#TPS3175

A first-in-human Phase I dose-escalation trial of the B7-H6/CD3 T-cell engager BI 765049 ± ezabenlimab (BI 754091) in patients with advanced solid tumors expressing B7-H6

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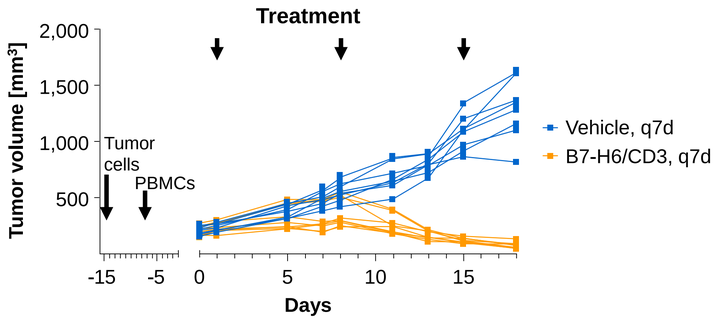
Introduction

- B7-H6 is a member of the B7 family of immune receptors, which is expressed in several solid tumor types; however, very little expression can be detected in normal tissues[1,2]
- BI 765049 is a novel immunoglobulin G-like bispecific T-cell engager designed to bind simultaneously to B7-H6 on tumor cells and CD3 on T cells, resulting in cytolytic synapse formation, local activation and proliferation of T cells, and cytokine secretion, converting a non-inflamed (cold) tumor environment into an inflamed (hot) tumor environment
- Preclinical studies have demonstrated that:
  - BI 765049 monotherapy induced dose-dependent antitumor activity in humanized *in vivo* CRC models and infiltration of T cells[3]
  - Activation of tumor-infiltrating T cells is associated with upregulation of the PD-L1 pathway

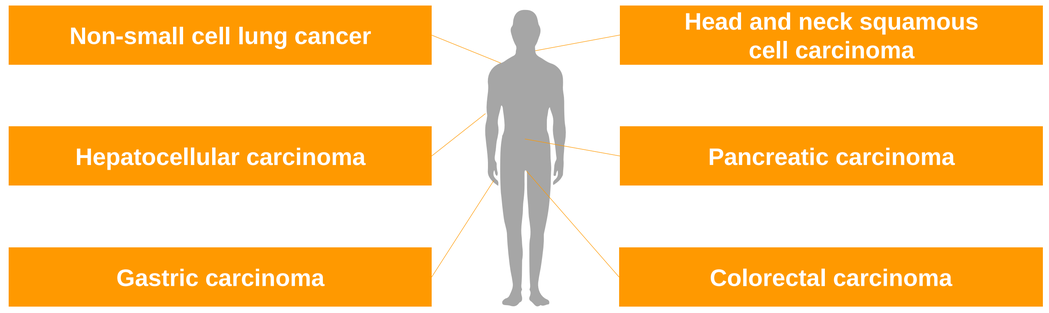
Tumor regression in HCT-15 CDX model following BI 765049 treatment[2]



B7-H6/CD3 monotherapy treatment induced regression in all treated HCT-15 (CRC) tumor-bearing mice

CD3, cluster of differentiation 3; CDX, cell-derived xenograft; CRC, colorectal cancer; PD-L1, programmed death-ligand 1; PBMC, peripheral blood mononuclear cells; q7d, every 7 days

- Potential indications for BI 765049 include:



- BI 765049 is currently undergoing clinical investigation in a Phase I study (NCT04752215) as a monotherapy and in combination with ezabenlimab (BI 754091) in patients with CRC or other B7-H6-positive tumors (NSCLC, HCC, HNSCC, gastric carcinoma, and pancreatic carcinoma)

CRC, colorectal cancer; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancer

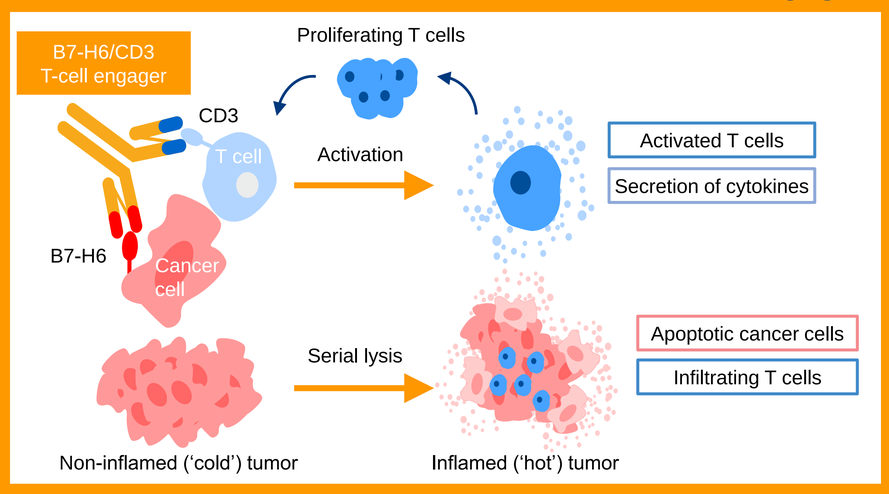
Objectives

- The primary objective is to determine the MTD or recommended dose for expansion based on the number of patients with DLTs during the MTD evaluation period
- Further objectives are to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy

DLTs, dose-limiting toxicities; MTD, maximum tolerated dose

Summary

Mechanism of action of BI 765049, a novel T-cell engager:[3]



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Key points:

- **NCT04752215 is a first-in-human, open-label, dose-escalation trial of BI 765049 ± ezabenlimab in patients with advanced CRC or other B7-H6-positive tumors**
- **The primary objective is to determine the MTD of BI 765049 ± ezabenlimab based on the number of patients with DLTs during the MTD evaluation period**

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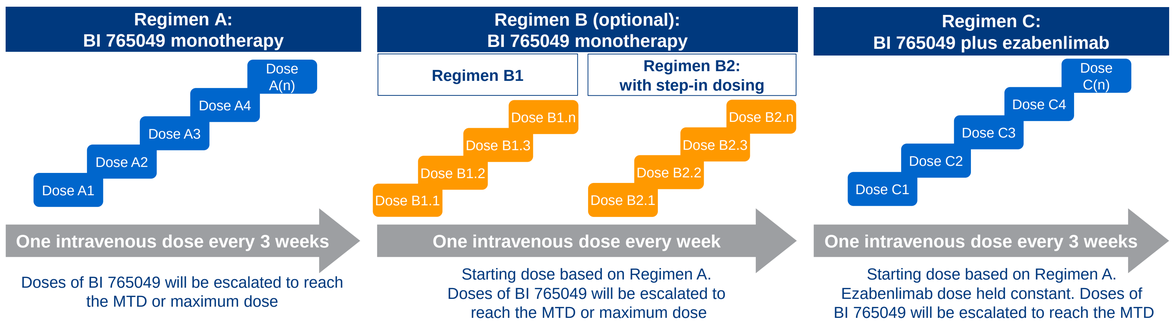
NCT04752215 Study design



- Dose escalation will be guided by a Bayesian Logistic Regression Model with overdose control that will be fitted to binary toxicity outcomes using a hierarchical modelling approach to jointly model all dosing regimens
- Treatment will be allowed to continue until confirmed progressive disease, unacceptable toxicity, or other withdrawal criteria, with a maximum duration of 36 months

Endpoints

Primary endpoints	Secondary endpoints
MTD based on number of patients with DLTs	Objective response based on RECIST v1.1
Number of patients with DLTs in the MTD evaluation period	Pharmacokinetic parameters (C_{max} and AUC_T) after first and multiple doses in all regimens

AUC_T, area under the concentration-time curve of the analyte over a uniform dosing interval$_T$; C_{max}, maximum measured concentration; RECIST v1.1, Response Evaluation Criteria In Solid Tumours version 1.1

Inclusion and exclusion criteria

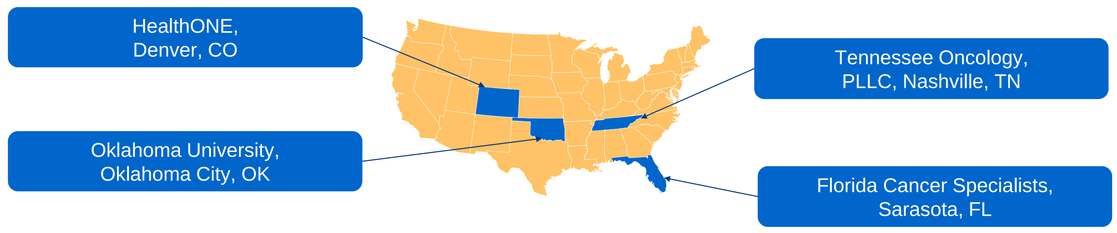
Key inclusion criteria
Adult patients (≥18 years old)
Patients with confirmed, advanced, unresectable and/or metastatic CRC, or patients with confirmed* B7-H6-positive NSCLC, HCC, HNSCC, gastric carcinoma, or pancreatic carcinoma
Patient has progressed on/is ineligible for available standard therapies
≥1 evaluable lesion (modified RECIST v1.1) outside of CNS
Adequate liver, bone marrow and renal function
ECOG PS 0/1

Key exclusion criteria
Previous treatment with B7-H6-targeting agents
Persistent toxicity from previous treatment that has not resolved to ≤CTCAE grade 1†
Anticoagulant treatment that cannot be safely interrupted if medically needed for a study procedure (e.g. biopsy)
Diagnosis of immunodeficiency or receiving immunosuppressive therapy within 7 days
Prior anticancer therapy within 3 weeks/5 half-life periods or extensive field radiotherapy within 2 weeks

*B7-H6 positivity confirmed by central testing; †Except for alopecia, CTCAE grade 2 neuropathy or endocrinopathies controlled by replacement therapy or grade 1 asthenia or fatigue.
CNS, central nervous system; CTCAE, Common Terminology Criteria for Adverse Events; ECOG PS, Eastern Cooperative Oncology Group performance status

Study status

- As of January 2022, patients are being recruited in early dose-escalation cohorts in the US



References

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SC-US-74410 **Presented at the American Society for Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA, June 3–7, 2022**

This study was funded by Boehringer Ingelheim. The authors were fully responsible for all content and editorial decisions, were involved at all stages of poster development and have approved the final version.
The authors did not receive payment related to the development of the poster. Medical writing support for the development of this poster, under the direction of the authors, was provided by Jo Badawy, BSc, of Ashfield MedComms, an Ashfield Health company, and funded by Boehringer Ingelheim