Multiple Myeloma: Diagnosis and Primary Treatment

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City of Hope Comprehensive Cancer Center
Educational Objectives

• Discuss considerations required for diagnosing and managing MM

• Individualize treatment for patients with MM

• Analyze recently updated clinical practice guidelines for MM

• Assess the safety, efficacy, and mechanism of actions of current and emerging treatments for patients with MM

• Identify strategies for anticipating, preventing, and treating adverse effects including patients with MM, including dose-modifying strategies
The Cause
Multiple Myeloma

- Approximately 30,000* new cases (second most frequent hematologic malignancy after NHL)
  - Accounts for 10-15% of hematologic cancers
  - Survival 4-6 years; considered incurable
- More common in men vs. women
- Incidence in African Americans is about twice that of Caucasians
- Median age at diagnosis is 70 years
- Over 70% of patients had a detectable M protein previously
  - MGUS > 3% over age 50

Myeloma: Clinical Features

- Constitutional weakness, fatigue, and weight loss
- Renal disease
- Anemia
- Bone pain, often with loss of height
- Infections: neutropenia/hypogammaglobulinemia
- Hypercalcemia
- Hyperviscosity
- Neurologic dysfunction: spinal cord or nerve root compression
INITIAL DIAGNOSTIC WORKUP

- History and physical exam
- CBC, differential, platelet count
- Serum BUN/creatinine, electrolytes, albumin, and calcium
- Serum LDH and beta-2 microglobulin
- 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)
- Serum free light chain (FLC) assay
- Skeletal survey
- Unilateral bone marrow aspirate + biopsy, including bone marrow immunohistochemistry and/or bone marrow flow cytometry
- Metaphase cytogenetics on bone marrow
- Plasma cell FISH [del 13, del 17p13, t(4;14), t(11;14), t(14;16), 1q21 amplification]

Useful Under Some Circumstances

- Whole body low-dose CT scan
- Whole body MRI or whole body PET/CT scan
- Tissue biopsy to diagnose a solitary osseous or extraosseous plasmacytoma
- Bone densitometry
- Plasma cell proliferation
- Staining of marrow and fat pad for amyloid
- Serum viscosity
- HLA typing

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Case Study

- 59-year-old patient presents with back pain and fatigue
- Hemoglobin 8 g/dL, calcium 11.5 mg/dL, creatinine 1.4 mg/dL, albumin 3.2 g/dL, total protein 10 g/dL
- β-2 microglobulin 5.8 mg/L, SPEP shows M spike of 7.2 g/dL, IFE IgGk
- Bone marrow with 70% monoclonal plasma cells
- Cytogenetics: Del(13), FISH t(4:14)
- Skeletal survey: multiple lytic lesions
### STAGING SYSTEMS FOR MULTIPLE MYELOMA

<table>
<thead>
<tr>
<th>Stage</th>
<th>International Staging System (ISS)</th>
<th>Revised-ISS (R-ISS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Serum beta-2 microglobulin &lt;3.5 mg/L, Serum albumin ≥3.5 g/dL</td>
<td>ISS stage I and standard-risk chromosomal abnormalities by iFISH and Serum LDH ≤ the upper limit of normal</td>
</tr>
<tr>
<td>II</td>
<td>Not ISS stage I or III</td>
<td>Not R-ISS stage I or III</td>
</tr>
<tr>
<td>III</td>
<td>Serum beta-2 microglobulin ≥5.5 mg/L</td>
<td>ISS stage III and either high-risk chromosomal abnormalities by iFISH or Serum LDH &gt; the upper limit of normal</td>
</tr>
</tbody>
</table>


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**MYEL-B**

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### Updated IMWG Criteria for Diagnosis of Multiple Myeloma

**MGUS**
- Myeloma protein < 3 g/dL
- Bone marrow clonal involvement < 10%
- No myeloma defining events*

**Smoldering Myeloma**
- M protein ≥ 3 g/dL
- BM clonal involvement ≥ 10-60%
- No Myeloma Defining Events*

*C: Calcium elevation (> 11 mg/dL or > 1 mg/dL higher than ULN)
R: Renal insufficiency (CrCl < 40 mL/min or serum creatinine > 2 mg/dL)
A: Anemia (Hb < 10 g/dL or 2 g/dL < normal)
B: Bone disease (≥ 1 lytic lesions on skeletal radiography, CT, or PET/CT)

## Risk Factors for MGUS Progression

<table>
<thead>
<tr>
<th>Factor, %</th>
<th>2-Yr Progression</th>
</tr>
</thead>
<tbody>
<tr>
<td>High levels of circulating plasma cells</td>
<td>80</td>
</tr>
<tr>
<td>Bone marrow plasma cell proliferative rate</td>
<td>80</td>
</tr>
<tr>
<td>Transformation into smoldering multiple myeloma</td>
<td>65</td>
</tr>
<tr>
<td>Abnormal plasma cell phenotype ≥ 95% plus immunoparesis</td>
<td>50</td>
</tr>
<tr>
<td>t(4;14), 1q amp, del(17p)</td>
<td>50</td>
</tr>
<tr>
<td>Decreased clearance by ≥ 25% and rise in urinary monoclonal protein or serum free light-chain concentrations</td>
<td>NA</td>
</tr>
</tbody>
</table>

DEFINITION OF MULTIPLE MYELOMA (SMOLDERING AND ACTIVE)

**Smoldering (Asymptomatic) Myeloma**
- 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 skeletal survey negative, assess for bone disease with whole body MRI or PET/CT

**Active (Symptomatic) Myeloma**
- 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 mg/L (involved kappa) or ≤0.01 (involved lambda)
  - >1 focal lesions on MRI studies ≥5 mm

MYEL-A
Revised ISS Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Serum albumin ≥ 3.5 g/dL AND β₂-M ≤ 3.5 mg/L</td>
</tr>
<tr>
<td></td>
<td>Normal LDH</td>
</tr>
<tr>
<td></td>
<td>No t(4;14), t(14;16), or del(17p)</td>
</tr>
<tr>
<td>2</td>
<td>Not stage I or III</td>
</tr>
<tr>
<td>3</td>
<td>β₂-M ≥ 5.5 mg/dL PLUS</td>
</tr>
<tr>
<td></td>
<td>High LDH, OR</td>
</tr>
<tr>
<td></td>
<td>t(4;14), t(14;16), or del(17p)</td>
</tr>
</tbody>
</table>

Frontline Treatment Options

- Is autologous stem cell transplant (ASCT) considered an option?
- New paradigm: include novel agents in induction, followed by ASCT, consolidation, and maintenance
  - Aim for complete response
  - Is there a need to improve develop new approaches of ASCT?
  - Have we improved efficacy in patients who are not eligible for transplant?
## NCCN Guidelines Version 1.2017
### Multiple Myeloma

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

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Standard IMWG response criteria</strong></td>
<td></td>
</tr>
<tr>
<td>Stringent complete response</td>
<td>Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (k/λ ratio ≤4:1 or ≥1:2 for k and λ patients, respectively, after counting ≥100 plasma cells)</td>
</tr>
<tr>
<td>Complete response</td>
<td>Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and &lt;5% plasma cells in bone marrow aspirates</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level &lt;100 mg per 24 h</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>≥50% reduction of serum M-protein plus reduction in 24-h urinary M-protein by ≥90% or to &lt;200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (sum of the products of the maximal perpendicular diameters [SPD] of measured lesions) of soft tissue plasmacytomas is also required</td>
</tr>
</tbody>
</table>

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## Multiple Myeloma

### Response Criteria for Multiple Myeloma

*Revised based on the new criteria by International Myeloma Working Group (IMWG)*

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Minimal response</strong></td>
<td>≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50%–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in SPD of soft tissue plasmacytomas is also required</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease</td>
</tr>
</tbody>
</table>
| **Progressive disease** | Any one or more of the following criteria: 
  - Increase of 25% from lowest confirmed response value in one or more of the following criteria: 
    - Serum M-protein (absolute increase must be ≥0.5 g/dL); 
    - Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; 
    - Urine M-protein (absolute increase must be ≥200 mg/24 h); 
  - In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); 
  - In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); 
  - Appearance of a new lesion(s), ≥50% increase from nadir in SPD of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; 
  - ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease |

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<tr>
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</table>
| Clinical relapse   | - Clinical relapse requires one or more of the following criteria:  
- Direct indicators of increasing disease and/or end organ dysfunction (calcium elevation, renal failure, anemia, lytic bone lesions [CRAB features]) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;  
- Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);  
- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥1 cm) increase as measured serially by the SPD of the measurable lesion;  
- Hypercalcemia (>11 mg/dL);  
- Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions;  
- Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;  
- Hyperviscosity related to serum paraprotein |
| Relapse from complete response (to be used only if the endpoint is disease-free survival) | - Any one or more of the following criteria:  
- Reappearance of serum or urine M-protein by immunofixation or electrophoresis;  
- Development of ≥5% plasma cells in the bone marrow;  
- Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia) |

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<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
</table>
| Relapse from MRD negative (to be used only if the endpoint is disease-free survival) | Any one or more of the following criteria:  
  - Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma);  
  - Reappearance of serum or urine M-protein by immunofixation or electrophoresis;  
  - Development of ≥5% clonal plasma cells in the bone marrow;  
  - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia) |


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## NCCN Guidelines Version 1.2017
### Multiple Myeloma

### Myeloma Therapy
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)

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bortezomib/cyclophosphamide/dexamethasone</td>
<td>- Bortezomib/dexamethasone (category 1)</td>
</tr>
<tr>
<td>- Bortezomib/doxorubicin/dexamethasone (category 1)</td>
<td>- Carfilzomib/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>- Bortezomib/lenalidomide/dexamethasone (category 1)</td>
<td>- Ixazomib/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td></td>
<td>- Lenalidomide/dexamethasone (category 1)</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Other Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Bortezomib/cyclophosphamide/dexamethasone</td>
<td>- Bortezomib/dexamethasone</td>
</tr>
<tr>
<td>- Bortezomib/lenalidomide/dexamethasone (category 1)</td>
<td>- Carfilzomib/lenalidomide/dexamethasone (category 2B)</td>
</tr>
<tr>
<td>- Lenalidomide/low-dose dexamethasone (category 1)</td>
<td>- Ixazomib/lenalidomide/dexamethasone</td>
</tr>
</tbody>
</table>

#### Maintenance Therapy
- Bortezomib
- Lenalidomide (category 1)
Patients with sCR have a significantly better outcome: estimated 5-yr OS 80% with sCR vs 53% with CR or 47% with nCR

Randomized, controlled phase III trial exploring utility of high-dose melphalan + ASCT consolidation ± lenalidomide maintenance vs MPR consolidation ± lenalidomide maintenance in newly diagnosed MM

^ ASCT: Autologous Stem Cell Transplantation; M: melphalan; P: prednisone; R: lenalidomide

A randomized, controlled phase III trial comparing high-dose melphalan + ASCT vs cyclophosphamide + Rd* consolidation in newly diagnosed MM

- Increased grade 3/4 AEs with ASCT vs CRd, but similar serious hematologic (0% vs 2%; \( P = .49 \)) and nonhematologic (7% vs 10%; \( P = .393 \)) AEs

Phase III IFM/DFCI 2009: Frontline RVd* ± ASCT in Younger Pts (< 65 Yrs) With MM

N = 700 previously untreated patients younger than 65 yrs of age

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>RVd + ASCT (n = 350)</th>
<th>RVd Only (n = 350)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-yr PFS</td>
<td>47</td>
<td>35</td>
<td>0.69 (0.56-0.84; (P &lt; .001))</td>
</tr>
<tr>
<td>4-yr OS</td>
<td>81</td>
<td>83</td>
<td>1.2 (0.7-1.8; (P = \text{NS}))</td>
</tr>
<tr>
<td>Second Primary</td>
<td>5</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>ORR</td>
<td>99</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>88</td>
<td>78</td>
<td>(P = .001)</td>
</tr>
</tbody>
</table>

PFS benefit in ASCT arm uniform across subgroups

- Age (≤ or > 60 yrs), sex, Ig isotype (IgG or others), ISS stage (I or II or III), cytogenetics (standard or high risk), and response after the 3 first cycles of RVd (CR or not)


N = 700 previously untreated patients younger than 65 yrs of age

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## Phase III EMN02/HO95 Trial: Upfront ASCT vs VMP in Newly Diagnosed MM: Efficacy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>VMP</th>
<th>ASCT</th>
<th>HR (95% CI; P Value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall population, n</td>
<td>497</td>
<td>695</td>
<td>0.73 (0.59-0.90; .003)</td>
</tr>
<tr>
<td>Median, mos</td>
<td>44</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>3 yr, %</td>
<td>57.5</td>
<td>66.1</td>
<td></td>
</tr>
<tr>
<td>Standard-risk cytogenetics, n</td>
<td>220</td>
<td>290</td>
<td>0.68 (0.47-0.98; .034)</td>
</tr>
<tr>
<td>Median, mos</td>
<td>46</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>3 yr, %</td>
<td>69.6</td>
<td>76.6</td>
<td></td>
</tr>
<tr>
<td>High-risk cytogenetics, n</td>
<td>181</td>
<td>292</td>
<td>0.69 (0.52-0.92; .010)</td>
</tr>
<tr>
<td>Median, mos</td>
<td>32</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>3 yr, %</td>
<td>43.2</td>
<td>55.2</td>
<td></td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td>(n = 451)</td>
<td>(n = 641)</td>
<td>--</td>
</tr>
<tr>
<td>VGPR or better, %</td>
<td>73.8</td>
<td>85.5</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

- Median follow-up: 26 mos (range: 19-37 mos)

TMI with Helical Tomotherapy and ASCT Following high-Dose Mel and ASCT as Part of TASCT for Patients with MM

Figure 1. Treatment plan dose distribution color wash from a patient treated with 1,600 cGy of TMI.

TOXICITIES

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cycle 1 Mel (n=54)</th>
<th>Cycle 2 TMI (cGy; n=44)</th>
<th>200 mg/m²</th>
<th>1000</th>
<th>1200</th>
<th>1400</th>
<th>1600</th>
<th>1800</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>54</td>
<td>3 4 3 28 6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>6</td>
<td>1 1 0 1 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue/anorexia</td>
<td>5</td>
<td>1 0 0 0 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/emaesis</td>
<td>2</td>
<td>0 0 0 3 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteritis/colitis</td>
<td>3</td>
<td>1 0 0 0 2*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Engraftment syndrome</td>
<td>0</td>
<td>1 0 0 0 0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>0</td>
<td>0 0 0 0 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHF/Hypotension</td>
<td>1</td>
<td>0 0 0 0 1*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic/electrolyte</td>
<td>10</td>
<td>1 1 0 7 4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Second malignancies: non-melanoma skin:2, thyroid:1, breast cancer:1, AML:1

OS at 5yrs: 63% (95% CI: 0.51-0.78)
PFS at 5yrs: 41% (95% CI: 0.29-0.57)

Somlo et al Proceedings ASCO 2015. abst 8581
CALGB 100104: Lenalidomide vs Placebo Maintenance Following ASCT for Myeloma

- Phase III trial with D-S stage I-III pts; < 71 yrs of age and > 2 cycles of induction with SD or better (N = 460)
- PFS: ITT analysis with median follow-up from transplant of 34 mos
  - Estimated HR: 0.48 (95% CI: 0.36-0.63); median TTP: 46 vs 27 mos
- OS: 35 deaths with lenalidomide and 53 deaths with placebo
  - 3-yr OS: 88% vs 80%; HR: 0.62 or a 38% reduction in death with the cross over

Lenalidomide Maintenance After ASCT in MM: Overall Survival

- Lenalidomide maintenance significantly improved survival after ASCT
  - 7-yr OS: 62% vs 50% in the control arm; Median OS: not estimable vs 86.0 mos in control arm (median follow-up: 80 mos);

- Lenalidomide maintenance benefit seen in most subgroups except high-risk cytogenetics
  - HR: 1.18 (95% CI: 0.66-2.10)

- Mean duration of maintenance: 25 mos in IFM trial, 30 mos in CALGB trial

- Incidence of second primary malignancies significantly higher with lenalidomide maintenance
  - Hematologic: HR: 2.03 (95% CI: 1.14-3.61; \( P = .015 \))
  - Solid tumor: HR: 1.71 (95% CI: 1.04-2.79; \( P = .032 \))

HOVON-65: Bortezomib in Induction and Maintenance for Newly Diagnosed MM

- CR/nCR superior with PAD induction (30% vs 15% with VAD) and by best response (35% vs 49% with VAD) ($P < .001$ for both)\textsuperscript{[1]}
- PFS and OS superior with bortezomib-based treatment regimen\textsuperscript{[1]}
- Bortezomib significantly improved OS for pts presenting with renal failure ($P < .001$)\textsuperscript{[2]}

**MYELOMA THERAPY**
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.

<table>
<thead>
<tr>
<th>Preferred Regimens:</th>
<th>Other Regimens:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Repeat primary induction therapy (if relapse at &gt;6 mo)</td>
<td>• Bendamustine</td>
</tr>
<tr>
<td>• Bortezomib/dexamethasone (category 1)</td>
<td>• Bendamustine/bortezomib/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dexamethasone</td>
<td>• Bendamustine/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
<td>• Bortezomib/liposomal doxorubicin (category 1)</td>
</tr>
<tr>
<td>• Carfilzomib/dexamethasone (category 1)</td>
<td>• Cyclophosphamide/lenalidomide/dexamethasone</td>
</tr>
<tr>
<td>• Carfilzomib/lenalidomide/dexamethasone (category 1)</td>
<td>• Elotuzumab/bortezomib/dexamethasone</td>
</tr>
<tr>
<td>• Daratumumab</td>
<td>• High-dose cyclophosphamide</td>
</tr>
<tr>
<td>• Daratumumab/bortezomib/dexamethasone (category 1)</td>
<td>• Ixazomib/dexamethasone</td>
</tr>
<tr>
<td>• Dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP)</td>
<td>• Panobinostat/bortezomib/dexamethasone (category 1)</td>
</tr>
<tr>
<td>• Dexamethasone/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide (DT-PACE) ± bortezomib (VTD-PACE)</td>
<td>• Panobinostat/carfilzomib</td>
</tr>
<tr>
<td>• Elotuzumab/lenalidomide/dexamethasone (category 1)</td>
<td>• Pomalidomide/cyclophosphamide/dexamethasone</td>
</tr>
<tr>
<td>• Ixazomib/lenalidomide/dexamethasone (category 1)</td>
<td></td>
</tr>
<tr>
<td>• Lenalidomide/dexamethasone (category 1)</td>
<td></td>
</tr>
<tr>
<td>• Pomalidomide/dexamethasone (category 1)</td>
<td></td>
</tr>
<tr>
<td>• Pomalidomide/bortezomib/dexamethasone</td>
<td></td>
</tr>
<tr>
<td>• Pomalidomide/carfilzomib/dexamethasone</td>
<td></td>
</tr>
</tbody>
</table>
Case Study

- 75-year-old patient presents with back pain and fatigue
- Hemoglobin 8 g/dL, calcium 11.5 mg/dL, creatinine 2.4 mg/dL, albumin 3.2 g/dL, total protein 10 g/dl
- Co-morbidities: HTN, IDDM, lower extremity neuropathy, severe preexisting osteoarthritis, COPD
- β₂ microglobulin 5.8 mg/L, SPEP shows M spike of 7.2 g/dL, IFE IgGk
- Bone marrow with 70% monoclonal plasma cells
- Cytogenetics: Del(13), FISH t(4:14)
- Skeletal survey: multiple lytic lesions
### SWOG S0777: RVd\(^\wedge\) vs Rd in Pts With Newly Diagnosed Multiple Myeloma

<table>
<thead>
<tr>
<th>Confirmed Response, %</th>
<th>RVd ((n = 216^*))</th>
<th>Rd ((n = 214^*))</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (PR or better)</td>
<td>81.5</td>
<td>71.5</td>
</tr>
<tr>
<td>• CR</td>
<td>15.7</td>
<td>8.4</td>
</tr>
<tr>
<td>• VGPR</td>
<td>27.8</td>
<td>23.4</td>
</tr>
<tr>
<td>• PR</td>
<td>38.0</td>
<td>39.7</td>
</tr>
<tr>
<td>SD or better</td>
<td>97.2</td>
<td>95.8</td>
</tr>
<tr>
<td>• SD</td>
<td>15.7</td>
<td>24.3</td>
</tr>
<tr>
<td>PD or death</td>
<td>2.8</td>
<td>4.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Survival, Mos</th>
<th>RVd ((n = 242))</th>
<th>Rd ((n = 229))</th>
<th>HR ((0.560-0.906))</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS</td>
<td>43</td>
<td>30</td>
<td>0.712</td>
<td>.0018</td>
</tr>
<tr>
<td>Median OS</td>
<td>75</td>
<td>64</td>
<td>0.709</td>
<td>.025</td>
</tr>
</tbody>
</table>

\(^\wedge\)RVd: lenalidomide, bortezomib, dexamethasone)  
*Assessable.  
Long-term Survival in Elderly Patients Treated With Novel Agents

Retrospective analysis: 3 randomized trials of GIMEMA and HOVON (N = 1175)

First-line treatment: MP (n = 332), MPT (n = 332), VMP (n = 257), VMPT-VT (n = 254)


Probability of PFS

All Pts

Pts Older Than 75 Yrs of Age

Probability of OS

Mos

CR
VGPR
PR

CR
VGPR
PR

CR
VGPR
PR

CR
VGPR
PR
## Age-Adjusted Dose Reduction in Patients With Myeloma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Younger Than 65 Yrs</th>
<th>65-75 Yrs</th>
<th>Older Than 75 Yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone</td>
<td>40 mg/day on Days 1-4, 15-18 q4w or Days 1, 8, 15, 22 q4w</td>
<td>40 mg/day on Days 1, 8, 15, 22 q4w</td>
<td>20 mg/day on Days 1, 8, 15, 22 q4w</td>
</tr>
<tr>
<td>Melphalan</td>
<td>0.25 mg/kg on Days 1-4 q6w</td>
<td>0.25 mg/kg on Days 1-4 q6w or 0.18 mg/kg on Days 1-4 q4w</td>
<td>0.18 mg/kg on Days 1-4 q6w or 0.13 mg/kg on Days 1-4 q4w</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>300 mg/day on Days 1, 8, 15, 22 q4w</td>
<td>300 mg/day on Days 1, 8, 15 15 q4w or 50 mg/day on Days 1-21 q4w</td>
<td>50 mg/day on Days 1-21 q4w or 50 mg/day QOD on Days 1-21 q4w</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>200 mg/day</td>
<td>100 mg/day or 200 mg/day</td>
<td>50 mg/day to 100 mg/day</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>25 mg/day on Days 1-21 q4w</td>
<td>15-25 mg/day on Days 1-21 q4w</td>
<td>10-25 mg/day on Days 1-21 q4w</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>1.3 mg/m² bolus on Days 1, 4, 8, 11 q3w</td>
<td>1.3 mg/m² bolus on Days 1, 4, 8, 11 q3w or on Days 1, 8, 15, 22 q5w</td>
<td>1.0-1.3 mg/m² bolus on Days 1, 8, 15, 22 q5w</td>
</tr>
</tbody>
</table>

New Approvals for RRMM in 2015

- Panobinostat (HDAC inhibitor) + bort/dex
- Carfilzomib (proteasome inhibitor) + len/dex
- Daratumumab (CD38-targeted monoclonal antibody) as single agent
- Ixazomib (oral proteasome inhibitor) + len/dex
- Elotuzumab (anti-SLAMF7 monoclonal antibody) + len/dex
Promising Agents

- **Proteasome inhibitors**: Marizomib (NPI0052): orally available, irreversible nonpeptide PI; Oprozomib (ONX0912): orally available, irreversible carfilzomib derivative

- **HDAC inhibitors**: Vorinostat + bortezomib; Rocilinostat (ACY1215): selective HDAC-6 inhibitor

- **KSP inhibitors**: Filanesib (ARRY-520): inhibits spindle formation during mitosis, inducing cell death

- **Monoclonal antibodies**: Isatuximab (SAR650984): humanized anti-CD38 antibody; BT062: Conjugated anti-CD138 antibody

- Checkpoint inhibitors

Potential targetable Genomic Abnormalities/targeting agents

- t(4;14) FGFR    FGFR inhibitors
- t(11;14) Cyclin D1 celeciclib, binaciclib
- t(14;16) MAF    MEK inhibitors (selumetinib)
- B-RAF           vemurafenib
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 skeletal 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 for 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
- Pneumocystis jiroveci pneumonia (PJP), 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
- Full-dose aspirin recommended with immunomodulator-based therapy. Therapeutic anticoagulation recommended for those at high risk for thrombosis.
- See NCCN Guidelines for Venous Thromboembolic Disease
### IMWG: prophylaxis recommendations determined by number of risk factors

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>Risk assessment</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Hyperviscosity</td>
<td></td>
<td></td>
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<tr>
<td>• Obesity</td>
<td></td>
<td></td>
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<tr>
<td>• Previous VTE</td>
<td></td>
<td></td>
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<tr>
<td>• Central venous catheter or pacemaker</td>
<td></td>
<td></td>
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<tr>
<td>• Cardiac disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Chronic renal disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Myeloma therapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– High-dose dexamethasone*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– Doxorubicin</td>
<td></td>
<td></td>
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<tr>
<td>– Multiagent chemotherapy</td>
<td></td>
<td></td>
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<tr>
<td>• Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Acute infection</td>
<td></td>
<td></td>
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<tr>
<td>• Immobilization</td>
<td></td>
<td></td>
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<tr>
<td>• General surgery</td>
<td></td>
<td></td>
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<tr>
<td>• Any anesthesia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Trauma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Use of erythropoietin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Clotting disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 or 1 risk factor</td>
<td></td>
<td>Aspirin</td>
</tr>
<tr>
<td>2 or more risk factors</td>
<td></td>
<td>LMWH or warfarin†</td>
</tr>
</tbody>
</table>

LMWH: low-molecular-weight heparin
Obesity: body mass index \( \geq 30 \text{ kg/m}^2 \)
*\( \geq 480 \text{ mg per month} \).
†Full-dose warfarin (target INR 2-3).

Treating Patients with Renal Impairment

- Reversal of renal failure seen in up to 50% of newly-diagnosed patients receiving bortezomib-based regimens
  - can receive full doses

- Can use thalidomide, lenalidomide in renal failure but
  - Little efficacy data reported on renal improvement rates
  - dose-reduce lenalidomide due to increased myelosuppression:
    - CrCl 30-60 ml/min: 10 mg daily
    - Cr Cl <30 (not on dialysis): 15 mg every other day
    - Cr Cl <30 (on dialysis): 5 mg daily

- Consider dose-reduced melphalan
Future of Myeloma Therapy

- Incorporation of novel agents into induction, consolidation, and maintenance.
- Continue development of drugs with different mechanisms of action.
- Heterogeneous disease: have to match the mechanism with the biologic abnormality.
- ASCT is here to stay for now, but need to define better regimens and role of tandem ASCT.
- Further research is needed with CAR-T cell and other immunotherapies (check point inhibitors, vaccines, etc)
- Go for cure