Evolving Management of Multiple Myeloma: 2015

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Section of Hematology/Oncology
MULTIPLE MYELOMA

- Estimated 24,050 cases and 11,090 deaths in 2014\(^1\)
- Median age at diagnosis: 69 yrs\(^2\)
- 5-yr survival has improved substantially (45% in 2004-2010 vs 28% in 1987-1989\(^2\)) due to novel agents
- Sensitive to treatment, but not curable

Incidence over time of multiple myeloma vs overall cancer incidence in the US

Etiology of multiple myeloma has not been clearly defined

<table>
<thead>
<tr>
<th>Accepted risk factors</th>
<th>Possible risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasing age</td>
<td>Obesity</td>
</tr>
<tr>
<td>Male sex</td>
<td>Low fish/green vegetable consumption</td>
</tr>
<tr>
<td>African/African-American race</td>
<td>AIDS</td>
</tr>
<tr>
<td>Family history</td>
<td>Herpes zoster/shingles</td>
</tr>
<tr>
<td>MGUS</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inconsistent data on risk</th>
<th>Do not appear to be risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair dye use</td>
<td>Smoking</td>
</tr>
<tr>
<td>Farming occupation</td>
<td>Alcohol</td>
</tr>
<tr>
<td>Wood dust exposure</td>
<td>Pesticides</td>
</tr>
<tr>
<td>Chronic immune stimulation conditions</td>
<td>Organic solvents</td>
</tr>
<tr>
<td>Autoimmune diseases</td>
<td>Radiation</td>
</tr>
<tr>
<td></td>
<td>Asbestos</td>
</tr>
<tr>
<td></td>
<td>Allergic conditions</td>
</tr>
</tbody>
</table>
Description of multiple myeloma

- Multiple myeloma is a B-cell malignancy derived from antibody-producing plasma cells in the bone marrow.
- The proliferation of myeloma cells leads to excessive production of a monoclonal antibody (M-protein), as well as adverse events in various organ systems.

Basic antibody structure and components

- **Heavy chain:**
  - Defines class – IgG, IgD, IgA, IgM, or IgE

- **Light chain:**
  - Kappa (κ) or lambda (λ)

- **Variable (antigen-binding) region**

- **Constant region**

Myeloma plasma cell


**Common symptoms of multiple myeloma**

Bone pain is the most common symptom, occurring in approximately 70% of patients.

<table>
<thead>
<tr>
<th>System affected</th>
<th>Symptoms</th>
<th>Common cause(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>Fatigue</td>
<td>• Anemia, therapy</td>
</tr>
<tr>
<td></td>
<td>Recurrent infections</td>
<td>• Low uninvolved Ig, therapy</td>
</tr>
<tr>
<td>Kidneys</td>
<td>Nausea and vomiting</td>
<td>• Renal failure, hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Confusion and CNS symptoms</td>
<td>• Renal failure, hypercalcemia</td>
</tr>
<tr>
<td>Bone/spine</td>
<td>Bone pain</td>
<td>• Pathologic fracture, cord compression</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>• Nerve compression, amyloidosis, POEMS*, immune-mediated effects, therapy</td>
</tr>
</tbody>
</table>

*POEMS: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes

1. Adapted from DeVita et al, eds. Cancer: Principles and Practice of Oncology, 9th Ed.
Recommended workup

**Blood specimen**
- Chemistry screen, including calcium and creatinine
- Serum $\beta_2$-microglobulin, albumin, and lactate dehydrogenase
- Serum protein electrophoresis (SPEP), immunofixation
- Measurement of serum-free light chains
- Nephelometric quantification of serum immunoglobulins

**Urine specimen**
- Routine urinalysis
- 24-hour urine collection for electrophoresis and immunofixation

**Bone marrow specimen**
- Aspirate and/or biopsy

**Cytogenetics**
- Metaphase karyotype and FISH

**Radiologic skeletal bone survey**
- Magnetic resonance imaging in certain circumstances

Image: Steven Fruitsmaak
**Recommended workup (cont’d)**

<table>
<thead>
<tr>
<th>Blood specimen</th>
<th>Urine specimen</th>
<th>Bone (marrow) specimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Chemistry screen, including calcium and creatinine</td>
<td>• Routine urinalysis, 24-hour urine collection for electrophoresis and immunofixation</td>
<td>• Bone marrow aspirate and/or biopsy</td>
</tr>
<tr>
<td>• Serum β_2_-microglobulin, albumin, and lactate dehydrogenase</td>
<td></td>
<td>• Cytogenetics (metaphase karyotype and FISH)</td>
</tr>
<tr>
<td>• Serum protein electrophoresis (SPEP), immunofixation</td>
<td></td>
<td>• Radiologic skeletal bone survey; magnetic resonance imaging in certain circumstances</td>
</tr>
<tr>
<td>• Measurement of serum-free light chains</td>
<td></td>
<td></td>
</tr>
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<td></td>
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Recommended workup (cont’d)

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### Urine specimen
- Routine urinalysis, 24-hour urine collection for electrophoresis and immunofixation

### Bone (marrow) specimen
- Bone marrow aspirate and/or biopsy
- Cytogenetics (metaphase karyotype and FISH)
- Radiologic skeletal bone survey; magnetic resonance imaging in certain circumstances

---

## Differential diagnosis

<table>
<thead>
<tr>
<th>Serum monoclonal protein</th>
<th>Monoclonal gammopathy of undetermined significance (MGUS)</th>
<th>Asymptomatic (smoldering) myeloma</th>
<th>Symptomatic myeloma</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3 g/dL</td>
<td>&lt;3 g/dL</td>
<td>≥3 g/dL</td>
<td>Presence of serum and/or urinary monoclonal protein</td>
</tr>
<tr>
<td>&lt;10%</td>
<td>≥10%</td>
<td>And/or ≥10%</td>
<td>≥10%</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Present; Can be attributed to the underlying plasma cell proliferative disorder (CRAB symptoms)</td>
<td></td>
</tr>
</tbody>
</table>

### C: Serum Calcium ≥11.5 mg/dL
### R: Renal insufficiency: serum creatinine >2 mg/dL
### A: Anemia: Hb <10 g/dL or 2 g/dL below normal
### B: Bone lesions: lytic or osteopenic, or pathologic fractures

# Durie-Salmon Staging System for MM

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Myeloma Cell Mass $(\times 10^{12}$ cells/m$^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>All of the following: Hemoglobin $&gt;10$ g/dL; normal serum calcium or $&lt;10.5$ mg/dL; normal bone/solitary plasmacytoma; low M protein (IgG $&lt;5$ g/dL; IGA $&lt;3$ g/dL; Bence-Jones protein $&lt;4$ g/24 h)</td>
<td>$&lt;0.6$ (low)</td>
</tr>
<tr>
<td>II</td>
<td>Not fitting stage I or III</td>
<td>$0.6-1.2$ (intermediate)</td>
</tr>
<tr>
<td>III</td>
<td>Any of the following: Hemoglobin $&lt;8.5$ g/dL; serum calcium $&gt;12$ mg/dL; multiple lytic bone lesions; high M protein (IgG $&gt;7$ g/dL; IGA $&gt;5$ g/dL; Bence-Jones protein $&gt;12$ g/24 h)</td>
<td>$&gt;1.2$ (high)</td>
</tr>
</tbody>
</table>

**Subclassification Criterion**

- **A** Normal renal function (serum creatinine level $<2.0$ mg/dL)
- **B** Abnormal renal function (serum creatinine level $\geq 2.0$ mg/dL)

$M =$ monoclonal

# New MM Staging

## New International Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
<th>Median Survival (months)</th>
</tr>
</thead>
</table>
| I     | Serum $\beta_2$-microglobulin <3.5 mg/L  
         Serum albumin $\geq$3.5 g/dL | 62 |
| II    | Not stage I or III* | 44 |
| III   | Serum $\beta_2$-microglobulin $\geq$5.5 mg/L | 29 |

*There are two categories for stage II: serum $\beta_2$-microglobulin <3.5 mg/L but serum albumin <3.5 g/dL; or serum $\beta_2$-microglobulin 3.5 to <5.5 mg/L irrespective of the serum albumin level.

**mSMART 2.0: Classification of Active MM**

<table>
<thead>
<tr>
<th>High-risk 20%</th>
<th>Intermediate-risk 20%</th>
<th>Standard-risk 60%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FISH</strong></td>
<td><strong>FISH</strong></td>
<td>All others including:</td>
</tr>
<tr>
<td></td>
<td><strong>t(4;14)</strong>*</td>
<td>Hyperdiploid</td>
</tr>
<tr>
<td></td>
<td><strong>Cytogenetic deletion 13 or hypodiploidy</strong></td>
<td>t(11;14)</td>
</tr>
<tr>
<td></td>
<td><strong>PCLI &gt;3%</strong></td>
<td>t(6;14)</td>
</tr>
<tr>
<td><strong>GEP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>High-risk signature</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 years 4-5 years 8-10 years

MM Classification Over Time

- www.upci.upmc.edu/research/clinical/myeloma/
- Rossi, J Kowalski, L Boise
Clonal Tides Define Myeloma

6 unique clones at diagnosis

Variable chemotherapy response

Minor drug-resistant clone lethal
Implications

1. Multiple clones with variable drug sensitivity
   (Combination chemotherapy a necessity and continuous therapy logical)

2. Re-emergence of drug-sensitive clones
   (Once resistant not always resistant)

3. Minor clone is lethal (CR is a goal)
Minimal Residual Disease: New Definitions for CR

- Newly diagnosed: $1 \times 10^{12}$
- Disease burden
  - S.S. Patient
  - CR
  - Stringent CR
  - Molecular/flow CR
  - Sequencing CR
  - ?Cure?

Quantities:
- $1 \times 10^8$
- $1 \times 10^4$
- 0.0
Redefining Symptomatic Myeloma
Smoldering Myeloma

• No symptoms; no related organ/tissue impairment
• 10% to 20% of newly diagnosed myeloma\[^{[1]}\]
• Can remain indolent for yrs
• Progression rate: ~ 50% at 5 yrs\[^{[2]}\]
  – Progression rate in high-risk subgroup: 50% at 2 yrs\[^{[3]}\]
• Current question: *Who* should be treated?\[^{[4]}\]

Smoldering Myeloma
Prognostic Models

Mayo Clinic (N = 273)

<table>
<thead>
<tr>
<th>Risk Factors, n</th>
<th>Patients, n (%)</th>
<th>Progression at 5 Yrs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>81 (28)</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>114 (42)</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>78 (30)</td>
<td>76</td>
</tr>
</tbody>
</table>

PETHEMA Study Group (N = 89)

<table>
<thead>
<tr>
<th>Risk Factors, n</th>
<th>Patients, n (%)</th>
<th>Progression at 5 Yrs, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>28 (31)</td>
<td>4</td>
</tr>
<tr>
<td>1</td>
<td>22 (25)</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>39 (44)</td>
<td>72</td>
</tr>
</tbody>
</table>

- Risk factors
  - Mayo Clinic\(^1\)
    - BMPCs ≥ 10%
    - M-protein ≥ 3 g/dL
    - FLC ratio < 0.125 or > 8
  - PETHEMA\(^2\)
    - ≥ 95% abnormal plasma cells
  - Immunoparesis
  - University of Salamanca\(^3\)
    - BMPCs ≥ 10%
    - High M-protein: IgG ≥ 3 g/dL, IgA ≥ 2 g/dL, or Bence-Jones > 1 g/24 hrs

PETHEMA Phase III Trial: Len/Dex vs Observation in High-Risk SM

- Study limitation in assessing OS: patients received treatment off-protocol at the time of disease progression to symptomatic myeloma
  - 53% treated with either bortezomib-based regimens
  - 28% treated with induction therapy followed by autologous stem-cell transplantation
  - 19% treatment not reported

Active Myeloma

Not CRAB but now **SLiM CRAB**

- **S** (60% Plasmacytosis)
- **Li** (Light chains I/U >100)
- **M** (MRI 1 or more focal lesion)
- **C** (Calcium elevation)
- **R** (Renal insufficiency)
- **A** (Anemia)
- **B** (Bone disease)

Untreated Active Multiple Myeloma
Approved agents in multiple myeloma

- **Bortezomib**
- **Carfilzomib**
- **Platinum (PLD)**
- **Thalidomide**
- **Cyclophosphamide & Melphalan**
- **Lenalidomide**
- **Pomalidomide**

Timeline:
- Pre-2003
- 2003
- 2004
- 2005
- 2006
- 2007
- 2008
- 2009
- 2010
- 2011
- 2012
- 2013
Improving Survival in MM
Chemical Structure of Thalidomide, Lenalidomide, and Pomalidomide

Thalidomide
100–200 mg/d
- Neuropathy
- Constipation
- Sedation
- DVT

Lenalidomide
15–25 mg/d
- Myelosuppression
- Skin rash
- DVT

Pomalidomide
2–4 mg/d
- Myelosuppression

Side effects

Potency
Proteasome Inhibitors

Figure 1: Structure of the 26S Proteasome—Adapted from Marteijn JA et al. Leukemia. 2006.[42] © 2006. Reprinted by permission from Macmillan Publishers Ltd.
Comparison of Proteasome Inhibitors

Bortezomib (reversible)
Carfilzomib (irreversible)
CEP 18770 (reversible)
MLN9708 (reversible)
NPI-0052 (irreversible)
Initial Approach to Treatment of Myeloma

Nontransplant Candidate (based on age, performance status, and comorbidities)
- Induction treatment
- Maintenance

Transplant Candidate
- Induction treatment (4-6 cycles)
  - Stem cell harvest
  - Stem cell transplantation
  - Consolidation therapy?
  - Maintenance
FIRST: Lenalidomide/Dexamethasone vs MPT in NDMM SCT-Ineligible Patients

Active treatment + PFS follow-up phase

<table>
<thead>
<tr>
<th>Arm A</th>
<th>Len + LoDex</th>
<th>Continuously</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lenalidomide</td>
<td>25 mg Days 1-21/28</td>
</tr>
<tr>
<td></td>
<td>LoDex</td>
<td>40 mg Days 1, 8, 15, 22/28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm B</th>
<th>Len + LoDex</th>
<th>18 cycles (72 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lenalidomide</td>
<td>25 mg Days 1-21/28</td>
</tr>
<tr>
<td></td>
<td>LoDex</td>
<td>40 mg Days 1, 8, 15, 22/28</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Arm C</th>
<th>Mel + Pred + Thal</th>
<th>12 cycles (72 weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Melphalan</td>
<td>0.25 mg/kg Days 1-4/42</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
<td>2 mg/kg Days 1-4/42</td>
</tr>
<tr>
<td></td>
<td>Thalidomide</td>
<td>200 mg Days 1-42/42</td>
</tr>
</tbody>
</table>

Patients >75 years: LoDex 20 mg Days 1, 8, 15, 22/28; Thal³ 100 mg Days 1-42/42; Mel³ 0.2 mg/kg Days 1-4

Stratification: age, country, and ISS stage

NDMM = newly diagnosed MM; SCT = stem cell transplant.
FIRST Trial: Efficacy Analysis of Len/Dex vs MPT in SCT-Ineligible Patients With MM

Relapsed Multiple Myeloma
ASPIRE Study Design

Randomization
N=792

Stratification:
• β₂-microglobulin
• Prior bortezomib
• Prior lenalidomide

28-day cycles

**KRd**
- Carfilzomib 27 mg/m² IV (10 min)
- 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

After cycle 12, carfilzomib given on days 1, 2, 15, 16

After cycle 18, carfilzomib discontinued

**Rd**
- Lenalidomide 25 mg Days 1–21
- Dexamethasone 40 mg Days 1, 8, 15, 22

Primary Endpoint: Progression-Free Survival

*ITT Population (N=792)*

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>KRd (n=396)</th>
<th>Rd (n=396)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at Risk:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRd</td>
<td>396</td>
<td>332</td>
</tr>
<tr>
<td></td>
<td>332</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>279</td>
<td>222</td>
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<td></td>
<td>222</td>
<td>179</td>
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<td>179</td>
<td>112</td>
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<td></td>
<td>112</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1</td>
</tr>
<tr>
<td>Rd</td>
<td>396</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td>287</td>
<td>206</td>
</tr>
<tr>
<td></td>
<td>206</td>
<td>151</td>
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<td>151</td>
<td>117</td>
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<td></td>
<td>117</td>
<td>72</td>
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<tr>
<td></td>
<td>72</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>1</td>
</tr>
</tbody>
</table>

Median PFS, mo: 26.3 vs 17.6
HR (KRd/Rd) (95% CI): 0.69 (0.57–0.83)
P value (one-sided): <0.0001

Secondary Endpoints: Response

- Median duration of response was 28.6 months in the KRd group and 21.2 months in the Rd group


- **sCR**
  - 14.1% vs 4.3%
  - *P* < 0.0001

- **≥CR**
  - 31.8%

- **≥VGPR**
  - 69.9%
  - *P* < 0.0001

- **ORR (≥PR)**
  - 87.1%
  - 66.7%
  - *P* < 0.0001
Median OS was not reached; results did not cross the prespecified stopping boundary ($P=0.005$) at the interim analysis.
EORTC Global Health Status improved in the KRd group vs the Rd group over 18 cycles of treatment (P=0.0001).
Relapsed/Refractory Myeloma
Once Treatment Fails, Trouble Begins

Overall Survival From Start of Therapy by Regimen Number

Survival With Bz/Len Refractory Disease

Overall Survival
Events/N: 173/231
Median (months): 9 (7, 11)

Event-Free Survival
222/291
5 (4, 6)

Improving Survival in MM

25% of patients live less than 3 years

Follow up from diagnosis (Years)

Proportion surviving

1960-65
1965-70
1970-75
1975-80
1980-85
1985-90
1990-95
1995-00
2000-05
2005-10
Ixazomib (MLN9708)

• Ixazomib (MLN9708) is an investigational oral, reversible, and specific 20S proteasome inhibitor
  – The first oral proteasome inhibitor in clinical development
  – Physiochemical properties distinct from bortezomib
  – Activity in preclinical models of MM
Oral Ixazomib – Phase 1 Weekly

- Oral weekly administration
- 60 patients with heavily pretreated disease
- DLTs due to nausea, vomiting, diarrhea, and rash
- AEs – thrombocytopenia, diarrhea, nausea, fatigue, vomiting
- Neuropathy 20% (but only 1 grade 3)
- 18% response rate (PR or better), 27% at MTD

Ixazomib Treatment Duration and Response


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Ixazomib Summary

• Well tolerated
• Single-agent activity in both weekly and twice weekly administration
• Less effective than bortezomib?
• Low neuropathy rate is encouraging
• Attractive oral regimen (esp in combination) – see next slide
IRd (Ixazomib/Lenalidomide/Dex)- Best Percent Change in M-protein From Baseline in Response-Evaluable Patients

- 48% of patients achieved 100% reduction in M-protein
- Reductions were seen at multiple dose levels
Elotuzumab: Background

- Elotuzumab is a humanized IgG1 mAb-targeting human CS1, a cell surface glycoprotein\textsuperscript{1,2}
- CS1 is highly expressed on >95% of MM cells\textsuperscript{1,3}
  - Lower expression on NK cells
  - Little-to-no expression on normal tissues
- MoA of elotuzumab is primarily through NK cell-mediated ADCC against myeloma cells\textsuperscript{1,2}
- In a MM xenograft mouse model, the combination of elotuzumab + lenalidomide significantly reduced tumor volume compared with either agent alone\textsuperscript{4}

ADCC = antibody-dependent cellular cytotoxicity; DMSO = dimethyl sulfoxide; mAb = monoclonal antibody; MED = maximum efficacious dose; MoA = mechanism of action; NK = natural killer.

Daratumumab: A Human CD38 MAb With Broad-Spectrum Killing Activity

Maximal Reduction of Serum M-Component (Part 1)

Maximal Change in Paraprotein

*Data at baseline below limits for measurable disease. Results are before database lock.
A = serum M-component; B = urine M-component; C = free light chains (FLC).
CD38 Expressed in Hematological Malignancies

- Transmembrane glycoprotein and ectoenzyme
- High receptor density on MM cells

<table>
<thead>
<tr>
<th>Disease</th>
<th>CD38 + Expression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple myeloma</td>
<td>80-100(^1)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>30-80(^2,3)</td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>58(^4)</td>
</tr>
<tr>
<td>B chronic lymphocytic leukemia</td>
<td>20-25(^5)</td>
</tr>
</tbody>
</table>

SAR650984: Maximal Change in Paraprotein Myeloma Patients Treated at Doses of 1 mg/kg or Higher Every 2 Weeks

A = serum M component; B = urine M component; C = free light chains (FLC).
One patient at 3 mg/kg and 20 mg/kg with 0% change; one patient at 20 mg/kg not-evaluable.
Blockade of Ubiquitinated Protein Catabolism

HDAC6
Tubacin
LBH, vorinostat
Dynein
Microtubule

Protein
Protein aggregates (toxic)
26S Proteasome
Bortezomib

Aggresome
Lysosome
Autophagy

PANORAMA 2 Study Design: Phase 2, Simon 2-Stage Study in BTZ-Refractory MM

BTZ-refractory disease defined as relapse on or within 60 days of last BTZ-containing line of therapy

Screening
- Adult patients
- Relapsed and BTZ-refractory MM
- ≥2 prior lines of therapy
- Exposed to IMiDs

Treatment Phase 1
- Eight 3-week cycles
- Panobinostat
- Bortezomib
- Dexamethasone

Treatment Phase 2
- 6-week cycles until PD
- Panobinostat
- Bortezomib
- Dexamethasone

After 8 cycles, continuation into treatment Phase 2 in patients with clinical benefit

Primary endpoint: ORR (CR + nCR + PR)*

*Response measured according to modified European Group for Blood and Marrow Transplantation 1998 criteria.
Preliminary Response Data: Activity in Patients With Bortezomib-Refractory MM

<table>
<thead>
<tr>
<th>Best confirmed response (confirmed at 6 weeks)</th>
<th>N = 55</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response (CR + nCR + PR)</td>
<td>16 (29%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>–</td>
</tr>
<tr>
<td>Near complete response</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>14 (25%)</td>
</tr>
<tr>
<td>Clinical benefit (CR + nCR + PR + MR)</td>
<td>27 (49%)</td>
</tr>
<tr>
<td>Minimal response</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>VGPR</td>
<td>3 (6%)</td>
</tr>
</tbody>
</table>

- Responses were typically observed after 1 to 2 cycles
- Stable disease observed in 2 patients; progressive disease in 10 patients

Richardson PG et al. ASH 2011 Annual Meeting Abstract 814.
**PANORAMA 1 Study Design:** Randomized, Double-Blind, Phase 3 Study in Relapsed or RRMM

**Study conducted at 215 centers across 34 countries**

- **Patients (N = 768)**
  - Relapsed or Relapsed/Refractory MM (BTZ-refractory excluded)
  - 1-3 prior lines of therapy
  - Stratification factors
    - Prior lines of therapy
    - Prior BTZ

**Treatment Phase 1**
- Eight 21-day cycles (24 weeks)
  - Panobinostat + Bortezomib + Dexamethasone
  - Placebo + Bortezomib + Dexamethasone

**Treatment Phase 2**
- Four 42-day cycles (24 weeks)
  - Panobinostat + Bortezomib + Dexamethasone
  - Placebo + Bortezomib + Dexamethasone

Patients with clinical benefit* in Treatment Phase 1 can proceed to Treatment Phase 2

- **Follow-up**

**Primary endpoint:** PFS (per modified EBMT criteria; confirmed by IRC)\(^1,2\)

- **Key secondary endpoint:** OS

- **Other secondary endpoints:** ORR, nCR/CR rate, DoR, TTR, TTP, QoL, and safety

*Achieving ≥no change according to modified EBMT criteria (SD or better).
PANORAMA 1: Primary Endpoint Met (PFS)

- Primary endpoint was met ($P<0.0001$), with clinically relevant increase in median PFS of 3.9 months for PAN-BTZ-Dex arm

<table>
<thead>
<tr>
<th></th>
<th>Events</th>
<th>Median PFS months (95% CI)</th>
<th>HR (95% CI)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAN-BTZ-Dex</td>
<td>207/387</td>
<td>12.0 (10.3, 12.9)</td>
<td>0.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pbo-BTZ-Dex</td>
<td>260/381</td>
<td>8.1 (7.6, 9.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

• Prolonged duration of therapy results in longer remission duration and potentially improved overall survival.
  – FIRST Trial
  – Maintenance therapy post transplant
• Combination therapy results in improved progression free survival and potentially overall survival.
  – ASPIRE Trial
  – Clonal Tides Theory
• Novel agents will help transform relapsed/refractory disease.
  – Oral proteasome inhibitors
  – Monoclonal antibodies