Emerging Treatment Options in the Management of Relapsed/Refractory Multiple Myeloma

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Educational Objectives

• Assess the safety, efficacy, and mechanism of actions of current and emerging treatments for patients with relapsed/refractory MM
• Discuss considerations required for managing relapsed/refractory MM
• Individualize treatment for patients with refractory/relapsed MM with regards to special issues such as advanced age, comorbid conditions, prior treatments.
• Analyze recently updated clinical practice guidelines for relapsed/refractory MM
• Identify strategies for anticipating, preventing, and treating adverse effects including patients with MM, including dose-modifying strategies
The Cause

Myeloma: Clinical Features

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

- Approximately 25,000 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

## Risk Factors for MM

<table>
<thead>
<tr>
<th>Hyperdiploidy</th>
<th>Expected OS &gt; 6-7 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;14); t(6;14)</td>
<td>Expected OS 2-3 yrs</td>
</tr>
<tr>
<td>Normal cytogenetics/FISH</td>
<td>t(4;14); t(14;16); t(14;20)</td>
</tr>
<tr>
<td>Del(17p)</td>
<td>Del(1p-) and or amp 1p</td>
</tr>
<tr>
<td>Hypodiploidy</td>
<td>by FISH</td>
</tr>
<tr>
<td>Del(13) by cytogenetics</td>
<td>Elevated LDH, B2 microglobulin &gt; 5.5</td>
</tr>
<tr>
<td>GEP-high-risk signature</td>
<td></td>
</tr>
</tbody>
</table>
INITIAL DIAGNOSTIC WORKUP

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
- 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

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
- 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
### STAGING SYSTEMS FOR MULTIPLE MYELOMA

#### Stage I

- All of the following:
  - Hemoglobin value >10 g/dl
  - Serum calcium value normal or 12 mg/dl
  - Bone x-ray, normal bone structure, or solitary bone plasmacytoma only
  - Low M-component production rate
    - IgG value <5 g/dl
    - IgA value <3 g/dl
    - Bence Jones protein <4 g/24 h

#### Stage II

- Neither stage I nor stage III

#### Stage III

- One or more of the following:
  - Hemoglobin value <8.5 g/dl
  - Serum calcium value >12 mg/dl
  - Advanced lytic bone lesions
  - High M-component production rate
    - IgG value >7 g/dl
    - IgA value >5 g/dl
    - Bence Jones protein >12 g/24 h

#### Subclassification Criteria

- A. Normal renal function (serum creatinine level <2.0 mg/dl)
- B. Abnormal renal function (serum creatinine level ≥ 2.0 mg/dl)

### DEFINITION OF MULTIPLE MYELOMA (SMOLDERING AND ACTIVE)

**Active (Symptomatic) Myeloma**

Requires one or more of the following:

- Calcium elevation (>11.5 mg/dl) (>2.65 mmol/L)
- Renal insufficiency (creatinine >2 mg/dl) (>177 µmol/L or more)
- Anemia (hemoglobin <10 g/dl or hematocrit <30%)
- Bone disease (lytic or osteopenic)
- >1 focal lesions detected by functional imaging including PET/CT or whole body MRI

**Smoldering Myeloma**

Requires all of the following:

- Calcium ≤ 11.5 mg/dl
- Renal insufficiency (creatinine ≤ 2 mg/dl)
- Anemia (hemoglobin >10 g/dl and hematocrit >30%)
- Bone disease (lytic or osteopenic)
- >1 focal lesions detected by functional imaging including PET/CT or whole body MRI

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4. Other examples of active disease include: repeated infections, amyloidosis, or hyperviscosity.

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**MYEL-A**

**MYEL-B**
Frontline Treatment Options

- Is Transplant Considered an Option?

- New paradigm: include novel agents in induction, followed by autologous stem cell transplantation (SCT), consolidation, and maintenance
  - Aim for Complete Response
  - Is there a need to optimize SCT?
  - Have we improved efficacy in patients who are not eligible for transplant?

RESPONSE CRITERIA FOR MULTIPLE MYELOMA

(R revised Uniform Response Criteria by the International Myeloma Working Group)\(^1\)

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR, complete response</td>
<td>Negative immunofixation of serum and urine, disappearance of any soft tissue plasmacytomas, and &lt;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 165 in addition to CR criteria is required; two consecutive assessments are needed</td>
</tr>
<tr>
<td>sCR, stringent complete response</td>
<td>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</td>
</tr>
<tr>
<td>Immunophenotypic CR</td>
<td>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 &gt;four colors)</td>
</tr>
</tbody>
</table>

# RESPONSE CRITERIA FOR MULTIPLE MYELOMA

(Revised Uniform Response Criteria by the International Myeloma Working Group)\(^1\)

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular CR</td>
<td>CR as defined plus negative allele-specific oligonucleotide polymerase chain reaction sensitivity (10^{-5}).</td>
</tr>
<tr>
<td>VGPR, very good partial response</td>
<td>Serum and urine M component detectable by immunofixation but not on electrophoresis or 90% reduction in serum M component plus urine M component &lt;100 mg/24 h in patients for whom only measurable disease is by serum FLC level, &gt;80% decrease in difference between involved and uninvolved FLC levels. In addition, VGPR criteria is required; two consecutive assessments are needed.</td>
</tr>
<tr>
<td>MR, partial response</td>
<td>50% reduction of serum M-protein and reduction in 24-hour 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, 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.</td>
</tr>
<tr>
<td>SD, stable disease</td>
<td>Not meeting criteria for CR, VGPR, PR or progressive disease; no known evidence of progressive or new bone lesions if radiographic studies were performed.</td>
</tr>
</tbody>
</table>

Multiple Myeloma

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

<table>
<thead>
<tr>
<th>Response Category</th>
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</tr>
</thead>
<tbody>
<tr>
<td>PD, progressive disease</td>
<td>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 &gt; 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 &gt;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 &gt; 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</td>
</tr>
</tbody>
</table>


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

- Autologous stem cell transplant (category 1) or Therapy for previously treated myeloma on or off clinical trial
- + Progressive disease
- Therapy for previously treated myeloma on or off clinical trial
- + Allogeneic stem cell transplant
- Therapy for previously treated myeloma on or off clinical trial
- + Allogeneic stem cell transplant
- Palliative care (See NCCN Guidelines for Palliative Care)
### 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/dexamethasone (category 1)</td>
<td>Carfilzomib/lenalidomide/dex</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dex (category 1)</td>
<td>Dexamethasone (category 28)</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
<td>Liposomal doxorubicin/vincristine/dexamethasone (category 28)</td>
</tr>
<tr>
<td>• Bortezomib/thalidomide/dex (category 1)</td>
<td>Thalidomide/dex (category 28)</td>
</tr>
<tr>
<td>• Lenalidomide/dexamethasone (category 1)</td>
<td></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/dexamethasone</td>
<td>Dexamethasone (category 28)</td>
</tr>
<tr>
<td>• Bortezomib/cyclophosphamide/dex</td>
<td>Liposomal doxorubicin/vincristine/dexamethasone (category 28)</td>
</tr>
<tr>
<td>• Bortezomib/lenalidomide/dexamethasone</td>
<td>Melphalan/prednisone</td>
</tr>
<tr>
<td>• Lenalidomide/bw-dose dex (category 28)</td>
<td>Thalidomide/dexamethasone (category 28)</td>
</tr>
<tr>
<td>• Melphalan/prednisone/lenalidomide (category 1)</td>
<td>Vincristine/doxorubicin/dexamethasone (category 28)</td>
</tr>
<tr>
<td>• Melphalan/prednisone/thalidomide (category 1)</td>
<td></td>
</tr>
</tbody>
</table>

### Therapy for Previously Treated Multiple Myeloma

#### Preferred Regimens

- Repeat primary induction therapy (if >6 mo)
- Bortezomib (category 1)
- Bortezomib/dexamethasone
- Bortezomib/cyclophosphamide/dex
- Bortezomib/lenalidomide/dexamethasone
- Bortezomib/liposomal doxorubicin (category 1)
- Bortezomib/thalidomide/dexamethasone
- Carfilzomib
- Carfilzomib/dex
- Carfilzomib/lenalidomide/dex (category 1)
- Cyclophosphamide/lenalidomide/dex
- Dex/cyclophosphamide/etoposide/cisplatin
- Dex/thalidomide/cisplatin/doxorubicin/cyclophosphamide/etoposide ± bortezomib
- High-dose cyclophosphamide
- Lenalidomide/dexamethasone (category 1)
- Panobinostat/bortezomib/dex (category 1)
- Pomalidomide/dexamethasone
- Thalidomide/dexamethasone

#### Other Regimens

- Bendamustine
- Bortezomib/vorinostat
- Lenalidomide/bendamustine/dexamethasone
- Vincristine/doxorubicin/dexamethasone
ADJUNCTIVE TREATMENT

Bone Disease
• Bisphosphonates (pamidronate and zoledronic acid)
  • 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

Hypercaldemia
• 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 bortezomib

Renal Dysfunction
• Maintain hydration to avoid renal failure
• Avoid use of NSAIDs
Avoid IV contrast
• Plasmapheresis (category 28)
• Not a contraindication to transplant
• Monitor for renal dysfunction with chronic use of bisphosphonates

Coagulation/thrombosis
• Prophylactic anticoagulation recommended for patients receiving thalidomide-based, or
  lenalidomide with dexamethasone therapy
• See NCCN Guidelines for Venous Thromboembolic Disease
Suggested treatment approach for patients with relapse or progressive disease

Overview

- Scenarios for Treatment of Relapsed/Refractory Myeloma
- Lenalidomide-Containing Regimens
- Bortezomib-Containing Regimens
- Novel Agents
Clinical Indications for Salvage Therapy

- Disease progression following allogeneic or autologous stem cell transplantation
- Primary progressive disease following initial autologous or allogeneic stem cell transplantation
- Progressive or relapsing disease after initial induction in patients not eligible for stem cell transplantation
- Progressive disease following second- or third-line therapy

Response Criteria for Multiple Myeloma

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

<table>
<thead>
<tr>
<th>Relapse Subcategory</th>
<th>Relapse Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical relapse</td>
<td>Clinical relapse requires one or more of:</td>
</tr>
<tr>
<td></td>
<td>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features). 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</td>
</tr>
<tr>
<td></td>
<td>- Development of new soft tissue plasmacytomas or bone lesions</td>
</tr>
<tr>
<td></td>
<td>- 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</td>
</tr>
<tr>
<td></td>
<td>• Hypercalcemia (&gt;11.5 mg/dL [2.65 mmol/L])</td>
</tr>
<tr>
<td></td>
<td>• Decrease in hemoglobin of 2 g/dL [1.25 mmol/L]</td>
</tr>
<tr>
<td></td>
<td>• Rise in serum creatinine by 2 mg/dL or more [177 µmol/L or more]</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Relapse Subcategory</th>
<th>Relapse Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relapse from CR</td>
<td>Any one or more of the following:</td>
</tr>
<tr>
<td></td>
<td>• Reappearance of serum or urine M-protein by immunofixation or electrophoresis</td>
</tr>
<tr>
<td></td>
<td>• Development of 50% plasma cells in the bone marrow</td>
</tr>
<tr>
<td></td>
<td>• Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcemia)</td>
</tr>
</tbody>
</table>


MM-009/010: Phase III Study Design

Patients with relapsed MM following ≥ 1 treatment (N = 353)

Lenalidomide 25 mg, Days 1-21
Dexamethasone 40 mg PO, Days 1-4
(and Days 9-12 and 17-20 for first 4 cycles)
(n = 177)

Placebo, Days 1-21
Dexamethasone 40 mg PO, Days 1-4
(and Days 9-12 and 17-20 for first 4 cycles)
(n = 176)

Primary endpoint: time to disease progression
Secondary endpoints: OS, response rate

MM-009/010 Phase III Trials: Survival

**MM-009**

Median OS
Lenalidomide: 29.6 mo
Placebo: 20.2 mo
\( P < .001 \)

**MM-010**

Median OS
Lenalidomide: not reached
Placebo: 20.67 mo
\( P < .001 \)


Len/Dex in Relapsed/Refractory MM and Renal Impairment: MM-009/MM-010

<table>
<thead>
<tr>
<th>Grade 3/4 AE</th>
<th>Degree of Renal Impairment (CrCl mL/min), %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>None (≥ 80)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>31</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7</td>
</tr>
<tr>
<td>Anemia</td>
<td>4</td>
</tr>
<tr>
<td>VTE</td>
<td>11</td>
</tr>
<tr>
<td>GI disorders</td>
<td>12</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
</tr>
</tbody>
</table>

*\( P < .05 \) vs no renal impairment
†\( P < .001 \) vs no renal impairment

MM-009/010 Phase III Trials of Len/Dex in Relapsed/Refractory MM: Grade 3/4 AEs


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>
</tr>
<tr>
<td>Previous VTE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central venous catheter or pacemaker</td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<tr>
<td>- Multiagent chemotherapy</td>
<td></td>
<td></td>
</tr>
<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>
</tr>
<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>Aspirin</td>
<td>LMWH or warfarin*</td>
</tr>
<tr>
<td>2 or more risk factors</td>
<td>LMWH or warfarin*</td>
<td></td>
</tr>
</tbody>
</table>

LMWH: low-molecular-weight heparin

Obesity: body mass index ≥ 30 kg/m²

*400 mg per month.

†Full-dose warfarin (target INR 2-3).

Bortezomib-Containing Regimens

Phase III APEX Trial: Bortezomib vs High-Dose Dexamethasone in Relapsed MM

Patients with relapsed MM following 1-3 therapies, not refractory to dexamethasone (N = 669)

**Induction**
- Dexamethasone 40 mg PO\(^*\), Days 1-4, 9-12, and 17-20 for four 5-week cycles (n = 336)
- Bortezomib 1.3 mg/m\(^2\), IV Days 1, 4, 8, 11 for eight 3-week cycles (n = 333)

**Maintenance**
- Dexamethasone 40 mg PO, Days 1-4 for four 5-week cycles
- Bortezomib 1.3 mg/m\(^2\), IV Days 1, 8, 15, 22 for three 5-week cycles

Treatment for 280 days

*Patients who progressed on dexamethasone allowed to cross over to receive bortezomib in a companion study

Phase III APEX Trial: Overall Survival (Extended Follow-up)

- > 62% of dexamethasone-treated patients crossed over to receive bortezomib
  - 1-year survival rate: 80% for bortezomib vs 67% for dexamethasone ($P = .0001$)


Bortezomib ± PLD in Relapsed/Refractory Myeloma (MMY-3001 Phase III Trial)

- Primary endpoint: time to disease progression
- Secondary endpoints: OS, PFS, response rate, safety

Bortezomib ± PLD in Relapsed/Refractory Myeloma (MMY-3001): Time to Progression

![Graph showing time to progression with PLD + bortezomib, bortezomib, and censored data]


Bortezomib ± PLD in Relapsed/Refractory Myeloma (MMY-3001): Overall Survival

![Graph showing overall survival with PLD + bortezomib, bortezomib, and censored data]

Parameter, % PLD + Bort Bortezomib

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PLD + Bort</th>
<th>Bortezomib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Censored</td>
<td>82</td>
<td>75</td>
</tr>
<tr>
<td>Died</td>
<td>18</td>
<td>25</td>
</tr>
</tbody>
</table>

Peripheral neuropathy criteria updated (CTCAE v4.03)

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>Asymptomatic; clinical or diagnostic observations only; Sensory PN—Loss of deep tendon reflexes or paresthesia</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Moderate symptoms; limiting instrumental ADL</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Severe symptoms; limiting self-care ADL; assistance device indicated</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Life-threatening consequences; urgent intervention indicated</td>
</tr>
</tbody>
</table>

*ADL: activities of daily living.

Peripheral Neuropathy Following Bortezomib Treatment in Advanced Myeloma

- PN (treatment emergent or worsening of baseline PN) identified in 90 of 256 (35%) patients with relapsed/refractory multiple myeloma enrolled in 2 phase II trials of bortezomib
  - ~82% had preexisting PN
  - 4% of patients without preexisting PN developed grade 3 PN vs 14% with preexisting PN
  - Of 35 patients with ≥ grade 3 PN, 71% experienced improvement or resolution to baseline
  - PN led to dose reduction in 12% and discontinuation in 5%

- **Consider sc route**

Neuropathic pain management in multiple myeloma

<table>
<thead>
<tr>
<th>Drug Group</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin and analogue</td>
<td>Interaction with other meds, depression</td>
</tr>
<tr>
<td>Opioids (only by pain specialists)</td>
<td>Concomitant use with antidepressants, constipation, substance abuse, driving impairment during treatment</td>
</tr>
<tr>
<td>Calcium channel α2-δ ligands</td>
<td>Renal insufficiency</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Cardiac disease, glaucoma, depression, hepatic disease, renal insufficiency, concomitant use with other antidepressants, withdrawal symptoms</td>
</tr>
</tbody>
</table>

- Topical treatments like capsaicin or menthol creams, and emollients like cocoa butter, may be of benefit²

How do we decide on salvage?

- Prior treatments, responses/duration, completion of prior regimen
- Organ dysfunction (neuropathy, renal, hematopoiesis, etc)
- Age
- Prior transplant
- Route (toxicity-based, value-based, iv, sc, oral)
Carfilzomib

- Open Label single-arm trial
- 20 mg/m² twice weekly ¾ weeks (escalation to 27 mg/m²)
- 266 patients
- 95% refractory to prior Rx and
- 80% were refractory or intolerant to bortezomib and lenalidomide
- 74% had a prior stem cell transplant
- 5 prior lines of Rx
- Response Rate 23.7%  Clinical Benefit Rate: 37%
- Response Duration: 7.8 months OS: 15.6 months

Siegel et al. 2012 Blood 120 (14):2817-25

Carfilzomib in Relapsed/Refractory MM: Safety and Efficacy (Phase II Study)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>18/11</td>
</tr>
<tr>
<td>Anemia</td>
<td>46/24</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39/29</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49/7.5</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>11/1.9/0.8</td>
</tr>
<tr>
<td>CHF/MI arrest</td>
<td>3.8/2.3</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>34/3.4</td>
</tr>
<tr>
<td>Fever</td>
<td>31/1.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32/0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>28/1.9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4.9/0.8</td>
</tr>
<tr>
<td>Low phosphorus</td>
<td>12/6</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>12.4/1.1</td>
</tr>
</tbody>
</table>

Siegel et al. 2012 Blood 120 (14):2817-25
Pomalidomide + low-dose dex vs. high-dose dex alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomized (2:1), open-label, phase 3 trial

- N = 302:153 patients who failed both bortezomib and lenolidomide therapies
- Pom 4 mg/d x 21 days/28 day cycle plus dex 40 mg/day on days 1, 8, 15, 22
- or Dex 40 mg/d days 1-4, 9-12, 17-20
- Median follow-up: 10 months
- PFS: 4 months vs. 1.9 months


**Major Toxicities**

<table>
<thead>
<tr>
<th>Pom Dex Adverse Event, %</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>48</td>
</tr>
<tr>
<td>Anemia</td>
<td>33</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13</td>
</tr>
<tr>
<td>Bone pain</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
</tr>
<tr>
<td>Death on trial</td>
<td>4</td>
</tr>
<tr>
<td>Fever</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>1.9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.8</td>
</tr>
<tr>
<td>Low phosphorus</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>1.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DEX Adverse Event, %</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>37</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>26</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
</tr>
<tr>
<td>Bone pain</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6</td>
</tr>
<tr>
<td>Death on trial</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>1.9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.8</td>
</tr>
<tr>
<td>Low phosphorus</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Siegel et al. 2012 Blood 120 (14):2817-25
ENDEAVOR: Relapsed MM

- Randomized, open-label, multicenter phase III trial
  *Stratified by prior PI therapy, prior lines of treatment, ISS stage, and route of V administration (IV vs SC)*

- Primary endpoint: PFS
- Secondary endpoints: OS, ORR, DoR, grade ≥ 2 peripheral neuropathy, safety
- **Dose of CARFILZOMIB!!!**

Relapsed MM with 1-3 previous lines of therapy; prior bort or carfil if response occurred with no discontinuation due to toxicity (N = 929)

- Randomized, open-label, multicenter phase III trial
  - Stratified by prior PI therapy, prior lines of treatment, ISS stage, and route of V administration (IV vs SC)

- **Carfilzomib + Dexamethasone (Kd)** (n = 464)
- **Bortezomib + Dexamethasone (Vd)** (n = 465)

- **Until PD or unacceptable toxicity**

- ENDEAVOR: Carfilzomib/dex Results in 2-Fold Increase in Median Progression-Free Survival vs bortezomib/dex in Relapsed MM

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Carf/d (n = 464)</th>
<th>Bortez/d (n = 465)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS, mos</td>
<td>18.7</td>
<td>9.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td><strong>HR (95% CI)</strong></td>
<td>0.53 (0.44-0.65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ORR, %</td>
<td>77</td>
<td>63</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>≥ CR (≥ CR + CR)</td>
<td>13</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>54</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

- Significant PFS benefit with carfil vs bortezd observed across most subgroups, including age (including ≥ 75 yrs), renal function, risk, prior treatment (including prior bortezomib)
- OS data not mature (HR: 0.79; P = .066)
ENDEAVOR: Safety

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Carf/d (n = 464)</th>
<th>Bort/d (n = 465)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median treatment duration, wks (range)</td>
<td>40 (1-108)</td>
<td>27 (1-106)</td>
</tr>
<tr>
<td>Dose reduction due to AE, %</td>
<td>23</td>
<td>48</td>
</tr>
<tr>
<td>Treatment discontinuation due to AE, %</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Deaths due to AE, %</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Any AE/grade ≥ 3 AE/serious AE, %</td>
<td>98/73/48</td>
<td>98/67/36</td>
</tr>
<tr>
<td>Grade ≥ 3 hematologic AE, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Anemia</td>
<td>15.0</td>
<td>10.0</td>
</tr>
<tr>
<td>• Thrombocytopenia</td>
<td>8.0</td>
<td>9.0</td>
</tr>
<tr>
<td>• Neutropenia</td>
<td>2.2</td>
<td>2.2</td>
</tr>
<tr>
<td>• Febrile neutropenia</td>
<td>0.6</td>
<td>1.3</td>
</tr>
<tr>
<td>Most common grade ≥ 3 infections, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Pneumonia</td>
<td>7.0</td>
<td>8.0</td>
</tr>
<tr>
<td>• Upper respiratory tract infection</td>
<td>1.9</td>
<td>0.7</td>
</tr>
<tr>
<td>• Sepsis</td>
<td>1.3</td>
<td>0.4</td>
</tr>
<tr>
<td>• Herpes zoster</td>
<td>0</td>
<td>0.4</td>
</tr>
</tbody>
</table>

ENDEAVOR: Conclusion

- Phase III ENDEAVOR trial showed significant PFS improvement and higher response rates with Carfd vs Bortezd in relapsed MM
- PFS benefit seen across important subgroups, including older pts and those with prior bortezomib exposure
- Carfil/d associated with higher rates of grade ≥ 3 hypertension, dyspnea, cardiac failure but significantly lower rates of grade ≥ 2 PN and comparable rate of discontinuation due to AEs despite longer time on treatment in Kd arm (40 vs 27 wks)
- OS data not yet mature
- Investigators suggested Carfd is new standard of care in relapsed MM CAVEATS!
ASPIRE: Lenalidomide/Dexamethasone ± Carfilzomib in R/R MM

- Randomized, open-label, multicenter phase III trial previously published results; current study is a secondary analysis.
- Stratified by β2-microglobulin, prior bortezomib, and prior lenalidomide

CarRd
- Carfilzomib* 27 mg/m² IV Days 1, 2, 8, 9, 15, 16 (20 mg/m² Days 1, 2; cycle 1 only) +
- Lenalidomide 25 mg Days 1-21 +
- Dexamethasone 40 mg Days 1, 8, 15, 22
(n = 396)

Rd
- Lenalidomide 25 mg Days 1-21 +
- Dexamethasone 40 mg Days 1, 8, 15, 22
(n = 396)

**ASPIRE: Grade ≥ 3 Adverse Events**

<table>
<thead>
<tr>
<th>Grade ≥ 3 Adverse Event, %</th>
<th>1 Prior Line of Therapy</th>
<th>2 Prior Lines of Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KRd (n = 182)</td>
<td>Rd (n = 154)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>26.4</td>
<td>22.1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15.4</td>
<td>11.7</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>9.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.1</td>
<td>6.5</td>
</tr>
<tr>
<td>Cataract</td>
<td>5.5</td>
<td>2.6</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>4.4</td>
<td>2.6</td>
</tr>
<tr>
<td>Respiratory tract infection</td>
<td>4.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>4.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3.8</td>
<td>0.6</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>3.8</td>
<td>1.9</td>
</tr>
<tr>
<td>Cytopenia</td>
<td>3.8</td>
<td>1.9</td>
</tr>
</tbody>
</table>

**ASPIRE: Conclusions**

- Results from this post hoc analysis confirm previously published interim analysis data showing clinical benefit to KRd vs Rd in relapsed myeloma
- The use of KRd after first relapse associated with median PFS improvement of ~ 12 mos vs Rd in pts with 1 prior line of therapy
- ORRs significantly higher with KRd vs Rd regardless of whether pts had received 1 or ≥ 2 lines of prior therapy
  - CR rates 5-fold higher with KRd in pts with 1 prior line, and 3-fold higher with ≥ 2 lines
- Grade ≥ 3 AEs similar between KRd and Rd
- Favorable risk–benefit profile with 1 and ≥ 2 prior lines of therapy

Phase III PANORAMA 1: Bort/Dex ± Panobinostat in R/R Myeloma

- Randomized, double-blind trial

### Treatment Phase I:
- Eight 21-day cycles (24 wks)
  - Panobinostat 20 mg 3x/wk +
  - Bort 1.3 mg/m² IV Days 1, 4, 8, 11 +
  - Dex 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12
  - (n = 387)
  - Placebo 3x/wk +
  - Bort 1.3 mg/m² IV Days 1, 4, 8, 11 +
  - Dex 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12
  - (n = 381)

### Treatment Phase II:
- Four 42-day cycles (24 wks)
  - Panobinostat 20 mg 3x/wk +
  - Bort* 1.3 mg/m² IV +
  - Dex* 20 mg
  - Placebo 3x/wk +
  - Bort* 1.3 mg/m² IV +
  - Dex* 20 mg

*Reduced frequency.

---


---

### PANORAMA 1: PFS by Prior Therapy

<table>
<thead>
<tr>
<th>Median PFS by Prior Treatment, Mos</th>
<th>Panobinostat/Bortezomib/Dexamethasone</th>
<th>Bortezomib/Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMID</td>
<td>12.3</td>
<td>7.4</td>
</tr>
<tr>
<td>IMID + bortezomib</td>
<td>10.6</td>
<td>5.8</td>
</tr>
<tr>
<td>IMID + bortezomib with ≥ 2 prior lines</td>
<td>12.5</td>
<td>4.7</td>
</tr>
</tbody>
</table>

PANORAMA 1: Grade 3/4 AEs by Prior Treatment

<table>
<thead>
<tr>
<th>Select Grade 3/4 AEs (≥ 20% Incidence), %</th>
<th>Prior IMiD Pan/Bort</th>
<th>Bort/Dex</th>
<th>Prior IMiD + Bort Pan/Bort</th>
<th>Bort/Dex</th>
<th>Prior IMiD, Bort With Pan/Bort</th>
<th>Bort/Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Thrombocytopenia</td>
<td>67.2</td>
<td>35.7</td>
<td>68.5</td>
<td>48.0</td>
<td>68.1</td>
<td>44.4</td>
</tr>
<tr>
<td>▪ Leukopenia</td>
<td>23.7</td>
<td>10.0</td>
<td>19.6</td>
<td>12.1</td>
<td>20.8</td>
<td>11.0</td>
</tr>
<tr>
<td>▪ Lymphopenia</td>
<td>53.9</td>
<td>40.6</td>
<td>50.0</td>
<td>46.5</td>
<td>48.6</td>
<td>49.3</td>
</tr>
<tr>
<td>▪ Neutropenia</td>
<td>36.9</td>
<td>12.6</td>
<td>35.9</td>
<td>17.2</td>
<td>40.3</td>
<td>16.4</td>
</tr>
<tr>
<td>▪ Anemia</td>
<td>17.0</td>
<td>21.3</td>
<td>18.5</td>
<td>19.2</td>
<td>20.8</td>
<td>20.5</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>▪ Diarrhea</td>
<td>26.1</td>
<td>7.9</td>
<td>30.4</td>
<td>13.1</td>
<td>33.3</td>
<td>15.1</td>
</tr>
<tr>
<td>▪ Fatigue/asthenia</td>
<td>25.3</td>
<td>11.7</td>
<td>25.0</td>
<td>12.1</td>
<td>26.4</td>
<td>13.7</td>
</tr>
<tr>
<td>▪ PN</td>
<td>17.0</td>
<td>14.2</td>
<td>15.2</td>
<td>9.1</td>
<td>16.7</td>
<td>6.8</td>
</tr>
<tr>
<td>▪ Nausea</td>
<td>5.8</td>
<td>0.8</td>
<td>8.7</td>
<td>1.0</td>
<td>11.1</td>
<td>1.4</td>
</tr>
<tr>
<td>▪ Peripheral edema</td>
<td>1.7</td>
<td>0</td>
<td>2.2</td>
<td>0</td>
<td>2.8</td>
<td>0</td>
</tr>
</tbody>
</table>


PANORAMA 1: Conclusions

- Subgroup analyses confirmed PFS benefit with addition of panobinostat to bortezomib/dexamethasone maintained among pts with varying prior treatment
  - Prior IMiDs, prior IMiDs plus bortezomib, prior IMiDs plus bortezomib and ≥ 2 prior lines of therapy
- Magnitude of PFS benefit between arms in subgroups was clinically meaningful (difference in median PFS)
  - Prior IMiD: 4.9 mos
  - Prior IMiD plus bortezomib: 4.8 mos
  - Prior IMiD plus bortezomib and ≥ 2 prior lines of therapy: 7.8 mos
- Safety profiles of subgroups similar to overall population

ELOQUENT-2: Elotuzumab With Lenalidomide/Dexamethasone R/R MM

- Randomized, open-label, multicenter international phase III trial

- Primary endpoints: PFS, ORR
- Secondary endpoints: OS (data not mature), DoR, QoL, safety

*Premedication administered before elotuzumab.

R/R MM with 1-3 prior lines of therapy (prior lenalidomide exposure allowed in 10%) (N = 646)

Elo-Rd

Rd

Elo: 10 mg/kg IV QW in cycles 1, 2; q2w thereafter +
Lenalidomide 25 mg PO Days 1-21 +
Dexamethasone 40 mg/wk equiv
28-day cycles

Assessed q4w until PD; followed q12w thereafter for survival


ELOQUENT-2: PFS and OS

HR: 0.70 (95% CI: 0.57-0.85)
P = .0004
Median PFS, mos 19.4 14.9
(95% CI) 17.2 (16.6-22.2) (12.1-)

Elo-Rd

Rd

1-yr PFS
2-yr PFS

Elo-Rd

68% 57%
42% 27%

P = .0002

Elo-Rd

PR

Rd

OG* Combined Response (sCR + CR + VGPR)

CR (sCR + CR)†

VGPR

33 28 4 7 28 21 46 38

ELOQUENT-2: Safety

- Elotuzumab well tolerated, had no negative effect on QoL
- Infusion reactions reported in 10% of pts (9% grade 1/2; 1% grade 3); 70% occurred with initial dose

<table>
<thead>
<tr>
<th>Selected Grade 3/4 AEs, %</th>
<th>Elotuzumab-Rd (n = 318)</th>
<th>Rd (n = 317)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphopenia</td>
<td>77</td>
<td>49</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>34</td>
<td>44</td>
</tr>
<tr>
<td>Infection</td>
<td>28*</td>
<td>24*</td>
</tr>
<tr>
<td>Nonhematologic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Fatigue</td>
<td>9</td>
<td>8</td>
</tr>
<tr>
<td>- Pyrexia</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>- Diarrhea</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

*Incidence similar after controlling for duration of therapy.


ELOQUENT-2: Conclusions

- Addition of elotuzumab to lenalidomide/dexamethasone associated with statistically and clinically significant increase in PFS, ORR in pts with R/R MM
- PFS benefit with elotuzumab maintained across important subgroups, including high-risk and elderly pts
- Adding elotuzumab did not increase the incidence of AEs and without a negative effect on QoL
- OS data not yet mature
- Elotuzumab is first monoclonal antibody to show PFS benefit when added to lenalidomide/dexamethasone in randomized, phase III trial in R/R MM

SIRIUS: Study Design

- Open-label, international, multicenter, 2-stage study
- Pts with MM who had received ≥ 3 prior lines of therapy or were refractory to a PI and an IMiD (N = 53)
- Primary objective: ORR
- Secondary objectives: PFS, OS, duration of response, time to response, clinical benefit rate

![Stage 1: Response assessment](Stage 1 Diagram)

- Daratumumab 8 mg/kg q4w (n = 18)
- Daratumumab 16 mg/kg QW x 8 then q2w x 16, then q4w thereafter (n = 16)
- Daratumumab 16 mg/kg QW x 8 then q2w x 16, then q4w thereafter (n = 90)

SIRIUS: Efficacy

- Responses observed across subgroups
- Deepening of responses with continued treatment
  - Median time to response: 1 mo
  - Median DoR: 7.4 mos (95% CI: 5.5-NE)
  - Median PFS: 3.7 mos (95% CI: 2.8-4.6)
  - 1-yr OS: 65% (95% CI: 51.2% to 75.5%)

![Change in Paraprotein From Baseline](Graph)
SIRIUS: ORR

- ORR = 29%
  - sCR n = 3 (3%)
  - VGPR n = 10 (9%)
  - PR n = 18 (17%)

- ORR (%) by Subgroup

- Refractory to

- ORR (%) by Subgroup:
  - Aged ≥ 75 yrs
  - CrCl ≥ 60 mL/min
  - > 3 Lines of Therapy
  - Extramedullary Disease
  - High-Risk Cytogenetics
  - Pls and IMiDs
  - Carfilzomib
  - Pomalidomide
  - Carfilzomib + Pomalidomide
  - Bortezomib + Lenalidomide
  - Bortezomib + Lenalidomide + Pomalidomide

SIRIUS: Safety

- Most common grade 3/4 AEs: thrombocytopenia (25%), anemia (24%), neutropenia (14%)
  - Grade 3/4 anemia, thrombocytopenia more frequent in nonresponders
  - Note that trial allowed pts with hemoglobin > 7.5 g/dL, platelet count ≥ 50 x 10⁹/L at baseline
- Infusion-related reactions: 43%
  - Primarily grade 1/2, > 90% occurred during first infusion
  - 7% of pts had another infusion reaction beyond first dose
- No discontinuations due to treatment-related AEs, including infusion reactions

SIRIUS: Conclusion

- Daratumumab associated with single-agent activity in heavily pretreated MM; ORR 29%[1]
- Responses were rapid, appeared durable, and improved over time (appearance of sCRs, VGPR)
- Daratumumab was well tolerated, with no discontinuations due to AEs
  - Infusion reactions mild to moderate, manageable
- Investigators concluded daratumumab is a potential new standard of care in this population
- Study is currently ongoing[2]


Bisphosphonates an Renal Dysfunction, ONJ

- Potent inhibitors bone resorption
  - Pamidronate – Glomerular
  - Zoledronic acid – Tubular
  - Both effective agents to decrease SRE’s
- BASELINE DENTAL EXAM!
  - Acute Phase Reactions, albuminuria, creatinine
  - Dialysis (irreversibly), may use either zoledronic acid or pamidronate at same dose, infusion time and interval
- Poor renal function at diagnosis
  - No dose reduction recommended
  - Most wait until kidneys improve; treat Hyperca++ with fluids

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 oral melphalan

Conclusion

- The primary Rx is induction to accomplish remission, consolidation-including SCT, and maintenance; cure may be within reach..
- Regimens containing lenalidomide or bortezomib have shown efficacy in relapsed/refractory myeloma
- Selection of regimens should be a rational process, based upon patient characteristics
- Novel agents (carfilzomib, pomalidomide) are useful additions, other agents (elotuzumab, daratumumab, ixazomib) await analysis of completed phase III trials
- *Supportive care (bone health, renal, neuro-problems, DVT prophylaxis, infection prophylaxis) are important aspects of the care of these patients*