Safety and Efficacy of Daratumumab with Lenalidomide and Dexamethasone in Relapsed, or Relapsed and Refractory Multiple Myeloma

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Background

**Daratumumab**
- A human mAb that targets CD38-expressing tumor cells
- DARA+LEN enhanced killing of MM cells *in vitro* and is hypothesized to lead to synergistically higher efficacy in clinical setting

- Antibody-dependent cell-mediated cytotoxicity (ADCC)
- Antibody-dependent cellular phagocytosis (ADCP)
- Complement-dependent cytotoxicity (CDC)
- Apoptosis

*DARA: daratumumab; LEN: lenalidomide; mAB: monoclonal antibody; MM: multiple myeloma*
Background

- DARA plus LEN/DEX was well-tolerated in a very heavily pretreated patient population typical for MM (n=20) – *Data presented at ASCO 2014*
- Ongoing study with updated data for 45 patients (enrollment complete)

Objectives

- To establish the safety and efficacy profile of DARA in combination with LEN/DEX in relapsed, or relapsed and refractory (RR) MM
Study Design

Part 1: Dose escalation study (3×3 design) – 2-16 mg/kg dose; N=13

Part 2: Expansion cohort – 16 mg/kg dose; N=32
Key Eligibility

- Part 1: Relapsed and refractory MM following 2 – 4 prior lines of therapy
- Part 2: Relapsed and refractory MM following minimum 1 prior lines of therapy with no upper limit on number of prior therapy
- Measurable disease by M protein and light chain
- Adequate organ function
- Patients refractory or intolerant to LEN excluded

AE: adverse event; DARA: daratumumab; IMWG: International Myeloma Working Group; LEN: lenalidomide; MM: multiple myeloma; MR: minimal response; PD: progressive disease; PR: partial response
Results

Demographics & Baseline Characteristics

- Data from 45 patients (32 men, 13 women) are evaluable for safety
  - 11 patients evaluated for accelerated infusion
- Data from 43 patients are evaluable for efficacy
- Median age: 61 (41 to 76) years
- Median prior lines of therapy: 2 (1 to 4)
  - 91% patients had prior exposure to PI (bortezomib)
  - 80% patients had prior exposure to IMiD (lenalidomide and thalidomide)
  - 73% patients had prior exposure to autologous stem cell transplant
- 3 patients were lenalidomide refractory (according to IMWG criteria)

PI = proteasome inhibitor; IMiD = Immunomodulatory drug; IMWG: International Myeloma Working Group; MM: multiple myeloma;
Maximum % Change in M Protein from Baseline

**Part 1**
Dose Escalation Study
2-, 4-, 8- & 16 mg/kg dose
N=13

**Part 2**
Expansion Cohort Study
16 mg/kg dose
N=30

- Majority had >50% reduction of M protein
Best Response (PR or Better) and Duration of Follow-up

VGPR or better was 75% in patients who were treated for at least 6 months.

CR: complete response; PR: partial response; VGPR: very good partial response
Overall Best Response

- Mean duration of follow-up: 12.9 months (Part 1, range: 4.0-22.1) & 5.6 months (Part 2, range: 2.7 – 7.0)
- Median time to response: 1 month for 16 mg/kg in part 2
- Median time to CR in part 2 was 4.9 months
- As has been observed with other mAbs, DARA may interfere with IFE
  - Interference assay to be validated

CR: complete response; PR: partial response; VGPR: very good partial response.

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Safety

- Safety data collected from 45 patients
- No DLTs were reported

Part 1: 4 patients discontinued treatment:
  - 3 disease progression (1 each in 2-, 8- and 16-mg/kg dose cohort)
  - 1 AE (2-mg/kg dose cohort, cardiac disorder due to recurrence of low grade QT prolongation), unrelated to DARA

Part 2: 1 patient discontinued due to IRR (laryngeal edema)

AE: adverse event; DARA: daratumumab; DLT: dose limiting toxicity; IRR, infusion related reaction.
Most Common (Incidence in >10% Patients) Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Part 1 N=13</th>
<th>Part 2 N=32</th>
<th>Total N=45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with AEs, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>62</td>
<td>65</td>
<td>64</td>
</tr>
<tr>
<td>Muscle Spasms</td>
<td>62</td>
<td>38</td>
<td>44</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>54</td>
<td>18</td>
<td>31</td>
</tr>
<tr>
<td>Fatigue</td>
<td>62</td>
<td>16</td>
<td>29</td>
</tr>
<tr>
<td>Cough</td>
<td>31</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Constipation</td>
<td>54</td>
<td>13</td>
<td>27</td>
</tr>
<tr>
<td>Nausea</td>
<td>38</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>62</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Bone Pain</td>
<td>31</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Upper Respiratory Tract Infection</td>
<td>46</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Insomnia</td>
<td>31</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>23</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Anemia</td>
<td>31</td>
<td>19</td>
<td>11</td>
</tr>
</tbody>
</table>

AE: adverse event.
### Daratumumab Infusions

<table>
<thead>
<tr>
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<th>16 mg/kg</th>
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<tbody>
<tr>
<td></td>
<td>Current infusion program N=21</td>
</tr>
<tr>
<td>Total number of full infusions per patient, Mean (SD)</td>
<td>15.6 (2.77)</td>
</tr>
<tr>
<td>Median duration of first infusion (hours)</td>
<td>8.0</td>
</tr>
<tr>
<td>Median duration of second infusion (hours)</td>
<td>6.5</td>
</tr>
<tr>
<td>Median duration of subsequent infusions (hours)</td>
<td>5.5</td>
</tr>
</tbody>
</table>
Infusion-related Reactions

- **Majority grade 1 and 2**
- 19/45 patients reported infusion-related reactions
- Most infusion-related reactions (86%) occurred during first infusion
- 18/19 patients with infusion-related reactions recovered and were able to continue the subsequent infusion
Serious Adverse Events

- 15 SAEs reported:
  - Part 1: 7, all assessed as unrelated to DARA
  - Part 2: 8, 4 were DARA-related

- DARA related SAEs:
  - Pneumonia, neutropenia, diarrhea (1 patient each receiving 16 mg/kg, early infusion program)
  - Laryngeal edema (1 patient receiving 16 mg/kg, accelerated infusion program)

DARA: daratumumab; SAE: serious adverse events
Conclusions (1)

- ORR was 100% in part 1 (31% CR, 46% VGPR), and 87% in part 2 (7% CR, 43% VGPR)
  - VGPR or better was 75% in patients treated for at least 6 months
- Data from part 1 are mature and show impressive CR rates
- Early results from part 2 are consistent with part 1
  - Median follow-up <6 months with depth of response expected to further improve

CR: complete response; ORR: overall response rate; VGPR: very good partial response
Conclusions (2)

- Accelerated infusion was tolerable but associated with higher incidence of grade 1/2 AEs
  - Accelerated infusion will require further investigation

- DARA+LEN/DEX treatment demonstrated a favorable safety profile with manageable toxicities in relapsed and RR MM patients

- Phase 3 clinical development of DARA in combination with LEN/DEX is ongoing
  - MMY3003-POLLUX (relapsed/refractory), enrolling
  - MMY3008-MAIA (frontline), enrollment expected to start early 2015

AE: adverse event; DARA: daratumumab; DEX: dexamethasone; LEN: lenalidomide; MM: multiple myeloma; RR: relapsed refractory
Acknowledgements

- We thank the patients, their carers and investigators who participated in this study