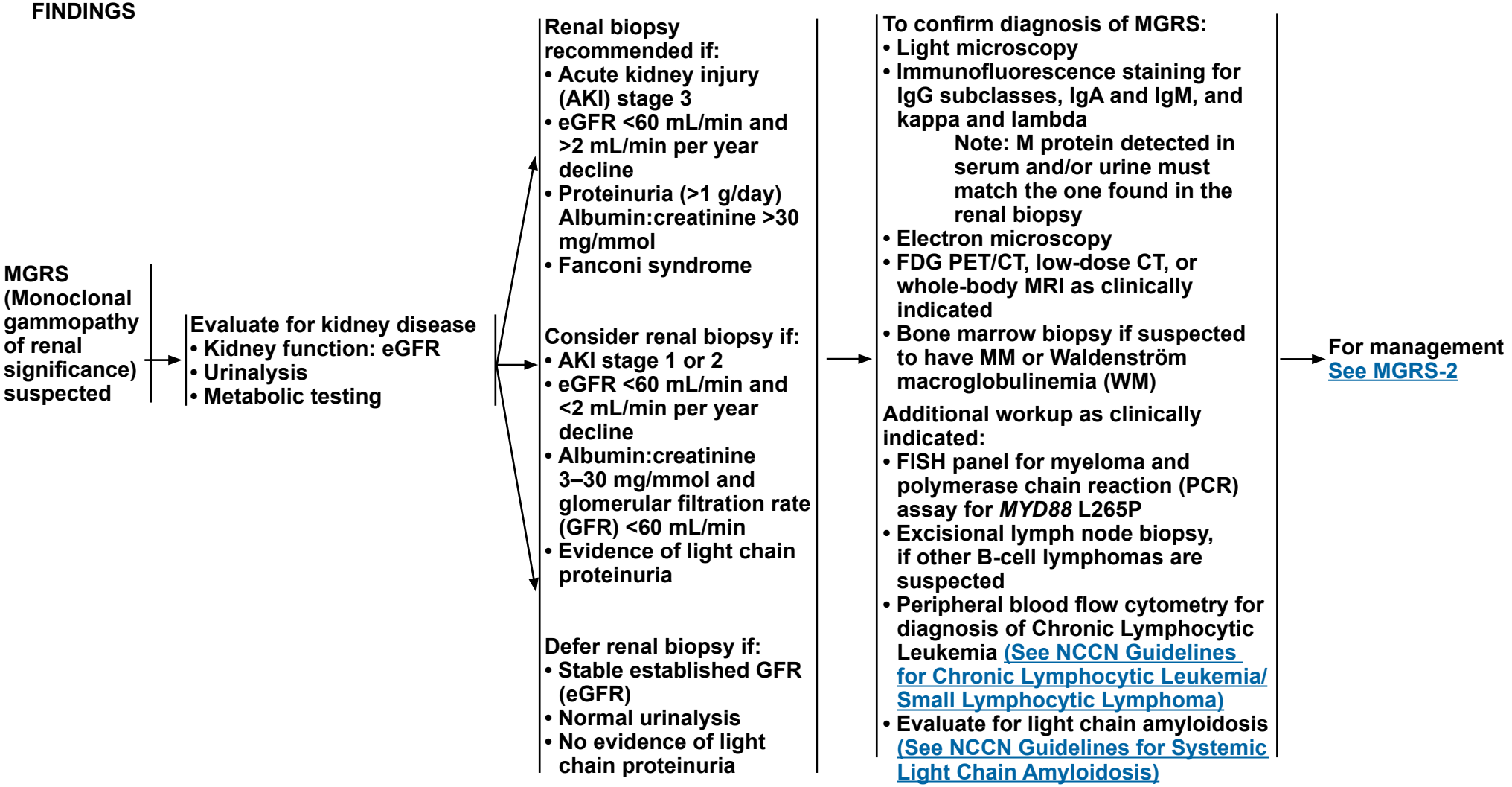
MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE
MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE



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MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE

MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE

TREATMENT

- For plasma cell-related MGRS, use the management algorithm for MM (See MYEL-4)
- For lymphoplasmacytic-related 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
  - evaluate bone marrow involvement or radiologic findings

→ Relapse →

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

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

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

MONOCLONAL GAMMOPATHY OF NEUROLOGICAL SIGNIFICANCE

IgM[a] MGNS (Monoclonal gammopathy of neurological significance) suspected

INITIAL WORKUP

- 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

CLINICAL FINDINGS

High suspicion
- Sensory predominant
- Length dependent
- Slow progression (years)
- Bilateral and symmetrical
- Antibodies present
- Demyelination by EMG/NCS

OR intermediate suspicion (not high or low suspicion) AND affecting activities of daily living (ADLs)

→ See NCCN Guidelines for Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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

OR intermediate/high suspicion AND not affecting ADLs

→ Observation

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

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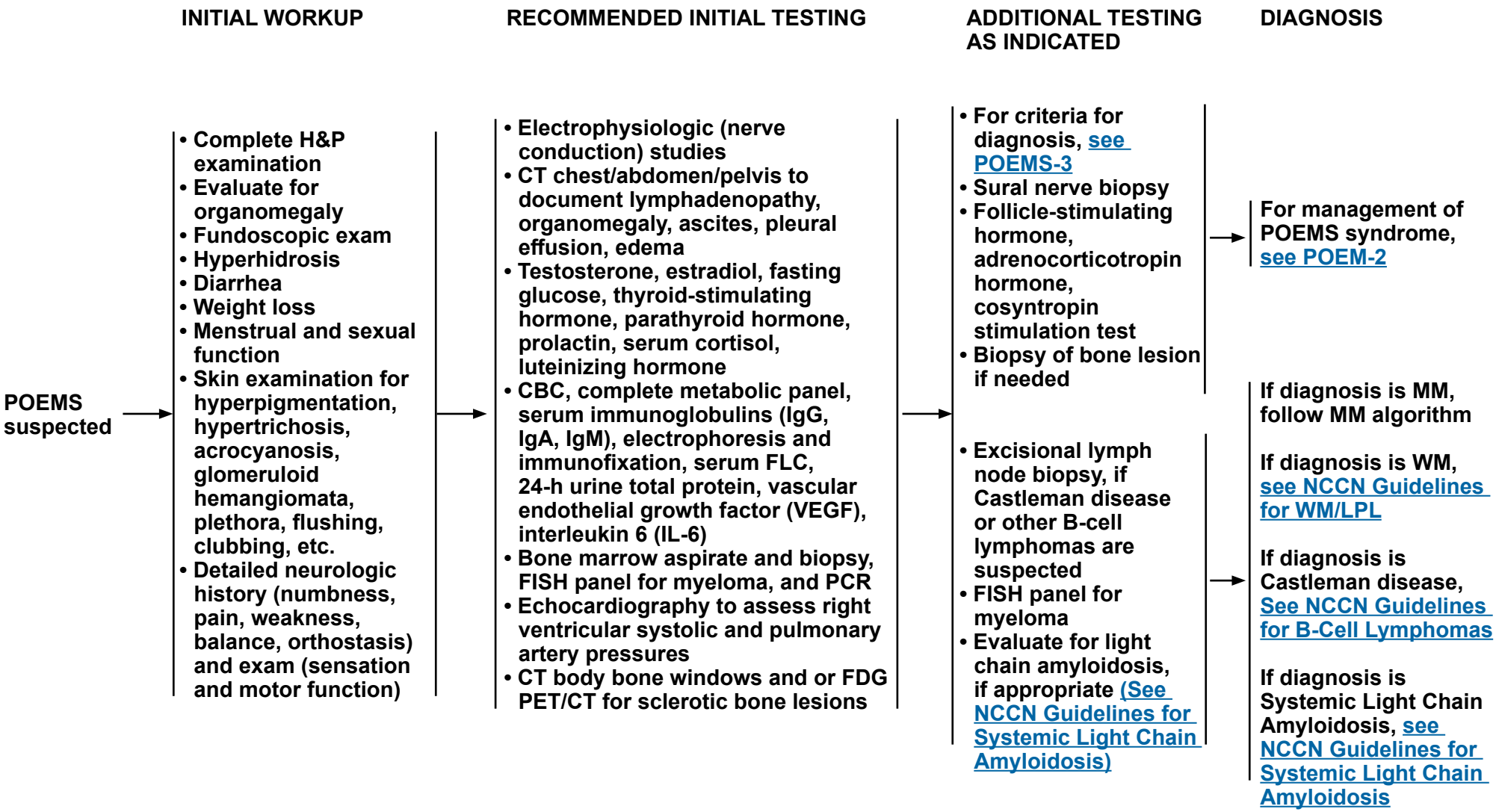
POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)



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

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

TREATMENT

- Radiation therapy alone to isolated bone lesion (<3 sites) in patients without clonal BMPC
- Autologous HCT 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

→ 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 hemangiomata, plethora, acrocyanosis, flushing, white nails)
	10. Papilledema
	11. Thrombocytosis/polycythemia[c]
Other signs and symptoms	**Clubbing, weight loss, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} 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.

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

Table 2 Response Criteria for POEMS Syndrome

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

Abbreviations:CTCAE, common terminology criteria for adverse events, IFE, immunofixation electrophoresis, ECHO RVSP, echocardiogram right ventricular systolic pressure, DLCO, diffusing capacity of carbon monoxide.

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

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ABBREVIATIONS

ADL	activities of daily living
AKI	acute kidney injury
AS-PCR	allele-specific polymerase chain reaction
BMPC	bone marrow plasma cell
BUN	blood urea nitrogen
BNP	b-type natriuretic peptide
CAR-T	chimeric antigen receptor T-cell therapy
CBC	complete blood count
CLcr	creatinine clearance
eGFR	established glomerular filtration rate
EMG	electromyogram
FDG	flurodeoxyglucose
FISH	fluorescence in situ hybridization
FLC	free light chain
FLCr	serum free light chain ratio
GFR	glomerular filtration rate
H&P	history and physical
HCT	hematopoietic cell transplant
HIV	human immunodeficiency virus
Ig	immunoglobulin
ISS	International Staging System
IMiD	Immunomodulatory drug
IMPEDE	IMiD, BMI, Pathologic fracture, ESA (erythropoietin stimulating agent), Dexamethasone/ Doxorubicin, Ethnicity
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
MFC	multicolor flow cytometry
MGUS	monoclonal gammopathy of undetermined significance
MM	multiple myeloma
MRD	minimal residual disease
MGRS	monoclonal gammopathy of renal significance
MGNS	monoclonal gammopathy of neurological significance
NGS	next generation sequencing
NGF	next-generation flow
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
NCS	nerve conduction study
POEMS	polyneuropathy, organomegaly, edocrinopathy, monoclonal protein, skin change
PFS	progression free survival
PI	proteasome-inhibitor
PR	partial response
PCR	polymerase chain reaction
OS	overall survival
R-ISS	revised International Staging System
SAVED	Surgery within 90 days, Asian race, Venous thromboembolism history, age over Eighty (80), dexamethasone
SIFE	serum immunofixation electrophoresis
SNP	single nucleotide polymorphism
SPEP	serum protein electrophoresis
SUV	standardized uptake value
UIFE	urine immunofixation electrophoresis
UPEP	urine protein electrophoresis
ULN	upper limit of normal
VTE	venous thromboembolism
VEGF	vascular endothelial growth factor
VGPR	very good partial response
WM/LPL	Waldenstrom Macroglobulinemia/ lymphoplasmacytic lymphoma

NCCN Categories of Evidence and Consensus	
Category 1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
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).*

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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).

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

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

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 **c**alcium levels (greater than 11.5 mg/dL), **r**enal insufficiency (creatinine greater than 2 mg/dL or creatinine clearance less than 40 mL/min), **a**nemia (hemoglobin less than 10 g/dL or 2 g/dL less than normal), and presence of **b**one 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, **Li**ght chain ratio, **M**RI) features include one or more of the following: greater than or equal to **s**ixty percent clonal plasma cells in the bone marrow; involved/uninvolved free **l**ight chain ratio of 100 or more with the involved FLC being greater than or equal 100 mg/L; or **M**RI with more than one focal marrow (non-osteolytic) lesion [34] 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

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.

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 great 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 20/2/20 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 was110 months.[35]

The Mayo 2018 20/2/20 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 20/2/20 criteria to stratify patients based on risk. According to the NCCN Panel, the low risk group should be managed by enrolling in a clinical trial or observe at 3- to 6-month intervals (category 1). For the high-risk group, the 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

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

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/m^2 vs. 5.2 mg/m^2).[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 daratumumab[63]. 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.

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 trial[65] 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

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%),

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 trial[69] 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.

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]

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/m^2 compared to those treated with twice weekly carfilzomib at a dose of 36 mg/m^2. The PFS and OS were also similar. The median PFS was 35.7 months in the once-weekly group and 35.5 months in the twice-weekly group (HR = 1.39; P = .26). The 3-year OS was 70% and 72%, respectively (HR = 1.27; P = .5).[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/m^2 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.

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 ≥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.

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/cyclophosphamide/bortezomib/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

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 trial[66] (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 trial[100] that included transplant-ineligible patients and the ECOG E4A03 trial[101] 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

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 al[76] 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

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 ≥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/

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

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

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]

None of these trials showed a significant improvement in OS. However, since the median follow-up in these trials ranged from 42 to 53 months, the lack of significant improvement is not surprising. The trial by Cavo et al[127] 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

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 studies[146-149] 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 allogenic curve was flat at 39%. This suggests that a proportion of these patients are long-term survivors. Thus, there is ongoing interest in myeloablative allogeneic HCT, particularly given the lack of a significant cure rate for single or tandem autologous HCT.

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

infusions to stimulate a beneficial graft-versus-myeloma effect[153-160] 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; $P <$

.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 al[122] (discussed in *Autologous Hematopoietic Cell Transplant*ation) 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

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 rates[81] (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

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 daratumuab-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

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 (≥ 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

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 trial[185] 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

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, trail (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

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

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

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]

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 (≥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/m^2). Toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients has reported that bendamustine is effective and tolerable in patients with advanced progressive MM, with an ORR of 36%.[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).

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

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/m^2 on a twice-weekly schedule and 2.97 mg/m^2 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 schedule[227] 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]

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,

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 al[244] 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

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.

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).

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 m^2 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]

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.

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.

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.

Monoclonal Gammopathy of Neurological Significance (MGNS)

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.

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