Phase Ia 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 Ang2 signaling have key roles in tumour angiogenesis**
  - Ang2 disrupts Tad signalling, promoting vessel remodelling and remodeling for VEGF-induced sprouting angiogenesis1,2
  - Preclinical data show that inhibition of both pathways is superior to targeting either pathway alone3
- **BI 836880 is a humanized bispecific nanobody**
  - BI 836880 has blocking domains that inhibit VEGFR2 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)**

Objectives

- **To assess the safety and anti-tumour activity of BI 836880 in combination with BI 754091 in patients with locally advanced/metastatic, non-squamous NSCLC and in those with other solid tumours**
  - **VEGF and Ang2 have distinct immunosuppressive effects on the tumour microenvironment**
    - VEGF inhibits dendritic cell maturation and T-cell function, and promotes activity of Tregs and MDSC3
    - Ang2 increases neutrophil recruitment and adhesion of neutrophils and Tregs to the endothelium4,5,6,7,8,9,10,11,12
  - Preclinical, combination of anti-VEG-F2 and anti-PD-1 therapy promotes an immunosuppressive state supportive of T-cell-mediated tumour cell killing5

Study design

- **Part 1:** dose escalation of BI 836880 + BI 754091 in patients with advanced/metastatic, PD-L1 positive, non-squamous NSCLC
  - **Primary objective of Part 1 is to determine the RP2D of BI 836880 + BI 754091 in patients with advanced/metastatic non-squamous NSCLC**
    - **Primary endpoint:** secondary endpoints
      - Time to disease progression or death
      - Objective response
      - Duration of response (≥6 months)
      - Disease control rate (CR, PR, SD, PD)
      - Progression-free survival
      - Tumour shrinkage
      - Pharmacokinetic parameters

Endpoints and assessments

- **Primary objective of Part 1 is to determine the RDD of BI 836880 in combination with BI 754091**
  - **Secondary endpoints:**
    - Pharmacokinetic parameters
    - Disease control (CR, PR, SD, PD)
    - Duration of OR
    - Tumour shrinkage
    - Pharmacokinetic parameters

Explosatory biomarker analysis and assessment of immunogenic response will be performed

- **Tumor 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)**

Key inclusion criteria

- **Part 1:**
  - Histologically confirmed locally advanced/metastatic non-squamous NSCLC and other solid tumours
  - Child-Pugh A or B, ECOG PS 0, no active infection or opportunistic infection
  - AECG from the last 2 cycles of 6 weeks, with relapse or relapse after ≥2 cycles of 1 line ant-PD-1 therapy permitted
  - No prior radiotherapy to the tumour region
  - No prior ant-angiogenesis treatment (ex. sorafenib/lenvatinib in HCC cohort)
  - Treatment with HCV anti-viral therapy within 4 weeks prior to study drug
  - HBV and HDV
  - Presence of diffuse leptomeningeal or extracranial disease
  - History of hepatic encephalopathy
  - Known fibromellular HCC, sarcomatoid HCC or mixed cholangiocarcinoma and HCC
  - Disease progression or relapse during or after ≥2 cycles of 1 line ant-PD-1 therapy
  - Pathologically confirmed locally advanced/metastatic non-squamous NSCLC
  - ≤1 prior CT ± CPI therapy
  - Histologically confirmed unresectable stage IV metastatic melanoma

Key exclusion criteria

- **Part 1:**
  - Prior anti-angiogenesis treatment (exc. sorafenib/lenvatinib in HCC cohort)
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