Phase I study of BI 836880, a VEGF/Ang2-blocking nanobody®, as monotherapy and in combination with BI 754091, an anti-PD-1 antibody, in Japanese patients with advanced solid tumors

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Introduction

Role of VEGF/Ang2 in tumor angiogenesis and the tumor microenvironment

• VEGF/VEGFR2 and Ang2/Tie2 signaling have complementary functions in tumor angiogenesis\(^1\)\(^–\)\(^4\)
  – Ang2 interrupts vascular tyrosine protein kinase receptor Tie2 signaling, promoting vessel remodeling and sensitizing it for VEGF-induced sprouting angiogenesis
  – VEGF signaling regulates endothelial cell proliferation and migration, and vessel sprouting
  – Preclinically, inhibition of both pathways is superior to targeting either pathway alone

• VEGF/Ang2 also have distinct immunosuppressive effects on the tumor microenvironment\(^5\),\(^6\)
  – VEGF inhibits dendritic-cell maturation and T-cell function, and promotes the activity of Tregs and MDSCs
  – Ang2 increases recruitment and adhesion of neutrophils and TEMs to the endothelium, and increases their conversion to the M2-like macrophage phenotype (TEMs secrete IL-10, which can promote the expansion of Tregs and inhibition of effector T cells)

Ang2, angiopoietin-2; IL-10, interleukin 10; MDSC, myeloid-derived suppressor cell; TEM, Tie2-expressing macrophage; Treg, regulatory T cell; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2
Introduction (cont’d)

Mechanism of action of BI 836880 and rationale for combining with anti-PD-1 therapy

- BI 836880 is a humanized bispecific nanobody® with two blocking domains that inhibit VEGF and Ang2, and a third domain that binds to albumin, to extend half-life in vivo\(^4\)

- Combining BI 836880 with an anti-PD-1 antibody, such as BI 754091, could enhance the tumor microenvironment to support T-cell-mediated destruction of tumor cells (see Figure)\(^1\)\(^-\)\(^4\)

PD-1, programmed cell death protein-1
Introduction (cont’d)

**Immunosuppressive effects of VEGF and Ang2**
- Immature dendritic cell
- Treg cell
- MDSC
- CD8+ T cell
- Tumor cell
- M2 tumor-associated macrophage (pro-tumor)

**Immunopermissive effects of inhibiting VEGF and Ang2**
- Mature dendritic cell
- Dying tumor cell
- M1 tumor-associated macrophage (antitumor)

**VEGF**
- VEGF
- VEGFR2
- Tie2

**BI 836880**

**BI 754091**

Anti-angiogenic normalization of tumor vasculature

Reprogramming of the tumor microenvironment

Adding PD-1 inhibitor drives T-cell-mediated tumor cell death

Figure from: [https://www.inoncology.com/compounds/investigational/vegf-ang2-inhibitor](https://www.inoncology.com/compounds/investigational/vegf-ang2-inhibitor). CD, cluster of differentiation
Trial: Study design

- Open-label, dose-escalation, Phase I study (NCT03972150) to assess BI 836880 as monotherapy (Part 1) and in combination with BI 754091 (Part 2) in Japanese patients with advanced solid tumors

- Dose escalation will be guided by Bayesian logistic regression models with overdose control

- Administration will continue until progressive disease, unacceptable toxicity, or other withdrawal criteria
Trial: Study design (cont’d)

**Part 1**
BI 836880  
Starting dose: 360 mg iv q3w  
~9  
Japanese patients with advanced solid tumors of any type

**Part 2**
BI 836880 + BI 754091  
Starting dose: BI 836880 120 mg iv q3w  
Fixed dose: BI 754091 240 mg iv q3w  
~15

iv, intravenous; q3w, every 3 weeks
Trial: Endpoints and assessments (Parts 1 and 2)

• Primary objective: determine MTD and/or RP2D of BI 836880 alone (Part 1) and in combination with BI 754091 (Part 2)

• Secondary objective: document safety and tolerability, and characterize PK of BI 836880 alone (Part 1) and in combination with BI 754091 (Part 2)

• Safety will be assessed by a descriptive analysis of incidence and severity of AEs (graded according to CTCAE v5), incidence of DLTs, laboratory data, and results of physical examinations

• Tumor response will be evaluated by the investigator every 2 cycles for the first 6 months, and every 3 cycles thereafter (per RECIST v1.1)

• PK parameters will be evaluated after the 1st, 2nd, and 4th infusion cycle in Part 1, and the 1st and 4th infusion in Part 2

AEs, adverse events; CTCAE, Common Terminology Criteria for Adverse Events; DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; PK, pharmacokinetic(s); RECIST, Response Evaluation Criteria in Solid Tumors; RP2D, recommended Phase II dose
## Trial: Endpoints and assessments (Parts 1 and 2; cont’d)

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*During the MTD evaluation period (1st 3-week cycle). OR, objective response; ORR, objective response rate*
## Trial: Patients

**Key inclusion criteria**

- Adult patients (≥20 years; no upper age limit)
- Advanced, unresectable, and/or metastatic solid tumor (any type)
- No therapy of proven efficacy available, or not amenable to standard therapies
- ECOG PS ≤1
- Adequate organ function

ECOG PS, Eastern Cooperative Oncology Group performance status
### Key exclusion criteria

- Known hypersensitivity to study drugs or their excipients
- History of severe hypersensitivity reactions to other mAbs
- Hematological malignancies
- Known HIV, HBV, or HCV infection
- Interstitial lung disease or pneumonitis within last 5 years
- Significant cardiovascular/cerebrovascular disease, or uncontrolled hypertension
- Severe hemorrhagic or thromboembolic event in past 12 months
- Active brain metastases
- Requirement for full-dose anticoagulation
- Any investigational or anti-tumor treatment within 4 weeks or 5 half-life periods prior to initiation of trial treatment
- Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to first dose of study drugs

HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; mAbs, monoclonal antibodies
Current status

- As of October 2019, three patients have been treated in Part 1; Part 2 will start after completion of Part 1
- Two sites are open for recruitment
Key points

• **Rationale:** VEGF/Ang2 inhibition (BI 836880) in combination with anti-PD-1 (BI 754091) is anticipated to enhance the tumor microenvironment to support T-cell-mediated destruction of tumor cells

• **Objectives:** Determine MTD/RP2D of BI 836880 alone and in combination with BI 754091 in Japanese patients with advanced solid tumors

• **Study:** Phase I, open-label, dose-escalation trial

• **Endpoints:** MTD/RP2D of BI 836880 alone and in combination with BI 754091 (primary); safety, PK, anti-tumor activity, and immunogenic response (secondary/further)

• **Status:** Part 1 ongoing (three patients treated); Part 2 will begin after Part 1 completed
References

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