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Phase Ib dose-escalation/expansion study of BI 836880, a VEGF/Ang2-blocking nanobody®, in combination with BI 754091, an anti-PD-1 antibody, in patients with advanced solid tumours

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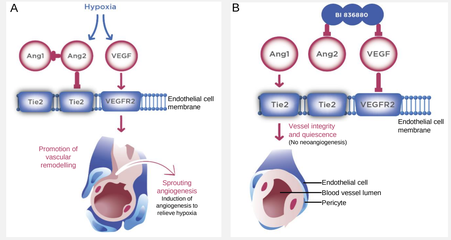
Introduction

- VEGF/VEGFR2 and Ang/Tie2 signalling have key roles in tumour angiogenesis[1,2]
  - Ang2 disrupts Tie2 signalling, promoting vessel remodelling and sensitising it for VEGF-induced sprouting angiogenesis[2,3]
  - Preclinical data show that inhibition of both pathways is superior to targeting either pathway alone[4]
- BI 836880 is a humanised bispecific nanobody[4]
  - BI 836880 has two blocking domains that inhibit VEGF and Ang2, and a third domain that binds to albumin, to extend half-life *in vivo*

VEGF/Ang2-induced angiogenesis (A) and inhibition by BI 836880 (B)[5]



- VEGF and Ang2 have distinct immunosuppressive effects on the tumour microenvironment[6]
  - VEGF inhibits dendritic cell maturation and T-cell function, and promotes activity of Tregs and MDSCs[7]
  - Ang2 increases neutrophil recruitment and adhesion of neutrophils and TEMs to the endothelium (TEMs secrete IL-10 which can promote expansion of Tregs and inhibition of effector T-cells)[6]
- Preclinically, combination of anti-VEGF/Ang 2 with anti-PD-1 therapy promotes an immunopermissive state supportive of T-cell-mediated tumour cell killing[8]
- BI 836880 and BI 754091, an anti-PD-1 antibody, have shown safety and preliminary anti-tumour activity as monotherapies in Phase I studies
  - RP2D: 720 mg iv q3w for BI 836880[9]
  - RP2D: 240 mg iv q3w for BI 754091[10]

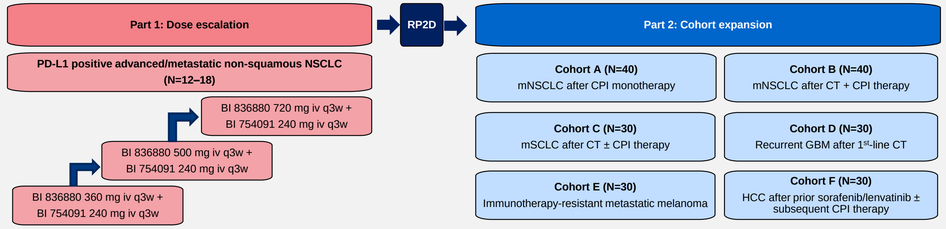
Ang2, angiopoietin 2; IL-10, interleukin 10; iv, intravenous; MDSCs, myeloid-derived suppressor cells; PD1, programmed cell death protein-1; q3w, every 3 weeks; RP2D, recommended phase 2 dose; TEM, Tie-2 expressing macrophages; Tregs, regulatory T-cells; VEGF, vascular endothelial growth factor; VEGFR2, VEGF receptor 2

Objectives

- To assess the safety and anti-tumour activity of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC and in those with other solid tumours

Study design

- This open-label Phase I trial (NCT03468426) is being conducted in two parts:
  - Part 1: dose escalation of BI 836880 + BI 754091 in patients with advanced/metastatic, PD-L1 positive, non-squamous NSCLC
  - Part 2: exploratory expansion cohorts (A–F) in 6 patient populations (expansion cohorts conducted in parallel)
- Dose escalation will be guided by a Bayesian logistic regression model with overdose control, and with oversight from a safety monitoring committee



CPI, checkpoint inhibitor; CT, chemotherapy; GBM, glioblastoma; HCC, hepatocellular carcinoma; mNSCLC, metastatic NSCLC; mSCLC, metastatic small-cell lung cancer; PD-L1, programmed cell death ligand 1

Endpoints and assessments

- Primary objective of Part 1 is to determine the RP2D of BI 836880 in combination with BI 754091
- Primary objective of Part 2 is to assess anti-tumour activity of BI 836880 in combination with BI 754091 in patients with locally advanced or metastatic non-squamous NSCLC and other solid tumours

	Primary endpoint	Secondary endpoints
Part 1	MTD (based on number of patients with DLTs*)	Safety
		Pharmacokinetic parameters
Part 2	OR (CR, PR)	Disease control (CR, PR, SD)
		Duration of OR
		PFS
		Tumour shrinkage
		Safety
		Pharmacokinetic parameters

Exploratory biomarker analysis and assessment of immunogenic response will also be performed

- Tumour response will be evaluated by the investigator according to RECIST version 1.1 and iRECIST
- Efficacy endpoints will be assessed every 2 cycles (6 weeks)
- Safety will be assessed by a descriptive analysis of incidence and severity of AEs graded according to CTCAE version 5.0, incidence of DLTs, laboratory data and results of physical examinations

*During the MTD evaluation period (1st 3-week cycle)
AE, adverse event; CR, complete response; CTCAE, Common Terminology Criteria for Adverse Events; DLT, dose-limiting toxicity; iRECIST, immune-related RECIST; MTD, maximum tolerated dose; OR, objective response; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease

Patients

Key inclusion criteria

≥18 years
- ECOG PS 0–1
- Measurable target lesion
- Adequate organ function

Part 1
- Pathologically confirmed locally advanced/metastatic non-squamous NSCLC (PD-L1 expression >1%)
- Disease progression or relapse during or after ≥2 cycles of 1st-line platinum-based CT ± CPI

Part 2 Cohorts A and B (NSCLC)
- Pathologically confirmed locally advanced/metastatic non-squamous NSCLC
- Cohort A: Prior 1st- or 2nd-line CPI monotherapy; ≤1 prior CT
- Cohort B: Prior 1st-line platinum-based CT and CPI combination

Part 2 Cohort C (SCLC)
- Pathologically confirmed locally advanced/metastatic SCLC
- Documented disease progression during or after 1st-line CT ± CPI

Part 2 Cohort D (GBM)
- Histologically confirmed de novo primary GBM
- Documented 1st progression after RT and concurrent/adjuvant CT (may have been operated for recurrence)

Part 2 Cohort E (Melanoma)
- Histologically confirmed unresectable stage IV metastatic melanoma
- Documented progression during or after CPI-based therapy

Part 2 Cohort F (HCC)
- Locally advanced/metastatic and/or unresectable histologically confirmed HCC, not eligible for surgical/locoregional therapies
- Progressed during or discontinued 1st-line sorafenib or lenvatinib. 2nd-line anti-PD-1 permitted
- Child-Pugh score class A and documented virology status of hepatitis

Key exclusion criteria

Part 2
- Prior anti-angiogenesis treatment (exc. sorafenib/lenvatinib in HCC cohort)

Part 2 Cohort D (GBM)
- Tumour primarily localised to brainstem/spinal cord
- Presence of diffuse leptomeningeal or extracranial disease

Part 2 Cohort E (Melanoma)
- Uveal or ocular melanoma

Part 2 Cohort F (HCC)
- Known fibromellar HCC, sarcomatoid HCC or mixed cholangiocarcinoma and HCC
- Untreated/incompletely treated varices with bleeding or high risk for bleeding
- History of hepatic encephalopathy
- Co-infection with HBV and HCV or HBV and HDV
- Untreated active HBV
- Treatment with HCV anti-viral therapy within 4 weeks prior to study drug

ECOG PS, Eastern Cooperative Oncology Group performance status; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; RT, radiotherapy

Current status

- As of August 2019, 9 patients have been treated in Part 1
  - Sites in France and Germany are open for recruitment
- Part 2 will begin once the RP2D is established in Part 1

Key points

- **Objectives:** Assess safety and anti-tumour activity of BI 836880 + BI 754091 in patients with locally advanced/metastatic non-squamous NSCLC and other solid tumours
- **Study:** Phase I, open-label, dose escalation (Part 1) and expansion (Part 2)
- **Endpoints:** Part 1: MTD; Part 2: OR (primary); disease control, duration of response, PFS and tumour shrinkage (secondary)
- **Status:** Part 1 ongoing in two countries (9 patients treated); Part 2 will begin when RP2D is established

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