Multiple Myeloma Updates 2007

Goals for today:

- Understand the staging systems for myeloma
- Understand prognostic factors in myeloma
- Review updates from ASH
Multiple Myeloma Staging History

- 1960 – Single prognostic factors
- 1970 – Durie Salmon tumor burden
- 1975 – Durie Salmon stage (in use today)
- 1980 – Beta 2 microglobulin and albumin
- 1990 – Other staging systems offered
Myeloma Staging Systems

- **Durie-Salmon.** Cancer 1975.
- **Bataille (BSS).** JCO 1986.
- **SWOG.** Br. J. Haematology 2003.
- **International Staging System (ISS).** JCO 2005.
Table 7. Myeloma Staging System

<table>
<thead>
<tr>
<th>Stage</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>I All of the following:</td>
<td>Measured myeloma cell mass (cells × 10¹²/m²)¹</td>
</tr>
<tr>
<td>1. Hemoglobin value &gt; 10 g/100 ml</td>
<td>&lt;0.6</td>
</tr>
<tr>
<td>2. Serum calcium value normal (≤ 12 mg/100 ml)</td>
<td></td>
</tr>
<tr>
<td>3. On roentgenogram, normal bone structure (scale 0) or solitary bone plasmacytoma only</td>
<td></td>
</tr>
<tr>
<td>4. Low M-component production rates (Low) a. IgG value &lt; 5 g/100 ml</td>
<td></td>
</tr>
<tr>
<td>b. IgA value &lt; 3 g/100 ml</td>
<td></td>
</tr>
<tr>
<td>c. Urine light chain M-component on electrophoresis &lt; 4 g/24 hours</td>
<td></td>
</tr>
<tr>
<td>II Fitting neither Stage I nor Stage III (Intermediate) 0.6–1.20</td>
<td></td>
</tr>
<tr>
<td>III One or more of the following:</td>
<td></td>
</tr>
<tr>
<td>1. Hemoglobin value &lt; 8.5 g/100 ml</td>
<td>&gt;1.20</td>
</tr>
<tr>
<td>2. Serum calcium value &gt; 12 mg/100 ml</td>
<td></td>
</tr>
<tr>
<td>3. Advanced lytic bone lesions (scale 3)</td>
<td></td>
</tr>
<tr>
<td>4. High M-component production rates (High) a. IgG value &gt; 7 g/100 ml</td>
<td></td>
</tr>
<tr>
<td>b. IgA value &gt; 5 g/100 ml</td>
<td></td>
</tr>
<tr>
<td>c. Urine light chain M-component on electrophoresis &gt; 12 g/24 hours</td>
<td></td>
</tr>
</tbody>
</table>

Why a New Staging System to Replace Durie Salmon as the International Standard?

- Difficult to remember cutoffs for DS Stage
- Subjective interpretation of bone lesions
- Relative good survival for DS Stage 3 patients
- $\beta_2$M based risk groups appropriately being used by investigators in clinical trials, rather than DS Stage, but no consensus on $\beta_2$M cutoffs
### Table 2. New International Staging System

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

*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.*

Griep et al. JCO 2005.
Fig 1. Training versus validation datasets. ISS, International Staging System. A is training dataset; B is validation dataset.
**IMF**

**International Staging System (ISS)**

*Staging for Multiple Myeloma*

| STAGE 1   | β2M < 3.5  
|           | ALB ≥ 3.5  
| STAGE 2   | β2M < 3.5  
|           | ALB < 3.5  
|           | or        
|           | β2M 3.5 – 5.5  
| STAGE 3   | β2M > 5.5  

Footnote: β2M = Serum β2 microglobulin in mg/dl  
ALB = Serum albumin in g/dl

**Good and Poor Risk Groups**

- **Age** is the only additional factor that significantly impacts outcome.

- **Survival for > 5 years** is associated with age < 60 years.

- **Survival for < 2 years** is associated with age > 60 years. Other correlations in this category include: platelet count < 130,000/mm³ and LDH serum level above normal.

- **Cytogenetics** do influence outcome, however, chromosome 13 deletion and presence of complex chromosome abnormalities do not add to the impact of age, β2M and ALB.
Multiple Myeloma

**Survival by ISS Staging System**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Deaths/N</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1320/2401</td>
<td>62 (59,64)</td>
</tr>
<tr>
<td>2</td>
<td>2172/3278</td>
<td>44 (42,48)</td>
</tr>
<tr>
<td>3</td>
<td>2083/2770</td>
<td>29 (27,31)</td>
</tr>
</tbody>
</table>

Logrank P-value < .0001

**Factors Predicting Very Low Risk**

(> 5 year survival)

<table>
<thead>
<tr>
<th>Category</th>
<th>Deaths/N</th>
<th>Median in Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk + Normal LDH</td>
<td>73/141</td>
<td>64 (53,77)</td>
</tr>
<tr>
<td>Low Risk + No T(4:14)</td>
<td>41/48</td>
<td>63 (50,77)</td>
</tr>
<tr>
<td>Low Risk + PLT&gt;200</td>
<td>287/434</td>
<td>63 (59,72)</td>
</tr>
<tr>
<td>Low Risk</td>
<td>480/711</td>
<td>62 (59,67)</td>
</tr>
<tr>
<td>Low Risk + No Fish 13</td>
<td>22/27</td>
<td>60 (53,77)</td>
</tr>
</tbody>
</table>

*Low Risk = Stage 1 Patients < Age 60*
Multiple Myeloma Staging

- Proposed molecular staging systems
  - Translocation and cyclin D or TC
  - Molecular classification
Multiple Myeloma
**A**

- **i**
  - Proportion of Patients vs. Months from Start of Therapy
  - Events/N:
    - PR: 20/29
    - LB: 7/31
    - MS: 32/44
    - HY: 24/66
    - CD-1: 7/22
    - CD-2: 10/43
    - MF: 10/21
  - *P* < 0.001

- **ii**
  - Deaths/N:
    - PR: 16/29
    - LB: 5/31
    - MS: 18/44
    - HY: 16/66
    - CD-1: 5/22
    - CD-2: 6/43
    - MF: 6/21
  - *P* = 0.002

**B**

- **i**
  - Proportion of Patients vs. Months from Start of Therapy
  - Events/N:
    - Low Risk: 48/162
    - High Risk: 62/94
  - *P* < 0.001

- **ii**
  - Deaths/N:
    - Low Risk: 32/162
    - High Risk: 40/94
  - *P* < 0.001
Multiple Myeloma Prognosis

- Modern Staging Systems
- Biochemical parameters
- Karyotype or cytogenetics
Multiple Myeloma Prognosis

- Biochemical markers
  - β2M, Albumin
  - Plasma cell labeling index (PCLI)
  - CRP, LDH
  - Plasmablastic morphology
Multiple Myeloma Prognosis

- Cytogenetics
  - P53 deletions (17)
  - t(4;14)
  - t(11;14)
  - del 13
  - 11q abnormalities
  - Hypodiploidy
  - 1q21 amplifications
Survival of Patients with MM
According to Cytogenetics (FISH)

Cytogenetic features:
Del 17p13, Del 13q14, *11q

Cumulative Proportion Surviving (%)

- n=37 (102.4 months)
- n=31 (29.6 months)
- n=21 (13.9 months)

p<0.001

Months survival
Multiple Myeloma

Plasma cell events:
- Translocations at 14q32 (50%)
- Deletion 13 (50%)
- Genomic instability

Microenvironment changes:
- ? infection
- ? inflammation

MGUS:
- N-Ras, K-Ras (30%)
- P16 methylation (40%)
- ? secondary translocations

Myeloma:
- Angiogenesis
- ↑ bone resorption (↑RANKL, ↓OPG, ↑MIP-1α)
- ↑IL-6, ↑VEGF
- ↓immune surveillance
First-Line Therapy and Issues in Transplantation
First-Line Therapy in MM: Introduction

- ASCT: standard of care for adults < 65 years of age with MM
  - Best response with initial therapy, followed by high-dose chemotherapy, then ASCT
- Patients > 65-70 years of age unlikely candidates for ASCT
- Optimal induction regimen not determined
  - Some regimens (ie, VAD) associated with low response and significant toxicity
- In recent years, many new active agents incorporated into treatment regimens for MM
  - Studies presented at ASH 2006 evaluated various agents in front-line, induction settings

IFM 2005-01 Trial: Study Design

Patients aged ≤ 65 years with newly diagnosed, symptomatic MM (N = 480)

Stratification by cytogenetics, β2-microglobulin level

- Four 21-day cycles; Stem cell collection between cycles 3, 4 after G-CSF

- VAD
  - DCEP (2 cycles)
    - Melphalan + ASCT*

- Bort/Dex
  - DCEP (2 cycles)
    - Melphalan + ASCT*

- Bort/Dex
  - Melphalan + ASCT*

*Second ASCT or reduced-intensity conditioning allogeneic transplantation if < VGPR.

Multiple Myeloma

IFM 2005-01 Trial: Objectives and Interim Results

- **Primary objective**: determine response (CR + nCR) with VAD vs bortezomib + dexamethasone
  - Preliminary analysis in 161 patients

- **Higher CR/nCR with bortezomib + dexamethasone vs VAD**

<table>
<thead>
<tr>
<th>Postinduction Response, %</th>
<th>Bortezomib + Dex (n = 79)</th>
<th>VAD (n = 82)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>CR</td>
<td>9</td>
<td>4</td>
</tr>
<tr>
<td>VGPR</td>
<td>23</td>
<td>17</td>
</tr>
<tr>
<td>CR + PR</td>
<td>82</td>
<td>67</td>
</tr>
</tbody>
</table>

IFM 2005-01 Trial: Objectives and Interim Results (cont’d)

- Bortezomib + dexamethasone also associated with higher CR/nCR in patients with del13q, β2-microglobulin > 3 mg/L
- Response also higher in patients receiving DCEP (n = 64) consolidation vs no DCEP (n = 78)
  - CR/nCR: 28% vs 11%
- Grade 3/4 adverse events
  - Bortezomib + dexamethasone vs VAD: 30% vs 36%
- Bortezomib + dexamethasone induction appears feasible
  - High postinduction CR/nCR may lessen probability for second ASCT

Tandem ASCT vs Delayed Second ASCT in MM

- Double ASCT established as option in first-line therapy of MM\(^1\)
  - Patients < 60 years of age with suboptimal response to first transplant

- Maintenance thalidomide after double ASCT improves survival\(^2\)

- Abdelkefi and colleagues\(^3\) investigated upfront tandem ASCT vs single ASCT + maintenance
  - Late second ASCT in maintenance group

Tandem ASCT vs Delayed Second ASCT in MM: Study Design

Patients with newly diagnosed, symptomatic MM < 60 years of age (N = 140)

First-line Thalidomide + Dexamethasone followed by PBSC collection
- First ASCT + Melphalan 200 mg/m² (n = 69)
- First ASCT + Melphalan 200 mg/m² (n = 71)

Second ASCT + Melphalan 200 mg/m² (n = 69)
- Maintenance Thalidomide 100 mg/d for 6 mos (n = 71)
- Second ASCT upon progression or relapse

Primary endpoint: OS
Secondary endpoint: PFS

Tandem ASCT vs Delayed Second ASCT in MM: Results

- 90% of patients in tandem ASCT group completed first transplant
  - 80% completed second transplant
- 86% of patients in delayed second ASCT group completed first transplant
  - 79% completed maintenance thalidomide

<table>
<thead>
<tr>
<th>CR/VGPR, %</th>
<th>Tandem ASCT (n = 69)</th>
<th>Delayed Second ASCT (n = 71)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After first ASCT</td>
<td>39</td>
<td>41</td>
<td>NS</td>
</tr>
<tr>
<td>After second ASCT (tandem) or maintenance (delayed second)</td>
<td>51</td>
<td>67</td>
<td>.04</td>
</tr>
</tbody>
</table>

Tandem ASCT vs Delayed Second ASCT in MM: Results (cont’d)

- No difference in OS between treatment arm
  - PFS trend favors maintenance group

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Tandem ASCT (n = 69)</th>
<th>Delayed Second ASCT (n = 71)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year OS</td>
<td>87</td>
<td>75</td>
<td>.19</td>
</tr>
<tr>
<td>3-year PFS</td>
<td>59</td>
<td>77</td>
<td>.08</td>
</tr>
</tbody>
</table>

- Delayed second ASCT possible global strategy for transplant-eligible MM patients

Bortezomib ± Dexamethasone as Frontline Induction

- Bortezomib ± dexamethasone effective induction regimen in MM
  - 88% response (median follow-up: 5.5 months)
- Long-term follow-up of phase II study (N = 49)
  - Primary endpoint: ORR, safety/tolerability

Bortezomib

1.3 mg/m²
Days 1, 4, 8, 11
3-week cycle
(N = 49)

If < PR after 2 cycles
or if < CR after 4 cycles

Bortezomib + Dexamethasone
40 mg PO
day of and day after bortezomib
(n = 36)

Up to 6 cycles

Bortezomib ± Dexamethasone as Frontline Induction: Results

- Most patients responded within 4 cycles
  - Median TTR: 1.9 months
- 36 patients received combination: 69% had improved response

<table>
<thead>
<tr>
<th>Response, %</th>
<th>Bortezomib Alone (2 Treatment Cycles)</th>
<th>Bortezomib + Dexamethasone (4 Treatment Cycles)</th>
<th>Bortezomib + Dexamethasone (6 Treatment Cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>49</td>
<td>78</td>
<td>88</td>
</tr>
<tr>
<td>PR</td>
<td>37</td>
<td>57</td>
<td>49</td>
</tr>
<tr>
<td>VGPR</td>
<td>2</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>CR/nCR</td>
<td>10</td>
<td>14</td>
<td>18</td>
</tr>
</tbody>
</table>

Bortezomib ± Dexamethasone as Frontline Induction: Results (cont’d)

- 51% of patients (n = 25) went on to HDT-SCT
- Estimated survival (median follow-up: 26.7 months)
  - 1 year: 92%
  - 2 year: 85%
  - Posttransplant 2-year survival: 91%
- No treatment-related mortality, DVT, PE
  - Grade 2-3 sensory neuropathy, 36%; fatigue, 20% (N = 49)
- Phase III study comparing bortezomib + dexamethasone with VAD as induction prior to HDT-SCT

Lenalidomide + Dexamethasone in Patients With Newly Diagnosed MM

- Phase II study investigated lenalidomide + dexamethasone in newly diagnosed MM (N = 34)
  - Lenalidomide: 25 mg PO, Days 1-21
  - Dexamethasone: 40 mg PO, Days 1-4, 9-12, 17-20
  - DVT prophylaxis: daily aspirin
- SCT allowed for responders
- Patients with PD taken off treatment
- Response and survival with combination assessed

### Lenalidomide + Dexamethasone in Patients With Newly Diagnosed MM

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>Lenalidomide + Dexamethasone (n = 21)</th>
<th>Lenalidomide + Dexamethasone With SCT (n = 13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (4 month)</td>
<td>90</td>
<td>100</td>
</tr>
<tr>
<td>CR/VGPR (4 month)</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>2-year OS</td>
<td>90</td>
<td>92</td>
</tr>
<tr>
<td>2-year PFS</td>
<td>59</td>
<td>83</td>
</tr>
</tbody>
</table>

- Aspirin effective as DVT prophylaxis; most events mild/moderate
- Adverse events
  - Grade 3/4 fatigue, neutropenia (21% for each)
  - 2 infection-related deaths

Lenalidomide + High- or Low-Dose Dexamethasone in MM*

**High-Dose Arm†**
- Lenalidomide 25 mg PO Days 1-21
- Dexamethasone 40 mg PO Days 1, 8, 15, 22
(n = 223)

**Low-Dose Arm†**
- Lenalidomide 25 mg PO Days 1-21
- Dexamethasone 40 mg PO Days 1, 8, 15, 22
(n = 222)

**Thalidomide + Dexamethasone x 4 cycles**

Primary endpoint: best response at 4 months (ITT)
Safety analysis performed

*DVT prophylaxis with aspirin initially recommended; required after September 2005.
†Treatment given for 4 cycles, every 28 days.

### Lenalidomide + High- or Low-Dose Dexamethasone: Results

- Increased nonhematologic toxicity in high-dose vs low-dose arm

<table>
<thead>
<tr>
<th>Grade 3/4 Adverse Events, %</th>
<th>High-Dose Arm (n = 223)</th>
<th>Low-Dose Arm (n = 222)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any nonhematologic</td>
<td>54.3</td>
<td>39.6</td>
<td>.002</td>
</tr>
<tr>
<td>Any toxicity (≥ grade 4)</td>
<td>19.3</td>
<td>11.3</td>
<td>.025</td>
</tr>
<tr>
<td>Death (grade 5)</td>
<td>4.9</td>
<td>0.5</td>
<td>.006</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>18.4</td>
<td>6.3</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Infection/pneumonia</td>
<td>16.1</td>
<td>9.0</td>
<td>.031</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11.7</td>
<td>4.1</td>
<td>.004</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>5.8</td>
<td>2.3</td>
<td>.090</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0.4</td>
<td>1.4</td>
<td>.372</td>
</tr>
</tbody>
</table>

Lenalidomide + High- or Low-Dose Dexamethasone: Results (cont’d)

- No differences in rate of hematologic toxicity between arms
  - Grade ≥ 3 neutropenia: ~ 3% in each arm
- Response assessment ongoing
- Conclusions
  - Lenalidomide + high-dose dexamethasone associated with greater toxicity
    - Increased thrombotic events
    - DVT prophylaxis recommended for all patients receiving lenalidomide + dexamethasone

Lenalidomide, Melphalan, and Prednisone in Untreated MM

- Thalidomide combined with MP: standard regimen for elderly MM patients

- Phase I/II study: lenalidomide + MP
  - 53 MM patients > 65 years of age
  - 4 dosing cohorts (prednisone dose: 2 mg/kg/d)

<table>
<thead>
<tr>
<th>Dosing Group (n)</th>
<th>Lenalidomide + Melphalan Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (6)</td>
<td>0.18 mg/kg + 5 mg/d</td>
</tr>
<tr>
<td>Cohort 2 (6)</td>
<td>0.25 mg/kg + 10 mg/d</td>
</tr>
<tr>
<td>Cohort 3 (6 + 15)</td>
<td>0.18 mg/kg + 10 mg/d</td>
</tr>
<tr>
<td>Cohort 4 (6 + 15)</td>
<td>0.25 mg/kg + 10 mg/d</td>
</tr>
</tbody>
</table>

Lenalidomide, Melphalan, and Prednisone in Untreated MM (cont’d)

- No DLT in cohorts 1 and 2
- DLTs observed in cohorts 3 and 4

<table>
<thead>
<tr>
<th>Dosing Group</th>
<th>DLT</th>
</tr>
</thead>
</table>
| Cohort 3     | Neutropenia  
|              | Grade 3 metabolic events |
| Cohort 4     | Grade 3 neutropenic fever, cutaneous events  
|              | Grade 4 thrombosis |

- MTD determined: 0.18 mg/kg + 10 mg/d (cohort 3)

Lenalidomide, Melphalan, and Prednisone in Untreated MM (cont’d)

- Response in cohort 3 and 4[1]
  - PR: 39%; VGPR: 44%

- Cohort 3 EFS compared favorably with thalidomide + MP historic control

- No difference in outcome for patients with unfavorable cytogenetics
  - Data suggest no benefit with higher melphalan doses in MM patients with abnormal cytogenetics[2]

- International, intergroup study will compare L-MP with MP

Multiple Myeloma

International, Intergroup MM-015 Trial: Study Design

Patients with newly diagnosed MM
(N = 450*)

- L-MP 9 courses
- L-MP 9 courses
- MP 9 courses

- Maintenance Lenalidomide
- No treatment
- No treatment

*Expected enrollment; study not yet recruiting.
Relapsed/Refractory Disease
Rationale for Bortezomib + PLD in Relapsed/Refractory MM

- Synergy between bortezomib, anthracyclines
  - May reduce resistance, augment anticancer effect[1]
- Phase I studies[2,3]
  - Bortezomib + PLD well tolerated
  - Associated with improved TTP
  - Enhanced response rate
- Phase III study assessed bortezomib + PLD vs bortezomib alone in relapsed/refractory MM

Bortezomib + PLD vs Bortezomib Alone in Relapsed/Refractory MM

Bortezomib-naive patients with relapsed/refractory MM; all patients received ≥ 1 prior therapy

(N = 646)

Bortezomib Monotherapy
Bortezomib 1.3 mg/m2,
Days 1, 4, 8, and 11,
every 21 days
(n = 322)

Continued treatment for 8 cycles or until CR, PD, or unacceptable toxicity

Bortezomib + PLD
Bortezomib 1.3 mg/m2,
Days 1, 4, 8, and 11
PLD at 30 mg/m2 given on Day 4 of every 21 days
(n = 324)

Primary endpoint: TTP
Secondary endpoints: ORR, OS, safety

Multiple Myeloma

Longer TTP With Bortezomib + PLD vs Bortezomib Alone


Bortezomib + PLD
Median TTP: 9.3 months

Bortezomib
Median TTP: 6.5 months

HR: 1.82 (95% CI: 1.41-2.35; P = 0.00004)
Bortezomib + PLD vs Bortezomib Alone: Clinical Outcomes

- Trend for improved OS with combination
- No difference in response
  - Longer duration of response with bortezomib + PLD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Bortezomib + PLD (n = 303)</th>
<th>Bortezomib (n = 310)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, %</td>
<td>91</td>
<td>88</td>
<td>.113</td>
</tr>
<tr>
<td>Total response (CR/PR/nCR), %</td>
<td>48</td>
<td>43</td>
<td>.251</td>
</tr>
<tr>
<td>CR + nCR, %</td>
<td>14</td>
<td>11</td>
<td>--</td>
</tr>
<tr>
<td>PR, %</td>
<td>34</td>
<td>32</td>
<td>--</td>
</tr>
<tr>
<td>Response duration, mos</td>
<td>10.2</td>
<td>7.0</td>
<td>.0008</td>
</tr>
</tbody>
</table>

Bortezomib + PLD vs Bortezomib Alone: Clinical Outcomes (cont’d)

- No additional benefit with PLD for del13q patients
- Manageable toxicity
- Most common serious adverse events in both arms
  - Thrombocytopenia: 22% with combination vs 15% for bortezomib
  - Neutropenia: 30% with combination vs 14% for bortezomib
- No increase in peripheral neuropathy with combination
- Cardiac events
  - 2% for combination vs 3% for monotherapy