First-in-human Phase I trial of BI 836880, a vascular endothelial growth factor (VEGF)/angiopoietin-2 (Ang-2)-blocking Nanobody®, given every 3 weeks in patients with advanced/metastatic solid tumors

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Background

- VEGF and Ang-2 are key angiogenic factors induced by hypoxia and are often overexpressed in cancer\textsuperscript{1,2}
  - Activation of the Ang-2/Tie-2 pathway promotes vascular destabilization, and enables VEGF-induced angiogenesis\textsuperscript{2}
  - Given the crosstalk between the VEGF/VEGFR2 and Ang-2/Tie-2 signaling pathways, it is hypothesized that inhibition of both pathways may be a superior approach compared to targeting either pathway alone\textsuperscript{4}

- BI 836880 is a humanized bispecific Nanobody\textsuperscript{®}
  - A Nanobody is an engineered antibody fragment consisting of one or more variable antibody domains\textsuperscript{3}
  - BI 836880 comprises two single variable domains that inhibit VEGF and Ang-2, and an additional albumin module (ALB11) that extends half-life \textit{in vivo}\textsuperscript{4}
Angiogenesis stimulated by VEGF and Ang-2 (left panel) and inhibited by BI 836880-mediated dual inhibition of the two pathways (right panel)\(^5\)
Background (cont’d)

- BI 836880 has demonstrated pre-clinical activity in cancer models
  - Data from models of pancreatic, lung, renal, ovarian and colon cancer have shown that BI 836880 can potently and selectively neutralize VEGF and Ang-2
- Here, we report the first-in-human Phase I trial of BI 836880 every 3 weeks (Q3W) in patients with advanced/metastatic solid tumors
**Methods**

**Patients** with advanced/metastatic solid tumors refractory after standard therapies or for whom no established treatment options were available  
(Clinicaltrials.gov: NCT02674152)

**Received** intravenous BI 836880 Q3W
- Starting dose: 40 mg Q3W  
- Dose escalation followed a Bayesian logistic regression model with overdose control

**Key inclusion and exclusion criteria:**
- ✓ Aged ≥18 years  
- ✓ ECOG PS ≤2  
- ✓ Life expectancy ≥3 months  
- ✓ Recovery from reversible AEs of previous anti-cancer therapies to baseline/grade 1*
- X Systemic anti-cancer therapy within 28 days/≥5 half lives prior to start of study treatment  
- X Serious concomitant disease  
- X Medical history including: QT prolongation and/or long QT syndrome or prolonged QTcF at baseline; and severe hemorrhagic or thromboembolic events  
- X Uncontrolled hypertension (blood pressure ≥140/≥90 mmHg [with or without medication])

*Except for alopecia (any grade) or sensory peripheral neuropathy (grade ≤2 or not clinically significant)

AEs; adverse events; ECOG PS, Eastern Cooperative Oncology Group performance status
Methods (cont’d)

Primary endpoint

• To assess the MTD, evaluated based on the number of patients with DLTs in the first 21-day cycle
  – The MTD was considered reached if there was a sufficiently large probability that the true DLT rate was in the target interval of 16–33%

Secondary endpoints

• TRAEs leading to dose reduction/discontinuation
• Exposure measures (AUC\textsubscript{0-tz}) after the first dose
• Disposition kinetic measures (t\textsubscript{1/2}) after the first dose

Further endpoint

• Best overall response

Data cut-off for this analysis was 02 May 2018

AUC\textsubscript{0-tz}, area under the plasma concentration–time curve of the analyte over the time interval from 0 up to the last quantifiable data point; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; t\textsubscript{1/2}, terminal half life; TRAE, treatment-related AE
Results

Baseline characteristics of 29 patients treated with BI 836880

**Gender**
- Female: 18 (62)
- Male: 11 (38)

**ECOG PS**
- PS 0: 11 (38)
- PS 1: 18 (62)
- PS 2: 0 (0)

**Region of primary site**
- Pancreas: 6 (21)
- Breast: 4 (14)
- Colon/rectum: 2 (7)
- Esophagus: 3 (10)
- Eye: 2 (7)
- Other*: 8 (28)
- Rhinopharynx/cavum: 2 (7)
- Thymus: 2 (7)

**Median age, years**
- Min.: 28
- Max.: 79

*Anal region, caecum, fossa iliaca left, ovary, proximal jejunum, sigmoid, uterus and unknown (each n=1)
Results (cont’d)

Treatment exposure

- At data cut-off, 2 patients remained on treatment
  - Reasons for treatment discontinuation were:
    PD (n=19); DLT (n=1); other AE or clinical progression (n=4); other (n=3)

*Patients who started the treatment cycle, including those who discontinued treatment before the planned 21-day cycle end. Two patients remain on treatment. PD, progressive disease
Results (cont’d)

Determination of the MTD based on the occurrence of DLTs in Cycle 1

DLT in 1000 mg dose cohort: Grade 3 pulmonary embolism

Total treated at 720 mg, n=17
Results (cont’d)

Most frequent AEs (occurring in ≥15% of patients, by max. CTCAE grade)

<table>
<thead>
<tr>
<th>AE</th>
<th>All grades</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>100</td>
<td>76</td>
</tr>
<tr>
<td>Hypertension</td>
<td>90</td>
<td>41</td>
</tr>
<tr>
<td>Asthenia</td>
<td>52</td>
<td>14</td>
</tr>
<tr>
<td>Nausea</td>
<td>45</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>38</td>
<td>3</td>
</tr>
<tr>
<td>Constipation</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>AST increased</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td>Anemia</td>
<td>28</td>
<td>3</td>
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<tr>
<td>Odema peripheral</td>
<td>24</td>
<td>3</td>
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<tr>
<td>Abdominal pain</td>
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<td>3</td>
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<tr>
<td>Dyspnea</td>
<td>24</td>
<td>10</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>17</td>
<td>3</td>
</tr>
<tr>
<td>ALT increased</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>17</td>
<td>7</td>
</tr>
</tbody>
</table>
Results (cont’d)

• TRAEs leading to dose reduction: 0
• TRAEs leading to treatment discontinuation: 2
  – Grade 3 pulmonary embolism, reported as DLT in 1000 mg dose cohort
  – Grade 3 myocarditis
Results (cont’d)

Anti-tumor activity

Best overall response regardless of confirmation
PD: n=6 (21%)
SD: n=13 (45%)
PR: n=3 (10%)
NE: n=7 (24%)

Minimum increase in SLD from baseline (%)

Subject index sorted by minimum increase (%)

Breast cancer
Duration of response: 39 days

Adenocarcinoma of the ovary
Duration of response: 92 days

Cavum carcinoma
Duration of response: 128 days

NE, not evaluable; PR, partial response; SD, stable disease; SLD, sum of target lesion diameters
Results (cont’d)

PK and PD analysis of 14 evaluable patients

gMean plasma concentration–time profile after first infusion (Cycle 1)

- BI 836880 plasma kinetics in Cycle 1 seemed to be dose proportional over 40–1000 mg
- The required trough values of 20 mg/L could be achieved at doses ≥720 mg

PD, pharmacodynamic; PK, pharmacokinetic
Results (cont’d)

Dose-normalized $C_{\text{max}}$ and $\text{AUC}_{0-504}$ after first infusion (Cycle 1)

$\text{AUC}_{0-504}$, area under the concentration–time curve over the time interval from 0 to 504 hours; $C_{\text{max}}$, maximum measured plasma concentration of BI 836880; $C_{\text{trough}}$, trough plasma concentration

Semi-log scale
Free systemic VEGF and Ang-2 levels after first infusion (Cycle 1)

- Systemic free VEGF was completely depleted (below the LLOQ of 0.1 pM or 0.00274 ngeq/ml) at the lowest dose of 40 mg
  - VEGF remained below the LOQ even before the start of the next treatment cycle.

LLOQ, lower limit of quantitation; LOQ, limit of quantitation
Results (cont’d)

Free systemic VEGF and Ang-2 levels after first infusion (Cycle 1)

- Systemic free Ang-2 was blocked in a dose-dependent manner.
- Complete inhibition of systemic Ang-2 below the LOQ of 1.4 pM (0.08 ngeq/ml) was achieved at doses ≥360 mg.
  - In these patients, Ang-2 levels remained below LOQ even before the start of the next treatment cycle.
Summary

- The MTD/recommended phase 2 dose of BI 836880 was determined as 720 mg Q3W
- The most frequently observed AEs were (any grade/grade ≥3) hypertension (90%/41%), asthenia (52%/14%) and nausea (45%/3%)
- PK/PD analysis supported BI 836880 720 mg Q3W as the biologically relevant dose
- Early signs of anti-tumor activity were observed
References


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