DARATUMUMAB, A CD38 MONOCLONAL ANTIBODY IN PATIENTS WITH MULTIPLE MYELOMA - DATA FROM A DOSE-ESCALATION PHASE I/II STUDY

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Daratumumab
A Human CD38 mAb with Broad-Spectrum Killing Activity

CD38 molecule

1. 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
   - CDC, ADCC & ADCP
   - Inhibition of CD38 enzymatic 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
   - Enhanced killing in combination with other novel agents

5. Currently in two clinical trials for multiple myeloma
Daratumumab: GEN501
Phase I/II Study of Monotherapy in Relapsed and Relapsed - Refractory Multiple Myeloma

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
Main Inclusion Criteria

- Patients with advanced Multiple Myeloma requiring systemic therapy
- Patients with relapsed or relapsed and refractory disease with at least 2 prior lines of therapy and without further established treatment options
- Patients with ECOG performance status of 0-2
- Patients having a life expectancy > 3 months
Daratumumab
Trial Design

Part 1
Open label, weekly i.v. infusion, 8 weeks
Dose-escalation: 3+3 scheme*
0.005 → 0.05 → 0.1 → 0.5 → 1.0 → 2.0 → 4.0 → 8.0 → 16.0 → 24.0 mg/kg

Part 2
Open label, single arm, i.v. infusion
weekly: 8 weeks
every other week: 16 weeks
every fourth week: up to 96 weeks
8 mg/kg, 16 patients

*: - start with pre-dose at 10% of the full dose, max 10 mg
- three weeks’ delay after first full dose
- governed by independent data monitoring committee
Daratumumab
Patient Characteristics

<table>
<thead>
<tr>
<th>Cohort</th>
<th>No. of subjects</th>
<th>Age(^a)</th>
<th>No. of treatments(^a)</th>
<th>Len(^b)</th>
<th>Thal(^b)</th>
<th>Bor(^b)</th>
<th>Dex/ Pred(^b)</th>
<th>Chemo(^b,c)</th>
<th>ASCT(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤1 mg/kg</td>
<td>17</td>
<td>63 (42-76)</td>
<td>5 (2-8)</td>
<td>88%</td>
<td>71%</td>
<td>100%</td>
<td>88%/41%</td>
<td>100%</td>
<td>65%</td>
</tr>
<tr>
<td>2 mg/kg</td>
<td>3</td>
<td>64 (60-71)</td>
<td>8 (6-10)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%/100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>4 mg/kg</td>
<td>3</td>
<td>64 (62-66)</td>
<td>6 (3-6)</td>
<td>100%</td>
<td>33%</td>
<td>100%</td>
<td>100%/33%</td>
<td>100%</td>
<td>67%</td>
</tr>
<tr>
<td>8 mg/kg</td>
<td>3</td>
<td>60 (56-68)</td>
<td>11 (5-12)</td>
<td>100%</td>
<td>67%</td>
<td>100%</td>
<td>100%/67%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>16 mg/kg</td>
<td>3</td>
<td>55 (54-59)</td>
<td>7 (4-8)</td>
<td>67%</td>
<td>67%</td>
<td>100%</td>
<td>100%/33%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>24 mg/kg</td>
<td>3</td>
<td>58 (50-69)</td>
<td>5 (4-6)</td>
<td>100%</td>
<td>67%</td>
<td>100%</td>
<td>100%/33%</td>
<td>100%</td>
<td>67%</td>
</tr>
</tbody>
</table>

ASCT=autologous stem cell transplant; Bor=bortezomib; Chemo=chemotherapy; Dex=dexamethasone; Len=lenalidomide; No.=number; Pred=prednisolone; Thal=thalidomide.
Note: These results are based on data before database lock.
\(a\) Median (range).
\(b\) Number of subjects exposed to the drug/treatment.
\(c\) Vincristine, doxorubicin, cyclophosphamide, melphalan, and others.
Daratumumab
Safety Findings

- Infusion-related reactions were observed during the initial infusions:
  - 9% during the pre-dose infusion
  - 26% during the first full infusion with a gradual decrease in frequency during the subsequent infusions
  - No dose relationship
  - Two events grade 3, the remaining grade 1-2
  - Onset of events within 3 to 4 hours of infusion
  - Five late reactions:
    - 2 events of bronchospasm, 1 event each of headache, dyspnoea and fever
    - Patients with bronchospasm had a medical history of chronic bronchitis and asthma
- No major changes in platelet count or hemoglobin were observed over time
- A dose-dependent decrease in NK cells as measured in the peripheral blood was observed, with full recovery after treatment
Daratumumab Safety Findings

- Six SAEs were assessed as related to daratumumab:
  - One patient: anemia grade 3 (DLT) and thrombocytopenia grade 4 (0.1 mg/kg)
  - One patient: AST grade 3 (DLT) (1 mg/kg)
  - One patient: cytokine release syndrome grade 2 (0.1 mg/kg)
  - One patient: bronchospasm grade 3 (2 mg/kg)
  - One patient: bronchospasm grade 2 (24 mg/kg)

- 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
Plasma peak levels after first full dose: as expected for IgG

Rapid clearance at low dose: indicates target-mediated clearance

High inter-patient variability suggests effect of tumor load on PK

2 mg/kg: pre-dose trough levels far below prediction

4 mg/kg and upwards: sustained trough levels > 10 µg/ml indicate that the impact of target-mediated clearance becomes negligible at higher doses

Daratumumab Pharmacokinetics

Red: observed daratumumab concentrations as measured by ELISA (day 21-56: trough levels only, no peak levels)

Blue: concentrations predicted using a 2-comp PK model with Vcen = 40ml/kg and elimination half life = 21 days
## Daratumumab Response

Max Reduction of M-Component/FLC/BM PCs and by IMWG Criteria

<table>
<thead>
<tr>
<th>Cohort (mg/kg)</th>
<th>N</th>
<th>Max. reduction in M-component (%)</th>
<th>Max. reduction in difference between involved and uninvolved FLC (%)</th>
<th>Max. reduction in plasma cells in BM smear (%) [Baseline value (%)]</th>
<th>Response according to IMWG^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>3</td>
<td>Serum: 49 100 64 87 *</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine: 87 * 96 *</td>
<td>*</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MR PR PR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>Serum: 4 39 *</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine: * * *</td>
<td>*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>-29 [14] 93 [7.5]</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>SD MR NE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>3</td>
<td>Serum: -3 50 *</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine: * * -12</td>
<td>*</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>100 [31.5]</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>PD MR SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>Serum: * 29b 58b</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Urine: * 89</td>
<td>80b *</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>51 [18.5] 17 [3.0]</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PR MR PR</td>
<td></td>
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</tbody>
</table>

**Notes:**
- * no measurable disease/normal at Baseline; —=data not available.
- a Evaluation based on maximal reduction in M-component or FLC, according to the consensus on uniform reporting of clinical trials
- b Follow-up still ongoing.
- c Data not yet available.
Daratumumab
Progression free survival vs. Exposure

![Graph showing progression free survival vs. exposure levels of Daratumumab]

- Low AUC [0.6, 280] μg*h/mL
- Mid AUC [280, 4326] μg*h/mL
- High AUC [4326, 63777] μg*h/mL

PFS (weeks)
Daratumumab
Conclusion 1/2

• Daratumumab has shown a favorable safety profile as monotherapy in relapsed or relapsed and refractory Multiple Myeloma patients

• In 15 of 32 (47%) heavily pre-treated evaluable Multiple Myeloma patients receiving 8 weeks of daratumumab as monotherapy in doses up to 24mg/kg, a reduction in paraprotein has been observed, corresponding to preliminary responses of:

  – 4 patients achieving PR (13%)
  – 6 patients achieving MR (19%)
  – 5 patients achieving SD (16%)

• At doses 4mg/kg and above, 8 of the 12 patients had at least MR (66%)
Biochemical response was accompanied by clearance of myeloma cells from the bone marrow.

At higher dose levels, observed plasma concentrations are close to those predicted.

MTD has not been reached.

Increased daratumumab exposure correlated with longer progression free survival.

Future directions: Extended exposure up to 24 months in MM patients with 8 mg/kg daratumumab as monotherapy and combination studies.
Acknowledgments

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