National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Multiple Myeloma

NCCN Evidence Blocks™

Version 3.2016

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NCCN Guidelines Version 3.2016 Panel Members
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Discussion

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NCCN Guidelines Panel Disclosures

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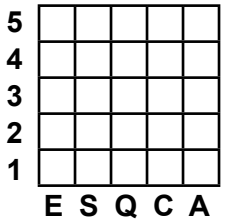
Clinical Trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN member institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

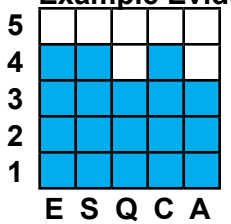
See NCCN Categories of Evidence and Consensus

NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS



E = Efficacy of Regimen/Agent
S = Safety of Regimen/Agent
Q = Quality of Evidence
C = Consistency of Evidence
A = Affordability of Regimen/Agent

Example Evidence Block



E = 4
S = 4
Q = 3
C = 4
A = 3

Efficacy of Regimen/Agent

5	**Highly effective:** Often provides long-term survival advantage or has curative potential
4	**Very effective:** Sometimes provides long-term survival advantage or has curative potential
3	**Moderately effective:** Modest, no, or unknown impact on survival but often provides control of disease
2	**Minimally effective:** Modest, no, or unknown impact on survival and sometimes provides control of disease
1	**Palliative:** Provides symptomatic benefit only

Safety of Regimen/Agent

5	**Usually no meaningful toxicity:** Uncommon or minimal side effects. No interference with activities of daily living (ADLs)
4	**Occasionally toxic:** Rare significant toxicities or low-grade toxicities only. Little interference with ADLs
3	**Mildly toxic:** Mild toxicity that interferes with ADLs is common
2	**Moderately toxic:** Significant toxicities often occur; life threatening/fatal toxicity is uncommon. Interference with ADLs is usual
1	**Highly toxic:** Usually severe, significant toxicities or life threatening/fatal toxicity often observed. Interference with ADLs is usual and/or severe

Note: For significant chronic or long-term toxicities, score decreased by 1

Quality of Evidence

5	**High quality:** Multiple well-designed randomized trials and/or meta-analyses
4	**Good quality:** Several well-designed randomized trials
3	**Average quality:** Low quality randomized trials or well-designed non-randomized trials
2	**Low quality:** Case reports or clinical experience only
1	**Poor quality:** Little or no evidence

Consistency of Evidence

5	**Highly consistent:** Multiple trials with similar outcomes
4	**Mainly consistent:** Multiple trials with some variability in outcome
3	**May be consistent:** Few trials or only trials with few patients; lower quality trials whether randomized or not
2	**Inconsistent:** Meaningful differences in direction of outcome between quality trials
1	**Anecdotal evidence only:** Evidence in humans based upon anecdotal experience

Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

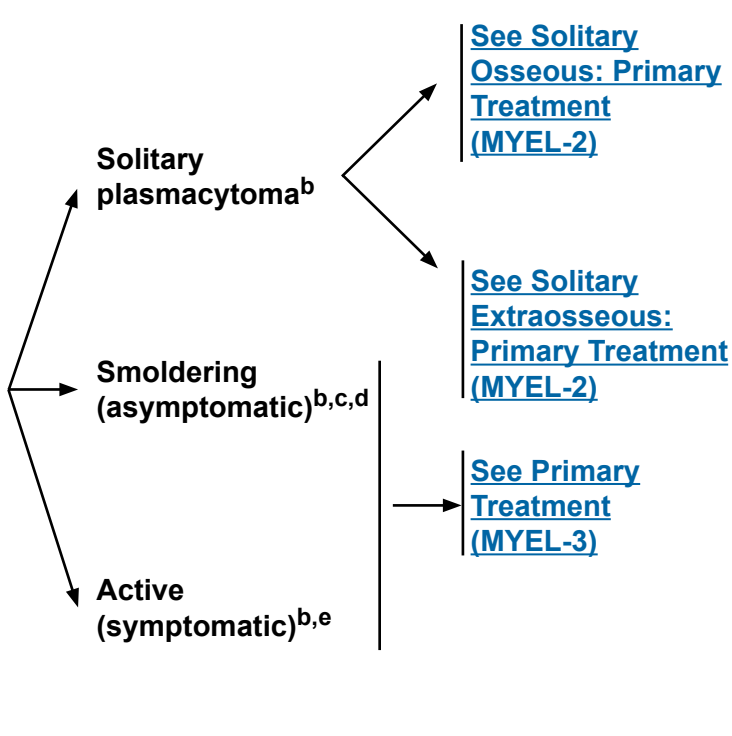
5	**Very inexpensive**
4	**Inexpensive**
3	**Moderately expensive**
2	**Expensive**
1	**Very expensive**

CLINICAL PRESENTATION

- **H&P**
- **CBC, differential, platelet count**
- **BUN/creatinine, electrolytes**
- **LDH**
- **Calcium/albumin**
- **Beta-2 microglobulin**
- **Serum free light chain (FLC) assay**
- **Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)**
- **24-h urine for total protein, urine protein electrophoresis (UPEP), urine immunofixation electrophoresis (UIFE)**
- **Skeletal survey**
- **Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry**
- **Cytogenetics**
- **FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 amplification]**

Useful Under Some Circumstances

- **Imaging with whole body MRI or PET/CT scan[a]**
- **Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma**
- **Bone densitometry**
- **Plasma cell labeling index**
- **Staining of marrow and fat pad for amyloid**
- **Serum viscosity**
- **HLA typing**



[a]Additional testing (whole body MRI or PET/CT scan) recommended to discern active from smoldering myeloma, if skeletal survey is negative.
[b]See Staging Systems for Multiple Myeloma (MYEL-A).
[c]See Smoldering Myeloma (Asymptomatic) (MYEL-B).
[d]Includes Durie-Salmon Stage I Myeloma.
[e]See Active Myeloma (Symptomatic) (MYEL-B).

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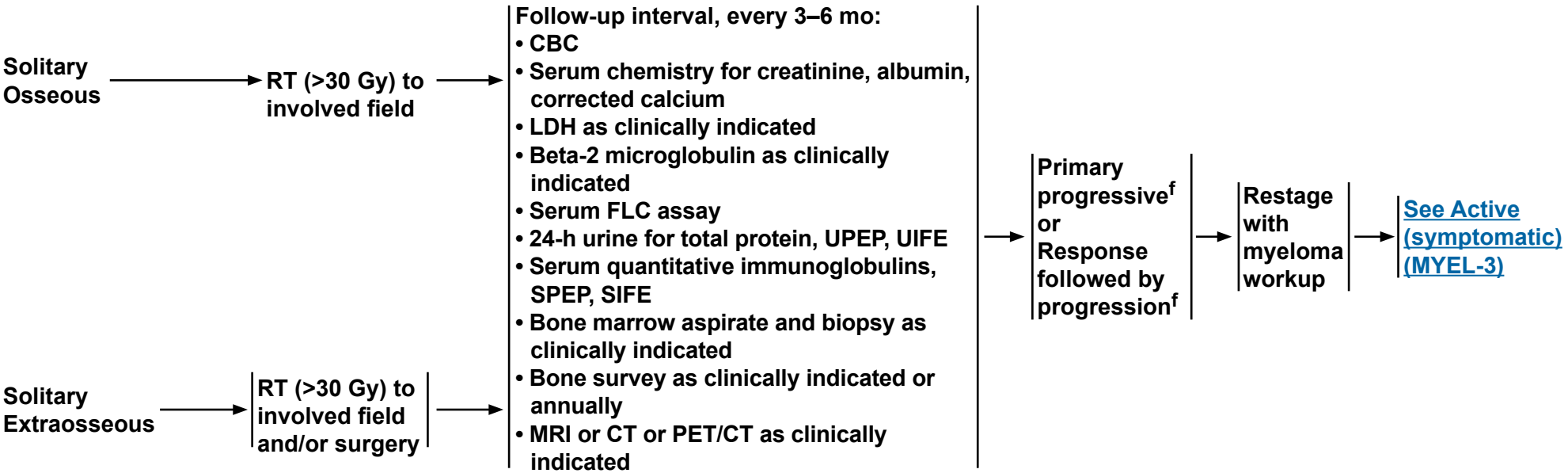

[f] See Response Criteria for Multiple Myeloma (MYEL-C).

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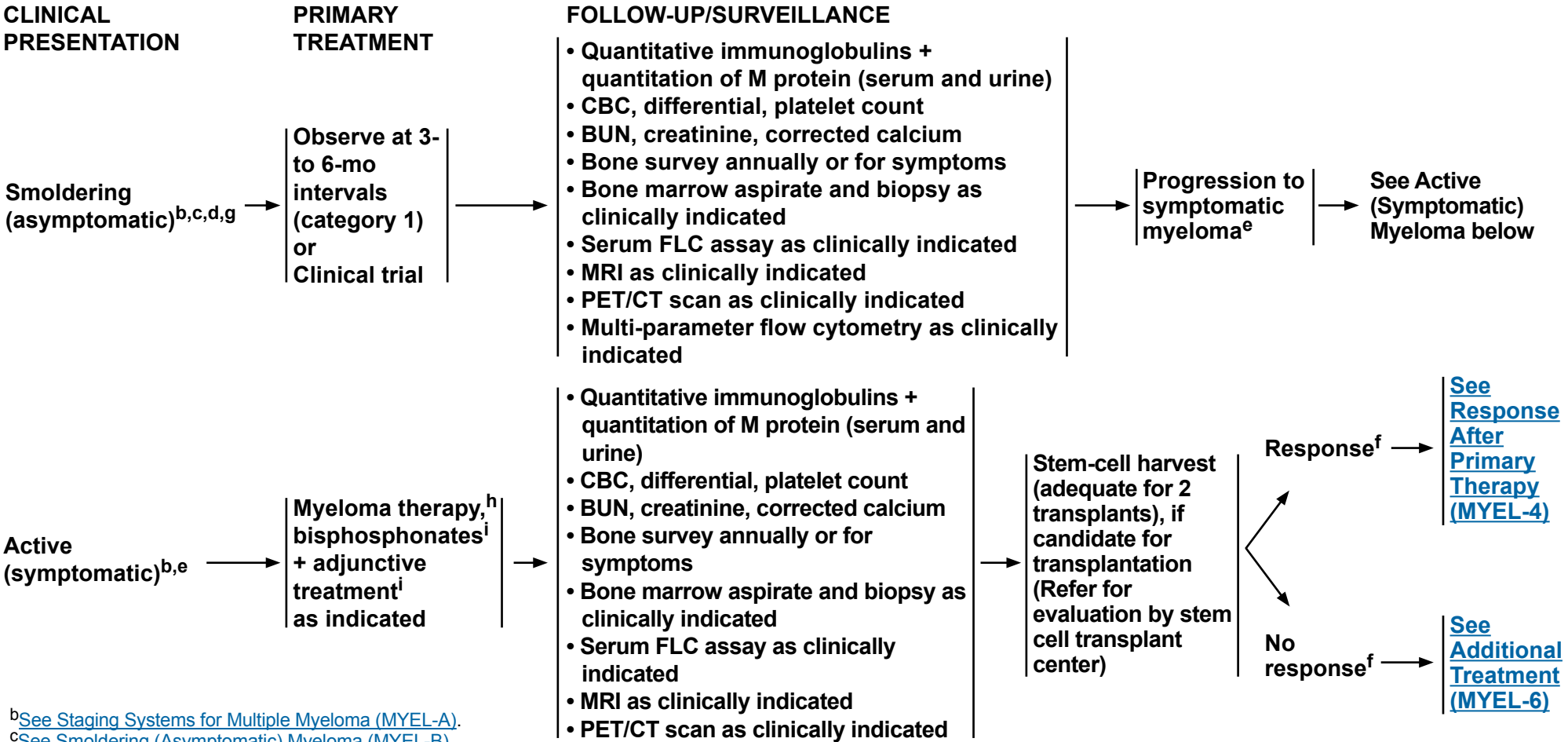

[b] See Staging Systems for Multiple Myeloma (MYEL-A).
[c] See Smoldering (Asymptomatic) Myeloma (MYEL-B).
[d] Includes Durie-Salmon Stage I Myeloma.
[e] See Active (Symptomatic) Myeloma (MYEL-B).
[f] See Response Criteria for Multiple Myeloma (MYEL-C).
[g] A relatively small randomized prospective study has shown benefit of early treatment with lenalidomide and dexamethasone for a subset of patients with smoldering myeloma with certain high-risk features predictive for early clinical progression (Mateos MV, Hernandez M, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-447). However, the high-risk criteria specified in the study are not in common use. Alternative criteria are under investigation (Dispienzeri A, Kyle R, Katzmann J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood 2008;111:785-789). The NCCN panel strongly recommends enrolling eligible smoldering myeloma patients with high-risk criteria in clinical trials.
[h] See Myeloma Therapy (MYEL-D).
[i] See Adjunctive Treatment (MYEL-E).

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ACTIVE (SYMPTOMATIC) MYELOMA

Response after primary therapy[f]

- **Autologous[j,k] stem cell transplant (category 1)**
- **OR**
- **Allogeneic[l,m] stem cell transplant**
- **OR**
- **Continue myeloma therapy until best response[f]**

FOLLOW-UP/SURVEILLANCE

- **Autologous[j,k] stem cell transplant (category 1)** and **Allogeneic[l,m] stem cell transplant** →
  - **Quantitative immunoglobulins + quantitation of M protein at least every 3 mo**
  - **CBC, differential, platelet count**
  - **BUN, creatinine, calcium**
  - **Bone survey annually or for symptoms**
  - **Bone marrow aspirate and biopsy as clinically indicated**
  - **Serum FLC assay as clinically indicated**
  - **MRI as clinically indicated**
  - **PET/CT scan as clinically indicated**

  → **See Additional Treatment (MYEL-5)**

- **Continue myeloma therapy until best response[f]** → **Monitor as above and/or maintenance therapy[h]** → **See Additional Treatment (MYEL-6)**

[f] See Response Criteria for Multiple Myeloma (MYEL-C).
[h] See Myeloma Therapy (MYEL-D).
[j] Autologous transplantation: Category 1 evidence supports proceeding straight after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival, although progression-free survival can be prolonged by an early transplant. (See Discussion section).
[k] Renal dysfunction and advanced age are not contraindications to transplant.
[l] Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.
[m] A prospective trial by Bruno et al found improved survival for patients receiving an autologous transplant followed by non-myeloablative allograft compared to patients who received tandem autologous grafts. In contrast, the IFM trial (99-03) and the BMT-CTN 0102 trial reported no overall survival or progression-free survival with autologous transplant followed by mini-allograft in high-risk myeloma patients.

Bruno B, Rotta M, Patriarca F, et al. A comparison of allografting with autografting for newly diagnosed myeloma. N Engl J Med 2007;356:1110-1120.
Garban F, Attal M, Michallet M, et al. Prospective comparison of autologous stem cell transplantation followed by dose-reduced allograft (IFM99-03 trial) with tandem autologous stem cell transplantation (IFM99-04 trial) in high-risk de novo multiple myeloma. Blood 2006;107:3474-3480.
Krishnan A, Pasquini MC, Logan B, et al. Autologous haemopoietic stem-cell transplantation followed by allogeneic or autologous haemopoietic stem-cell transplantation in patients with multiple myeloma (BMT CTN 0102): a phase 3 biological assignment trial. Lancet Oncol 2011;12:1195-1203.
Hegenbart U, et al. Tandem autologous/reduced-intensity conditioning allogeneic stem-cell transplantation versus autologous transplantation in myeloma: long-term follow-up. J Clin Oncol 2011;29:3016-3022.

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ACTIVE (SYMPTOMATIC) MYELOMA **ADDITIONAL TREATMENT**

Post-allogeneic stem cell transplant:

Progressive disease[f] → **Therapy for previously treated myeloma[h] on or off clinical trial or Donor lymphocyte infusion**

Response or stable disease[f] → **Maintenance therapy[h] on clinical trial or Observe** → **Progressive disease[f]** → **Therapy for previously treated myeloma[h] on or off clinical trial or Donor lymphocyte infusion**

Post-autologous stem cell transplant:

Progressive disease[f] → **Therapy for previously treated myeloma[h] on or off clinical trial or Allogeneic stem cell transplant[l]**

Response or stable disease[f] → **Maintenance therapy[h] or Second tandem transplant ± maintenance therapy[h,n] or Observe** → **Progressive disease[f]** → **Therapy for previously treated myeloma[h] on or off clinical trial ± additional autologous stem cell transplant[o,p] or Allogeneic stem cell transplant[l]**

[f]See Response Criteria of Multiple Myeloma (MYEL-C).
[h]See Myeloma Therapy (MYEL-D).
[k]Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.
[n]There is evidence from a randomized, phase III trial showing that maintenance therapy after tandem transplant significantly reduced the risk of disease progression (HR, 0.47).Palumbo A, Cavallo F, Gay F, et al. Autologous transplantation and maintenance therapy in multiple myeloma. N Engl J Med 2014;371:895-905.
[o]Additional autologous transplant on or off clinical trial is an option depending on the time interval between the preceding stem cell transplant and documented progression.
[p]Retrospective studies suggest a 2-3 y minimum length of remission for consideration of a second autologous stem cell transplant for salvage therapy (category 2B).

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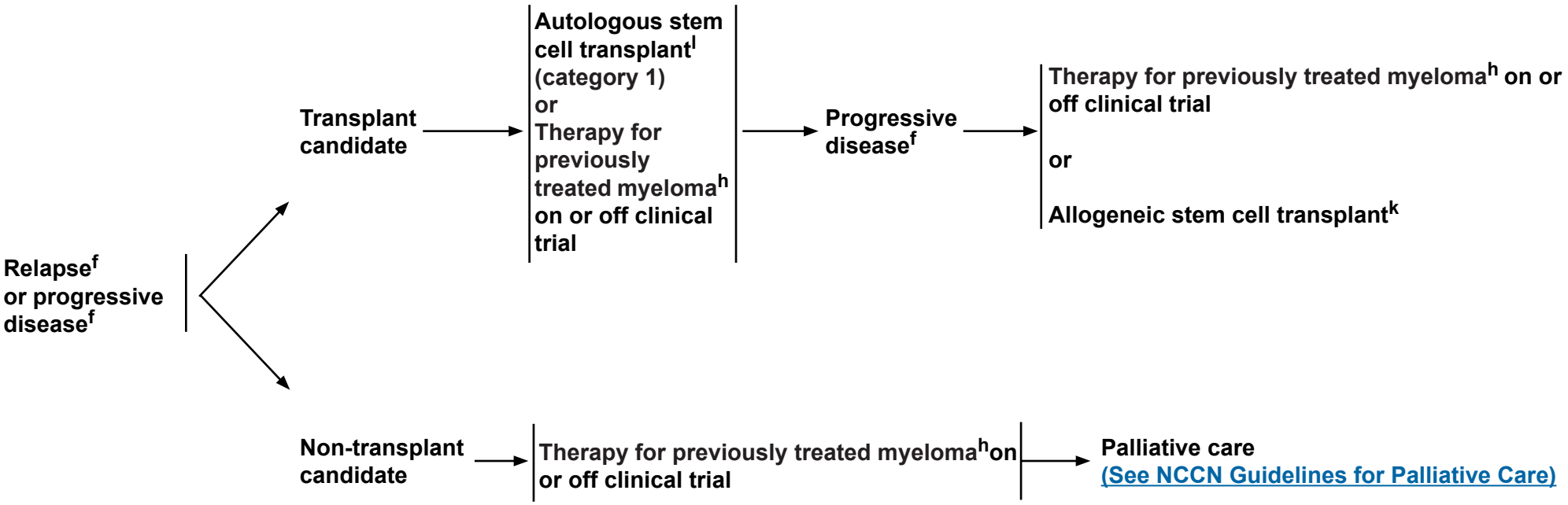
ACTIVE (SYMPTOMATIC) MYELOMA

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



[f] See Response Criteria for Multiple Myeloma (MYEL-C).
[h] See Myeloma Therapy (MYEL-D).
[k] Allogeneic stem cell transplant may include nonmyeloablative (mini) following autologous stem cell transplant or fully myeloablative preferably on a clinical trial. Current data do not support miniallografting alone.
[l] Autologous transplantation: Category 1 evidence supports proceeding straight after induction therapy to high-dose therapy and stem cell transplant versus saving the stem cell transplant for salvage therapy. Evidence suggests equivalent overall survival although progression-free survival can be prolonged by an early transplant.
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.
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.

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STAGING SYSTEMS FOR MULTIPLE MYELOMA[1]

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

Return to Clinical Presentation (MYEL-1)

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

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DEFINITION OF MULTIPLE MYELOMA (SMOLDERING AND ACTIVE)

Smoldering (Asymptomatic) Myeloma[1,2]

- **Serum monoclonal protein**
  - **IgG or IgA ≥3 g/dL;**

Or

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

And/Or

- **Clonal bone marrow plasma cells 10%–60%**

And

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

Active (Symptomatic) Myeloma[2,3]

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

And

Any one or more of the following myeloma defining events:

- **Calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)**
- **Renal insufficiency (creatinine >2 mg/dL) [>177 µmol/L] or creatinine clearance <40 mL/min**
- **Anemia (hemoglobin <10 g/dL or hemoglobin >2 g/dL below the lower limit of normal)**
- **One or more osteolytic bone lesions on skeletal radiography, CT, or PET-CT**
- **Clonal bone marrow plasma cells ≥60%**
- **Abnormal serum FLC ratio ≥100 (involved kappa) or <0.01 (involved lambda)**
- **>1 focal lesions on MRI studies > 5mm**

[1]The understanding of smoldering (asymptomatic) myeloma is evolving rapidly. Some studies have shown that patients with certain characteristics, including IgG levels of >3 g/dL, IgA of >2 g/dL, or urinary Bence Jones protein of >1 g/24 h (Mateos MV, Hernandez M, Giraldo P, et al. Lenalidomide plus dexamethasone for high-risk smoldering multiple myeloma. N Engl J Med 2013;369:438-447) or abnormal free light chain ratios (Dispienzeri A, Kyle R, Katzmann J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. Blood 2008;111:785-789), have an increased risk of progression to active (symptomatic) myeloma. It is also increasingly recognized, that the classical definition of smoldering myeloma using certain tests such as plain x-rays is outdated. Efforts to modify these criteria and reclassify some patients previously classified as “asymptomatic” to having “active disease” are underway.

[2]Rajkumar SV, Dimopoulos MA, Palumbo A, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 2014;Vol 15,e538-e548.

[3]Other examples of active disease include: repeated infections, amyloidosis, or hyperviscosity.

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Return to Clinical Presentation (MYEL-1)

RESPONSE CRITERIA FOR MULTIPLE MYELOMA
(Revised Uniform Response Criteria by the International Myeloma Working Group)[1]

Response Category	Response Criteria
CR, complete response	Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow; in patients for whom only measurable disease is by serum FLC level, normal FLC ratio of 0.26 to 1.65 in addition to CR criteria is required; two consecutive assessments are needed
sCR, stringent complete response	CR as defined plus normal FLC ratio and absence of clonal plasma cells by immunohistochemistry or two- to four-color flow cytometry; two consecutive assessments of laboratory parameters are needed
Immunophenotypic CR	sCR as defined plus absence of phenotypically aberrant plasma cells (clonal) in bone marrow with minimum of 1 million total bone marrow cells analyzed by multiparametric flow cytometry (with >four colors)
Molecular CR	CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction (sensitivity 10^{-5})
VGPR, very good partial response	Serum and urine M component detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M component plus urine M component <100 mg/24 h; in patients for whom only measurable disease is by serum FLC level, >90% decrease in difference between involved and uninvolved FLC levels, in addition to VGPR criteria, is required; two consecutive assessments are needed
PR, partial response	≥50% reduction of serum M-protein and 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, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required. Two consecutive assessments are needed; no known evidence of progressive or new bone lesions if radiographic studies were performed.
MR, minimal response for relapsed refractory myeloma only	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50% to 89% In addition, if present at baseline, 25% to 49% reduction in size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
SD, stable disease	Not meeting criteria for CR, VGPR, PR, or progressive disease; no known evidence of progressive or new bone lesions if radiographic studies were performed
PD, progressive disease	Increase of 25% from lowest response value in any of following: Serum M component with absolute increase ≥0.5 g/dL; serum M component increases ≥1 g/dL are sufficient to define relapse if starting M component is ≥5 g/dL and/or; Urine M component (absolute increase must be ≥200 mg/24 h) and/or; Only in patients without measurable serum and urine M-protein levels: difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); Only in patients without measurable serum and urine M-protein levels and without measurable disease by FLC level, bone marrow plasma cell percentage (absolute percentage must be ≥10%) Development of new or definite increase in size of existing bone lesions or soft tissue plasmacytoma Development of hypercalcemia that can be attributed solely to plasma cell proliferative disorder Two consecutive assessments before new therapy are needed

[1]From 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

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RESPONSE CRITERIA FOR MULTIPLE MYELOMA
(Uniform Response Criteria for Disease Relapse by the International Myeloma Working Group)[1]

Relapse Subcategory	Relapse Criteria
Clinical relapse[2]	**Clinical relapse requires one or more of:** **Direct indicators of increasing disease and/or end organ dysfunction (CRAB features).**[3] **It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice** **• Development of new soft tissue plasmacytomas or bone lesions** **• Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion** **• Hypercalcemia (>11.5 mg/dL) [2.85 mmol/L]** **• Decrease in hemoglobin of ≥2 g/dL [1.25 mmol/L]** **• Rise in serum creatinine by 2 mg/dL or more [177 µmol/L or more]**
Relapse from CR[3] **(To be used only if the endpoint studied is DFS, disease-free survival)**[5]	**Any one or more of the following:** **• Reappearance of serum or urine M-protein by immunofixation or electrophoresis** **• Development of ≥5% plasma cells in the bone marrow**[4] **• Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, hypercalcemia)**

[1]From Durie BG, Harousseau JL, Miguel JS, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.
[2]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[3]For progressive disease, serum M-component increases of ≥1 g/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.
[4]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[5]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria for progressive disease.

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

MYELOMA THERAPY[1-4]

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 transplants.

Primary Therapy for Transplant Candidates (Assess for response after 2 cycles)	
Preferred Regimens	**Other Regimens**
• Bortezomib/dexamethasone (category 1)	• Carfilzomib[5]/lenalidomide[6]/dexamethasone
• Bortezomib/cyclophosphamide/dexamethasone	• Dexamethasone (category 2B)
• Bortezomib/doxorubicin/dexamethasone (category 1)	• Ixazomib/lenalidomide[6]/dexamethasone
• Bortezomib/lenalidomide[6]/dexamethasone (categoy 1)	• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)
• Bortezomib/thalidomide/dexamethasone (category 1)	• Thalidomide/dexamethasone (category 2B)
• Lenalidomide[6]/dexamethasone (category 1)	

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.
[3]Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[4]Prophylactic anticoagulation recommended for patients receiving immunomodulator-based therapy.
[5]Optimal dosing in this regimen has not been defined.
[6]Consider harvesting peripheral blood stem cells prior to prolonged exposure to lenalidomide.

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

MYELOMA THERAPY[1-4]

Primary Therapy for Non-Transplant Candidates (Assess for response after 2 cycles)

Preferred Regimens	Other Regimens
• Bortezomib/dexamethasone	• Dexamethasone (category 2B)
• Bortezomib/cyclophosphamide/dexamethasone	• Ixazomib/lenalidomide/dexamethasone
• Bortezomib/lenalidomide/dexamethasone (category 1)	• Liposomal doxorubicin/vincristine/dexamethasone (DVD) (category 2B)
• Lenalidomide/low-dose dexamethasone (category 1)[8]	• Melphalan/prednisone (MP)
• Melphalan/prednisone/bortezomib (MPB) (category 1)	• Thalidomide/dexamethasone (category 2B)
• Melphalan/prednisone/lenalidomide (MPL) (category 1)	• Vincristine/doxorubicin/dexamethasone (VAD) (category 2B)
• Melphalan/prednisone/thalidomide (MPT) (category 1)	

Maintenance Therapy

Preferred Regimens	Other Regimens
• Bortezomib	• Bortezomib + prednisone (category 2B)
• Lenalidomide[7] (category 1)	• Bortezomib + thalidomide (category 2B)
• Thalidomide (category 1)	• Interferon (category 2B)
	• Dexamethasone (category 2B)
	• Prednisone (caegory 2B)
	• Thalidomide + prednisone (category 2B)

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.
[3]Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[4]Prophylactic anticoagulation recommended for patients receiving immunomodulator-based therapy.

[7] 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.
[8]Continuously until progression. Facon T, Dimopoulos MA, Dispenzieri A, et al. Continuous lenalidomide and low-dose dexamethasone demonstrates a significant PFS and OS advantage in transplant ineligible NDMM patients. The FIRST: MM-020/IFM0701 [oral]. Oral presented at: 55th Annual Meeting of the American Society of Hematology (ASH) 2013; December 7-10.

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MYELOMA THERAPY[1-4, 9]

Therapy for Previously Treated Multiple Myeloma

Preferred Regimens

- Repeat primary induction therapy (if relapse at >6 mo)
- Bortezomib (category 1)
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dexamethasone
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Bortezomib/thalidomide/dexamethasone
- Carfilzomib
- Carfilzomib/dexamethasone
- Carfilzomib/lenalidomide/dexamethasone (category 1)
- Cyclophosphamide/lenalidomide/dexamethasone
- Daratumumab[10]
- Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE)
- Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide/bortezomib (VTD-PACE)
- Elotuzumab[11]/lenalidomide/dexamethasone (category 1)
- Ixazomib[12]
- Ixazomib[12]/dexamethasone
- Ixazomib[12]/lenalidomide/dexamethasone (category 1)
- High-dose cyclophosphamide
- Lenalidomide/dexamethasone[13] (category 1)
- Panobinostat/bortezomib/dexamethasone[14] (category 1)
- Pomalidomide[15]/dexamethasone[13] (category 1)
- Thalidomide/dexamethasone[13]

Other Regimens

- Bendamustine
- Bortezomib/vorinostat
- Lenalidomide/bendamustine/dexamethasone
- Panobinostat[14]/carfilzomib

[1]Selected, but not inclusive of all regimens.
[2]Recommend herpes zoster prophylaxis for patients treated with proteasome inhibitors.
[3]Consider using subcutaneous bortezomib for patients with pre-existing or high-risk peripheral neuropathy.
[4]Prophylactic anticoagulation recommended for patients receiving immunomodulator-based therapy.
[9]Consideration for appropriate regimen is based on the context of clinical relapse.
[10]Indicated for the treatment of patients who have received at least three prior therapies, including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double refractory to a PI and immunomodulatory agent.
[11]Indicated in combination with lenalidomide and dexamethasone for the treatment of patients who have received one to three prior therapies.
[12]Indicated for the treatment of patients who have received at least one prior therapy.
[13]Consider single-agent lenalidomide, pomalidomide, or thalidomide for steroid-intolerant individuals.
[14]Indicated for the treatment of patients who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.
[15]Indicated for the treatment of patients who have received at least two prior therapies including bortezomib and an immunomodulatory agent and have demonstrated disease progression on or within 60 days of completion of the last therapy.

Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.
All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

ADJUNCTIVE TREATMENT

Bone Disease
- Bisphosphonates (pamidronate and zoledronic acid)[1]
  - All patients receiving primary myeloma therapy should be given bisphosphonates (category 1)
    - ◊ A dental exam is recommended before starting bisphosphonate therapy
  - Use of bisphosphonates in smoldering or stage I disease preferably in the context of a clinical trial. These patients should have bone survey annually and if symptomatic
  - Monitor for renal dysfunction with use of bisphosphonates
  - Monitor for osteonecrosis of the jaw
- RT
  - Low-dose RT (10–30 Gy) can be used as palliative treatment for uncontrolled pain, for impending pathologic fracture or impending cord compression
  - Limited involved fields should be used to limit the impact of irradiation on stem-cell harvest or impact on potential future treatments
- 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/furosemide, bisphosphonates (zoledronic acid preferred), steroids, and/or calcitonin.

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

Anemia
- See NCCN Guidelines for Cancer- and Chemotherapy-Induced Anemia
- Consider erythropoietin for anemic patients

Infection
- See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections
- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection
- Consider pneumococcal polysaccharide vaccine and influenza vaccine
- PCP, herpes, and antifungal prophylaxis if high-dose dexamethasone regimen
- Herpes zoster prophylaxis for patients treated with proteasome inhibitors

Renal Dysfunction
- Maintain hydration to avoid renal failure
- Avoid use of NSAIDs
- Avoid IV contrast
- Plasmapheresis (category 2B)
- Not a contraindication to transplant
- Monitor for renal dysfunction with chronic use of bisphosphonates

Coagulation/thrombosis
- Prophylactic anticoagulation recommended for patients receiving immunomodulator-based therapy
- See NCCN Guidelines for Venous Thromboembolic Disease

[1]Both pamidronate and zoledronic acid have shown equivalence in terms of reducing risk of skeletal-related events in randomized trials. In a recent MRC IX trial, in addition to benefits for bone health, zoledronic acid reduced mortality by 16% versus clodronic acid and extended median overall survival by 5.5 months. 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.

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All recommendations are category 2A unless otherwise indicated.
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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/22/15

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 noted.

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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. The American Cancer Society has estimated 26,850 new cancer cases in the United States in 2015, with an estimated 11,240 deaths.[1] The mean age of affected individuals is 62 years for men (75% >70 years of age) and 61 years for women (79% >70 years of age). The 5-year survival rate reported in the SEER database has increased from 25% in 1975 to 34% in 2003 due to newer and more effective treatment options available.

MM is typically sensitive to a variety of cytotoxic drugs, both as initial treatment or as treatment for relapsed disease. Unfortunately responses are transient, and MM is not considered curable with current approaches. However, treatment of MM has been rapidly evolving because of the introduction of new drugs, such as thalidomide, lenalidomide, and bortezomib.[2-4] In addition, there is emerging understanding of the microenvironment of the bone marrow, creating the rationale for new combinations of therapies and new drug development.[5,6] Studies of the associated cytogenetic abnormalities indicate that MM is a heterogeneous disease, suggesting that risk-adapted approaches and individualizing treatment will further help refine patient management.

These guidelines developed by the NCCN Multiple Myeloma Panel Members address diagnosis, treatment, and follow-up for patients with MM.

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Multiple Myeloma, an electronic search of the PubMed database was performed to obtain key literature in MM published between 04/08/2014 and 04/08/2015, using the following search terms: Smoldering Myeloma OR Multiple Myeloma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[7]

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

The PubMed search resulted in 611 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Any recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN webpage.

Initial Diagnostic Workup

The initial diagnostic workup in all patients should include a history and physical (H&P) examination and the following baseline blood studies and biological assessments to differentiate symptomatic and asymptomatic MM: a complete blood count (CBC) with differential and platelet counts; blood urea nitrogen (BUN); serum creatinine and serum electrolytes; serum calcium; albumin; lactate dehydrogenase (LDH); and beta-2 microglobulin. Increased BUN and creatinine indicate

decreased kidney function, whereas LDH levels help assess tumor cell burden. The level of beta-2 microglobulin reflects the tumor mass and is now considered a standard measure of the tumor burden.

The monoclonal protein (M-protein) component in serum and urine is detected and evaluated by the following urine and serum analyses. 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).

Serum analysis also includes quantitative immunoglobulin levels of different types of antibodies (IgG, IgA, and IgM); serum protein electrophoresis (SPEP); and serum immunofixation electrophoresis (SIFE) to obtain more specific information about the type of abnormal antibodies present. Assessing changes and proportions of various proteins, particularly the M-protein, helps track the progression of myeloma disease and response to treatment. Use of serum free light chain (FLC) assay along with SPEP and SIFE yields high sensitivity while screening for MM and related plasma cell disorders.[8] Therefore, this assay is now included as a part of the initial diagnostic workup in the NCCN Guidelines for Multiple Myeloma. The serum FLC assay also has prognostic value in plasma cell disorders, including monoclonal gammopathy of undetermined significance (MGUS), smoldering myeloma, active myeloma, immunoglobulin light chain amyloidosis, and solitary plasmacytoma.[8,9] The serum FLC assay also allows for quantitative monitoring of patients with light chain amyloidosis and oligosecretory myeloma. In addition to all of the above, the FLC ratio is required for documenting stringent complete response (sCR) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria.[10] The FLC assay cannot replace the 24-h UPEP for monitoring patients with measurable urinary M proteins.

Most patients have serum proteins with or without associated urinary protein. In the Mayo Clinic review of 1027 patients newly diagnosed with MM, 20% of patients had secretory urinary proteins; however, 3% of patients had neither serum nor urine proteins, and therefore had nonsecretory myeloma.[11] The serum FLC assay is useful to monitor disease response and progression in a proportion of patients with nonsecretory myeloma. Once the myeloma or M-protein is quantified, it is important to use the same test for serial studies to ensure accurate relative quantification.

To evaluate bone marrow plasma cell infiltration, bone marrow aspiration and biopsy is recommended to detect quantitative and/or qualitative abnormalities of bone marrow plasma cells. To evaluate lytic bone lesions, full skeleton radiographic survey is recommended.

Although MM may be morphologically similar, several subtypes of the disease have been identified at the genetic and molecular level. Bone marrow studies at initial diagnosis should include chromosome analysis by conventional karyotyping (cytogenetics) and fluorescence in situ hybridization (FISH) performed with the plasma cells obtained from bone marrow aspiration. Specific chromosomal abnormalities have been identified in patients with MM involving translocations, deletions, or amplifications.

Deletion of chromosome 13 [del(13)] seems to have an amplifying effect on cell cycle gene expression and is reported to be associated with short event-free survival (EFS) and overall survival (OS).[12] Deletion of 17p13 (the locus for the tumor-suppressor gene, p53) leads to loss of heterozygosity of *TP53* and is considered a high-risk feature in MM.[13-15] Other high-risk chromosomal aberrations in MM are characterized by structural changes that include specific rearrangements involving the IGH gene (encoding immunoglobulin heavy chain), located at 14q32.

Several subgroups of patients are identified on the basis of 14q32 translocations. The three main translocations are the t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23). From a clinical point of view, t(4;14) is the most important one. Several studies have confirmed that patients with this translocation have a poor prognosis.[16-18] Conflicting data exist regarding t(14;16); although one study showed no impact on prognosis,[19] some studies have shown a negative prognostic impact.[20,21]

A translocation between 11 and 14 [t(11;14)] has been reported to be associated with an improved survival.[22,23] Abnormalities of chromosome 1 are also among the frequent chromosomal alterations in MM.[24] The short arm is most often associated with deletions and the long arm with amplifications.[25] Gains/amplification of 1q21 increases the risk of MM progression and incidence of the amplification is higher in relapsed than in newly diagnosed patients.[24,26]

Stratification of patients into various risk groups based on the chromosomal markers is being utilized by some centers for prognostic counseling, selection, and sequencing of therapy approaches.[27,28] According to the NCCN Multiple Myeloma Panel Members, the FISH panel for prognostic estimation should include t(4;14), t(14;16), and 17p13 deletions, t(11;14), chromosome 13 deletion, and chromosome 1 amplification. The utility of this information is to determine biological subtype and for prognostic recommendations.

In addition to cytogenetic markers of prognosis, it is postulated that biological factors or gene expression signatures may be capable of discerning prognosis and helping rational therapeutic decisions.[29,30] Further understanding of the molecular subtypes of MM is emerging from the application of high-throughput genomic tools such as gene expression profiling (GEP).[31] With the currently available novel treatment approaches, a majority of patients with MM can now anticipate long-term disease control. However, patients with cytogenetically and molecularly defined high-risk disease do not receive the same benefit from certain approaches as the low-risk patients and need alternative therapies. GEP is a powerful and fast tool with the potential to provide additional prognostic value to further refine risk stratification, help therapeutic decisions, and inform novel drug design and development. Several groups have identified and developed 15-gene, 70-gene, and 92-gene models based on GEP signatures of MM cells.[32-34] Studies show that patients in the high-risk group based on the 15-gene,[32] 70-gene,[33] or 92-gene[34] models had shorter survival compared with the low-risk group. The NCCN Panel unanimously agreed that although GEP is not currently *routinely* used in clinical practice during diagnostic workup, GEP is a useful tool and may be helpful in selected patients to estimate the aggressiveness of the disease and individualize treatment.

Bone marrow immunohistochemistry may be useful in some cases to confirm presence of monoclonal plasma cells, to more accurately quantify plasma cell involvement, and bone marrow flow cytometry can help define the disease.

Additional Diagnostic Tests

The NCCN Multiple Myeloma Panel recommends additional tests that may be useful under some circumstances. These include MRI,[35] CT, or PET/CT scan.[36] Active myeloma is positive on PET scan.[37,38] PET/CT and MRI scans are more sensitive than plain radiographs and are only indicated when symptomatic areas show no abnormality on routine radiographs. A multivariate analysis showed persistent fluorodeoxyglucose PET/CT positivity before and after primary therapy and subsequent high-dose therapy, and is a predictor of prognosis in patients with symptomatic MM.[39,40]

A tissue biopsy may also be necessary to confirm the presence of plasmacytomas. Plasma cell labeling index may be helpful to identify the fraction of the myeloma cell population that is proliferating.[41] Also, bone marrow and fat pad staining for the presence of amyloid and serum viscosity should be evaluated if hyperviscosity is suspected.

In selected patients with MM, physicians may use allogeneic (ie, from someone else) transplantation. In this approach, physicians administer non-myeloablative or reduced intensity therapy and infuse stem cells (ie, peripheral blood or bone marrow) obtained from a donor, preferably a human leukocyte antigen (HLA) -identical sibling. In such cases, the patient will need to be HLA-typed.

Since bisphosphonate therapy is a consideration in patients with MM, a baseline bone densitometry test may be recommended.

Diagnostic Categories

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

The IMWG recently updated the disease definition of MM to include biomarkers in addition to existing requirements of CRAB features. [42] The CRAB criteria that define MM include: hypercalcemia [>11.5 mg/dL], renal insufficiency [creatinine >2 mg/dL, anemia [hemoglobin <10 g/dL or 2 g/dL < normal], and presence of bone lesions). The IMWG has also clarified that presence of one or more osteolytic lesions seen on skeletal radiography, whole body MRI or PET-CT fulfils the criteria for bone disease.[42] The MM defining biomarkers identified by the IMWG include one or more of the following: ≥ 60% clonal plasma cells in the bone marrow; involved/uninvolved free light chain (FLC) ratio of 100 or more with the involved free light chain being ≥100 mg/L; MRI with more than one focal lesion (involving bone or bone marrow).[42]

The criteria by the IMWG for smoldering (asymptomatic) patients include serum monoclonal protein (IgG or IgA) ≥30 g/L and/or clonal bone marrow plasma cells 10 to 60% *and* absence of myeloma defining events or amyloidosis.[42] The updated IMWG diagnostic criteria for MM helps to initiate therapy before end-organ damage on the basis of specific biomarkers, and also allows the use of sensitive imaging criteria to diagnose MM, including PET-CT and MRI.[42] Patients with high-risk soldering myeloma, who are being observed at 3-6 month intervals with sensitive imaging techniques as clinically indicated, can be initiated on therapy without waiting for CRAB features to appear.

Those with active myeloma can be categorized according to stage, based on either the Durie-Salmon staging system or the International Staging System (ISS).[43] The ISS system is based on easily obtained laboratory measures (serum beta-2 -microglobulin and serum albumin) and is easier to use than the Durie-Salmon staging system for patients with previously untreated MM.

Response Criteria

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

The IMWG response criteria were developed from the European Group for Blood and Marrow Transplant/International Bone Marrow Transplant Registry/Autologous Blood and Bone Marrow Transplant Registry (EBMT/IBMTR/ABMTR) response criteria,[44] with revisions and improvements to help uniform reporting.

The updated IMWG response criteria definitions[10,45,46] for complete response (CR), stringent CR (sCR), immunophenotypic CR, molecular CR, very good partial response (VGPR), partial response (PR), MR for relapsed refractory myeloma, stable disease (SD), and progressive disease (PD) are outlined in the NCCN Guidelines for Multiple Myeloma section titled *Response Criteria for Multiple Myeloma*. It is recommended that the IMWG uniform response criteria should be used in future clinical trials.

Solitary Plasmacytoma

The diagnosis of solitary plasmacytoma requires a thorough evaluation to rule out the presence of systemic disease, because many patients presumed to have solitary plasmacytomas are found to have occult disease. Solitary plasmacytomas are further categorized as osseous or extraosseous. Osseous plasmacytoma is defined as a plasmacytoma emanating from bone without other evidence of disease. Solitary plasmacytomas derived from soft tissue are termed extraosseous.[47] An analysis of the SEER database between 1992 and 2004 found that incidence of osseous plasmacytoma was 40% higher than extraosseous plasmacytoma ($P < .0001$).[48]

Primary Therapy for Solitary Plasmacytoma

The treatment and follow-up options for osseous and extraosseous plasmacytomas are similar. Radiation therapy has been shown to provide excellent local control of solitary plasmacytomas.[49-55] The largest retrospective study (N = 258) included patients with solitary plasmacytoma (n = 206) or extramedullary plasmacytoma (n = 52).[56] 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%. Patients who received localized RT had a lower rate of local relapse (12%) than those who did not (60%).[55]

The optimal radiation dose for treatment of solitary plasmacytomas is not known. The median dose used in most published papers is 40 Gy with doses ranging from 30 to 60 Gy.[54,55,57]

For those patients with osseous plasmacytoma, the NCCN Panel recommends that primary radiation therapy (> 30 Gy to the involved field).to the involved field is the initial treatment and is potentially curative. For extraosseous plasmacytomas primary treatment is radiation therapy (> 30 Gy to the involved field) [52] to the involved field followed by surgery[58] if necessary.

Surveillance/Follow-up Tests for Solitary Plasmacytoma

Follow-up and surveillance tests for both solitary plasmacytoma and extraosseous plasmacytoma consist of blood and urine tests. Serial and frequent measurements of M-protein are required to confirm disease sensitivity.

The blood tests include CBC; serum chemistry for creatine, albumin, and corrected calcium; serum quantitative immunoglobulins, SPEP, and SIFE; and serum FLC assay. Testing for LDH levels and beta-2 microglobulin may be useful under some circumstances.

The urine tests include 24-hour urine assay for total protein, UPEP, and UIFE.

Bone marrow aspirate and biopsy, and imaging studies using MRI and/or CT and/or PET/CT are recommended as clinically indicated. PET imaging may detect early bone marrow involvement in patients with solitary plasmacytoma.[38,59,60] Bone survey is recommended annually or as clinically indicated.

If PD emerges, then the patient should be re-evaluated as described in the Discussion section, *Initial Diagnostic Workup*, and systemic therapy must be administered as indicated.

Smoldering (Asymptomatic) Myeloma

Smoldering (asymptomatic) myeloma describes a stage of disease with no symptoms and no related organ or tissue impairment.[61] Patients with Durie-Salmon stage I myeloma with low amounts of M-protein without significant anemia, hypercalcemia, or bone disease would be included in this category. Patients with asymptomatic smoldering MM may have an indolent course for many years without therapy.

Primary Therapy for Smoldering (Asymptomatic) Multiple Myeloma

Patients with smoldering myeloma, including Durie-Salmon stage I, do not need primary therapy as it may take many months to years before the disease progresses. The risk of transformation to symptomatic myeloma[62] in these patients is life long and therefore should be followed closely.

A relatively small, randomized, prospective, phase III study by the PETHEMA group investigated whether early treatment with lenalidomide and dexamethasone in patients (n = 125) with smoldering myeloma, at high risk of progression to active MM, prolongs the time to progression.[63] 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. At a median follow-up of 40 months (range, 27–57 months), treatment with lenalidomide and dexamethasone delayed median time to progression to symptomatic disease compared to no treatment (time to progression was not reached in the treatment arm compared to 21 months in the observation arm; HR 0.18; 95% CI, 0.09–0.32; $P < .001$). 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; $P = .03$).[63]

According to the NCCN Panel, the high-risk criteria specified in the study are not currently in common use. Based on the criteria used in the trial, some patients with active myeloma were classified as having high-risk smoldering myeloma. This fact is evident from the striking differences in outcome seen between patients who were treated and those who were only observed. The NCCN Panel strongly believes there is need to re-evaluate the definition of high-risk smoldering myeloma. The panel believes that it is too early to begin treating *all* patients with smoldering myeloma at high risk (as defined in the trial) of progression to active MM with any anti-myeloma therapy. The NCCN Multiple Myeloma Panel recommends that patients with smoldering myeloma should initially be observed at 3- to 6-month intervals (category 1 recommendation) or strongly recommends enrolling eligible patients with smoldering myeloma in clinical trials.

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

The surveillance/follow-up tests include CBC; serum chemistry for creatinine, albumin, LDH, calcium, and beta-2 microglobulin; serum quantitative immunoglobulins, SPEP, and SIFE; and serum FLC assay. The urine tests include 24-hour urine assay for total protein, UPEP, and UIFE.

Bone survey is recommended annually or as clinically indicated. Bone marrow aspiration and biopsy and imaging studies with MRI and/or CT and/or PET/CT are recommended as clinically indicated.[64] PET imaging

seems to reliably predict active myeloma; by virtue of FDG uptake, low-level smoldering myeloma is consistently negative on the PET scan.[37] It can also assess the extent of active disease, detect extramedullary involvement, or evaluate treatment response.[38,65-67]

Multiparameter flow cytometry is a newly available tool that can help individualize the follow-up/surveillance strategy for patients with smoldering myeloma. It measures abnormal cells in the bone marrow and provides information regarding the risk of progression to active myeloma. A high proportion of abnormal plasma cells within the bone marrow plasma cell compartment (>95%) has been shown to predict the risk of progression in patients with smoldering myeloma or MGUS, as has quantity and type of M protein (non-IgG) and abnormal serum FLC assay.[68,69] According to the NCCN Multiple Myeloma Panel Members, multiple parameter flow cytometry information may be a useful consideration in the follow-up/surveillance plan of patients with smoldering myeloma. Since this test is not standardized and widely available, they recommend that it should only be performed in laboratories with experience.

If the disease progresses to symptomatic myeloma, then patients should be treated according to the guidelines for symptomatic MM. The IMWG definition for PD is in the section titled *Response Criteria for Multiple Myeloma* in the NCCN Guidelines for Multiple Myeloma.

Active (Symptomatic) Multiple Myeloma

Primary Therapy for Active (Symptomatic) MM

Patients presenting with active (symptomatic) myeloma are initially treated with primary therapy and, in selected patients, primary therapy is followed by high-dose chemotherapy with autologous stem cell support. Stem cell toxins, such as nitrosoureas or alkylating agents, may compromise stem cell reserve, and regimens with these agents (notably melphalan) should be avoided in patients who are potential candidates for stem cell transplant (SCT). Therefore, one of the first steps in evaluating patients with advanced MM is to determine whether they are candidates for high-dose therapy and transplant, based on age and comorbidities. However, it should be noted that advanced age and renal dysfunction are not absolute contraindications to transplant. 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. Bone disease, renal dysfunction, and other complications such as hypercalcemia, hyperviscosity, and coagulation/thrombosis should be treated with appropriate adjunctive measures (see *Adjunctive Treatment for Multiple Myeloma*. In all patients, careful attention to supportive care is critical to avoid early complications that may compromise therapeutic outcome.

The page titled *Myeloma Therapy* in the guidelines has a list of primary therapy regimens recommended by the NCCN Multiple Myeloma Panel Members for transplant and non-transplant candidates and also lists drugs recommended for maintenance therapy. The list is selected and not inclusive of all regimens. The NCCN Multiple Myeloma Panel Members have classified the regimens either as “preferred regimens” or “other regimens” on the basis of a balance of efficacy and toxicity. Research into various primary regimens has focused on improving the CR rates in both transplant and non-transplant candidates. The NCCN Panel Members have noted that it is important to assess for response to primary therapy after 2 cycles.

Lenalidomide is a potent analogue of thalidomide. Both lenalidomide and thalidomide possess immunomodulatory properties.[70] Prophylaxis with an anticoagulation agent is recommended for patients receiving thalidomide- or lenalidomide-based therapy.

Bortezomib-based regimens may be of value in patients with renal failure, and in those with certain adverse cytogenetic features.[71] Bortezomib treatment has been associated with an increased incidence of herpes zoster.[72-74] The incidence of bortezomib-associated herpes zoster may be reduced with the use of prophylactic acyclovir.[75] The risk of deep vein thrombosis (DVT) is low with bortezomib; however, peripheral neuropathy and gastrointestinal disturbance can be higher. Bortezomib-related adverse events are predictable and managed with patient monitoring and appropriate supportive care.[76]

Preferred Primary Therapy Regimens for Transplant Candidates

Bortezomib/Dexamethasone

In the IFM cooperative group trial, 482 transplant-eligible patients were randomized to one of the following four primary therapy arms: vincristine, doxorubicin, and dexamethasone (VAD) (n = 121) alone; or VAD plus consolidation therapy with dexamethasone, cyclophosphamide, etoposide, cisplatin (DCEP; n = 121); or bortezomib and dexamethasone (n = 121); or bortezomib, dexamethasone plus consolidation with DCEP (n = 119). [77] The primary endpoint was assessing response rate after primary therapy. The investigators evaluated the response according to modified EBMT criteria,[44] including additional categories of near CR (CR but immunofixation-positive)[78] and VGPR (serum M-protein reduction ≥90%; urine light chain <100 mg/24 hours).[10] After primary therapy, the overall response rate (ORR) (78.5% vs. 62.8%) and the rates of CR/near CR (14.8% vs. 6.4%) and VGPR (37.7% vs. 15.1%) were significantly higher with bortezomib plus dexamethasone versus VAD.[77] At a median follow-up of 32.2 months, median progression-free survival (PFS) was modestly but not statistically significantly prolonged, with 36.0 months with bortezomib and dexamethasone versus 29.7 months with VAD.[77] Use of DCEP as consolidation therapy after primary therapy did not have a significant impact on response rates.[77] Bortezomib and dexamethasone regimen was equally effective in patients with high-risk MM, including those with ISS stage III disease and poor-risk cytogenetic abnormalities. The incidence of severe adverse events reported was similar between the two groups. Hematologic toxicity and deaths related to toxicity were more frequent with VAD versus bortezomib and dexamethasone (7 vs. 0). The rates of grade 2 (20.5% vs. 10.5%) and grades 3 to 4 (9.2% vs. 2.5%) peripheral neuropathy during induction through first transplantation were significantly higher with bortezomib and dexamethasone compared to VAD.[77]

The IFM conducted a phase III randomized trial comparing bortezomib and dexamethasone with a combination of reduced doses of bortezomib and thalidomide plus dexamethasone.[79] The response rates achieved in the comparing bortezomib and dexamethasone arm seen in this study match those described in previous trials comparing VAD with bortezomib and dexamethasone.[77]

Patients with either t(4;14) or del(17p) are known to have a short EFS and OS. A study analyzed a large series of patients (younger 65 years) with newly diagnosed transplant-eligible MM treated and t(4;14) or del(17p) treated with bortezomib and dexamethasone versus VAD as primary therapy before treatment.[71] The analysis demonstrated that bortezomib improves the prognosis (in terms of both EFS and OS; $P < .001$ and $P < .001$, respectively) of patients with t(4;14) compared with patients treated with VAD primary therapy.[71]

Based on these data and the uniform consensus among the NCCN Multiple Myeloma Panel Members, bortezomib and dexamethasone is listed as a category 1 primary therapy option for transplant-eligible patients with MM. The panel recommends herpes prophylaxis in patients receiving bortezomib therapy.

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 the bortezomib, doxorubicin, and dexamethasone versus VAD, and this superior response rate (CR + near CR was 31% vs. 15%; *P* < .001) was maintained even after SCT with significantly higher ORR.[80] 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).[80] After a median follow-up of 41 months, PFS in patients treated with bortezomib, doxorubicin, and dexamethasone as primary therapy followed by SCT and bortezomib maintenance was 35 months versus 28 months in patients treated with VAD followed by SCT and maintenance with thalidomide. Patients treated with bortezomib, doxorubicin, and dexamethasone had a significantly better PFS (hazard ratio [HR], 0.75; 95% CI, 0.62–0.90; *P* = .002).[80] The OS was also found to be better in the bortezomib, doxorubicin, and dexamethasone arm (HR, 0.77; 95% CI, 0.60– 1.00; *P* = .049). In high-risk patients presenting with increased creatinine more than 2 mg/dL, bortezomib significantly improved PFS from a median of 13 months to 30 months (HR, 0.45; 95% CI, 0.26–0.78; *P* = .004) and OS from a median of 21 months to 54 months (HR, 0.33; 95% CI, 0.16– 0.65; *P* < .001). A benefit in terms of increased PFS was also observed in patients with deletion of 17p13.[80] 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.[80]

Based on data from the HOVON-65/GMMG-HD4 trial and the uniform consensus among the NCCN Multiple Myeloma Panel Members, the bortezomib, doxorubicin, and dexamethasone regimen is a category 1 option for primary therapy for transplant-eligible patients with MM.

Bortezomib/Thalidomide/Dexamethasone

Thalidomide attacks multiple targets in the microenvironment of the myeloma cell, producing apoptosis, inhibition of angiogenesis, and cytokine circuits, among others. The GIMEMA Italian Multiple Myeloma Network reported results of a phase III trial investigating bortezomib, thalidomide, and dexamethasone (n = 241) versus thalidomide and dexamethasone (n = 239) as primary therapy, followed by tandem autologous SCT with high-dose melphalan and then consolidation therapy with the same primary regimen.[81] The addition of bortezomib to thalidomide and dexamethasone significantly improved ORR after primary treatment. After primary therapy, CR/near CR was achieved in 73 patients (31%, 95% CI 25.0–36.8) receiving bortezomib, thalidomide, and dexamethasone, and 27 patients (11%, CI 7.3–15.4) on thalidomide/dexamethasone.[81] Rates of CR/near CR and VGPR or better continued to be significantly higher in the bortezomib, thalidomide, and dexamethasone group than in the thalidomide/dexamethasone group after the first and second autologous SCT, and subsequent consolidation therapy.[81] Patients receiving the bortezomib-containing regimen experienced grade 3/4 peripheral neuropathy.

Data from a single-institution retrospective study are similar to the interim data from the GIMEMA trial.[82] The findings of this analysis demonstrate that ORR after primary therapy with bortezomib, thalidomide, and dexamethasone was 94% of the patients (32 of 34 patients showed some response, including a VGPR rate ≥56%).[82]

The results of the randomized phase III trial by the Spanish Myeloma Group (PETHEMA/GEM) also demonstrated a significantly higher CR

rate with bortezomib, thalidomide, and dexamethasone as primary therapy overall (35% vs. 14%, *P* =.001) and in patients with high-risk cytogenetics (35% vs. 0%, *P* = .002).[83] The CR rate continued to be significantly higher after autologous SCT (46% vs. 24%) in patients treated with bortezomib, thalidomide, and dexamethasone versus thalidomide and dexamethasone as primary therapy.[83]

Based on the above data and the uniform consensus among the NCCN Multiple Myeloma Panel Members the bortezomib, thalidomide, and dexamethasone regimen is a category 1 option as primary therapy for transplant-eligible patients with MM.

Cyclophosphamide/Bortezomib/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.[84-86] 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.[84] 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%).[84] 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).[87]

Analysis of the German DSMM XIa study also demonstrated high responses with CyBorD as primary treatment (ORR was 84%; with 74% PR rate and 10% CR rate). High response rates were seen in patients with unfavorable cytogenetics.[85]

In the updated results of the phase II EVOLUTION study, primary treatment with CyBorD demonstrated ORR of 75% (22% CR and 41% ≥VGPR), and one-year PFS rate was 93%.[86]

Based on data from these three phase II studies, the NCCN Multiple Myeloma Panel has now included the combination of cyclophosphamide/bortezomib/dexamethasone as a category 2A recommendation to the list of primary treatment options available for transplant candidates.

Twice-weekly bortezomib can be associated with toxicities that may limit efficacy caused by treatment delays or discontinuation. Therefore, Reeder et al modified the regimen to a once-weekly schedule of bortezomib.[88] In the study, patients treated with weekly bortezomib achieved responses similar to the twice-weekly schedule (ORR 93% vs. 88%, VGPR 60% vs. 61%). In addition, they experienced less grade 3/4 adverse events (37%/3% vs. 48%/12%). Fewer dose reductions of bortezomib and 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).[88]

Lenalidomide/Dexamethasone

Lenalidomide is a potent analogue of thalidomide. Like thalidomide it is believed to attack multiple targets in the microenvironment of the myeloma cell, producing apoptosis and inhibition of angiogenesis and cytokine circuits, among others. Lenalidomide received approval from the U.S. Food and Drug Administration (FDA) for the treatment of relapsed/refractory MM in combination with dexamethasone (discussed further under *Salvage Therapy*). Lenalidomide and dexamethasone have also been investigated as primary therapy. The phase III randomized controlled study, S0232, by Southwest Oncology Group

(SWOG) compared dexamethasone single agent with dexamethasone plus lenalidomide for patients newly diagnosed with MM.[89] This trial was halted at interim analysis and patients on dexamethasone alone were allowed to switch to lenalidomide with dexamethasone. The SWOG data and safety monitoring committee based its recommendation to permanently close enrollment based on the preliminary results from the ECOG phase III study (E4A03).[90] At the time the SWOG trial was halted, at the end of one year, the lenalidomide plus dexamethasone arm showed improved CR rate compared to dexamethasone alone (22.1% vs. 3.8%).[89]

In an open-label trial, 445 newly diagnosed patients with MM were randomly assigned to high-dose or low-dose regimens. The response was superior with high-dose dexamethasone. One hundred sixty-nine (79%) of 214 patients receiving high-dose therapy and 142 (68%) of 205 patients on low-dose therapy had CR or PR within four cycles.[91] However, the high response rates did not result in superior time to progression, PFS, or OS compared with low-dose dexamethasone. The trial was stopped after one year. Patients on high-dose therapy were allowed to cross over to the low-dose arm since the OS rate was significantly higher in that arm. At 1-year interim analysis, OS was 96% in the low-dose dexamethasone group compared with 87% in the high-dose group (P = .0002); 2-year OS was 87% versus 75%, respectively.

The cause of inferior OS with high-dose dexamethasone seems to be related to increased deaths caused by toxicity. Fifty-two percent of patients on the high-dose regimen compared with 35% on the low-dose regimen had grade 3 or worse toxic effects in the first 4 months, including DVT (26% vs. 12%); infections including pneumonia (16 vs. 9%); and fatigue (15% vs. 9%). The 3-year OS of patients who received four cycles of primary treatment with either dose followed by autologous SCT was 92%, suggesting that lenalidomide and dexamethasone is a reasonable choice for primary therapy before SCT. However, it should be noted that the choice to proceed to SCT was not randomized but based on physician and patient preference.

A retrospective analysis of 411 newly diagnosed patients treated with either the lenalidomide and dexamethasone regimen (n = 228) or the thalidomide and dexamethasone regimen (n = 183) was performed at the Mayo Clinic.[92] In a matched-pair analysis, the differences between the two arms were similar for age, sex, transplantation status, and dexamethasone dose. The proportion of patients achieving at least a PR to lenalidomide and dexamethasone was 80.3% versus 61.2% with thalidomide/dexamethasone; VGPR rates were 34.2% and 12.0%, respectively. Patients receiving lenalidomide and dexamethasone had longer time to progression (median, 27.4 vs. 17.2 months; P = .019), longer PFS (median, 26.7 vs. 17.1 months; P = .036), and better OS (median not reached vs. 57.2 months; P = .018).[92] Grade 3 or 4 adverse events (57.5% vs. 54.6%, P = .568) were seen in a similar proportion of patients in both groups. Grade 3 or 4 toxicities of lenalidomide and dexamethasone were hematologic, mainly neutropenia (14.6% vs. 0.6%, P < .001); the most common toxicities in thalidomide and dexamethasone were venous thromboembolism (VTE) (15.3% vs. 9.2%, P = .058) and peripheral neuropathy (10.4% vs. 0.9%, P < .001). Based on the results of this meta-analysis lenalidomide and dexamethasone seems well-tolerated and more effective than thalidomide and dexamethasone.[92] However, randomized prospective trials are needed to confirm these results.

The incidence of DVT is low with single-agent lenalidomide or lenalidomide plus low-dose dexamethasone, but risk rises when combined with high-dose dexamethasone. According to a recent report, patients treated with lenalidomide and high-dose dexamethasone that

developed a VTE did not experience shorter OS or time to progression.[93] Prophylactic anticoagulation is recommended in patients receiving this therapy.[76,94]

A decrease in CD34-positive cells collected after prolonged lenalidomide treatment has been reported.[95,96] Guidelines by the IMWG suggest that patients treated with lenalidomide and dexamethasone should have stem cells collected within the first 4 cycles of therapy.[97] This inability to collect stem cells may be overcome by chemo-mobilization.[98] There are data indicating successful stem cell harvest with the addition of plerixafor when conventional mobilization methods fail.[99,100]

The NCCN Multiple Myeloma Panel recommends harvesting peripheral blood early in the course of primary treatment with lenalidomide. Lenalidomide and dexamethasone is listed as a category 1 primary treatment option in the NCCN Guidelines. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Bortezomib/Lenalidomide/Dexamethasone

Phase I/II study results have shown that primary therapy with bortezomib, lenalidomide, and dexamethasone is active and well tolerated in newly diagnosed patients with MM.[101] Response rate is 100% with 74% VGPR or better and 52% CR/near CR. Given this high extent and frequency of response, a randomized trial is now evaluating this regimen with or without high-dose melphalan and stem cell support in newly diagnosed transplant candidates.

The benefits of bortezomib, lenalidomide, and dexamethasone as primary therapy were also seen in the results of the phase II IFM 2008 trial[102] and phase II EVOLUTION trial.[86] In the phase II IFM 2008 trial, patients received bortezomib, lenalidomide, and dexamethasone as induction therapy followed by stem cell transplantation. Patients subsequently received two cycles of bortezomib, lenalidomide, and dexamethasone as consolidation cycles and 1-year lenalidomide maintenance. Very good partial response rate or better at the completion of induction was 58%. After transplantation and consolidation therapy the rate of VGPR or better was 70%, and 87%, respectively. The phase II EVOLUTION trial was designed to examine the tolerability and efficacy of combining bortezomib, cyclophosphamide, lenalidomide, and dexamethasone versus bortezomib, lenalidomide, and dexamethasone versus cyclophosphamide, bortezomib, and dexamethasone in a randomized multicenter setting. The ORR after primary treatment followed by maintenance with bortezomib for four 6-week cycles was 85% (51% ≥ VGPR and 24% CR) with one-year PFS of 83% for the bortezomib, lenalidomide, and dexamethasone arm.[86]

The NCCN Panel included the bortezomib, lenalidomide, and dexamethasone regimen as a category 2A option for primary treatment of transplant eligible patients with MM.

Other Primary Therapy Regimens for Transplant Candidates

Thalidomide/Dexamethasone

Rajkumar et al reported the results of a study involving 207 patients with newly diagnosed MM randomized to receive thalidomide and dexamethasone or dexamethasone alone.[103] The response rate to the combined therapy was significantly higher compared to those receiving dexamethasone alone (63% vs. 41%, respectively). Stem cells for subsequent transplant were also successfully collected. However, increased toxicity is associated with thalidomide, specifically DVT; therefore, prophylactic anticoagulation is recommended if thalidomide and dexamethasone are given.[94] Other side effects of thalidomide

included rash, gastrointestinal disturbance, peripheral neuropathy, or somnolence.[76] The use of thalidomide requires individual patient consideration, and the higher response rate of the thalidomide and dexamethasone combination must be weighed against the increased side effects.

Thalidomide in combination with dexamethasone as a primary regimen is a category 2B recommendation in the NCCN Guidelines. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy.

Single-Agent Dexamethasone

Dexamethasone alone may be an option as short-term primary therapy for a highly selected group of patients (eg, in those with renal failure, hypercalcemia, cord compromise requiring radiation therapy, cytopenia).

Single-agent dexamethasone as primary treatment is a category 2B recommendation in the NCCN Guidelines.

Liposomal Doxorubicin/Vincristine/Dexamethasone

In a non-inferiority trial, newly diagnosed patients with active MM (n = 192) were randomized to receive pegylated liposomal doxorubicin (PLD), vincristine, and dexamethasone regimen (DVD) or VAD regimen.[104] The primary endpoints were response and toxicity. Objective response, PFS, and OS were similar between the treatment groups. However, pegylated DVD was associated with less toxicity compared with VAD.[104] Data from this and other recent studies suggest that VAD should no longer be recommended, as most patients respond to induction regimen based on novel drug combinations.

The DVD regimen is listed as a category 2B recommendation for primary treatment in the NCCN Guidelines.

Carfilzomib/Lenalidomide/Dexamethasone

Carfilzomib is a second-generation proteosome inhibitor that binds highly selectively and irreversibly to the proteasome. It is administered intravenously. Preclinical studies with carfilzomib show lack of neurodegeneration in vitro[105] and less neurotoxicity in animal studies.[106] Carfilzomib has demonstrated antimyeloma activity in patients with relapsed and/or refractory MM with an acceptable tolerability profile, including limited neuropathy after prolonged treatment.[107-109]

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

First, a multicenter phase I/II trial evaluated the combination of carfilzomib, lenalidomide, and dexamethasone in newly diagnosed patients with MM.[110] In this trial, patients (n =53) received carfilzomib (20, 27, or 36 mg/m^2 on days 1, 2, 8, 9, 15, and 16 and days 1, 2, 15, 16 after cycle 8) with lenalidomide 25 mg/day on days 1 to 21 and dexamethasone 40 mg weekly for cycles 1 to 4 then 20 mg weekly for cycles 5 to 8 in 28-day cycles. After 8 cycles, patients received the regimen every other week (days 1, 2, 15, and 16 of 28-day cycles) for 8 cycles. After 24 cycles of therapy, maintenance with single-agent lenalidomide was recommended off study. After a median of 12 cycles, 62% achieved at least a near-CR and 42% achieved a sCR. In 36 patients who completed 8 or more cycles, 78% achieved at least a near CR and 61% achieved a sCR. With median follow-up of 13 months, 24-month PFS was estimated at 92%.The most common grade 3 and 4 toxicities in ≥10% of patients included hypophosphatemia (25%), hyperglycemia (23%), anemia (21%), thrombocytopenia (17%), and

neutropenia (17%). Peripheral neuropathy was limited to grade 1/2 (23%).[110] An updated follow up analyses of the subset of 23 elderly patients (age ≥65 years) showed that use of the carfilzomib, lenalidomide, and low dose dexamethasone regimen for an extended period of time resulted in deep and durable responses. All patients achieved at least a PR and with a median follow up of 30.5 months, PFS rate reported was 79.6% (95%CI: 53.5–92.0) and OS was100%.[111]

The second phase II trial also evaluated the same regimen (carfilzomib in combination with lenalidomide and dexamethasone) in newly diagnosed patients (n=45) with MM. The dosing in this study was carfilzomib 20 or 36 mg/m^2 (20 mg/m^2 on days 1 and 2 of cycle 1 only) on days 1, 2, 8, 9, 15, and 16, with lenalidomide 25 mg/day on days 1 to 21 and dexamethasone 20 mg on days 1 2, 8, 9, 15, 16, 22, and 23 for cycles 1 to 4, then decreased to 10 mg for cycles 5 to 8 (28-day cycles). After 8 cycles of treatment, patients with stable disease received up to 24 cycles of lenalidomide 10 mg/day on days 1 to 21.[112] Thirty-eight patients are evaluable for response and toxicity. After 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 study after initial therapy. The most common non hematologic and hematologic toxicities (≥ grade 3) in > 10% of patients included electrolyte disturbances (18%), liver function tests elevation (13%), rash/pruritus (11%), fatigue (11%), lymphopenia (63%), anemia (16%), leukopenia (13%), and thrombocytopenia (11%).[113]

Based on the above data, the NCCN Panel has included the carfilzomib, lenalidomide, and dexamethasone regimen as a category 2A option for primary treatment of transplant-eligible patients with MM.

Preferred Primary Therapy Regimens for Non-transplant Candidates

Many of the regimens described above for transplant candidates are also options for non-transplant candidates. The regimens containing melphalan compromise stem cell reserve, and thus are options only for non-transplant candidates.

Melphalan/Prednisone/Thalidomide

Melphalan and prednisone (MP) has been a standard treatment of MM since 1960. A review of the clinical trials reported that MP results in a 60% response rate with duration of 18 months and an OS of 24 to 36 months.[114] Palumbo and colleagues were the first to report that when thalidomide was combined with melphalan and prednisone (MPT), combined near-CR and CR rates were 27.9% for MPT compared to 7.2% for MP.[115] In the updated analysis, after a median follow-up of 38.1 months, the median PFS was 21.8 months for MPT and 14.5 months for MP (*P* = .004). The median OS was 45.0 months for MPT and 47.6 months for MP (*P* = .79).[116]

Subsequently, several phase III trials have reported significantly higher ORR with MPT versus MP (57%–76% vs. 31%–48%); including a higher CR or VGPR rate (7%–15.5%).[116-119] The impact of MPT on survival is not clear, as only the IFM studies[117,118] have reported a survival advantage in patients on MPT.

The phase III IFM 01-01 study compared the standard MP versus MPT in 232 newly diagnosed elderly (age ≥75 years) patients with MM.[118] After a median follow-up time of 47.5 months, median OS was significantly prolonged in the MPT group (44.0 months; 95% CI, 33.4–58.7) compared with the MP group (29.1 months; 95% CI, 26.4–34.9) (HR, 0.68 in favor of MPT; *P* = .028). Median PFS time was significantly longer in the MPT group versus MP (24.1 months; 95% CI, 19.4–29.0

vs. 18.5 months; 95% CI,14.6–21.3; HR, 0.62 in favor of MPT; *P* = .001).[118]

The phase III study by the HOVON group compared the standard MP versus MPT in 333 newly diagnosed elderly patients with MM. [119] Significantly higher response rates were seen with MPT-treated patients compared to MP and were comparable with response rates seen in the French and Italian trials described above. With MPT, the ORR (CR+VGPR+PR) was 66% versus 45% with MP. The percentage of patients whose disease did not respond to therapy or those with PD was 55% with MP and 34% with MPT. The EFS was 13 months with MPT versus 9 months with MP, and OS was 40 months with MPT versus 31 months with MP.[119] Comparisons between these studies are difficult because of differences in patient populations, duration of treatment, and use of maintenance regimens.

A meta-analysis has demonstrated that in previously untreated, transplant-ineligible, elderly patients with MM, MPT results in significantly improved response rates and PFS with a trend towards improvement in OS compared with MP alone.[120]

Based on the significantly higher ORR consistently seen in all these studies, the NCCN Panel has included MPT as a category 1 primary treatment in transplant-ineligible patients with MM. The panel cautions that there is a significant risk of DVT with thalidomide-based therapy; therefore, use of thromboprophylaxis in patients on MPT therapy is highly recommended.

Melphalan/Prednisone/Lenalidomide

Melphalan and prednisone in combination with lenalidomide (MPL) was initially studied in 54 patients with newly diagnosed MM.[121] Although there were concerns about myelosuppression with lenalidomide, therapy with oral MPL produced high response rates. Eighty-one percent of patients achieved at least a PR, 47.6% achieved a VGPR, and 24% achieved a CR (immunofixation-negative). One-year EFS in all patients was 92% and OS was 100%. Common grade 3/4 toxicities seen in patients were neutropenia (52%), thrombocytopenia (24%), and anemia (5%). In another phase I/II trial of newly diagnosed patients with MM not eligible for autologous SCT (median age 74 years), MPL regimen showed substantial activity (CR was 12%, ORR was 69%) with a manageable toxicity profile.[122] The most common grade 3/4 toxicities were neutropenia (58% of patients) and thrombocytopenia (27%).[122]

A subsequent phase III, multicenter, randomized, double-blind, placebo-controlled trial (MM-015), compared MPL induction followed by lenalidomide maintenance with MPL or MP followed by placebo in patients 65 years of age or older with newly diagnosed MM.[123] The primary endpoint of the trial was PFS. A total of 459 patients were randomly assigned to receive MPL induction followed by lenalidomide maintenance (152 patients), MPL (153 patients), or MP (154 patients). MPL as an induction regimen had higher speed of response, ORR, and response quality compared with MP. For patients in the study of age 65 to 75 years, MPL provided a significant PFS benefit (HR, 0.62; *P* = .006). MPL did not improve PFS as compared with MP in patients older than 75 years of age.[123]

In the recently reported randomized, multicenter, phase III trial (E1A06) MPT was compared with MPL as primary treatment in newly diagnosed, non-transplant patients (n= 306) with MM. The median age of patients was 75.7 years, and patients were followed for a median of 40.7 months. The study found no significant difference between the response rates, PFS, and OS in the two arms.[124] However, several differences with respect to toxicity were found. Patients in the MPT arm had significantly more grade 3 or higher overall toxicity (73% vs. 58%; *P* =

.007) and grade 3 or higher non-hematologic toxicity (59% vs. 40%; *P* = .001) compared with patients in the MPL arm.

The MPL regimen is a category 1 primary treatment option for patients ineligible for transplant in the NCCN Guidelines for Multiple Myeloma.

Melphalan/Prednisone/Bortezomib

Addition of bortezomib to MP (MPB) was investigated in a large, randomized, international phase III VISTA (Velcade as Initial Standard Therapy in Multiple Myeloma) trial.[125] The trial evaluated MP (n = 338) versus MPB (n = 344) in previously untreated patients with MM who were 65 years of age or older, or patients who were younger than 65 years of age and transplant ineligible. The regimen was well tolerated. The addition of bortezomib resulted in high rates of CR and significant prolongation of time to disease progression, PFS, OS, and time to next treatment. Importantly, adverse cytogenetics, advanced age, and renal function had no impact on the efficacy of the bortezomib-containing regimen.

The final analysis of the phase III VISTA trial with median follow-up of 60.1 months (range, 0–74 months), showed a 31% reduced risk of death with MPB versus MP (HR, 0.695; *P* < .001).[126] Reported median OS was 56.4 months with MPB versus 43.1 months with MP, with 5-year OS rates of 46.0% with MPB versus 34.4% with MP.[126] No OS benefit was seen with the use of bortezomib among the small subgroup of patients with documented high-risk cytogenetics. Another interesting finding from this study was that patients relapsing after bortezomib-based therapy were not resistant to subsequent therapies and could be successfully treated with immunomodulatory drug-based therapies. Among patients who received subsequent therapies, survival from start of subsequent therapy was similar after treatment with MPB (median, 28.1 months) or MP (median, 26.8 months; HR, 0.914).These findings support the strategy of using bortezomib-based treatment as first-line therapy instead of reserving it for as therapy for relapsed/refractory disease. In addition, no increased risk of second primary malignancies was observed with MPB versus MP.[126] The incidence of hematologic malignancies and solid tumors was similar in both arms, and was consistent with background incidence rate of for all cancers in the general U.S. population of similar age group.[126]

There is no randomized head-to-head study comparing MPT and MPB; however, a meta-analysis of the phase III studies has demonstrated that better response rates could be expected with MPB than with MPT.[127] Existing data on MP, MPT, and MPB were compared, and analysis showed 81% probability that MPB was the most efficacious among the three regimens in terms of ORR, with a greater than 99% probability that it was also the most efficacious in terms of CR.[127]

Advantages of MPB over MPT for transplant-ineligible patients include more rapid response and higher rates of CR, with improved survival.[128] No difference was seen in OS and PFS between MPB and MPT regimens. Based on the VISTA trial results, the MPB regimen is now a NCCN category 1 primary treatment option for transplant-ineligible patients with MM.

Lenalidomide/Low-dose Dexamethasone

The results of the SWOG SO232 trial[89] that included transplant-ineligible patients and the ECOG E4A03 trial[129] that included elderly patients with MM demonstrate that lenalidomide in combination with low-dose dexamethasone is a well-tolerated and effective regimen for these groups of patients. In the ECOG E4A03 trial the OS rate was significantly higher in the lenalidomide plus low-dose dexamethasone arm compared with the lenalidomide plus high-dose dexamethasone arm (also discussed under *Preferred Primary Therapy Regimens for*

Transplant Candidates).[91] The inferior survival outcome seen with high-dose dexamethasone was greatest in patients 65 years and older. At 2 years, patients who did not proceed to transplant had an OS rate of 91% with lenalidomide and low-dose dexamethasone.[91]

The international, multicenter trial (FIRST trial) evaluated efficacy and safety of lenalidomide/dexamethasone given continuously or for 72 weeks with MPT in elderly (n= 1623) transplantation-ineligible patients with newly diagnosed MM.[130] 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, $P < .001$). [130] 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, $P = .02$).[130]

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.[131-134] 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.[130]

Lenalidomide in combination with low-dose dexamethasone is considered a category 1 option by the NCCN Multiple Myeloma Panel for transplant-ineligible patients with MM. The panel recommends appropriate thromboprophylaxis for patients receiving this therapy. Based on the results of the FIRST trial, the NCCN Panel recommends considering treatment with continuous lenalidomide/dexamethasone until disease progression for patients who are not eligible for transplant.

Bortezomib/Dexamethasone

A U.S. community-based, randomized, open-label, multicenter phase IIIb UPFRONT trial compared safety and efficacy of three highly active bortezomib-based regimens in previously untreated elderly patients with MM ineligible for SCT.[135] The patients with symptomatic, measurable MM were randomized (1:1:1) to one of the following regimens: bortezomib and dexamethasone (n = 168); bortezomib, thalidomide, and dexamethasone (n = 167); or MPB (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 ORR of 73% (bortezomib and dexamethasone), 80% (bortezomib, thalidomide, and dexamethasone), and 69% (MPB) during the treatment period.[135] After a median follow-up of 21.8 months, no significant difference in PFS was observed between the treatment arms.[135] Response rates, including CR and ≥VGPR, improved after bortezomib maintenance, with no concomitant increase in the incidence of peripheral neuropathy.

The NCCN Multiple Myeloma Panel has included bortezomib and dexamethasone as a category 2A primary therapy option for patients with MM who are ineligible for transplant.

Bortezomib/Lenalidomide/Dexamethasone

Phase II study results have shown that primary therapy with bortezomib, lenalidomide, and dexamethasone is active and well

tolerated in all newly diagnosed patients with MM regardless of autologous SCT status.[101]
A post-hoc analysis of the study showed a low risk of progression after 1 year of initiation of therapy regardless of ASCT status.The18-month PFS rate of 75% and OS rate of 97% after lenalidomide, bortezomib, dexamethasone with or without autologous SCT.

The NCCN Panel included the bortezomib, lenalidomide, and dexamethasone regimen as a category 2A option for patients with MM not eligible for SCT.

Cyclophosphamide/Bortezomib/Dexamethasone
The role of CyBorD as initial therapy for patients with MM ineligible for transplant was studied in a small phase II trial (n = 20). The median age of patients in this study was 76 years (range 66-90). At a median follow-up of 9.5 months, the OS was 100% and at median of 12 month, and 5 had disease progression. With respect to toxicity, 6 patients experienced non-hematological grade 3/4 adverse events (20%), including muscle weakness, sepsis and pneumonia. Neutropenia and thrombocytopenia were seen in 2 patients (10%).[136] Based on the above and the results from the EVOLUTION trial (described earlier) that did not exclude transplant ineligible patients, the NCCN panel has included CyBorD as a primary therapy option (category 2A) for non-transplant candidates.

Other Primary Therapy Regimens for Non-transplant Candidates
Both MPT and MPB regimens have reported superior responses compared to MP. However, MP may still have a role in patients who do not have access to novel agents. According to the NCCN Multiple Myeloma Panel, MP is a category 2A recommendation. The other NCCN category 2B options for patients not eligible for SCT include thalidomide and dexamethasone, single-agent dexamethasone, DVD, and VAD.

Follow-Up of Transplant and Non-transplant Candidates After Primary Therapy

Patients on treatment should be monitored for response to therapy, for response to primary therapy, and for symptoms related to disease and/or treatment. It is recommended to re-evaluate (after 2 cycles) with the laboratory tests, bone survey, and bone marrow aspiration and biopsy to determine treatment response, or whether the primary disease is progressive. Potential transplant candidates must undergo a stem cell harvest, collecting enough stem cells for two transplants in anticipation of a tandem transplant or a second transplant as subsequent therapy. Alternatively, all patients may consider continuation of primary therapy till 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.

Follow-up tests include those used for initial diagnosis: a CBC with differential and platelet counts; BUN; serum creatinine and corrected serum calcium; and quantification of M-protein and immunoglobulins. The serum FLCs may be assessed as clinically indicated (especially in patients with oligo- or non-secretory MM). According to the NCCN Panel, response should be assessed using the IMWG criteria.[10]

Stem Cell Transplants

Introduction

High-dose therapy with stem cell support is a critical component in the treatment plan for eligible, newly diagnosed patients with MM. The types of SCT may be single autologous SCT, a tandem SCT (a planned

second course of high-dose therapy and SCT within 6 months of the first course), or an allogeneic SCT. An allogeneic SCT can be performed after prior myeloablative therapy or after nonmyeloablative therapy. Nonmyeloablative therapy, also referred to as "mini transplant," has been investigated as a technique to decrease toxicity of the allotransplant while preserving the alloimmune graft-versus-myeloma effect.[137,138] An allogeneic SCT may also follow an autologous SCT.

The NCCN Guidelines for Multiple Myeloma indicate that all types of SCT are appropriate in different clinical settings; these indications are discussed further below. In general, all candidates for high-dose chemotherapy must have sufficient liver, renal, pulmonary, and cardiac function. However, renal dysfunction is not absolute contraindication to transplant. Earlier studies of autologous transplant included total body irradiation (TBI) as a component of the preparative regimen. Regimens with chemotherapy have only recently been shown to have equivalent efficacy and less toxicity than TBI. TBI regimens have now been abandoned,[139] but newer, potentially less toxic radiation techniques aimed to deliver total marrow irradiation while reducing toxicities to non-target organs are currently undergoing evaluation in clinical trials.[140]

Autologous Stem Cell Transplants

Autologous SCT results in high response rates and remains the standard of care after primary therapy for eligible patients. In 1996, results of the first randomized trial were reported; this trial demonstrated that autologous SCT is associated with statistically significant higher response rates and increased OS and EFS when compared with the response of similar patients treated with conventional therapy.[141] 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).[142] The benefit was more pronounced for higher-risk patients. Barlogie and colleagues reported on the results of an American trial that randomized 510 patients to receive high-dose therapy with autologous stem cell support or standard therapy.[143] With a median follow-up of 76 months, there were no differences in response rates, PFS, or OS between the two groups. The reason for the discrepant results are not clear, but may be related to differences in the specific high-dose and conventional regimens between the American and French study. For example, the American study included TBI as part of the high-dose regimen; TBI has subsequently been found to be inferior to high-dose melphalan.[139]

Another trial included 190 patients 55 to 65 years of age randomized to standard or high-dose therapy.[144] 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 whereas 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 (TWiSTT) 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. However, this study[145] also showed that a transplant performed at relapse has a similar OS compared to an early transplant. The choice of early versus late transplant was examined in a randomized French trial, and the results in both arms are comparable with respect to OS.[146] However, early SCT was superior in terms of

quality of life, assessed as time without symptoms and side effects from therapy.[146]

It should be noted that all randomized studies of autologous SCT after primary therapy were designed and implemented before the availability of thalidomide, lenalidomide, or bortezomib. Therefore, the role of transplant may evolve in the future. The results of the PETHEMA trial strongly support the use of upfront autologous SCT for MM even in the era of novel agents.[83] The response rates were evaluated after induction therapy and after autologous SCT. Taking into consideration patients who actually underwent the autologous SCT, the CR rates were increased from 35% pre-transplant to 57% post-transplant, in the group treated with bortezomib, thalidomide, and dexamethasone as induction therapy and from 14% to 40% in the group treated with thalidomide and dexamethasone as induction therapy.[83]

A recent phase III study compared high-dose melphalan followed by autologous SCT with MPL. Patients (n = 402) were randomly assigned (in a 1:1:1:1 ratio) to one of the four groups: high-dose therapy and SCT followed by maintenance with lenalidomide; high-dose therapy and SCT alone; primary therapy with MPL followed by lenalidomide; and primary therapy with lenalidomide alone. The primary study endpoint was PFS. Secondary endpoints included OS, the ORR, the time to a response, and safety.[147] The comparison of the group treated with high-dose melphalan therapy followed by stem-cell transplantation with MPL shows that high-dose melphalan therapy followed by stem-cell transplantation was associated with a significant reduction in the risk of progression or death (HR, 0.44) and prolonged OS (HR for death, 0.55).[148]

Results from the IFM 2005/01 study of patients with symptomatic myeloma receiving primary therapy with either bortezomib and dexamethasone versus VAD showed a marked improvement in ORR with bortezomib and dexamethasone over VAD (discussed under section titled *Preferred Primary Therapy Regimens for Transplant Candidates*).[77] Responses were evaluated after primary treatment and post-autologous SCT. After the first autologous SCT, CR/near-CR rates were 35.0% in the bortezomib plus dexamethasone arm, compared with 18.4% in the VAD arm.[77] 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.[77] Also, PFS was also significantly longer in the patients achieving greater than or equal to a VGPR after primary treatment than in patients achieving a less than VGPR (median 36 vs. 29.7 months). [77]

In another study, 474 patients were randomized to primary therapy with bortezomib, dexamethasone, and thalidomide (n = 236) or thalidomide and dexamethasone (n = 238) before double autologous SCT.[149] The three-drug regimen yielded high response rates compared with the two-drug regimen, with a CR rate of 19% (vs. 5%) and ≥-VGPR of 62% (vs. 31%). After SCT, improved incremental responses were still seen with bortezomib/dexamethasone/thalidomide compared with thalidomide plus dexamethasone. Taken together, these studies suggest that improved responses with the primary regimen result in improved outcomes after transplantation.

Studies have found that PD emerging after primary therapy does not preclude a good response to autologous SCT.[143,150,151] For example, Kumar and colleagues reported on a case series of 50 patients with primary progressive MM receiving an autologous SCT.[151] Results were compared to 100 patients with responsive disease undergoing autologous SCT. The one-year PFS from the time of transplant was 70% in the primary progressive group compared to 83% in the chemosensitive group. For this reason, the NCCN Guidelines indicate

autologous SCT as a category 1 option for treatment of primary progressive or refractory disease post primary treatment.

Tandem Stem Cell Transplants

Tandem SCT refers to a planned second course of high-dose therapy and SCT within 6 months of the first course. Planned tandem transplants have been studied in several randomized trials. The IFM94 trial reported by Attal et al randomized newly diagnosed patients with MM to single or tandem autologous transplants.[152] A total of 78% of patients assigned to the tandem transplant group received the second transplant at a median time of 2.5 months after the first. A variety of options for therapy of relapsed disease were provided. For example, relapsing patients in either group underwent either no therapy, additional conventional therapy, or another SCT. The probability of surviving event free for seven years after the diagnosis was 10% in the single transplant group compared to 20% in the double transplant group. An accompanying editorial by Stadtmauer questions whether the promising results might be related to regimens used, rather than to the effect of two courses of high-dose therapy.[153] For example, patients in the single transplant arm received 140 mg/m^2 melphalan plus TBI, whereas those in the tandem arm received the same dose without TBI for the initial transplant and with TBI for the second transplant. As noted above, TBI has been shown to be more toxic without providing additional benefit. Based on this, the editorial suggests that the increased survival in IFM94's tandem arm may have resulted from greater cumulative exposure to melphalan (280 vs. 140 mg/m^2). In a subset analysis, those patients who did not achieve a complete CR or a 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.[144,154-156] 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[154] found that patients not in CR or near-CR after the first transplant benefited the most from a second transplant. This confirms the observations of the IFM94 trial using non-TBI–based high-dose regimens.

In both the French and Italian trials, the benefit of a second autologous SCT was seen in patients who do not achieve a CR or VGPR (greater than 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.[157] Also, post-relapse survival was longer when EFS was sustained for at least 3.5 years after tandem transplantation.[157] The NCCN Multiple Myeloma Panel recommends collecting enough stem cells for two transplants in *all* eligible patients. According to the NCCN Multiple Myeloma Panel, a tandem transplant with or without maintenance therapy can be considered for all patients who are candidates for SCT, and is an option for patients who do not achieve at least a VGPR after the first autologous SCT. The support for use of maintenance therapy after tandem transplant comes from the study by Palumbo et al[147] (discussed in the previous section, page MS-20) addressed the role of maintenance therapy with lenalidomide after autologous transplantation.[147] Although associated with more frequent grade 3 or 4 neutropenia and infections, maintenance therapy with lenalidomide was

found to significantly reduced risk of disease progression or death (HR, 0.47) after both single and tandem transplantation compared with no maintenance.[147]

The benefit from the second transplant in patients, who are in CR, or VGPR, and also in those who achieve less than VGPR after the first SCT, should preferably be answered in a clinical trial. In fact, such a randomized prospective NIH- and Intergroup-supported trial is currently ongoing. The other options for this group of patients include maintenance therapy or observation.

A retrospective case-matched control analysis was performed comparing patients who underwent a second autologous SCT to those treated with conventional chemotherapy for relapsed MM.[158] Similar to previously published smaller studies,[159-161] this retrospective analysis demonstrated that a second autologous SCT is associated with superior relapse-associated mortality compared with conventional chemotherapy (68% vs. 78%), along with improved OS (32% vs. 22%) at 4 years. In this analysis, factors associated with improved OS and PFS included younger age (<55 years), beta-2 microglobulin <2.5 mg/L at diagnosis, a remission duration of >9 months, and a greater than PR to their first autologous SCT. This analysis indicates that a second autologous transplant, for relapsed or progressive MM, may be an option for carefully selected patients. Some of these patients can achieve durable complete or partial remission.[161,162]

A multicenter, randomized phase III trial compared treatment with high-dose melphalan plus second autologous SCT with cyclophosphamide in patients with relapsed MM who had received autologous SCT as primary treatment.[163] The patients included in the study were greater than 18 years of age and needed treatment for progressive or relapsed disease at least 18 months after a previous autologous SCT. All patients first received bortezomib/doxorubicin/dexamethasone induction therapy. Patients with adequately harvested stem cells then were randomized to high-dose melphalan plus second autologous SCT (n = 89) or oral cyclophosphamide (n = 85). The primary endpoint was time to disease progression.[163] After a median follow-up of 31 months, median time to progression in patients who underwent second autologous SCT after induction therapy was 19 months versus 11 months for those treated with cyclophosphamide (HR, 0.36 [95% CI, 0.25–0.53]; $P < .0001$). Grade 3–4 neutropenia (76% vs. 13%) and thrombocytopenia (51% vs. 5%) were higher in the group that underwent autologous SCT versus cyclophosphamide. [163]

According to the NCCN Multiple Myeloma Panel, repeat autologous SCT for relapsed disease may be considered either on or off clinical trial depending on the time interval between the preceding SCT and documented progression (category 2A). Based on the data from retrospective studies,[164-167] the NCCN Panel suggests 2 to 3 years as the minimum length of remission for consideration of second autologous SCT for relapsed disease (category 2B).

Allogeneic Stem Cell Transplant

Allogeneic SCT includes either myeloablative or nonmyeloablative (ie, “mini” transplant) transplants. Allogeneic SCT has been investigated as an alternative to autologous SCT both to avoid the contamination of re-infused autologous tumor cells, but also to take advantage of the beneficial graft-versus-tumor effect associated with allogeneic transplants. However, lack of a suitable donor and increased morbidity has limited this approach, particularly for the typical older MM population. Non-myeloablative transplants are designed to decrease the morbidity of the high-dose chemotherapy but preserve the beneficial graft-versus-tumor effect. Therefore, the principal difference between

myeloablative and nonmyeloablative transplants relates to the chemotherapy regimen used. Specific preparatory regimens have not been a focus of the NCCN Guidelines, and therefore these Guidelines do not make a distinction between these approaches.

Given the small candidate pool, it is not surprising that there have been no randomized clinical trials comparing myeloablative allogeneic to autologous SCT, but multiple case series have been published describing allogeneic SCT as an initial or as therapy for relapsed/refractory MM. In a 1999 review, Kyle reported a mortality rate of 25% within 100 days and overall transplant-related mortality of approximately 40% and few patients were cured.[168] Other reviews have also reported increased morbidity without convincing proof of improved survival.[150,169] However, there are intriguing data from the SWOG randomized trial of autologous transplant versus conventional chemotherapy.[143] 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. With seven years of follow-up the OS of the conventional chemotherapy, autologous, and allogeneic arms were all identical at 39%. The autologous and conventional chemotherapy arms do not demonstrate a plateau, whereas the allogenic curve was flat at 39%. This suggests that a proportion of these patients are long-term survivors. Thus, there is ongoing interest in myeloablative allogeneic SCT, particularly given the lack of a significant cure rate for single or tandem autologous SCT.

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

Another strategy that has been investigated is initial autologous SCT followed by a mini-allogeneic transplant. A prospective trial by Bruno et al[170] showed that, among patients (<65 years) with HLA-matched siblings who received an autograft-allograft regimen, CR rate after allografting was 55%, compared with 26% after double autograft in patients without HLA-matched siblings. Median OS was higher (80 vs. 54 months). In the prospective PETHEMA trial in patients who do not achieve at least near-CR with a first autologous SCT, there was no significant difference in OS after double autologous SCT versus autologous SCT followed by mini-allogeneic transplant. However, a trend toward a longer PFS was observed in the group treated with autologous SCT followed by mini-allogeneic transplant.[171] In contrast, the IFM trial (99-03) by Garban et al[172] and the BMT-CTN 0102 trial[173] reported no OS or PFS advantage with autologous transplant followed by allogeneic transplant in patients with high risk.

In a prospective study of patients with previously untreated MM, patients were selected for treatment with autologous SCT followed by reduced-intensity conditioning allogeneic SCT or autologous SCT based on the availability of an HLA-identical sibling.[174] The induction chemotherapy in this study consisted of the chemotherapy that was standard at the time- the VAD or VAD-like regimen. After 60 months, the incidence of relapse/progression was 49% in the group treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT versus 78% in the autologous SCT group. AT 60 months, the OS and CR rates were 65% and 51%, respectively, for patients treated with autologous SCT followed by reduced-intensity conditioning allogeneic SCT compared with 58% and 41% for those treated with autologous SCT. Based on these study results, patients who have an HLA-identical sibling may be considered candidates for reduced-intensity allogeneic SCT as part of their first-line treatment.

Mini-allogeneic transplants have also been investigated as therapy for relapsed/refractory disease by virtue of their graft-versus-myeloma effect. Responsive disease to prior transplantation and younger age are associated with better response and OS rates.[175-178] In a case series report, 54 patients with previously treated relapsed or PD were treated with an autologous SCT followed by a mini-allogeneic transplant.[176] There was a 78% OS at a median 552 days after the mini-allogeneic transplant, with a 57% CR rate and an ORR of 83%. This study concluded that this approach reduced the acute toxicities of a myeloablative allogeneic SCT while preserving anti-tumor activity. The largest case series was reported by the EBMT.[177] In this heterogeneous population of 229 patients, the 3-year OS and PFS were 41% and 21%, respectively. Adverse OS was associated with chemoresistant disease and more than 1 prior transplant, whereas improved OS was associated with graft-versus-host disease, confirming the importance of a graft-versus-leukemia effect. This study concluded that mini-allogeneic transplantation is feasible, but heavily pretreated and patients with PD are unlikely to benefit.

Patients whose disease either does not respond to or relapses after allogeneic stem cell grafting may receive donor lymphocyte infusions to stimulate a beneficial graft-versus-myeloma effect[179-186] or other myeloma therapies on or off a clinical trial.

Maintenance Therapy

Thalidomide as Maintenance Therapy After Autologous SCT

Thalidomide as maintenance therapy after a prior autologous SCT has been studied in retrospective and independent randomized trials. In a retrospective review of 112 patients undergoing autologous SCT, Brinker and colleagues reported on the outcomes of 36 patients who received thalidomide as maintenance compared to 76 patients who received no post-transplant therapy.[187] The median survival in the thalidomide group was 65.5 months compared to 44.5 months in the no treatment group (P = .9). Attal et al randomized 597 patients to one of three different strategies after tandem autologous SCT: either no maintenance, pamidronate alone, or pamidronate combined with thalidomide.[188] There was a highly significant EFS and OS advantage in the thalidomide and pamidronate arm. The group that appeared to benefit the most was one that had patients who achieved only a PR after transplantation. In another randomized trial, thalidomide maintenance induced improvement in PFS in patients achieving less than a VGPR after autologous SCT with no survival benefit.[189] Thalidomide has also been used before, during, and after tandem autologous SCT.[143,190] In a randomized study of 668 newly diagnosed patients, half received thalidomide throughout the course of the tandem autologous SCT. Thalidomide was incorporated into primary therapy, continued between the tandem autologous SCT, and incorporated into consolidation therapy and continued as maintenance therapy.[190] The group that was not treated with thalidomide received the same core therapy. After a median follow-up of 42 months, the group that received thalidomide had improved CR rates (62% vs. 43%) and five-year EFS rates (56% vs. 44%). However, the OS rate was approximately 65% in both groups. Patients who did not receive thalidomide throughout therapy benefited from thalidomide therapy at relapse. The results of this study suggest that sequencing drugs may be important. For example, if thalidomide is used as part of primary therapy, another drug should be considered for maintenance therapy.

An Australian study compared thalidomide plus prednisone versus prednisone alone as maintenance therapies post autologous SCT. The results confirm that thalidomide added to maintenance is superior to prednisone alone.[191] A recent analysis of the Canadian NCIC

randomized study comparing thalidomide and prednisone with observation after autologous SCT showed that thalidomide and prednisone improves the duration of disease control, but is associated with lower patient-reported quality of life and no OS benefit.[192]

Based on the above evidence, the NCCN Multiple Myeloma Panel has listed single-agent thalidomide as a category 1 option under *Preferred Maintenance Regimens*. Thalidomide in combination with prednisone is included under *Other Maintenance Regimens* and is a category 2A. There are concerns about the cumulative toxicity with thalidomide. For example, peripheral neuropathy observed with thalidomide is related to the duration of treatment and is cumulative. The benefits and risks of maintenance therapy with thalidomide should be discussed with patients.

Lenalidomide as Maintenance Therapy After Autologous SCT
Lenalidomide as maintenance therapy after autologous transplantation has been evaluated in two independent randomized phase III studies.[131,132]

In The CALGB 100104 trial, patients were randomized to maintenance therapy with lenalidomide (n = 231) versus placebo (n = 229) after autologous SCT.[132] At a median follow-up of 34 months, 37% of the patients who received lenalidomide versus 58% who received placebo had disease progression or died. The median time to progression in the lenalidomide group was 46 months versus 27 months in the placebo group ($P < .001$). Second primary cancers occurred in 18 patients who received lenalidomide (8%) and in 6 patients who received placebo (3%).[132]

Data from the international, randomized, double-blind phase III IFM 2005-02 trial (n = 614) show that patients treated with lenalidomide as consolidation therapy after an autologous SCT followed by lenalidomide as maintenance therapy had upgraded responses. Of the 614 patients enrolled in the trial, 307 were randomly assigned to lenalidomide maintenance therapy and 307 to placebo. Maintenance treatment was continued until the patient withdrew consent, the disease progressed, or unacceptable toxic effects occurred. The final analysis of the IFM 2005-02 trial was performed after a median follow-up of 30 months and 264 patients had disease progression (104 in the lenalidomide group and 160 in the placebo group). The median PFS was 41 months in the lenalidomide group, compared with 23 months in the placebo group (HR, 0.50; $P < .001$; median follow-up period was 30 months). The probability of surviving without progression for 3 years after randomization was 59% in those treated with lenalidomide and 35% in those who received the placebo. The benefit of lenalidomide maintenance therapy, evidenced by rate of PFS at 3 years after randomization, was higher in all patients who received lenalidomide maintenance therapy, compared with those who received placebo. This benefit was observed in patients who had a VGPR at randomization (64% vs. 49%, $P = .006$) and those who did not (51% vs. 18%, $P < .001$).[131] 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).[131]

In a phase II study by the IFM group, lenalidomide maintenance was shown to upgrade responses seen in 27% of patients (8 out of 31 patients) after induction therapy with lenalidomide, bortezomib, and dexamethasone followed by autologous transplant.[102]

The study by Palumbo et al[147] (discussed in *Autologous Stem Cell Transplants*) showed that although maintenance therapy with lenalidomide, is associated with more frequent grade 3 or 4 neutropenia

and infections, it significantly reduced risk of disease progression or death (HR, 0.47) compared with no maintenance.[147]

A report from the HOVON 76 trial indicates that lenalidomide maintenance may not be a feasible option after mini-allogeneic SCT.[193] However, another recently reported study has shown the feasibility of maintenance therapy with low-dose lenalidomide after allogeneic SCT in patients with high-risk MM.[194]

Lenalidomide as Maintenance Therapy After Non-transplant Active Primary Treatment

Data from the phase III MM-015 study show that lenalidomide maintenance after MPL primary therapy significantly reduced the risk of disease progression and also increased PFS.[123] 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.[123]

Based on the evidence from the phase III trials,[123,131,132] the NCCN Multiple Myeloma Panel lists single-agent lenalidomide as one of the preferred maintenance regimens (category 1). Lenalidomide lacks the neurologic toxicity seen with thalidomide. However, there seems to be an increased risk for secondary cancers, especially post-transplantation,[131,132,195] or after a melphalan-containing regimen.[134] 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.[130]

A meta-analysis of 4 randomized controlled trials examined patients treated with lenalidomide maintenance versus patients with no maintenance or placebo in both the transplant and non-transplant settings.[196] The analysis showed that patients treated with lenalidomide maintenance had significantly improved PFS (HR, 0.49; *P* < .001) and a trend toward OS (HR, 0.77; *P* = .071) versus no maintenance or placebo.[196] There was significantly more grade 3/4 neutropenia with the use of lenalidomide and a 2-fold increased risk of secondary malignancies.

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

Bortezomib as Maintenance Therapy after Autologous SCT

The results from the HOVON study show that maintenance with single-agent bortezomib after autologous SCT is well tolerated and is associated with improvement of ORR.[80] Patients in the HOVON trial were randomly assigned to one of the two arms consisting of either primary treatment with vincristine/doxorubicin/dexamethasone followed by autologous SCT and maintenance with thalidomide or with bortezomib/doxorubicin/dexamethasone followed by autologous SCT and bortezomib as maintenance therapy for 2 years. The study reported high near-CR/CR rates after primary treatment with the bortezomib-based regimen. Bortezomib as maintenance therapy was well tolerated and associated with additional improvement of response rates[80] (see *Preferred Primary Therapy Regimens for Transplant Candidates).*

A multicenter phase III trial in newly diagnosed patients with MM showed that consolidation with bortezomib after autologous SCT, improved PFS only in patients not achieving at least VGPR after autologous SCT.[197] There was no difference in PFS in patients with ≥VGPR after autologous SCT.

Bortezomib as Maintenance Therapy After Non-transplant Active Primary Treatment

The preliminary 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.[198] Newly diagnosed patients with MM ineligible for high-dose therapy and SCT enrolled in the UPFRONT trial were randomized (1:1:1) and treated with one of the following bortezomib-based primary regimens: bortezomib and dexamethasone; bortezomib in combination with thalidomide and dexamethasone; or bortezomib with melphalan and prednisone followed by maintenance treatment with bortezomib. The updated results show that the response rates, including CR and ≥VGPR, improved after bortezomib maintenance in all arms, with no concomitant increase in the incidence of peripheral neuropathy.[198]

The NCCN Multiple Myeloma Panel Members have added bortezomib to the list of preferred maintenance regimens with a category 2A designation.

Other Maintenance Therapy Regimens

Several other maintenance therapies, such as steroids (dexamethasone) and interferon, have been investigated in patients whose disease responds to high-dose therapy followed by autologous or allogeneic SCT.[199] At the present time, the role of interferon[200] or steroid maintenance therapy[201] in general is uncertain. Therefore, these are category 2B recommendations as maintenance therapy in the NCCN Guidelines for Multiple Myeloma.

Patients enrolled in the PETHEMA trial were randomized to maintenance with thalidomide plus bortezomib, thalidomide, or alfa-2b-interferon after treatment with induction therapy and autologous SCT.[202] Maintenance with bortezomib plus thalidomide increased the post-transplant CR rate by 21% compared with maintenance with either thalidomide or alfa-2b interferon, each of which increased the CR rate by 15%. After a median follow-up of 34.9 months, PFS from start of maintenance was significantly longer with bortezomib plus thalidomide versus thalidomide or alfa-2b-interferon (P = .0009); there was no significant difference in OS (P = .47) between the three arms. Rates of grade 3 and 4 thrombocytopenia were 10% with bortezomib plus thalidomide versus 2% with thalidomide (P = .01). Rates of grade 3 peripheral neuropathy were 15%, 14%, and 0% in the bortezomib plus thalidomide arm, thalidomide arm, and alfa-2b-interferon arm, respectively.[202]

Transplant-ineligible patients from the Spanish GEM2005MAS65 phase III trial were randomized to maintenance with bortezomib plus thalidomide or bortezomib plus prednisone after bortezomib-based primary therapy.[203] After a median of 38 months from the start of maintenance the results reported that overall CR rate increased from 24% after primary therapy to 42% (the difference in CR between the two maintenance regimens was not significant for bortezomib plus thalidomide: 46%; bortezomib plus prednisone: 39%).[203]

After a median follow-up of 46 months from initiation of primary therapy, median PFS among all patients receiving maintenance was 35 months (39 months in patients receiving bortezomib plus thalidomide and 32 months in patients receiving bortezomib plus prednisone; P = .1). The

5-year median OS rate was 59% (69% in those receiving bortezomib plus thalidomide, and 50% in those receiving bortezomib plus prednisone; *P* = .1). Rates of non-hematologic grade 3 and 4 adverse events with bortezomib and thalidomide versus bortezomib and prednisone were 17% versus 5% (*P* = .009), including 9% versus 3% grade 3 and 4 peripheral neuropathy.[203]

Based on the above data, the NCCN Multiple Myeloma Panel Members have added bortezomib plus thalidomide and bortezomib plus prednisone as options for maintenance therapy (category 2B).

Treatment of Progressive or Relapsed Myeloma

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

A variety of therapies are available as options for previously treated MM. If the relapse occurs at greater than 6 months after completion of the initial primary therapy, patients may be retreated with the same primary regimen.

Preferred Regimens for Previously Treated Multiple Myeloma

The phase III APEX trial compared bortezomib versus high-dose dexamethasone as therapy for relapsed disease.[74] Among the 669 participants, patients randomized to bortezomib had a combined CR and PR rate 38% vs. 18% for those receiving dexamethasone), improved median time to progression (6.22 vs 3.49 months) and one-year survival (80% vs. 66%). In an updated efficacy analysis,[204] the response rate was 43% with bortezomib versus 18% for dexamethasone (*P* < .0001). A CR or near-CR was observed in 16% versus 0% of relapsed patients, respectively. Median OS was 29.8 months with bortezomib and 23.7 months with dexamethasone, despite nearly two thirds of patients' crossing over to bortezomib. Survival rates after one year were 80% and 67%, respectively (*P* = .00002). Patients with poor prognostic factors also benefited from bortezomib. Patients with del(13q) had worse survival when treated with dexamethasone than those without the deletion. However, for bortezomib-treated patients, the outcome was the same for those with or without the deletion.[205] Based on the above phase III trial data, the NCCN Multiple Myeloma Panel Members have included bortezomib monotherapy as a category 1 option for patients with relapsed/refractory myeloma.

A randomized trial, MMY-3021, of 222 patients compared single-agent bortezomib administered by the conventional intravenous (IV) route versus by subcutaneous route.[206] The findings from the phase III MMY-3021 study demonstrate non-inferior efficacy with subcutaneous versus intravenous bortezomib with regard to the primary endpoint (ORR after 4 cycles of single-agent bortezomib). Consistent results were shown with regard to secondary endpoints.[206] The results showed no significant differences in terms of time to progression or in one-year OS between groups.[206,207] However, patients receiving bortezomib subcutaneously had a significant reduction in peripheral neuropathy. The NCCN Panel has noted in a footnote that subcutaneous bortezomib may be considered for patients with pre-existing or high-risk peripheral neuropathy.

Bortezomib with 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 1 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).[208] 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 PLD regimen as a category 1 option for patients with relapsed/refractory MM.

Addition of dexamethasone to bortezomib in patients with relapsed/ refractory myeloma who had PD during bortezomib monotherapy resulted in improvement of response in 18% to 34% of patients.[209-211] The NCCN Multiple Myeloma Panel Members have included the bortezomib and dexamethasone regimen as an option for patients with relapsed/refractory myeloma (category 2A).

Lenalidomide combined with dexamethasone received approval from the FDA as a treatment option for patients with MM who had received at least one prior treatment. This was based on the results of two studies of a total of 692 patients randomized to receive dexamethasone either with or without lenalidomide. The primary efficacy endpoint in both studies was time to progression. A pre-planned interim analysis of both studies reported that the median time to progression was significantly longer in the lenalidomide arm compared to the control group.[212,213] 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.[213] Similar results were seen in the international trial MM-010.[212] Patients in both of these trials had been heavily treated before enrollment. Many had three or more prior lines of therapies with other agents and more than 50% of patients having undergone SCT.[212,213] Most adverse events and Grade 3/4 adverse events were more frequent in patients with MM who received the combination of lenalidomide/ dexamethasone compared to placebo and dexamethasone. Thrombocytopenia (61.5%) and neutropenia (58.8%) were the most frequently reported adverse events observed. The NCCN Multiple Myeloma Panel now considers this regimen as a category 1 option as therapy for patients with relapsed/refractory MM. Lenalidomide monotherapy has also been investigated and found effective in patients with relapsed/refractory MM.[214] The NCCN Multiple Myeloma Panel suggests considering lenalidomide monotherapy for steroid-intolerant individuals.

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, and 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 SCT.[215,216] The updated data after over 2 years of follow-up report a median PFS of 9.5 months and median OS of 26 months, with 12- and 24-month OS rates of 86% and 55%, respectively.[217] The NCCN Multiple Myeloma Panel Members have included bortezomib, lenalidomide, and dexamethasone as a category 2A option for relapsed/refractory MM.

The effects of adding of an alkylating agent (such as cyclophosphamide) and a novel agent (such as lenalidomide or bortezomib) to dexamethasone have been investigated for patients with relapsed/refractory MM. 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.[218] The combination of bortezomib, dexamethasone, and cyclophosphamide was found to be effective in patients with relapsed/refractory myeloma with an acceptable toxicity profile.[219,220] The NCCN Multiple Myeloma

Panel Members have included cyclophosphamide, and dexamethasone in combination with either lenalidomide or bortezomib, to the list of options for relapsed/refractory MM.

The addition of dexamethasone to thalidomide to treat patients with relapsed/refractory MM has been reported to have higher response rates of approximately 50% when compared to thalidomide alone.[221-224] Furthermore, combination therapy of dexamethasone and thalidomide along with infusional chemotherapy such as cisplatin, doxorubicin, cyclophosphamide, and etoposide (DT-PACE regimen) was also found to be effective, especially in patients with PD.[225] Both the above regimens have been included in NCCN Guidelines for Multiple Myeloma as category 2A options for relapsed/refractory myeloma. Thalidomide monotherapy has also been shown to be effective in refractory/relapsed myeloma, with 20% to 48% of the patients obtaining at least a PR.[226-230] Thalidomide-based combination regimens are more effective than thalidomide monotherapy; however, for steroid-intolerant individuals, the NCCN Multiple Myeloma Panel suggests considering thalidomide monotherapy.

An international randomized, controlled, open-label study randomized 269 patients, with progressive or relapsed MM after at least one autologous SCT, to receive bortezomib with thalidomide and dexamethasone or thalidomide and dexamethasone.[231] Patients receiving the triple drug combination of bortezomib with thalidomide and dexamethasone had significantly better outcomes. Median time to progression was significantly longer (19.5 vs. 13.8) and PFS was also significantly longer (18.3 months vs. 13.6 months) compared with thalidomide and dexamethasone. The CR + near-CR rate was higher in patients receiving bortezomib, thalidomide, and dexamethasone compared to thalidomide and dexamethasone (45% vs. 25%; *P* = .001). No significant difference was seen in OS between the two arms over a median follow-up of 30 months. The most clinically significant adverse event was Grade 3 peripheral sensory neuropathy in 29% of patients on bortezomib, thalidomide, and dexamethasone versus 12% on thalidomide and dexamethasone.[231] The bortezomib, thalidomide, and dexamethasone regimen is included as an option for relapsed/refractory MM (category 2A).

Results of an open-label, single-arm, phase II study in which 266 patients received single-agent carfilzomib intravenously two times a week for 3 of 4 weeks[232] showed that 95% of the evaluable patients were refractory to their last therapy; 80% were refractory to both bortezomib and lenalidomide. Patients had a median of 5 prior lines of therapy, including bortezomib, lenalidomide, and thalidomide. The primary endpoint of this trial was ORR and secondary endpoints included duration of response, clinical benefit response rate (≥minimal response), PFS, OS, and safety. The ORR seen in the trial was 23.7%, median duration of response was 7.8 months, and median OS was 15.6 months.[232] No cumulative toxicities were reported. Common adverse events reported in this trial were fatigue (49%), anemia (46%), nausea (45%), and thrombocytopenia (39%). Treatment-related peripheral neuropathy occurred in 12.4% of patients overall. This is substantially lower than incidence of peripheral neuropathy seen in the study evaluating subcutaneous bortezomib.[206,207] The rate of cardiac events observed in this study was within the expected range for this population and also it was not greater than previously reported with bortezomib.[74,78] The safety and efficacy data of carfilzomib seen in this trial is comparable to those reported by other phase II trials.[108,233] A sub-group analysis of this study in the patients in whom the FISH/conventional cytogenetic profiles were available (n=229) *suggests* that carfilzomib may have the potential to overcome the impact of high-risk cytogenetics in heavily pre-treated patients with MM.[234] A number of phase 3 studies

with carfilzomib as a single agent or in combination with other drugs are currently underway and should provide more definitive data on the impact of carfilzomib in patients with high-risk abnormalities (Clinical Trial ID: NCT01302392,[235] NCT01818752[236]). A phase 3 clinical trial, known as the FOCUS trial, will evaluate single-agent carfilzomib versus best supportive care in patients with relapsed and refractory MM who have received three or more prior therapies.[235]

The available data indicate that carfilzomib produces durable responses with an acceptable tolerability profile in heavily pretreated patients with MM. Based on this, the NCCN Panel has included single-agent carfilzomib as a therapeutic option for patients who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy (category 2A).

A randomized, multicenter phase III trial of 792 patients (ASPIRE), studied combination of lenalidomide and dexamethasone with or without carfilzomib in patients with relapsed/refractory myeloma, who had received one to three prior lines of therapy. The primary end point 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 to 0.83; *P* = .0001). The median duration of treatment was longer in the in the carfilzomib group (88.0 weeks vs. 57 weeks). The incidence of peripheral neuropathy was nearly identical in both arms (17.1% in the carfilzomib group vs. 17.0%). Non-hematologic adverse effects (≥ grade 3) that were higher in the carfilzomib group compared with lenalidomide and dexamethasone included dyspnea (2.8% vs. 1.8%), cardiac failure (3.8% vs.1.8%), and hypertension (4.3% and 1.8%). There were fewer discontinuations due to side effects in the carfilzomib arm (15.3% vs. 17.7%). Patients in the carfilzomib arm reported superior health-related quality of life than those who received lenalidomide and dexamethasone.[237]

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

The results of the phase III ENDEAVOR trial in patients with relapsed refractory MM treated with multiple prior lines of therapy showed a 2 fold improvement in median PFS with carfilzomib and dexamethasone compared to bortezomib and dexamethasone (18.7 months vs. 9.4 months; HR = 0.53; P < .0001).[238] Adverse events (grade 3 or higher) in the carfilzomib arm compared to the bortezomib arm included hypertension (8.9% vs 2.6%), dyspnea (5.6% vs 2.2%), cardiac failure (4.8% vs 1.8%), and acute renal failure (4.1% vs 2.6%).[238]

The NCCN Myeloma panel has included the combination of carfilzomib and dexamethasone as an option for patients with relapsed/refractory myeloma.

Pomalidomide, like lenalidomide, is an analogue of thalidomide. It possesses potent immunomodulatory and significant anti-myeloma properties.[239] The results of a phase I study of pomalidomide (4 mg orally on days 1– 21 of each 28-day cycle), with or without dexamethasone (40 mg/week), showed encouraging activity with manageable toxicity in patients with relapsed refractory MM, including those refractory to both lenalidomide and bortezomib.[240] A subsequent phase II randomized, open-label study evaluated the combination of pomalidomide and low-dose dexamethasone versus single-agent pomalidomide in patients with relapsed, refractory MM who had received a trial of lenalidomide and bortezomib.[241] Of the 221 patients

who were evaluated after a median follow-up of 14.2 months, the median PFS was 4.2 months in patients treated with pomalidomide plus low-dose dexamethasone compared with 2.7 months in patients treated with pomalidomide (HR, 0.68; *P* = .003).[242] The median OS was 16.5 months compared to 13.6 months with pomalidomide alone.[242] Grade 3 to 4 neutropenia occurred in 41% of patients treated with pomalidomide plus low-dose dexamethasone versus 48% of patients treated with pomalidomide monotherapy. No grade 3 to 4 peripheral neuropathy was reported.

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.[243] After a median follow-up of 10 months, PFS, the primary endpoint of the study, was significantly longer in patients who received pomalidomide and low-dose dexamethasone compared with those who received high-dose dexamethasone (4.0 vs. 1.9 months; HR, 0.45; *P* < .0001).[244] 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=.74; *P* = .0285).[244] The most common hematologic grade 3 and 4 adverse effects found higher with the low-dose dexamethasone compared with the high-dose were neutropenia and pneumonia.[244] 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).[245] The median PFS reported was 4.2 months and OS was 11.9 months. Whether the patients received prior lenalidomide or bortezomib, the PFS, OS, and ORR reported were similar.[245] The results of this trial are consistent with those observed in the pivotal MM-003 trial.[244]

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.[246] ORR was 35% and 34% for patients in the 21-day and 28-day groups, respectively. With median follow-up of 23 months, median duration of response, PFS, and OS were 7.3, 4.6, and 14.9 months across both groups, respectively. All patients experienced similar adverse events in both groups. The adverse events were primarily due to myelosuppression.[246] 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).[247] 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.[247]

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 immunomodulatory agent and bortezomib, and have demonstrated disease progression on or within 60 days of completion of the last therapy (category 1). For steroid-intolerant individuals, the NCCN Multiple Myeloma Panel suggests considering pomalidomide monotherapy.

Panobinostat is a pan-deacetylase inhibitor that epigenetically modulates class I and II histone deacetylase (HDAC) enzymes.[248] Recently, the FDA approved the use of panobinostat in combination with bortezomib and dexamethasone for patients with relapsed/refractory MM who have had at least two prior therapies with regimens containing an immunomodulatory agent and bortezomib.

The approval was based on the results of a randomized placebo-controlled phase III study, PANORAMA-1. The study randomized 768 patients with MM who had received prior treatment with an immunomodulatory agent and bortezomib to receive bortezomib and dexamethasone along with either panobinostat or placebo. The results showed an improved median PFS with panobinostat containing regimen compared with the control arm (11.99 months [95% CI; 10.33–12.94 months] vs. 8.08 months [95% CI; 7.56–9.23 months]; HR= 0.63, 95% CI; 0.52–0.76; *P* <. 0001) along an increased depth of response.[249] The final OS data from this study are not yet available.

The regimen containing panobinostat is associated with significant toxicity. Serious adverse events were reported in 228 (60%) of 381 patients in the panobinostat group and 157 (42%) of 377 patients in the placebo group. Common grade 3–4 laboratory abnormalities and adverse events were more in the panobinostat group versus the control group including thrombocytopenia 67% vs. 31%), lymphopenia (53% vs. 40%), diarrhoea (26% vs. 8%), fatigue (4% vs. 2%), and peripheral neuropathy (18% vs. 5%).[249]

The PANORAMA-2 is a phase II single arm, multicenter trial that evaluated combination of panobinostat with bortezomib and dexamethasone in patients who had relapsed disease, refractory to bortezomib (N= 55).[250] Patients on this study achieved an ORR of 34.5% with the panobinostat containing regimen. [250] The median PFS was 5.4 months and OS had not been reached after at a median follow-up of 8.3 months. [250] Common grade 3/4 adverse events included thrombocytopenia (63.6%), fatigue (20.0%), and diarrhea (20.0%)..[250]

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

In addition, the NCCN Guidelines include the regimens containing high-dose (non-marrow ablative) cyclophosphamide[251]; DCEP[252,253]; and VTD-PACE (bortezomib, thalidomide, dexamethasone, cisplatin, doxorubicin, cyclophosphamide, and etoposide) as preferred therapy options for patients with previously treated MM.[21]

Other Regimens for Previously Treated MM

In a trial by Knop and colleagues, 31 patients who had experienced relapse after high-dose chemotherapy and autologous transplantation were enrolled to receive increasing doses of bendamustine.[254] The ORR was 55%, with a median PFS of 26 weeks for all patients and 36 weeks for patients who received higher doses of bendamustine (90–100 mg/m^2). Toxicity was mild and mainly hematologic. A retrospective analysis of 39 patients has reported that bendamustine is effective and

tolerable in patients with advanced progressive MM, with an ORR of 36%.[255] Bendamustine is currently a NCCN category 2A treatment option for relapsed/refractory MM.

A multicenter phase I/II trial investigated the combination of bendamustine, lenalidomide, and dexamethasone as treatment for patients (n = 29) with relapsed refractory MM.[256] PR rate was seen in 52% (n = 13) of patients, with VGPR in 24% (n = 6) of patients. The median PFS in the trial was 6.1 months (95% CI, 3.7–9.4 months), and the one-year PFS rate was 20% (95% CI, 6%–41%).[256] The NCCN Panel has included lenalidomide in combination with bendamustine and dexamethasone as a treatment option for relapsed/refractory MM (category 2A).

Vorinostat is an oral inhibitor of histone deacetylase class I and class II proteins. It regulates genes and proteins involved in tumor growth and survival. The synergistic effects of vorinostat and bortezomib have been shown in preclinical studies and were confirmed in independent phase 1 trials in patients with relapsed/refractory MM, showing ORR of up to 42%.[257] An international, multi-centered, open-label, single-arm phase IIb trial called Vantage 095 studied the combination of vorinostat and bortezomib in bortezomib–refractory patients and patients considered refractory, intolerant, or ineligible for immunomodulatory drug-based regimens. The combination of vorinostat and bortezomib was found to be active and well-tolerated. The ORR in the Vantage 095 study was 17%.[258] The median OS observed was 11.2 months with a 2-year OS rate of 32%.[258] Another international, multicenter, randomized, double-blind, phase II trial studied vorinostat and bortezomib compared with bortezomib and placebo in patients with relapsed/refractory MM.[259] The ORR seen in patients treated with vorinostat and bortezomib was 56% versus 41% in those treated with bortezomib and placebo. The median PFS was 7.63 versus 6.83 months for vorinostat in combination with bortezomib versus bortezomib plus placebo-treated patients, respectively. Based on these data, the NCCN Panel has included vorinostat in combination with bortezomib as a treatment option for relapsed/refractory MM (category 2A).

Adjunctive Treatment for Multiple Myeloma

Important advances have been made in adjunctive treatment/supportive care of patients with MM. This involves careful patient education about the probable side effects of each drug and the drug combinations being used, and the supportive care measures required. Supportive care can be categorized into those measures required for all patients and those that address specific drugs.

Bony manifestations of myeloma, in the form of diffuse osteopenia and/or osteolytic lesions, develop in 85% of patients. Related complications are the major cause of limitations in quality of life and performance status in patients with MM. A large, double-blind, randomized trial has shown that monthly use of intravenous 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.[260,261] Zoledronic acid has equivalent benefits.[262] Results from the study conducted by Zervas et al[263] show a 9.5-fold greater risk for the development of osteonecrosis of the jaw with zoledronic acid compared to pamidronate. Patients who are on bisphosphonates should have their renal function monitored. They should have dental exam prior to start of bisphosphonate therapy and be monitored for osteonecrosis of the jaw.

The 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.[264] 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 confirmed osteonecrosis of the jaw than was clodronic acid.[264-266] The study reanalyzed and recently reported survival outcomes. After an extended follow-up (median, 5.9 years), in addition to PFS, the OS was also significantly improved (52 vs. 46 months; HR, 0.86; *P* =.01) compared with clodronic acid.[267] The long-term rates of osteonecrosis of the jaw were also observed to be higher with zoledronic acid compared with clodronate (3.7% vs. 0.5%; *P* = .0001). [267]

A recent meta-analysis of 20 randomized controlled trials of 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. Whether zoledronate is superior to pamidronate and other bisphosphonates remains to be determined.[268]

The NCCN Guidelines for Multiple Myeloma recommend bisphosphonates for all patients receiving myeloma therapy for symptomatic disease regardless of documented bone disease (category 1). In patients with smoldering or stage I MM, according to the NCCN Panel, bisphosphonates may be considered but preferably in a clinical trial. Skeletal survey annually or as clinically indicated is recommended for these patients. Bone densitometry or other metabolic studies should be reserved for clinical trials.

Low-dose radiation therapy (10–30 Gy) is used for the palliative treatment of uncontrolled pain, impending pathologic fracture, or impending spinal cord compression.[50] Limited involved fields should be used to limit the effect of irradiation on stem cell harvest or its effect on potential future treatments; the radiation doses administered should not preclude stem cell collection in potential candidates for high-dose therapy and hematopoietic SCT. Orthopedic consultation should be obtained for impending or actual fractures in weight-bearing bones, bony compression of the spinal cord, or vertebral column instability. Either vertebroplasty or kyphoplasty should be considered for symptomatic vertebral compression fractures.

Excess bone resorption from myeloma bone disease can lead to excessive release of calcium into the blood, contributing to hypercalcemia. Symptoms include polyuria and gastrointestinal disturbances, with progressive dehydration and decreases in glomerular filtration rate. Hypercalcemia should be treated with hydration and furosemide, bisphosphonates, 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.[269-271]

Plasmapheresis should be used as adjunctive therapy for symptomatic hyperviscosity.[272] Institutions differ in their use of plasmapheresis for adjunctive treatment of renal dysfunction.

Erythropoietin therapy should be considered for anemic patients, especially those with renal failure. Measuring endogenous erythropoietin levels may also be helpful in treatment planning[273,274] (see NCCN Guidelines for Cancer and Treatment-Related Anemia).

To prevent infection: 1) intravenous immunoglobulin therapy should be considered for recurrent, life-threatening infections; 2) pneumococcal and influenza vaccine should also be considered; and 3) *Pneumocystis*

carinii pneumonia (PCP), herpes, and antifungal prophylaxis is recommended if a high-dose regimen is used. Bortezomib treatment has been associated with an incidence of herpes zoster.[73,74] Herpes prophylaxis is recommended in patients receiving bortezomib therapy.[72] (See NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections).

Thrombosis is relatively common when thalidomide or lenalidomide is used with steroids, and is particularly frequent when treating newly diagnosed patients. Use of prophylactic anticoagulation agents (see NCCN Guidelines for Venous Thromboembolic Disease) is recommended when immunomodulatory drugs are used in combination therapy during induction.[94,275,276]

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

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