Comparative Effectiveness of Pomalidomide Plus Low-Dose Dexamethasone (POM+LoDEX) in Relapsed and Refractory Multiple Myeloma: Use of Real-World Data in the Absence of Head-to-Head Studies

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Disclosures

• HG: Has received research support from Celgene, Janssen, Chugai, Novartis, BMS, Millennium, Served on the advisory boards at Celgene, Janssen, Novartis, Onyx, Amgen, Takeda, BMS and received honoraria from Celgene, Janssen, Novartis, Chugai, Onyx, Millennium

• DL, RH: Consultant/advisor for Celgene

• SD: Employment by and equity ownership of Celgene

• PM: Received honoraria from Celgene

• SS: Has no relevant conflicts of interest to declare

• LP: Has no relevant conflicts of interest to declare

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• GC: Disclosures have been requested
Background

• The MM-003 study demonstrated a clinically and statistically significant survival benefit with POM+LoDEX vs high-dose dexamethasone (HiDEX) in relapsed and refractory multiple myeloma (RRMM) following prior treatment with both bortezomib (BORT) and lenalidomide (LEN)\textsuperscript{1,2}:
  – Median increase 4.6 months overall survival (OS) unadjusted for crossover (12.7 vs 8.1 months; HR 0.74 [95% CI, 0.56-0.97])\textsuperscript{1} based on the March 2013 data cut
  – Median increase 7.0 months OS adjusted for crossover (12.7 vs 5.7 months; HR 0.52 [95% CI, 0.39-0.68])\textsuperscript{2} based on the March 2013 data cut
  – Median increase 5.0 months OS unadjusted for crossover (13.1 vs 8.1 months; HR 0.52 [95% CI, 0.39-0.68])\textsuperscript{3} based on the September 2013 data cut

• Increasingly, access to innovative medicines requires a demonstration of increased benefit vs current care by reimbursement bodies

• Although HiDEX was standard of care when MM-003 was designed, in the treatment setting immediately following BORT and LEN, DEX is now mostly used with palliative intent or as an add-on to other treatments

• Current European standard of care in this setting primarily comprises combinations including bendamustine (BEN), BORT retreatment, or LEN retreatment
Objectives

- The objective of this study was to estimate the comparative effectiveness of POM+LoDEX vs other active treatments in patients with RRMM who had previous failure of LEN and BORT treatment using statistical analyses performed on time-to-event individual patient data (IPD).

- A secondary objective was to estimate long-term OS outcomes based on standard extrapolation methods.
Inclusion/Exclusion Criteria

- IPD for current care treatments was sourced from 5 EU countries (United Kingdom, France, Spain, Italy, Germany) using the following inclusion/exclusion criteria to allow for appropriate comparisons:
  - However, for the current analysis and results, only the UK data was available to report.

Table 1. Inclusion/Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subsequent therapy received following previous treatment with both BORT and LEN</td>
<td>Missing OS information</td>
</tr>
<tr>
<td>Information collected on the following potentially prognostic covariates:</td>
<td>Missing covariate information</td>
</tr>
<tr>
<td>- Age</td>
<td></td>
</tr>
<tr>
<td>- Disease duration</td>
<td></td>
</tr>
<tr>
<td>- ISS stage</td>
<td></td>
</tr>
<tr>
<td>- Receipt of prior SCT</td>
<td></td>
</tr>
<tr>
<td>- Receipt of prior thalidomide</td>
<td></td>
</tr>
<tr>
<td>- Treatment regimen received post BORT and LEN</td>
<td></td>
</tr>
<tr>
<td>- Refractoriness to BORT and LEN</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subsequent POM received</td>
</tr>
</tbody>
</table>

ISS, International Staging System; SCT, stem cell transplant.
Methods

- IPD for POM+LoDEX was sourced from the MM-002 and MM-003 trials
- Available data were included in a time-to-event regression model, adjusting for 8 covariates selected based on prognostic value in the MM-003 trial and clinician advice
  - Age (years)
  - Disease duration (years)
  - ISS stage (1/2/3)
  - Receipt of prior thalidomide (yes/no)
  - Receipt of prior stem cell transplant (yes/no)
  - Refractory to BORT (yes/no)—defined as progression on or within 60 days of treatment
  - Refractory to LEN (yes/no)—defined as progression on or within 60 days of treatment
  - Treatment (POM+LoDEX/other active treatments)
- OS and progression-free survival (PFS) were measured from the start of the treatment line of interest to the analysis, ie, the first line of therapy post BORT and LEN
Data Analysis

- As a large proportion of patients in this setting received treatment with BEN, the difference in survival with POM+LoDEX vs BEN vs other therapies was investigated using Cox regression analysis.
- Adjusted Kaplan-Meier plots stratified by treatment were then generated for:
  - OS
  - PFS
  - Time to treatment failure (TTF)
- Five parametric curves (exponential, Weibull, log-logistic, log-normal and extreme value) were fitted to the adjusted Kaplan-Meier data to predict long-term survival.
- Goodness of fit was assessed in accordance with NICE Decision Support Unit guidance\textsuperscript{4} based on statistical goodness of fit (Akaike Information Criteria [AIC], Bayesian Information Criteria [BIC]), visual fit, and clinical validity.
### Table 2. Provides a summary of the trial design for datasets

<table>
<thead>
<tr>
<th>Dataset</th>
<th>Number of Relevant Patients</th>
<th>Trial Design</th>
<th>Dates of Data</th>
<th>Datasets Considered</th>
<th>Inclusion Criteria</th>
<th>Included in This Analysis?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current Care</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gooding et al⁵</td>
<td>30</td>
<td>Retrospective chart review using pharmacy-generated lists of sequential LEN recipients</td>
<td>Jan 2011 to Jul 2013</td>
<td>BEN containing BEN containing DT-PACE LEN containing No treatment</td>
<td>Progressive or refractory disease following receipt of BORT and LEN</td>
<td>Y</td>
</tr>
<tr>
<td>Tarant et al⁷</td>
<td>26</td>
<td></td>
<td>Jan 2007 to Sep 2012</td>
<td>BEN containing BEN containing LEN containing Clinical trials Other chemotherapies</td>
<td>Progressive disease following receipt sequentially THAL, BORT, then LEN</td>
<td>Y</td>
</tr>
<tr>
<td>Musto et al⁶</td>
<td>41</td>
<td>Retrospective, real-life analysis of Italian patients with RRMM who had received salvage therapy with BEN as single agent or in combination with other drugs, within a national, compassionate-use program (18 centers)</td>
<td>Jan 2011 to 2014</td>
<td>BEN containing</td>
<td>Progressive disease following receipt of THAL, BORT, and LEN</td>
<td>N—missing covariate information Used for validation</td>
</tr>
<tr>
<td>EU Therapy Monitor</td>
<td>≈ 200</td>
<td>Retrospective chart review via survey of European centers (≈ 20 per country) in France, Germany, Italy and Spain</td>
<td>Jan 2012 to 2014</td>
<td>POM containing BEN containing Other active treatment</td>
<td>Receipt of BORT and LEN Died in 2015 from MM</td>
<td>N—planned for inclusion in future analysis</td>
</tr>
<tr>
<td>Pomalidomide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MM-002²</td>
<td>113</td>
<td>Randomized open-label Phase II study 18 centers in the USA and Canada</td>
<td>Dec 2009 to Feb 2013</td>
<td>POM+LoDEX arm</td>
<td>Progressive disease following ≥ 2 cycles of LEN and ≥ 2 cycles of BORT</td>
<td>Y</td>
</tr>
<tr>
<td>MM-003¹</td>
<td>302</td>
<td>Randomized open-label Phase III study 93 centers in Europe, Russia, Australia, Canada, and the USA</td>
<td>Mar 2011 to Sep 2013</td>
<td>POM+LoDEX arm</td>
<td>Progressive or refractory disease following ≥ 2 cycles of LEN and ≥ 2 cycles of BORT Progressive disease ≤ 6 months after achieving partial response to BORT or intolerance of BORT ≥ 6 cycles of alkylator treatment, or progressive disease after ≥ 2 cycles of alkylator treatment</td>
<td>Y</td>
</tr>
</tbody>
</table>

**THAL,** thalidomide.
Summary of Patient Characteristics in Datasets Included in This Analysis

- In Table 3, the datasets available for current care include patients with a similar age and number of prior therapies to the patients from the trials for POM+LoDEX, however, substantially fewer patients in the current care trials were refractory to either BORT or LEN

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>No. of Pts</th>
<th>ISS stage (% 1,2,3; n)</th>
<th>Prior THAL (% yes)</th>
<th>Prior SCT (% yes)</th>
<th>Refractory to BORT (% yes)</th>
<th>Refractory to LEN (% yes)</th>
<th>Age, (yrs) (mean)</th>
<th>Disease Duration (yrs)</th>
<th>Un-adjusted Median Survival (mos)</th>
<th>No of Pts in Analysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gooding et al⁵</td>
<td>Current UK standard of care</td>
<td>30</td>
<td>21.7, 34.8, 43.5; 23</td>
<td>83.3</td>
<td>46.7</td>
<td>10.0</td>
<td>16.7</td>
<td>67.6</td>
<td>4.5</td>
<td>5.3</td>
<td>21</td>
</tr>
<tr>
<td>Tarant et al⁷</td>
<td>Current UK standard of care</td>
<td>26</td>
<td>58.8, 35.3, 5.9; 17</td>
<td>76.9</td>
<td>65.4</td>
<td>3.8</td>
<td>7.7</td>
<td>64.3</td>
<td>6.3</td>
<td>8.4</td>
<td>15</td>
</tr>
<tr>
<td>MM-002⁸</td>
<td>POM+ LoDEX</td>
<td>113</td>
<td>7.1, 25.7, 67.3; 113</td>
<td>68.1</td>
<td>74.3</td>
<td>72.6</td>
<td>77.0</td>
<td>64.4</td>
<td>6.2</td>
<td>16.5</td>
<td>113</td>
</tr>
<tr>
<td>MM-003¹</td>
<td>POM+ LoDEX</td>
<td>302</td>
<td>27.9, 40.0, 32.1; 290</td>
<td>57.2</td>
<td>70.9</td>
<td>78.8</td>
<td>94.7</td>
<td>63.6</td>
<td>6.2</td>
<td>13.1</td>
<td>290</td>
</tr>
</tbody>
</table>

* Includes only patients meeting the study inclusion/exclusion criteria.
Within the current care datasets, no significant difference in survival prospects was found between BEN and other forms of active treatments (HR=0.98, 95% CI [0.50, 1.94]). This led to all active treatments being assessed as a whole rather than by individual treatment.

Figure 1. Kaplan-Meier Curves for BEN vs Other Standard Care Treatments

- This led to all active treatments being assessed as a whole rather than by individual treatment
Survival of POM+LoDEX vs Other Active Treatments

- Once adjusted for baseline patient demographics, POM+LoDEX showed even greater survival prospects vs other active treatments (Figure 2, HR, 0.33 [95% CI, 0.18-0.59]); median OS was 14.4 and 4.6 months, respectively.

**Figure 2. Kaplan-Meier Curves for OS, Stratified by Treatment Arm**
RESULTS

All curves fitted the adjusted survival data well. The log-normal curve produced the lowest AIC and BIC values and yielded a mean OS of 28.7 vs 9.6 months with POM+LoDEX vs other active treatments respectively.
Conclusions

• Based on this analysis, POM+LoDEX showed greater OS vs other active treatments, with the predicted median remaining in line with published estimates for patients in this hard-to-treat group who have received prior therapy with both LEN and BORT.\textsuperscript{4,5,8}

• A limitation of this analysis is that randomization is not preserved due to data arising from different center and studies; however, the method of covariate adjustment used can account for some imbalances that arise from the use of different populations. Additionally, the sample size available for the current analysis is relatively small. Additional datasets are being sought to validate the outcomes observed here with a larger sample size.

• Data sourcing is ongoing, and results from any additional datasets identified will be reported subsequently.
References

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