Overcoming Current Challenges in the Management of De Novo and Relapsed/Refractory Multiple Myeloma

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Objectives

1. Provide background and management strategies for newly diagnosed multiple myeloma
2. Compare and contrast efficacy and safety data on current treatments for patients with relapsed/refractory multiple myeloma
3. Analyze recent data on therapeutic options currently undergoing late stage clinical trials
4. Select appropriate treatments tailored to the individualized needs of patients with relapsed/refractory MM, taking into consideration factors such as risk stratification, transplant eligibility, and comorbidities
5. Review current clinical trial options for patients with relapsed/refractory multiple myeloma
6. Discuss the recently updated clinical practice guidelines for relapsed/refractory multiple myeloma
Multiple Myeloma

- Approximately 24,000 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

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

Risk Factors in MM

- Expected OS >6-7 yrs
  - t(11;14); t(6:14)
  - Hyperdiploidy
  - Normal cytogenetics/FISH

- Expected OS 2-3 yrs
  - t(4;14); t(14;16); t(14;20)
  - Del(17p)
  - Del(1p-) and or amp 1p by FISH
  - Del(13) by cytogenetics
  - Hypodiploidy
  - GEP-high-risk signature

Elevated LDH, B2 microglobulin > 5.5
Multiple Myeloma
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INITIAL DIAGNOSTIC WORKUP
• H&P
• CBC, differential, platelets
• BUN/creatinine, electrolytes
• LDH
• Calcium/albumin
• Beta-2 microglobulin

Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
• 24h urine for total protein, urine protein electrophoresis, and immunofixation electrophoresis
• Skeletal survey
• Unilateral bone marrow aspirate + biopsy including bone marrow immunohistochemistry and bone marrow flow cytometry
• Cytogenetics
• FISH [del 13, del 17, t(4;14), t(11;14), t(14:16)]

Useful Under Some Circumstances
• MRI for suspected vertebral compression
• CT scan (avoid contrast)
• PET/CT scan
• Tissue biopsy to diagnose a solitary osseous or extraneous plasmacytoma
• Bone densitometry
• Plasma cell labeling index
• Staining of marrow and fat pad for amyloid
• Serum free light chain assay
• Serum viscosity
• HLA typing

Multiple Myeloma
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STAGING SYSTEMS FOR MULTIPLE MYELOMA

<table>
<thead>
<tr>
<th>Stage</th>
<th>Durie-Salmon Criteria 1</th>
<th>ISS Criteria 2</th>
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<tbody>
<tr>
<td>I</td>
<td>All of the following:</td>
<td>Serum beta-2 microglobulin</td>
</tr>
<tr>
<td></td>
<td>Hemoglobin value &gt; 10 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum calcium value normal or ≤12 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low M-component production rate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgG value &lt; 6 g/dL;</td>
<td></td>
</tr>
<tr>
<td></td>
<td>IgA value ≤ 3 g/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bence Jones protein &lt; 4 g/24 h</td>
<td></td>
</tr>
</tbody>
</table>

|       | Serum albumin ≥ 3.5 g/dL |

| II    | Neither stage I nor stage III |

| III   | One or more of the following: |
|       | Hemoglobin value < 8.5 g/dL |
|       | Serum calcium value > 12 mg/dL |
|       | Advanced lytic bone lesions (scale 3) |
|       | High M-component production rate |
|       | IgG value > 7 g/dL; |
|       | IgA value ≤ 5 g/dL |
|       | Bence Jones protein > 12 g/24 h |

<table>
<thead>
<tr>
<th>Subclassification Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>A Normal renal function (serum creatinine level &lt; 2.0 mg/dL)</td>
</tr>
<tr>
<td>B Abnormal renal function (serum creatinine level ≥ 2.0 mg/dL)</td>
</tr>
</tbody>
</table>


MYEL-A
Frontline Treatment Options

- Transplant is considered a preferred option
- Old paradigm: Chemotherapy followed by SCT alkylator- and corticosteroid-based therapy
  - VAD or Dexamethasone pulse, or melphalan/other alkylator-based therapy
- New paradigm
  - Include novel agents in induction, followed by SCT, consolidation, and maintenance
  - Aim for CR or PR

Autologous transplantation and maintenance therapy in multiple myeloma

- 273 patients randomized to induction with lenalidomide/dex x 4, followed by tandem melphalan and autologous transplant vs. melphalan, lenalidomide, dex (mpr) followed by a second randomization of lenalidomide maintenance vs no maintenance.

  - Median follow-up: 51.2 months

<table>
<thead>
<tr>
<th></th>
<th>melphalan auto</th>
<th>MPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td>43 months</td>
<td>22.4 months</td>
</tr>
<tr>
<td>OS at 4-years</td>
<td>81.6 %</td>
<td>65.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>lenalidomide maintenance</th>
<th>yes</th>
<th>no</th>
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</thead>
<tbody>
<tr>
<td>PFS</td>
<td>41.9 months</td>
<td>21.6 months</td>
</tr>
<tr>
<td>OS</td>
<td>88%</td>
<td>79.2 % (NS)</td>
</tr>
</tbody>
</table>

- Palumbo et al, NEJM, 2014 371:895-905
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
- $\beta_{2}$ 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
Induction with Combinations of Proteosome Inhibiting (PI) and/or Immune Modulatory (ImID) Agents
**Bortezomib/Dex vs VAD Induction**

Response to Induction, first and second transplant

<table>
<thead>
<tr>
<th>ITT Analysis, %</th>
<th>VAD (n = 242)</th>
<th>Vel/Dex (n = 240)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>1.4</td>
<td>6.1</td>
<td>.0109</td>
</tr>
<tr>
<td>CR + nCR</td>
<td>6.7</td>
<td>15.0</td>
<td>.0035</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>16.0</td>
<td>39.0</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>65.0</td>
<td>82.0</td>
<td>&lt; .0001</td>
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Post First ASCT Response

<table>
<thead>
<tr>
<th></th>
<th>VAD (n = 101)</th>
<th>Vel/Dex (n = 101)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + nCR</td>
<td>19</td>
<td>37</td>
<td>.0016</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>38</td>
<td>57</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>≥ PR</td>
<td>79</td>
<td>84</td>
<td>NS</td>
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</table>

Post Second ASCT Response

<table>
<thead>
<tr>
<th></th>
<th>VAD (n = 101)</th>
<th>Vel/Dex (n = 101)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + nCR</td>
<td>32</td>
<td>39</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td>≥ VGPR</td>
<td>47</td>
<td>68</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>


**PFS: 2-Yr Median Follow-up**

![Graph showing PFS: 2-Yr Median Follow-up](image)

- Bort/dex: 71 events
- Median PFS: NR; 2-yr PFS: 69%
- VAD: 101 events
- Median PFS: 28 mos; 2-yr PFS: 60%

Phase III E4A03: Len + High-Dose Dex vs Len + Low-Dose Dex in Newly Diagnosed Pts

- Primary endpoint: response at 4 mos
- Equivalence: ORR in the Rd arm < 15%


Pts with newly diagnosed myeloma

RD: Lenalidomide 25 mg PO Days 1-21 and high-dose dexamethasone*

RD: Lenalidomide 25 mg PO Days 1-21 and low-dose dexamethasone†

Thal/Dex (4 cycles)

Off study for SCT or continue at physician’s discretion

CR/PR/SD

* Dexamethasone given on Days 1-4, 9-12, 17-20 for a total of 480 mg.
† Dexamethasone given on Days 1, 8, 15, 22 for a total of 160 mg.

- Primary endpoint: response at 4 mos
- Equivalence: ORR in the Rd arm < 15%


E4A03: OS Landmark Analysis Transplant or Primary Therapy After 4 Cycles

Transplantation Following 4 Cycles of RD vs Rd

Primary Therapy Beyond 4 Cycles of RD vs Rd

Survival Probability

<table>
<thead>
<tr>
<th>Pts at Risk, n</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
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<tbody>
<tr>
<td>RD</td>
<td>50</td>
<td>50</td>
<td>49</td>
<td>48</td>
<td>47</td>
<td>35</td>
<td>20</td>
</tr>
<tr>
<td>Rd</td>
<td>40</td>
<td>40</td>
<td>38</td>
<td>37</td>
<td>32</td>
<td>21</td>
<td></td>
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</table>

Transplant N = 99 (median age: 57 yrs)

Survival Probability

<table>
<thead>
<tr>
<th>Pts at Risk, n</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
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</thead>
<tbody>
<tr>
<td>RD</td>
<td>108</td>
<td>108</td>
<td>103</td>
<td>97</td>
<td>90</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>Rd</td>
<td>140</td>
<td>140</td>
<td>139</td>
<td>133</td>
<td>128</td>
<td>95</td>
<td>51</td>
</tr>
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</table>

RD n = 108 (median age: 65 yrs)
Rd n = 140 (median age: 66 yrs)

Rajkumar V, et al. ASH/ASCO Joint Symposium at ASH08.
Strategy: Transplant Eligible Pt with MM

- ISS Stage I-III, DS Stage I-III, SYMPTOMATIC
- Induction with:
  - VRd or CyBorD or doublet len-dex or bor/dex
  - Transplant
- Maintenance

Case Presentation: non-transplant candidate

- 75-year-old woman presents with generalized aches, fatigue
- Hemoglobin 8 g/dL, calcium 12.5 mg/dL, creatinine 1.8 mg/dL, albumin 3.0 g/dL
- $\beta_2$ microglobulin 7 mg/L, SPEP shows M spike of 6.2 g/dL
- Bone marrow with 50% monoclonal plasma cells
- Cytogenetics: hyperdiploid
- Skeletal survey: multiple small lytic lesions
Phase III VISTA Study: VMP vs MP in Untreated MM Pts Ineligible for HDT-ASCT

- Pts (N = 682): symptomatic MM/end-organ damage with measurable disease; ≥ 65 yrs or < 65 yrs of age but not transplant eligible; ≥ 75 yrs of age: 31% in VMP arm, 30% in MP arm KPS ≥ 60%

- VMP (n = 344)
  - Cycles 1-4
    - Bortezomib 1.3 mg/m² IV Days 1, 4, 8, 11, 22, 25, 29, 32
    - Melphalan 9 mg/m² IV and prednisone 60 mg/m² IV Days 1-4
  - Cycles 5-9
    - Bortezomib 1.3 mg/m² IV Days 1, 8, 22, 29
    - Melphalan 9 mg/m² IV and prednisone 60 mg/m² IV Days 1-4

- MP (n = 338)
  - Cycles 1-9
    - Melphalan 9 mg/m² IV and prednisone 60 mg/m² IV Days 1-4

Primary endpoint: TTP
- Secondary endpoints: CR rate, ORR, time to response, DOR, time to next therapy, OS, PFS, QoL (PRO)


VMP vs MP in Untreated Myeloma: Efficacy Data

- ORR: VMP 71%, MP 35%
- CR: VMP 30%, MP 4%
- TTP: ~52% reduced risk of progression on VMP
- OS: ~36% reduced risk of death on VMP
- Median follow-up: 25.9 mos
  - 3-year OS:
    - VMP: 72%
    - MP: 59%

- 43% of MP patients received bortezomib upon progression
- OS with > 4 cycles bortezomib: 98.5% at 1 yr, 89% at 2 yrs
- Treatment-related death: 2% in both arms

**Phase III Study Schema**

N=459, 82 centers in Europe, Australia and Israel

**Randomization**

- **MPR-R**
  - M: 0.18 mg/kg, days 1-4
  - P: 2 mg/kg, days 1-4
  - R: 10 mg/day po, days 1-21
  - Lenalidomide Continued Tx

- **MP**
  - M: 0.18 mg/kg, days 1-4
  - P: 2 mg/kg, days 1-4
  - R: 10 mg/day po, days 1-21

- **Placebo**
  - days 1-21

**Cycles (28-day) 1-9**

- **Disease progression**
- Lenalidomide (25 mg/day) +/- dexamethasone

**Cycles 10+**

**RANDOMIZATION**

- **Double-Blind Treatment Phase**
- **Open-Label Extension/ Follow-Up Phase**

• Stratified by age (≤ 75 vs. > 75 years) and stage (ISS 1,2 vs. 3)

M, melphalan; P, prednisone; R, lenalidomide; PBO, placebo.

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**Best Response**

**Best Overall Response**

- a. As measured using EBMT criteria
- b. Immunofixation negative with or without bone marrow confirmation
- c. VGPR: >90% reduction in M-protein

<table>
<thead>
<tr>
<th></th>
<th>MPR-R N=152</th>
<th>MPR N=153</th>
<th>MP N=154</th>
<th>P Value (MPR-R vs. MP)</th>
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<tbody>
<tr>
<td>ORR</td>
<td>77%</td>
<td>67%</td>
<td>49%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRb</td>
<td>18%</td>
<td>13%</td>
<td>5%</td>
<td>&lt;0.001</td>
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<tr>
<td>≥ VGPRc</td>
<td>32%</td>
<td>33%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PR</td>
<td>45%</td>
<td>34%</td>
<td>37%</td>
<td>---</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
<td>---</td>
</tr>
<tr>
<td>Median time to first response, months</td>
<td>1.9</td>
<td>1.9</td>
<td>2.8</td>
<td>&lt;0.001</td>
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</tbody>
</table>

Progression-Free Survival
First Interim Analysis
50% Reduced Risk in PFS

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>MPR-R</th>
<th>MP</th>
</tr>
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<tbody>
<tr>
<td>at Risk</td>
<td>152</td>
<td>154</td>
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<tr>
<td>115</td>
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<tr>
<td>11</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
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</tr>
</tbody>
</table>

HR 0.499
95% CI [0.330, 0.755]
Logrank P<0.001

Median PFS Not reached
13.0 months

Median follow up: 9.4 mos

• Patients without Event (%)

Median follow up: 9.4 mos

Initial Treatment: not Transplant Eligible

- MPT (GIMEMA, IFM-99-06, IFM 01-01, Nordic)
  PFS: 3-28 months vs 9-19 months
  OS: 29-52 months vs 29-48 months
- MPB vs MP (VISTA Trial)
  PFS: 24 vs 16.6 months
  OS 82.6% vs. 69.5%
- or VRD (high risk), or MP-Len and maintenance Len or BD or Len-Bortezomib

Palumbo et al, ASH 2009
Novel/newer effective regimens

RVD, CyBord, PAD, CVD, CVRD

Overall response Rates: UP TO 100%
CR/VGPR: 30-45%      VGPR 60-75% -70%

• Stewart et al. Blood 2008;114:5436-43
Multiple Myeloma
Clinical Practice Guidelines in Oncology – v.3.2010

FOLLOW-UP/SURVEILLANCE

- Quantitative immunoglobulins + quantitation of M protein at least every 3 mo
- CBC, differential, platelets
- BUN, creatinine, calcium
- Bone survey annually or for symptoms
- Bone marrow biopsy as clinically indicated
- Consider free light chain
- Consider MRI
- Consider PET/CT scan

Active (symptomatic) myeloma: Response after induction therapy

- Allogeneic stem cell transplant in clinical trial or
- Autologous stem cell transplant or
- Continue induction chemotherapy to plateau

See Additional Treatment

MYEL-4

Additional Treatment

Salvage therapy on or off clinical trial or
Allogeneic stem cell transplant on clinical trial
(category 3 for conventional vs clinical trial)

Post-autologous stem cell transplant:

Salvage therapy on or off clinical trial or
Allogeneic stem cell transplant on clinical trial

- Refractory disease
- Observe or Second tandem transplant or Maintenance therapy

Stable disease

Progressive disease

(Continued)

Salvage therapy on or off clinical trial or
Allogeneic stem cell transplant on clinical trial or
Additional autologous stem cell transplant on clinical trial
(category 2B)

MYEL-5
BMT-CTN Study 0102: no difference between autologous transplant followed by non-myeloablative allogeneic transplant vs. tandem autologous transplant

- Collect
  - > 4 mill CD34/kg
  - Melphalan 200
  - + 2 mill CD34

  - HLA = sibling
  - Nonmyeloablative allograft
    - 200 cGy TBI
    - MMF/CSA

  - No HLA = sibling
  - Melphalan 200
    - No maintenance
    - Maintenance 1 yr
      - Thalidomide 200/day/Dex 40 x 4 days/mo

Krishnan Lancet Oncol 2012

Bortezomib induction, reduced-intensity transplantation, and lenalidomide consolidation-maintenance for myeloma: updated results

- Characteristics: Age 65-75 n:102 median follow-up: 66 months
  - Bortezomib, Peg-doxorubicin, dexamethasone x 4
  - Tandem melphalan 100 mg/m2 followed by ASCT: CR 33%
  - Lenalidomide-prednisone x 4: CR 48%
  - Lenalidomide maintenance till progression: CR 55%

- Time to Progression (TTP): 55 mos ; Progression-Free Survival (PFS): 48 mos
- Median Overall Survival not reached, 5-year OS: 63%
- In CR patients: TTP: 70 mos ; 5-year OS: 83%
- Median survival from relapse: 28 mos
  - Treatment-related mortality: 8/102 (5/26 in aged < 70 vs 3/26 in >70)

**BMT CTN 0702: SCHEMA**

- Register and randomize
- MEL 200 mg/m²
- VRD x 4
- MEL 200 mg/m²
- Lenalidomide maintenance
- Lenalidomide maintenance

* *Bortezomib 1.3 mg/m² Days 1, 4, 8, 11.
† Lenalidomide 10 mg/day x 3 mos, then 15 mg/day x 3 yrs
• Lenalidomide 15 mg Days 1-15
  Dexamethasone 40 mg Days 1, 8, 15

**IFM/DFCI Trial**

- Induction 4 cycles of RVD
- Mobilization Cy 3 g/m²
- MEL 200 mg/m²
- RVD x 2
- RVD x 4
- Lenalidomide maintenance
- Lenalidomide maintenance

• **Lenalidomide 10 mg/day x 3 mos, then 15 mg/day**
Suggested treatment approach for patients with relapse or progressive disease

Overview

- Scenarios for Treatment of Relapsed/Refractory Myeloma
  - May repeat primary/prior therapy if relapse > 6 months since completion and there are no other contraindications
  - Lenalidomide–containing regimens
  - Bortezomib-containing regimens
  - DCEP, DT-PACE, bendamustine
  - New Aspects in Supportive Care
  - Novel Agents: carfilzomib, pomalidomide, vorinostat
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

Definitions of Relapse

- New plasmacytoma or new bone metastatic site
- Increase in bone/plasmacytoma site of > 1cm
- Hypercalemia
- Progressive Anemia
- New or recurrent renal dysfunction
- Reappearance/rise in M protein level or doubling of M protein at 2 consecutive time points (absolute $\geq 1$ g/dl in blood or $> 500$ mg/24 hr in urine, or involved FLC $> 20$ mg/dl with abnormal ration or $> 25\%$ increase)
Thalidomide- and Lenalidomide-Containing Regimens

Lenalidomide + Dexamethasone: Recommendations for Patient Selection

<table>
<thead>
<tr>
<th>Baseline Factor(s)</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_2$-M levels</td>
<td>Not exclusion criteria</td>
</tr>
<tr>
<td>Cytogenetic factors, or Previous treatments</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Not exclusion criterion. Monitoring of patients ≥ 65 yrs is recommended. Fragile patients &gt; 75 yrs, dexamethasone dose may need to be reduced to avoid toxicity</td>
</tr>
<tr>
<td>Renal Impairment</td>
<td>Not exclusion criterion. Care should be taken in dose selection; it would be prudent to monitor renal function; monitor counts. Dose reductions might be needed when toxicity occurs</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


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**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>
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</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>
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<tr>
<td>Anemia</td>
<td>4</td>
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<tr>
<td>VTE</td>
<td>11</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

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


## Bortezomib-Containing Regimens

### Bortezomib in Myeloma Patients with Renal Impairment

<table>
<thead>
<tr>
<th>CrCl, mL/min</th>
<th>Overall response rate, %</th>
<th>Grade 3/4 AEs, %</th>
<th>Discontinuation, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 50 (n = 42)</td>
<td>25</td>
<td>Thrombocytopenia: 33 Neutropenia: 17 Peripheral neuropathy: 13</td>
<td>38</td>
</tr>
<tr>
<td>51-80 (n = 99)</td>
<td>33</td>
<td>Thrombocytopenia: 27 Neutropenia: 15 Peripheral neuropathy: 9</td>
<td>22</td>
</tr>
<tr>
<td>&gt; 80 (n = 105)</td>
<td>45</td>
<td>Thrombocytopenia: 30 Neutropenia: 12 Peripheral neuropathy: 11</td>
<td>28</td>
</tr>
</tbody>
</table>

**Bortezomib and Del(13) in Myeloma**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Treatment</th>
<th>N (Evaluable Pts)</th>
<th>Cytogenetics</th>
<th>Del(13), n</th>
<th>No Del(13), n</th>
</tr>
</thead>
<tbody>
<tr>
<td>SUMMIT</td>
<td>II</td>
<td>Bortezomib</td>
<td>20</td>
<td>Metaphase (n = 147)</td>
<td>26</td>
<td>121</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APEX</td>
<td>III</td>
<td>Bortezomib</td>
<td>33</td>
<td>Metaphase (n = 74)</td>
<td>11</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dex</td>
<td>33</td>
<td>Metaphase (n = 94)</td>
<td>13</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FISH (n = 65)</td>
<td>18</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>FISH (n = 73)</td>
<td>22</td>
<td>51</td>
</tr>
</tbody>
</table>

- SUMMIT trial: matched pair analysis by metaphase cytogenetics
- Del(13) had no significant effect on response rate or survival
- APEX trial: matched pair analysis of 21 del(13) patients vs 41 without del(13)
- Response rate not significantly different between groups in either treatment arm
- Del(13) associated with significant decrease in survival in dexamethasone arm
- Del(13) had no effect on survival


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

**Induction**
- Dexamethasone 40 mg PO*, Days 1-4, 9-12, and 17-20 for four 5-week cycles (n = 336)
- Bortezomib 1.3 mg/m², 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/m², IV Days 1, 8, 15, 22 for three 5-week cycles

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

*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)

Patients with relapsed/refractory MM, PS 0-1, bort-naive (N = 646)

- Bortezomib 1.3 mg/m², Days 1, 4, 8, 11 (n = 322)
- Bortezomib 1.3 mg/m², Days 1, 4, 8, 11, PLD 30 mg/m², Day 4 (n = 324)

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

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


Median TTP: Bort 6.5 months
Median TTP: Bort + PLD 9.3 months

Parameter, % PLD + Bort Bortezomib
Censored 82 75
Died 18 25

P = .000004
HR (95% CI): 1.82 (1.41 to 2.35)

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

VMPT in Relapsed/Refractory Myeloma

VMPT (bortezomib, melphalan, prednisone, thalidomide) evaluated as second-line (n = 14) or third-line (n = 16) therapy for relapsed/refractory myeloma

- Bortezomib MTD: 1.3 mg/m²
- Grade 3/4 AEs in ≥ 5% of patients
  - Neutropenia (43%)
  - Thrombocytopenia (33%)
  - Anemia (16%)
  - Herpes zoster (7%)


Supportive Therapies in Myeloma

- **Bone disease**
  - Analgesics for bone pain (avoid NSAIDs)
  - Radiotherapy for palliation of bone pain
  - Vertebroplasty or kyphoplasty for persistent pain
  - Bisphosphonates
- **Anemia**: transfusions and/or RBC growth factors
  - Consider EPO trial in patients with symptomatic anemia
- **Hypercalcemia**: rehydration, bisphosphonates
- **Renal dysfunction or hyperviscosity**
  - Rehydration, treat infection, plasmapheresis
- **Infections**: antibiotics, influenza vaccination

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>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 benefit

•
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>

*Adapted from Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03.
*ADL: activities of daily living.

Len/Dex: Cytopenia Management

- **Monitoring FBCs**
  - If normal at baseline, biweekly monitoring; If abnormal at baseline due to MM infiltration, pursue treatment with full-dose and at least weekly monitoring
  - Standard dose-reduction for all other causes of abnormal baseline and follow-up

- **Neutropenia**
  - For grade ≥ 3, monitor and consider G-CSF prophylaxis of lenalidomide dose reduction

- **Febrile neutropenia**
  - Antibiotic prophylaxis if patients receive lenalidomide with high-dose dexamethasone; patients should seek medical care within 3 hours if febrile while neutropenic

- **Thrombocytopenia**
  - For grade ≥ 3, monitor and consider interrupting treatment or dose reductions

- **Anemia**
  - Use ESAs for Hgb < 10 g/dL and if symptomatic with Hgb < 12 g/dL, which is target of treatment and should not be exceeded

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>
</tr>
<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>LMWH: low-molecular-weight heparin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immobilization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery</td>
<td></td>
<td></td>
</tr>
<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>
</tbody>
</table>

0 or 1 risk factor ➞ Aspirin

2 or more risk factors ➞ LMWH or warfarin

Obesity: body mass index ≥ 30 kg/m²

* ≥480 mg per month.

† Full-dose warfarin (target INR 2-3).

Adapted from Palumbo et al.

LMWH: low-molecular-weight heparin

How do we decide on salvage?

- Prior responses/duration, completion of prior regimen
- Organ dysfunction (neuropathy, renal, hematopoiesis, etc)
- Age
- Prior transplant
- Route (iv, sc, oral)
## Novel Agents

- Carfilzomib: selective proteasome inhibitor (in phase 3 trials)
- Pomalidomide: immunomodulatory lenalidomide analogue (in phase III trials)
- Ixazomib: oral proteasome inhibitor
- CNTO 328: anti-IL 6 antibody (phase II with dex)
- Vorinostat: HDAC inhibitor (phase III with bortezomib)
- Elotuzumab (CS1 anti-adhesion) in phase III trials with len dex and RVD
- CD38 and CD-138 antibodies

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

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Any Grade</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>46</td>
<td>24</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>39</td>
<td>29</td>
</tr>
<tr>
<td>Fatigue</td>
<td>49</td>
<td>7.5</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>45/22</td>
<td>1.9/0.8</td>
</tr>
<tr>
<td>CHF/Marrest</td>
<td>3.8</td>
<td>2.3</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>34</td>
<td>3.4</td>
</tr>
<tr>
<td>Fever</td>
<td>31</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>32</td>
<td>0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>28</td>
<td>1.9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4.9</td>
<td>0.8</td>
</tr>
<tr>
<td>Low phosphorus</td>
<td>12</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>12.4</td>
<td>1.1</td>
</tr>
</tbody>
</table>

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

Pomalidomide + Low-Dose Dex in Relapsed/Refractory MM: Safety & Efficacy

<table>
<thead>
<tr>
<th>Grade 3/4 Adverse Event</th>
<th>Patients, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>19</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>10</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2</td>
</tr>
<tr>
<td>Fatigue</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>3</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Cardiovascular thrombosis</td>
<td>1</td>
</tr>
</tbody>
</table>

63% ORR
40% ORR

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 lenolidamide 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</th>
<th>Grade 3/4</th>
<th>DEX</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse Event, %</td>
<td></td>
<td>Adverse Event, %</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>48</td>
<td>Neutropenia</td>
<td>16</td>
</tr>
<tr>
<td>Anemia</td>
<td>33</td>
<td>Anemia</td>
<td>37</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22</td>
<td>Thrombocytopenia</td>
<td>26</td>
</tr>
<tr>
<td>pneumonia</td>
<td>13</td>
<td>pneumonia</td>
<td>8</td>
</tr>
<tr>
<td>Bone pain</td>
<td>7</td>
<td>Bone pain</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>Fatigue</td>
<td>6</td>
</tr>
<tr>
<td>Death on trial</td>
<td>4</td>
<td>Death on trial</td>
<td>5</td>
</tr>
<tr>
<td>Fever</td>
<td>1.5</td>
<td>Fever</td>
<td>1.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.8</td>
<td>Diarrhea</td>
<td>0.8</td>
</tr>
<tr>
<td>Headache</td>
<td>1.9</td>
<td>Headache</td>
<td>1.9</td>
</tr>
<tr>
<td>Renal failure</td>
<td>0.8</td>
<td>Renal failure</td>
<td>0.8</td>
</tr>
<tr>
<td>Low phosphorus</td>
<td>6</td>
<td>Low phosphorus</td>
<td>6</td>
</tr>
<tr>
<td>Peripheral Neuropathy</td>
<td>1.1</td>
<td>Peripheral Neuropathy</td>
<td>1.1</td>
</tr>
</tbody>
</table>

Siegel et al. 2012 Blood 120 (14):2817-25
Vorinostat or placebo in combination with bortezomib in patients with multiple myeloma (Vantage 088): a multicentre, randomised, double-blind study

- Non-refractory (previously responded but now progressing, and not progressing on bortezomib) MM patients
- N = 317  Bort: days 1,4,8,11; V 400 mg days 1-14 (21-day cycles)
- N = 320  Bort: days 1,4,8,11 (21-day cycles)
- PFS 7.67 vs. 6.87 months P: 0.01
- Grade ¾ toxicities
  - Neutropenia 28% 25%
  - Thrombocytopenia 45% 24%
  - Anemia 17% 13%


Myeloma Trials Currently Available at COH

- Newly Diagnosed
  - A Randomized Phase I/II Study of Optimal Induction Therapy of Bortezomib, Dexamethasone and Lenalidomide with or without Elotuzumab (NSC-764479) for Newly Diagnosed High Risk Multiple Myeloma (SWOG S1211). Status: Open to Accrual

- Transplant
  - Phase I Study of Bortezomib With or Without Total Marrow Irradiation in Combination with Fludarabine (FLU) and Melphalan (MEL) as a Preparative Regimen for Allogeneic Hematopoietic Stem Cell (HSC) Transplantation in Patients with High Risk Multiple Myeloma. Status: Open to Accrual
  - Phase I/IIa open label, Multiple Site Clinical Trial Evaluating the Safety and Activity of Engineered Autologous T cells Expressing an Affinity-enhanced TCR specific for NY-ESO-1 and LAGE-1, in Patients with Relapsed or Progressive Disease in Multiple Myeloma (Adaptimmune Ltd). Status: Open to Accrual
  - A Phase II Study of IRD (Ixazomib, Lenalidomide, & Dexamethasone) for Consolidation Therapy Post Autologous Stem Cell Transplantation followed by Maintenance Ixazomib or Lenalidomide for Multiple Myeloma
- Relapsed/Refractory
  - A Phase I Study of ARRY-520 and Bortezomib plus Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma (MMRC - Array BioPharma, Inc.). Status: Open to Accrual
  - A Phase I/IIa multi-dose escalation study of BT062 in combination with Lenalidomide and Dexamethasone in subjects with relapsed or relapsed/refractory Multiple Myeloma (Anti CD138). Status: Accrual on hold (may re-open)
  - Phase II/II Trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma (MMRC - COH IIT). Status: Open to Accrual
  - A Multicenter Phase II Study of Single-agent Filanesib (ARRY-250) in Patients with Advanced Multiple Myeloma. Status: Pending
  - A Phase 1, Dose-Escalation/Dose-Expansion Study Evaluating the Safety, Pharmacokinetics, and Pharmacodynamic Effects of Orally Administered CB-5083 in Patients with Relapsed/Refractory Multiple Myeloma (Cleave). Status: Open to Accrual

- Amyloidosis
  - A Multicenter Phase 1/2b Study of the Bruton’s Tyrosine Kinase Inhibitor, Ibrutinib (PCI-32765), in Combination with Carfilzomib (Kyprolis™) in Subjects with Relapsed or Relapsed and Refractory Multiple Myeloma (Pharmacyclics). Status: Pending (SIV 10/8/2014)
  - A Phase I Dose-Escalation Study of Carfilzomib in Patients with Previously-Treated Systemic Light-Chain (AL) Amyloidosis. (AMyC 11-MM-02). Status: Open to Accrual
  - IRB# 14150:
  - Pilot Study of Leflunomide Plus or Minus Dexamethasone for Relapsed/Refractory Myeloma
Other Novel Agents

- Potential targetable Genomic Anomalies
  - \( t(4;14) \) \( FGFR \) FGFR inhibitors
  - \( t(11;14) \) \( Cyclin\ D1 \) celecilib, binaciclib
  - \( t(14;16) \) \( MAF \) MEK inhibitors (selumetinib)
  - \( B-RAF \) vemurafenib

Conclusion

- 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 need further testing in ongoing and planned clinical trials
- Supportive care is an important aspect of the care of these patients