PK/PD properties of BI 836880, a vascular endothelial growth factor (VEGF)/angiopoietin-2 (Ang-2)-blocking Nanobody®, in patients with advanced/metastatic solid tumors

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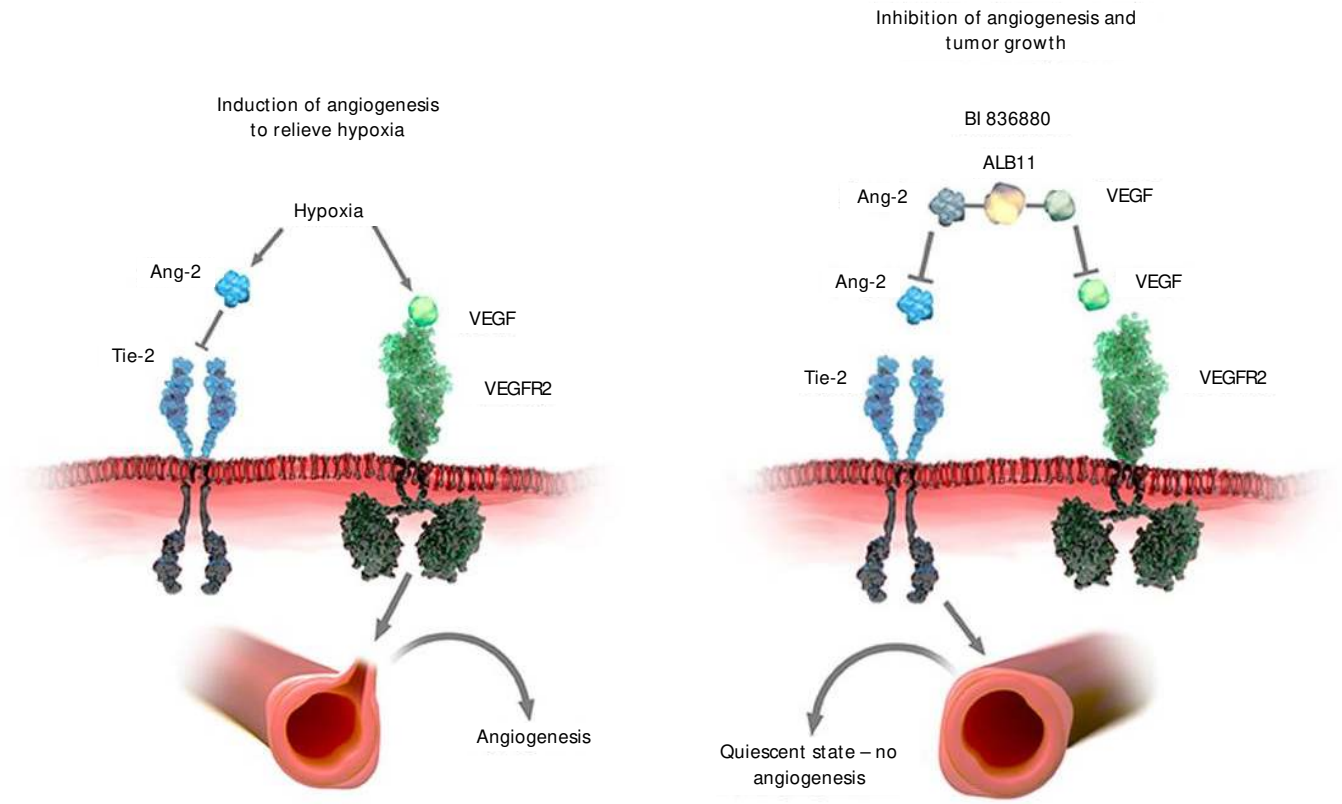
Background

- VEGF and Ang-2 are key angiogenic factors induced by hypoxia and are often overexpressed in cancer[1,2]
  - Activation of the Ang-2/Tie-2 pathway promotes vascular destabilization, therefore allowing for VEGF-induced angiogenesis[2]
  - Given the synergy and crosstalk between the VEGF/VEGFR2 and Ang-2/Tie-2 signaling pathways, there is a rationale for dual inhibition[3]
- BI 836880 is a humanized bispecific Nanobody®
  - A Nanobody is an engineered antibody fragment consisting of one or more variable antibody domains[4]
  - BI 836880 consists of two single variable domains that inhibit VEGF and Ang-2, and an additional albumin module (ALB11) for half-life extension *in vivo*[3]
  - Based on the inhibition of two pathways, BI 836880 is expected to demonstrate clinical efficacy superior to anti-angiogenic monotherapies, especially when given in combination with standard-of-care treatments

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)[5]

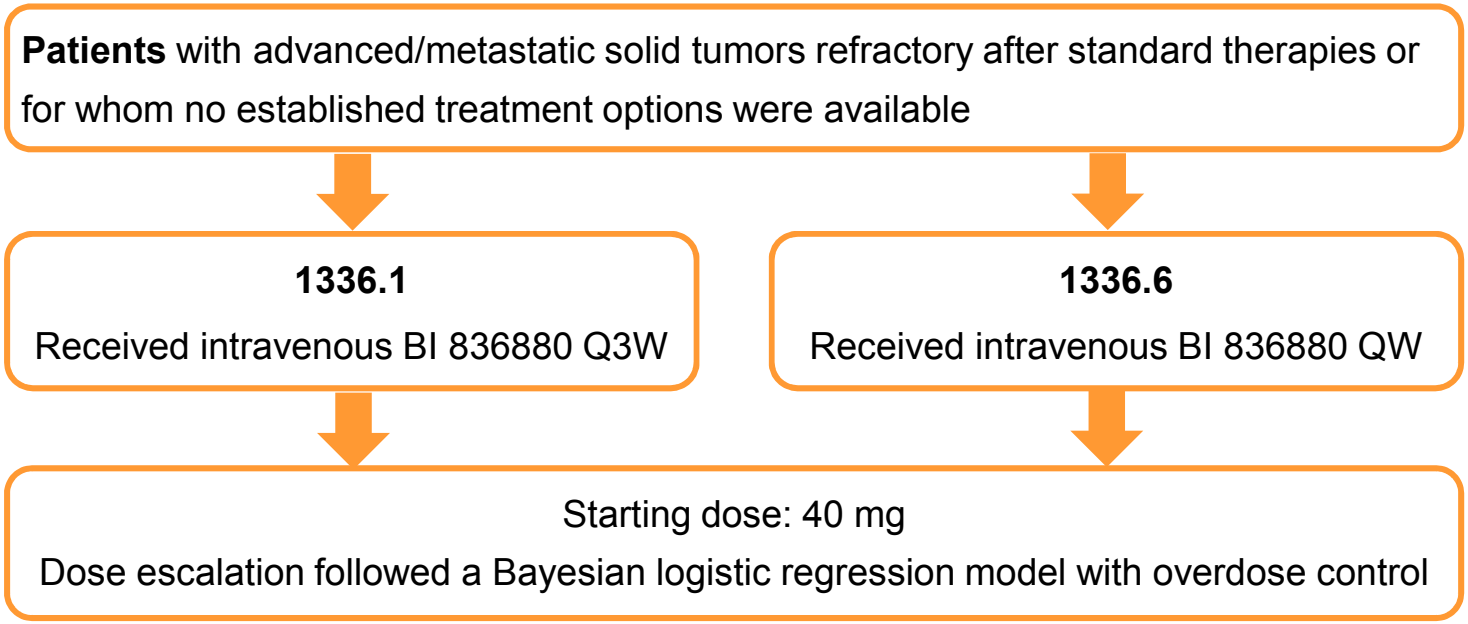


Background (cont'd)

- 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[3]
  - In a 13-week toxicology study, BI 836880 was well tolerated when administered once weekly to cynomolgus monkeys
- Here, we report the exploratory pharmacokinetic (PK) and pharmacodynamics (PD) analysis of two Phase I studies, one with a 3-weekly dosing schedule (1336.1) and one with a weekly dosing schedule (1336.6) to support the dose selection of BI 836880 for future combination therapy trials

Further 1336.1 information:

Methods



Q3W, once every 3 weeks; QW, once every week

Further 1336.1 information:

Methods (cont'd)

Analyte assessments

- PK profiles of BI 836880 in plasma were assessed after the first, and repeated, doses
- Systemic BI 836880: Levels of BI 836880 in plasma were analyzed using a LC-MS/MS method, via monitoring a unique peptide of BI 836880 (LLOQ 0.5 mg/L)
- Total and free systemic Ang-2 in EDTA plasma were analyzed using ELISAs (LLOQs 0.1 and 0.08 µg equivalents [µgeq]/L, respectively)
- Free systemic VEGF in EDTA plasma was analyzed using ECLIA with LLOQ 2.7 ngeq/L
- Total VEGF-A: Human plasma samples were mixed with isotopically labelled VEGF-A protein as internal standard. Unlabeled, recombinant VEGF-A was used to create a calibration curve. Samples were denatured and digested before VEGF-A peptides were enriched by an immunocapture step. After further SPE clean up, samples were analyzed with a Qexactive™ HF system connected to a nanoLC system.
- Capillary permeability, as an anti-angiogenic marker, was assessed by DCE-MRI analysis[5] in 8 pts of the 1336.1 arm

DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; ECLIA, electro-chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; LC-MS/MS, liquid chromatography tandem-mass spectrometry; LLOQ, lower limit of quantitation; SPE, solid phase extraction

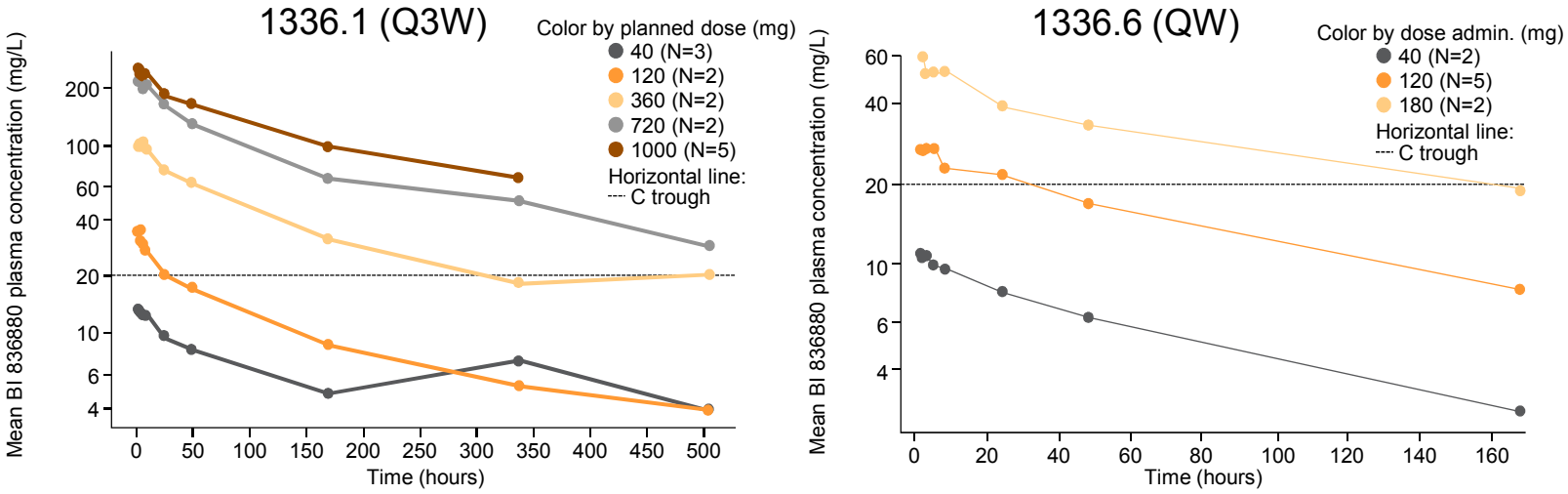
Results

- This preliminary analysis was based on planned times and included evaluable data from 23 patients (14 in 1336.1 and 9 in 1336.6) over at least 1 treatment cycle
  - 9 patients in 1336.1 and 6 patients in 1336.6 continued treatment up to at least cycle 2 (6 patients and 3 patients continued to cycle 4, respectively)
  - Data from 5 patients in 1336.1 and 2 patients in 1336.6 were available over 6 or more treatment cycles
- Dosing was as follows:
  - 1336.1 (Q3W): 40 mg (n=3); 120 mg (n=2); 360 mg (n=2); 720 mg (n=2), 1000 mg (n=5)
  - 1336.6 (QW): 40 mg (n=2), 120 mg (n=5), 180 mg (n=2)

Results (cont'd)

BI 836880 plasma kinetics

- Plasma kinetics appeared to be dose-proportional over 40–1000 mg Q3W and 40–180 mg QW
- Accumulation ratios were between 1 and 2



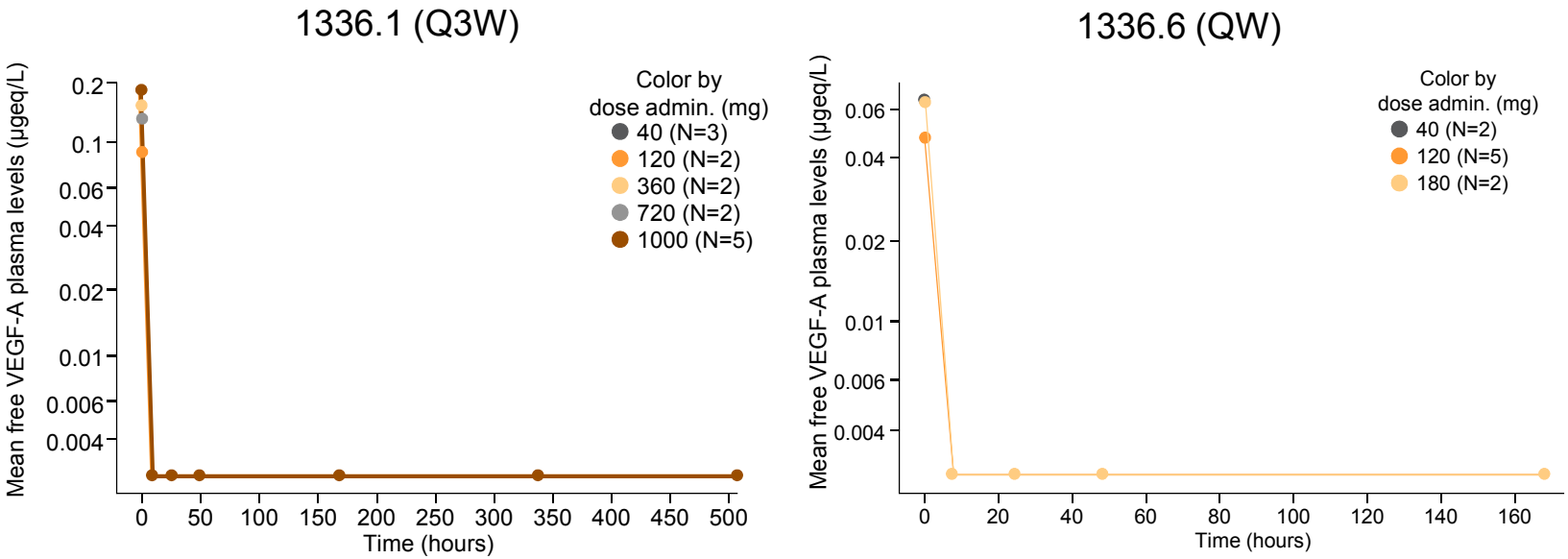
- Required trough values (20 mg/L) as predicted from pre-clinical models were achieved at doses ≥720 mg Q3W

C trough, trough plasma concentration

Results (cont'd)

Free VEGF levels

- Pre-dose free VEGF levels were 0.022–0.669 µgeq/L
- Individual patient PK/PD profiles showed that systemic free VEGF was completely blocked (below LLOQ) at the lowest dose
- Free VEGF remained blocked until next treatment cycle

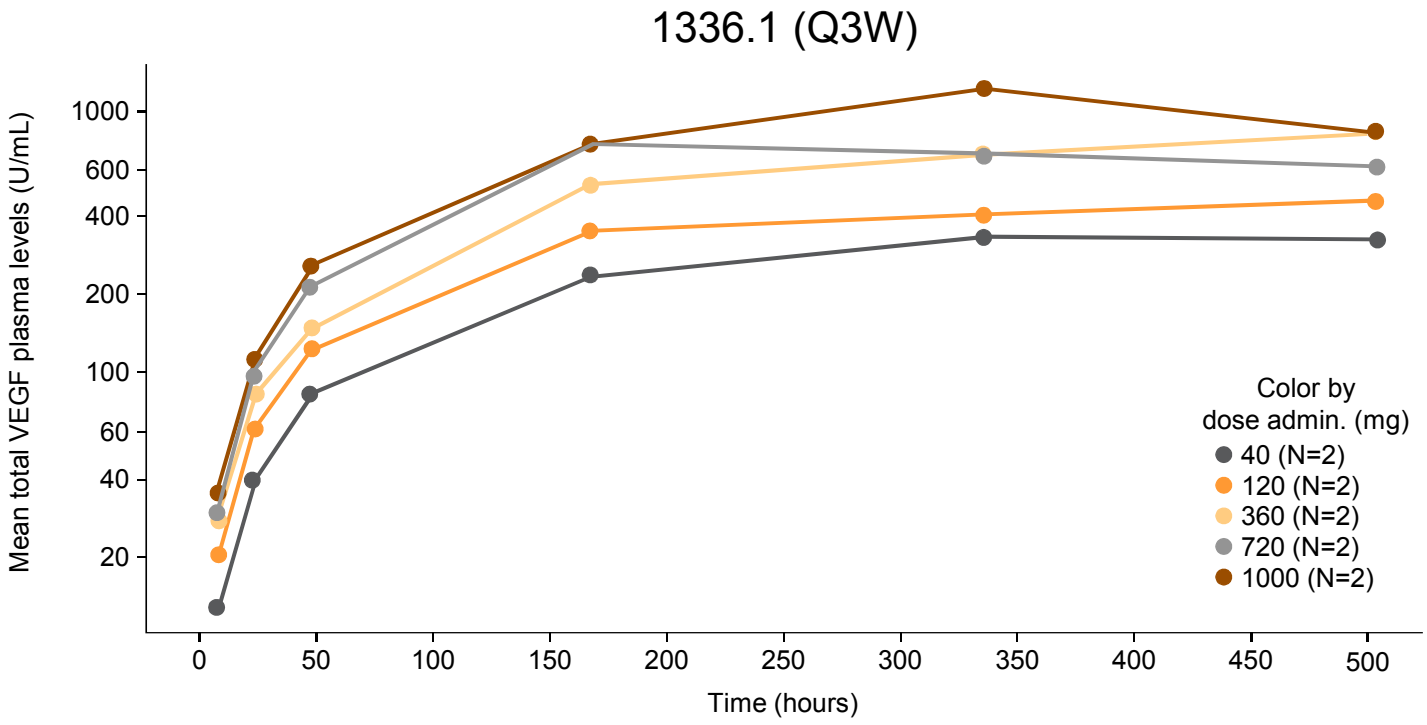


µgeq/L, µg equivalents/L

Results (cont'd)

Total VEGF levels

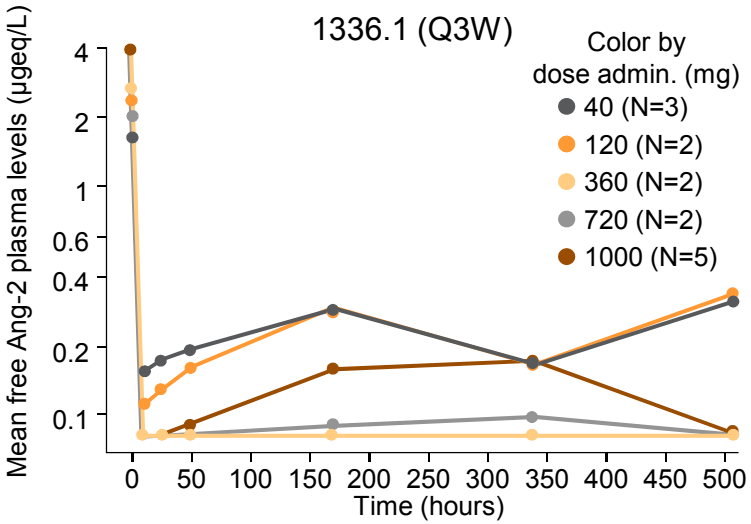
- Total VEGF levels appeared to reach saturation at ≥360 mg Q3W

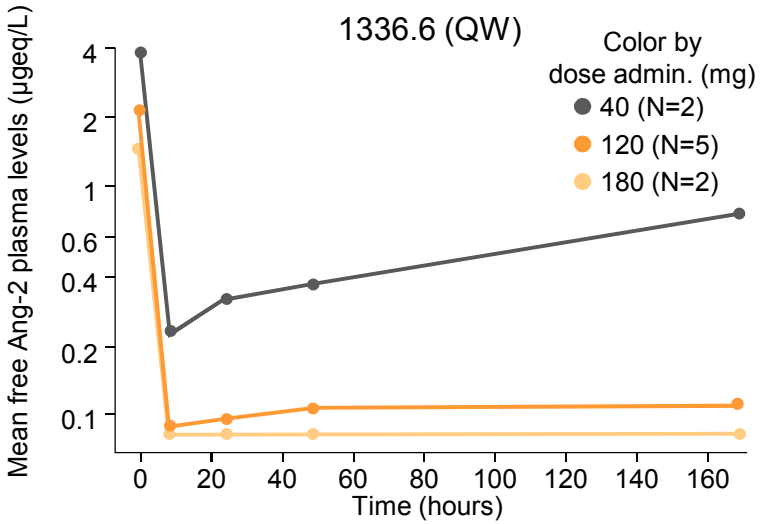


Results (cont'd)

Free Ang-2 levels

- Pre-dose free Ang-2 levels were 0.72 to >15 µgeq/L
- Free Ang-2 was dose-dependently blocked
- Strong inhibition of free Ang-2 at dosages ≥360 mg Q3W or ≥120 mg QW
  - At 1000 mg Q3W, free Ang-2 was not fully depleted in 2 patients, which may be due to slower BI836880 PK in these patients
  - Free Ang-2 remained blocked until the next treatment cycle

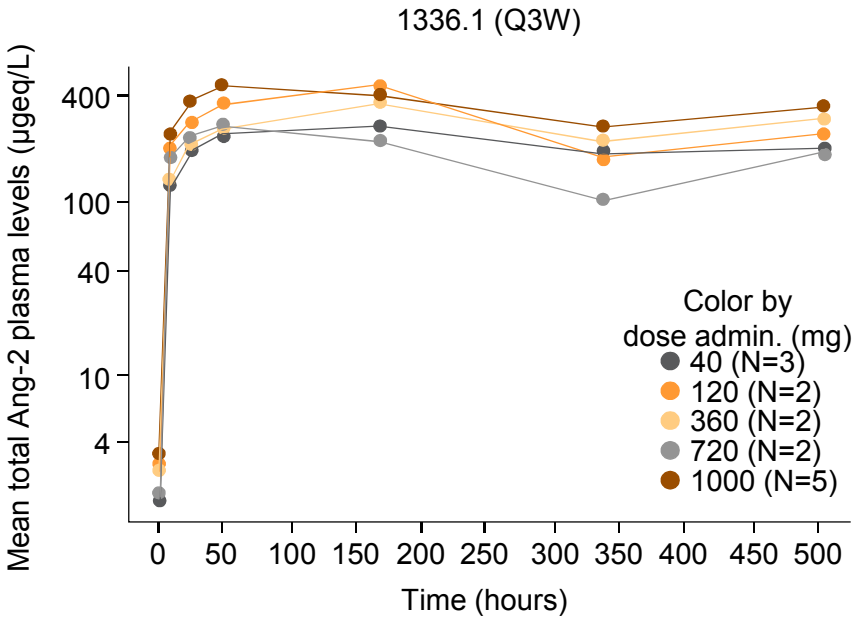


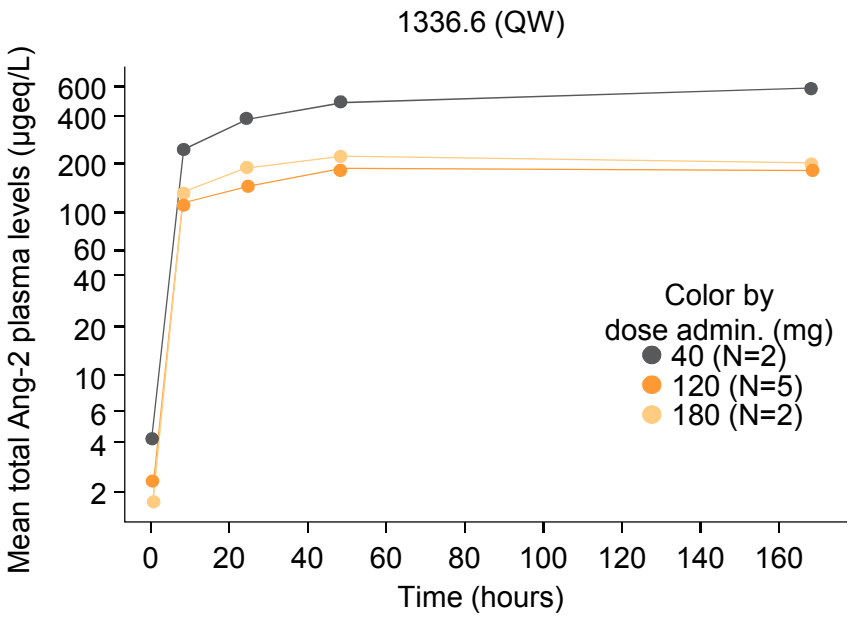


Results (cont'd)

Total Ang-2 levels

- Total Ang-2 increased 100–1000 fold above pre-dose levels

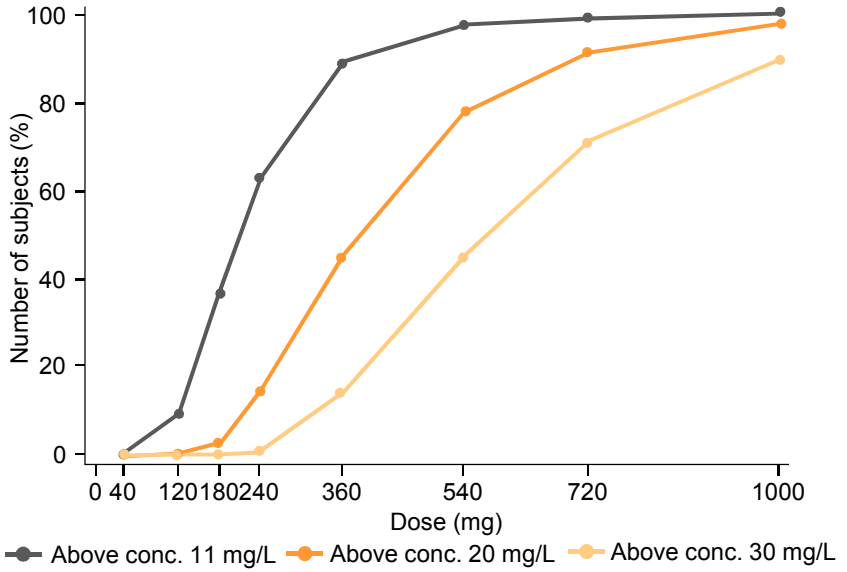




Results (cont'd)

BI 836880 population PK modelling

- Two additional potential trough concentration targets were established with an exploratory model of human plasma free Ang-2 inhibition vs. BI 836880 concentrations
- These interim results indicated 95%, 97% and 98% relative free-Ang2 inhibition with BI 836880 trough concentrations of 11, 20 and 30 mg/L, respectively
- Together with the interim population PK model, developed for the Q3W dosing schedule, the percentage of subjects who reached these target trough values after 3 and 6 weeks of treatment were assessed



- With doses ≥360 mg Q3W, ~90% of simulated subjects (n=1000) have a trough concentration above 11 mg/L at 6 weeks of treatment

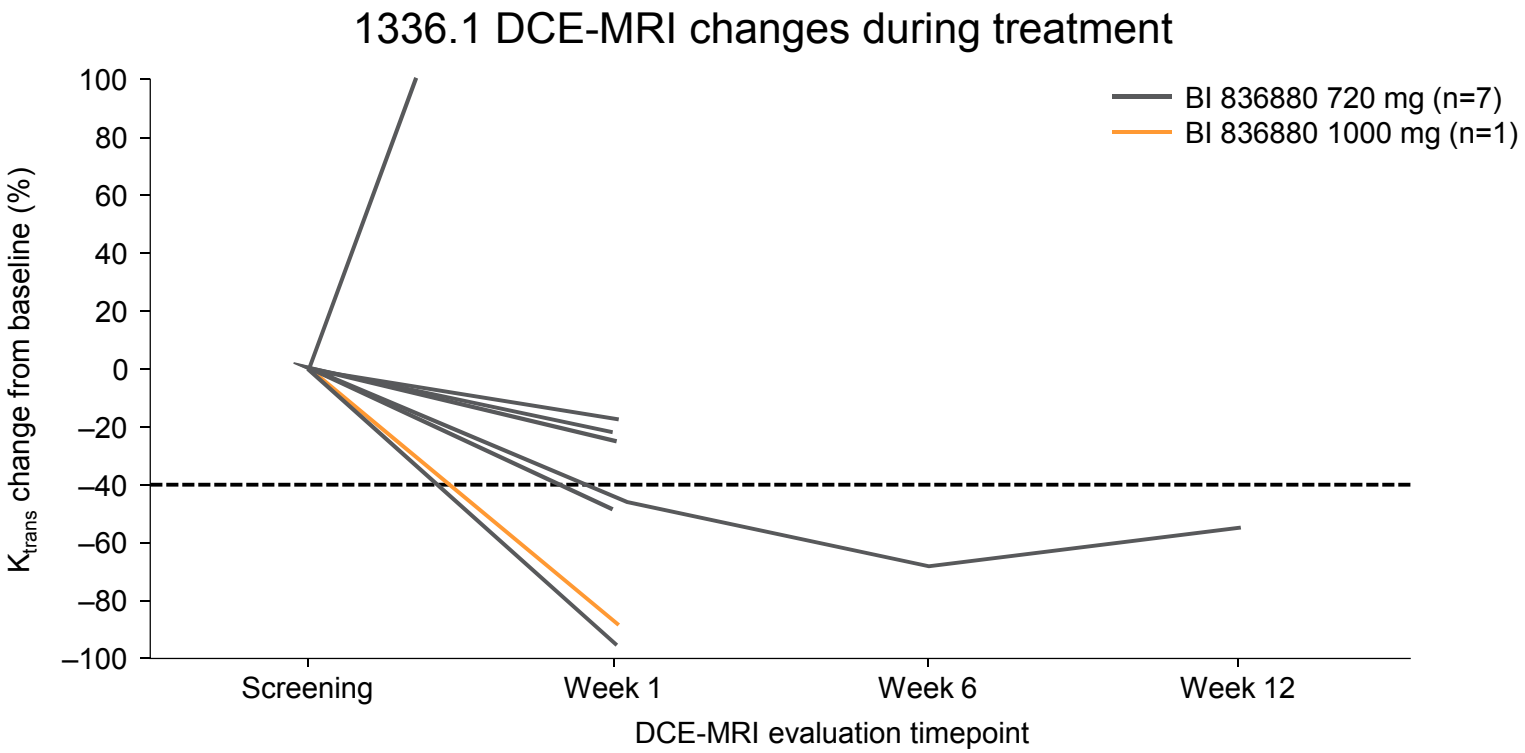
Results (cont'd)

DCE-MRI evaluation

- DCE-MRI is a well established imaging method to assess treatment-induced changes of vascular permeability in anti-angiogenesis projects[6]
- A large number of clinical trials have used DCE-MRI, e.g. several clinical studies with bevacizumab
- K_{trans} is a well-established kinetic parameter used to quantify vascular permeability and changes thereof

Results (cont'd)

DCE-MRI evaluation (cont'd)



- Relevant K_{trans} decreases (≥40%)[5] were observed in 3/8 patients
- K_{trans} decreases of 20–40% were demonstrated in 2 additional patients

Summary

- Free VEGF, but not free Ang-2, was depleted from the lowest dose of BI 836880
- PK/PD analysis supported BI 836880 720 mg Q3W as the biologically relevant dose
  - Depletion of free Ang-2 was achieved at ≥360 mg Q3W
  - Total VEGF levels appeared to reach saturation with ≥360 mg Q3W
- DCE-MRI analysis confirmed the anti-angiogenic activity in the tumor at this dose
- These data are exploratory and will be updated at final analysis

References

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