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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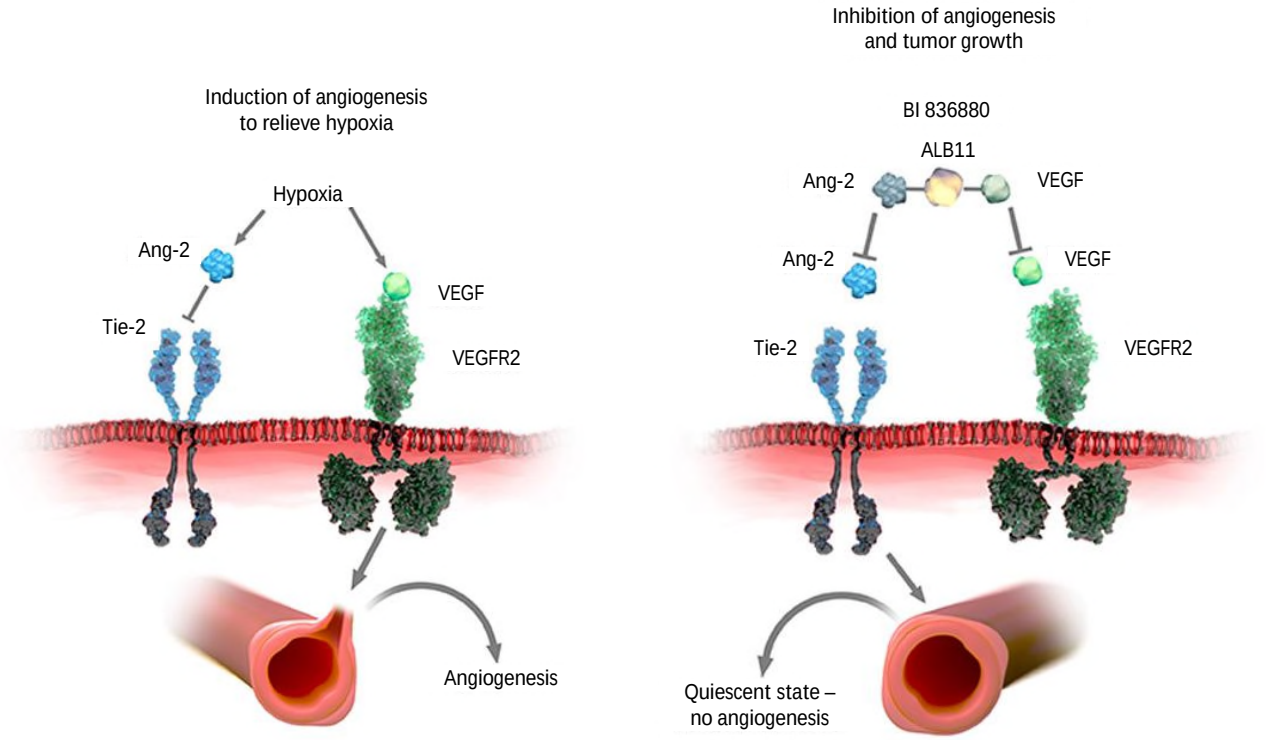
Background

- VEGF and Ang-2 are key angiogenic factors induced by hypoxia and are often overexpressed in cancer[1,2]
  - Activation of the Ang-2/Tie-2 pathway promotes vascular destabilization, and enables VEGF-induced angiogenesis[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[4]

- BI 836880 is a humanized bispecific Nanobody®
  - A Nanobody is an engineered antibody fragment consisting of one or more variable antibody domains[3]
  - BI 836880 comprises two single variable domains that inhibit VEGF and Ang-2, and an additional albumin module (ALB11) that extends half-life *in vivo*[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)[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[4]
- 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%

Further information: DLT definition

Secondary endpoints

- TRAEs leading to dose reduction/discontinuation
- Exposure measures ($AUC_{0\text{-}tz}$) 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

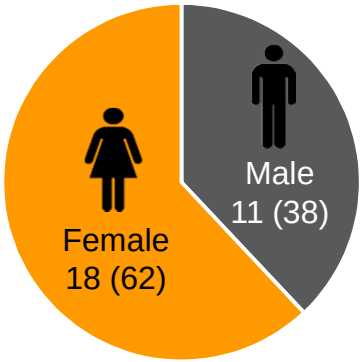
$AUC_{0\text{-}tz}$, area under the plasma concentration–time curve of the analyte over the time interval from 0 up to the last quantifiable data point; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; $t_{1/2}$, terminal half life; TRAE, treatment-related AE

Results

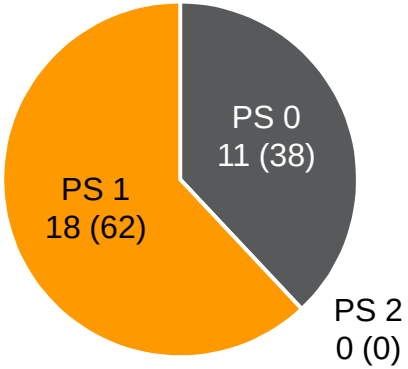
Baseline characteristics of 29 patients treated with BI 836880

Data are n (%)

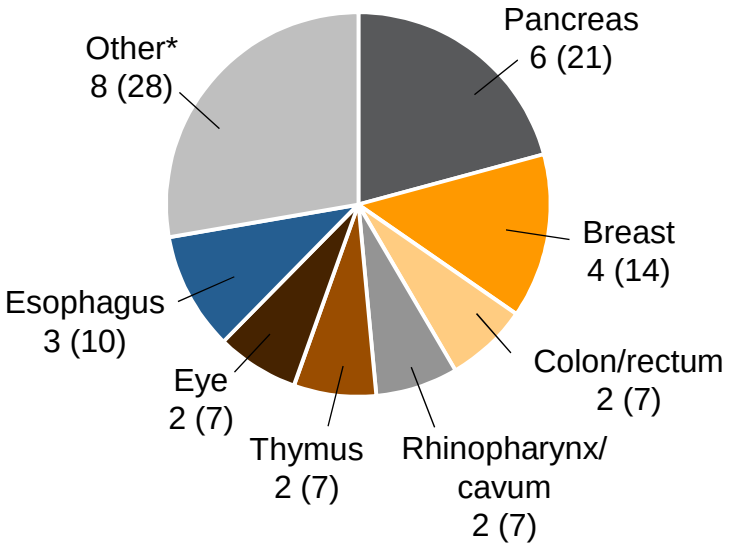
Gender



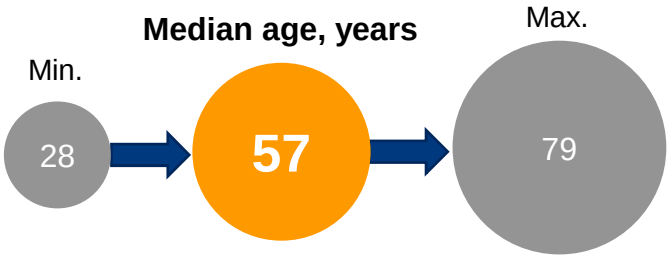
ECOG PS



Region of primary site



Median age, years

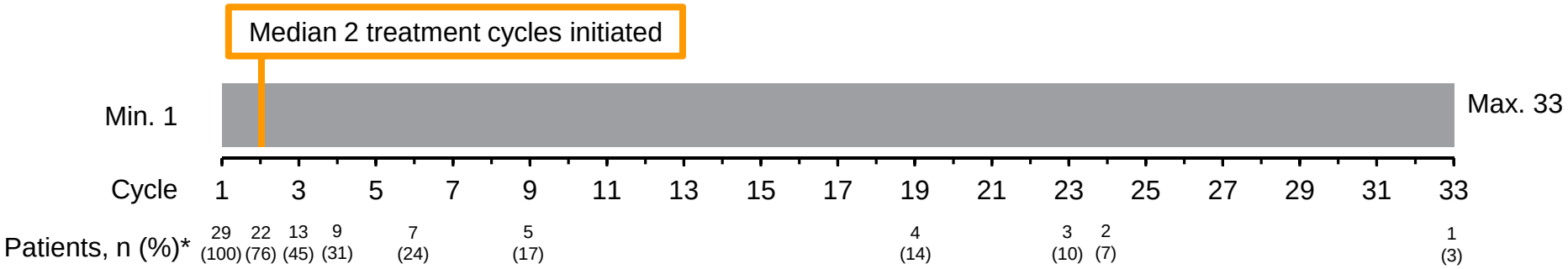


*Anal region, caecum, fossa iliaca left, ovary, proximal jejunum, sigmoid, uterus and unknown (each n=1)

Results (cont'd)

Treatment exposure

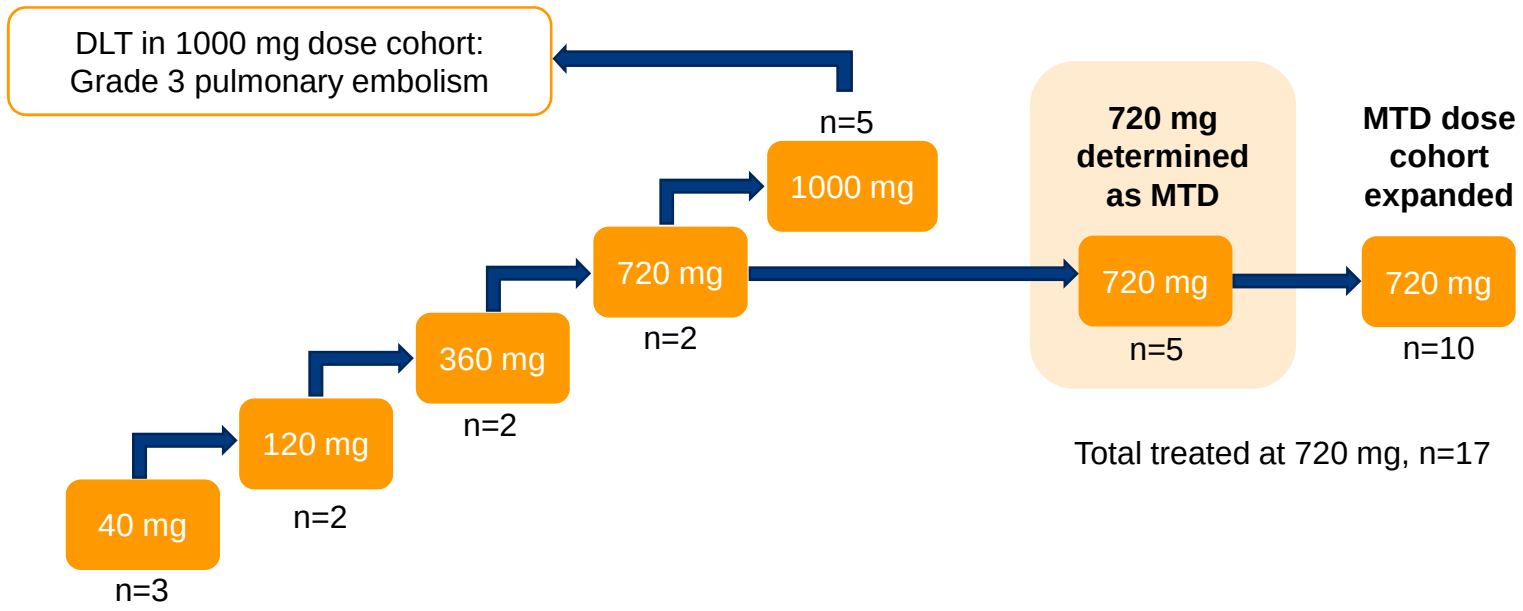
- At data cut-off, 2 patients remained on treatment
  - Reasons for treatment discontinuation were:
    PD (n=19); DLT (n=1); other AE or clinical progression (n=4); other (n=3)



*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

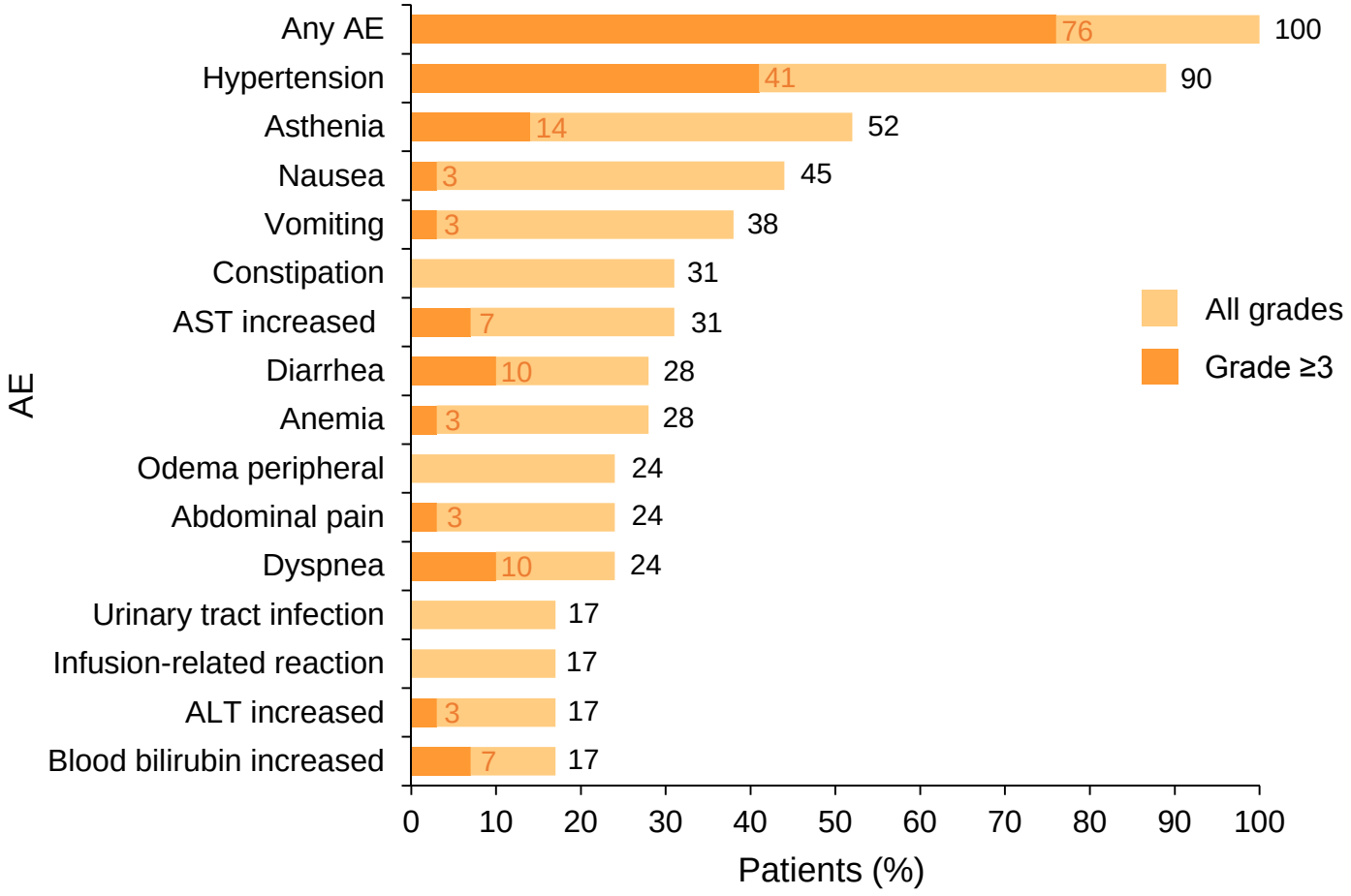
Results (cont'd)

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



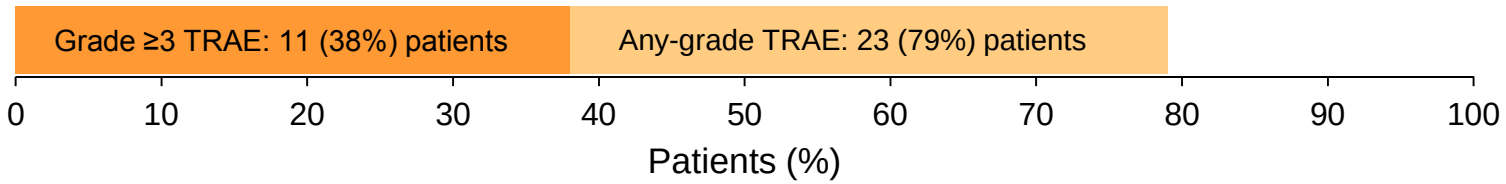
Results (cont'd)

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



Results (cont'd)

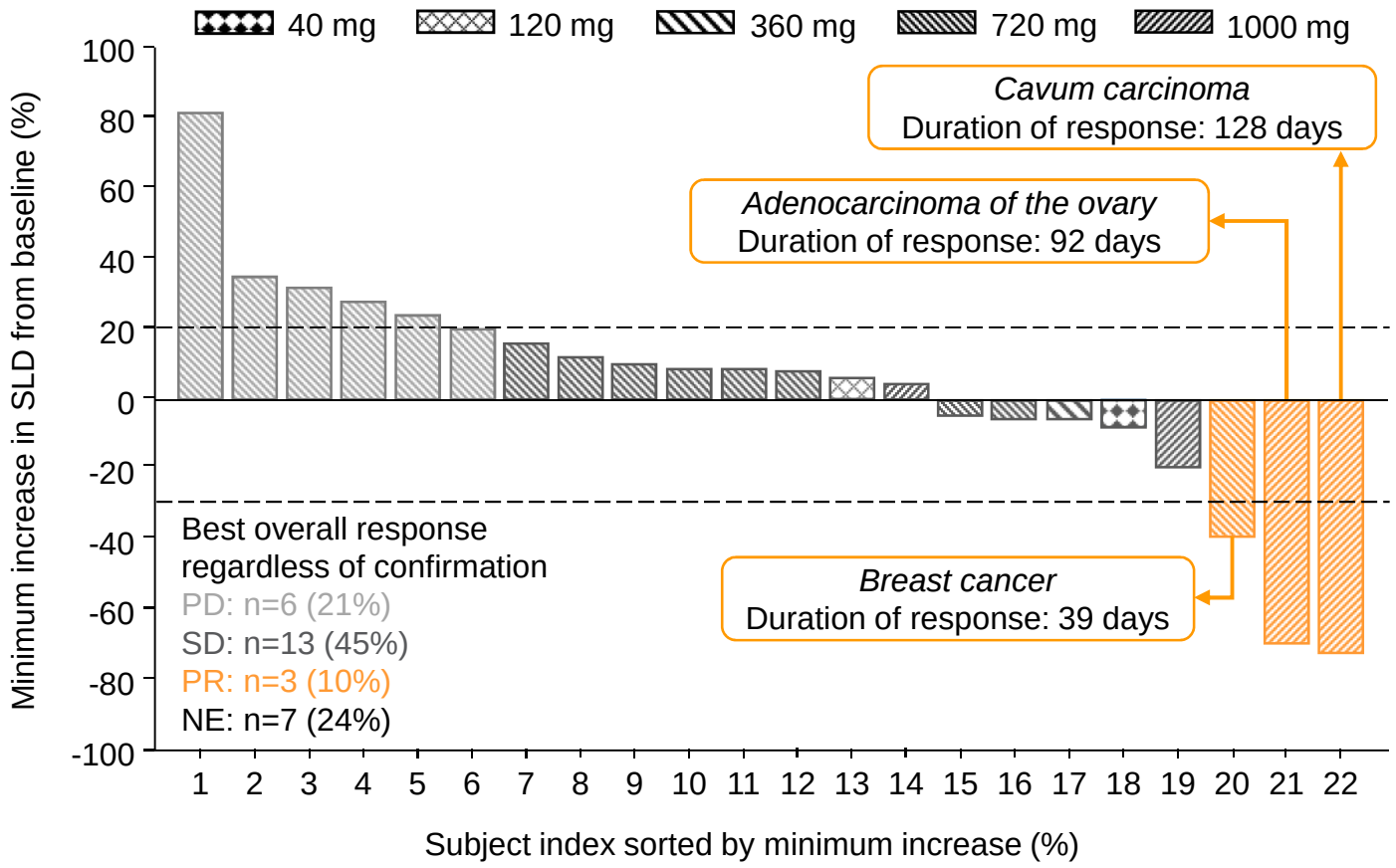
TRAEs



- **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



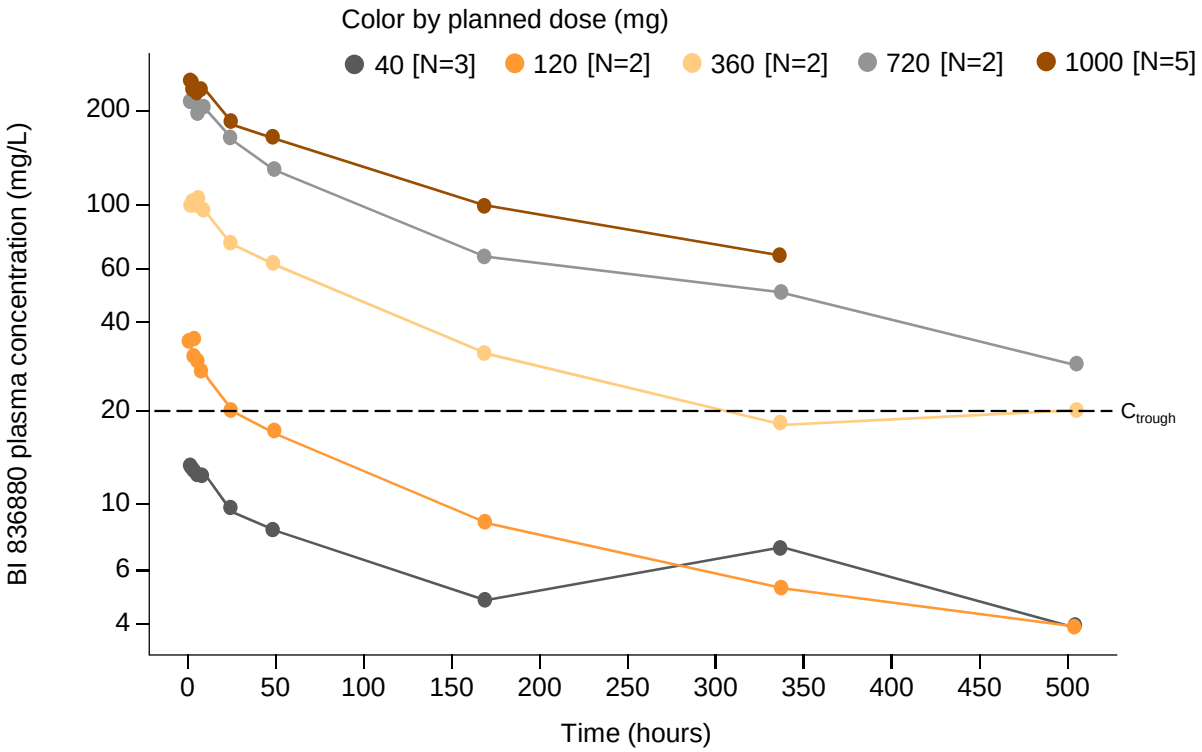
NE, not evaluable; PR, partial response; SD, stable disease; SLD, sum of target lesion diameters

Further PK/PD information: Poster #349

Results (cont'd)

PK and PD analysis of 14 evaluable patients

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



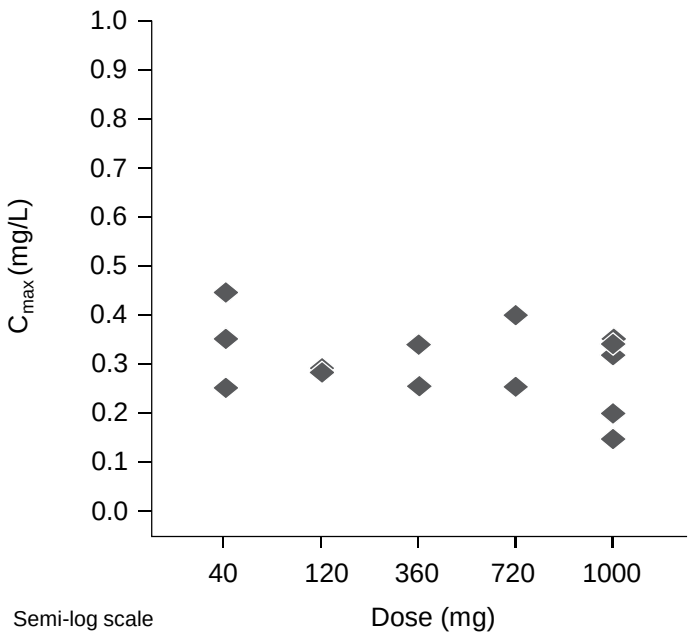
- BI 836880 plasma kinetics in Cycle 1 seemed to be dose proportional over 40–1000 mg
- The required trough values of 20 mg/L could be achieved at doses ≥720 mg

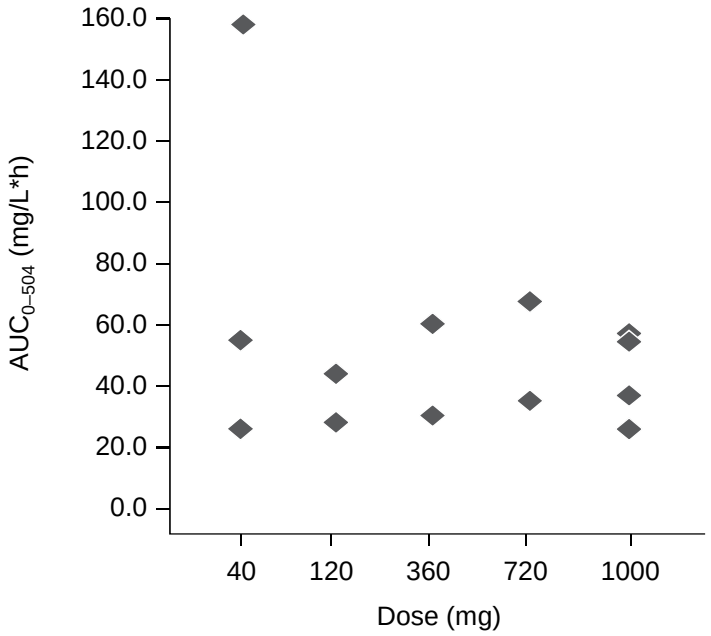
PD, pharmacodynamic; PK, pharmacokinetic

Further PK/PD information: Poster #349

Results (cont'd)

Dose-normalized C_{max} and $AUC_{0–504}$ after first infusion (Cycle 1)

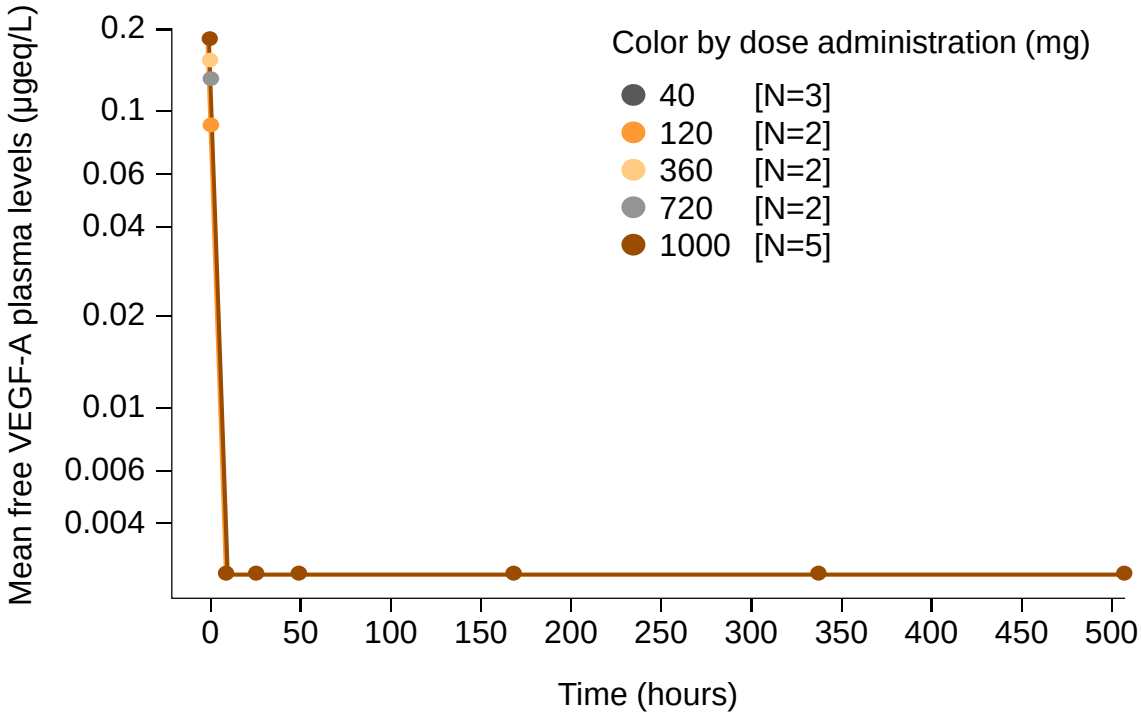




$AUC_{0–504}$, area under the concentration–time curve over the time interval from 0 to 504 hours; C_{max}, maximum measured plasma concentration of BI 836880; C_{trough}, trough plasma concentration

Results (cont'd)

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

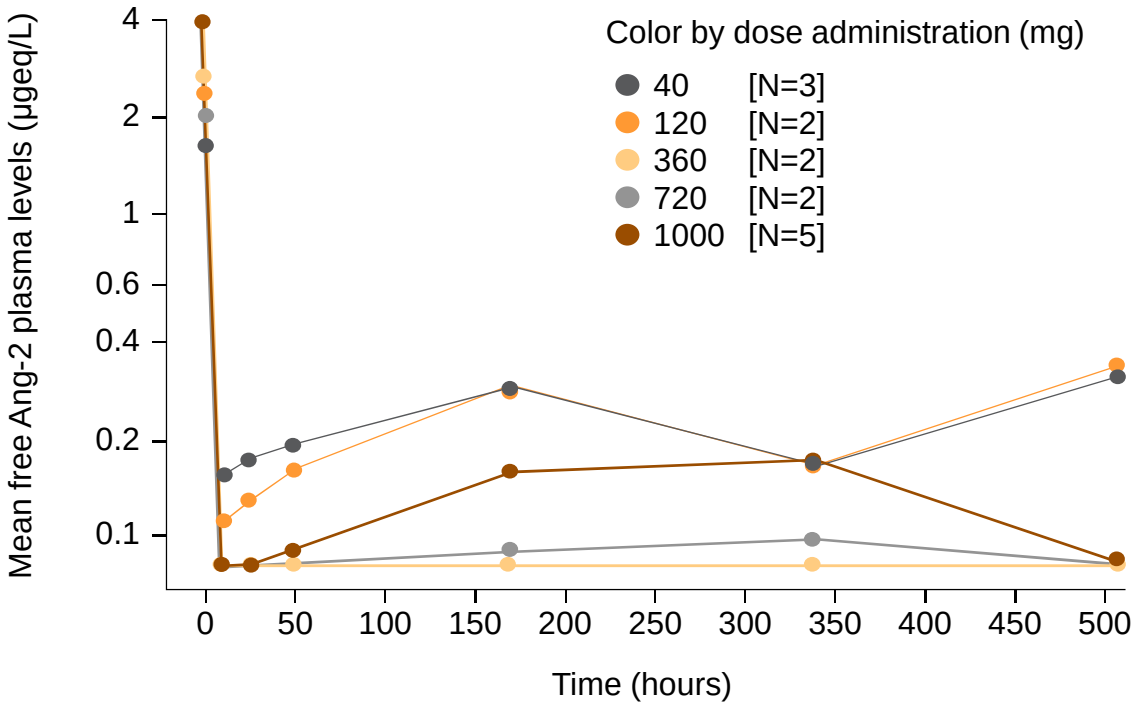


- Systemic free VEGF was completely depleted (below the LLOQ of 0.1 pM or 0.00274 ngeq/ml) at the lowest dose of 40 mg
  - VEGF remained below the LOQ even before the start of the next treatment cycle

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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