National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Multiple Myeloma

Version 4.2024 — April 26, 2024

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

See NCCN Categories of Evidence and Consensus.

NCCN Categories of Preference: All recommendations are considered appropriate.

See NCCN Categories of Preference.

The NCCN Guidelines® are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use or application and disclaims any responsibility for their application or use in any way. The NCCN Guidelines are copyrighted by National Comprehensive Cancer Network®. All rights reserved. The NCCN Guidelines and the illustrations herein may not be reproduced in any form without the express written permission of NCCN. ©2024.

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Terminologies in all NCCN Guidelines are being actively modified to advance the goals of equity, inclusion, and representation.

Updates in Version 4.2024 of the NCCN Guidelines for Multiple Myeloma from Version 3.2024 include:

MYEL-G (3 of 5)

- Preferred regimens table
  - New row added: CAR T-cell Therapy
    - ◊ After one prior therapy including IMiD and a PI, and refractory to lenalidomide
      - – Ciltacabtagene autoleucel (category 1)
    - ◊ After two prior therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI
      - – Idecabtagene vicleucel (category 1)

Updates in Version 3.2024 of the NCCN Guidelines for Multiple Myeloma from Version 2.2024 include:

MYEL-H, MYEL-K

- Footnote c added: An FDA-approved biosimilar is an appropriate substitute.

Updates in Version 2.2024 of the NCCN Guidelines for Multiple Myeloma from Version 1.2024 include:

MS-1

- The Discussion sections have been updated to reflect the changes in the algorithm

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Updates in Version 1.2024 of the NCCN Guidelines for Multiple Myeloma from Version 4.2023 include:

MYEL-1

- Useful In Certain Circumstances
  - 3rd bullet removed: Plasma cell proliferation
  - 5th bullet removed: Human leukocyte antigen (HLA) typing

MYEL-2

- Follow-up/Surveillance
  - 1st bullet, 2nd sub-bullet modified: Serum chemistry for creatinine, ~~albumin~~, and corrected calcium
  - 2nd bullet, 4th sub-bullet removed: Serum LDH and beta-2 microglobulin
- 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 (*If whole-body MRI is not available, then consider* MRI of the spine and pelvis, whole-body FDG-PET/CT, or low-dose whole-body CT ~~under certain circumstances~~)...
- Footnote k modified: All criteria must be present for the diagnosis. For diagnostic criteria, *see Definitions of Smoldering and Multiple Myeloma (MYEL-C)* ~~please refer to Rajkumar SV, et al. Lancet Oncol 2014;15:e538-e548~~.

MYEL-3

- Smoldering myeloma (asymptomatic): Follow-up/Surveillance
  - 3rd bullet modified: Whole-body ~~imaging with~~ MRI without contrast, low-dose CT ~~scan~~, FDG-PET/CT annually or as needed, ideally with the same technique used at diagnosis
- Footnote u added: Consider consultation for hematopoietic cell transplant (HCT) and consider collection of hematopoietic stem cells (for more than one transplants, if appropriate).

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UPDATES

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Updates in Version 1.2024 of the NCCN Guidelines for Multiple Myeloma from Version 4.2023 include:

MYEL-4

- MM (symptomatic): Follow-up/Surveillance
  - 5th bullet modified: Whole-body ~~imaging with~~ MRI without contrast, low-dose CT ~~scan~~, FDG-PET/CT annually or as…
  - 7th bullet modified: Consider MRD *testing* as indicated for prognostication after shared decision with patient
  - Footnote aa modified: Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and HCT. *Delayed HCT can be considered in select patients*. See Discussion. (Also for MYEL-5)

MYEL-6

- Relapse or progressive disease: Additional Treatment
  - 1st bullet: Consider referral to CAR T-cell therapy specialist ~~for consideration for CAR T-cell therapies~~

MYEL-A

- Definitions of Smoldering and Multiple Myeloma
  - Smoldering Myeloma (Asymptomatic): 3rd bullet, 1st sub-bullet modified: ~~If skeletal survey negative~~, Assess for bone disease with whole-body low-dose CT, FDG-PET/CT, or whole-body MRI *without contrast* ~~FDG-PET/CT, or low-dose CT scan~~. *If unable to perform, consider skeletal survey.*

MYEL-B 1 of 2

- Disease Staging and Risk Stratification Systems for Multiple Myeloma
  - Page extensively modified.

MYEL-B 2 of 2

- Disease Staging and Risk Stratification Systems for Multiple Myeloma
  - New section of table add for R2-ISS.
  - Footnote c added: For R2-ISS classification a numerical value is assigned to each risk factor based on their influence on OS: ISS-III is 1.5 points, ISS-II is 1 point, del(17p) is 1 point, t(4;14) is 1 point, 1q+ is 0.5 points, and serum LDH > the upper limit of normal is 1 point.
  - Footnote d added: D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma: A European Myeloma Network (EMN) report within the harmony project. J Clin Oncol 2022;40:3406-3418.

MYEL-C 1 of 2

- Principles of Imaging
  - This page was extensively revised. Information was moved to Discussion section.

MYEL-D

- Principles of Radiation Therapy: This section was extensively revised

MYEL-F 1 of 2

- General Considerations for Myeloma Therapy
  - This page was extensively revised.
  - Screening and prophylaxis recommendations were moved; see Management of Infections in Patients with Multiple Myeloma (MYEL-I).

MYEL-F 2 of 2

- General Considerations for Myeloma Therapy
  - Dosing and administration; 5th bullet added: *Steroids should be reduced to 20 mg weekly in older patients and should be decreased or discontinued with treatment response plateau and/or toxicity*
- Side Effects and Lab Interference
  - 3rd bullet added: *Monoclonal antibodies can produce a false positive serum immunofixation if the monoclonal protein is IgG kappa and special interference testing or mass spectrometry based assessment can differentiate between the two.*
  - 4th bullet modified: Agents such as bendamustine can impact the ability to collect T cells for CAR T-cell therapy. See *NCCN Guidelines for Management of Immunotherapy-Related Toxcities*.

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UPDATES

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Updates in Version 1.2024 of the NCCN Guidelines for Multiple Myeloma from Version 4.2023 include:

MYEL-G 1 of 5
- Primary Therapy for Transplant Candidates: Page was extensively revised.

MYEL-G 2 of 5
- Primary Therapy for Non-transplant Candidates
  - Other Recommended Regimens: Ixazomib/lenalidomide/dexamethasone (category 1) moved to Therapy for Previously Treated Multiple Myeloma Relapsed/Refractory Disease After 1–3 Prior Therapies: Other Recommended Regimens
  - Maintenance Therapy; Other Recommended Regimens: Ixazomib (category 2b) moved to Useful in Certain Circumstances.
- Footnote e modified: Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to ~~bortezomib~~ *PI*/lenalidomide/dexamethasone. Consider switching to ~~bortezomib~~ *PI*/lenalidomide/dexamethasone after renal function improves.
- Footnote k added: Ixazomib may be substituted for carfilzomib in select patients.

MYEL-G 3 of 5
- Page extensively revised.

MYEL-G 4 of 5
- Page extensively revised.

MYEL-G 5 of 5
- Page extensively revised.

MYEL-H
- Supportive Care for Multiple Myeloma
  - Bone disease: 1st bullet, 5th sub-bullet modified: 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, *and agent used*. Continuing beyond 2 years should be based on clinical judgment.
- Infection:
  - Bullets 1–4: moved to MYEL-I
  - 7th bullet modified: ~~See MYEL-F for myeloma therapy-specific prophylaxis~~ *For prophylaxis and management of infections in patients with multiple myeloma, see MYEL-I*
- Footnote d added: *Increased risk of VTE has been reported in patients receiving erythropoiesis-stimulating agents (ESAs).*

MYEL-I
- New section added: Management of Infections in Patients with Multiple Myeloma.

MGRS-1
- Monoclonal Gammopathy of Clinical Significance
  - Additional Workup; To confirm diagnosis of MGRS: 4th bullet modified: FDG-PET/CT, low-dose CT, or whole-body MRI *without contrast* as clinically indicated

MGNS-1
- Monoclonal Gammopathy of Neurological Significance; Initial Workup; 7th bullet modified: ~~Chest/abdominal/pelvic~~ Chest/abdomen/pelvis CT with contrast when possible

POEMS-1
- POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Protein, Skin Changes)
  - Recommended Initial Testing; 5th bullet modified: Bone marrow aspirate and biopsy, *with* FISH panel for myeloma, ~~and PCR~~

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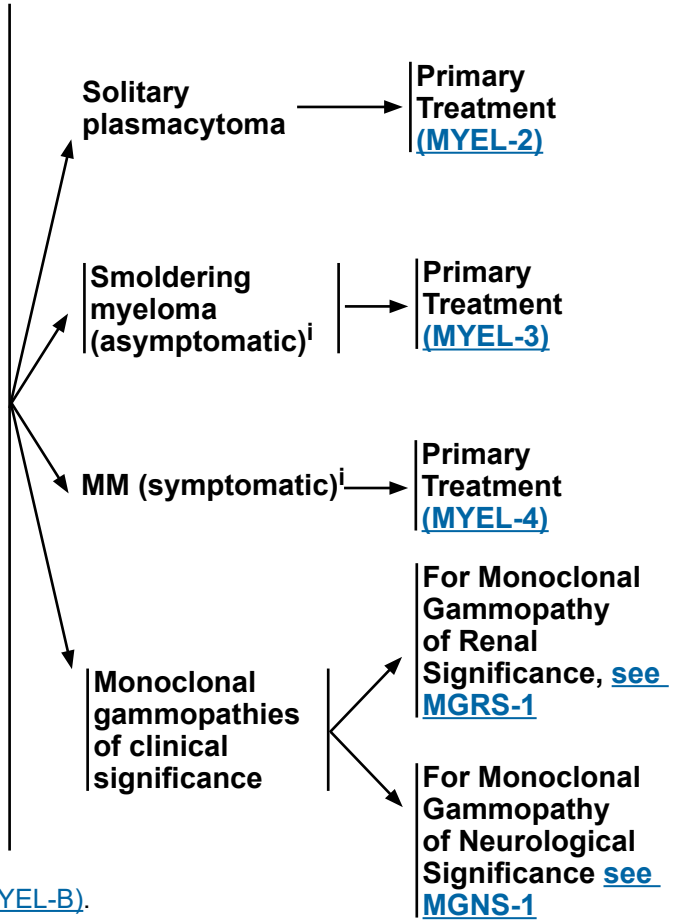
INITIAL DIAGNOSTIC WORKUP[a]

- 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 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[g], 1p deletion]
- 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
- Serum viscosity
- Hepatitis B and hepatitis C testing and HIV screening as required
- Echocardiogram
- Evaluation for light chain amyloidosis, if appropriate (NCCN Guidelines for Systemic Light Chain Amyloidosis)
- Single nucleotide polymorphism (SNP) array on bone marrow,[f] and/or next-generation sequencing (NGS) panel on bone marrow[f]
- Consider baseline clone identification and storage of aspirate sample for future minimal residual disease (MRD) testing by NGS
- Assess for circulating plasma cells as clinically indicated

CLINICAL FINDINGS



[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] These tests are essential for R-ISS staging. See Disease Staging and Risk Stratification for Multiple Myeloma (MYEL-B).
[c] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[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] Principles of Imaging (MYEL-C).
[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] Definitions of Smoldering and Multiple Myeloma (MYEL-A).

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.

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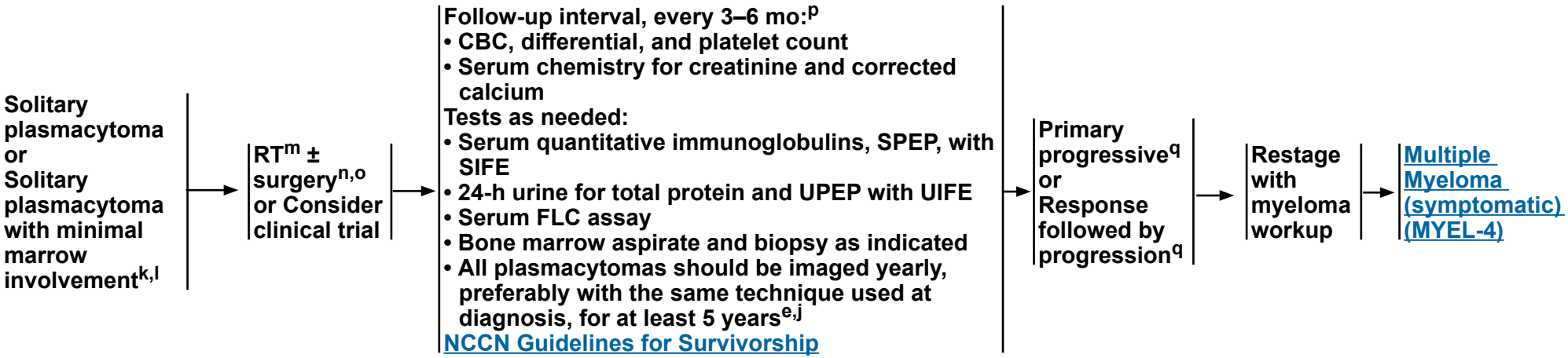

[e] Principles of Imaging (MYEL-C).
[j] Whole-body MRI (or PET/CT if MRI is not available) is the first choice for initial evaluation of solitary osseous plasmacytoma (If whole-body MRI is not available, then consider MRI of the spine and pelvis, whole-body FDG-PET/CT, or low-dose whole-body CT). Whole-body 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, see Definitions of Smoldering and Multiple Myeloma (MYEL-B).
[l] Solitary plasmacytoma with 10% or more clonal plasma cells is regarded as active (symptomatic) MM and systemic therapy should be considered.
[m] 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] Response Criteria for Multiple Myeloma (MYEL-E).

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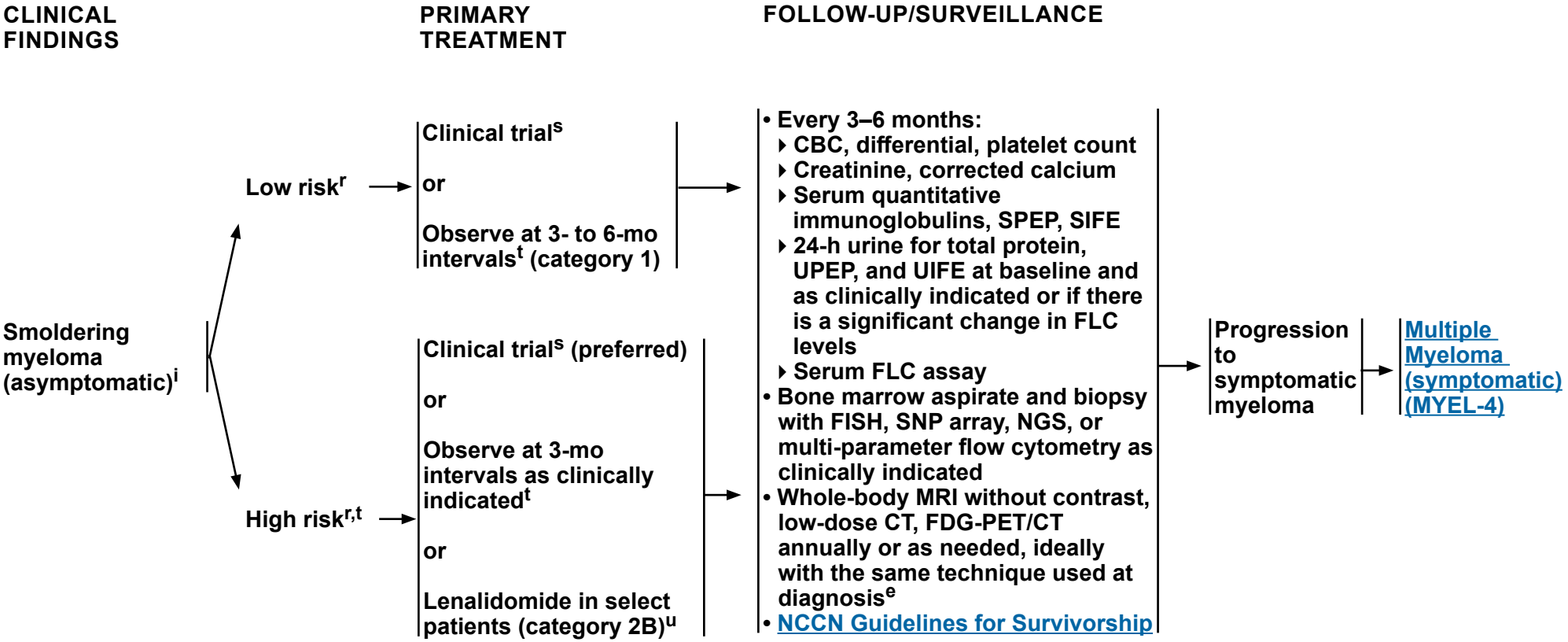

[e] Principles of Imaging (MYEL-C).
[i] Definitions of Smoldering and Multiple Myeloma (MYEL-A).
[r] Bone marrow plasma cells (BMPCs) >20%, M-protein >2 g/dL, and serum FLC ratio (FLCr) >20 are variables used to risk stratify patients at diagnosis. Patients with two or more of these risk factors are 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.
[u] Consider consultation for hematopoietic cell transplant (HCT) and consider collection of hematopoietic stem cells (more than one transplant, if appropriate).

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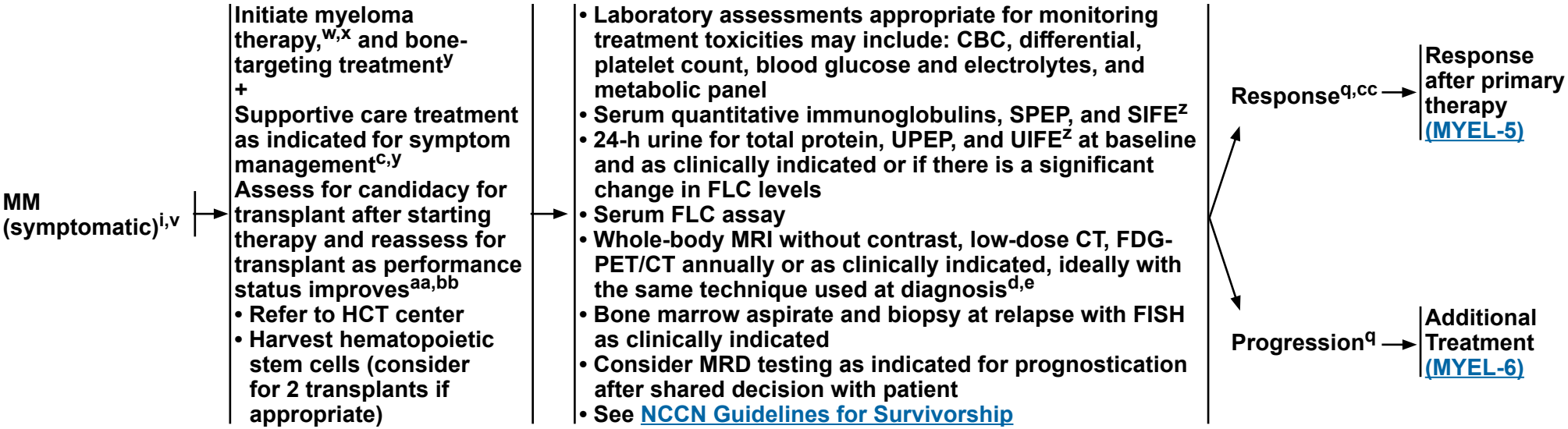

[c] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[d] Skeletal survey is acceptable in certain circumstances. However, it is significantly less sensitive than whole-body low-dose CT and FDG-PET/CT. If whole-body FDG-PET/CT or low-dose CT has been performed, then skeletal survey is not needed.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

Note: All recommendations are category 2A unless otherwise indicated.
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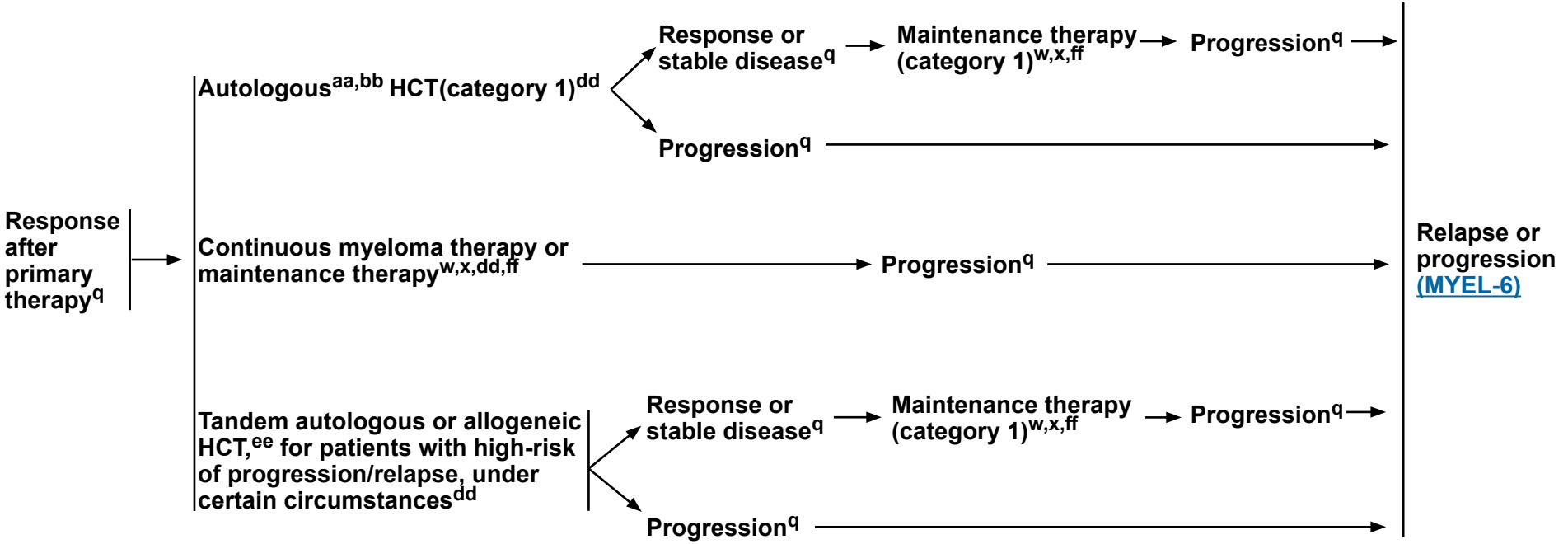
MULTIPLE MYELOMA (SYMPTOMATIC)

FOLLOW-UP/SURVEILLANCE



[q] Response Criteria for Multiple Myeloma (MYEL-E).
[w] Myeloma Therapy (MYEL-G).
[x] General Considerations for Myeloma Therapy (MYEL-F).
[aa] Autologous transplantation: Category 1 evidence supports proceeding directly after induction therapy to high-dose therapy and HCT. Delayed HCT can be considered in select patients. See Discussion.
[bb] Renal dysfunction and advanced age are not contraindications to transplant.
[dd] Follow up with the tests listed on MYEL-4 under Follow-up/Surveillance.
[ee] Allogeneic HCT should preferentially be done in the context of a trial when possible.
[ff] 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,dd] →

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

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

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

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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**
  - **Assess for bone disease with whole-body low-dose CT, FDG-PET/CT, or whole-body MRI without contrast. If unable to perform, consider skeletal survey.**

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 (FLCr) ≥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, Rajkumar SV, Buadi FK, et al. Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. 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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DISEASE STAGING AND RISK STRATIFICATION SYSTEMS FOR MULTIPLE MYELOMA

Factors Considered as High Risk for Progression/Relapse	
For Those with Newly Diagnosed MM	**For Those with Relapsed MM**

• R-ISS III (MYEL-B 2 of 2)
• Extramedullary disease
• Circulating plasma cells[a]
• Cytogenetic abnormalities
  ▸ Del(1p32)
  ▸ t(4;14)
  ▸ t(14;16)
  ▸ t(14;20)
  ▸ Del(17p)/monosomy 17/*TP53* mutation
  ▸ 1q21 gain/1q21 amplification[b]
  ▸ MYC translocation
• High-risk gene expression profile
	• Disease relapse within 2 years of initial therapy when transplant and maintenance are used.
	
	• Relapse within 18 mo in case of non-transplant–based treatment.
	
	• Acquisition of 1q gain/amplification and/or del(17p)/*TP53* mutation
	
	• Extramedullary disease at relapse

[a] Presence of ≥5% of plasma cells in circulation is defined as plasma cell leukemia.
[b] 1q21 gain/amplification alone is not considered high-risk for progression/relapse.

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DISEASE STAGING AND RISK STRATIFICATION SYSTEMS FOR MULTIPLE MYELOMA

Stage	International Staging System (ISS)	Revised-ISS (R-ISS)[1]	R2-ISS[2,c]
I	Serum beta-2 microglobulin <3.5 mg/L, Serum albumin ≥3.5 g/dL	ISS stage I and standard-risk chromsomal abnormalities by FISH and Serum LDH ≤ the upper limit of normal	Low-risk: 0 points[d] • Not ISS stage II or III • Serum LDH ≤ the upper limit of normal • del(17p), t(4;14), 1q+: Not detected
II	Not ISS stage I or III	Not R-ISS stage I or III	Low-intermediate risk: 0.5–1 points[d] • ISS stage II or • Serum LDH > the upper limit of normal or • del(17p) or t(4;14) or 1q+: Detected
III	Serum beta-2 microglobulin ≥5.5 mg/L	ISS stage III and either high-risk chromosomal abnormalities by FISH or Serum LDH > the upper limit of normal	Intermediate-high risk: 1.5–2.5 points[d] • Any combination of high-risk features which equals a score of 1.5–2.5
IV			High-risk: 3–5 points[d] • Any combination of high-risk features which equals a score of 3–5

[1] 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.

[2] D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second revision of the international staging system (R2-ISS) for overall survival in multiple myeloma: A European Myeloma Network (EMN) report within the harmony project. J Clin Oncol 2022;40:3406-3418.

[c] R2-ISS is only validated for newly diagnosed Multiple Myeloma.

[d] For R2-ISS classification a numerical value is assigned to each risk factor based on their influence on OS: ISS-III is 1.5 points, ISS-II is 1 point, del(17p) is 1 point, t(4;14) is 1 point, 1q+ is 0.5 points, and serum LDH > the upper limit of normal is 1 point

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PRINCIPLES OF IMAGING

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

- **Whole-body 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.**
- **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 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.**
- **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.[1]**

Imaging for Follow-up of Smoldering Myeloma

- **Advanced whole-body imaging (ie, MRI without contrast, low-dose CT, FDG-PET/CT) is recommended annually or as clinically indicated. 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, 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.[2-5]**

References:

[1] Paiva B, Chandia M, Vidriales MB, et al. Multiparameter flow cytometry for staging of solitary bone plasmacytoma: new criteria for risk of progression to myeloma. Blood 2014;124:1300-1303.
[2] Walker R, Barlogie B, Haessler J, et al. Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. J Clin Oncol 2007;25:1121-1128.
[3] Bartel TB, Haessler J, Brown TL, et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009;114:2068-2076.
[4] Zamagni E, Nanni C, Mancuso K, et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. Clin Cancer Res 2015;21:4384-4390.
[5] Moreau P, Attal M, Caillot D, et al. Prospective evaluation of magnetic resonance imaging and [(18)F]fluorodeoxyglucose positron emission tomography-computed tomography at diagnosis and before maintenance therapy in symptomatic patients with multiple myeloma included in the IFM/DFCI 2009 trial: Results of the IMAJEM study. J Clin Oncol 2017;35:2911-2918.

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PRINCIPLES OF RADIATION THERAPY

Solitary Plasmacytoma

General Principles:

- **Radiation therapy (RT) is the intervention of choice for solitary plasmacytoma.**
- **Treatment of solitary plasmacytomas should be performed using modern treatment principles including imaging-based delineation (MRI, CT with contrast, and/or FDG-PET/CT) of a gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) and adjacent organs at risk (OARs). CTV expansions should generally include at least 0.5 cm of margin for microscopic extent, and up to 2–3 cm for involvement of long bones. PTV margins should be minimized using modern daily image guidance. Treatment of adjacent vertebral bodies for spine lesions is not required if there is no suspicion of clinical involvement.**

- **RT should be utilized with advanced technology (ie, intensity-modulated RT [IMRT], volumetric modulated arc therapy [VMAT], protons) when these modalities can help limit radiation doses to surrounding OARs. Principles of involved-site RT (ISRT) should be used to avoid large radiation fields and inappropriately including uninvolved sites, which will increase the risk of toxicity.**

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.**
  - **Treatment with 35–40 Gy is an acceptable alternative for solitary plasmacytomas <5 cm in size, due to the high rates of local control reported for smaller tumors.**

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PRINCIPLES OF RADIATION THERAPY

Multiple Myeloma

General Principles:

- **RT is primarily used for palliation in patients with MM.**
- **Careful planning in defining the radiation field and radiation technique must be utilized to minimize toxicity to the spinal cord, brain, bone marrow, and adjacent OARs as patients may be treated multiple times during their disease course.**
- **Careful planning of radiation fields for cord compression in the thoracic area at the level of the heart should be utilized to avoid radiation dose exiting into the heart structures, which could lead to cardiac toxicity.**

Timing and Sequencing of Therapy:

- **Systemic therapy should not be delayed for RT, and can often be given concurrently.**
- **Data suggest that systemic therapy (carfilzomib, bortezomib, or daratumumab) and palliative RT can be used concurrently without evidence of increased toxicity, but that patients should be carefully monitored for toxicities.**
- **If urgent surgical intervention is indicated, RT should be delivered postoperatively to improve pain control and prevent local recurrence. Patients in a resource-limited setting with access to systemic therapy may consider forgoing postoperative RT.**
- **If surgical intervention is not indicated for impending fracture, structural instability, or emergent decompression it should be avoided to avoid potential complications and delays in systemic therapy. RT can result in functional re-ossification in a large proportion of patients.**

Palliative RT Dosing for MM:

- **Low-dose RT (8 Gy x 1 fraction) or 20–30 Gy in 5–10 total fractions can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or for impending cord compression. Moderately fractionated courses of 20-25 Gy in 8-10 fractions are generally preferred over higher doses (30 Gy) absent extenuating circumstances (e.g., severe symptomatic cord compression) to limit unnecessary toxicity and reduce risk of future treatment of adjacent or overlapping organs at risk (e.g., spinal cord).**
- **Limited involved sites should be used to limit the impact of irradiation on hematopoietic stem cell harvest or impact on potential future treatments.**
- **For RT dose constraint suggestions regarding bone marrow and other OARs, see NCCN Guidelines for Hodgkin Lymphoma.**

References:

Elhammali A, Amini B, Ludmir EB, et al. New paradigm for radiation in multiple myeloma: lower yet effective dose to avoid radiation toxicity. Haematologica. 2020;105(7):e355-e357

Guerini AE, Tucci A, Alongi F, et al. RR Myelo POINT: A Retrospective Single-Center Study Assessing the Role of Radiotherapy in the Management of Multiple Myeloma and Possible Interactions with Concurrent Systemic Treatment. Cancers (Basel). 2022;14(9):2273

Resende Salgado L, Wang S, Adler A, et al. The Safety Profile of Concurrent Therapy for Multiple Myeloma in the Modern Era. Adv Radiat Oncol. 2018;4(1):112-117.

Tsang RW, Campbell BA, Goda JS, et al. Radiation Therapy for Solitary Plasmacytoma and Multiple Myeloma: Guidelines From the International Lymphoma Radiation Oncology Group Int J Radiat Oncol Biol Phys. 2018;101(4):794-808.

Tsang RW, Gospodarowicz MK, Pintilie M, et al. Solitary plasmacytoma treated with radiotherapy: impact of tumor size on outcome. Int J Radiat Oncol Biol Phys. 2001;50(1):113-120

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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
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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 ratioof 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:

- **Systemic therapy should not be delayed for advanced imaging if diagnosis of active myeloma is otherwise clear.**
- **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.**
- **Frailty assessment should be considered in older adults. see NCCN Guidelines for Older Adult Oncology.**
- **For the Myeloma Frailty Score Calculator developed by IMWG for the prognosis of elderly myeloma patients, see http://www.myelomafrailtyscorecalculator.net/[1]**
- **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).**

Additional Consideration for Relapsed/Refractory Disease

- **Consideration for appropriate regimen in previously treated myeloma should be based on the context of clinical relapse.**
- **For relapsed disease, if relapse is greater than 6 months after the end of primary treatment, the regimen used for primary therapy may be repeated.**
- **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.**
- **Intravenous immunoglobulin (IVIG) should be considered for patients with an IgG <400 mg/dL prior to the administration of bispecfic T-cell antibodies and CAR T-cell therapy.**

For HCT and Stem Cell Storage:

- **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 HCT.**
- **Consider harvesting peripheral blood stem cells within the first 6 cycles of therapy initiation prior to prolonged exposure to lenalidomide and/or daratumumab in patients for whom HCT is being considered.**
- **If delayed HCT is considered then stem cells should be collected and stored.**

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

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

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GENERAL CONSIDERATIONS FOR MYELOMA THERAPY

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.**
- **Steroids should be reduced to 20 mg weekly in older patients and should be decreased or discontinued with treatment response plateau and/or toxicity.**

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.**
- **Monoclonal antibodies can produce a false positive serum immunofixation if the monoclonal protein is IgG kappa and special interference testing or mass spectrometry based assessment can differentiate between the two.**
- **Carfilzomib can potentially cause cardiac and pulmonary toxicity, especially in older patients.**
- **Agents such as bendamustine can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guidelines for Management of Immunotherapy-Related Toxcities.**

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

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

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[e] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to proteasome inhibitor (PI)/lenalidomide/dexamethasone. Consider switching to PI/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] Two drug maintenance recommended for high-risk MM
[k] Ixazomib may be substituted for carfilzomib in select patients

Note: All recommendations are category 2A unless otherwise indicated.
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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[k]	• Daratumumab/cyclophosphamide/bortezomib/dexamethasone
Useful In Certain Circumstances • Lenalidomide/low-dose dexamethasone (category 1)[m] • Bortezomib/cyclophosphamide/dexamethasone[e] • Bortezomib/dexamethasone	• Bortezomib/lenalidomide/dexamethasone (VRD-lite) for frail patients • Carfilzomib/cyclophosphamide/dexamethasone[f,k] • Lenalidomide/cyclophosphamide/dexamethasone

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

[a] Selected, but not inclusive of all regimens. The regimens under each preference category are listed by order of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[e] Preferred primarily as initial treatment in patients with acute renal insufficiency or those who have no access to PI/lenalidomide/dexamethasone. Consider switching to PI/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] Ixazomib may be substituted for carfilzomib in select patients.
[m] Continuously until progression. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917.

Note: All recommendations are category 2A unless otherwise indicated.
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THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o,q]
Relapsed/Refractory Disease After 1–3 Prior Therapies

Preferred Regimens*
Order of regimens does not indicate comparative efficacy

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

CAR T-Cell Therapy
After one prior therapy including IMiD and a PI, and refractory to lenalidomide
▸ **Ciltacabtagene autoleucel (category 1)**

After two prior therapies including an IMiD, an anti-CD38 monoclonal antibody and a PI
▸ **Idecabtagene vicleucel (category 1)**

* For Other Recommended Regimens and for regimens Useful in Certain Circumstances for Relapsed/Refractory Disease After 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 of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[n] 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.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[p] Regimens without anti-CD38 should be considered for those refractory to anti-CD38 antibody as long as they have not received or are refractory to other agents in the regimen.
[q] If relapse occurs >6 months after stopping treatment, the primary regimen could be considered.

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THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-r] Relapsed/Refractory Disease After 1–3 Prior Therapies	
Other Recommended Regimens	
• **Carfilzomib (twice weekly)/dexamethasone (category 1)** • **Elotuzumab/lenalidomide/dexamethasone (category 1)** • **Ixazomib/lenalidomide/dexamethasone (category 1)** • **Bortezomib/cyclophosphamide/dexamethasone** • **Bortezomib/lenalidomide/dexamethasone** • **Carfilzomib/cyclophosphamide/dexamethasone** • **Daratumumab/cyclophosphamide/bortezomib/dexamethasone** • **Elotuzumab/bortezomib/dexamethasone** • **Ixazomib/cyclophosphamide/dexamethasone** • **Lenalidomide/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**
Useful in Certain Circumstances	
• **Bortezomib/dexamethasone (category 1)** • **Bortezomib/liposomal doxorubicin/dexamethasone (category 1)** • **Lenalidomide/dexamethasone (category 1)** • **Carfilzomib/cyclophosphamide/thalidomide/dexamethasone** • **Carfilzomib (weekly)/dexamethasone** • **Selinexor/carfilzomib/dexamethasone** • **Selinexor/daratumumab/dexamethasone** • **Venetoclax/dexamethasone ± daratumumab or PI 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)** ▸ **Ixazomib/pomalidomide/dexamethasone** ▸ **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 of NCCN Category of Evidence and Consensus alphabetically.
[b] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[n] 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.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[q] If relapse occurs >6 months after stopping treatment, the primary regimen could be considered.
[r] Consider single-agent lenalidomide or pomalidomide for patients with steroid intolerance.

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THERAPY FOR PREVIOUSLY TREATED MULTIPLE MYELOMA[a-d,n-o]
Relapsed/Refractory Disease After 3 Prior Therapies

Preferred Regimens

After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD[s]

- *CAR T-cell Therapy:*
  - **Ciltacabtagene autoleucel**
  - **Idecabtagene vicleucel**
- *Bispecific Antibodies:*
  - **Elranatamab-bcmm**
  - **Talquetamab-tgvs**
  - **Teclistamab-cqyv**

Other Recommended Regimens

- **Bendamustine**[t]
- **Bendamustine/bortezomib/dexamethasone**[t]
- **Bendamustine/carfilzomib/dexamethasone**[t]
- **Bendamustine/lenalidomide/dexamethasone**[t]
- **High-dose or fractionated cyclophosphamide**

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**

Useful in Certain Circumstances

After at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD

- **Belantamab mafodotin-blmf (if available through compassionate use program)**

[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] Supportive Care Treatment for Multiple Myeloma (MYEL-H).
[c] General Considerations for Myeloma Therapy (MYEL-F).
[d] Management of Renal Disease in Multiple Myeloma (MYEL-K).
[n] 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.
[o] Autologous HCT should be considered in patients who are eligible and have not previously received HCT or had a prolonged response to initial HCT.
[s] Patients can receive more than one B-cell maturation antigen (BCMA) targeted therapy, but optimal sequencing is unclear.
[t] Agents such as bendamustine can impact the ability to collect T cells for CAR T-cell therapy. See NCCN Guideline for Management of Immunotherapy-Related Toxicities.

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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,c]).
  - 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[c]) for up to 2 years. The frequency of dosing (monthly vs. every 3 months) would depend on the individual patient criteria, response to therapy, and agent used. Continuing beyond 2 years should be based on clinical judgment.
  - Patients receiving denosumab[c] for bone disease who subsequently discontinue therapy should be given maintenance denosumab[c] every 6 months or a single dose of bisphosphonate to mitigate risk of rebound osteoporosis.[d]
- For RT recommendations 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[c], 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.[e]

Infections

- See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.
- See CDC for Use of COVID-19 Vaccines in the US.
- For prophylaxis and management of infections in patients with multiple myeloma, see MYEL-I.

Renal Dysfunction

- See Management of Renal Disease in Multiple Myeloma (MYEL-K).

Venous Thromboembolism (VTE)

- For management of VTE, risk stratification, and VTE prophylaxis, see MYEL-J.

[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] An FDA-approved biosimilar is an appropriate substitute.
[d] 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.
[e] Increased risk of VTE has been reported in patients receiving erythropoiesis-stimulating agents (ESAs).

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MANAGEMENT OF INFECTIONS IN PATIENTS WITH MULTIPLE MYELOMA[1]

The following treatments are associated with an increased risk of infections in patients with MM:
- **Autologous HCT**
- **Bispecific antibody (BsAb) therapy**
- **CAR T-cell therapy**
- **Cytotoxic chemotherapy**

In addition:
- **New diagnosis of MM has an increased risk of bacterial infection.**
- **Proteasome inhibitors and monoclonal antibodies have an increased risk of viral infection.**
- **High-dose steroids have an increased risk of fungal infections.**

Common Bacterial Infections	
Interventions & Prophylaxis	**Indications & Duration**
Levofloxacin 500 mg PO daily. Alternatives: Cefdinir 300 mg PO twice a day or augmentin 875 mg PO twice a day.	**• Newly diagnosed MM: Consider levofloxacin for 12 weeks after diagnosis[2] • CAR T-cell: Start when ANC <500 or per clinician discretion and continue until neutrophil recovery. • BsAb: Consider starting with therapy and administer throughout the first cycle.**
IVIG: Suggested dose is 400 mg/kg once every 4 weeks.	**• IVIG replacement is indicated for IgG <400 mg/dL and recurrent life-threatening infections.[a] Note: IVIG replacement during CAR T-cell and BsAb therapies is not guided by presence of infections. Duration: • Patients at high risk for infections[b]: At day +30 until end of therapy or serum IgG >400 mg/dL. • CAR T-cell[a]: Day +30 through 1 year. After 1 year continue until serum IgG >400 mg/dL. • BsAb[a]: Start at second cycle of therapy and continue until end of therapy or serum IgG >400 mg/dL (whichever is longer).**
Pneumococcal vaccination	**The CDC recommends 1 dose of PCV20 or 1 dose of PCV15 followed by 1 dose of PPSV23 at least 1 year later. CAR T-cell and/or autologous HCT: Revaccination starting 3–6 months after treatment. BsAb: Update vaccination status prior to starting BsAb treatment.**

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Footnotes
(MYEL-I 2 of 2)
Continued

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MANAGEMENT OF INFECTIONS IN PATIENTS WITH MULTIPLE MYELOMA[1]

Common Viral and Fungal Infections	
Interventions & Prophylaxis	**Indication & Duration**
Herpes simplex virus or Varicella-zoster virus: Acyclovir 400–800 mg PO twice/day or valacyclovir 500 mg PO once or twice/day. Continue as clinically indicated	**While recieving a regimen with PIs or monoclonal antibody and for at least 3 months beyond end of therapy or per institutional practice. CAR T-cell: A minimum of one year; indefinite (preferred), irrespective of vaccination status. BsAb: Indefinite, irrespective of vaccination status. Autologous HCT: for 1 year post-HCT or as clinically indicated**
Hepatitis B virus and HIV: Screen for and treat as outlined in the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections	**CAR T-cell or BsAb: Patients HBsAg-positive or HBsAg-negative, HBcAb-IgG positive. See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections for treatment duration.**
Pneumocystis jiroveci pneumonia (PJP): Trimethoprim-sulfamethoxazole (TMP-SMX) therapy or pentamidine or atorvaquone	**• CAR T-cell or BsAb: Start with therapy and continue until end of therapy or until CD4 ≥200/mm³ (whichever is longer). • For other myeloma therapy (Non CAR T-cell/BsAb: When equivalent dexamethasone dosing is >40 mg/day for 4 days per week or as clinically indicated per institutional practice.**
SARS-CoV-2: COVID-19 vaccination	**Autologous HCT and/or CAR T-cell: Revaccination 3–6 months after therapy. Per CDC for patients who are immunosuppressed.**
Influenza virus: Vaccination	**Per CDC for patients who are immunosuppressed.**
RSV: Bivalent vaccine	**Single dose of bivalent vaccine for MM patients aged ≥60 years. See CDC guidance for all other patient populations.**
Adenovirus, CMV, EBV, JC virus, parvovirus: No prophylaxis	**Routine monitoring of viral load is not recommended. Monitor viral load (by PCR) only in patients with suspected CMV-related disease (eg, colitis, pneumonitis, hepatitis) or otherwise unexplained fever and/or cytopenias or in patients with high risk of infections.[b]**
Yeast: Fluconazole 400 mg PO daily	**Start when ANC <500 or per clinician discretion and continue until neutrophil recovery.**
Mold: Azole	**In patients with high risk of infections[b]: Consider ongoing prophylaxis with anti-mold azole.**

[1] Mohan Mohan M, Nagavally S, et al. Blood Adv. 2022; 6: 2466–70.
[2] Drayson MT, et al. Lancet Oncol 2019;20:1760-1772.
[a] Discount/subtract monoclonal component that may be responsible for disease-related IgG elevation.
[b] Patients receiving CAR T-cell and BsAb treatment, recipients of >1 dose of tocilizumab, use of second line agents such as anakinra or siltuximab for management of CRS and ICANS, prolonged and/or high-dose steroid use (requiring >3 days of 10 mg dexamethasone per day with a 7-day period or receiving higher doses of methylprednisone >1 g per day) are at high risk of infection.

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MANAGEMENT OF VENOUS THROMBOEMBOLISM (VTE) IN MULTIPLE MYELOMA

VTE RISK STRATIFICATION USING IMPEDE OR SAVED SCORING SYSTEM

IMPEDE Score[1] 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[2] 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

[1] Adapted from Sanfilippo KM, et al. Am J Hematol 2019;94:1176-1184.
[2] 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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MANAGEMENT OF VENOUS THROMBOEMBOLISM (VTE) IN MULTIPLE MYELOMA

General Principles:

- **The 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 (see VTE-A within 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:

Carrier M, Abou-Nassar K, Mallick R, et al. Apixaban to Prevent Venous Thromboembolism in Patients with Cancer. N Engl J Med. 2019;380(8):711-719.
Khorana AA, Soff GA, Kakkar AK, et al. Rivaroxaban for Thromboprophylaxis in High-Risk Ambulatory Patients with Cancer. N Engl J Med. 2019;380(8):720-728.
Kristinsson SY. Thrombosis in multiple myeloma. Hematology Am Soc Hematol Educ Program. 2010;2010:437-444.
Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22(2):414-423.
Piedra K, Peterson T, Tan C, et al. Comparison of venous thromboembolism incidence in newly diagnosed multiple myeloma patients receiving bortezomib, lenalidomide, dexamethasone (RVD) or carfilzomib, lenalidomide, dexamethasone (KRD) with aspirin or rivaroxaban thromboprophylaxis. Br J Haematol. 2022;196(1):105-109.
Wang TF, Zwicker JI, Ay C, et al. The use of direct oral anticoagulants for primary thromboprophylaxis in ambulatory cancer patients: Guidance from the SSC of the ISTH. J Thromb Haemost. 2019;17(10):1772-1778. Note: The AVERT apixaban trial had only 2.6% myeloma patients, and myeloma patients were excluded from the CASSINI rivaroxaban trial.

Note: All recommendations are category 2A unless otherwise indicated.
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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[a]**
• 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)

[a] 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[c]
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[d]

[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] An FDA-approved biosimilar is an appropriate substitute.
[d] Patients with creatinine clearance <30 cc/min can experience severe hypocalcemia and should be monitored.

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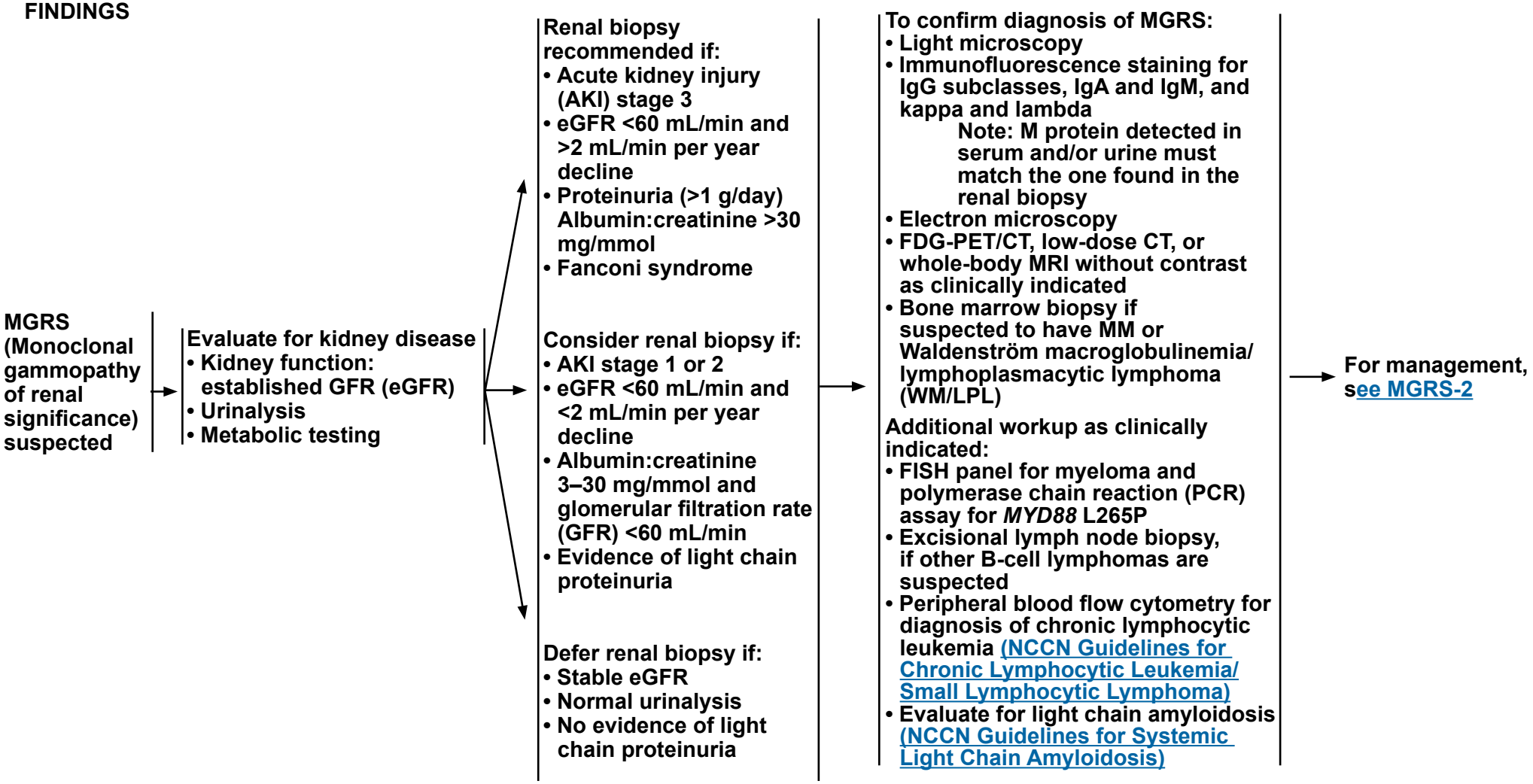
MONOCLONAL GAMMOPATHY OF CLINICAL SIGNIFICANCE
MONOCLONAL GAMMOPATHY OF RENAL SIGNIFICANCE



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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 (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 (NCCN Guidelines for Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma)
- For FLC-associated MGRS, use the response criteria for amyloidosis (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] 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, (NCCN Guidelines for Systemic Light Chain Amyloidosis), WM (NCCN Guidelines for WM/LPL), or POEMS (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/abdomen/pelvis 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)

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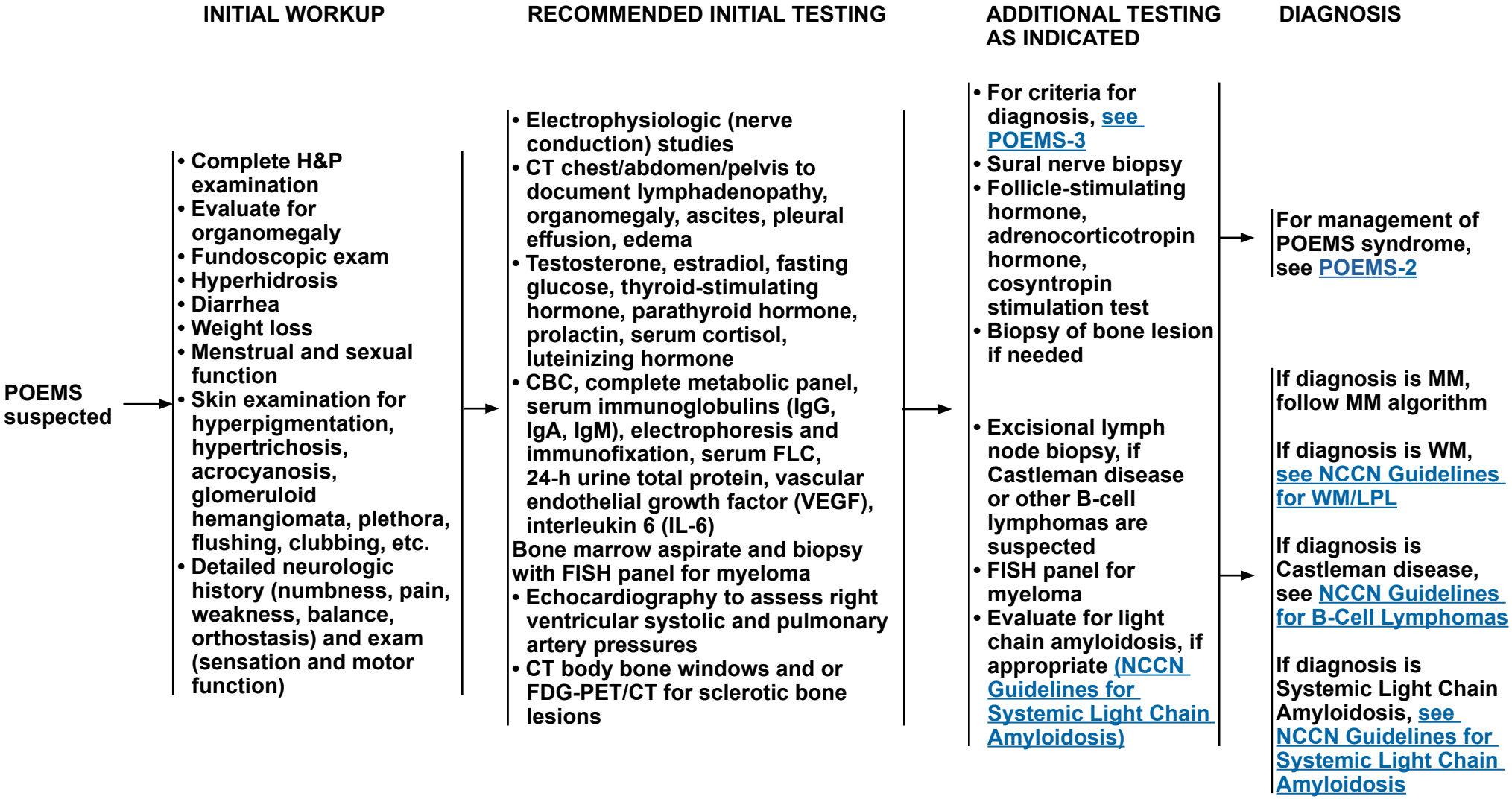
POEMS (POLYNEUROPATHY, ORGANOMEGALY, ENDOCRINOPATHY, MONOCLONAL PROTEIN, SKIN CHANGES)



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

TREATMENT

- RT 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.

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

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

Mandatory major criteria	**1. Polyneuropathy (typical demyelinating)**
	2. Monoclonal plasma cell-proliferative disorder (almost always λ)
Other major criteria (one required)	**3. Castleman 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

ADLs	activities of daily living
AKI	acute kidney injury
AS-PCR	allele-specific polymerase chain reaction
ANC	absolute neutrophil count
BCMA	B-cell maturation antigen
BMPC	bone marrow plasma cell
BUN	blood urea nitrogen
BNP	b-type natriuretic peptide
BsAb	bispecific antibody
CAR	chimeric antigen receptor
CBC	complete blood count
CL_{cr}	creatinine clearance
CMV	cytomegalovirus
CTV	clinical target volume
EBV	Epstein-Barr virus
eGFR	established glomerular filtration rate
EMG	electromyogram
ESA	erythropoiesis-stimulating agent
FDG	fluorodeoxyglucose
FISH	fluorescence in situ hybridization
FLC	free light chain
FLCr	serum free light chain ratio
GFR	glomerular filtration rate
GTV	gross tumor volume
H&P	history and physical
HCT	hematopoietic cell transplant
HIV	human immunodeficiency virus
Ig	immunoglobulin
IHC	immunohistochemistry
ISS	International Staging System
IMiD	immunomodulatory drug
IMPEDE	IMiD, BMI, Pathologic fracture, ESA (erythropoietin stimulating agent), Dexamethasone/ Doxorubicin, Ethnicity
IMRT	intensity-modulated radiation therapy
INR	international normalized ratio
ISRT	involved-site radiation therapy
IVIG	intravenous immunoglobulin
JC	John Cunningham
LDH	lactate dehydrogenase
LMWH	low-molecular-weight heparin
MBL	monoclonal B-cell lymphocytosis
MFC	multicolor flow cytometry
MGNS	monoclonal gammopathy of neurological significance
MGRS	monoclonal gammopathy of renal significance
MGUS	monoclonal gammopathy of undetermined significance
MRD	minimal residual disease
MM	multiple myeloma
NGS	next-generation sequencing
NGF	next-generation flow
NT-proBNP	N-terminal pro hormone B-type natriuretic peptide
NCS	nerve conduction study
OAR	organs at risk
OS	overall survival
PI	proteasome inhibitor
POEMS	polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes
PR	partial response
PCR	polymerase chain reaction
PCV	pneumococcal conjugate vaccine
PJP	pneumocystis jirovecii pneumonia
PTV	planning target volume
R-ISS	Revised International Staging System
RSV	respiratory syncytial virus
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
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
VEGF	vascular endothelial growth factor
VGPR	very good partial response
VMAT	volumetric modulated arc therapy
VTE	venous thromboembolism
WM/LPL	Waldenström macroglobulinemia/ lymphoplasmacytic lymphoma

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

All recommendations are category 2A unless otherwise indicated.

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

All recommendations are considered appropriate.

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National Comprehensive Cancer Network®

NCCN Guidelines Version 4.2024
Multiple Myeloma

Discussion

This discussion corresponds to the NCCN Guidelines for Multiple Myeloma. Last updated: 10/31/2023

Table of Contents

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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 is most frequently diagnosed among people aged 65 to 74 years, with the median age being 69 years.[1] The American Cancer Society has estimated 35,730 new MM cases and an estimated 12,590 deaths in the United States in 2023.[2]

Guidelines Update Methodology

The complete details of the development and update of the NCCN Guidelines are available at www.NCCN.org.

Literature Search Criteria

Prior to the annual update of the NCCN Guidelines for Multiple Myeloma, an electronic search of the PubMed database was performed to obtain key literature published since the previous update, using the following search terms: Smoldering Multiple Myeloma, Solitary Plasmacytoma, Multiple Myeloma, Monoclonal Gammopathy of Undetermined Significance, and POEMS syndrome. The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.

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; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these guidelines as discussed by the panel have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

Sensitive/Inclusive Language

NCCN Guidelines strive to use language that advances the goals of equity, inclusion, and representation. NCCN Guidelines endeavor to use language that is person-first; not stigmatizing; anti-racist, anti-classist, anti-misogynist, anti-ageist, anti-ableist, and anti-weight-biased; and inclusive of individuals of all sexual orientations and gender identities. NCCN Guidelines incorporate non-gendered language, focusing on organ-specific recommendations. This language is accurate and inclusive and can help fully address the needs of individuals of all sexual orientations and gender identities. NCCN Guidelines will continue to use the terms men, women, female, and male when citing statistics, recommendations, or data from organizations or sources that do not use inclusive terms. Most studies do not report how sex and gender data are collected and use these terms interchangeably or inconsistently. If sources do not differentiate gender from sex assigned at birth or organs present, the information is presumed to predominantly represent cisgender individuals. NCCN encourages researchers to collect more specific data in future studies and organizations to use more inclusive and accurate language in their future analyses.

Diagnosis and Workup

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

The initial diagnostic workup in all patients should include a history and physical examination. To differentiate symptomatic and asymptomatic MM the following baseline laboratory studies are needed: a complete blood count (CBC) with differential; examination of peripheral blood smear; blood urea nitrogen (BUN); serum creatinine; creatinine clearance (calculated or measured directly) and serum electrolytes; liver function tests; serum

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calcium; serum uric acid; albumin; lactate dehydrogenase (LDH); and beta-2 microglobulin.

Peripheral smear may show abnormal distribution of red blood cells (RBCs) such as the Rouleaux formation (red cells taking on the appearance of a stack of coins) due to elevated serum proteins.[3] Increased BUN and creatinine indicate decreased kidney function, whereas LDH and beta-2 microglobulin levels reflect tumor cell characteristics. NT-proBNP is also recommended, and if N-terminal prohormone of brain natriuretic peptide N-terminal prohormone of brain natriuretic peptide (NT-proBNP) is not available BNP can be performed.

Serum and Urine Analysis: Serum analysis includes quantitative immunoglobulin levels (IgG, IgA, and IgM); serum protein electrophoresis (SPEP) for quantitation of M 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 free light chain (FLC) assay along with serum M protein analyses (SPEP and SIFE) yield high sensitivity while screening for MM and related plasma cell disorders.[4-6] It is also helpful in prognostication of monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, active MM, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.[6,7] 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.[8] 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 individuals are found to have an M protein, light chain abnormalities, or both, the same studies should be used serially. Patients with a negative UPEP do not need this study repeated, except to confirm remission or if the clinical situation changes.

Bone Marrow Evaluation: The percentage of clonal bone marrow plasma cells (BMPCs; ≥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.[9] The cytoplasm of abnormal plasma cells contains either kappa or lambda light chains, and predominance of one or the other light chain expressing plasma cells indicates clonality. Specific immunophenotypic profiles of the myeloma cells may have prognostic implications.[10]

Cytogenetic Studies: Although MM may be morphologically similar, several subtypes of the disease have been identified at the genetic and molecular levels. 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 is not recommended unless myelodysplasia is suspected. Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications. According to the NCCN Multiple Myeloma Panel members, the FISH panel for prognostic estimation of plasma cells should be examined 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.

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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.[11-13]

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.[14-17]

Abnormalities of chromosome 1 are also among the frequent chromosomal alterations in MM.[18] The short arm is most often associated with deletions and the long arm with amplifications.[19] Gains/amplification of 1q21 increases the risk of MM progression and incidence of the amplification is higher in relapsed than in newly diagnosed patients.[18,20]

Risk stratification based on the chromosomal markers is being utilized for prognostic counseling, selection, and sequencing of therapy.[21-23]

Imaging: A skeletal survey has been the standard for decades for assessing bone disease for any individual with suspected MM.[24] 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. A multicenter analysis by the IMWG compared conventional skeletal survey 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 the spine and pelvis.[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 the 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 FDG-PET/CT is chosen instead of whole-body low-dose CT, the imaging quality of the CT part of the FDG-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 generally be 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 and PET are 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] PET is used specifically to rule out lytic bone disease as well as extramedullary involvement. 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.

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A tissue biopsy may also be necessary to confirm the diagnosis of suspected plasmacytomas, particularly extramedullary deposits. 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.

Hepatitis B and C testing and human immunodeficiency virus (HIV) screening should be done as required.

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

The panel also suggests baseline clone identification or storage of bone marrow aspirate sample for clone identification for future minimal residual disease (MRD) testing by NGS if required and assessment for circulating plasma cells in peripheral blood, as clinically indicated. Risk assessment by gene expression profiling can also be considered.[33]

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 organ dysfunction related to the monoclonal gammopathy have been variably classified as having monoclonal gammopathy of clinical significance (MGCS) or monoclonal gammopathy of renal significance (MGRS), depending on the nature of organ involvement.

Staging and Risk Stratification Systems for MM

Definitions: The IMWG definition of MM includes biomarkers in addition to requirements of CRAB features.[34] The CRAB criteria that define MM include: increased **c**alcium levels (>11.5 mg/dL), **r**enal insufficiency (creatinine >2 mg/dL or creatinine clearance <40 mL/min), **a**nemia (hemoglobin <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) 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. Asymptomatic patients fulfilling these criteria should be treated as having active MM.

The criteria by the IMWG for patients with smoldering (asymptomatic) MM include serum M protein (IgG or IgA) greater than or equal to 30 g/L and/or clonal BMPCs 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 M protein greater than 2 g/dL, FLCr of greater than 20, and plasma cells greater than 20% as important risk factors for progression. Patients with 2 or more of these features had a

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median time to progression (TTP) of 29 months.[35] Mateos et al in an analysis of 2004 patients found that the presence of t(4;14), t(14;16), 1q amp/gain, or del(13q) was a further risk factor and patients with one of these findings, along with all 3 of the 20/2/20 model had a risk of progression of 67% at 2 years.[36]

Risk Stratification: The NCCN Panel has provided a list of factors that put patients at high risk of disease progression and/or relapse. For patients with newly diagnosed MM, these factors include being diagnosed as R-ISS III, having extramedullary disease,[37] having circulating plasma cells,[38] have certain cytogenetic abnormalities [eg, del(1p32), t(4;14), t(14;14), t (14;20), del(17p)/monosomy 17; 1q21 gain/1q21 amplification; MYC translocation][39]; or high-risk gene expression profile.[33]

The NCCN Panel has also listed factors for risk of disease progression in those with relapsed MM. These include disease relapse within 2 years of initial therapy with hematopoietic cell transplant (HCT) and maintenance regimens or with 6 months of primary induction therapy with HCT; acquisition of 1q gain and/or del(17p)[39]; or presence of extramedullary disease at relapse.[37]

These factors are useful for counseling patients regarding prognosis and for selection and sequencing of subsequent therapy.

Staging Systems: Those with active MM can be staged using the International Staging System (ISS).[40] The ISS identifies three stages based on serum beta-2 microglobulin and serum albumin.
The revised ISS (R-ISS) includes serum beta-2 microglobulin, serum albumin, and prognostic information 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.[41] 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. The R-ISS also identifies three stages: 1) R-ISS I, which includes ISS I standard risk chromosomal abnormalities or evaluated LDH levels; 2) R-ISS III, which includes ISS III and either high-risk chromosomal abnormalities or elevated LDH levels; and 3) R-ISS II, which includes all the other possible combinations and is neither R-ISS I nor R-ISS II.

The main limitation of the R-ISS is that most of the patients were classified as R-ISS II or the intermediate-risk group; it therefore included patients with large variations in risk of progression/death.

In the second revision of the R-ISS (R2-ISS), the intermediate-risk group has been further divided into low- and high-risk groups.[23]

Therefore, the R2-ISS identifies four risk groups by assigning a numerical value to each risk factor based on their influence on overall survival (OS): ISS-III is 1.5 points, ISS-II is 1 point, del(17p) is 1 point, t(4;14) is 1 point, 1q+ is 0.5 points, and serum LDH > the upper limit of normal is 1 point. The low-risk group is 0 points, low-intermediate-risk group is 0.5–1 points; intermediate high-risk group is 1.5–2.5 points, and high-risk group is 3–5 points.[23] The limitation of R2-ISS is that it has only been validated in newly diagnosed MM.

Solitary Plasmacytoma

The diagnosis of solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement 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.[42,43]

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.

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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.[24]

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.[44,45] 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%).[46] 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.[47]

Primary Therapy for Solitary Plasmacytoma

The treatment and follow-up options for solitary plasmacytoma or solitary plasmacytoma with minimal marrow involvement (<10% plasma cells in bone marrow) are similar. RT has been shown to provide excellent local control of solitary plasmacytomas.[48-54] The largest retrospective study (N = 258) included patients with solitary plasmacytoma (n = 206) or extramedullary plasmacytoma (n = 52).[55] Treatments included RT alone (n = 214), RT plus chemotherapy (n = 34), and surgery alone (n = 8). Five-year OS was 74%, disease-free survival was 50%, and local control was 85%.[55]

Patients with solitary plasmacytoma (n = 206) who received localized RT (varying doses) had a lower rate of local relapse (12% in those who received between 40–50 Gy) than those who did not receive RT and were treated with surgery (80%).[54]

According to the NCCN Panel, treatment planning of solitary plasmacytomas should be performed using modern treatment principles including imaging-based delineation (MRI, CT with contrast, and/or FDG-PET CT) of a gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV) and adjacent organs at risk (OARs). CTV expansions should generally include at least 0.5 cm of margin for microscopic extent, and up to 2 to 3 cm for involvement of long bones. PTV margins should be minimized using modern daily image guidance. Treatment of adjacent vertebral bodies for spine lesions is not required if there is no suspicion of clinical involvement. In addition, advanced technology (ie, intensity-modulated RT [IMRT], volumetric modulated arc therapy [VMAT], protons) should be used when feasible to limit radiation doses to surrounding OARs. Principles of involved-site RT (ISRT) should be used to avoid large radiation fields and inappropriately including uninvolved sites that would increase the risk of toxicity.

The dose used in most published papers ranges from 30 to 60 Gy.[53,54,56]

The recommended RT dose by the NCCN Panel is 40 to 50 Gy in 1.8 to 2.0 Gy fractions (20–25 total fractions) to the involved site. The panel also recommends treatment with 35 to 40 Gy as an alternative for solitary plasmacytomas less than 5 cm in size, due to the high rates of local control reported for smaller tumors.[51,57-59]

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The response to RT should be assessed after at least 3 months of completion of RT.

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 RT. The recommended follow-up interval for patients with plasmacytoma after RT is every 3 to 6 months. The imaging results may not be accurate if the scans are performed sooner than 3 months of RT. However, patients with soft tissue and head/neck plasmacytoma could be followed less frequently after an initial 3-month follow-up. All plasmacytomas should be imaged yearly, preferably with the same technique used at diagnosis, for at least 5 years.

The blood tests include CBC with differential and platelet count, serum chemistry for creatinine, and corrected calcium. Serum FLC assay, serum quantitative immunoglobulins, and SPEP with SIFE may be performed as needed.

The urine tests as needed include 24-hour urine assay for total protein, UPEP, and UIFE. Bone marrow aspirate and biopsy are recommended as clinically indicated.

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.[60] 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.[61] However, the rate of progression varies from months to several years based on certain risk features.[61]

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.[62] The high-risk group in the study was defined using the following criteria: plasma cell bone marrow infiltration of at least 10% and/or a monoclonal component (defined as an IgG level of ≥3 g/dL, an IgA level of ≥2 g/dL, or a urinary Bence Jones protein level of >1 g per 24 hours); and at least 95% phenotypically aberrant plasma cells in the bone marrow infiltrate. The OS reported in the trial at 3 years was higher in the group treated with the lenalidomide and dexamethasone arm (94% vs. 80%; HR, 0.31; 95% CI, 0.10–0.91; P = .03).[62] 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).[63] 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

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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.[64] Grade 3 or 4 adverse events were reported in 41% of patients treated with lenalidomide.[64] 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.[64]

The Mayo 2018 20/2/20 criteria stratify patients based on risk. The criteria take into consideration the following risk factors: percentage of BMPCs 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.[65] The estimated progression rates at 2 years among those with low-, intermediate-, and high-risk disease were 5%, 17%, and 46%, respectively.[65]

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 enrolled in a clinical trial or observed at 3- to 6-month intervals (category 1). For the high-risk group, the NCCN Panel prefers enrollment in an ongoing clinical trial (strongly recommended and preferred option) or observation at 3-month intervals, as clinically indicated or treatment with single-agent lenalidomide only in carefully selected patients (category 2B).[62,64] Those with rising markers or high-risk factors must be monitored closely. It is important to note that patients can evolve from having low-risk to high-risk SMM over time, requiring recalibration of follow-up strategies.

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.

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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 HCT in transplant-eligible patients.

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 a patient is eligible for HCT is important.

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. If delaying HCT, then stem cells should be collected and stored. The panel recommends harvesting peripheral blood stem cells within the first 6 cycles of therapy initiation prior to prolonged exposure to lenalidomide and/or daratumumab if HCT is being considered.

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 PFS or OS seen with 3-drug regimens in clinical trials. Frailty assessment should be performed in older adults, as well as consideration of dose modifications, particularly steroids, based on functional status and age.

The doublet regimens are no longer recommended for transplant candidates with the rationale that doublets would be recommended for patients who would not be considered for initial treatment with a 3-drug regimen, such as those not initially eligible for transplant. Patients with poor performance status or who are frail can be started on a 2-drug regimen, with a third drug added after 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.

General Considerations for Dosage and Administration of Commonly Used Agents:

While weekly and twice-weekly dosing schemas of bortezomib are acceptable and supported by data, 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 CyBorD regimen to a once-weekly schedule of bortezomib.[66] In the study, patients treated with weekly bortezomib achieved responses similar to the twice-weekly schedule (overall response rate [ORR], 93% vs. 88%; very good partial response [VGPR], 60% vs. 61%). In addition, they experienced fewer grade 3/4 adverse events (37%/3% vs. 48%/12%). Fewer dose reductions of

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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).[66]

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 IV route or by subcutaneous route.[67] The findings from the study demonstrate non-inferior efficacy with subcutaneous versus IV bortezomib with regard to the primary endpoint (ORR after 4 cycles of single-agent bortezomib). The results showed no significant differences in terms of PFS or 1-year OS between groups.[67,68] However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy.

Carfilzomib can potentially cause cardiac, renal, and pulmonary toxicities. Careful assessment before initiating treatment with carfilzomib and close monitoring during treatment is recommended. Regarding dosing and administration, the panel notes that carfilzomib may be used once or twice weekly and at different doses. Ixazomib may be substituted for carfilzomib in select patients.

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 IV daratumumab.[69] 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.

Prolonged use of steroids can be detrimental in frail patients >60 years of age. Therefore, the NCCN Panel recommends a tailored approach of reducing the dose to 20 mg weekly and discontinuing with either treatment response plateau or toxicity.[70,71]

By binding to CD38 expressed on the surface of RBCs, daratumumab and isatuximab-irfc may result in false-positive indirect antiglobulin test (indirect Coombs test). The binding of these antibodies to RBCs masks detection of antibodies to minor antigens in the patient's serum and interferes with serologic testing. Therefore, type and screen should be performed before using daratumumab or isatuximab-irfc.

The monoclonal antibodies used for myeloma treatment can produce a false-positive serum immunofixation, if the M protein is IgG kappa. In such instances, special interference testing or mass spectrometry-based assessment may be used to differentiate between the two.
Bone disease, renal dysfunction, and other complications such as infections, hypercalcemia, hyperviscosity, and coagulation/thrombosis should be treated with appropriate adjunctive measures (see *Supportive Care for Multiple Myeloma* in this Discussion).

Preferred Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

The preferred primary therapy options for patients who are HCT eligible include bortezomib/lenalidomide/dexamethasone (category 1) and carfilzomib/lenalidomide/dexamethasone (category 2A).

Bortezomib/Lenalidomide/Dexamethasone
Phase II and III study 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.

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In the first phase I/II prospective study of lenalidomide/bortezomib/dexamethasone in patients with newly diagnosed MM, the rate of partial response (PR) was 100%, with 74% VGPR or better and 52% complete response (CR)/near CR.[72]

The benefits of bortezomib/lenalidomide/dexamethasone as primary therapy were also seen in the results of the phase II IFM 2008 trial[73] and phase II EVOLUTION trial.[74] In the phase II IFM 2008 trial, patients received bortezomib, lenalidomide, and dexamethasone as induction therapy followed by HCT.[73] Patients subsequently received 2 cycles of bortezomib/lenalidomide/dexamethasone as consolidation cycles and 1-year lenalidomide maintenance. VGPR rate or better at the completion of induction was 58%.[73] After transplantation and consolidation therapy the rate of VGPR or better was 70% and 87%, respectively.[73]

Bortezomib/lenalidomide/dexamethasone was compared to lenalidomide/dexamethasone in the multicenter phase III SWOG S077 trial.[75] 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).[75] As expected, ≥ grade 3 neuropathy was more frequent in the bortezomib-containing arm (24% vs. 5%; $P < .0001$) as bortezomib was administered twice weekly and intravenously in this study.[75]

With longer-term follow-up (median 84 months), the benefits of adding bortezomib to lenalidomide and dexamethasone were seen to be maintained.[76] The PFS with bortezomib/lenalidomide/dexamethasone was 41 months versus 29 months for lenalidomide/dexamethasone.[76] The OS was not yet reached (>84 months) with the bortezomib regimen versus 69 months for lenalidomide/dexamethasone.[76]

A randomized multicenter phase III 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.[77] 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.[77]

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).[78] The VRd-lite regimen included subcutaneous bortezomib (1.3 mg/m^2) on days 1, 8, 15, and 22, and oral dexamethasone (20 mg) on the day of and the day after bortezomib administration. Lenalidomide was omitted on days 1, 8, and 15, which are the days of bortezomib administration. The ORR after 4 cycles of VRd-lite was 83%, including a CR of 25%. The ORR and VGPR or better were further improved to 100% and 74%, in those who received autologous HCT.[78]

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

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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.[79] In this trial, patients (n = 53) received carfilzomib with lenalidomide and low-dose dexamethasone. After 4 cycles, hematopoietic cells were collected from eligible patients.[79] Out of 35 patients from whom hematopoietic cells were collected, 7 proceeded to transplantation, and the remainder continued with carfilzomib/lenalidomide/dexamethasone.[79] With a 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%).[79]

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.[80] 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%).[80] This study also accessed MRD. The PFS was found to be longer in patients with negative MRD.[81]

Another phase II study examined patients (n = 76) with newly diagnosed MM who received carfilzomib/lenalidomide/dexamethasone primary therapy followed by HCT. The primary endpoint of sCR after 8 cycles of therapy was met, with a 60% sCR rate in the overall population. In a median follow-up of 56 months, median PFS and OS were not reached. The estimated 5-year PFS rate was 72%, and the estimated 5-year OS rate was 84% in the intention to treat population. Adverse events of grade 3 to 4 included neutropenia (34%), lymphopenia (32%), infection (22%), and cardiac events (3%).[82]

The results of the phase III ENDURANCE trial[77] 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.[77] Based on the data from the above studies, the NCCN Panel has included the carfilzomib/lenalidomide/dexamethasone regimen as a preferred option for primary treatment of transplant-eligible patients with MM.

The NCCN Panel has included in a footnote that ixazomib may be substituted for carfilzomib in select patients receiving the carfilzomib/lenalidomide/dexamethasone regimen. The data from this comes from the phase III TOURMALINE-MM2 trial, which evaluated the addition of ixazomib to lenalidomide and dexamethasone versus lenalidomide/dexamethasone plus placebo in newly diagnosed MM patients not eligible for autologous HCT.[83] Higher rates of CR were reported with the addition of ixazomib to lenalidomide/dexamethasone (26% vs. 14%; OR, 2.10; $P < .001$). The median TTP was longer in the ixazomib arm (45.8 months vs. 26.8 months; HR, 0.738).[83] The primary endpoint was PFS, and median PFS was increased by 13.5 months with the addition

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of ixazomib (35.3 months vs. 21.8 months; HR, 0.830; *P* = .073).[83] This trial, however, did not meet its pre-specified primary endpoint of improved PFS as the data did not meet the threshold for statistical significance.[84]

Other Recommended Primary Therapy Regimens for Newly Diagnosed Transplant Candidates

Daratumumab/Lenalidomide/Bortezomib/Dexamethasone

The benefit of adding a fourth drug for the primary treatment of transplant-eligible patients is emerging. In the phase II 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.[85] The sCR rate after autologous HCT and consolidation with the 4-drug regimen was 42% versus 32% with the 3-drug regimen.[85] Follow-up after a median of 22 months showed further improved sCR rates for the daratumumab-containing 4-drug regimen (62.6% vs. 45.4%; *P* = .0177).[85] Although the hematologic toxicities were higher with the 4-drug regimen, no major safety concerns were reported in the study.[85]

Subsequent analysis showed that the benefit persisted after longer follow-up. After 24 months, the rate of sCR was 66% for the daratumumab-containing 4-drug regimen compared with 47% for bortezomib/lenalidomide/dexamethasone (*P* = .0096). In those who received the 4-drug regimen, the MRD-negative status for ≥12 months was seen in 44% vs.12.6% with the 3-drug combination (*P* < .0001). [86]

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

Regimens Useful In Certain Circumstances for Newly Diagnosed Transplant Candidates

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.[74,87,88] 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.[87] 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%).[87] 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).[89]

Analysis of the German DSMM XIa study also demonstrated high responses with CyBorD as primary treatment (ORR was 84%, with a 71.5% PR rate and 12.5% CR rate). High response rates were seen in patients with unfavorable cytogenetics.[88]

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%.[74]

Based on data from these and other phase II studies, the NCCN Multiple Myeloma Panel has now included the combination of bortezomib/cyclophosphamide/dexamethasone to the list of primary treatment available for transplant candidates. This is designated as a regimen that may be useful in certain circumstances, including in patients with acute renal insufficiency or those who do not have access to bortezomib/lenalidomide/dexamethasone. According to the NCCN Panel,

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one can consider switching to bortezomib/lenalidomide/dexamethasone after renal function improves.

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.[90] No unexpected toxicities occurred, and del(13q) did not have a significant impact on response. Response rates improved with bortezomib maintenance (34% vs. 49%; $P < .001$).[90] 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; $P = .002$).[90] 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 myeloma 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.[90] 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.[90]

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 regimen that may be useful in certain circumstances 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.[91,92] 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; $P = .5$).[93]

Consistent with the above results, a phase Ib study, CHAMPION-2, evaluated the safety and tolerability of twice-weekly carfilzomib (three 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.[94]

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. The panel

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notes carfilzomib may be substituted with ixazomib in select patients. A multicenter, phase II trial investigated the efficacy and toxicity of ixazomib, cyclophosphamide and low-dose dexamethasone as induction, followed by single-agent ixazomib maintenance, in older, transplant-ineligible, newly diagnosed patients.[95] 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.[95]

Daratumumab/Bortezomib/Thalidomide/Dexamethasone

In the CASSIOPEIA trial, patients with newly diagnosed MM (n = 1085) were first randomly assigned to receive induction with 4 cycles of bortezomib/thalidomide/dexamethasone with or without daratumumab, followed by autologous HCT plus 2 cycles of consolidation with the induction regimen.[96] The primary endpoint of the first part of this trial was assessment of response 100 days after transplantation.

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

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 the CASSIOPEIA trial and FDA approval for this indication.

Daratumumab/Carfilzomib/Lenalidomide/Dexamethasone

A non-randomized clinical trial (n = 41) examined adding daratumumab to the 3-drug combination regimen of carfilzomib/lenalidomide/dexamethasone without HCT. The primary endpoint of MRD rate was achieved in 71% of patients, with a PFS rate of 98% and an OS rate of 100% at a median of 11 months follow-up. The most common grade 3/4 adverse events included neutropenia (27%), rash (9%), lung infection (7%), and increased alanine aminotransferase levels (4%).[97]

The phase II MASTER trial studied daratumumab, carfilzomib, lenalidomide, and dexamethasone in newly diagnosed MM and used MRD status by NGS to determine whether additional consolidation with the induction regimen after autologous HCT is needed, depending on whether the subject had two consecutive MRD-negative results at a level of 10^{-5}.

At a median follow-up of 25 months, 80% of the overall population reached MRD negativity, with a PFS of 87%. The most common serious adverse events included pneumonia and venous thromboembolism.[98]
The NCCN Panel has included daratumumab/carfilzomib/lenalidomide/dexamethasone as a primary therapy option for transplant-eligible patients with MM under the category useful in certain circumstances (category 2A) based on the above data.

Daratumumab/Bortezomib/Cyclophosphamide/Dexamethasone

Patients with MM (n = 101) including newly diagnosed patients (*n* = 87) and patients with relapsed MM (*n* = 14) received daratumumab/bortezomib/cyclophosphamide/dexamethasone.[99] In newly diagnosed patients, after 4 cycles of induction therapy, VGPR or better was seen in 44.2% and the ORR observed was 79.1%.[99] 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%).[99] Efficacy was also observed in patients with relapsed MM.

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Based on the above results, NCCN Panel has included daratumumab/bortezomib/cyclophosphamide/dexamethasone for newly diagnosed patients with MM (transplant eligible and ineligible patients) as an option under 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.[100] 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.

Isatuximab/Bortezomib/Lenalidomide/Dexamethasone

The GMMG-HD7 evaluated the benefit of the addition of isatuximab to bortezomib/lenalidomide/dexamethasone. The study randomized patients (n = 662) to receive bortezomib/lenalidomide/dexamethasone or isatuximab/bortezomib/lenalidomide/dexamethasone.[101] With respect to MRD negativity, the percentage of patients achieving the MRD-negative status at the end of induction was higher with the addition of isatuximab (50.1% vs. 35.6%; OR, 1.83; 95% CI, 1.34–2.51; $P < .001$). The rates of VGPR or better were also significantly higher with the addition of isatuximab (60.5% vs. 77.3%; $P < .001$) and overall adverse events and serious adverse events reported were similar between the arms.[101]

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, 3-drug regimens are preferred by the NCCN Panel as these regimens have been shown to induce higher response rates and depth of response in clinical trials. The 2-drug regimens are reserved for older and/or frail patients. The list of preferred options for non-transplant candidates includes: bortezomib/lenalidomide/dexamethasone and daratumumab/lenalidomide/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.[72]

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.[75,76]

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 orally on days 1–21; bortezomib 1.3 mg/m^2 subcutaneously on 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.[102]

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The NCCN Panel included the bortezomib/lenalidomide/dexamethasone regimen as a category 1, preferred option for patients with MM not eligible for HCT, as well as the VRD-lite regimen as an option useful in certain circumstances for patients who are frail and not eligible for HCT.

Daratumumab/Lenalidomide/Dexamethasone

In transplant-ineligible patients (n = 737) with newly diagnosed MM, a phase III trial (MAIA) compared daratumumab/lenalidomide/dexamethasone to lenalidomide/dexamethasone. The addition of daratumumab to lenalidomide/dexamethasone resulted in median PFS not being reached at a median follow-up of 56.2 months compared to a median PFS of 34.4 months in the control group (HR, 0.68; $P < .0001$). The rates of several adverse events were higher in the daratumumab group compared to the control group, including neutropenia (54% vs. 37%), pneumonia (19% vs. 11%), and lymphopenia (16% vs. 11%). Treatment-related deaths occurred in 4% of patients in the daratumumab group and 3% of patients in the control group. Based on the results of this study the FDA has approved the use of daratumumab/lenalidomide/dexamethasone in this setting.[103]

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

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

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.[104] 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.

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.[79] An updated follow-up analysis of the subset of 23 older 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%.[105]

The phase II trial by Korde et al[81] 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, and the regimen was found to be effective in individuals with high-risk disease.[81]

Based on the above phase II studies that did not exclude transplant-ineligible patients, the NCCN Panel has included carfilzomib/

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

The panel has noted in a footnote that ixazomib may be substituted for carfilzomib in select patients. The evidence for this comes from a phase I/II study (discussed in the previous section for HCT-eligible candidates) that 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.[106] 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.

Daratumumab/Bortezomib/Cyclophosphamide/Dexamethasone
Based on the results of the LYRA study (described above),[99] the NCCN Panel has included daratumumab/bortezomib/cyclophosphamide/dexamethasone as a treatment option for non-transplant settings.

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

Lenalidomide/Low-Dose Dexamethasone
The results of the SWOG SO232 trial[107] that included transplant-ineligible patients and the ECOG E4A03 trial[108] that included older 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.[108] The inferior survival outcome seen with high-dose dexamethasone was greatest in patients aged ≥65 years. At 2 years, patients who did not proceed to transplant had an OS rate of 91% with lenalidomide and low-dose dexamethasone.[108]

The international, multicenter trial (FIRST trial) evaluated efficacy and safety of lenalidomide/dexamethasone given continuously for 72 weeks with melphalan/prednisone/thalidomide (MPT) in older (n = 1623) transplantation-ineligible patients with newly diagnosed MM.[109] 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; $P < .001$).[109] 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; $P = .02$).[109]

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.[110-113] 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.[109] 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.[114]

Lenalidomide/low-dose dexamethasone is considered an option useful in certain circumstances (category 1) by the NCCN Multiple Myeloma Panel

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for transplant-ineligible patients with MM. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Based on the results of the FIRST trial,[109,115] the NCCN Panel recommends considering treatment with continuous lenalidomide/dexamethasone until disease progression for patients who are not eligible for transplant.

Lenalidomide/Cyclophosphamide/Dsexamethasone

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).[116]

[117]The Myeloma XI trial compared responses to cyclophosphamide/lenalidomide/dexamethasone with cyclophosphamide/thalidomide/dexamethasone.[118] The results reported that the combination of cyclophosphamide/lenalidomide/dexamethasone was associated with significantly longer PFS (median 36 vs. 33 months, *P* = .0116) and OS at 3 years (82.9% vs. 77.0%, *P* = .0072). [118]

The NCCN Panel included lenalidomide/cyclophosphamide/dexamethasone as a primary therapy option for patients with MM who are not eligible for transplant under the category useful in certain circumstances (category 2A).

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 older patients with MM ineligible for HCT.[119] 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.[120] After a median follow-up of 42.7 months, the median PFS and OS were not significantly different between the three treatment arms.[119] Response rates, including CR and greater than or equal to 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, older 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.

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).[121] 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%).[121]

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Based on the above *and* the results from the EVOLUTION trial[74] (described earlier) that had included transplant-ineligible patients and the above phase II trial results,[121] the NCCN Panel has included bortezomib/cyclophosphamide/dexamethasone as an option useful in certain circumstances for non-transplant candidates. This option may be considered especially in patients with acute renal insufficiency or for patients who have no access to a PI in combination with lenalidomide/dexamethasone. According to the NCCN Panel, one can consider switching to PI/lenalidomide/dexamethasone after renal function improves.

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.[91] Out of 55 patients, 52 (95%) had at least a PR, 39 of 55 (71%) patients had at least a VGPR, 27 of 55 (49%) patients had a near CR or CR, and 11 of 55 (20%) patients had an sCR. After a median follow-up of 18 months, the 2-year PFS and OS rates were 76% and 87%, respectively.[91] 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 useful in certain circumstances for treatment of patients with newly diagnosed MM not eligible for HCT with renal insufficiency and/or peripheral neuropathy.

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[8,122,123] for CR, sCR, 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 updated to include measures of MRD assessments. It is recommended that the IMWG uniform response criteria should be used in all clinical trials.[124] According to the NCCN Panel, response should be assessed using the IMWG criteria.[8]

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, blood glucose, electrolytes, and metabolic panel.

Assessing changes in levels of various proteins, particularly the M protein, helps track disease progression and response to treatment. SPEP is used to track for quantitative immunoglobulins and 24-hour urine UPEP helps track total protein.

The FLCr is required for documenting sCR according to the IMWG Uniform Response Criteria.[8] 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.

Bone marrow aspirate and biopsy with FISH should be performed as clinically indicated, especially at relapse.

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Follow-up with advanced whole-body imaging (ie, FDG-PET/CT, low-dose CT, 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.[125-128] Zamagni et al reported PFS of 44 months in patients with residual focal lesions on FDG-PET/CT versus 84 months for those without residual focal lesions on FDG-PET/CT after systemic treatment (P = .0009).[127] In the IMAJEM trial, both PFS and OS were significantly better in patients with negative FDG-PET/CT results before initiation of maintenance therapy (P = .011 and P = .033, respectively).[128] An analysis by Walker et al showed that conventional MRI normalizes over a prolonged period of time making FDG-PET/CT superior in this regard.[125] 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.[129-131] Furthermore, unlike FDG-PET/CT, MRI does not expose the patient to radiation.

A meta-analysis of 14 studies has shown that MRD negativity predicts improved PFS and OS, including in those who achieved CR.[132] Therefore, the NCCN Panel recommends consideration of MRD testing as indicated for prognostication after shared decision-making.

Hematopoietic Cell Transplantation

The NCCN Panel recommends considering harvesting peripheral blood hematopoietic stem cells prior to prolonged exposure to lenalidomide and/or daratumumab (ie, optimally 4 or fewer induction cycles) 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, boost after cellular therapy, 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.

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 HCT 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.[133] 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).[134]

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Barlogie and colleagues reported on the results of an American trial that randomized 510 patients to receive high-dose therapy with autologous HCT or standard therapy.[135] 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.[136]

Another trial included 190 patients 55 to 65 years of age randomized to standard or high-dose therapy.[137] 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.[138] 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).[138]

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*).[139] 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.[139] 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.[139] Also, PFS was also significantly longer in patients achieving greater than or equal to VGPR after primary treatment than in patients achieving less than VGPR (median 36 vs. 29.7 months).[139]

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.[140] 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 VGPR of 62% (vs. 31%). After HCT, improved incremental responses were still seen with bortezomib/dexamethasone/thalidomide compared with thalidomide plus dexamethasone.[140] 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.[141] The reported CR rate was 48% in the group that received induction therapy alone

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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).[141] 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.[141] 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.[141] 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.[142] 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.[137,143-145] 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[143] 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.[146] Also, post-relapse survival was longer when EFS was sustained for at least 3.5 years after tandem transplantation.[146-147] 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.[148] In another more recent study, after initial HCT patients were

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randomly assigned to receive a second HCT followed by lenalidomide maintenance; or 4 cycles of bortezomib, lenalidomide, and dexamethasone followed by lenalidomide maintenance; or lenalidomide maintenance alone.[149] At 38 months, all three arms showed similar PFS and OS.[149]

The NCCN Multiple Myeloma Panel recommends collecting enough hematopoietic stem cells for at least one HCT in *all* eligible patients, and for two transplants in the younger patients if tandem transplant or repeat 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,[138] which addressed the role of maintenance therapy with lenalidomide after autologous transplantation.[138] 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.[138]

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.[150] Similar to previously published smaller studies,[151-153] 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.[153,154]

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.[155] The patients included in the study were >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.[155] 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.[155] Median OS in the HCT group was 67 months versus 52 months in the cyclophosphamide maintenance group.[156]

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.[157-161] Data from retrospective

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studies[162-165] 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 et al reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured.[166] Other reviews have also reported increased morbidity without convincing proof of improved survival.[167,168] However, there are intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.[135] 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[169-176] 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. MRD assessment is indicated for prognostication. Studies have shown that MRD negativity after autologous HCT translates to significantly improved PFS and OS rates.[177-179] 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.[180] The NCCN Panel recommends assessing for MRD during follow-up as indicated prognostication after shared decision-making with patient.[124]

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.

Maintenance Therapy: Preferred Regimen

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Lenalidomide as Maintenance

Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in two independent randomized phase III studies.[110,111]

In the CALGB 100104 trial, patients were randomized to maintenance therapy with lenalidomide (n = 231) versus placebo (n = 229) after autologous HCT.[111] 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%).[111]

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%, $P < .001$).[110] 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).[110] 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; $P < .0001$).[181] 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%).[181]

The study by Palumbo et al[138] (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.[138]

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.[182] 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.

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A report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option after mini-allogeneic HCT.[183] 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.[184]

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.[185] 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.[185] In the FIRST trial, use of lenalidomide indefinitely until progression was associated with a superior PFS compared with a fixed duration of 18 months.

The GMMG-MM5 trial (n = 502) examined maintenance therapy with lenalidomide following induction therapy and HCT in newly diagnosed MM patients. Patients received lenalidomide for a fixed duration of 2 years or until either CR. The primary endpoint was PFS, which was not significantly different between arms after a median follow-up of 60.1 months. Higher OS was seen with lenalidomide given for 2 years than for lenalidomide given until CR (HR, 1.42; 95% CI, 1.04–1.93; *P*= .03). Serious adverse events were more common in the group that received lenalidomide for 2 years versus until CR (77.6% vs. 58.2%) and included infections, cardiac disorders, neuropathy, and thromboembolic events.[186]

Based on the evidence from the phase III trials,[110,111,185] the NCCN Multiple Myeloma Panel lists single-agent lenalidomide as one of the preferred maintenance regimens (category1) for both transplant-eligible and transplant-ineligible patients. Lenalidomide lacks the neurologic toxicity seen with thalidomide. However, there seems to be an increased risk for secondary cancers, especially post-transplantation,[110-112] or after a melphalan-containing regimen.[113] 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.[109]

A meta-analysis of randomized controlled trials examined patients treated with lenalidomide maintenance versus patients with no maintenance or placebo in the transplant setting.[182] The analysis showed that patients treated with lenalidomide maintenance had significantly improved PFS (HR, 0.48; 95% CI, 0.41–0.55) and a trend toward OS with lenalidomide maintenance (HR, 0.75; 95% CI, 0.63–0.90; *P* = .001) versus no maintenance or placebo. [182]

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.[187] The NCCN Panel notes that the benefits and risks of maintenance therapy with lenalidomide versus secondary cancers should be discussed with patients.

Other Recommended Regimen for Maintenance Therapy

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.[90] 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

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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[90] (see *Preferred Primary Therapy Regimens for Newly Diagnosed 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.[188] There was no difference in PFS in patients with greater than or equal to VGPR after autologous HCT.

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.[119] 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 greater than or equal to VGPR, improved after bortezomib maintenance in all arms, with no concomitant increase in the incidence of peripheral neuropathy.[119]

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

Maintenance Regimens Useful in Certain Circumstances

Bortezomib/Lenalidomide

Patients with high-risk cytogenetics have been shown to benefit from a combination of PI and IMiD as maintenance therapy.[189,190] The study by Joseph et al of patients (n = 1000) with newly diagnosed MM treated with lenalidomide, bortezomib, and dexamethasone induction therapy and risk-adapted maintenance showed that early transplantation and maintenance with doublet therapy (lenalidomide plus bortezomib) improves outcomes for those with high-risk myeloma.[190]

Carfilzomib/Lenalidomide as Maintenance

Patients enrolled in the FORTE trial (described above) were randomized to receive carfilzomib/lenalidomide maintenance therapy or lenalidomide alone as maintenance therapy.[191] After a median duration of follow-up of 37 months, 3-year PFS was 75% in the carfilzomib/lenalidomide group versus 65% in the lenalidomide alone group (HR, 0.64; 95% CI, 0.44–0.94; *P* = .023). Most common grade 3–4 adverse events in the carfilzomib/lenalidomide group versus the lenalidomide group included neutropenia (20% vs. 23%), infections (5% vs. 7%), and vascular events (7% vs. 1%), with one treatment-related adverse event leading to death in the carfilzomib/lenalidomide group.[191]

The NCCN Panel has included carfilzomib/lenalidomide maintenance therapy as an option useful in certain circumstances for transplant-eligible candidates.

Daratumumab with or without Lenalidomide as Maintenance Therapy After Autologous HCT

The second randomization of the CASSIOPEIA trial (results of first randomization described above) compared daratumumab maintenance for up to 2 years with observation following primary therapy with bortezomib/thalidomide/dexamethasone in transplant-eligible patients with

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newly diagnosed MM.[192] At a median follow-up of 35.4 months from the second randomization, the primary endpoint of PFS was not reached in the daratumumab versus 46.7 months in the observation-only group (HR 0.53; 95% CI, 0.42–0.68; *P* < .0001). The most common grade 3 or 4 adverse events in the daratumumab maintenance group included lymphopenia (4%), hypertension (3%), and neutropenia (2%). Serious adverse events were more common in the daratumumab group (23% vs. 19%), with two treatment-related deaths in the daratumumab group. [192]

In the randomized, phase II GRIFFIN study described in a section above, daratumumab in combination with lenalidomide, bortezomib, and dexamethasone, followed by maintenance therapy with daratumumab and lenalidomide was compared to lenalidomide, bortezomib, and dexamethasone followed by maintenance therapy with lenalidomide alone, in newly diagnosed, transplant-eligible patients with MM. The addition of daratumumab to primary therapy, followed by daratumumab/lenalidomide maintenance therapy, led to deep and durable responses including high rates of sCR and MRD negativity.[86]

The NCCN Panel has added daratumumab alone (based on the CASSIOPEIA trial data) and daratumumab with lenalidomide maintenance therapy (based on the GRIFFIN trial data) as options useful in certain circumstances after autologous HCT.

Ixazomib as Maintenance Therapy After Autologous HCT

The TOURMALINE-MM3 trial studied 2 years of maintenance with ixazomib versus placebo in patients who had achieved at least a PR following induction therapy and a single autologous HCT. After a median follow-up of 31 months, a 28% reduction in median PFS was observed with ixazomib versus placebo (median PFS was 26.5 months vs. 21.3 months; HR, 0.72; 95% CI, 0.58–0.89; *P* = .0023).[193] A subsequent analysis of the same study demonstrated a higher rate of deepening responses with ixazomib versus placebo maintenance therefore prolonging PFS.[194] The median PFS in patients with VGPR/PR was 26.2 with ixazomib maintenance versus 18.5 months with placebo (HR, 0.636; *P* < .001).[194]

The TOURMALINE-MM4 trial is similar to TOURMALINE-MM3, but examined patients who were not receiving transplant. The study randomized patients who were not undergoing transplant and had achieved at least a PR following standard induction therapy to receive either ixazomib maintenance therapy or placebo. The primary endpoint was PFS since time of randomization. The primary endpoint was met, with a median PFS of 17.4 months in the ixazomib group versus 9.4 months in the placebo group (HR, 0.659; 95% CI, 0.542–0.801; *P* < .001). Grade 3 treatment-related adverse events were more common with ixazomib (36.6%) than placebo (23.2%). The most common any grade adverse events included nausea, vomiting, and diarrhea.[195] While both TOURMALINE-MM3 and TOURMALINE-MM4 have demonstrated statistically significant improvement in PFS, the OS data for MM3 and MM4 have not demonstrated a statistically significant difference.[196]

Based on the above data, the NCCN Panel has included ixazomib as a category 2B recommendation useful in certain circumstances maintenance option for both transplant-eligible and transplant-ineligible patients.

Therapy for Previously Treated Multiple Myeloma

A variety of therapies are available for previously treated or relapsed/refractory MM. The choice of appropriate therapy for a specific patient depends on the context of clinical relapse such as prior treatment and duration of response.

The therapeutic options for previously treated MM include systemic therapy; autologous hematopoietic cell transplant (HCT) for eligible

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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 stable disease, consideration may be given to a second transplantation at the time of relapse/disease progression. As a general principle, 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. This however does not apply to HCT where a longer remission would be needed to justify another transplant.

Preferred Regimens for Previously Treated Multiple Myeloma – After One to Three Prior Therapies

For patients that are still sensitive to bortezomib and/or lenalidomide, any of the regimens listed below may be appropriate. Since, however, bortezomib-containing or lenalidomide-containing regimens are often given as induction therapy, and it is likely that at relapse the disease is refractory to these agents, especially if relapse is well within 6 months of primary treatment completion other combinations are preferred.

The NCCN Panel has provided a list of regimens for bortezomib-refractory and lenalidomide-refractory disease after one to three prior therapies.

Preferred Regimens for Bortezomib or Lenalidomide-Refractory Disease

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 overall response rate (ORR) was 84%. In the overall treatment population, while the median progression free survival (PFS) was not reached, the 12-month and 18-month PFS rates were 74% and 66%, respectively.[197] In a multicenter, open-label phase 3 trial (CANDOR), the addition of daratumumab to carfilzomib plus dexamethasone showed deeper responses and improved PFS.[198] This response has been shown to be maintained with longer follow up analyses of about 27 months. PFS was 28.6 months in the daratumumab group versus 15.2 months in the carfilzomib alone group (Hazard ratio (HR) HR, 0.59; 95 CI, 0.45–0.78; $P < .0001$).[199] Based on the above data and the FDA approval, the NCCN Panel has included this regimen as a category 1, preferred option for relapsed/refractory MM, for patients with relapsed or refractory MM.

Isatuximab-irfc/Carfilzomib/Dexamethasone

A prospective, randomized, open label, phase 3 study (IKEMA) examined the utility of isatuximab/carfilzomib/dexamethasone vs carfilzomib/dexamethasone in 302 patients with relapsed/refractory MM who had received one to three prior lines of therapy (median two prior lines of therapy). Treatment was continued until disease progression or unacceptable toxicity, with the primary endpoint being PFS. Median PFS was 35.7 months in the isatuximab/carfilzomib/dexamethasone group vs a median PFS of 19.15 months in the carfilzomib/dexamethasone group (HR 0.53; 99% CI, 0.32-0.89, $P = .0007$). Grade 3 or higher treatment related adverse events occurred in 77% of patients in the isatuximab group vs 67% of patients in the control group. [200] Based on this data, the NCCN Panel has included isatuximab-irfc/carfilzomib/dexamethasone as a category 1, preferred regimen option for relapsed or refractory MM.

Carfilzomib/Pomalidomide/Dexamethasone

A phase II trial investigated carfilzomib/pomalidomide/dexamethasone followed by continuous pomalidomide/dexamethasone as second line therapy for relapsed/refractory MM in patients who had progression during lenalidomide maintenance therapy. Patients who were eligible for transplant and had not received it previously received HCT. On this regimen, 75% of patients had a VGPR, and 37% displayed CR. At 40-months of follow up, the median PFS was 26 months for patients who

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received therapy with HCT, and 17 months for patients who received carfilzomib/pomalidomide/dexamethasone therapy without HCT. The median OS was 67 months, with the most common grade 3 and 4 adverse events related to treatment including hematologic toxicity (41%), cardiovascular (6%) and respiratory (3%) events, and infections (17%).[201] Based on these data, the NCCN Panel has included carfilzomib/pomalidomide/dexamethasone as a preferred regimen option for relapsed or 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).[202] At a median follow-up of 13.1 months, the ORR was 60%. The median PFS and OS were 8.8 and 17.5 months, respectively, and estimated survival at 1 year was 66%.[202] Toxicities reported were similar to those seen in other trials of pomalidomide and daratumumab, except for increase in neutropenia.[202]

The open label phase III APOLLO trial randomly assigned patients with relapsed/refractory disease and at least one previous line of therapy (n=304) to receive pomalidomide/dexamethasone or daratumumab/pomalidomide/dexamethasone. With a median follow up time of 16.9 months, there was a statistically significant improvement in the primary endpoint of PFS for the added daratumumab group (12.4 months vs 6.9 months, *P* = .0018). Serious adverse events occurred in 50% of patients in the daratumumab group compared to 39% of patients in the pomalidomide/dexamethasone group, the most common being pneumonia and lower respiratory tract infections.[203]

The MM-014 study evaluated 112 patients with relapsed/refractory MM who had previously been treated with lenalidomide and assigned them to a regimen containing daratumumab/pomalidomide/dexamethasone. The primary endpoint was ORR which was achieved in 77.7% of patients in a median follow up of 17.2 months (median PFS was not reached at time of follow up). The most common adverse event of grade 3 or higher was infection, which developed in 31.3% of patients (13.4% with grade 3 or higher pneumonia).[204]

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 one prior therapy including an IMiD and a PI.

Isatuximab-irfc/pomalidomide/dexamethasone

In an open-label, multicenter, phase III 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.[205] 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) were 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.[206]

The NCCN Panel has included isatuximab-irfc/pomalidomide/dexamethasone as a category 1, preferred option for the treatment of patients with relapsed/refractory MM after two prior therapies including lenalidomide and a PI.

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Ixazomib/Pomalidomide/Dexamethasone

In the phase I/II Alliance A061202 study (n=29), patients with lenalidomide/PI refractory MM were treated with ixazomib/pomalidomide/dexamethasone- with 51.7% of patients having a PR or better, a median PFS of 4.4 months, a median response duration of 16.8 months, and a median OS of 34.3 months. Common adverse events included hematologic toxicity, and gastrointestinal events.[207]

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.[208] The ORR was 33% and 40% with two different doses of ixazomib.[208]

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.

Additional Preferred Regimens for Bortezomib-Refractory Disease:

In addition to the regimens listed in the section above, the following two lenalidomide-containing regimens may be used for lenalidomide-sensitive or naïve and bortezomib-refractory disease.

Daratumumab/Lenalidomide/Dexamethasone

In a multicenter, open-label phase 3 trial (POLLUX), patients (n= 569) with relapsed/refractory MM were randomized to receive lenalidomide/dexamethasone with or without daratumumab until disease progression or unacceptable toxicity.[209]

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% vs. 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 had received daratumumab.[209]

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 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 (PFS 16.7 vs. 7.1 months; HR, 0.31; 95%; CI, 0.25-0.40; $P < .0001$). In a subgroup of patients with one prior line of therapy, the median PFS was 27.0 months with daratumumab versus 7.9 months with daratumumab 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 the daratumumab-regimen was 92% compared with 74% in those receiving daratumumab/dexamethasone.[210]

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

The randomized, multicenter, phase III ASPIRE trial, studied the combination of lenalidomide and dexamethasone with or without carfilzomib in patients (n=792) with relapsed/refractory MM who had

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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 alone.[211]

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.

Additional Preferred Regimens for Lenalidomide refractory Disease

In addition to the regimens listed in the section for bortezomib- and lenalidomide refractory disease, the following bortezomib-containing regimens may be used for bortezomib-sensitive or naïve and lenalidomide-refractory disease.

Daratumumab/Bortezomib/Dexamethasone

A phase III trial showed that adding daratumumab to bortezomib and dexamethasone markedly improved outcomes for patients with recurrent/refractory MM.[212] 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).[212] 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%).[212] 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).[212] 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.[213,214]

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).[215] Patients who received one 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.

Pomalidomide/Bortezomib/Dexamethasone

A phase 3 open-label, multicenter, randomized, trial (OPTIMISMM) evaluated pomalidomide/bortezomib/dexamethasone (n=281) versus bortezomib/dexamethasone in patients (n= 278) with relapsed or refractory MM who previously received lenalidomide.[216] 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

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treatment-related adverse events in the pomalidomide arm reported in this trial were neutropenia, infections, and thrombocytopenia.[216] A post-hoc subgroup analysis of the OPTIMISSM trial evaluated outcomes in 226 patients at first relapse that had only received one prior line of therapy. Analyses were conducted by lenalidomide-refractory status, prior bortezomib exposure, and prior HCT. There were statistically significant improvements in PFS in both lenalidomide refractory (17.8 vs 9.5 months, *P* = .0276) and lenalidomide non-refractory (22.0 vs 12.0 months, *P* = .0491) patients. There were also statistically significant improvements in PFS in patients who had received prior bortezomib (17.8 vs. 12 months), and patients with (22 vs. 13.8 months) and without (16.5 vs 9.5 months) prior HCT. [217]

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

Selinexor/Bortezomib/Dexamethasone

An ongoing phase 3, randomized open label trial (BOSTON) compared selinexor/bortezomib/dexamethasone with bortezomib/dexamethasone in patients with previously treated MM (one to three prior lines of therapy, including PIs). Four hundred two patients were randomized to the selinexor/bortezomib/dexamethasone and 206 to the bortezomib/dexamethasone group. After a median follow up duration of 13.2 months in the selinexor/bortezomib/dexamethasone group, the median PFS was 13.93 months compared to a median follow up duration of 16.5 months and median PFS of 9.46 months in the bortezomib/dexamethasone group (HR 0.70; 95% CI, 0.53 – 0.93; *P*=.0075). The most frequent adverse events of grade 3-4 that were more common in the selinexor/bortezomib/dexamethasone group were thrombocytopenia (39% vs. 17%), fatigue (13% vs 1%), and anemia (16% vs 10%).[218]

Based on the above data the NCCN Panel has included once weekly selinexor in combination with bortezomib and dexamethasone as a category 1, other recommended regimen 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 elotuzumab/pomalidomide/dexamethasone.[219] 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%).[219] Median OS was also significantly improved with elotuzumab/pomalidomide/dexamethasone compared with pomalidomide/dexamethasone (29.8 months vs. 17.4 months; HR 0.59 (95% CI, 0.37 to 0.93; *P* = .0217).[220]

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.

Preferred CAR T-Cell Therapies for Relapse After One to Three Prior Therapies

Update to this section is in progress.

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Other Recommended Regimens for Relapse After One to Three Prior Therapies

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; $P < .0001$).[221] 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. The 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.[221]

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]; $P = .010$).[222] 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%).[222] Rates of thrombocytopenia, pneumonia, and fatigue were similar in both groups.[222]

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.

Elotuzumab/Lenalidomide/Dexamethasone

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.[223]

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).[223] 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.[223] 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.[223]

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.[224]

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 one to three prior lines of therapy (48.3 months vs. 39.6 months).[225]

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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.

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. See nccn.org*).[106]

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).[226] 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).[226] 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%).[226] 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[226] the NCCN Panel has included ixazomib/lenalidomide/dexamethasone as a category 1, preferred regimen option for previously treated MM after one to three prior therapies.

Bortezomib/Cyclophosphamide/Dexamethasone

The effects of adding 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.[227,228] The NCCN Multiple Myeloma Panel members have included bortezomib/cyclophosphamide/dexamethasone as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

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.[229,230] 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).[230] The NCCN Multiple Myeloma Panel members have included bortezomib/lenalidomide/dexamethasone as other recommended regimen for relapsed/refractory MM after one to three prior therapies.

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Carfilzomib/Cyclophosphamide/Dexamethasone

Carfilzomib/cyclophosphamide/dexamethasone has been shown to be well tolerated with the toxicity profile of carfilzomib being similar to that seen in other trials.[231]

A phase II trial (MUKfive) compared the safety and toxicity of carfilzomib/cyclophosphamide/dexamethasone with bortezomib/cyclophosphamide/dexamethasone in patients with relapsed/refractory MM, who had received one prior regimen.[231] A higher proportion of patients receiving carfilzomib achieved VGPR or better and was non-inferior to bortezomib. Carfilzomib/cyclophosphamide/dexamethasone was well tolerated with the toxicity profile of carfilzomib being similar to that seen in other trials.[231] This study also included a maintenance phase and demonstrated a median PFS of 11.9 versus 5.6 months in favor of carfilzomib maintenance versus observation.

Another phase II trial compared treatment with cyclophosphamide plus carfilzomib and dexamethasone to treatment with carfilzomib and dexamethasone in patients (n=197) with relapsed/refractory MM after one to three prior lines.[232] After a median follow-up of 37 months, median PFS was 19.1 with the 3-drug regimen compared to 16.6 months with the 2-drug regimen (*P*= .577).[232] The combination of cyclophosphamide with carfilzomib and dexamethasone did not improve outcomes significantly compared with carfilzomib and dexamethasone alone in the overall population. However, in a sub-group analysis of the lenalidomide-refractory population, the addition of cyclophosphamide to carfilzomib and dexamethasone resulted in a PFS benefit of 18.4 versus 11.3 months (HR, 1.7; 95% CI, 1.1–2.7; *P* = .043).[232]

The NCCN Panel has included carfilzomib/cyclophosphamide/dexamethasone as treatment as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

Daratumumab/Cyclophosphamide/Bortezomib/Dexamethasone

In the LYRA study,[99] 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.[99] 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%).[99]

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

Elotuzumab/Bortezomib/Dexamethasone

Numerous randomized trials have shown that three-drug combinations are 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.[233]

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).[233]

Based on the above phase II trial data, the NCCN Panel has included elotuzumab/bortezomib/dexamethasone as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

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Ixazomib/cyclophosphamide/dexamethasone

This regimen has been shown to be tolerable and efficacious in newly diagnosed patients.[95,234] 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).[235] The NCCN Panel has included this all oral regimen under the list of "other recommended regimens" for relapsed/refractory MM.

Lenalidomide/Cyclophosphamide/Dexamethasone

A retrospective analysis to assess the efficacy of lenalidomide in combination with cyclophosphamide and dexamethasone showed that this regimen is effective in heavily pre-treated patients with manageable adverse effects.[236] The NCCN Panel has included cyclophosphamide/lenalidomide/dexamethasone treatment as an other recommended regimen for relapsed/refractory MM after one to three prior therapies.

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.[237]

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.[237] 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.[238] Response to the triple-drug regimen was 63%, with nearly half of patients (42%) 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.[238]

Based on the above phase II trial data, the NCCN Panel has included pomalidomide/cyclophosphamide/dexamethasone as other recommended treatment option for patients with relapsed/refractory MM who have received two prior therapies, including an IMiD and a PI and disease progression on/within 60 days of completion of last therapy.

Regimens Useful In Certain Circumstances for Previously Treated MM – Early Relapse (one to three prior therapies)

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).[239] 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 that is useful in certain circumstances for patients with relapsed/refractory MM.

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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.[240-242] The NCCN Multiple Myeloma Panel members have included the bortezomib and dexamethasone regimen as an option that is useful in certain circumstances 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.[243,244] 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.[244] Similar results were seen in the international trial MM-010.[243] 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 had undergone HCT.[243,244] 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 that is useful in certain circumstances for patients with relapsed/refractory MM.

Carfilzomib/Cyclophosphamide/Thalidomide/Dexamethasone:

The results of the phase I/II trial showed that this 4-drug regimen is efficacious with an ORR of 91%, with 59% achieving VGPR or greater after 4 cycles in patients with MM.[245] The PFS and OS at 24 months (median 17.5 months) was 76% and 96%, respectively.[245] This regimen has now been included under the list of regimens “useful in certain circumstances” for relapsed/refractory MM.

Carfilzomib (weekly)/dexamethasone

In the phase III A.R.R.O.W. trial, patients (n = 578) with relapsed and refractory MM previously treated with two or three treatments, including PI and IMiD were randomly assigned (1:1) to receive carfilzomib once a week (70 mg/m2) or twice a week (27 mg/m2). All patients received dexamethasone. The media PFS was higher in the once weekly (11.2 months) compared with those who received twice weekly carfilzomib (7. 6 months; HR 0.69, 95% CI 0.54-0.83; *P*=.0029). The overall safety was comparable between the two groups.[246] The NCCN panel has included this combination on the list of regimens “useful in certain circumstances” for relapsed/refractory MM.

Selinexor/daratumumab/dexamethasone

A phase Ib/II trial assessed the safety and efficacy of adding daratumumab to selinexor dexamethasone. Patients (n=34) enrolled in the trial had received three or more prior lines of therapy, including a PI and an IMiD. In daratumumab naïve patients, the ORR was 73%, with 11 VGPR, and 11 PR. The median PFS was 12.5 months. This regimen has been included under the list of regimens useful in certain circumstances for relapsed/refractory MM.

Selinexor/Carfilzomib/Dexamethasone

In a study of 32 patients who had received a median of four prior therapies were assigned to receive once weekly selinexor, carfilzomib, and

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dexamethasone. The ORR was 78% with a median PFS of 15 months. The most common grade 3 or higher treatment-related adverse events were thrombocytopenia (47%), nausea (6%), anemia (19%), and fatigue (9%).[247]

Another analysis of a subset of this patient population that had triple class refractory MM also showed an ORR of 66.7% with a median PFS of 13.8 months, and median OS of 33 months.[248]

This regimen has now been included under the list of regimens "useful in certain circumstances" for relapsed/refractory MM.

Venetoclax/Dexamethasone with or without Daratumumab or PI for t(11;14) Patients

A phase I study of patients (n=66) with relapsed/refractory MM who received a median of 5 prior lines of therapy studied venetoclax monotherapy and 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 t(11:14) (40% vs. 6%).[249] Similar higher response rates have been found in patients with t(11:14) in real-world experience as well.[250] An open label phase I/II study examined venetoclax/dexamethasone in heavily pretreated t(11;14) patients. In this phase II part of the study, patients had received a median of 5 prior lines of therapy. At a median follow-up of 9.2 months, the ORR was 48%, with a median TTP of 10.8 months.[251]

Several prospective trials have reported on the efficacy and tolerability of venetoclax/dexamethasone containing combination regimens in relapsed t(11;14) MM. A phase I study found that venetoclax/dexamethasone in combination with daratumumab with or without bortezomib produced high rates of durable responses in patients with relapsed or refractory MM with t(11;14) translocation.[252]

In patients with no prior treatment with carfilzomib, venetoclax/dexamethasone plus carfilzomib was found to be safe and efficacious especially in those with t(11;14) translocations.[253] This finding has been supported by case studies.[254]

The NCCN Panel had included venetoclax/dexamethasone with or without daratumumab or a PI as options for patients with t(11:14) translocation.

Pomalidomide/Dexamethasone

Pomalidomide, like lenalidomide, is an analogue of thalidomide. It possesses potent immunomodulatory and significant anti-myeloma properties.[255]

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.[256] 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; $P < .0001$).[256] 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; $P = .0285$).[256] 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.[256] 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).[257] 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

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reported were similar.[257] The results of this trial are consistent with those observed in the pivotal MM-003 trial.[256]

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.[258] 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.[258] 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).[259] 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.[259]

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 a PI, and have demonstrated disease progression on or within 60 days of completion of the last therapy (category 1).

Selinexor/Pomalidomide/Dexamethasone

An abstract presented at the 2021 ASCO Annual Meeting presented data from an ongoing phase I/II clinical trial that contains one arm evaluating the regimen of selinexor/pomalidomide/dexamethasone (NCT02343042). Sixty-five patients were enrolled initially in phase I with a median of three prior lines of therapy. After determining a recommended phase II dose, it was administered to 20 patients. Among these patients, the ORR was 65% and the median PFS was not reached in a median follow up of 3.9 months.[260] Based on the above data, the NCCN Panel has included selinexor/pomalidomide/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).

Daratumumab

Daratumumab is a human IgG kappa monoclonal antibody that targets the CD38 surface protein on myeloma cells.[213] 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). Findings from 106 patients who received 16 mg/kg noted an ORR of 29.2% in 31 patients (3 sCR, 10 VGPR, and 18 PR). The median duration of response was 7.4 months and median TTP was 3.7 months. The estimated 1-year OS rate was 65%.[214] 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.[214]

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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.

DCEP and VTD-PACE for Aggressive MM

Patients with an aggressive relapse may need multi-drug combinations such as DCEP,[261-263] TD-PACE (thalidomide, dexamethasone, cisplatin, doxorubicin, high-dose cyclophosphamide, and etoposide),[264,265] and VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide)[266-268] for effective disease control.

Preferred Regimens for Relapse After Four Prior Therapies

Currently there are three bispecific antibodies (elranatamab-bcmm, talquetamab-tgvs, and teclistamab-cqyv) and two chimeric antigen receptor (CAR) T-cell therapies (idecabtagene vicleucel and ciltacabtagene autoleucel) approved by the FDA and included as preferred options by the NCCN Panel for relapsed/refractory MM after at least four prior therapies including an anti-CD38 monoclonal antibody, a PI, and an IMiD.

Bispecific Antibodies:

Elranatamab-bcmm: Elranatamab-bcmm is a bispecific T-cell engager (BiTE) that binds CD3 on T cells and to B-cell maturation antigen (BCMA) on myeloma cells. In the phase II, MagnetisMM-3 trial, patients with relapsed/refractory MM received subcutaneous elranatamab once weekly.[269] The primary population in whom the efficacy was seen were patients (n= 123) without prior BCMA-directed therapy. The findings indicated an ORR of 61.0% (75/123) and 35.0% greater than or equal to CR. Fifty responders switched to biweekly dosing, and 40 of those (80.0%) improved or maintained their response for ≥ 6 months. Common adverse events reported were infections, cytokine release syndrome, anemia, and neutropenia. With biweekly dosing, grade 3–4 adverse events decreased from 58.6% to 46.6%.[269]

Talquetamab-tgvs: Talquetamab is a T cell redirecting bispecific antibody targeting both GPRC5D and CD3 on T cells. In the single-arm, open-label, multicenter trial, MMY1001 (MonumenTAL-1) patients (n=187) who had previously received at least four prior systemic therapies received talquetamab-tgvs subcutaneously weekly or talquetamab-tgvs biweekly until disease progression or unacceptable toxicity.[270]The most common adverse reactions reported with weekly and biweekly dosing were cytokine release syndrome (in 77% and 80% of the patients, respectively), skin-related events (in 67% and 70%), and dysgeusia (in 63% and 57%).[270]

Teclistamab-cqyv: Teclistamab-cqyv, similar to elranatamab-bcmm, is a BiTE that binds to CD3 on T cells and BCMA on myeloma cells. A phase I/II study examined the T-cell-redirecting bispecific antibody teclistamab-cqyv in 165 patients who had triple class refractory disease, with a median of five prior lines of therapy. [271] After a median follow up of 14.1 months, the ORR was 63% and 39.4% of patients demonstrated a CR or better. The median PFS was 11.3 months, with a median response duration of 18.4 months. Common adverse events included cytokine release syndrome in 72.1% of patients (0.6% grade 3) and grade 3 or 4 hematologic toxicity including neutropenia (64.2%), anemia (37%), and thrombocytopenia (21.2%). Infections were also common, with grade 3 or 4 infection occurring in 44.8% of patients.

CAR T-Cell Therapies:

Idecabtagene vicleucel: Idecabtagene vicleucel is a BCMA-directed CAR-T cell therapy. In a phase II study (n=128) patients with relapsed and refractory MM who had received at least three prior regimens (including a PI, an IMiD, and an anti-CD38 antibody) received idecabtagene vicleucel.

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Patients had received a median of 6 previous regimens for MM and 94% had received HCT. In this population of heavily pretreated patients, after a median 13 months follow up, 73% of patients demonstrated response, with 33% having a CR or better. The median time to response was 1 month and median time to a CR or better was 2.8 months. High response rates (> 50%) were found in several examined subgroups including older patients, patients with high-risk cytogenetic abnormalities, penta-refractory disease, and high tumor burden. Adverse events at grade 3 or 4 were common and included neutropenia (91%), anemia (70%), and thrombocytopenia (63%). Twenty eight patients were retreated with idecabtagene vicleucel following disease progression and 21% demonstrated a second response. Grade 3 or 4 adverse events were common and were reported in 99% of patients. The most common adverse events were related to hematologic toxicity such as neutropenia (89%), anemia (60%), and thrombocytopenia (52%). Infections (69%) and cytokine release syndrome (84%) were also common treatment related adverse events, although the incidence of grade 3 or higher cytokine release syndrome was lower (5%).[272] The NCCN Panel has included idecabtagene vicleucel as an option for patients who have received at least four prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.

Ciltacabtagene autoleucel: Ciltacabtagene autoleucel is another BCMA directed CAR T-cell therapy. The CARTITUDE-1 trial (n=97) was an open label phase Ib/II study that looked to assess the safety and efficacy of ciltacabtagene autoleucel in patients with relapsed or refractory MM who had received three or more previous lines of therapy (including an IMiD, PI, and andti-CD38 antibody).[273] The median amount of prior therapies was six. After a median 12.4 months of follow up, the ORR was 97%, with 67% of patients achieving sCR. The PFS rate was 77% with an 89% OS rate. Adverse events included neutropenia in 95% of patients and anemia in 68%. Other common adverse events included thrombocytopenia (60%), leukopenia (61%), and lymphopenia (50%). Cytokine release syndrome also occurred in 95% of patients. There were six deaths due to treatment related adverse events.[273] A follow up analysis at 18 months showed that responses were durable; 18-month PFS and OS rates were 66.0% and 80.9% respectively, with no new observed safety signals.[274]

Other Recommended Regimens for Relapse After Three Prior Therapies

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.[275] 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). The 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%.[276]

The ECOG studied treatment with high-dose cyclophosphamide in patients with poor-risk features who had disease that was refractory to prior chemotherapy.[277] The ORR reported was 43% (29% response rate in patients refractory to prior therapy with cyclophosphamide).[277] Bendamustine is currently a treatment option for relapsed/refractory MM.

Bendamustine/Bortezomib/Dexamethasone

A phase II study evaluated bendamustine/bortezomib/dexamethasone administered over six 28-day cycles and then every 56 days for 6 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).

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At 12-month follow-up, median TTP was 16.5 months, and 1-year OS was 78%.[278]

Bendamustine/carfilzomib/dexamethasone

A multicenter trial evaluated combination therapy with bendamustine/carfilzomib/and dexamethasone in 63 patients with relapsed/refractory MM (with at least two lines of prior therapy). Fifty two percent of patients achieved a PR or better and 32% achieved a VGPR or better. After a median follow up of 22 months, the median PFS was 11.6 months with a median OS of 30.4 months. The most common adverse events of grade 3 or higher included lymphopenia (29%), neutropenia (25%), and thrombocytopenia (22%).[279] The NCCN Panel has included carfilzomib in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM.

Bendamustine/Lenalidomide/Dexamethasone

A multicenter phase I/II trial investigated the combination of bendamustine, lenalidomide, and dexamethasone as treatment for patients (n = 29) with relapsed/refractory MM.[280] PR 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%).[280] The NCCN Panel has included lenalidomide in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM.

High Dose or Fractionated Cyclophosphamide

Studies have reported that high-dose cyclophosphamide or hyperfractionated cyclophosphamide is efficacious particularly in patients needing immediate disease control who have received multiple prior treatments.[281,282] Therefore the NCCN Panel has included high dose or fractionated cyclophosphamide as an option for relapsed/refractory MM.

Selinexor/Dexamethasone:

Selinexor in combination with dexamethasone was studied in a phase IIb trial (STORM) in patients with relapsed/refractory MM.[283] 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% CI, 19- 35 with sCR 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 other recommended options for patients with relapsed/refractory MM who have received at least four prior therapies and whose disease is refractory to at least two PI, at least two immunomodulatory agents, and an anti-CD38 monoclonal antibody.[247]

Regimens Useful in Certain Circumstances for Relapse After Four Prior Therapies

Belantamab Mafodotin-blmf

Belantamab mafodotin-blmf is a 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.[284] The most common grade 3/4 adverse events in the safety population were keratopathy, thrombocytopenia, and anemia.[284]

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In November 2022, it was announced that belantamab mafodotin-blmf is being withdrawn as it did not meet the primary end point of having a superior PFS compared to pomalidomide/dexamethasone in the DREAMM-3 trial (HR 1.03; 95% CI, 0.72–1.47). The PFS with belantamab mafodotin-blmf was 11.2 months compared with 7 months for pomalidomide plus dexamethasone, however this was not statistically significant. Since, patients already receiving belantamab mafodotin-blmf and those enrolled on the FDA Risk Evaluation and Mitigation Strategy (REMS) program have been able to continue to receive the drug through a compassionate use program. There are other ongoing trials with belantamab mafodotin-blmf, the NCCN Panel has included this as an option useful in certain circumstance for those after 4 prior therapies (including a PI, an IMiD, and an anti-CD38 monoclonal antibody).

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.[285,286] Zoledronic acid has equivalent benefits.[287] Results from the study conducted by Zervas et al[288] 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.[289] 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.[290] 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.[291] 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).[291]

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.[292] It did not find a particular bisphosphonate to be superior to another.[292] In a multicenter trial (CALGB 70604), patients with MM or bone metastases from a solid malignancy were randomly assigned to zoledronic acid either monthly or every 3 months for 2 years.[293] The rates of skeletal-related events (SRE) 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 3 months.[293]

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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 SRE and OS were 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.[294]

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.

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,[294] 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.[287,295,296]

The NCCN Panel has provided general principles of palliative RT for patients with MM. Careful planning of the radiation field and radiation technique is important to minimize toxicity to the spinal cord, brain, bone marrow, and adjacent organs at risk (OAR) as patients with MM may be treated multiple times during their disease course. The panel has noted that initiation of systemic therapy should not be delayed for RT and can often be given concurrently and that patients should be carefully monitored for toxicities.[297,298] Low-dose RT (8 Gy x 1 fraction) or 20–30 Gy in 5–10 total fractions can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture, or for impending cord compression. Moderately fractionated courses of 20-25 Gy in 8-10 fractions are generally preferred over higher doses (30 Gy) absent extenuating circumstances (e.g., severe symptomatic cord compression) to limit unnecessary toxicity and reduce risk of future treatment of adjacent or overlapping OAR (e.g., spinal cord).[299] For RT dose constraint suggestions regarding bone marrow and other OAR, see NCCN Guidelines for Hodgkin Lymphoma.

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.[300] 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[301,302] (see NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections). Daratumumab can interfere with cross-matching and RBC antibody screening. The NCCN Panel recommends performing type and screen prior to receiving daratumumab to inform future matching.

The highest risk for venous thromboembolism (VTE) is in the first 6 months following new diagnosis of MM. The NCCN Panel has outlined management of VTE, risk stratification, and VTE prophylaxis in a separate section in the NCCN Guidelines for Multiple Myeloma (see nccn.org) and VTE prophylaxis is administered to all patients, assuming there are no contraindications to anticoagulation agents or anti-platelets (see NCCN Guidelines for Cancer-Associated Venous Thromboembolic Disease).

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To prevent infections in patients with MM, the panel recommends referring to the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections, the CDC recommendations for CDC for Use of COVID-19 Vaccines in the US, and in the most recent update, the panel has outlined recommendations for prophylaxis and management of infections in patients undergoing treatment with CAR T-cell and bispecific antibody.

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% to 50% of patients with MM and has been observed to negatively affect outcomes.[303-305] 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) less than 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, electrolyte measurements, eGFR, electrophoresis of a sample from a 24-hour urine collection, serum electrophoresis, and serum FLC measurement. If proteinuria predominantly consists of light chains with high serum levels of FLC, and the cause of renal insufficiency can be attributed to MM, a renal biopsy may not be necessary. However, 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: Bortezomib and/or a daratumumab-containing regimen can be administered in patients with severe renal impairment and also those on dialysis and does not require renal dose adjustment.[306-310] Once the renal function improves or stabilizes, one can switch to other regimens.

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.[311] 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.[312] Patients with renal insufficiency had higher rates of thrombocytopenia and lenalidomide discontinuation than seen in patients without renal insufficiency. The NCCN Panel has 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

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sqm, and those requiring dialysis) and full-dose pomalidomide of 4 mg daily was found to be safe in all three groups.[313]

Supportive Care: IV 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 FLCs has not been established, there is limited evidence for the use of plasmapheresis or high-cutoff dialysis to reduce pathogenic light chains.

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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 BMPCs less than 10%. The prevalence of MGUS in the general population is about 0.7%, and it increases with age.

MGCS refers to the potentially organ-toxic properties of M protein. Typically, the M protein in MGCS does not meet the diagnostic criteria for MM and Waldenström macroglobulinemia (WM). Previously MGCS were all grouped under MGUS. Monoclonal gammopathy affects the renal function, and it is referred to as MGRS. Peripheral neuropathy mediated by a M 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 for MGUS but demonstrate renal injury attributable to the underlying M protein.[314]

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 M protein. The biopsy may be deferred if the eGFR is stable, the urinalysis is normal, or there is no evidence of proteinuria (it is 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 M 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.

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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 FLC assay; and serum creatinine.

Monoclonal Gammopathy of Neurological Significance (MGNS)

MGNS is a subset of MGCS that is predominantly characterized by neurologic symptoms (such as peripheral neuropathy) and the presence of M protein without evidence of active MM or WM.

Patients with MGNS may have varying electrophysiologic features. A single-center retrospective analysis suggests that approximately 69% of patients with MGNS showed demyelinating features while 26% showed axonal features.[315] As a precursor state to numerous B-cell disorders, suspected MGNS does not always necessitate pharmacotherapy, but does warrant additional workup and evaluation to rule out other causes of neuropathy and inform clinical decision-making.

Initial Workup

MGNS may be the result of other comorbidities or conditions such as diabetes, cobalamin deficiency, thyroid dysfunction, Lyme disease, HIV infection, syphilis, autoimmune disease, or cryoglobulinemia. A comprehensive assessment of other causes of neuropathy is needed, including an evaluation for light chain amyloidosis, WM, or POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, Skin changes) syndrome. Additional components of an initial workup include anti-MAG antibodies, ganglioside antibody panel, nerve conduction study (NCS) or electromyogram (EMG), neurology consult, and chest/abdominal/pelvic CT with contrast (if possible). Sural nerve biopsy may be considered in certain circumstances. A nerve biopsy is a less desirable diagnostic method due to the association with pain and potential permanent sensory or motor deficits.[316]

MYD88 L265P allele-specific PCR testing of bone marrow is included in the initial workup of a patient with suspected MGNS. A study analyzed the correlation of *MYD88* L265P mutation in a large number of tumor samples across a variety of B-cell disorders and reported higher levels of IgM ($P < .0001$) and higher frequency of proteinuria ($P = .002$) in patients with the mutation compared to patients with wild-type *MYD88*. The incidence of *MYD88* L265P mutation was reported in 100% of patients with WM, 47% of patients with MGUS, 6% with splenic marginal zone lymphoma, and 4% of patients with B-cell chronic lymphoproliferative disorders.[317] Subsequent studies have also reported the strong correlation of *MYD88* mutation status in MGNS and WM.[318-320] It should be noted that wild-type *MYD88* occurs in less than 10% of patients and should not be used to exclude diagnosis of WM if other criteria are met.

CXCR4 gene mutation testing may be considered in certain circumstances due to its prevalence in MGNS. Several studies reported *CXCR4* gene mutation as a common somatic mutation that has been linked with the *MYD88* L265P mutation.[319-323] Notably, however, a study reported that *CXCR4* mutation status had no impact on risk of death.[320] Therefore, *CXCR4* gene mutation testing may be included in the initial workup of a patient with suspected MGNS but should be interpreted in the context of other clinical findings to confirm diagnosis.

Clinical Findings

If there is either low suspicion or intermediate suspicion of MGNS that does not affect activities of daily living (ADLs), observation and follow-up as clinically indicated is appropriate. A low suspicion of MGNS may be determined if the following clinical findings are present: motor/pain predominant, non-length dependent, rapid progression (weeks to months),

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unilateral or asymmetrical, antibodies not present, and no demyelination confirmed by EMG/NCS.

If there is either intermediate suspicion that affects ADLs or high suspicion of MGNS, please refer to the NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma. A high suspicion of MGNS may be determined if the following clinical findings are present: sensory predominant, length dependent, slow progression (years), bilateral and symmetrical, antibodies present, and demyelination confirmed by EMG/NCS. Presence of the *MYD88* L265P and/or *CXCR4* mutations should also be considered in the further diagnosis of WM.

POEMS Syndrome

POEMS syndrome is a rare plasma cell disorder that is characterized by the dominant presence of demyelinating peripheral neuropathy and confirmed clonal plasma cell proliferation. The etiology is not well understood, but it is believed to be correlated with inflammatory cytokines, such as vascular endothelial growth factor (VEGF). Despite the individual components of the acronym, not all of the features are necessary to make a diagnosis of POEMS syndrome. There are also other important features that are not included in the acronym. Because of its rarity, POEMS syndrome may be underdiagnosed and mistaken for other chronic inflammatory syndromes.[324-326]

The diagnosis of POEMS syndrome is confirmed when both mandatory major criteria, one of the other three major criteria, and one of the six minor criteria are present. The mandatory major criteria for diagnosis of POEMS syndrome include the presence of polyneuropathy (typical demyelinating) and monoclonal plasma cell proliferative disorder [almost always λ (lambda)]. Additionally, at least one of the following major criteria is required: Castleman disease, sclerotic bone lesions, and/or VEGF elevation. Minor criteria for diagnosis that may be present include organomegaly (ie, splenomegaly, hepatomegaly, lymphadenopathy), extravascular volume overload (eg, edema, pleural effusion, ascites), endocrinopathy (ie, adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic), skin changes (ie, hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails), papilledema, and/or thrombocytosis/polycythemia. Other signs and symptoms may include clubbing, weight loss, hyperhidrosis, pulmonary hypertension, restrictive lung disease, thrombotic diatheses, diarrhea, and/or low vitamin B12 levels.[325]

Initial Workup

If POEMS syndrome is suspected, a complete history and physical examination is warranted. Clinical findings should be evaluated for potential correlation to organomegaly (including splenomegaly, hepatomegaly, and lymphadenopathy). Presentation of symptoms such as hyperhidrosis, diarrhea, weight loss, and menstrual/sexual dysfunction should be accounted for in the initial workup. Fundoscopic, skin, and neurologic examinations may be performed to identify abnormalities. [325]

Recommended initial testing beyond the initial workup includes electrophysiologic (nerve conduction) studies, CT of the chest/abdomen/pelvis (for lymphadenopathy, organomegaly, ascites, pleural effusion, and/or edema), echocardiography (for right ventricular systolic and pulmonary artery pressures), and CT body bone windows and/or FDG-PET/CT (for sclerotic bone lesions). Laboratory testing should include a CBC, complete metabolic panel, fasting glucose, serum immunoglobulins (ie, IgG, IgA, IgM), electrophoresis and immunofixation, serum FLC, 24-hour urine total protein, VEGF, interleukin-6 (IL-6), and numerous hormones (ie, testosterone, estradiol, thyroid-stimulating hormone, parathyroid hormone, prolactin, serum cortisol, luteinizing hormone). A bone marrow aspirate and biopsy, FISH panel, and PCR should be done to assess for MM.[325]

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Additional testing may be considered, if indicated. These additional tests include sural nerve biopsy, follicle-stimulating hormone, adrenocorticotropin hormone, cosyntropin stimulation test, biopsy of bone lesion (if needed), and excisional lymph node biopsy (if Castleman disease or other B-cell lymphomas suspected).[325]

Treatment

For a confirmed diagnosis of POEMS syndrome, treatment options may include RT, autologous transplant, and/or systemic therapy. RT alone is recommended for isolated bone lesions (defined as <3 sites) in patients without clonal BMPCs.

Autologous transplant is recommended in patients who are eligible as sole therapy or as consolidation after induction therapy. Patients who are not eligible for transplant should receive induction therapy as treatment. Induction therapy options regardless of transplant eligibility include lenalidomide/dexamethasone, bortezomib/dexamethasone, melphalan/dexamethasone, cyclophosphamide/dexamethasone, or pomalidomide/dexamethasone.

Patients who progress after initial therapy should receive individualized treatment based on response and toxicity of prior therapy, with consideration of the patient's performance status at the time of progression.

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References

1. SEER Stat Fact Sheets: Myeloma. Available at: http://seer.cancer.gov/statfacts/html/mulmy.html.

2. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin 2023;73:17-48. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36633525.

3. Kyle RA, Gertz MA, Witzig TE, et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003;78:21-33. Available at: https://www.ncbi.nlm.nih.gov/pubmed/12528874.

4. Dispenzieri A, Kyle RA, Katzmann JA, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood 2008;111:785-789. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17942755.

5. Dispenzieri A, Zhang L, Katzmann JA, et al. Appraisal of immunoglobulin free light chain as a marker of response. Blood 2008;111:4908-4915. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18364469.

6. Dispenzieri A, Kyle R, Merlini G, et al. International Myeloma Working Group guidelines for serum-free light chain analysis in multiple myeloma and related disorders. Leukemia 2009;23:215-224. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19020545.

7. Kuhnemund A, Liebisch P, Bauchmuller K, et al. 'Light-chain escape-multiple myeloma'-an escape phenomenon from plateau phase: report of the largest patient series using LC-monitoring. J Cancer Res Clin Oncol 2009;135:477-484. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18802723.

8. Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-1473. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16855634.

9. Craig FE, Foon KA. Flow cytometric immunophenotyping for hematologic neoplasms. Blood 2008;111:3941-3967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18198345.

10. Paiva B, Vidriales MB, Perez JJ, et al. Multiparameter flow cytometry quantification of bone marrow plasma cells at diagnosis provides more prognostic information than morphological assessment in myeloma patients. Haematologica 2009;94:1599-1602. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19880781.

11. Xiong W, Wu X, Starnes S, et al. An analysis of the clinical and biologic significance of TP53 loss and the identification of potential novel transcriptional targets of TP53 in multiple myeloma. Blood 2008;112:4235-4246. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18337559.

12. Drach J, Ackermann J, Fritz E, et al. Presence of a p53 gene deletion in patients with multiple myeloma predicts for short survival after conventional-dose chemotherapy. Blood 1998;92:802-809. Available at: https://www.ncbi.nlm.nih.gov/pubmed/9680348.

13. Avet-Loiseau H, Attal M, Moreau P, et al. Genetic abnormalities and survival in multiple myeloma: the experience of the Intergroupe Francophone du Myelome. Blood 2007;109:3489-3495. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17209057.

14. Gertz MA, Lacy MQ, Dispenzieri A, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. Blood 2005;106:2837-2840. Available at: https://www.ncbi.nlm.nih.gov/pubmed/15976175.

15. Gutierrez NC, Castellanos MV, Martin ML, et al. Prognostic and biological implications of genetic abnormalities in multiple myeloma undergoing autologous stem cell transplantation: t(4;14) is the most relevant adverse prognostic factor, whereas RB deletion as a unique abnormality is not associated with adverse prognosis. Leukemia 2007;21:143-150. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17024116.

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16. Ross FM, Chiecchio L, Dagrada G, et al. The t(14;20) is a poor prognostic factor in myeloma but is associated with long-term stable disease in monoclonal gammopathies of undetermined significance. Haematologica 2010;95:1221-1225. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20410185.

17. Ross FM, Avet-Loiseau H, Ameye G, et al. Report from the European Myeloma Network on interphase FISH in multiple myeloma and related disorders. Haematologica 2012;97:1272-1277. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22371180.

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

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

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

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

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

23. D'Agostino M, Cairns DA, Lahuerta JJ, et al. Second Revision of the International Staging System (R2-ISS) for Overall Survival in Multiple Myeloma: A European Myeloma Network (EMN) Report Within the HARMONY Project. J Clin Oncol 2022;40:3406-3418. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35605179.

24. Hillengass J, Moulopoulos LA, Delorme S, et al. Findings of Whole Body Computed Tomography Compared to Conventional Skeletal Survey in Patients with Monoclonal Plasma Cell Disorders - a Study of the International Myeloma Working Group [Abstract]. Blood 2016;128:4468. Available at: http://www.bloodjournal.org/content/128/22/4468.

25. Kropil P, Fenk R, Fritz LB, et al. Comparison of whole-body 64-slice multidetector computed tomography and conventional radiography in staging of multiple myeloma. Eur Radiol 2008;18:51-58. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17924119.

26. Princewill K, Kyere S, Awan O, Mulligan M. Multiple myeloma lesion detection with whole body CT versus radiographic skeletal survey. Cancer Invest 2013;31:206-211. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23406213.

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

28. Siontis B, Kumar S, Dispenzieri A, et al. Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: identification of patients needing therapy. Blood Cancer J 2015;5:e364. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26495861.

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

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30. Hillengass J, Fechtner K, Weber MA, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J Clin Oncol 2010;28:1606-1610. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20177023.

31. Merz M, Hielscher T, Wagner B, et al. Predictive value of longitudinal whole-body magnetic resonance imaging in patients with smoldering multiple myeloma. Leukemia 2014;28:1902-1908. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24535407.

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

33. van Beers EH, van Vliet MH, Kuiper R, et al. Prognostic Validation of SKY92 and Its Combination With ISS in an Independent Cohort of Patients With Multiple Myeloma. Clin Lymphoma Myeloma Leuk 2017;17:555-562. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28735890.

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

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

36. Mateos MV, Kumar S, Dimopoulos MA, et al. International Myeloma Working Group risk stratification model for smoldering multiple myeloma (SMM). Blood Cancer J 2020;10:102. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33067414.

37. Touzeau C, Moreau P. How I treat extramedullary myeloma. Blood 2016;127:971-976. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26679866.

38. Granell M, Calvo X, Garcia-Guinon A, et al. Prognostic impact of circulating plasma cells in patients with multiple myeloma: implications for plasma cell leukemia definition. Haematologica 2017;102:1099-1104. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28255016.

39. Schavgoulidze A, Talbot A, Perrot A, et al. Biallelic deletion of 1p32 defines ultra-high-risk myeloma, but monoallelic del(1p32) remains a strong prognostic factor. Blood 2023;141:1308-1315. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36375118.

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

41. Palumbo A, Avet-Loiseau H, Oliva S, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. J Clin Oncol 2015;33:2863-2869. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26240224.

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

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

44. Zamagni E, Nanni C, Patriarca F, et al. A prospective comparison of 18F-fluorodeoxyglucose positron emission tomography-computed tomography, magnetic resonance imaging and whole-body planar radiographs in the assessment of bone disease in newly diagnosed multiple myeloma. Haematologica 2007;92:50-55. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17229635.

45. Fonti R, Salvatore B, Quarantelli M, et al. 18F-FDG PET/CT, 99mTc-MIBI, and MRI in evaluation of patients with multiple myeloma. J Nucl

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Med 2008;49:195-200. Available at: https://www.ncbi.nlm.nih.gov/pubmed/18199607.

46. Nahi H, Genell A, Walinder G, et al. Incidence, characteristics, and outcome of solitary plasmacytoma and plasma cell leukemia. Population-based data from the Swedish Myeloma Register. Eur J Haematol 2017;99:216-222. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28544116.

47. Paiva B, Chandia M, Vidriales MB, et al. Multiparameter flow cytometry for staging of solitary bone plasmacytoma: new criteria for risk of progression to myeloma. Blood 2014;124:1300-1303. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24876564.

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

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

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

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

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

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

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

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

56. Sasaki R, Yasuda K, Abe E, et al. Multi-institutional analysis of solitary extramedullary plasmacytoma of the head and neck treated with curative radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:626-634. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21277117.

57. Tsang RW, Gospodarowicz MK, Pintilie M, et al. Solitary plasmacytoma treated with radiotherapy: impact of tumor size on outcome. Int J Radiat Oncol Biol Phys 2001;50:113-120. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11316553.

58. Tsang RW, Campbell BA, Goda JS, et al. Radiation Therapy for Solitary Plasmacytoma and Multiple Myeloma: Guidelines From the International Lymphoma Radiation Oncology Group. Int J Radiat Oncol Biol Phys 2018;101:794-808. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29976492.

59. Gerry D, Lentsch EJ. Epidemiologic evidence of superior outcomes for extramedullary plasmacytoma of the head and neck. Otolaryngol Head Neck Surg 2013;148:974-981. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23482476.

60. Group TIMW. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. British Journal of Haematology

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2003;121:749-757. Available at: http://dx.doi.org/10.1046/j.1365-2141.2003.04355.x.

61. Kyle RA, Remstein ED, Therneau TM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med 2007;356:2582-2590. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17582068.

62. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-447. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23902483.

63. Mateos MV, Hernandez MT, Giraldo P, et al. Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. Lancet Oncol 2016;17:1127-1136. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27402145.

64. Lonial S, Jacobus S, Fonseca R, et al. Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma. J Clin Oncol 2020;38:1126-1137. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31652094.

65. San Miguel J, Mateos M-V, Gonzalez V, et al. Updated risk stratification model for smoldering multiple myeloma (SMM) incorporating the revised IMWG diagnostic criteria. Journal of Clinical Oncology 2019;37:8000-8000. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2019.37.15_suppl.8000.

66. Reeder CB, Reece DE, Kukreti V, et al. Once- versus twice-weekly bortezomib induction therapy with CyBorD in newly diagnosed multiple myeloma. Blood 2010;115:3416-3417. Available at: https://www.ncbi.nlm.nih.gov/pubmed/20413666.

67. Moreau P, Pylypenko H, Grosicki S, et al. Subcutaneous versus intravenous administration of bortezomib in patients with relapsed multiple myeloma: a randomised, phase 3, non-inferiority study. Lancet Oncol 2011;12:431-440. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21507715.

68. Arnulf B, Pylypenko H, Grosicki S, et al. Updated survival analysis of a randomized phase III study of subcutaneous versus intravenous bortezomib in patients with relapsed multiple myeloma. Haematologica 2012;97:1925-1928. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22689676.

69. Mateos MV, Nahi H, Legiec W, et al. Subcutaneous versus intravenous daratumumab in patients with relapsed or refractory multiple myeloma (COLUMBA): a multicentre, open-label, non-inferiority, randomised, phase 3 trial. Lancet Haematol 2020;7:e370-e380. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32213342.

70. Nair V, Mohammed H, Mahmood S, et al. Assessing Steroid Toxicity in the Elderly with Multiple Myeloma. Blood 2019; 134 (Supplement_1): 5557. Available at: https://doi.org/10.1182/blood-2019-125442.

71. Larocca A, Bonello F, Gaidano G, et al. Dose/schedule-adjusted Rd-R vs continuous Rd for elderly, intermediate-fit patients with newly diagnosed multiple myeloma. Blood 2021;137:3027-3036. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33739404.

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

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

74. Kumar S, Flinn I, Richardson PG, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib,

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dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood 2012;119:4375-4382. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22422823.

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

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

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

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

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

80. Korde N, Zingone A, Kwok M, et al. Phase II clinical and correlative study of carfilzomib, lenalidomide, and dexamethasone (CRd) in newly diagnosed multiple myeloma (MM) patients [abstract]. j Clin Oncol 2012;30:e18568. Available at: http://meeting.ascopubs.org/cgi/content/abstract/30/15_suppl/e18568.

81. Korde N, Roschewski M, Zingone A, et al. Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma. JAMA Oncol 2015;1:746-754. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26181891.

82. Jasielec JK, Kubicki T, Raje N, et al. Carfilzomib, lenalidomide, and dexamethasone plus transplant in newly diagnosed multiple myeloma. Blood 2020;136:2513-2523. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32735641.

83. Facon T, Venner, CP. Bahlis, NJ. et al Ixazomib Plus LenalidomideDexamethasone (IRd) vs. PlaceboRd for Newly Diagnosed Multiple Myeloma (NDMM) Patients Not Eligible for Autologous Stem Cell Transplant: The Double-Blind, Placebo-Controlled, Phase 3 TOURMALINE-MM2 Trial [Abstract]. Abstract MM-347 presented at Society of Hema-to-logic Oncology (SOHO) Eighth Annual Meeting 2020. Available at: https://clml-soho2020.elsevierdigitaledition.com/306/index.html#zoom=z.

84. Facon T, Venner CP, Bahlis NJ, et al. Oral ixazomib, lenalidomide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. Blood 2021;137:3616-3628. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33763699.

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

86. Laubach JP, Kaufman JL, Sborov DW, et al. Daratumumab (DARA) plus lenalidomide, bortezomib, and dexamethasone (RVd) in patients

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(Pts) with transplant-eligible newly diagnosed multiple myeloma (NDMM): Updated analysis of Griffin after 24 months of maintenance. Blood 2021;138:79-79. Available at: https://www.sciencedirect.com/science/article/pii/S0006497121020693.

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

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

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

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

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

92. Bringhen S, D'Agostino M, De Paoli L, et al. Phase 1/2 study of weekly carfilzomib, cyclophosphamide, dexamethasone in newly diagnosed transplant-ineligible myeloma. Leukemia 2018;32:979-985. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29263440.

93. Bringhen S, Mina R, Petrucci MT, et al. Once-weekly versus twice-weekly carfilzomib in patients with newly diagnosed multiple myeloma: a pooled analysis of two phase I/II studies. Haematologica 2019;104:1640-1647. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30733270.

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

95. Dimopoulos MA, Grosicki S, Jedrzejczak WW, et al. All-oral ixazomib, cyclophosphamide, and dexamethasone for transplant-ineligible patients with newly diagnosed multiple myeloma. Eur J Cancer 2019;106:89-98. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30471652.

96. Moreau P, Attal M, Hulin C, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet 2019;394:29-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31171419.

97. Landgren O, Hultcrantz M, Diamond B, et al. Safety and Effectiveness of Weekly Carfilzomib, Lenalidomide, Dexamethasone, and Daratumumab Combination Therapy for Patients With Newly Diagnosed Multiple Myeloma: The MANHATTAN Nonrandomized Clinical Trial. JAMA Oncol 2021;7:862-868. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33856405.

98. Costa LJ, Chhabra S, Medvedova E, et al. Daratumumab, Carfilzomib, Lenalidomide, and Dexamethasone With Minimal Residual Disease Response-Adapted Therapy in Newly Diagnosed Multiple Myeloma. J Clin Oncol 2022;40:2901-2912. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34898239.

99. Yimer H, Melear J, Faber E, et al. Daratumumab, bortezomib, cyclophosphamide and dexamethasone in newly diagnosed and

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relapsed multiple myeloma: LYRA study. Br J Haematol 2019;185:492-502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30828799.

100. Barlogie B, Anaissie E, van Rhee F, et al. Incorporating bortezomib into upfront treatment for multiple myeloma: early results of total therapy 3. Br J Haematol 2007;138:176-185. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17593024.

101. Goldschmidt H, Mai EK, Bertsch U, et al. Addition of isatuximab to lenalidomide, bortezomib, and dexamethasone as induction therapy for newly diagnosed, transplantation-eligible patients with multiple myeloma (GMMG-HD7): part 1 of an open-label, multicentre, randomised, active-controlled, phase 3 trial. Lancet Haematol 2022;9:e810-e821. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36328040.

102. O'Donnell EK, Laubach JP, Yee AJ, et al. A phase 2 study of modified lenalidomide, bortezomib and dexamethasone in transplant-ineligible multiple myeloma. Br J Haematol 2018;182:222-230. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29740809.

103. Facon T, Kumar SK, Plesner T, et al. Daratumumab, lenalidomide, and dexamethasone versus lenalidomide and dexamethasone alone in newly diagnosed multiple myeloma (MAIA): overall survival results from a randomised, open-label, phase 3 trial. Lancet Oncol 2021;22:1582-1596. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34655533.

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

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

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

107. Zonder JA, Crowley J, Hussein MA, et al. Superiority of lenalidomide (Len) plus high-dose dexamethasone (HD) compared to HD alone as treatment of newly-diagnosed multiple myeloma (NDMM): Results of the randomized, double-blinded, placebo-controlled SWOG Trial S0232 [abstract]. Blood 2007;110:Abstract 77. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/110/11/77.

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

109. Benboubker L, Dimopoulos MA, Dispenzieri A, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med 2014;371:906-917. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25184863.

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

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

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

113. Palumbo A, Bringhen S, Kumar SK, et al. Second primary malignancies with lenalidomide therapy for newly diagnosed myeloma: a

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meta-analysis of individual patient data. Lancet Oncol 2014;15:333-342. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24525202.

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

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

116. Kumar SK, Lacy MQ, Hayman SR, et al. Lenalidomide, cyclophosphamide and dexamethasone (CRd) for newly diagnosed multiple myeloma: results from a phase 2 trial. Am J Hematol 2011;86:640-645. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21630308.

117. Pawlyn C, Brioli A, Gregory W, et al. Lenalidomide Combined With Cyclophosphamide and Dexamethasone Is Effective and Well Tolerated Induction Treatment For Newly Diagnosed Myeloma Patients Of All Ages. Blood 2013;122:540-540. Available at: https://doi.org/10.1182/blood.V122.21.540.540.

118. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide before and after autologous stem cell transplantation for transplant-eligible patients of all ages in the randomized, phase III, Myeloma XI trial. Haematologica 2021;106:1957-1967. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32499244.

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

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

121. Zepeda J, H. V, Duggan P, et al. Cyclophosphamide, bortezomib and dexamethasone (CyBORD) is a feasible and active regimen for non-transplant eligible multiple myeloma patients [Abstract}. Blood 2014;124:5751-5751. Available at: http://www.bloodjournal.org/content/124/21/5751.

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

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

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

125. Walker R, Barlogie B, Haessler J, et al. Magnetic resonance imaging in multiple myeloma: diagnostic and clinical implications. J Clin Oncol 2007;25:1121-1128. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17296972.

126. Bartel TB, Haessler J, Brown TL, et al. F18-fluorodeoxyglucose positron emission tomography in the context of other imaging techniques and prognostic factors in multiple myeloma. Blood 2009;114:2068-2076. Available at: https://www.ncbi.nlm.nih.gov/pubmed/19443657.

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127. Zamagni E, Nanni C, Mancuso K, et al. PET/CT Improves the Definition of Complete Response and Allows to Detect Otherwise Unidentifiable Skeletal Progression in Multiple Myeloma. Clin Cancer Res 2015;21:4384-4390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26078390.

128. Moreau P, Attal M, Caillot D, et al. Prospective Evaluation of Magnetic Resonance Imaging and [(18)F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study. J Clin Oncol 2017;35:2911-2918. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28686535.

129. Pawlyn C, Fowkes L, Otero S, et al. Whole-body diffusion-weighted MRI: a new gold standard for assessing disease burden in patients with multiple myeloma? Leukemia 2016;30:1446-1448. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26648535.

130. Rasche L, Angtuaco E, McDonald JE, et al. Low expression of hexokinase-2 is associated with false-negative FDG-positron emission tomography in multiple myeloma. Blood 2017;130:30-34. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28432222.

131. Rasche L, Alapat D, Kumar M, et al. Combination of flow cytometry and functional imaging for monitoring of residual disease in myeloma. Leukemia 2019;33:1713-1722. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30573775.

132. Munshi NC, Avet-Loiseau H, Rawstron AC, et al. Association of Minimal Residual Disease With Superior Survival Outcomes in Patients With Multiple Myeloma: A Meta-analysis. JAMA Oncol 2017;3:28-35. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27632282.

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

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

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

136. Moreau P, Facon T, Attal M, et al. Comparison of 200 mg/m(2) melphalan and 8 Gy total body irradiation plus 140 mg/m(2) melphalan as conditioning regimens for peripheral blood stem cell transplantation in patients with newly diagnosed multiple myeloma: final analysis of the Intergroupe Francophone du Myelome 9502 randomized trial. Blood 2002;99:731-735. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11806971.

137. Fermand JP, Katsahian S, Divine M, et al. High-dose therapy and autologous blood stem-cell transplantation compared with conventional treatment in myeloma patients aged 55 to 65 years: long-term results of a randomized control trial from the Group Myelome-Autogreffe. J Clin Oncol 2005;23:9227-9233. Available at: https://www.ncbi.nlm.nih.gov/pubmed/16275936.

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

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

140. Cavo M, Pantani L, Petrucci MT, et al. Bortezomib-thalidomide-dexamethasone is superior to thalidomide-dexamethasone as consolidation therapy after autologous hematopoietic stem cell

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transplantation in patients with newly diagnosed multiple myeloma. Blood 2012;120:9-19. Available at: https://www.ncbi.nlm.nih.gov/pubmed/22498745.

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

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

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

144. Sonneveld P, van der Holt B, Segeren C, et al. Intensive versus double intensive therapy in untreated multiple myeloma: Updated analysis of the randomized phase III study HOVON 24 MM [abstract]. Blood 2004;104:Abstract 948. Available at: http://abstracts.hematologylibrary.org/cgi/content/abstract/104/11/948.

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

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

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

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

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

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

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

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

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

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

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

156. Cook G, Ashcroft AJ, Cairns DA, et al. The effect of salvage autologous stem-cell transplantation on overall survival in patients with relapsed multiple myeloma (final results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. Lancet Haematol 2016;3:e340-351. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27374467.

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

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

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

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

161. Bygrave C, Pawlyn C, Davies F, et al. Early relapse after high-dose melphalan autologous stem cell transplant predicts inferior survival and is associated with high disease burden and genetically high-risk disease in multiple myeloma. Br J Haematol 2021;193:551-555. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32524584.

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

163. Jimenez-Zepeda VH, Mikhael J, Winter A, et al. Second autologous stem cell transplantation as salvage therapy for multiple myeloma: Impact on progression-free and overall survival. Biol Blood Marrow Transplant 2012;18:773-779. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22062804.

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

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

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

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

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

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

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

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

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

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

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

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

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

177. Munshi NC, Avet-Loiseau H, Anderson KC, et al. A large meta-analysis establishes the role of MRD negativity in long-term survival outcomes in patients with multiple myeloma. Blood Adv 2020;4:5988-5999. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33284948.

178. Rawstron AC, Child JA, de Tute RM, et al. Minimal residual disease assessed by multiparameter flow cytometry in multiple myeloma: impact on outcome in the Medical Research Council Myeloma IX Study. J Clin Oncol 2013;31:2540-2547. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23733781.

179. Hahn TE, Wallace PK, Fraser R, et al. Minimal Residual Disease (MRD) Assessment before and after Autologous Hematopoietic Cell Transplantation (AutoHCT) and Maintenance for Multiple Myeloma (MM): Results of the Prognostic Immunophenotyping for Myeloma Response (PRIMeR) Study. Biology of Blood and Marrow Transplantation 2019;25:S4-S6. Available at: https://doi.org/10.1016/j.bbmt.2018.12.687.

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

181. Holstein SA, Jung SH, Richardson PG, et al. Updated analysis of CALGB (Alliance) 100104 assessing lenalidomide versus placebo maintenance after single autologous stem-cell transplantation for multiple

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myeloma: a randomised, double-blind, phase 3 trial. Lancet Haematol 2017;4:e431-e442. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28826616.

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

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

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

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

186. Goldschmidt H, Mai EK, Durig J, et al. Response-adapted lenalidomide maintenance in newly diagnosed myeloma: results from the phase III GMMG-MM5 trial. Leukemia 2020;34:1853-1865. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32034285.

187. Musto P, Anderson KC, Attal M, et al. Second primary malignancies in multiple myeloma: an overview and IMWG consensus. Ann Oncol 2017;28:228-245. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27864218.

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

189. Nooka AK, Kaufman JL, Muppidi S, et al. Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients. Leukemia 2014;28:690-693. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24220275.

190. Joseph NS, Kaufman JL, Dhodapkar MV, et al. Long-Term Follow-Up Results of Lenalidomide, Bortezomib, and Dexamethasone Induction Therapy and Risk-Adapted Maintenance Approach in Newly Diagnosed Multiple Myeloma. J Clin Oncol 2020;38:1928-1937. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32298201.

191. Gay F, Musto P, Rota-Scalabrini D, et al. Carfilzomib with cyclophosphamide and dexamethasone or lenalidomide and dexamethasone plus autologous transplantation or carfilzomib plus lenalidomide and dexamethasone, followed by maintenance with carfilzomib plus lenalidomide or lenalidomide alone for patients with newly diagnosed multiple myeloma (FORTE): a randomised, open-label, phase 2 trial. Lancet Oncol 2021;22:1705-1720. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34774221.

192. Moreau P, Hulin C, Perrot A, et al. Maintenance with daratumumab or observation following treatment with bortezomib, thalidomide, and dexamethasone with or without daratumumab and autologous stem-cell transplant in patients with newly diagnosed multiple myeloma (CASSIOPEIA): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:1378-1390. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34529931.

193. Dimopoulos MA, Gay F, Schjesvold F, et al. Oral ixazomib maintenance following autologous stem cell transplantation (TOURMALINE-MM3): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2019;393:253-264. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30545780.

194. Goldschmidt H, Dimopoulos MA, Rajkumar SV, et al. Deepening responses associated with improved progression-free survival with

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ixazomib versus placebo as posttransplant maintenance in multiple myeloma. Leukemia 2020;34:3019-3027. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32327729.

195. Dimopoulos MA, Spicka I, Quach H, et al. Ixazomib as Postinduction Maintenance for Patients With Newly Diagnosed Multiple Myeloma Not Undergoing Autologous Stem Cell Transplantation: The Phase III TOURMALINE-MM4 Trial. J Clin Oncol 2020;38:4030-4041. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33021870.

196. Dimopoulos MA, Rajkumar SV, Lonial S, et al. Interim Analyses of Overall Survival (OS) from the TOURMALINE MM3 & MM4 Studies of Ixazomib Maintenance Following Primary Therapy in Multiple Myeloma (MM). Blood 2021;138:1656-1656. Available at: https://doi.org/10.1182/blood-2021-150476.

197. Chari A, Martinez-Lopez J, Mateos MV, et al. Daratumumab plus carfilzomib and dexamethasone in patients with relapsed or refractory multiple myeloma. Blood 2019;134:421-431. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31113777.

198. Dimopoulos M, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet 2020;396:186-197. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32682484.

199. Usmani SZ, Quach H, Mateos MV, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. Lancet Oncol 2022;23:65-76. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34871550.

200. Moreau P, Dimopoulos MA, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet 2021;397:2361-2371. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34097854.

201. Sonneveld P, Zweegman S, Cavo M, et al. Carfilzomib, Pomalidomide, and Dexamethasone As Second-line Therapy for Lenalidomide-refractory Multiple Myeloma. Hemasphere 2022;6:e786. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36204691.

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

203. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol 2021;22:801-812. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34087126.

204. Siegel DS, Schiller GJ, Samaras C, et al. Pomalidomide, dexamethasone, and daratumumab in relapsed refractory multiple myeloma after lenalidomide treatment. Leukemia 2020;34:3286-3297. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32376855.

205. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. Lancet 2019;394:2096-2107. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31735560.

206. Dimopoulos MA, Leleu X, Moreau P, et al. Isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma patients with renal impairment: ICARIA-MM subgroup analysis. Leukemia 2021;35:562-572. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32444867.

207. Voorhees PM, Suman VJ, Tuchman SA, et al. A phase I/II study of ixazomib, pomalidomide, and dexamethasone for lenalidomide and

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proteasome inhibitor refractory multiple myeloma (Alliance A061202). Am J Hematol 2021;96:1595-1603. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34559902.

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

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

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

211. Stewart AK, Rajkumar SV, Dimopoulos MA, et al. Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-152. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25482145.

212. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. N Engl J Med 2016;375:754-766. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27557302.

213. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. N Engl J Med 2015;373:1207-1219. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26308596.

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

215. Mateos MV, Sonneveld P, Hungria V, et al. Daratumumab, Bortezomib, and Dexamethasone Versus Bortezomib and Dexamethasone in Patients With Previously Treated Multiple Myeloma: Three-year Follow-up of CASTOR. Clin Lymphoma Myeloma Leuk 2020;20:509-518. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32482541.

216. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:781-794. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31097405.

217. Dimopoulos M, Weisel K, Moreau P, et al. Pomalidomide, bortezomib, and dexamethasone for multiple myeloma previously treated with lenalidomide (OPTIMISMM): outcomes by prior treatment at first relapse. Leukemia 2021;35:1722-1731. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32895455.

218. Grosicki S, Simonova M, Spicka I, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet 2020;396:1563-1573. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33189178.

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

220. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab Plus Pomalidomide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: Final Overall Survival Analysis From the Randomized Phase II ELOQUENT-3 Trial. J Clin Oncol 2023;41:568-578. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35960908.

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221. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016;17:27-38. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26671818.

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

223. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med 2015;373:621-631. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26035255.

224. Dimopoulos MA, Lonial S, White D, et al. Elotuzumab plus lenalidomide/dexamethasone for relapsed or refractory multiple myeloma: ELOQUENT-2 follow-up and post-hoc analyses on progression-free survival and tumour growth. Br J Haematol 2017;178:896-905. Available at: https://www.ncbi.nlm.nih.gov/pubmed/28677826.

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

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

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

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

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

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

231. Yong KL, Hinsley S, Auner HW, et al. Carfilzomib or bortezomib in combination with cyclophosphamide and dexamethasone followed by carfilzomib maintenance for patients with multiple myeloma after one prior therapy: results from a multicenter, phase II, randomized, controlled trial (MUKfive). Haematologica 2021;106:2694-2706. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33910333.

232. Puertas B, Gonzalez-Calle V, Sureda A, et al. Randomized phase II study of weekly carfilzomib 70 mg/m(2) and dexamethasone with or without cyclophosphamide in relapsed and/or refractory multiple myeloma patients. Haematologica 2023;108:2753-2763. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37102598.

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

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

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

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

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

238. Garderet L, Polge E, Gueye mS, et al. Pomalidomide, Cyclophosphamide and Dexamethasone for Relapsed/Refractory Multiple Myeloma: A Retrospective Single Center Experience. Blood 2015;126:1858-1858. Available at: https://doi.org/10.1182/blood.V126.23.1858.1858.

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

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

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

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

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

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

245. Mikhael JR, Reeder CB, Libby EN, et al. Phase Ib/II trial of CYKLONE (cyclophosphamide, carfilzomib, thalidomide and dexamethasone) for newly diagnosed myeloma. Br J Haematol 2015;169:219-227. Available at: https://www.ncbi.nlm.nih.gov/pubmed/25683772.

246. Moreau P, Mateos MV, Berenson JR, et al. Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study. Lancet Oncol 2018;19:953-964. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29866475.

247. Gasparetto C, Schiller GJ, Tuchman SA, et al. Once weekly selinexor, carfilzomib and dexamethasone in carfilzomib non-refractory multiple myeloma patients. Br J Cancer 2022;126:718-725. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34802051.

248. Schiller GJ, Tuchman SA, Callander N, et al. Once Weekly Selinexor, Carfilzomib and Dexamethasone (XKd) in Triple Class Refractory Multiple Myeloma. Blood 2022;140:10050-10053. Available at: https://doi.org/10.1182/blood-2022-158011.

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249. Kumar S, Kaufman JL, Gasparetto C, et al. Efficacy of venetoclax as targeted therapy for relapsed/refractory t(11;14) multiple myeloma. Blood 2017;130:2401-2409. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29018077.

250. Basali D, Chakraborty R, Rybicki L, et al. Real-world data on safety and efficacy of venetoclax-based regimens in relapsed/refractory t(11;14) multiple myeloma. Br J Haematol 2020. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32012228.

251. Kaufman JL, Gasparetto C, Schjesvold FH, et al. Targeting BCL-2 with venetoclax and dexamethasone in patients with relapsed/refractory t(11;14) multiple myeloma. Am J Hematol 2021;96:418-427. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33368455.

252. Bahlis NJ, Baz R, Harrison SJ, et al. Phase I Study of Venetoclax Plus Daratumumab and Dexamethasone, With or Without Bortezomib, in Patients With Relapsed or Refractory Multiple Myeloma With and Without t(11;14). J Clin Oncol 2021;39:3602-3612. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34388020.

253. Costa LJ, Stadtmauer EA, Morgan G, et al. Phase 2 Study of Venetoclax Plus Carfilzomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma. Blood 2018;132:303. Available at: https://www.sciencedirect.com/science/article/pii/S0006497119363529.

254. Abuelgasim KA, Alherz N, Alhejazi A, Damlaj M. Venetoclax in combination with carfilzomib and dexamethasone in relapsed/refractory multiple myeloma harboring t(11,14)(q13;q32): two case reports and a review of the literature. J Med Case Rep 2020;14:54. Available at: https://www.ncbi.nlm.nih.gov/pubmed/32321588.

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

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

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

258. Leleu X, Attal M, Arnulf B, et al. Pomalidomide plus low-dose dexamethasone is active and well tolerated in bortezomib and lenalidomide-refractory multiple myeloma: Intergroupe Francophone du Myelome 2009-02. Blood 2013;121:1968-1975. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23319574.

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

260. White D, Chen C, Baljevic M, et al. Oral selinexor, pomalidomide, and dexamethasone (XPd) at recommended phase 2 dose in relapsed refractory multiple myeloma (MM). Journal of Clinical Oncology 2021;39:8018-8018. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.8018.

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

262. Dadacaridou M, Papanicolaou X, Maltesas D, et al. Dexamethasone, cyclophosphamide, etoposide and cisplatin (DCEP) for

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relapsed or refractory multiple myeloma patients. J BUON 2007;12:41-44. Available at: https://www.ncbi.nlm.nih.gov/pubmed/17436400.

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

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

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

266. Buda G, Orciuolo E, Galimberti S, et al. VDTPACE As salvage therapy for heavily pretreated MM patients. Blood 2013;122:5377-5377. Available at: https://doi.org/10.1182/blood.V122.21.5377.5377.

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

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

269. Lesokhin AM, Tomasson MH, Arnulf B, et al. Elranatamab in relapsed or refractory multiple myeloma: phase 2 MagnetisMM-3 trial results. Nat Med 2023;29:2259-2267. Available at: https://www.ncbi.nlm.nih.gov/pubmed/37582952.

270. Chari A, Minnema MC, Berdeja JG, et al. Talquetamab, a T-Cell-Redirecting GPRC5D Bispecific Antibody for Multiple Myeloma. N Engl J Med 2022;387:2232-2244. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36507686.

271. Moreau P, Garfall AL, van de Donk N, et al. Teclistamab in Relapsed or Refractory Multiple Myeloma. N Engl J Med 2022;387:495-505. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35661166.

272. Munshi NC, Anderson LD, Jr., Shah N, et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma. N Engl J Med 2021;384:705-716. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33626253.

273. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet 2021;398:314-324. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34175021.

274. Martin T, Usmani SZ, Berdeja JG, et al. Updated Results from CARTITUDE-1: Phase 1b/2Study of Ciltacabtagene Autoleucel, a B-Cell Maturation Antigen-Directed Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma. Blood 2021;138:549-549. Available at: https://www.sciencedirect.com/science/article/pii/S0006497121025416.

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

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

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

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278. Offidani M, Corvatta L, Maracci L, et al. Efficacy and tolerability of bendamustine, bortezomib and dexamethasone in patients with relapsed-refractory multiple myeloma: a phase II study. Blood Cancer J 2013;3:e162. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24270324.

279. Gay F, Gunther A, Offidani M, et al. Carfilzomib, bendamustine, and dexamethasone in patients with advanced multiple myeloma: The EMN09 phase 1/2 study of the European Myeloma Network. Cancer 2021;127:3413-3421. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34181755.

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

281. Rivell GL, Brunson CY, Milligan L, et al. Effectiveness and safety of high-dose cyclophosphamide as salvage therapy for high-risk multiple myeloma and plasma cell leukemia refractory to new biological agents. Am J Hematol 2011;86:699-701. Available at: https://www.ncbi.nlm.nih.gov/pubmed/21630309.

282. Shank BR, Primeaux B, Yeung EK, et al. Hyperfractionated Cyclophosphamide and Dexamethasone Alone or in Combination with Daratumumab and/or Carfilzomib for the Treatment of Relapsed or Refractory Multiple Myeloma: A Single-Center Retrospective Analysis. Clin Lymphoma Myeloma Leuk 2023;23:279-290. Available at: https://www.ncbi.nlm.nih.gov/pubmed/36797154.

283. Chari A, Vogl DT, Gavriatopoulou M, et al. Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. N Engl J Med 2019;381:727-738. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31433920.

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

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

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

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

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

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

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

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

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

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

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

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

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

297. Resende Salgado L, Wang S, Adler A, et al. The Safety Profile of Concurrent Therapy for Multiple Myeloma in the Modern Era. Adv Radiat Oncol 2019;4:112-117. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30706018.

298. Guerini AE, Tucci A, Alongi F, et al. RR Myelo POINT: A Retrospective Single-Center Study Assessing the Role of Radiotherapy in the Management of Multiple Myeloma and Possible Interactions with Concurrent Systemic Treatment. Cancers (Basel) 2022;14. Available at: https://www.ncbi.nlm.nih.gov/pubmed/35565401.

299. Elhammali A, Amini B, Ludmir EB, et al. New paradigm for radiation in multiple myeloma: lower yet effective dose to avoid radiation toxicity. Haematologica 2020;105:e355-e357. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31919088.

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

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

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

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

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

305. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group.

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Eur J Haematol 2000;65:175-181. Available at: https://www.ncbi.nlm.nih.gov/pubmed/11007053.

306. Dimopoulos MA, Roussou M, Gavriatopoulou M, et al. Bortezomib-based triplets are associated with a high probability of dialysis independence and rapid renal recovery in newly diagnosed myeloma patients with severe renal failure or those requiring dialysis. Am J Hematol 2016;91:499-502. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26890495.

307. Monge J, Solomon RS, Flicker K, et al. Daratumumab in Patients with Multiple Myeloma and Renal Impairment - Real-World Data from a Single-Center Institution. Blood 2019;134:5563-5563. Available at: https://doi.org/10.1182/blood-2019-127697.

308. Jeyaraman P, Bhasin A, Dayal N, et al. Daratumumab in dialysis-dependent multiple myeloma. Blood Res 2020;55:65-67. Available at:

309. Kuzume A, Tabata R, Terao T, et al. Safety and efficacy of daratumumab in patients with multiple myeloma and severe renal failure. British Journal of Haematology 2021;193:e33-e36. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1111/bjh.17412.

310. Niewinski M, Chin-Hon J, Akerman M, et al. Safety and efficacy of daratumumab use in patients with renal impairment and hemodialysis. Journal of Clinical Oncology 2022;40:8026-8026. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2022.40.16_suppl.8026.

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

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

313. Dimopoulos M, Weisel K, van de Donk N, et al. Pomalidomide Plus Low-Dose Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma and Renal Impairment: Results From a Phase II Trial. J Clin Oncol 2018;36:2035-2043. Available at: https://www.ncbi.nlm.nih.gov/pubmed/29394124.

314. Leung N, Bridoux F, Hutchison CA, et al. Monoclonal gammopathy of renal significance: when MGUS is no longer undetermined or insignificant. Blood 2012;120:4292-4295. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23047823.

315. Mani AM, Devasia AJ, Nair A, et al. Monoclonal Gammopathies of 'Neurological Significance': Paraproteinemic Neuropathies. Can J Neurol Sci 2021;48:616-625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33397535.

316. Castillo JJ, Callander NS, Baljevic M, et al. The evaluation and management of monoclonal gammopathy of renal significance and monoclonal gammopathy of neurological significance. Am J Hematol 2021;96:846-853. Available at: https://www.ncbi.nlm.nih.gov/pubmed/33709474.

317. Varettoni M, Arcaini L, Zibellini S, et al. Prevalence and clinical significance of the MYD88 (L265P) somatic mutation in Waldenstrom's macroglobulinemia and related lymphoid neoplasms. Blood 2013;121:2522-2528. Available at: https://www.ncbi.nlm.nih.gov/pubmed/23355535.

318. Xu L, Hunter ZR, Yang G, et al. Detection of MYD88 L265P in peripheral blood of patients with Waldenstrom's Macroglobulinemia and IgM monoclonal gammopathy of undetermined significance. Leukemia 2014;28:1698-1704. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24509637.

319. Hunter ZR, Xu L, Yang G, et al. The genomic landscape of Waldenstrom macroglobulinemia is characterized by highly recurring MYD88 and WHIM-like CXCR4 mutations, and small somatic deletions associated with B-cell lymphomagenesis. Blood 2014;123:1637-1646. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24366360.

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320. Treon SP, Cao Y, Xu L, et al. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood 2014;123:2791-2796. Available at: https://www.ncbi.nlm.nih.gov/pubmed/24553177.

321. Bagratuni T, Ntanasis-Stathopoulos I, Gavriatopoulou M, et al. Detection of MYD88 and CXCR4 mutations in cell-free DNA of patients with IgM monoclonal gammopathies. Leukemia 2018;32:2617-2625. Available at: https://www.ncbi.nlm.nih.gov/pubmed/30026568.

322. Xu L, Hunter ZR, Tsakmaklis N, et al. Clonal architecture of CXCR4 WHIM-like mutations in Waldenstrom Macroglobulinaemia. Br J Haematol 2016;172:735-744. Available at: https://www.ncbi.nlm.nih.gov/pubmed/26659815.

323. Ballester LY, Loghavi S, Kanagal-Shamanna R, et al. Clinical Validation of a CXCR4 Mutation Screening Assay for Waldenstrom Macroglobulinemia. Clin Lymphoma Myeloma Leuk 2016;16:395-403 e391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/27268124.

324. Bardwick PA, Zvaifler NJ, Gill GN, et al. Plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes: the POEMS syndrome. Report on two cases and a review of the literature. Medicine (Baltimore) 1980;59:311-322. Available at: https://www.ncbi.nlm.nih.gov/pubmed/6248720.

325. Dispenzieri A. POEMS Syndrome: 2019 Update on diagnosis, risk-stratification, and management. Am J Hematol 2019;94:812-827. Available at: https://www.ncbi.nlm.nih.gov/pubmed/31012139.

326. Khouri J, Nakashima M, Wong S. Update on the Diagnosis and Treatment of POEMS (Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal Gammopathy, and Skin Changes) Syndrome: A Review. JAMA Oncol 2021;7:1383-1391. Available at: https://www.ncbi.nlm.nih.gov/pubmed/34081097.

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