IMiDs (Immunomodulatory drugs) and Multiple Myeloma

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## Disclosure of Conflict of Interest (List)

<table>
<thead>
<tr>
<th>Company</th>
<th>Nature of Conflict</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celgene</td>
<td>Lecture fees, board, other honorarium</td>
</tr>
<tr>
<td>Janssen</td>
<td>Lecture fees, board</td>
</tr>
<tr>
<td>Millenium/Takeda</td>
<td>Lecture fees, board</td>
</tr>
<tr>
<td>Onyx/Amgen</td>
<td>Lecture fees, board</td>
</tr>
<tr>
<td>LeoPharma</td>
<td>Lecture fees, board</td>
</tr>
<tr>
<td>Novartis</td>
<td>Lecture fees</td>
</tr>
</tbody>
</table>
Approval of Novel Agents has Improved OS

Overall Survival from Time of Diagnosis 1971–2006

- Approval of Bort-, Thal-, and Len-containing regimens occurred during this time.
- Sustained improvement in OS seen over the 2006-2010 diagnosis period
- Improvement in OS over this period attributed to use of novel agents and ASCT

<table>
<thead>
<tr>
<th>Diagnosis Period</th>
<th>Median OS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1971–1996(^1)</td>
<td>30 months</td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>1996–2006(^1,a)</td>
<td>45 months</td>
<td></td>
</tr>
<tr>
<td>2001–2005(^2)</td>
<td>55 months</td>
<td>p = 0.002</td>
</tr>
<tr>
<td>2006-2010(^2)</td>
<td>73 months</td>
<td></td>
</tr>
</tbody>
</table>

\(^{1}\) Approval of Bort-, Thal-, and Len-containing regimens occurred during this time.

Continued Improvement in OS in Novel-Agent Era

- There are 1038 patients grouped into 2001–2005 and 2006–2010 cohorts
- Use of novel agents in treatment regimens improved OS

<table>
<thead>
<tr>
<th></th>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS, years</td>
<td>4.6</td>
<td>6.1</td>
<td>0.002</td>
</tr>
<tr>
<td>6-year estimated OS, %</td>
<td>40</td>
<td>51</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Approval Timelines (EU) for Novel Therapies

Approved for RRMM

- 20 April 2005
  Bort (IV) as monotherapy for RRMM patients who received ≥ 1 prior treatment and who have undergone or are ineligible for BMT

- 26 April 2004
  Bort (IV) approved for RRMM patients who failed to respond to ≥ 2 prior treatment

Approved for NDMM

- 14 June 2007
  Len in combination with DEX in RRMM patients who received ≥ 1 prior treatment

- 16 April 2008
  Thal in combination with MP in NDMM patients aged ≥ 65 years or ineligible for HDT

- 29 August 2008
  Bort (IV) in combination with MP approved for NDMM patients ineligible for HDT with BMT

- 20 September 2012
  Bort (SC) as monotherapy for RRMM patients who received ≥ 1 prior treatment and who have undergone or are ineligible for BMT

- 20 May 2009
  Bort (SC) approved for NDMM patients ineligible for HDT with BMT

- 14 June 2007
  Len in combination with DEX in RRMM patients who received ≥ 1 prior treatment

- 16 April 2008
  Thal in combination with MP in NDMM patients aged ≥ 65 years or ineligible for HDT

- 28 June 2013
  Bort in combination with TD approved for SCT-eligible NDMM patients

- 5 August 2013
  Pom + LoDex in relapsed and refractory patients with ≥ 2 prior regimens including Len and Bort

EMA approval dates can only be verified from 2004 to the present.

BMT, bone marrow transplant; EMA, European Medicines Agency; EU, European Union; IV, intravenous; SC, subcutaneous.

IMiDs (Immunomodulatory drugs)

- **Thalidomide**
  - Dose: 100–200 mg/d
  - Side effects: Neuropathy, Constipation, Sedation, DVT

- **Lenalidomide**
  - Dose: 15–25 mg/d
  - Side effects: Myelosuppression, Skin rash, DVT

- **Pomalidomide**
  - Dose: 2–4 mg/d
  - Side effect: Myelosuppression
IMiDs share a Phtaloyl ring

- Thalidomide
- Lenalidomide
- Pomalidomide
IMiDs share mechanism of action: Overview

**Anti-myeloma**
- Tumour suppressor gene upregulation and oncogene inhibition\(^1\)\(^–\)\(^4\)
- Induction of cell-cycle arrest and apoptosis\(^1\)\(^–\)\(^5\)
- Effects in drug-sensitive and drug-resistant cells\(^1\)\(^–\)\(^5\)

**Stromal inhibition**
- Inhibition of osteoclast differentiation\(^6\),\(^7\)
- Inhibition of growth factor production\(^8\)
- Inhibition of angiogenesis\(^9\)

**Immunomodulatory**
- Enhanced immune function\(^8\),\(^10\)\(^–\)\(^14\)
- Increased NK-mediated MM lysis\(^14\),\(^15\)

IMiDs: Pomalidomide

MM, multiple myeloma; NK, natural killer.
Molecular Structure of IMiDs (Immunomodulatory drugs)

Thalidomide
100–200 mg/d
Neuropathy
Constipation
Sedation
DVT

Lenalidomide
15–25 mg/d
Myelosuppression
Skin rash
DVT

Pomalidomide
2–4 mg/d
Myelosuppression
Antitumor Activity of Thalidomide in Refractory Multiple Myeloma

Seema Singhal, et al

1999;341:1565
Glasmacher A, Br J Haematol 2005

- 42 communications (24 full papers)
- 1629 patients
- median dose > 200 mg/d in 86% of cases

CR or VGPR (> 90%) 1.6
PR (>50%) 27.8 43.2%
MR 13.8

- Survival data
1 year EFS 35 %, median EFS : 3 to 16 months
1 year SV 60 %, median SV : 14 months
Melphalan and prednisone plus thalidomide versus melphalan and prednisone alone or reduced-intensity autologous stem cell transplantation in elderly patients with multiple myeloma (IFM 99–06): a randomised trial

MP versus MPT and MP versus MEL100 in newly diagnosed elderly MM patients: response*

**Overall survival**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>PFS, months</th>
<th>p value</th>
<th>OS, months</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MP (n = 196)</td>
<td>17.8 ± 1.4</td>
<td>&lt; 0.0001</td>
<td>33.2 ± 5.8</td>
<td>0.001</td>
</tr>
<tr>
<td>MPT (n = 125)</td>
<td>27.5 ± 2.1</td>
<td>0.0002</td>
<td>51.6 ± 4.5</td>
<td>0.004</td>
</tr>
<tr>
<td>MEL100 (n = 126)</td>
<td>19.4 ± 1.0</td>
<td></td>
<td>38.3 ± 2.7</td>
<td></td>
</tr>
</tbody>
</table>

* Median follow-up time: 51.5 months (IQR 34.4–63.2).

MPT vs MP for previously untreated elderly patients with MM: Meta-analysis of 1685 individual-patient data from 6 randomized trials

**PFS**
- Median 20.3 mos (18.8-21.6)
- Median 14.9 mos (14.0-16.6)
- HR=0.67 in favor of MPT, p<0.0001

**OS**
- Median 39.3 mos (35.6-44.6)
- Median 32.7 mos (30.5-36.6)
- HR=0.83 in favor of MPT, p=0.005*

* Cox model for treatment, with analysis stratified by study using a random effects (frailty) model

Fayers et al. Blood 2011;118:1239-1247
Phase III trial of Thal + Dex compared with Dex alone in NDMM (MM-003)

Multi-centre phase III study

Thal/Dex (n = 235)
Thalidomide: 50 mg/day escalating to 100 mg/day on day 15, and to 200 mg/day from day 1 of cycle 2 + dexamethasone: 40 mg on days 1–4, 9–12, and 17–20 (cycles 1–4), and days 1–4 (cycle 5+)

Placebo/Dex (n = 235)
Placebo: as for thalidomide above + dexamethasone: as for above

- 28-day cycles repeated until disease progression or unacceptable toxicity
- Stratification according to age, ECOG performance status, and β2-microglobulin
- Primary end-point TTP

470 patients with untreated symptomatic MM

ECOG = Eastern Cooperative Oncology Group; NDMM = newly diagnosed MM.
Thal + Dex vs Dex in newly diagnosed MM (MM-003): TTP and overall survival

Time to progression (TTP)

HR (95% CI): 0.43 (0.32–0.58)

Proportion of subjects with no progression

- Thal + Dex
- Placebo + Dex
- Censored

p < 0.001

Thal + Dex median time to progression: 22.6 months
Placebo + Dex median time to progression: 6.5 months

Overall survival

<table>
<thead>
<tr>
<th>Event</th>
<th>MP (N=193)</th>
<th>MPT (N=124)</th>
<th>MEL100 (N=122)</th>
<th>p</th>
<th>MP vs MPT</th>
<th>MP vs MEL100</th>
<th>MPT vs MEL100</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Haematological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>27 (14%)</td>
<td>17 (14%)</td>
<td>122 (100%)</td>
<td>0.94</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>51 (26%)</td>
<td>60 (48%)</td>
<td>122 (100%)</td>
<td>&lt;0.0001</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>19 (10%)</td>
<td>11 (14%)</td>
<td>122 (100%)</td>
<td>0.29</td>
<td>*</td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Severe hemorrhage†</td>
<td>3 (1.5%)</td>
<td>0</td>
<td>4 (3%)</td>
<td></td>
<td></td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>Thrombosis or embolism</strong></td>
<td>8 (4%)</td>
<td>16 (12%)</td>
<td>10 (8%)</td>
<td>0.008</td>
<td>0.13</td>
<td>0.31</td>
<td></td>
</tr>
<tr>
<td>Peripheral neuropathy</td>
<td>0</td>
<td>8 (6%)</td>
<td>0</td>
<td>0.001</td>
<td>*</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Somnolence/fatigue/dizziness</td>
<td>0</td>
<td>10 (8%)</td>
<td>0</td>
<td>&lt;0.0001</td>
<td>*</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever of unknown origin</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
<td>26 (21%)</td>
<td>0.32</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>5 (2.5%)</td>
<td>9 (7%)</td>
<td>11 (9%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septicaemia</td>
<td>6 (3%)</td>
<td>4 (3%)</td>
<td>22 (18%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningitis</td>
<td>0</td>
<td>2 (2%)</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>6 (3%)</td>
<td>1 (1%)</td>
<td>14 (11%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>6 (3%)</td>
<td>3 (2.5%)</td>
<td>4 (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1 (0.5%)</td>
<td>2 (2%)</td>
<td>12 (10%)</td>
<td>*</td>
<td>&lt;0.0001</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction/angina</td>
<td>0</td>
<td>2 (2%)</td>
<td>4 (3%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>0</td>
<td>0</td>
<td>2 (2%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>3 (2.5%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (1%)</td>
<td>1 (1%)</td>
<td>9 (7%)</td>
<td></td>
<td></td>
<td>0.004</td>
<td>0.01</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>1 (10%)</td>
<td>0</td>
<td>&lt;0.0001</td>
<td>*</td>
<td>0.0004</td>
<td></td>
</tr>
<tr>
<td>Mucositis</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>7 (6%)</td>
<td></td>
<td></td>
<td>*</td>
<td>0.006</td>
</tr>
<tr>
<td>Bleeding</td>
<td>2 (1%)</td>
<td>0</td>
<td>2 (2%)</td>
<td></td>
<td></td>
<td>*</td>
<td>0.007</td>
</tr>
<tr>
<td><strong>Any grade ≥3 non-haematological toxic effect</strong></td>
<td>30 (16%)</td>
<td>5 (42%)</td>
<td>71 (58%)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>
Molecular Structure of Imids (Immunomodulatory drugs)

Thalidomide
100–200 mg/d
Neuropathy
Constipation
Sedation
DVT

Lenalidomide
15–25 mg/d
Myelosuppression
Skin rash
DVT

Pomalidomide
2–4 mg/d
Myelosuppression
Lenalidomide plus Dexamethasone for Relapsed or Refractory Multiple Myeloma

Meletios Dimopoulos, M.D., Andrew Spencer, M.D., Michael Attal, M.D., H. Miles Prince, M.D., Jean-Luc Harousseau, M.D., Anna Dmoszynska, M.D., Jesus San Miguel, M.D., Andrzej Hellmann, M.D., Thierry Facon, M.D., Robin Foà, M.D., Alessandro Corso, M.D., Zvenyslava Masliak, M.D., Marta Olesnyckyj, R.N., Zhinuan Yu, Ph.D., John Patin, M.S., Jerome B. Zeldis, M.D., Ph.D., and Robert D. Knight, M.D., for the Multiple Myeloma (010) Study Investigators*

Lenalidomide + Dexamethasone in RRMM: Two Phase 3 Trials

- North American MM-009 (48 centres in the US, Canada; n = 353)\(^1\)
- International MM-010 (50 centres in Europe, Australia, Israel; n = 351)\(^2\)
- Mean follow-up length of MM-009: 17.6 months, MM-010: 16.4 months

**Len:** 25 mg, Days 1–21\(^a\)

**Dex:** 40 mg, Days 1–4, 9–12, 17–20 for the first 4 cycles; 40 mg, Days 1–4 for subsequent cycles

Continue until disease progression

**Placebo:** Days 1–21\(^a\)

\(^a\)Each course of treatment lasted 28 days.

Len, Lenalidomide; Dex, dexamethasone

Lenalidomide + Dexamethasone Significantly Prolonged TTP vs Placebo + Dexamethasone$^{1,2}$

- TTP with Lenalidomide + dexamethasone was significantly longer compared to placebo + dexamethasone in both trials ($p < 0.001$)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>Median TTP</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MM-009</td>
<td>Len + Dex</td>
<td>177</td>
<td>11.1 months$^1$</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>MM-009</td>
<td>Placebo + Dex</td>
<td>176</td>
<td>4.7 months$^1$</td>
<td></td>
</tr>
<tr>
<td>MM-010</td>
<td>Len + Dex</td>
<td>176</td>
<td>11.3 months$^2$</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>MM-010</td>
<td>Placebo + Dex</td>
<td>175</td>
<td>4.7 months$^2$</td>
<td></td>
</tr>
</tbody>
</table>

Pooled MM-009/MM-010 Analysis: Lenalidomide + Dexamethasone Significantly Prolonged OS

- Cross-over rate from Placebo + dexamethasone to Lenalidomide-based therapy was 47.6%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Median OS</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Len + Dex</td>
<td>38.0 months</td>
<td>0.045</td>
</tr>
<tr>
<td>Placebo + Dex</td>
<td>31.6 months</td>
<td></td>
</tr>
</tbody>
</table>

Safety Profile of Lenalidomide + Dexamethasone in RRMM

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Lenalidomide + Dex</th>
<th>Placebo + Dex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>125 (35.4)**</td>
<td>12 (3.4)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>46 (13.0)**</td>
<td>22 (6.3)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>38 (10.8)*</td>
<td>21 (6.0)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>32 (9.1)</td>
<td>19 (5.4)</td>
</tr>
<tr>
<td>All thromboembolic events</td>
<td>56 (15.9)**</td>
<td>19 (5.4)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>27 (7.6)</td>
<td>27 (7.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>23 (6.5)</td>
<td>17 (4.9)</td>
</tr>
</tbody>
</table>

- Pooled analysis from MM-009 and MM-010: grade ≥3 AEs occurring in more than 5% of patients

*p < 0.001; **p < 0.05.

Hazard Rates of Haematologic AEs in Patients Continuously Treated With Lenalidomide + Dexamethasone

MM-009 and MM-010 Subgroup Analysis: 212 (of 353) Patients Who Achieved ≥ PR

<table>
<thead>
<tr>
<th>Time, Months</th>
<th>Neutropenia</th>
<th>Thrombocytopenia</th>
<th>Thrombotic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.038</td>
<td>0.022</td>
<td>0.011</td>
</tr>
<tr>
<td>6</td>
<td>0.022</td>
<td>0.009</td>
<td>0.005</td>
</tr>
<tr>
<td>9</td>
<td>0.011</td>
<td>0.006</td>
<td>0.003</td>
</tr>
<tr>
<td>12</td>
<td>0.006</td>
<td>0.003</td>
<td>0.001</td>
</tr>
<tr>
<td>15</td>
<td>0.004</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>18</td>
<td>0.003</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>21</td>
<td>0.002</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>24</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>27</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Neuropathy Risk Decreased During Lenalidomide + Dexamethasone Treatment Regardless of History of Neuropathy

MM-009 and MM-010 Subgroup Analysis

With History of Neuropathy

Without History of Neuropathy

Incidence Rate (per 100 Person-Months)

Time, Months

Severity

Grade 1

Grade 2

Grade 3

Severity

Grade 1

Grade 2

Grade 3

MM-009/010: Trend Toward Improved Median Survival With Continued Therapy After Achievement of Response

Patients discontinuing Len + Dex (n = 38)

Patients continuing Len + Dex (n = 174)

Median OS: 50.9 vs 35.0 months; p = 0.0594

Continuous Treatment With Lenalidomide and Dexamethasone Did Not Increase the Incidence of Gr≥3 AEs

<table>
<thead>
<tr>
<th>Grade ≥ 3 Adverse Event, n (%)</th>
<th>Patients (n = 174)</th>
<th>Total population (n= 351)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>72 (41)</td>
<td>125 (35)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>20 (12)</td>
<td>46 (13)</td>
</tr>
<tr>
<td>Thrombotic events</td>
<td>19 (11)</td>
<td>56 (16)</td>
</tr>
<tr>
<td>Hyperglycaemia</td>
<td>15 (9)</td>
<td>27 (8)</td>
</tr>
<tr>
<td>Anaemia</td>
<td>13 (8)</td>
<td>38 (11)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13 (8)</td>
<td>32 (9)</td>
</tr>
<tr>
<td>Hypokalaemia</td>
<td>10 (6)</td>
<td>20 (6)</td>
</tr>
</tbody>
</table>

- 112 patients (64%) required lenalidomide dose reductions/interruptions due to adverse events
- 42 patients (24%) received G-CSF support

G-CSF, granulocyte-colony stimulating factor.

MM-015: Study Design

- Newly diagnosed
- Transplant-ineligible multiple myeloma
- Stratified by age (65-75 vs > 75 years) and disease stage (ISS I/II vs III)

N = 459

Double-Blind Treatment

**MPR-R (n = 152)**
- M: 0.18 mg/kg, days 1-4
- P: 2 mg/kg, days 1-4
- R: 10 mg/day po, days 1-21

**MPR (n = 153)**
- M: 0.18 mg/kg, days 1-4
- P: 2 mg/kg, days 1-4
- R: 10 mg/day po, days 1-21

**MP (n = 154)**
- M: 0.18 mg/kg, days 1-4
- P: 2 mg/kg, days 1-4
- PBO: days 1-21

Maintenance
- Lenalidomide 10 mg/day days 1-21
- Placebo

Disease Progression
- Placebo

Cycles (28-day) 1-9
- Cycles 10+

Open-Label

Lenalidomide 25 mg/day ± Dex

* All patients received thromboprophylaxis during induction; thromboprophylaxis could be continued during maintenance at physician’s discretion.


MM-015: Progression-Free Survival

- MPR-R significantly extended median PFS vs. MP and MPR

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR-R</td>
<td>31 months</td>
</tr>
<tr>
<td>MPR</td>
<td>14 months</td>
</tr>
<tr>
<td>MP</td>
<td>13 months</td>
</tr>
</tbody>
</table>

HR: hazard ratio; MP: melphalan-prednisone; MPR: melphalan-prednisone-Lenalidomide; MPR-R: melphalan-prednisone-Lenalidomide followed by Lenalidomide maintenance; N/A: not applicable; PFS: progression-free survival.

• After a median follow-up of 30 months, the number of deaths was low (31% event rate) and comparable across all arms.

**HR (P value)**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR-R vs. MPR</td>
<td>0.79</td>
<td>0.25</td>
</tr>
<tr>
<td>MPR-R vs. MP</td>
<td>0.95</td>
<td>0.81</td>
</tr>
</tbody>
</table>

**3-year OS**

<table>
<thead>
<tr>
<th>Arm</th>
<th>OS Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR-R</td>
<td>70%</td>
</tr>
<tr>
<td>MPR</td>
<td>62%</td>
</tr>
<tr>
<td>MP</td>
<td>66%</td>
</tr>
</tbody>
</table>

HR: hazard ratio; MP: melphalan-prednisone; MPR: melphalan-prednisone-Lenalidomide; MPR-R: melphalan-prednisone-Lenalidomide followed by Lenalidomide maintenance; N/A: not applicable; OS: overall survival.

FIRST Trial: Study Design

**Randomization 1:1:1**

- **Arm A**
  - Continuous Rd
  - LEN + Lo-DEX Continuously
    - LENALIDOMIDE 25mg D1-21/28
    - Lo-DEX 40mg D1,8,15 & 22/28

- **Arm B**
  - Rd18
  - LEN + Lo-DEX: 18 Cycles (72 wks)
    - LENALIDOMIDE 25mg D1-21/28
    - Lo-DEX 40mg D1,8,15 & 22/28

- **Arm C**
  - MPT
  - MEL + PRED + THAL 12 Cycles\(^1\) (72 wks)
    - MELPHALAN 0.25mg/kg D1-4/42
    - PREDNISONE 2mg/kg D1-4/42
    - THALIDOMIDE 200mg D1-42/42

**PD or Unacceptable Toxicity**

- PD, OS and Subsequent anti-MM Tx

- **Pts > 75 yrs**: Lo-DEX 20 mg D1, 8, 15 & 22/28; THAL\(^2\) (100 mg D1-42/42); MEL\(^2\) 0.2 mg/kg D1–4

- **Stratification**: age, country and ISS stage

ISS, International Staging System; LT, long-term; PD, progressive disease; OS, overall survival

FIRST Trial: Final Progression-free Survival

Median PFS

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd</td>
<td>25.5 mos</td>
</tr>
<tr>
<td>Rd18</td>
<td>20.7 mos</td>
</tr>
<tr>
<td>MPT</td>
<td>21.2 mos</td>
</tr>
</tbody>
</table>

Hazard ratio

Rd vs. MPT: 0.72; $P = 0.00006$
Rd vs. Rd18: 0.70; $P = 0.00001$
Rd18 vs. MPT: 1.03; $P = 0.70349$

mos, months; MPT, melphalan, prednisolone, thalidomide; PFS, progression-free survival; Rd, lenalidomide plus low-dose dexamethasone.
FIRST Trial: Overall Survival Interim Analysis

574 deaths (35% of ITT)

4-year OS

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>4-year OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rd</td>
<td>535</td>
<td>59.4%</td>
</tr>
<tr>
<td>Rd18</td>
<td>541</td>
<td>55.7%</td>
</tr>
<tr>
<td>MPT</td>
<td>547</td>
<td>51.4%</td>
</tr>
</tbody>
</table>

Overall survival (months)

Hazard ratio

Rd vs. MPT: 0.78; \( P = 0.0168 \)
Rd vs. Rd18: 0.90; \( P = 0.307 \)
Rd18 vs. MPT: 0.88; \( P = 0.184 \)

**IFM 2005-02: Study Design and Endpoints**

- **Primary endpoint:** PFS
- **Secondary endpoints:** ORR, EFS, OS

**N = 614**
- NDMM; < 65 years of age
- ≥ SD within 6 months of ASCT
- Stratified according to β2-M, del(13),* ≥ VGPR post-ASCT

**Consolidation†‡**
- 2 × 28-day cycles

**Lenalidomide 25 mg/day days 1-21**

**Maintenance‡**
- until progression

**Lenalidomide 10-15 mg § daily**
- (n = 307)

**Placebo**
- (n = 307)

---

* As measured by FISH; † Consolidation phase added at first protocol amendment (Sept 2006); ‡ Thromboprophylaxis was not mandatory; § 10 mg/day for the first 3 months, then increased to 15 mg/day if tolerated.

ASCT: autologous stem cell transplant; β2-M: β2-microglobulin; del: deletion; EFS: event-free survival; FISH: fluorescence in situ hybridisation; IFM: Intergroupe Francophone du Myélome; NDMM: newly diagnosed multiple myeloma; ORR: overall response rate; OS: overall survival; PFS: progression-free survival; R: randomisation; SD: stable disease; VGPR: very good partial response.

IFM 2005-02: Progression-Free Survival

- Lenalidomide maintenance significantly prolonged median PFS vs. placebo

**Cut-off: July 2010**

<table>
<thead>
<tr>
<th></th>
<th>Median PFS</th>
<th>HR (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN</td>
<td>41 months</td>
<td>0.50 (&lt; 0.001)</td>
</tr>
<tr>
<td>PBO</td>
<td>23 months</td>
<td>N/A</td>
</tr>
</tbody>
</table>

**Cut-off: Oct 2011**

<table>
<thead>
<tr>
<th></th>
<th>4-year PFS</th>
<th>HR (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEN</td>
<td>43%</td>
<td>0.50 (&lt; 0.001)</td>
</tr>
<tr>
<td>PBO</td>
<td>22%</td>
<td>N/A</td>
</tr>
</tbody>
</table>

HR: hazard ratio; IFM: Intergroupe Francophone du Myélome; LEN: Lenalidomide; N/A: not applicable; PBO: placebo; PFS: progression-free survival.

Poor Prognosis in Patients Ineligible for Novel Agents

- RRMM patients who are intolerant of or refractory to treatment with Lenalidomide, thalidomide, or bortezomib have a poor prognosis
  - Median EFS: 5 months
  - Median OS: 9 months

Kumar SK. Leukemia. 2012; 26:149-57.
Molecular Structure of Imids (Immunomodulatory drugs)

Thalidomide
100–200 mg/d
Neuropathy
Constipation
Sedation
DVT

Lenalidomide
15–25 mg/d
Myelosuppression
Skin rash
DVT

Pomalidomide
2–4 mg/d
Myelosuppression
**MM-003 Design: POM + LoDEX vs. HiDEX**

**RANDOMIZATION 2:1**

28-day cycles

(n = 302)

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

Follow-Up for OS and SPM Until 5 Years Post Enrollment

(n = 153)

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

Companion trial MM-003C
POM 21/28 days

Thromboprophylaxis was required for those receiving POM or at high risk for DVT

**Stratification**

- **Age** (≤ 75 vs. > 75 yrs)
- **Number of prior Tx** (2 vs. > 2)
- **Disease population** (primary refractory vs. relapsed/refractory vs. intolerance/failure)

*a* Progression of disease was independently adjudicated in real time.

Dimopoulos MA, et al. Updated Analysis, Cytogenetics, Long-Term Treatment, and Long-Term Survival in MM-003, A Phase 3 Study Comparing Pomalidomide + Low-Dose Dexamethasone (POM + LoDEX) vs High-Dose Dexamethasone (HiDEX) in Relapsed/Refractory Multiple Myeloma (RRMM). *Oral presentation at: American Society of Hematology. 2013; December 7-10; New Orleans, LA.*
MM-003: Overall Survival (ITT)

<table>
<thead>
<tr>
<th></th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>POM + LoDEx (n = 302)</td>
<td>13.1 mos</td>
</tr>
<tr>
<td>HiDEx (n = 153)</td>
<td>8.1 mos</td>
</tr>
</tbody>
</table>

HR = 0.72
P = .009

• 85 pts (56%) on the HiDEx arm received subsequent POM

Dimopoulos MA, et al. Updated Analysis, Cytogenetics, Long-Term Treatment, and Long-Term Survival in MM-003, A Phase 3 Study Comparing Pomalidomide + Low-Dose Dexamethasone (POM + LoDEx) vs High-Dose Dexamethasone (HiDEx) in Relapsed/Refractory Multiple Myeloma (RRMM). Oral presentation at: American Society of Hematology. 2013; December 7-10; New Orleans, LA.
MM-003. OS – Forest Plot of Subgroup Analyses
Updated March 1 2013

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95%CI)</th>
<th>POM + LoDEX*</th>
<th>HiDEX*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITT Population</td>
<td>0.74 (0.56-0.97)</td>
<td>145/302</td>
<td>82/153</td>
</tr>
<tr>
<td>LEN and BORT Refractory</td>
<td>0.77 (0.56-1.05)</td>
<td>113/225</td>
<td>62/113</td>
</tr>
<tr>
<td>LEN as Last Prior Tx</td>
<td>0.53 (0.33-0.87)</td>
<td>41/85</td>
<td>29/49</td>
</tr>
<tr>
<td>BORT as Last Prior Tx</td>
<td>0.87 (0.56-1.36)</td>
<td>56/132</td>
<td>30/66</td>
</tr>
</tbody>
</table>

Favors POM + LoDEX  Favors HiDEX

* Number of events/number of pts
San Miguel JF, et al. ASCO 2013 [abstract 8510].
# MM-003 Phase 3: Safety

<table>
<thead>
<tr>
<th>Event</th>
<th>POM + LoDEX (N = 300)</th>
<th>HiDEX (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Grade 3/4 haematological AEs, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>48</td>
<td>16</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>33</td>
<td>37</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td><strong>Grade 3/4 non-haematological AEs, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>13</td>
<td>8</td>
</tr>
<tr>
<td>Bone pain</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Asthenia</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Glucose intolerance</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td><strong>Grade 3/4 AEs of interest, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DVT/PE</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Peripheral neuropathy&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Discontinuation due to AEs, %</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>
Pomalidomide superior to any approach post Bortezomib and Lenalidomide

![Graph showing survival distribution function estimates for TTP (time-to-progression) for last prior line, pomalidomide, and IRC responders, with time from first intake in weeks on the x-axis and survival distribution function estimate on the y-axis.]

IRC = Independent review committee; ITT = intent-to-treat; TTP = time-to-progression.
<table>
<thead>
<tr>
<th>Category</th>
<th>Drugs and Clinical Trials</th>
</tr>
</thead>
</table>
| **Proteasome inhibitors** | • Rd + **carfilzomib** in RRMM, phase 3 (US/EU), phase 1/2 (US)  
                             • Rd + **MLN9708** in RRMM: phase 3 (USA, Canada, EU)  
                             • Rd + **MLN9708** in NDMM: phase 3 (USA, Canada, France, Belgium, Japan) |
| **HDAC inhibitors**       | • Rd + **vorinostat** in RRMM: multiple phase 1/2 (US, EU), 1 phase 3 (USA)  
                             • Rd + **panobinostat** in RRMM: 2 phase1/2 (USA, Australia, EU)  
                             • Rd + **ACY-1215** in RRMM: phase 1 (USA)                           |
| **Monoclonal antibodies** | • Rd + **elotuzumab** in RRMM: multiple phase 1/2 (EU, USA, Japan), 1 phase 3 (ELOQUENT-2)  
                             • Rd + **elotuzumab** in NDMM: phase 3 (ELOQUENT-1)  
                             • Rd + **daratumumab** in RRMM: 1 phase 3  
                             • Rd + **SAR650984** in RRMM: phase 1 (USA)  
                             • Rd + **IPH2101** in RRMM: phase 1 (USA)                         |
# IMiDs in numbers

## Trials (as per clinicaltrials.gov, dd 12 May 2014)

<table>
<thead>
<tr>
<th></th>
<th>Open</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>Thalidomide</td>
<td>136</td>
<td>330</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>117</td>
<td>254</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>29</td>
<td>45</td>
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## Publications (as per pubmed, dd 12 May 2014)

<table>
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<th>2012</th>
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<tr>
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<td>299</td>
<td>315</td>
<td>2422</td>
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<tr>
<td>Lenalidomide</td>
<td>275</td>
<td>244</td>
<td>1232</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td>53</td>
<td>21</td>
<td>132</td>
</tr>
</tbody>
</table>
Model of the disease course in multiple myeloma

Multiple myeloma: changing the paradigm in the RRMM setting

Active MM

MGUS or SMM

M-protein (g/L)

100

50

20

First-line therapy

Second-line therapy

Third-line therapy

Plateau remission

First relapse

Second relapse

Third relapse

Pomalidomide

Lenalidomide

Active MM

REFRACTORY RELAPSE

Proposed “Updated” Model
Never give up!

We will make it...

Thank you for your attention