A Phase III Study to Determine the Efficacy and Safety of Lenalidomide in Combination with Melphalan and Prednisone Followed by Lenalidomide (MPR-R) in Patients ≥ 65 Years with Newly Diagnosed Multiple Myeloma (NDMM)

Palumbo A et al.

Proc ASH 2009;Abstract 613.
Introduction

- Prolonged lenalidomide therapy has been shown to improve overall survival in patients with relapsed/refractory multiple myeloma (ASH 2008;Abstract 3702).
- Phase I/II study has demonstrated that MPR is an effective therapy with manageable toxicity for patients with NDMM (Clin Lymphoma Myeloma 2009;9:145).
- **Current study objective:**
  - Compare the efficacy and safety of MPR with or without lenalidomide maintenance with that of MP alone in patients with NDMM.

Phase III, Multicenter, Randomized Trial of MPR in Elderly Patients with NDMM

Newly diagnosed MM  
Age ≥ 65 years

Randomization 1:1:1

MPR-R (n = 152)  
MPR q28 days x 9
R q28 days  
Cycles 10+

MPR (n = 153)  
MPR q28 days x 9
Placebo  
Cycles 10+

MP (n = 154)  
MP Placebo: d1-28  
q28 days x 9
Placebo  
Cycles 10+

Primary trial comparison
• MPR-R vs MP

Secondary trial comparison
• MPR-R vs MPR

### Clinical Response

<table>
<thead>
<tr>
<th>Best overall response*</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>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response rate</td>
<td>77%</td>
<td>67%</td>
<td>48%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complete response</td>
<td>18%</td>
<td>13%</td>
<td>5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥Very good partial response</td>
<td>32%</td>
<td>33%</td>
<td>11%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Partial response</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</td>
<td>1.9 mo</td>
<td>1.9 mo</td>
<td>2.8 mo</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Measured by EBMT criteria*

Primary Analysis MPR-R vs MP

- **MPR-R**: Not reached
- **MP**: 13.0 months

Secondary Analysis MPR-R vs MPR

- **MPR-R**: Not reached
- **MPR**: 13.2 months

**PFS Time (months)**
- **HR 0.499 [0.330, 0.755]**
- **HR 0.530 [0.350, 0.802]**

With permission from Palumbo A et al. *Proc ASH* 2009; Abstract 613.
Conclusions

- Continuous lenalidomide is superior to regimens of limited duration in patients ≥65 years with NDMM.
- MPR-R resulted in an approximately 50% reduced risk of progression compared to MP.
- MPR-R had a tolerable safety profile (data not shown).
  - No Grade 3/4 peripheral neuropathy
  - Grade 4 neutropenia: 36%
- MPR-R is a potential new standard treatment option for elderly patients with NDMM.

A Prospective, Multicenter, Randomized Trial of Bortezomib/Melphalan/Prednisone (VMP) versus Bortezomib/Thalidomide/Prednisone (VTP) as Induction Therapy Followed by Maintenance Treatment with VT versus VP in Elderly Untreated Patients with Multiple Myeloma Older than 65 Years

Mateos MV et al.  
Proc ASH 2009;Abstract 3.
VMP is tolerable and effective in elderly patients.
- 89% ≥ PR; 32% CR (Blood 2006;108:2165)
- Median PFS = 25 months (Haematologica 2008;93:560)
- Overall survival = 50 months
- 17% GIII-IV peripheral neuropathy

Current study objectives:
- Compare the efficacy (ORR and CR rate) of VMP vs VTP when used as induction therapy
- Assess if maintenance therapy (VT vs VP) can improve response rates with a favorable toxicity profile
  - Increase CR by 15% (from 20-35% to 35-40%)

Induction with VMP versus VTP Followed by Maintenance with VT versus VP for Untreated MM in Patients > 65 Years

Bortezomib (V): Induction phase, 1.3 mg/m² twice weekly during a 6-week first cycle, then weekly during subsequent cycles; maintenance phase, 1.3 mg/m² twice weekly days 1, 4, 8 and 11 every 3 months

# Induction: Response and Toxicity Profile

## Response Rate (EBMT criteria)

<table>
<thead>
<tr>
<th>Response Rate (EBMT criteria)</th>
<th>VMP</th>
<th>VTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR</td>
<td>80%</td>
<td>81%</td>
</tr>
<tr>
<td>CR immunofixation (CRIF)-negative</td>
<td>20%</td>
<td>27%</td>
</tr>
<tr>
<td>CRIF-positive</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>PR</td>
<td>48%</td>
<td>46%</td>
</tr>
</tbody>
</table>

## Select Adverse Events (≥G3-4)

<table>
<thead>
<tr>
<th>Select Adverse Events (≥G3-4)</th>
<th>VMP</th>
<th>VTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
<td>7%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>Cardiologic events</td>
<td>0%</td>
<td>8%</td>
</tr>
</tbody>
</table>

### Maintenance: Response and Toxicity Profile

<table>
<thead>
<tr>
<th>Response Rate (EBMT criteria)</th>
<th>VT (n = 91)</th>
<th>VP (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>59%</td>
<td>55%</td>
</tr>
<tr>
<td><strong>CRIF-negative</strong></td>
<td><strong>44%</strong></td>
<td><strong>39%</strong></td>
</tr>
<tr>
<td>CRIF-positive</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>PR</td>
<td>39%</td>
<td>44%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Select Adverse Events (&gt;G3-4)</th>
<th>VT (n = 91)</th>
<th>VP (n = 87)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral neuropathy</td>
<td>5%</td>
<td>2%</td>
</tr>
<tr>
<td>Cardiologic events</td>
<td>2%</td>
<td>1%</td>
</tr>
</tbody>
</table>

Median PFS by Induction-Maintenance Treatment Cohorts (n = 178)

With permission from Mateos MV et al. *Proc ASH* 2009;Abstract 3.
Two-Year Overall Survival According to Cytogenetic Risk Profile (VMP or VTP Followed by VT or VP)

From 1st Randomization
- Standard risk: 77%
- High-risk: 74%

From 2nd Randomization
- Standard risk: 84%
- High-risk: 82%

With permission from Mateos MV et al. Proc ASH 2009;Abstract 3.
Survival According to MRD* After Induction Therapy (VMP or VTP Followed by VT or VP)

* Minimal residual disease (MRD) assessed by immunophenotyping in bone marrow

With permission from Mateos MV et al. *Proc ASH* 2009;Abstract 3.
Conclusions

- Weekly bortezomib dosing resulted in less peripheral neuropathy compared to rates seen with historical biweekly administration.
- Maintenance therapy increased the CR rate with an acceptable toxicity profile.
- Progression-free survival with induction VMP followed by maintenance VT is significantly superior to VPT-TP.
- The bortezomib-based combinations appeared to overcome the poor prognosis of high-risk cytogenetics.
- Alkylating agents remain effective drugs for elderly patients with previously untreated multiple myeloma.

A Phase III Study of Double Autotransplantation Incorporating Bortezomib-Thalidomide-Dexamethasone (VTD) or Thalidomide-Dexamethasone (TD) for Multiple Myeloma: Superior Clinical Outcomes with VTD Compared to TD

Cavo M et al.

Proc ASH 2009;Abstract 351.
Newly diagnosed multiple myeloma; ≤65 years old

Induction (n = 241)
VTD, three 21-d cycles

Consolidation
VTD, two 35-d cycles

Induction (n = 239)
TD, three 21-d cycles

Melphalan 200 mg/m²
Double autologous stem cell transplantation (ASCT)

Consolidation
TD, two 35-d cycles

Maintenance with dexamethasone

## Response to Induction Therapy

**Intent-to-Treat Analysis**

<table>
<thead>
<tr>
<th></th>
<th>VTD (n = 241)</th>
<th>TD (n = 239)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>57%</td>
<td>31%</td>
<td>0.0001</td>
</tr>
<tr>
<td>CR + nCR</td>
<td>70%</td>
<td>51%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>88%</td>
<td>72%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥PR</td>
<td>95%</td>
<td>89%</td>
<td>0.01</td>
</tr>
</tbody>
</table>

CR, complete response; nCR, near complete response; VGPR, very good partial response; PR, partial response

*Responses were centrally reassessed and defined by EBMT criteria.*

Progression-Free Survival (PFS)

With permission from Cavo M et al. Proc ASH 2009;Abstract 351.
## PFS in Patients with High-Risk Cytogenetic Profiles*

<table>
<thead>
<tr>
<th></th>
<th>VTD</th>
<th></th>
<th>TD</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Events</td>
<td>22.7%</td>
<td>12.1%</td>
<td>36%</td>
<td>20.3%</td>
</tr>
<tr>
<td>PFS at 24 mo</td>
<td>73%</td>
<td>83%</td>
<td>53%</td>
<td>77%</td>
</tr>
<tr>
<td>PFS at 30 mo</td>
<td>60%</td>
<td>67%</td>
<td>42%</td>
<td>59%</td>
</tr>
<tr>
<td>p-value</td>
<td>0.16</td>
<td></td>
<td>0.02</td>
<td></td>
</tr>
</tbody>
</table>

*Patients with t(4;14) ± del(17p)*

Conclusions

- VTD plus double ASCT provided superior short- and long-term outcomes to TD plus double ASCT.
  - The rates of CR + nCR/≥VGPR were significantly improved with VTD vs TD.
  - PFS was significantly improved with VTD vs TD.
- The toxicity of VTD as an induction and consolidation therapy was relatively low (data not shown).
- The VTD regimen may be considered as a new standard treatment option for younger ASCT-eligible patients with multiple myeloma.

Lenalidomide Plus High-Dose Dexamethasone versus Lenalidomide Plus Low-Dose Dexamethasone as Initial Therapy for Newly Diagnosed Multiple Myeloma: An Open-Label Randomised Controlled Trial

Rajkumar SV et al.
In newly diagnosed multiple myeloma (MM), the response rate with lenalidomide (R) plus high-dose dexamethasone (D) is 91% (Blood 2005;106:4050).

**Current study objective:**
- Assess if R plus low-dose dexamethasone (Rd) can preserve the efficacy of RD but with reduced toxicity
- Primary study endpoint: Overall response rate (ORR) in first 4 cycles of treatment
- Survival analysis of patients who received transplant after 4 cycles vs patients who continued Rd beyond 4 cycles

Open-Label Trial of RD versus Rd in MM

**Accrual: 445**

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>R 25 mg/d + D 40 mg/d d1-4, 9-12, 17-20 q 28 days* (n = 223) x 4 cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurable, untreated symptomatic MM or bone marrow plasmacytosis or plasmacytoma</td>
<td>R 25 mg/d + d 40 mg/d d1, 8, 15, 22 q 28 days* (n = 222) x 4 cycles</td>
</tr>
<tr>
<td>Hgb &gt; 70g/L, platelet ≥ 75x10⁹/L, neutrophil &gt; 1x10⁹/L</td>
<td></td>
</tr>
</tbody>
</table>

*After 4 cycles, patients may proceed to stem cell transplant (SCT); patients with progression or no response may receive thalidomide + dexamethasone.*

## Select Adverse Events (AE) in First Four Months

<table>
<thead>
<tr>
<th>AE</th>
<th>RD (n = 223)</th>
<th>Rd (n = 220)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;Grade 3</td>
<td>52%</td>
<td>35%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Deaths</td>
<td>5%</td>
<td>0.4%</td>
<td>0.003</td>
</tr>
<tr>
<td>Deep vein thrombosis or pulmonary embolism</td>
<td>26%</td>
<td>12%</td>
<td>0.0003</td>
</tr>
<tr>
<td>Infections or pneumonia</td>
<td>16%</td>
<td>9%</td>
<td>0.04</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15%</td>
<td>9%</td>
<td>0.08</td>
</tr>
</tbody>
</table>

## Primary Study Results:
### Overall Response and Survival

<table>
<thead>
<tr>
<th></th>
<th>RD (n = 214)</th>
<th>Rd (n = 208)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR (complete plus partial) at 4 cycles</td>
<td>79%</td>
<td>68%</td>
<td>0.008</td>
</tr>
<tr>
<td>1-year overall survival (OS)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years old</td>
<td>87%</td>
<td>96%</td>
<td>0.0002</td>
</tr>
<tr>
<td>≥ 65 years old</td>
<td>91%</td>
<td>98%</td>
<td></td>
</tr>
<tr>
<td>2-year OS*</td>
<td>83%</td>
<td>94%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>87%</td>
<td></td>
</tr>
<tr>
<td>Successful stem cell mobilization (n = 167)</td>
<td></td>
<td>163 (98%)</td>
<td></td>
</tr>
</tbody>
</table>

*Not a protocol-specified endpoint; study stopped at 12.5 months follow-up because of higher OS with Rd. Patients on RD crossed over to Rd.*

### Survival Outcome with Post-Induction SCT, No SCT or Continued Primary Therapy*

<table>
<thead>
<tr>
<th>Three-year overall survival</th>
<th>RD</th>
<th>Rd</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No SCT after 4 cycles of primary therapy (n = 54, 39)</td>
<td>55%</td>
<td>55%</td>
<td>0.631</td>
</tr>
<tr>
<td>SCT after 4 cycles of primary therapy (n = 50, 40)</td>
<td>92%</td>
<td>92%</td>
<td>0.528</td>
</tr>
<tr>
<td>Primary therapy beyond 4 cycles (n = 108, 140)</td>
<td>79%</td>
<td>79%</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

*At four months, 183 of 431 patients alive discontinued from study +/- subsequent SCT and 248 continued primary therapy in the absence of SCT.

Conclusions

- Primary analysis of induction RD vs Rd
  - ORR RD vs Rd: 79% vs 69% (absolute difference within prespecified margin of noninferiority)
  - Lower toxicity and treatment-related mortality with Rd (0.5% vs 5.0%)
  - Greater 2-year OS with Rd (87% vs 75%)

- Impact of SCT and continued primary therapy on outcome
  - Lenalidomide plus dexamethasone may be a good option for pretransplant induction therapy (3-year OS: 92%)
  - Continued primary therapy (>4 cycles) with Rd seems effective and tolerable as a front-line regimen for myeloma, particularly in the elderly

Lenalidomide Plus Dexamethasone versus Thalidomide Plus Dexamethasone in Newly Diagnosed Multiple Myeloma: A Comparative Analysis of 411 Patients

Gay F et al.  
Introduction

- Lenalidomide and thalidomide are each active in combination with dexamethasone for the treatment of multiple myeloma (MM).
  - Lenalidomide is more potent in preclinical assays than thalidomide, but causes more hematologic side effects (Blood 2002;100:3063; NEJM 2007;357:2123).
- No randomized trial of thalidomide/dexamethasone (Thal/Dex) versus lenalidomide/dexamethasone (Len/Dex) has been reported or is ongoing/planned.

- **Current study objective:**
  - Compare the efficacy and toxicity of Len/Dex or Thal/Dex as initial therapy for MM using a retrospective analysis.

Methods

- Case-control retrospective study conducted using data from 411 consecutive patients from the Mayo Clinic with newly diagnosed MM.
  - Patients treated with Thal/Dex: 183 (110 received SCT)
  - Patients treated with Len/Dex: 228 (111 received SCT)
- All patients were administered either:
  - High-dose dexamethasone (40 mg orally, twice weekly)
  - Low-dose dexamethasone (40 mg orally, weekly)
- Risk stratification of patients:
  - High risk: del 17p, t(4;14), t(14;16) by FISH or loss of chromosome 13 by metaphase cytogenetics
  - Standard risk: Patients without any of the above

**Efficacy Outcomes**

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>Thal/Dex (n = 183)</th>
<th>Len/Dex (n = 228)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>3.3%</td>
<td>13.6%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥VGPR</td>
<td>12.0%</td>
<td>34.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥PR</td>
<td>61.2%</td>
<td>80.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median time to progression</td>
<td>17.2 mo</td>
<td>27.4 mo</td>
<td>0.019</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>17.1 mo</td>
<td>26.7 mo</td>
<td>0.036</td>
</tr>
</tbody>
</table>

*CR = complete response; VGPR = very good partial response; PR = partial response*

Median Overall Survival with Len/Dex versus Thal/Dex

Regardless of dexamethasone dose

- **Len/dex**
- **Thal/dex**

**Median NR**
- Median = 57.2 m

**HR 0.60**
- *p* = 0.018

**High-dose dexamethasone only**

- **Len/dex**
- **Thal/dex**

**Median NR**
- Median = 50.0 m

**HR 0.35**
- *p* = 0.002

*NR = not reached*

With permission from Blood, through Copyright Clearance Center Inc.
Overall Survival with Respect To Transplantation Status

Patients with transplant

- Len/dex
- Thal/dex

Median = 80.6 m

Median NR

HR 0.54
p = 0.075

Patients without transplant

Median = 42.2 m

Median NR

HR 0.53
p = 0.023

With permission from Blood, through Copyright Clearance Center Inc.
## Grade 3 and 4 Adverse Events

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Thal/Dex (n = 183)</th>
<th>Len/Dex (n = 228)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>0%</td>
<td>4.4%</td>
<td>0.003</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0%</td>
<td>4.8%</td>
<td>0.002</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.6%</td>
<td>14.0%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>10.4%</td>
<td>0.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Constipation</td>
<td>4.9%</td>
<td>0%</td>
<td>0.001</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0%</td>
<td>3.5%</td>
<td>0.01</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>15.3%</td>
<td>9.2%</td>
<td>0.058</td>
</tr>
<tr>
<td>Infections</td>
<td>8.2%</td>
<td>13.1%</td>
<td>0.109</td>
</tr>
</tbody>
</table>

Summary

- Len/Dex appears superior to Thal/Dex in all efficacy outcomes including overall survival.
- Outcomes remain superior with Len/Dex after adjusting for the dose of dexamethasone and for transplantation status.
- Differences in the adverse events with the two regimens are consistent with what has been previously reported.
  - Hematological side effects were more common with lenalidomide; peripheral neuropathy was more common with thalidomide.
- Randomized trials are required for confirmation of these results.

High Complete and Very Good Partial Response Rates with Bortezomib-Dexamethasone as Induction Prior to ASCT in Newly Diagnosed Patients with High-Risk Myeloma: Results of the IFM2005-01 Phase 3 Trial

Harousseau J-L et al.  
*Proc ASH* 2009;Abstract 353.
Newly diagnosed multiple myeloma; ≤ 65 years old

Randomization 1:1:1:1

VAD = vincristine/doxorubicin/dexamethasone
VD = bortezomib/dexamethasone

Induction

VAD x 4
VAD x 4

Consolidation

VD x 4
VD x 4

Transplant 1

DCEP x 2
DCEP x 2

Melphalan + ASCT
Melphalan + ASCT

2nd ASCT or allo-RIC-SCT if >VGPR

### Clinical Response (≥VGPR)

<table>
<thead>
<tr>
<th></th>
<th>VAD (n = 218)</th>
<th>VD (n = 223)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>After induction</td>
<td>16%</td>
<td>39%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>After ASCT 1</td>
<td>37%</td>
<td>54%</td>
<td>0.0003</td>
</tr>
<tr>
<td>After ASCT 2</td>
<td>47%</td>
<td>68%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

A higher response rate was achieved in patients on the VD arm receiving induction therapy despite:

- A slightly higher proportion of patients with poor-risk cytogenetics
- A smaller proportion of patients having received a second ASCT

### Progression-Free Survival (PFS)
**Median Follow-Up 32 Months**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>VAD</th>
<th>VD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 242, 240)</td>
<td>30 mo</td>
<td>36 mo</td>
<td>0.057</td>
</tr>
<tr>
<td>Patients with ISS Stage II-III (n = 136, 133)</td>
<td>23 mo</td>
<td>33 mo</td>
<td>0.006</td>
</tr>
<tr>
<td>Patients with poor cytogenetics* (n = 29, 40)</td>
<td>24 mo</td>
<td>33.5 mo</td>
<td>0.113</td>
</tr>
</tbody>
</table>

*Patients with poor cytogenetics were defined as having t(4;14) and/or del(17p).*

# Impact of Post-Induction VGPR or Better on PFS

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>≥VGPR</th>
<th>&lt;VGPR</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients (n = 117, 324)</td>
<td>41 mo</td>
<td>30 mo</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with ISS Stage II-III (n = 65, 204)</td>
<td>Not reached</td>
<td>23 mo</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Patients with poor cytogenetics* (n = 21, 48)</td>
<td>37 mo</td>
<td>24 mo</td>
<td>0.0036</td>
</tr>
</tbody>
</table>

*Patients with poor cytogenetics were defined as having t(4;14) ± del(17p).*

Conclusions

- Pre-ASCT induction therapy with VD versus VAD resulted in:
  - Longer PFS, irrespective of cytogenetic risk profile
  - Higher rates of complete response and VGPR
- Achieving at least VGPR after induction therapy appears to be a major prognostic factor for improved PFS, especially in patients with high-risk multiple myeloma.

Reversibility of Symptomatic Peripheral Neuropathy with Bortezomib in the Phase III APEX Trial in Relapsed Multiple Myeloma: Impact of a Dose-Modification Guideline

Richardson PG et al.  
APEX Trial Comparing Bortezomib with Dexamethasone

Eligibility (n = 669)
- Relapsed multiple myeloma
- 1-3 prior therapies
- ≥Grade 2 peripheral neuropathy excluded

Bortezomib (n = 333)
Dexamethasone (n = 336)

Bortezomib 1.3 mg/m² on d1, 4, 8 and 11 for eight 21-d cycles, and then on d1, 8, 15 and 22 for three 35-d maintenance cycles

Dose-Modification Guideline in APEX Trial for Bortezomib-Associated Neuropathy

- Grade 1 without pain
  - No action
- Grade 1 with pain or Grade 2
  - Reduce bortezomib dosage to 1.0 mg/m$^2$
- Grade 2 with pain or Grade 3
  - Withhold bortezomib until toxicity resolves, then reinitiate at a dose of 0.7 mg/m$^2$ once weekly
- Grade 4
  - Discontinue bortezomib

**Neuropathy in APEX Trial**

<table>
<thead>
<tr>
<th></th>
<th>All patients with ≥G 2 neuropathy (n = 91)</th>
<th>≥G 2 neuropathy; dose modification (n = 72)</th>
<th>≥G 2 neuropathy; no dose modification (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement/resolution of neuropathy</td>
<td>58 (64%)</td>
<td>49 (68%)</td>
<td>9 (47%)</td>
</tr>
<tr>
<td>No improvement/resolution of neuropathy</td>
<td>33 (36%)</td>
<td>23 (32%)</td>
<td>10 (53%)</td>
</tr>
</tbody>
</table>

*Mostly sensory neuropathy (98%) observed; incidence and severity was independent of age, prior thalidomide or vincristine therapy, and diabetes history.*

91/331 (27%) patients developed ≥ G2 neuropathy.
- 72/91 had dose modifications per guidelines.
- 19/91 had no dose modifications (protocol violations).
49/72 (68%) patients who had dose modifications experienced improvement or resolution of their neuropathy.
9/19 (47%) patients who did not have dose modifications experienced resolution of their neuropathy.

## Effect of Dose Modification for Neuropathy on Outcome

<table>
<thead>
<tr>
<th>Evaluable patients</th>
<th>RR (CR + PR)</th>
<th>CR</th>
<th>Median TTP (mo)</th>
<th>Median OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All (N = 315)</td>
<td>43%</td>
<td>9%</td>
<td>6.2</td>
<td>29.7</td>
</tr>
<tr>
<td>No neuropathy (n = 196)</td>
<td>38%</td>
<td>6%</td>
<td>5.6</td>
<td>23.2</td>
</tr>
<tr>
<td>G ≥ 2 neuropathy (n = 86)</td>
<td>50%</td>
<td>14%</td>
<td>6.3</td>
<td>Not estimable</td>
</tr>
<tr>
<td>Dose modified (n = 68)</td>
<td>59%</td>
<td>16%</td>
<td>6.9</td>
<td>Not estimable</td>
</tr>
<tr>
<td>No dose modification (n = 18)</td>
<td>17%</td>
<td>6%</td>
<td>2.9</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Summary and Conclusions

- Bortezomib-associated neuropathy is predominantly sensory and is reversible in the majority of patients.
- Bortezomib-associated neuropathy is unaffected by age, prior therapies with neurotoxic agents or history of diabetes and thus may be mechanistically distinct.
- Bortezomib dose modification may ameliorate bortezomib-associated neuropathy.
- Bortezomib dose modification for peripheral neuropathy does not appear to adversely affect efficacy or outcome.

Bortezomib Plus Melphalan and Prednisone Compared with Melphalan and Prednisone in Previously Untreated Multiple Myeloma: Updated Follow-Up and Impact of Subsequent Therapy in the Phase III VISTA Trial

Mateos M-V et al.

Introduction

- Overall survival has been shown to be improved with VMP compared with MP in previously untreated patients with multiple myeloma (MM) ineligible for transplant (*NEJM* 2008;359:906).
- Rescue therapies may affect overall survival in longer follow-up.
- **Current study objective:**
  - Examine updated survival analysis of bortezomib (V) with melphalan/prednisone (MP) versus MP alone in patients with untreated MM ineligible for high-dose therapy

VISTA Trial Schema

Eligibility (n = 682)
Previously untreated multiple myeloma ineligible for high-dose therapy

VMP (n = 344)
Bortezomib* + MP x 9 cycles

MP (n = 338)
MP x 9 cycles

* Bortezomib administered on standard twice-weekly schedule during cycles 1-4. Bortezomib administered on weekly schedule during cycles 5-9.

Subsequent Therapy

- 52% of patients on VMP and 69% on MP have received subsequent therapy.
- Among patients who received subsequent therapy, 24% on VMP arm and 50% on MP arm received bortezomib.
- Median time to next treatment (TTNT) and treatment free interval (TFI) were significantly longer with VMP.
  - 43% and 18% of VMP and MP patients, respectively, had TFI $\geq$ 2 years

3 yr OS: 68.5% with VMP; 54% with MP
VMP: Median OS not reached (109 deaths)
MP: Median OS 43.1 months (148 deaths)
HR 0.653 (95% CI: 0.508, 0.840), \( p = 0.0008 \)

Subset Analyses

- Among those patients who received subsequent therapy, the survival benefit with VMP over MP was retained.
- A trend of improved survival from start of subsequent therapy was observed (HR 0.815, \( p = 0.21 \)) in all patients who received subsequent therapy.
- In the VMP subgroup, OS was better among patients aged < 75 vs \( \geq 75 \) years (HR 1.664, \( p = 0.011 \)).
- No statistically significant difference in overall survival among patients treated with VMP was apparent when results were analyzed by baseline renal function or cytogenetic risk profile.

Conclusions

- Updated analysis confirms that VMP results in significantly improved survival compared to MP.
- Survival benefit is seen both overall and also in patients who had received subsequent therapy.
- VMP results in significantly longer TTNT and TFI.
- Salvage therapies are similarly effective following VMP and MP, suggesting that bortezomib use as initial therapy does not induce more resistant relapse.

Influence of Cytogenetics in Patients with Relapsed or Refractory Multiple Myeloma Treated with Lenalidomide Plus Dexamethasone: Adverse Effect of Deletion 17p13

Reece D et al.  
Introduction

- Poor prognosis exists for patients with multiple myeloma (MM) carrying t(4;14) or del(17p13) (*Blood* 2007;109:3489).
- Limited data exist on the role of lenalidomide in patients with “high-risk” cytogenetic abnormalities.
- **Current study objective:**
  - Determine effects of del(13q), t(4;14) and del(17p13) in patients treated with lenalidomide (R) and dexamethasone (D) for relapsed or refractory MM.

Methods

- Post hoc subanalysis was performed on 130 patients from three Canadian centers in the Expanded Access Program database (MM-016 study), with available FISH studies for del(13q), t(4;14) and del(17p13).
  - Median follow-up at 19.7 months
  - Primary outcome: Time to progression (TTP)
  - Secondary outcome: Overall survival (OS)
- Matched pair analysis was performed for the subgroup of patients with t(4;14) to address the inherent imbalance in clinical characteristics and short period of follow-up.

### Effect of Cytogenetics on Treatment Efficacy

<table>
<thead>
<tr>
<th></th>
<th>All patients (n = 130)</th>
<th>del(13q) (n = 54)</th>
<th>del(17p13) (n = 12)</th>
<th>t(4;14) (n = 28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response (&gt;minimal)</td>
<td>83.1%</td>
<td>77.8% (p = 0.007)</td>
<td>58.3% (p &lt; 0.001)</td>
<td>78.5% (p = 0.06)</td>
</tr>
<tr>
<td>Median TTP (mo)</td>
<td>7.1</td>
<td>5.9 (HR = 1.42; p = 0.09)</td>
<td>2.22 (HR = 2.82; p &lt; 0.001)</td>
<td>8.0 (HR = 1.44; p = 0.137)</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>22.7</td>
<td>14.7 (HR = 1.43; p = 0.152)</td>
<td>4.67 (HR = 3.23; p &lt; 0.001)</td>
<td>23.7 (HR = 1.04; p = 0.910)</td>
</tr>
</tbody>
</table>

*Hazard ratio (HR) and p-values for abnormality versus none (matched)*

The combination of lenalidomide and dexamethasone is an effective therapy for relapsed/refractory MM.

- Patients with either del(13q) or t(4;14) experienced median TTP and OS comparable to those without the corresponding cytogenetic abnormality.

- Patients with del(17p13), however, had significantly worse outcomes (TTP = 2.2 mo; OS = 4.67 mo).

- Lenalidomide appears to be ineffective in patients with del(17p13), and novel therapeutic approaches are needed for this subgroup.

Safety and Efficacy of Single-Agent Lenalidomide in Patients with Relapsed and Refractory Multiple Myeloma

Richardson P et al.

Introduction

- Lenalidomide has demonstrated clinical benefit in the treatment of relapsed or refractory multiple myeloma (MM) as monotherapy and in combination with dexamethasone (Blood 2002;100:3063; Blood 2006;108:3458).

- Significant adverse events resulted from the addition of dexamethasone to lenalidomide, including:
  - Deep vein thrombosis, infections and hyperglycemia

- **Current study objective:**
  - Efficacy and safety of single-agent lenalidomide, 30 mg once daily, as therapy for relapsed and refractory MM
  - Primary endpoint: At least partial response

Eligibility (n = 222)

- Relapsed and refractory MM
- Disease progression during or within 60 days of salvage regimen
- ≥2 prior treatment regimens, not including SCT

Lenalidomide, 30 mg once daily, d1-21 q 28 days until progression or unacceptable toxicity

# Clinical Response (Intent to Treat)

<table>
<thead>
<tr>
<th>Category</th>
<th>&lt;2 Prior Treatment Regimens (n = 73)</th>
<th>&gt;3 Prior Treatment Regimens (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR + PR</td>
<td>26%</td>
<td>26%</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>25%</td>
<td>23%</td>
</tr>
<tr>
<td>Minimal response (MR)</td>
<td>19%</td>
<td>17%</td>
</tr>
<tr>
<td>Stable disease</td>
<td>48%</td>
<td>48%</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

### Efficacy (Intent to Treat)

<table>
<thead>
<tr>
<th></th>
<th>Overall (n = 222)</th>
<th>CR + PR (n = 58)</th>
<th>CR + PR + MR (n = 98)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median PFS (mo)</td>
<td>4.9*</td>
<td>14.5</td>
<td>10.4</td>
</tr>
<tr>
<td>Median TTP (mo)</td>
<td>5.2†</td>
<td>14.5</td>
<td>10.4</td>
</tr>
<tr>
<td>Median OS (mo)</td>
<td>23.2‡</td>
<td>33.9</td>
<td>28.0</td>
</tr>
<tr>
<td>1-year survival rate</td>
<td>67%</td>
<td>73%</td>
<td>79%</td>
</tr>
</tbody>
</table>

* 73% of patients had disease progression or died.
† 69% of patients had disease progression.
‡ 60% of patients died.

Lenalidomide monotherapy at 30 mg/day is an active therapy with long-term benefit in patients with relapsed and refractory MM.

Similar response was obtained in patients who received prior thalidomide, bortezomib or after prior stem cell transplant, respectively.

- ORR = 41%, 46% and 39%, respectively (data not shown)

Toxicity was acceptable. Common Grade 3/4 adverse events were neutropenia (60%), febrile neutropenia (4%), thrombocytopenia (39%) and anemia (20%).

These data support the treatment option of single-agent lenalidomide.

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010

Summary of the Guidelines Update

### Treatments Placed in New Categories:
#### Primary Induction Therapy for Transplant Candidates

<table>
<thead>
<tr>
<th>Regimen (supporting trial)</th>
<th>Current category*</th>
<th>Previous category*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib/dexamethasone (<em>Harousseau et al. ASCO 2008</em>)</td>
<td>1</td>
<td>2B</td>
</tr>
<tr>
<td>Bortezomib/doxorubicin/dexamethasone (<em>Sonneveld et al. ASH 2008</em>)</td>
<td>1</td>
<td>2B</td>
</tr>
<tr>
<td>Bortezomib/thalidomide/dexamethasone (<em>Cavo et al. ASH 2008</em>)</td>
<td>1</td>
<td>2B</td>
</tr>
<tr>
<td>Lenalidomide/dexamethasone (<em>Zonder et al. ASH 2007</em>)</td>
<td>1</td>
<td>2B</td>
</tr>
</tbody>
</table>

*Category 1 = uniform consensus, high evidence quality; 2B = nonuniform consensus, lower evidence quality*
### Treatments Placed in New Categories:

### Primary Induction Therapy for Transplant Candidates (continued)

<table>
<thead>
<tr>
<th>Regimen (supporting trial)</th>
<th>Current category*</th>
<th>Previous category*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone (Rajkumar et al. JCO 2006)</td>
<td>2B</td>
<td>2A</td>
</tr>
<tr>
<td>Thalidomide/dexamethasone (Rajkumar et al. JCO 2006)</td>
<td>2B</td>
<td>2A</td>
</tr>
<tr>
<td>Liposomal doxorubicin/vincristine/dexamethasone (Rifkin et al. Cancer 2006)</td>
<td>2B</td>
<td>2A</td>
</tr>
</tbody>
</table>

*Category 2A = uniform consensus, lower evidence quality; 2B = nonuniform consensus, lower evidence quality*
<table>
<thead>
<tr>
<th>Regimen (supporting trial)</th>
<th>Current category</th>
<th>Previous category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melphalan/prednisone/thalidomide (MPT) ((Multiple randomized trials compared MPT to MP))</td>
<td>1</td>
<td>2A</td>
</tr>
<tr>
<td>Melphalan/prednisone/bortezomib (MPB) (San Miguel et al. NEJM 2008 VISTA trial)</td>
<td>1</td>
<td>2A</td>
</tr>
<tr>
<td>Lenalidomide/low-dose dexamethasone (Rd) (Rajkumar et al. Lancet 2010)</td>
<td>1</td>
<td>2B</td>
</tr>
<tr>
<td>Melphalan/prednisone (MP) (Multiple trials compared MP to either MPT or MPB)</td>
<td>2A</td>
<td>1</td>
</tr>
</tbody>
</table>

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.
Treatments Placed in New Categories:
Primary Induction Therapy for Nontransplant Candidates (continued)

<table>
<thead>
<tr>
<th>Regimen (supporting trial)</th>
<th>Current category</th>
<th>Previous category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalidomide/dexamethasone <em>(Rajkumar et al. JCO 2006)</em></td>
<td>2B</td>
<td>2A</td>
</tr>
<tr>
<td>Dexamethasone <em>(Rajkumar et al. JCO 2006)</em></td>
<td>2B</td>
<td>2A</td>
</tr>
<tr>
<td>Vincristine/doxorubicin/dexamethasone *(VAD)*¹</td>
<td>2B</td>
<td>2A</td>
</tr>
</tbody>
</table>

Category 2A: Uniform consensus, lower evidence quality

¹ VAD is now category 2B; no specific reference has been cited for the change.

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.
Maintenance Therapy

- Three independent trials with lenalidomide maintenance have recently reported improvement in disease progression.
  - CALGB-100104: 58% reduction in disease progression (ASH 2009;Abstract 3416.)
  - IFM 2005-02: Improved PFS and sCR/CR (ASH 2009;Abstract 529.)
  - MM-015: 75% reduction in disease progression (ASH 2009;Abstract 613.)
- Lenalidomide maintenance added (Category 2A).
- Thalidomide alone or with prednisone (Category 1 and 2B respectively).

NCCN Practice Guidelines in Oncology — Multiple Myeloma v.3.2010.
International Myeloma Working Group Guidelines for the Management of Multiple Myeloma Patients Ineligible for Standard High-Dose Chemotherapy with Autologous Stem Cell Transplantation

Palumbo A et al.

Introduction

- Prior guidelines were published in 2005.
- Current update conducted by a panel of clinical and statistical experts who reviewed articles from 2004-2008 and abstracts from 2006-2008.
- No changes to guidances on diagnosis, indications to start therapy or monitoring of myeloma.
- Changes in specific areas of multiple myeloma are summarized.

Cytogenetics and/or FISH should be performed in all patients at diagnosis and at the time of relapse.

IMWG criteria should be used to assess response (Leukemia 2006;20:1467).
  - Response criteria of stringent CR and VGPR have been added.
  - Serum free light chain assay is used to determine stringent CR.

Front-Line Therapy

- IMWG considers MPT and VMP as standard treatment for initial induction therapy in patients ineligible for transplantation and Rd for patients who wish to postpone transplantation.
- Major trials reviewed:
  - RD vs Rd (Rajkumar et al. ASCO 2008)
  - MPT vs MP (Palumbo et al. Blood 2008)
  - MPT vs MP (Facon et al. Lancet 2007)
  - MPT vs MP (Hulin et al. ASH 2007)
  - VMP vs MP (San Miguel et al. NEJM 2008)

Therapy for Relapsed Myeloma

- In the relapsed setting, IMWG recommends:
  - Bortezomib with or without dexamethasone or in combination with liposomal doxorubicin
  - Lenalidomide in combination with dexamethasone
- Choice of salvage therapy depends on earlier exposure to a particular drug and concomitant comorbidities.

Supportive Care In Myeloma

- Bisphosphonates are recommended in patients with osteolytic lesions.
  - Comprehensive dental examination should be done before starting bisphosphonate therapy.
  - Continue bisphosphonates for two years. However, one year is sufficient for patients in CR/nCR.
- Vertebral fracture:
  - Balloon kyphoplasty has shown a marked reduction in back disability and pain in a randomized Phase III trial and should be considered as a standard approach if appropriate (*Clinical Lymphoma Myeloma* 2009;Abstract 204).

International Myeloma Working Group Molecular Classification of Multiple Myeloma: Spotlight Review

Fonseca R et al.

Multiple myeloma (MM) is a clonal B-cell disorder with heterogeneity in outcome among different patients. Several subtypes have been identified at the genetic and molecular level. Genetic and molecular subtypes are associated with unique clinicopathologic features and have prognostic implications.

### Genetic Classification

<table>
<thead>
<tr>
<th>Hyperdiploid (h) MM</th>
<th>Nonhyperdiploid (nh) MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>● 45% of all MM</td>
<td>● 40% of all MM</td>
</tr>
<tr>
<td>● Numerous chromosome trisomies</td>
<td>● Highly enriched for IgH translocations</td>
</tr>
<tr>
<td>● More favorable outcome</td>
<td>● Overall less favorable outcome</td>
</tr>
<tr>
<td>● Slightly more common in males</td>
<td>● Examples include t(11;14), t(4;14), t(14;16), del(17p)</td>
</tr>
<tr>
<td>● More common in elderly</td>
<td></td>
</tr>
</tbody>
</table>

*Remaining 15% of MM is either with overlap or unclassified in the two major genetic categories.*

Molecular Subtypes of MM

- **t(11;14)**
  - 15% of all MM
  - Hyposecretory disease
  - Associated with IgM myeloma
  - Prognosis neutral

- **t(14;16)**
  - 5-7% of all MM
  - High prevalence of concomitant chromosome 13 deletion
  - Higher frequency of IgA isotype
  - Aggressive clinical course

Molecular Subtypes of MM

- **del(17p13)**
  - Most aggressive disease
  - Higher prevalence of extramedullary disease
  - Short duration of response after transplant

- **t(4;14)**
  - 15% of all MM
  - High prevalence of concomitant chromosome 13 abnormalities
  - Poor outcome
  - Bortezomib may overcome the poor prognosis of this subgroup

Molecular Subtypes of MM

- Chromosome 13 abnormalities
  - Present in 50% of MM and 90% of t(4;14) and t(14;16)
  - Significance is considered as of surrogate association with nh MM
- Chromosome 1 abnormalities
  - Emerging marker
  - Negative prognostic association in some reports

University of Arkansas and IFM (Intergroupe Francophone du Myélome) have identified gene signatures that can provide prognostic discrimination.

There is minimal overlap between these two signatures, and both will need validation.

It is conceivable that gene signatures may become predictive markers in the future.

Summary and Recommendations

- Baseline genetic information should be obtained in all MM cases.
- FISH testing must be done on purified plasma cells and not on unsorted samples.
- Minimal panel required for prognostication should include t(4;14), t(14;16) and del(17p13).
- A more comprehensive panel should include testing for t(11;14), chromosome 13 deletion, ploidy category and chromosome 1 abnormalities.
- Gene expression signatures should be incorporated in all clinical trials.

International Myeloma Working Group Guidelines for Serum-Free Light Chain Analysis in Multiple Myeloma and Related Disorders

Dispenzieri A et al.

Introduction

- Serum free light chain (FLC) assay was developed in early 2000s.
- Assay consists of quantitating circulating free κ and λ light chain immunoglobulin as well as providing κ/λ FLC ratio (rFLC).
- This review describes uses in which FLC has proven its utility and areas in which it is still investigational.

Gold standard for plasma cell disorders screening is immunofixation electrophoresis (IFE) of serum and urine. A prior study identified 428 patients in the Mayo Clinic database who had positive urinary IFE (u IFE) and also had serum IFE (sIFE), serum protein electrophoresis (SPEP) and serum rFLC done (*Mayo Clin Proc* 2006;81:1575).

<table>
<thead>
<tr>
<th>Laboratory test</th>
<th>% Abnormal</th>
<th>% Missed if urinary IFE was not done</th>
</tr>
</thead>
<tbody>
<tr>
<td>sIFE or SPEP</td>
<td>93.5</td>
<td>6.5</td>
</tr>
<tr>
<td>sIFE or rFLC</td>
<td>99.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Prognostic Value of Serum FLC Assay

- MGUS/Smoldering Myeloma/Solitary Plasmacytoma: Abnormal rFCL is an independent predictor for higher rate of progression.
- Multiple Myeloma: Highly abnormal rFLC (<0.03 or >32) predicts inferior outcomes when compared to those with less severe abnormality (Leukemia 2008;22:1933).
- Amyloidosis: Baseline FLC correlates with the risk of death (Blood 2006;107:3378).

Monitoring and Response Assessment with Serum FLC Assay

- **Amyloidosis:**
  - FLC response has been shown to correlate with survival (*BJH* 2003;122:78).

- **Oligosecretory myeloma/light chain deposition disease:**
  - No data suggest that FLC changes correlate with disease status or outcome.
  - However, anecdotal reports exist in the literature to support a role of FLC in this population, and authors confirm their personal experience of use in follow-up of such patients.

Active Multiple Myeloma:
- There is no data to suggest routine use except to document stringent CR in a patient who has already attained CR.
- FLC half-life is 2 to 4 hours, while that of IgG is 8 to 21 days.
- FLC may detect an early response or an early relapse.
- No data is currently available to show that early detection of response or relapse may change the patient’s outcome.

Summary and Recommendations

- Serum FLC assay in combination with serum IFE is sufficient for screening plasma cell disorders.
- Serum FLC assay should be measured at diagnosis for prognostic purposes for all plasma cell disorders.
- Serum FLC assay should be conducted in the follow-up of patients with amyloidosis, oligosecretory myeloma and light chain-only myeloma and should also be conducted in patients with active multiple myeloma who have achieved a CR to determine a stringent CR.

The Use of Bisphosphonates in Multiple Myeloma: Recommendations of an Expert Panel on Behalf of the European Myeloma Network

Terpos E et al.

Bone destruction occurs in 90% of patients with MM (Oncologist 2007;12:62).

Bisphosphonates have become the standard of care in MM to reduce and delay the skeletal morbidity.

Recommendations developed by an expert panel after multiple rounds of review of associated evidence are summarized.

# Major Double Blind Trials of Bisphosphonates in MM

<table>
<thead>
<tr>
<th>Bisphosphonate/Control</th>
<th>Manuscript</th>
<th>N</th>
<th>Reduction of pain</th>
<th>Reduction of skeletal related events (SRE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate (IV) vs Placebo</td>
<td><em>JCO</em> 1998;16:593</td>
<td>392</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zoledronic Acid (IV) vs Pamidronate (IV)</td>
<td><em>Cancer</em> 2001;91:1191</td>
<td>108</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Zoledronic Acid (IV) vs Pamidronate (IV)</td>
<td><em>Cancer</em> 2003;98:1735</td>
<td>513</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Renal Impairment with Bisphosphonates

- Serum creatinine should be monitored before each dose.
- Patients with renal impairment should have creatinine clearance rates, serum electrolytes and albuminuria also monitored.
  - Moderate renal impairment (creatinine clearance 30-60 mL/min):
    - Lower doses and longer infusions of pamidronate
    - Lower doses with no changes in infusion time with zoledronic acid
  - Severe renal impairment (creatinine clearance < 30 mL/minute): Should not receive bisphosphonates

Osteonecrosis of Jaw (ONJ) with Bisphosphonates

- Preventive dentistry with ongoing dental evaluation has shown a 75% reduction in ONJ (Annals of Oncology 2009;20:137).
- A comprehensive dental examination should be done before initiating bisphosphonates.
- Existing/high-risk dental conditions should be treated before starting bisphosphonates.
- Bisphosphonates should be stopped if a patient develops ONJ.

Bisphosphonates should be administered to patients with MM with osteolytic lesions or osteopenia.
- Bisphosphonates should be continued for 2 years, and administration beyond 2 years is not recommended.

After 2 years, bisphosphonates should be reinitiated in patients with pain or documented progression in bone involvement.

Patients with MGUS, asymptomatic multiple myeloma or solitary plasmacytoma should not receive bisphosphonates.

Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma

Lacy MQ et al.

Introduction

- A curative therapy for multiple myeloma (MM) does not exist and most patients relapse.
- Pomalidomide is a new immunomodulatory drug demonstrated to be highly potent in vitro (*Blood* 2006;107:3098; *Leukemia* 2003;17:41).
- Pomalidomide dosed from 1 to 5 mg/mL has been shown to be well tolerated in Phase I trials in patients with relapsed MM (*Br J Haematol* 2008;141:41).
- **Current study objective:**
  - Assess the efficacy and safety of pomalidomide plus dexamethasone therapy for patients with relapsed MM.

Phase II Trial of Pomalidomide Plus Low-Dose Dexamethasone in Patients with Relapsed Multiple Myeloma

Protocol ID: NCT00558896

Eligibility (n = 60)

- Relapsed/refractory multiple myeloma
- At least one but no more than three prior regimens
- No deep vein thrombosis without prior therapeutic anticoagulation

Pomalidomide + dexamethasone* (dose adjustments allowed based on toxicity)

* Pomalidomide 2 mg/day oral, d1-28 q28 days
  Dexamethasone 40 mg/day oral, d1, 8, 15, 22 q28 days

### Confirmed Responses in Patients with Refractory Disease

<table>
<thead>
<tr>
<th>Response</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (n = 60)</td>
<td>5%</td>
<td>28%</td>
<td>30%</td>
<td>63%</td>
</tr>
<tr>
<td>Bortezomib refractory (n = 10)</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
<td>60%</td>
</tr>
<tr>
<td>Lenalidomide refractory (n = 20)</td>
<td>0%</td>
<td>5%</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>Bortezomib and lenalidomide refractory (n = 5)</td>
<td>0%</td>
<td>20%</td>
<td>40%</td>
<td>60%</td>
</tr>
</tbody>
</table>

CR = complete response; VGPR = very good partial response; PR = partial response; RR = response rate (CR + VGPR + PR)

**Confirmed Responses in Patients at High Risk**

<table>
<thead>
<tr>
<th>Response</th>
<th>CR</th>
<th>VGPR</th>
<th>PR</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All high risk* (n = 19)</td>
<td>5%</td>
<td>27%</td>
<td>42%</td>
<td>74%</td>
</tr>
<tr>
<td>Deletion 13 (n = 4)</td>
<td>0%</td>
<td>25%</td>
<td>75%</td>
<td>100%</td>
</tr>
<tr>
<td>t(14;16) (n = 3)</td>
<td>0%</td>
<td>0%</td>
<td>67%</td>
<td>67%</td>
</tr>
<tr>
<td>17p- (n = 5)</td>
<td>0%</td>
<td>60%</td>
<td>40%</td>
<td>100%</td>
</tr>
<tr>
<td>PCLI ≥ 3% (n = 8)</td>
<td>12.5%</td>
<td>25%</td>
<td>25%</td>
<td>63%</td>
</tr>
</tbody>
</table>

*Only one patient with t(14;16) achieved stable disease.*  
*Two patients had two high-risk factors; PCLI = plasma cell labeling index*

Conclusions

- The pomalidomide plus low-dose dexamethasone combination was highly active as a treatment for relapsed/refractory MM.
  - RR in patients with refractory MM: 63%
  - RR in patients with high-risk MM: 74%

- Toxicity was mild and consisted mainly of Grade 3/4 neutropenia (data not shown).

- Additional Phase II trials are planned with this treatment combination to better define response rates in patients with lenalidomide- and bortezomib-refractory MM.

PX-171-004, an Ongoing Open-Label Phase II Study of Single-Agent Carfilzomib (CFZ) in Patients with Relapsed or Refractory Myeloma (MM): Updated Results from the Bortezomib-Treated Cohort

Siegel D et al.

Proc ASH 2009;Abstract 303.
CFZ may provide greater, more sustained proteasomal inhibition than bortezomib (BTZ):
- Durable responses and disease control were observed in a Phase II study for progressive MM (ASCO 2009;Abstract 8504).

**Current study objective:**
- Evaluate patient responses by IMWG criteria from the bortezomib-treated cohort of the PX-171-004 study
- Primary objective: Overall response rate (ORR), defined as ≥partial response

Phase II Study of CFZ for Relapsed or Refractory MM (BTZ-Treated Cohort)

Protocol ID: PX-171-004

**Eligibility**

Relapsed/refractory MM (<25% response or progressed during therapy)

1-3 prior treatment regimens

**BTZ-treated cohort (n = 35)**

CFZ 20 mg/m² IV bolus Days 1, 2, 8, 9, 15 and 16 q 28 days up to 12 cycles

## Efficacy of CFZ Therapy in BTZ-Treated Cohort (n = 33*)

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Very good partial response</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Minimal response (MR)</td>
<td>4 (12%)</td>
</tr>
<tr>
<td>Stable disease ≥6 weeks</td>
<td>13 (39%)</td>
</tr>
</tbody>
</table>

**ORR (≥PR) = 18%; CBR (≥MR) = 30%; disease control = 70%**

Duration of ≥MR = 9.0 mo; duration of ≥PR = 10.6 mo
Median TTP = 5.3 mo at 11.5-month follow-up; * Evaluable patients

Select ≥Grade 3 Adverse Events*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>5 (14%)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (11%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2 (6%)</td>
</tr>
</tbody>
</table>

*Includes related and nonrelated Grade 3 or 4 events in >5% of patients

Conclusions

- CFZ (20 mg/m\(^2\)) achieves durable responses and disease control in patients with MM despite prior bortezomib treatment.
  - 18% ORR; 70% disease control; TTP = 5.3 mo
- Adverse events are mild and manageable.
  - Tolerability permits long-term treatment — 23% completed 12 cycle protocol (~ 1 year therapy; data not shown).
  - Peripheral neuropathy is rare, mild and does not limit therapy despite preexisting symptoms (data not shown).
- These data support the continuing evaluation of CFZ as a treatment option for MM.
  - Ongoing Phase II trial (PX-171-003 A1, n = 269) is further studying this agent in relapsed and refractory MM.