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}
Background (cont’d)

Angiogenesis stimulated by VEGF and Ang-2 (left panel) and inhibited by BI 836880-mediated dual inhibition of the two pathways (right panel).
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*

✗ Systemic anti-cancer therapy within 28 days/≥5 half lives prior to start of study treatment
✗ Serious concomitant disease
✗ Medical history including: QT prolongation and/or long QT syndrome or prolonged QTcF at baseline; and severe hemorrhagic or thromboembolic events
✗ 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)
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\(_{0-tz}\)) after the first dose
• Disposition kinetic measures (t\(_{1/2}\)) after the first dose

Further endpoint
• Best overall response

Data cut-off for this analysis was 02 May 2018
AUC\(_{0-tz}\), 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\(_{1/2}\), 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%)
- Eye: 2 (7%)
- Esophagus: 3 (10%)
- 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
Determination of the MTD based on the occurrence of DLTs in Cycle 1

DLT in 1000 mg dose cohort: Grade 3 pulmonary embolism

MTD dose cohort expanded

Total treated at 720 mg, n=17
Most frequent AEs (occurring in ≥15% of patients, by max. CTCAE grade)

- Any AE
- Hypertension
- Asthenia
- Nausea
- Vomiting
- Constipation
- AST increased
- Diarrhea
- Anemia
- Odema peripheral
- Abdominal pain
- Dyspnea
- Urinary tract infection
- Infusion-related reaction
- ALT increased
- Blood bilirubin increased
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

Minimum increase in SLD from baseline (%)

-100 -80 -60 -40 -20 0 20 40 60 80 100

Subject index sorted by minimum increase (%)

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22

Cavum carcinoma
Duration of response: 128 days

Adenocarcinoma of the ovary
Duration of response: 92 days

Breast cancer
Duration of response: 39 days

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

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
Results (cont’d)

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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