Phase I, first-in-human trial evaluating BI 1387446 (STING agonist) alone and in combination with ezabenlimab (BI 754091; anti-PD-1) in solid tumors

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Introduction

• Activation of the STING pathway in intratumoral immune cells leads to increased type I interferon production, promoting recruitment and priming of T cells against tumor antigens, and providing anti-tumor activity.
• BI 1387446 potently and highly selectively activates the STING pathway (Figure 1).

Intratumoral administration of STING agonists has resulted in notable therapeutic activity in animal models:
• Intratumoral administration of BI 1387446 resulted in dose-dependent local tumor control and induction of immunological memory:
  - Delay in tumor growth was seen in non-injected lesions, indicative of an abscopal effect
  - Systemic anti-tumor effect was further enhanced with PD-1 inhibition
• Ezabenlimab (BI 754091) is a humanized IgG4 anti-PD-1 monoclonal antibody
  - IgG4, immunoglobulin G4; PD-1, programmed cell death protein-1; STING, stimulator of interferon genes

Study design

• First-in-human, Phase I, open-label, multicenter trial (NCT04147234)
  - The study will consist of two arms: Arm A and Arm B (with a potential third arm: Arm C)
  - Arm B will open at the starting dose level once the starting dose level in Arm A is considered safe by the SMC; Arm C may open at the starting dose level (or higher) once this dose level is considered safe in Arm B

Study uses a Bayesian logistic regression model with overdose control to investigate a range of dose levels

Objectives and inclusion/exclusion criteria

• To characterize safety and determine the MTD for BI 1387446 and ezabenlimab

Key Inclusion criteria

- Adult patients (≥18 years of age)
- Diagnosis of advanced, unresectable and/or metastatic malignant solid tumor and indication for treatment
- Patient must have exhausted established treatment options known to meaningfully prolong survival
- ≥1 Tumor lesion suitable for injection
- ECOG PS 0/1

Key exclusion criteria

- History or evidence of active, non-tumor-related autoimmune disease, except for endocrinopathies
- History or evidence of pneumonitis related to prior immunotherapy
- Presence of other active invasive cancers other than the one treated in this trial within 5 years prior to enrollment

Endpoints and assessments

- Number of patients with DLTs in the MTD evaluation period
- Best percentage change from baseline in size of target lesions
- Best percentage change from baseline in size of injected lesions
- OR, objective response rate
- RECIST Response Evaluation Criteria in Solid Tumors

Outcomes

• The study of biomarkers (in plasma, blood and tumor samples) will be hypothesis-generating and will substantially contribute to the understanding of the BI 1387446 mode of action (additional content can be accessed via the QR code)

The trial is currently open for recruitment in six sites in Europe and the USA

As of February 2021, 10 patients have been treated

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References


Studies

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Key points

- BI 1387446 administered intratumorally into superficial lesions
- BI 1387446 administered intratumorally into superficial lesions, in combination with ezabenlimab (240 mg q3w) IV
- BI 1387446 administered intratumorally into deep/visceral lesions
- BI 1387446 administered intratumorally into superficial lesions, in combination with ezabenlimab (240 mg q3w) IV

Abbreviations

- RP2D, recommended phase 2 dose
- SMC, Safety Monitoring Committee

Figure 1: Intratumoral/intracystic administration of BI 1387446 in solid tumors

• Tumor associated immune cells
- Tumor cell
- Tumor necrosis
- Eczematized
- Fibrotic
- Non-inflamed tumor microenvironment
- T-cell-inflamed tumor microenvironment
- Tumor associated immune cells

Tumor 
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Tumor associated immune cells
Ezabenlimab 
Inflammation 
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• CD8+ T cells and mast cells infiltrate lesions, indicative of an abscopal effect

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- Tumor cell
- Tumor necrosis
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Figure 1: Intratumoral/intracystic administration of BI 1387446 in solid tumors

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