Abstract #8019
Daratumumab – a CD38 mAb – for the Treatment of Relapsed/Refractory Multiple Myeloma Patients: Preliminary Efficacy Data from a Multicenter Phase I/II Study

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Disclosures

Consultant for Genmab. Member of Advisory Boards for Janssen and Celgene. Investigator for Genmab, Janssen, Celgene, Bristol Myers Squibb, Novartis, Roche, Nordic Myeloma Study Group, HOVON, German CLL Study Group. Teacher for Janssen, Celgene, Novartis and Norpharma/ Mundipharma. Recipient of research grants from Janssen, Celgene, Roche and Novartis.
Daratumumab

1. CD38 molecule
   CD38 is expressed on multiple myeloma, various leukemias (B-CLL, AML, B-ALL, plasma cell leukemia), NHL including DLBCL

2. Human CD38 antibody generated in transgenic mice

3. Potent
   - ADCC & CDC
   - Inhibition of CD38 enzyme activity
   - Apoptosis after cross-linking
   - In vivo efficacy: active at very low doses in mouse models

4. Effectively kills CD38^+ tumor cells, e.g. in multiple myeloma
   Additive/synergistic effects with novel agents

5. Currently in a Phase I/II clinical trial for multiple myeloma
Daratumumab
A human CD38 mAb with broad-spectrum killing activity
Daratumumab
Induces Potent CDC of patient MM tumor cells

Representative example of DARA-induced lysis

De Weers et al, J Immunol 186, 1840-1848 (2011)
Daratumumab
ADCC Induced in the Presence or Absence of BMSCs

Primary MM cells (9 patients)  
Dexamethasone-resistant cell line (MM1R)

Daratumumab: GEN501 - Phase I/II Study of Monotherapy in Relapsed and Relapsed, Refractory MM; Objectives

Primary
• Establishment of the safety profile of daratumumab

Secondary
• To establish the pharmacokinetic profile of daratumumab
• Evaluation of the efficacy of daratumumab according to International Myeloma Workshop Consensus Panel 1, Blood 2011;117:4691-5
• Evaluation of the immunogenicity of daratumumab.
Daratumumab
GEN501 - Ongoing Study in MM; Study Design

- GEN501 First In Human, daratumumab monotherapy in relapsed or relapsed, refractory MM, phase I/II
  - Part 1: ongoing: determine MTD, safety
  - Part 2: cohort expansion at MTD or dose chosen by IDMC/sponsor, for safety & efficacy

**Part 2**
Open label, single-arm
MTD from Part 1 chosen by DMC

**Part 1**
Open Label,
Dose Escalation

24 weeks of treatment

8 weeks of treatment

Maximum Tolerated Dose 16 pts

Dosing 0.005–24mg/kg

Weekly Infusions

10% Pre-infusion

Intermediate dose levels possible
Patient Characteristics
(Part 1; N=29)

• Patients [pts] with advanced Multiple Myeloma

• Relapsed or relapsed and refractory disease with at least 2 prior lines of therapy and without further established treatment options

• All IMiD, Bortezomib exposed.

• 76 % of pts had received a SCT before entering study incl 1 allo

<table>
<thead>
<tr>
<th>Cohort/ pt number</th>
<th>Age (yrs)</th>
<th>Number of prior lines of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 mg/kg (n=17)</td>
<td>63*</td>
<td>5*</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>64*</td>
<td>8*</td>
</tr>
<tr>
<td>Pt 018</td>
<td>60</td>
<td>6</td>
</tr>
<tr>
<td>Pt 019</td>
<td>64</td>
<td>10</td>
</tr>
<tr>
<td>Pt 020</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>64*</td>
<td>6*</td>
</tr>
<tr>
<td>Pt no 21</td>
<td>64</td>
<td>6</td>
</tr>
<tr>
<td>Pt no 22</td>
<td>62</td>
<td>6</td>
</tr>
<tr>
<td>Pt no 23</td>
<td>66</td>
<td>3</td>
</tr>
<tr>
<td>8 mg/kg</td>
<td>60*</td>
<td>11*</td>
</tr>
<tr>
<td>Pt no 26</td>
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<td>11</td>
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<tr>
<td>Pt no 27</td>
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<td>12</td>
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<tr>
<td>Pt no 28</td>
<td>56</td>
<td>5</td>
</tr>
<tr>
<td>16 mg/kg</td>
<td>55*</td>
<td>7*</td>
</tr>
<tr>
<td>Pt no 29</td>
<td>59</td>
<td>4</td>
</tr>
<tr>
<td>Pt no 30</td>
<td>55</td>
<td>7</td>
</tr>
<tr>
<td>Pt no 31</td>
<td>54</td>
<td>8</td>
</tr>
</tbody>
</table>

* median

• Patients with advanced Multiple Myeloma

• Relapsed or relapsed and refractory disease with at least 2 prior lines of therapy and without further established treatment options

• All IMiD, Bortezomib exposed.

• 76 % of pts had received a SCT before entering study incl 1 allo

PRESSENTED AT: ASCO Annual Meeting
Adverse Events [AEs] (reported in > 1 patient) across all cohorts; all grades (CTC 4.0)

**AEs primarily related to Infusion*:**
- pyrexia (31%)
- cough (21%)
- hypo/hypertension (7%/14%)
- nausea (14%)
- dizziness (10%)
- influenza-like illness (10%)
- rash (10%)
- arthralgia (7%)
- flushing (7%)
- chest pain (7%)
- fatigue (7%)
- headache (7%)
- tachycardia (7%)
- hypersensitivity (7%)
- cytokine release syndrome (7%)

**Other Treatment Emergent Laboratory AE’s :**
- monochytopenia (21%)
- lymphopenia (21%)
- free hemoglobin (17%)
- anemia (17%)
- hemolysis (14%)
- thrombocytopenia (7%)

**Other AEs:**
- diarrhea (10%)
- pneumonia (7%)
- vomiting (7%)

* Reduced with subsequent premeds
Daratumumab: Related Serious Adverse Events [SAEs]

• Five SAEs assessed as related to daratumumab:
  – One pt: anemia grade 3 (DLT) and thrombocytopenia grade 4
  – One pt: AST grade 3 (DLT)
  – One pt: bronchospasm grade 3
  – One pt: cytokine release syndrome grade 2
• In total, 2 DLT events reported; 3 more patients were enrolled in the 0.1 mg/kg and 1.0 mg/kg cohorts
• All patients recovered after relevant treatment
• No serious infusion-related AEs reported after implementation of relevant pre-medication and dilution of trial drug
• No major changes in platelet count or hemoglobin observed over time
Serum M-Component Results in Patients Treated with Daratumumab 4mg/kg (n=3)

- Treatment Period
- Arrows indicate last dose

Patient no. 021, 022, 023
Maximal Reduction of Serum M-Component (Part 1)
## Daratumumab: Max Reduction of M-Component/FLC and BM Plasma Cells (Part 1)

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n/N</th>
<th>Max reduction in M-component</th>
<th>Max reduction of plasma cells in BM smear</th>
<th>Responses according to IMWG Uniform Criteria[^4]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Serum</td>
<td>Urine</td>
<td>Reduction %</td>
</tr>
<tr>
<td>≤0.5 mg/kg</td>
<td>6/11</td>
<td>12%</td>
<td>3%[^5]</td>
<td>22%[^*]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50%</td>
<td></td>
<td>50%[^*]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0%</td>
<td>0%</td>
<td>0%[^*]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>14%</td>
<td>25%</td>
<td></td>
</tr>
<tr>
<td>1 mg/kg</td>
<td>3/6</td>
<td>24%[^1]</td>
<td>33%[^5]</td>
<td>1%[^*]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9%[^*]</td>
<td>19%</td>
<td></td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>1/3</td>
<td>67%[^2]</td>
<td>55%</td>
<td>-</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>3/3</td>
<td>49%</td>
<td>100%</td>
<td>87%[^*]</td>
</tr>
<tr>
<td></td>
<td></td>
<td>64%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>8 mg/kg</td>
<td>3/3</td>
<td>4%[^*]</td>
<td>39%</td>
<td>2%[^*]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>100%[^2]</td>
<td>93%[^1]</td>
</tr>
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</tr>
<tr>
<td>16 mg/kg</td>
<td>2/3</td>
<td>50%[^*]</td>
<td>33%[^3]</td>
<td>100%[^3]</td>
</tr>
<tr>
<td></td>
<td></td>
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</tbody>
</table>

[^*]: Not measurable at baseline; -: Not available; NA: not applicable; Explorer: Normal at baseline; 2: FLC only measurable; 3: Dosing ongoing; 4: Evaluation based on maximal reduction in M-component or for FLC according to consensus of uniform reporting of clinical trials (Rajkumar et al. Blood 2011;117:4691-5); 5: Based on only one measurement (no consecutive measurements); SD: stable disease; MR: minimal response; PR: partial response; VGPR: very good partial response
Conclusions/Future Directions

• Daratumumab has shown a favorable safety profile as monotherapy in relapsed and relapsed/refractory MM patients
• MTD has not yet been established/reached
• In 18 of 29 heavily pretreated MM patients receiving 8 weeks of daratumumab as monotherapy in doses up to 16mg/kg, a marked reduction in M-component has been observed, corresponding to preliminary responses of:
  – 5 patients achieving PR
  – 4 patients achieving MR
  – 9 patients achieving SD
• Biochemical responses were accompanied by clearance of myeloma cells from the bone marrow
• Dose escalation is ongoing and will be followed by a 24 week study (Part 2) to evaluate long-term safety and efficacy
• Continuous therapy studies and combination strategies planned (e.g. with bortezomib plus dex; lenalidomide plus dex)
Acknowledgments

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