Novel Agents in Relapsed or Refractory Multiple Myeloma

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Natural History of Multiple Myeloma

- MGUS or smoldering myeloma
- Asymptomatic
- Symptomatic

**Active Myeloma**
- M Protein (g/L)
- 20
- 50
- 100

1. Relapse
2. Relapse
Refractory relapse

First-line therapy (the majority receives novel agent-based therapies)
Plateau remission
Second-line therapy
Third-line therapy

MGUS or smoldering myeloma
Refractory relapse
When to Start Treatment in RR Myeloma?

1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, CT or MRI
2. Definite increase (ie at least 50% increase and at least 1 cm) of existing plasmacytomas or bone lesions
3. Hypercalcemia (11.5 mg/dl)
4. Decrease in hemoglobin of >2g/dl or to less than 10 gm/dL
5. Rise in serum creatinine by 2 mg/dl or more
6. Hyperviscosity

Consider treatment if a significant monoclonal protein relapse, defined as doubling in two consecutive measurements separated by ≤ 2 months
Considerations in Patients With Relapsed/Refractory Myeloma

- Previous therapy
- Response to previous therapy
- Patient characteristics and other prognostic factors
  - Older than 65 yrs of age
  - Increased $\beta_2$-M, decreased serum albumin, low platelet count
  - Cytogenetic abnormalities: del(13q), t(4;14)
  - Renal dysfunction
    - Up to 50% of patients with MM have renal dysfunction
    - Between 20% and 30% of patients have concomitant renal failure
  - Extensive bone disease; extramedullary MM

APEX Efficacy: VD vs. high-dose Dex

ORR with bortezomib improved from 38% to 43%

Updated analysis

- Bortezomib: 27% PR, 7% nCR, 9% CR
- Dex: 25% PR, 7% nCR, 6% CR

Primary analysis

- Bortezomib: 43% ORR
- Dex: 18% ORR

Richardson et al. Blood 2007;110:3557-60
APEX Data: Survival
TTP (n=669)

Median TTP: bortezomib 6.2 months; dexamethasone 3.5 months

78% improvement in median TTP with bortezomib

1-yr OS rate: 80% vs 67%; P = 0.0002

Superior survival despite > 62% of HD dex pts crossing over to bortezomib

Richardson et al. Blood 2007;110:3557-60
RD vs. high-dose Dex
MM-009 and MM-010: Response Rates

EBMT response data

Longer TTP and OS with Len + Dex vs Dex alone in relapsed/refractory patients

**MM-009 and MM-010: pooled analysis**

**Time to progression**
- Median 4.6 months (Len + Dex)
- Median 13.4 months (Dex)

**Overall survival**
- Median 31.6 months (Len + Dex)
- Median 38.0 months (Dex)

\[ p < 0.001 \] \[ p = 0.045 \]

Despite 47.6% cross-over of patients who were randomized to dexamethasone-placebo.

Treatment with Len + Dex at first relapse achieves ≥ VGPR in 40% of patients.

CR or VGPR rate were significantly higher with second-line vs later therapy (39.8% vs 27.7%; p = 0.028)

Longer TTP and OS when Lenalidomide + Dex was used at first relapse rather than as salvage therapy

**MM-009 and MM-010: pooled analysis**

- **1 prior therapy (Lenalidomide + Dex)**, median TTP 17.1 months
- **≥ 2 prior therapies (Lenalidomide + Dex)**, median TTP 10.6 months

- **1 prior therapy (Lenalidomide + Dex)**, median OS 42.0 months
- **≥ 2 prior therapies (Lenalidomide + Dex)**, median OS 35.8 months

\[ p = 0.026 \]
\[ p = 0.041 \]

Continuous treatment with Len + Dex improves the quality of the response

MM-009 and MM-010: CR or VGPR achieved in 114 of 353 patients treated with Len + Dex

Continuing Len + Dex treatment results in additional late CR or VGPR

Patients having a VGPR or better with Len + Dex treatment have longer TTP

Pooled analysis of MM-009 and MM-010 (N = 114)

Median follow-up 48 months

CR or VGPR
PR

27.7 months vs 12.0 months

p < 0.001

18% of Patients Have a PFS ≥ 2 years with RD (pooled MM-009 and MM-010 Data)

- 50 patients with PFS ≥ 2 years (n = 64), 100% of which achieved ≥ PR.
- 33 patients with PFS ≥ 2 years (n = 64), 60% of which achieved ≥ PR.
- 16 patients with all patients (N = 353), 60% of which achieved ≥ PR.

Dimopoulos et al. ASH 2011; poster 2929
## EU-PASS Study: Safety and tolerability

<table>
<thead>
<tr>
<th></th>
<th>Len (n = 2,164)</th>
<th>Bort (n = 842)</th>
<th>Thal (n = 114)</th>
<th>Overall (N = 3,236)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Incidence of grade 3/4 AEs</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any AE, %</td>
<td>51</td>
<td>41</td>
<td>44</td>
<td>47</td>
</tr>
<tr>
<td>Drug-related AE, %</td>
<td>34</td>
<td>26</td>
<td>19</td>
<td>nr</td>
</tr>
<tr>
<td>Drug-related serious AE, %</td>
<td>16</td>
<td>10</td>
<td>11</td>
<td>nr</td>
</tr>
<tr>
<td><strong>Grade 3/4 AEs observed in &gt; 5% of patients</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Haematological AEs, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>341 (16)</td>
<td>34 (4)</td>
<td>6 (5)</td>
<td>391 (12)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>188 (9)</td>
<td>68 (8)</td>
<td>4 (4)</td>
<td>264 (8)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>162 (8)</td>
<td>32 (4)</td>
<td>5 (4)</td>
<td>204 (6)</td>
</tr>
<tr>
<td>Non-haematological AEs, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>92 (4)</td>
<td>24 (3)</td>
<td>9 (8)</td>
<td>128 (4)</td>
</tr>
<tr>
<td><strong>Treatment discontinuation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Discontinuations, n (%)</td>
<td>1,702 (79)</td>
<td>737 (88)</td>
<td>103 (90)</td>
<td>2,647 (82)</td>
</tr>
<tr>
<td>Due to AE</td>
<td>399 (18)</td>
<td>156 (19)</td>
<td>22 (19)</td>
<td>587 (18)</td>
</tr>
<tr>
<td>Due to PD</td>
<td>504 (23)</td>
<td>130 (15)</td>
<td>24 (21)</td>
<td>685 (21)</td>
</tr>
</tbody>
</table>

Management of neutropenia: consensus panel opinion

If ANC < 500/µL

Suspend lenalidomide and add G-CSF

At the start of next cycle

ANC > 1,000/µL

Resume lenalidomide at same dose level

ANC < 1,000/µL

Aggressive disease?

Yes

Resume lenalidomide at same dose level with G-CSF

No

Resume lenalidomide at 1 dose level lower

Management of thrombocytopenia

- When platelet level first falls to < $30 \times 10^9/L$
  - interrupt lenalidomide treatment
- When platelet level returns to $\geq 30 \times 10^9/L$
  - resume lenalidomide at dose level 1
- For each subsequent drop to < $30 \times 10^9/L$
  - interrupt lenalidomide treatment
- Upon return to $\geq 30 \times 10^9/L$
  - resume lenalidomide at next lower dose level
- Do not dose below 5 mg once daily

<table>
<thead>
<tr>
<th>Starting dose</th>
<th>25 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level 1</td>
<td>15 mg</td>
</tr>
<tr>
<td>Dose level 2</td>
<td>10 mg</td>
</tr>
<tr>
<td>Dose level 3</td>
<td>5 mg</td>
</tr>
</tbody>
</table>

Revlimid® SmPC. Celgene Europe Limited (Windsor, UK). Last updated 31/01/2011.
Management of thrombocytopenia

- When platelet level first falls to < 30 × 10⁹/L
  - interrupt lenalidomide treatment

- When platelet level returns to ≥ 30 × 10⁹/L
  - resume lenalidomide at dose level 1

- For each subsequent drop to < 30 × 10⁹/L
  - interrupt lenalidomide treatment

- Upon return to ≥ 30 × 10⁹/L
  - resume lenalidomide at next lower dose level

- Do not dose below 5 mg once daily

---

Starting dose | 25 mg
Dose level 1   | 15 mg
Dose level 2   | 10 mg
Dose level 3   | 5 mg

Adjustment of lenalidomide dose according to renal function, neutropenia or thrombocytopenia

<table>
<thead>
<tr>
<th>Renal function</th>
<th>Creatinine clearance</th>
<th>Lenalidomide starting dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline ANC(^2)</strong></td>
<td>Normal (CL_{Cr} \geq 50\text{ml/min})</td>
<td>25 mg once daily</td>
</tr>
<tr>
<td>&gt; 1,000 (\mu l) and platelets &gt; 50,000 (\mu l)</td>
<td>Moderate RI (30\text{ml/min} \leq CL_{Cr} &lt; 50\text{ml/min})</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td></td>
<td>Severe RI (CL_{Cr} &lt; 30\text{ml/min})</td>
<td>15 mg every other day</td>
</tr>
<tr>
<td></td>
<td>End-stage renal disease (CL_{Cr} &lt; 30\text{ml/min}) (requiring dialysis)</td>
<td>5 mg once daily</td>
</tr>
<tr>
<td>&lt; 1,000 (\mu l) or platelets &lt; 50,000 (\mu l)</td>
<td>15 mg once daily (GF support / platelet transfusion as needed; monitor frequently)</td>
<td>15 mg every other day (GF support / platelet transfusion as needed; monitor frequently)</td>
</tr>
<tr>
<td></td>
<td>5 mg once daily (GF support / platelet transfusion as needed; monitor frequently)</td>
<td>5 mg every other day (GF support / platelet transfusion as needed; monitor frequently)</td>
</tr>
</tbody>
</table>

Adjust the dose at each cycle if changes in \(CL_{Cr}\) or blood cell count occurs.
Management and prevention of peripheral neuropathy

- Lenalidomide can be given to patients with existing neuropathy or a history of peripheral neuropathy (PN)\(^1\)
- Lenalidomide rarely exacerbates pre-existing PN\(^1,2\)
- For agents that are associated with PN, assessment before every dose is recommended\(^3\)
- If PN occurs, prompt intervention is crucial to enable the improvement/reversal of symptoms\(^3\)
- In patients with pre-existing PN, the use of drugs without neurotoxic potential such as Lenalidomide is preferred\(^3\)

Management and prevention of VTE: consensus panel opinion

- Thromboprophylaxis should be considered for patients treated with Lenalidomide + Dex and should continue for the entire duration of treatment*

- Lenalidomide + Dex should be resumed in patients considered stable on anticoagulation therapy

- Aspirin prophylaxis is appropriate for patients with standard VTE risk; LMWH is recommended for patients with higher risk of VTE*

- LMWH prophylaxis should continue for at least the first 4 cycles of therapy; thereafter, patients may be switched to aspirin prophylaxis*

* Not in line with SmPC; opinion of consensus panel.
Management and prevention of other AEs during Lenalidomide + Dex: consensus panel opinion

- Limited, localized rash
  - antihistamines and topical steroids
- Diffuse, desquamating, exfoliative, bullous rash
  - discontinue lenalidomide
- Infection
  - routine antibiotic prophylaxis for first 3 cycles of therapy
- Muscle cramps
  - magnesium supplementation
- Dex-related symptoms (myopathy, non-neutropenic infection, psychological changes, hyperglycaemia)
  - consider reduction in Dex dose

A Multicenter, Open-Label Phase 2 Study of Lenalidomide Plus Low-Dose Dexamethasone in Chinese Patients With Relapsed/Refractory Multiple Myeloma: The MM-021 Trial
Investigators

Jian Hou¹, Xin Du², Jie Jin³, Zhen Cai³, Fangping Chen⁴, Dao-bin Zhou⁵, Li Yu⁶, Xiaoyan Ke⁷, Xiao Li⁸, Depei Wu⁹, Fanyi Meng¹⁰, Huisheng Ai¹¹, Jianmin Wang¹², Jingshan Zhang¹³, Honeylet Wortman-Vayn¹³, Nianhang Chen¹³, Jay Mei¹³

¹Shanghai Changzheng Hospital, Shanghai, China; ²Guangdong General Hospital, Guangzhou, China; ³The 1st Hospital, Zhejiang University, Hangzhou, China; ⁴Xiangya Hospital of Central South University, Changsha, China; ⁵Peking Union Medical College Hospital, Beijing, China; ⁶The 301 Military Hospital, Beijing, China; ⁷Peking University Third Hospital, Beijing, China; ⁸Shanghai 6th Hospital, Shanghai, China; ⁹The 1st Affiliated Hospital of Soochow University, Suzhou, China; ¹⁰Nanfang Hospital, Southern Medical University, Guangzhou, Guangzhou, China; ¹¹The 307 PLA Hospital, Beijing, China; ¹²Changhai Hospital, Shanghai, China; ¹³Celgene Corporation, Summit, NJ, USA
Study Design

- Phase 2, multicenter, single-arm, open-label
- Patients with RRMM received:
  - LEN (25 mg/day on days 1–21)
  - and LoDEX (40 mg on days 1, 8, 15, and 22)
  - in 28-day treatment cycles until disease progression
  - Starting dose of DEX adjusted according to patient age:
    - 40 mg/day (≤ 75 years)
    - 20 mg/day (> 75 years)
- Thromboembolic prophylaxis
Summary of Baseline Characteristics

• High percentage of pts with advanced disease and high number of prior therapies
  – 86% with Durie-Salmon Stage III disease
  – 57% had received ≥ 4 prior therapies
  – 69% with prior THAL, 64% with prior BORT, and 46% had received both

• Unusually high proportion (5%) with IgD subtype Associated with more severe disease and lower response rates than other types of MM

**Similar Pharmacokinetics in Chinese MM patients**

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59 (40–69)</td>
<td>63 (43–66)</td>
<td>55 (44–68)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>82 (50–118)</td>
<td>59 (48–75)</td>
<td>65 (54–84)</td>
</tr>
<tr>
<td>CrCl (mL/min)</td>
<td>101</td>
<td>91</td>
<td>95</td>
</tr>
<tr>
<td>(\text{AUC}_\infty) (ng•h/mL)</td>
<td>2,124</td>
<td>2,305</td>
<td>2,202</td>
</tr>
<tr>
<td>(C_{\text{max}}) (ng/mL)</td>
<td>487</td>
<td>572</td>
<td>596</td>
</tr>
<tr>
<td>(T_{\text{max}}) (h)</td>
<td>1.0</td>
<td>1.0</td>
<td>0.93</td>
</tr>
<tr>
<td>(t_{\frac{1}{2}}) (h)</td>
<td>3.18</td>
<td>2.70</td>
<td>3.18</td>
</tr>
</tbody>
</table>

Despite lower body weight
Results

Response Rates and Comparison

Data from Dimopoulos M, et al. Leukemia., 2009
Responses by Prior Therapy

1-2 prior (n=50):
- PR-VGPR: 50.0%
- CR: 14.0%

> 2 prior (n=137):
- PR-VGPR: 45.0%
- CR: 5.0%
Responses comparable Regardless of Renal Impairment

Renal impairment categories defined as: none-to-mild (CrCl ≥ 60 mL/min); moderate (CrCl ≥ 30 to < 60 mL/min); and severe (CrCl < 30 mL/min).
Safety
Grade 3-4 AEs in $\geq 5\%$ of Patients

<table>
<thead>
<tr>
<th>AEs</th>
<th>N = 199</th>
</tr>
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<tbody>
<tr>
<td><strong>Hematological, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>24.6 %</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>23.6 %</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14.6 %</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>9.5 %</td>
</tr>
<tr>
<td>Febrile neutropenia (1 pt)</td>
<td>0.5 %</td>
</tr>
<tr>
<td><strong>Non-Hematological, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>DVT (1 pt)</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Duodenal tumor (1 pt)</td>
<td>0.5 %</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>12.6 %</td>
</tr>
</tbody>
</table>
## Safety

### Comparison to Phase III Trials

**Grade 3-4 AEs in ≥ 2% of Patients**

<table>
<thead>
<tr>
<th></th>
<th>MM-009/010*</th>
<th></th>
<th>MM-021</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>REV/DEX (n=353)</td>
<td>Placebo/DEX (n=351)</td>
<td>REV/DEX (n=199)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>35.4 %</td>
<td>3.4 %</td>
<td>23.6 %</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13.0 %</td>
<td>6.3 %</td>
<td>14.6 %</td>
</tr>
<tr>
<td>Anemia</td>
<td>10.8 %</td>
<td>6.0 %</td>
<td>24.6 %</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9.1 %</td>
<td>5.4 %</td>
<td>12.6 %</td>
</tr>
<tr>
<td><strong>All thrombotic events</strong></td>
<td>15.9 %</td>
<td>5.4 %</td>
<td><strong>0.5 %</strong></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7.6 %</td>
<td>7.7 %</td>
<td>2.5 %</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6.5 %</td>
<td>4.9 %</td>
<td>4.0 %</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>5.7 %</td>
<td>3.1 %</td>
<td>NR</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>5.7 %</td>
<td>1.4 %</td>
<td>7.0 %</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4.8 %</td>
<td>15.1 %</td>
<td>NR</td>
</tr>
</tbody>
</table>

Dose Level Used According to Time

% of Treated Patients on Each Lenalidomide Dose

Cycle

10 mg
15 mg
20 mg
25 mg
MM-021 Trial
Conclusions

• Largest registration trial for RR MM Chinese patients

• Overall response rates
  – 54% in predominantly heavily pre-treated pts
  – 64% in pts treated earlier (i.e. 1-2 prior therapies)
  – Consistent with those observed in pivotal phase III trials in caucasians
  – Regardless of the severity of disease
  – Consistent across subgroups including patients with renal impairment
MM-021 Trial
Conclusions (cont.)

• PK profile similar to that seen in prior studies of Caucasian and Japanese patients

• Len + low dose dex is tolerable
  – No DVT challenge in Chinese patients
  – No Peripheral Neuropathy Challenge
  – No special dose-adaptation required in Chinese patients

*Rd regimen will address the unmet clinical need for effective treatment of Chinese patients with RRMM*
Is retreatment with novel agents feasible?
2nd-line combinations after bortezomib-based therapies: data from VISTA trial

- Bortezomib mono or combination (n = 107)
- Thalidomide combination (n = 155)
- Lenalidomide combination (n = 36)
- MPV (n = 129)
- MP (n = 194)

Overall response* rate (%)

- 73
- 67
- 37
- 47
- 41
- 59

*Responses ≥ PR.
Studies of bortezomib retreatment: results of a meta-analysis presented at ASH 2012

<table>
<thead>
<tr>
<th></th>
<th>ORR, %</th>
<th>TTP, mos</th>
<th>OS, mos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All patients</strong></td>
<td>39</td>
<td>7.5</td>
<td>16.6</td>
</tr>
<tr>
<td><strong>BTZ-refractory:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0% (relapsed only)*</td>
<td>57</td>
<td>8.5</td>
<td>19.7</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>28</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>≥50%</td>
<td>19</td>
<td>5.9</td>
<td>20.4</td>
</tr>
<tr>
<td>100% (refractory only)</td>
<td>23</td>
<td>–</td>
<td>11.2</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>49</td>
<td>6.0</td>
<td>–</td>
</tr>
<tr>
<td><strong>Prior therapies:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤4</td>
<td>43</td>
<td>8.2</td>
<td>13.3</td>
</tr>
<tr>
<td>&gt;4</td>
<td>29</td>
<td>7.1</td>
<td>20.0</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>45</td>
<td>5.6</td>
<td>–</td>
</tr>
<tr>
<td><strong>Time since last BTZ:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9 months</td>
<td>49</td>
<td>9.5</td>
<td>19.7</td>
</tr>
<tr>
<td>≥9 months</td>
<td>43</td>
<td>7.3</td>
<td>–</td>
</tr>
<tr>
<td><strong>Unknown</strong></td>
<td>30</td>
<td>5.9</td>
<td>15.4</td>
</tr>
<tr>
<td><strong>Therapy:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTZ ± dex</td>
<td>51</td>
<td>7.9</td>
<td>19.2</td>
</tr>
<tr>
<td>Combination</td>
<td>36</td>
<td>7.1</td>
<td>16.1</td>
</tr>
</tbody>
</table>

Knopf et al. ASH 2012 (Abstract 1863), poster presentation
## Retreatment with IMiDs

### Retrospective study
- Median of 2 treatments prior to IMiD based salvage therapy
- Median time from diagnosis to repeat exposure to IMiD: 28 months

<table>
<thead>
<tr>
<th></th>
<th>Len → Len</th>
<th>Len → Thal</th>
<th>Thal → Len</th>
<th>Thal → Thal</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=140</td>
<td>n=48</td>
<td>n=11</td>
<td>n=58</td>
<td>n=23</td>
</tr>
<tr>
<td>ORR (≥PR) to repeat IMiD therapy</td>
<td>54%</td>
<td>20%</td>
<td>48%</td>
<td>30%</td>
</tr>
<tr>
<td>Median TTP from start of repeat IMiD therapy</td>
<td>16 months</td>
<td>3 months</td>
<td>9 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>

- Repeat therapy with IMiDs feasible
- Response rates with lenalidomide retreatment higher than with repeat thal administration

Madan et al. IMW 2011 (abstract P-134); poster presentation
MM-015: Response to 2nd Line LEN (OLEP)

LEN maintenance (MPR-R) did not appear to induce resistant relapses

<table>
<thead>
<tr>
<th></th>
<th>Patients (%)</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR-R (n=21)</td>
<td>19</td>
<td>33</td>
<td>43</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>MPR (n=53)</td>
<td>11</td>
<td>28</td>
<td>47</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>MP (n=79)</td>
<td>13</td>
<td>42</td>
<td>34</td>
<td>11</td>
<td></td>
</tr>
</tbody>
</table>

≥ PR\(^a\): 53%

≥ PR\(^a\): 40%

≥ PR: 55%

\(^a\)Discrepancies in total percentages are due to rounding effects.

Unmet Clinical Needs for RR MM

- Multiple myeloma refractory to both lenalidomide- and bortezomib- based regimens
- Plasmacytoma relapses
- High risk features, i.e. del17p

- Important for treatments to target tumour growth and concomitant immunosuppression while being easy to administer and well tolerated for long-term use
Novel Drugs for Relapsed/Refractory Myeloma
Pomalidomide: a novel IMiD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pomalidomide + Low-Dose Dexamethasone</th>
<th>Pomalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>(n = 113)</td>
<td>(n = 108)</td>
</tr>
<tr>
<td>▪ ORR, %</td>
<td>34</td>
<td>13</td>
</tr>
<tr>
<td>▪ Median time to response, mos</td>
<td>1.9</td>
<td>2.9</td>
</tr>
<tr>
<td>▪ Median duration of response, mos</td>
<td>7.9</td>
<td>8.5</td>
</tr>
<tr>
<td>▪ Median PFS, mos</td>
<td>4.7</td>
<td>2.7</td>
</tr>
<tr>
<td>▪ Median OS, mos</td>
<td>16.9</td>
<td>14</td>
</tr>
<tr>
<td>• For patients with PD as best response</td>
<td></td>
<td>5.4</td>
</tr>
<tr>
<td>Double-refractory population</td>
<td>(n = 69)</td>
<td>(n = 64)</td>
</tr>
<tr>
<td>▪ ORR, %</td>
<td>30</td>
<td>16</td>
</tr>
<tr>
<td>▪ Median time to response, mos</td>
<td>1.8</td>
<td>2.0</td>
</tr>
<tr>
<td>▪ Median duration of response, mos</td>
<td>6.5</td>
<td>8.3</td>
</tr>
<tr>
<td>▪ Median PFS, mos</td>
<td>3.9</td>
<td>2.0</td>
</tr>
<tr>
<td>▪ Median OS, mos</td>
<td>13.7</td>
<td>12.7</td>
</tr>
<tr>
<td>• For patients with PD as best response</td>
<td></td>
<td>4.6</td>
</tr>
</tbody>
</table>

**MM-003 Design: POM + LoDEX vs HiDEX**

*Refractory MM Pts Who Have Failed BORT and LEN*

- **Randomization 2:1**
- **Follow-Up for OS and SPM Until 5 Years Post Enrollment**

**Randomization**

- **POM:**
  - 4 mg/day D1-21 +
  - LoDEX:
    - 40 mg (≤ 75 yrs)
    - 20 mg (> 75 yrs)
  - D1, 8, 15, 22

- **HiDEX:**
  - 40 mg (≤ 75 yrs)
  - 20 mg (> 75 yrs)
  - D1-4, 9-12, 17-20

**Stratification**

- Age (≤ 75 vs > 75 yrs)
- Number of prior Tx (2 vs > 2)
- Disease population

**Thromboprophylaxis**

- Indicated for those receiving POM or with DVT history

**Companion trial MM-003C**

- POM 21/28 days

Dimopoulos et al. ASH 2012 (Abstract LBA-6), oral presentation
Figure 3: Ongoing Evaluation of Response by IRAC

<table>
<thead>
<tr>
<th></th>
<th>Response (%)</th>
<th>POM + LoDEX (n=302)</th>
<th>HiDEX (n=153)</th>
<th>POM + LoDEX (n=204)</th>
<th>HiDEX (n=99)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≥ PR = 21%</td>
<td>18</td>
<td>52</td>
<td>21</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>≥ MR = 37%</td>
<td>16</td>
<td>1</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>≥ MR = 3%</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>≥ MR = 8%</td>
<td>1</td>
<td>2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dimopoulos et al. IMW 2013 (Abstract 311)
MM-003: Progression-Free Survival

Progression-Free Survival (months)

Proportion of Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median PFS</th>
<th>HR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 302)</td>
<td>3.6 months</td>
<td>0.45</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>HiDEX (n = 153)</td>
<td>1.8 months</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dimopoulos et al. ASH 2012 (Abstract LBA-6), oral presentation
MM-003: Progression-Free Survival

Patients Refractory to Both LEN and BORT

Proportion of Patients

Progression-Free Survival (months)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 221)</td>
<td></td>
<td>3.2 months</td>
</tr>
<tr>
<td>HiDEX (n = 108)</td>
<td></td>
<td>1.7 months</td>
</tr>
</tbody>
</table>

HR = 0.48

$P < .001$

Based on adjudicated data; IMWG criteria

MM-003: Overall Survival

- Median OS (95% CI)
  - POM + LoDEX (n = 302): Not Reached (11.1-NE)
  - HiDEX (n = 153): 7.8 months (5.4-9.2)

- HR = 0.53, P < .001

- 29% of pts received POM after progression on HiDEX

Dimopoulos et al. ASH 2012 (Abstract LBA-6), oral presentation
MM-003: Overall Survival

Patients Refractory to Both LEN and BORT

- 29% of pts received POM after progression on HiDEX

**Overall Survival**

**Proportion of Patients**

**Median OS (95% CI)**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEX (n = 221)</td>
<td>Not Reached (8.5-NE)</td>
</tr>
<tr>
<td>HiDEX (n = 108)</td>
<td>7.4 months (4.3-9.2)</td>
</tr>
</tbody>
</table>

**HR = 0.56**,  
**P = .003**

## MM-003: Safety Profile

<table>
<thead>
<tr>
<th></th>
<th>POM + LoDEX (n = 300)</th>
<th>HiDEX (n = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3/4 hematologic AEs, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42</td>
<td>15</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Anemia</td>
<td>27</td>
<td>29</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td><strong>Grade 3/4 non-hematologic AEs, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>24</td>
<td>23</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Any grade AEs of interest, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VTE</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td><strong>Discontinuation due to AEs, %</strong></td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

# Carfilzomib

<table>
<thead>
<tr>
<th>Trial</th>
<th>N*</th>
<th>Population</th>
<th>Previous Lines, n</th>
<th>ORR, %</th>
<th>MR/SD%</th>
<th>Median TTP, Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td>003-A0[^1]</td>
<td>39</td>
<td>Relapsed/ refractory</td>
<td>&gt; 2</td>
<td>18</td>
<td>8/41</td>
<td>6.2</td>
</tr>
<tr>
<td>004 (Bz exposed)[^3]</td>
<td>35</td>
<td>Relapsed/ refractory</td>
<td>1-3</td>
<td>21</td>
<td>12/35</td>
<td>8.1</td>
</tr>
<tr>
<td>004 (Bz naive)[^4] 20 mg/m²</td>
<td>59</td>
<td>Relapsed/ refractory</td>
<td>1-3</td>
<td>42</td>
<td>17/22</td>
<td>8.3</td>
</tr>
<tr>
<td></td>
<td>67</td>
<td>Relapsed/ refractory</td>
<td></td>
<td>52</td>
<td>12/15</td>
<td>NR</td>
</tr>
<tr>
<td>006 (combo with len/dex)[^5]</td>
<td>50</td>
<td>Relapsed/ refractory</td>
<td>1-3</td>
<td>78</td>
<td>2/8</td>
<td>--</td>
</tr>
</tbody>
</table>

*Evaluable for response.

**Neuropathy from phase II experience**
9.6% grades 1/2 and 1.4% grade 3

PX-171-006: Phase II Trial of Carfilzomib Plus Len/Dex in Relapsed/Refractory MM

Carfilzomib
20/27 mg/m² IV

D1/D2
D8/D9
D15/D16

Week 1
Week 2
Week 3

*20 mg/m² cycle 1 days 1 and 2 only, 27 mg/m² thereafter

Lenalidomide D1-D21
25 mg/d PO

Dexamethasone
40 mg/d PO

Response (N = 51)

<table>
<thead>
<tr>
<th>Response</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/nCR</td>
<td>12 (24)</td>
</tr>
<tr>
<td>VGPR</td>
<td>9 (18)</td>
</tr>
<tr>
<td>PR</td>
<td>19 (37)</td>
</tr>
<tr>
<td>MR</td>
<td>1 (2)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (6)</td>
</tr>
<tr>
<td>ORR</td>
<td>40 (78)</td>
</tr>
</tbody>
</table>

## Monoclonal Antibodies in RR MM

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Target</th>
<th>N</th>
<th>Phase</th>
<th>Preliminary Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jagannath et al[1]</td>
<td>BT062</td>
<td>Syndecan-1, CD138</td>
<td>32</td>
<td>I</td>
<td>Acceptable toxicity profile</td>
</tr>
<tr>
<td>Fanale et al[2]</td>
<td>Lucatumumab</td>
<td>CD40</td>
<td>164</td>
<td>I</td>
<td>MTD for MM: 4.5 mg/kg/wk</td>
</tr>
<tr>
<td>Mahadevan et al[3]</td>
<td>Samalizumab</td>
<td>CD200</td>
<td>3</td>
<td>I/II</td>
<td>MTD not yet established</td>
</tr>
<tr>
<td>Raje et al[4]</td>
<td>Tabalumab</td>
<td>BAFF</td>
<td>48</td>
<td>I</td>
<td>CR 4%, VGPR 8%, PR 33% TTP 4.9m, DOR 7.3m</td>
</tr>
<tr>
<td>Rossi et al[5]</td>
<td>BOR + siltuximab</td>
<td>IL6</td>
<td>21</td>
<td>I/II</td>
<td>ORR: 57% TTP: 8.7 mos</td>
</tr>
<tr>
<td>Jakubowiak et al[6]</td>
<td>BOR + elotuzumab</td>
<td>CS1</td>
<td>28</td>
<td>I</td>
<td>ORR: 48% TTP: 9.4 mos</td>
</tr>
<tr>
<td>Lonial et al[7]</td>
<td>Elotuzumab + len + dex</td>
<td>CS1</td>
<td>55</td>
<td>II</td>
<td>ORR: 82%</td>
</tr>
<tr>
<td>Plesner et al[8]</td>
<td>Daratumumab</td>
<td>CD38</td>
<td>32</td>
<td>I/II</td>
<td>At doses 4mg/kg and above, 8 of the 12 patients had at least a MR</td>
</tr>
</tbody>
</table>

Lenalidomide Can Enhance the efficacy of Monoclonal Antibodies in Myeloma

A

Target: 12BM

% Specific Lysis

E/T Ratio

Target: 28BM

% Specific Lysis

E/T Ratio

B

Patient 1

% Specific Lysis

Patient 2

% Specific Lysis

Patient 3

% Specific Lysis

# Efficacy: Best Response

## Phase II (Study 1703)

<table>
<thead>
<tr>
<th></th>
<th>Elotuzumab 10 mg/kg</th>
<th>Elotuzumab 20 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, n</td>
<td>36</td>
<td>37</td>
<td>73</td>
</tr>
<tr>
<td>ORR (≥PR), n (%)</td>
<td>33 (92)</td>
<td>28 (76)</td>
<td>61 (84)</td>
</tr>
<tr>
<td>CR/stringent CR, n (%)</td>
<td>5 (14)</td>
<td>4 (11)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>VGPR, n (%)</td>
<td>17 (47)</td>
<td>14 (38)</td>
<td>31 (43)</td>
</tr>
<tr>
<td>PR, n (%)</td>
<td>11 (31)</td>
<td>10 (27)</td>
<td>21 (29)</td>
</tr>
<tr>
<td>&lt;PR, n (%)</td>
<td>3 (8)</td>
<td>9 (24)</td>
<td>12 (16)</td>
</tr>
</tbody>
</table>

- Overall median time to response: 1 mo (range, 0.7-19.2); 1 deepening response was observed in the 20mg/kg arm since the previous data cut (April 27, 2012)

- Overall median time to best response: 2.5 mo (range, 0.7-24.7)

- Median duration of objective response: 17.8 mo (range, 1.0-30.4)

---

Progression Free Survival
Phase II (Study 1703)

At a median follow-up of 20.8 mo, median PFS has not been reached in the 10 mg/kg arm

In the abstract, a preliminary median PFS of 26.9 mo was reported; however, no disease progression/death has been reported since then; continued maturation of the results has increased the number of patients at risk post the preliminary median PFS (in the denominator). Therefore, in this updated dataset the median has not been crossed.
Daratumumab: A human CD38 mAb with broad-spectrum killing activity
Maximal Change in Paraprotein

Data at baseline below limits for measurable disease

Results are before database lock

Lokhorst et al.
EHA 2012;Abstract 1143
Algorithm for the Management of Patients with RR Myeloma: the European Approach

Frontline treatment with novel agent?

- Yes
  - PN in frontline treatment?
    - Yes
      - Len/dex
      - Cy/dex
      - Bortezomib combos (eg, RVD); modified dose & schedule
      - Bendamustine (EU)
      - Clinical trials (eg, pomalidomide, carfilzomib, elotuzumab, daratumumab)
    - No
      - Bortezomib/dex
      - Bortezomib/PL doxorubicin
      - Clinical trials
  - No
    - Consider auto-SCT or allo-SCT

Repeat or change frontline treatment?

- Yes
  - Long remission
  - Short frontline treatment duration
  - No toxicity concerns from first line treatment
- No
  - Short remission
  - Long-term treatment
  - Toxicity

Frontline was

- MPT
  - Bortezomib/dex
  - Bortezomib/PL doxorubicin
  - Clinical trials
- MPV
  - Len/dex
  - CVD
  - PAD

Switch drug class after:

- Short remission
- Long-term treatment
- Toxicity

Repeat treatment after:

- Long remission
- Short frontline treatment duration
- No toxicity concerns from first line treatment

Use novel agents

- Survival is extended with novel therapies
  - Len/dex
  - Bortezomib/PL doxorubicin
  - Bortezomib/dex
  - RVD
  - CTD
  - VTD
  - CVD
  - PAD
  - Clinical trials

Conclusions

- The combination of lenalidomide and dexamethasone is associated with the highest response and the longest TTP reported so far from large randomized trials.

- When lenalidomide and dexamethasone is administered as second-line therapy, response rates are even higher and TTP is even longer.

- Pomalidomide and carfilzomib may be effective in both bortezomib and lenalidomide refractory patients.

- Novel monoclonal antibodies (daratumumab, elotuzumab) in combination with PIs, IMiDs or conventional chemotherapy show promise for the management of RR myeloma patients.