Phase I Study of Tabalumab, a Human Anti-BAFF Antibody, and Bortezomib in Patients with Previously Treated Multiple Myeloma

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BAFF: (B-cell Activating Factor of the Tumor Necrosis Factor Family)

- BAFF binds to three receptors found on plasma cells in marrow: BCMA, TACI and BAFF-R
- BAFF promotes survival and proliferation of plasma cells in marrow
- BAFF-stimulated MM cells are resistant to dexamethasone-induced apoptosis
- BAFF is elevated in sera from patients with multiple myeloma (MM)

Adapted from F. Mackay & C Ambrose, Cytokine & Growth Factor Rev. 2003;14:311-24
Plasma BAFF Levels are Elevated in Patients with Multiple Myeloma


Additional evidence that BAFF is involved in B cell malignancies (including B-chronic lymphocytic leukemia, non-Hodgkin’s lymphoma and MM):

- Malignant B cells express BAFF receptors
- Some malignant B cells produce BAFF as an autocrine survival factor
- BAFF-neutralization by BAFF mAb improved survival in a preclinical MM xenograft model
Tabalumab

- Human IgG₄κ monoclonal Ab that neutralizes membrane-bound and soluble BAFF
- Contains an S-to-P mutation in the hinge region to prevent formation of half antibodies
- Has activity in xenograft models of multiple myeloma (MM)
- Is in Phase III trials for rheumatoid arthritis + systemic lupus erythematosus

**Parameter** | **Result**
---|---
Kₐ: Binding affinity for soluble human BAFF | 126 pM
Half-life (human) | 15.1 days (0.5 mg/kg i.v.)
| 18.2 days (2 mg/kg i.v.)
| 25.3 days (8 mg/kg i.v.)
Aim

- To study the combination of BAFF inhibitor tabalumab with bortezomib in a Phase I trial

Primary objective

- To identify a recommended Phase II dose of tabalumab with bortezomib for previously treated patients with multiple myeloma
Study Design

**Dose escalation**

3 pt. cohorts + 3 pts. if DLT* occurs (up to 30 pts.)
Cycle=21 days

Dose levels 1-5: 1mg, 10 mg, 30 mg, 100 mg, and 300 mg.

*DLT=dose limiting toxicity:
  • ≥Grade 3 nonhematological toxicity
  • Thrombocytopenia with platelets <10,000/μL on ≥2 occasions despite transfusion support
  • Grade 4 neutropenia lasting >5 days +/or neutropenic fever ≥101°F
  • >7-day delay in ability to receive Day 1 dose for Cycle 2 due to toxicity

**Schedule**

<table>
<thead>
<tr>
<th>Cycle #</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Tabalumab</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dexamethasone**</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Bortezomib 1.3 mg/m² administered as a 3- to 5-sec bolus on Days 1, 4, 8, and 11 of indicated cycles
Tabalumab administered as 30-min infusion on Day 1 of indicated cycles (on Day 2 in Part B1 for DDI assessment)
**Dexamethasone 20 mg po on Days 1, 2, 4, 5, 8, 9, 11, and 12 of indicated cycles

Tabalumab 100 mg i.v.

**Part A**
Dose Escalation

**Part B1**
Tabalumab on Day 2

**Part B2**
Safety Expansion

**Part B3**
Tabalumab 100 mg i.v. + dexamethasone**
PK of Tabalumab in Patients With Multiple Myeloma

Tabalumab serum levels after a single dose

Peak - trough fluctuation at steady state (%)

Parameter | Estimate (%SEE) | %IIV (%SEE)
--- | --- | ---
CL (L/day) | 0.15 (11.2) | 61% (20.8)
V1 (L) | 3.4 (4.0) | 26% (26.4)
Q(L/day) | 0.7 (13.3) | ---
V2 (L) | 2.9 (7.9) | 30% (35.3)
CL\(\text{SAT}\) (L/day) | 1.2 (112) | ---
C\(\text{50}\) (ng/mL) | 161 (125) | ---
\(\sigma_{\text{prop}}\) (%CV) | 18.5 (26) |
\(\sigma_{\text{add}}\) (ng/mL) | 47.4 (44) |
Patient Demographics and Prior Treatments

Patients who were enrolled met standard eligibility criteria and had relapsed or refractory MM treated with at least 1 prior regimen

### Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>All Patients (%) (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (44)</td>
</tr>
<tr>
<td>Female</td>
<td>27 (56)</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>65.7</td>
</tr>
<tr>
<td>Range</td>
<td>(41-84)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>38 (79)</td>
</tr>
<tr>
<td>Black</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Asian</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (27)</td>
</tr>
<tr>
<td>1</td>
<td>34 (71)</td>
</tr>
<tr>
<td>2</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

### Prior Therapy

<table>
<thead>
<tr>
<th>Prior Therapy</th>
<th>All Patients (%) (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Prior Therapy</td>
<td>48 (100)</td>
</tr>
<tr>
<td>Transplant</td>
<td>25 (52)</td>
</tr>
<tr>
<td>Bortezomib</td>
<td>36 (75)</td>
</tr>
<tr>
<td>IMiD</td>
<td>42 (87.5)</td>
</tr>
<tr>
<td>IMiD or Bortezomib</td>
<td>48 (100)</td>
</tr>
<tr>
<td>Median Prior Treatments (range)</td>
<td>3 (1-10)</td>
</tr>
</tbody>
</table>
Summary of ≥Grade 3 Adverse Events (AEs)

22 additional ≥Grade 3 AEs* were reported by one patient each. Examples include respiratory related events and infections (upper respiratory tract infection [URTI], acute respiratory distress syndrome [ARDS]), electrolyte imbalances, and pain.

*Treatment-emergent adverse events regardless of relationship
## Deaths on Study and Treatment-related Serious Adverse Events

<table>
<thead>
<tr>
<th>Related Serious Adverse Events* (Preferred Term)</th>
<th>All (%) (n=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with at least 1 event*</td>
<td>4 (8.3)</td>
</tr>
<tr>
<td>Nausea</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Clostridium Difficile Colitis</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>ARDS</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Syncope</td>
<td>1 (2.1)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Deaths Cohort (mg)</th>
<th>Cycles</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>30</td>
<td>5</td>
<td>Progressive Disease</td>
</tr>
<tr>
<td>Part B2 No Dex</td>
<td>3</td>
<td>Adverse Event (ARDS)**</td>
</tr>
</tbody>
</table>

**Patient also had progressive disease

*Possibly related
Summary of Best Confirmed IURC Response

<table>
<thead>
<tr>
<th>M-protein Best Response</th>
<th>Serum</th>
<th>Urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Very Good Partial</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Partial Response</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

*22 patients achieved a confirmed partial response or better

<table>
<thead>
<tr>
<th>% of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>n=2</td>
</tr>
</tbody>
</table>

Total n=48*
Time to Progression and Duration of Response

**Time to Progression (TTP)**

- Total patients: 47*
- Censored: 14
- Median TTP (95%CI): 4.9 (4.0-8.0) months

**Duration of Response (DoR)**

- Total patients: 22
- Censored: 6
- Median DoR (95%CI): 7.3 (3.5-13.9) months

*Data was not available for 1 patient
Percent Change from Baseline - B-cells (CD19+) and Immunoglobulins

PCB = percent change from baseline
The bottom and top edges of the boxes are 25th and 75th percentiles of the sample
Baseline BAFF Expression

Each ▲ or ● represents one patient.
Phase I Study Summary

- Phase I study of BAFF inhibitor tabalumab with bortezomib enrolled 48 patients with relapsed or refractory MM treated with at least 1 prior regimen
- Treatment-related SAEs occurred in 4 (8.3%) patients; 2 deaths on study occurred
- The median time to progression was 4.9 months (4.0 – 8.0)
- The median duration of response was 7.3 months (3.5 – 13.9)
- 22 patients achieved a confirmed partial response or better
- A Phase II study randomly assigning patients to the combination of bortezomib, dexamethasone and tabalumab 100 mg vs. 300 mg vs. placebo is currently enrolling
Ongoing Study

Eligibility:
Relapsed/refractory
multiple myeloma
treated with 1-3
prior lines of therapy

Randomize 1:1:1

Phase II

Arm A (control):
- Dexamethasone PO
- Placebo i.v.
- Bortezomib SQ

Arm B (experimental):
- Dexamethasone PO
- Tabalumab i.v. 100mg
- Bortezomib SQ

Arm C (experimental):
- Dexamethasone PO
- Tabalumab i.v. 300mg
- Bortezomib SQ

Interim Analysis
Tabalumab
dose selection

Starting treatment dosages and schedule:
Dexamethasone 20 mg PO days 1, 2, 4, 5, 8, 9, 11, 12 every 21 days for up to 10 cycles
Placebo i.v. OR Tabalumab 100 mg i.v. OR Tabalumab 300 mg i.v. on day 1 every 21 days for up to 10 cycles
Bortezomib 1.3 mg/m² SQ days 1, 4, 8, 11 every 21 days for up to 10 cycles

SQ= subcutaneously
Acknowledgements

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