

Phase I dose escalation study in patients with advanced solid tumours receiving first-in-class BI 765063, a selective signal-regulatory protein α (SIRP α) inhibitor, in combination with ezabenzimab (BI 754091), a programmed cell death protein-1 (PD-1) inhibitor

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Introduction

- BI 765063 is a first-in-class, humanised IgG4 monoclonal antibody (mAb) antagonist of signal-regulatory protein α (SIRP α) that blocks the "don't eat me" signal of the SIRP α /CD47 axis, enhancing tumour cell phagocytosis and increasing antigen presentation to drive anti-tumour responses.^{1,2}
- BI 765063 strongly binds to the V1 SIRP α allele but lacks SIRP α binding, thereby preserving T-cell activation³
- In the first-in-human trial assessing BI 765063 (NCT03990233), preliminary results from the monotherapy arm of the trial demonstrated that BI 765063 was well tolerated with no dose-limiting toxicities (DLTs), and showed anti-tumour activity, including one patient experiencing an ongoing partial response (PR) for >1 year³
- Here we report an update from the trial on dose escalation results of the combination of BI 765063 + ezabenzimab (BI 754091; a programmed death protein-1 [PD-1] inhibitor) in patients with advanced solid tumours

Figure 1. BI 765063 (anti-SIRP α) mechanism of action



Objectives and Methods

Objectives

- This dose escalation/expansion trial aims to evaluate the safety and efficacy of BI 765063 alone and in combination with ezabenzimab in adult patients with advanced solid tumours

Methods

- This is a two-step, open-label, multicentre Phase I trial in patients genetically homozygous or V1/V2 heterozygous with advanced solid tumours who had failed or were ineligible for standard therapy
- Step 1 (completed):** dose escalation monotherapy³ or in combination with ezabenzimab (presented here)
- Step 2 (recruiting):** dose confirmation/expansion in patients with microsatellite stable (MSS) colorectal cancer (CRC) and endometrial cancer
- In the escalation combination, two BI 765063 dose levels (18 and 24 mg/kg IV q3w) were evaluated with ezabenzimab (240 mg, IV q3w)
- Primary endpoints were: DLTs, maximum tolerated dose (MTD) and recommended Phase II dose (RP2D)
- Secondary and further endpoints included: adverse events (AEs), objective response rate (ORR; RECIST 1.1 and iRECIST) and pharmacokinetics (PK)

Patient demographics and disease characteristics

- A total of 18 patients received ≥ 1 dose of BI 765063 (18/24 mg/kg q3w) and ezabenzimab (240 mg q3w): nine V1/V1 patients and nine V1/V2 patients
- 16 patients were evaluable for efficacy
- The most frequent tumours included: CRC (n=4), endometrial cancer (n=3), liver cancer (n=2) and cervical cancer (n=2)

Table 1. Patient demographics and disease characteristics

	All patients (N=18)
Median age, years (range)	62 (26–78)
Female, n (%)	15 (83.3)
White, n (%)	18 (100.0)
Metastatic disease at screening, n (%)	18 (100.0)
V1/V1 SIRP α polymorphism, n (%)	9 (50.0)
ECOG PS at baseline, n (%)	
0	6 (33.3)
1	11 (61.1)
2	1 (5.6)
Median prior lines of systemic therapy, n (range)	3.5 (1.0–6.0)
Prior anti-PD-L1 therapy, n (%)	8 (44.4)

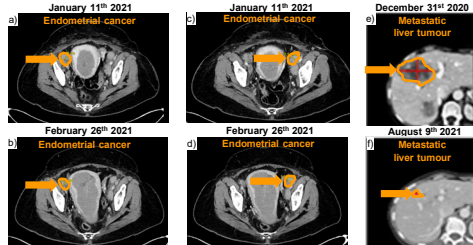
Key findings and conclusions

- The first-in-class, selective SIRP α inhibitor BI 765063 in combination with the PD-1 inhibitor ezabenzimab was well tolerated with no DLTs
- One patient had grade 2 anaemia, but no other haematological AEs frequently associated with CD47-targeting therapies were reported
- The RP2D of BI 765063 was 24 mg/kg q3w with full RO saturation
- Preliminary antitumour activity was observed, with three patients with advanced colorectal or endometrial cancer experiencing confirmed (i)PRs;
- An additional patient with HCC had SD; notably, AFP levels were normalised in this patient
- The trial is currently recruiting patients with MSS CRC and endometrial cancer in the expansion phase



Efficacy

Please scan the QR code for additional efficacy results



- Figure 4 shows CT scans of a V1/V2 heterozygous 72-year-old female patient with endometrial cancer (maximum target lesion shrinkage: 37%; from 43 mm to 27 mm) and another with MSS CRC (maximum target lesion shrinkage: 50%; from 186 mm to 93 mm)

Safety

- No DLTs were reported; the MTD was not reached. No BI 765063-treatment-related thrombocytopenia, and only one case of anaemia (grade 2), was observed
- All BI 765063-treatment-related AEs (TRAEs) were grade 1 or 2, except grade 3 rash maculo-papular in one patient; no grade 4/5 TRAEs were reported

Table 2. Summary of BI 765063-TRAEs (n ≥ 3 patients)

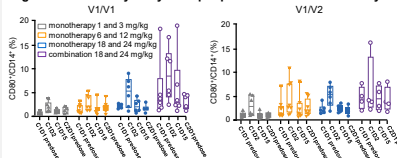
Patients (N=18) with:	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Total with TRAEs ^a	12 (66.7)	2 (11.1)	8 (44.4)	1 (5.6)
Infusion-related reaction	5 (27.8)	2 (11.1)	3 (16.7)	0
Fatigue	5 (27.8)	3 (16.7)	2 (11.1)	0
Arthralgia ^a	4 (22.2)	2 (11.1)	1 (5.6)	0
Rash maculo-papular	4 (22.2)	3 (16.7)	0	1 (5.6)
Pruritus	3 (16.7)	3 (16.7)	0	0

^aIncludes one patient with arthralgia of unknown grade

Efficacy and biomarker results

- BI 765063 showed dose-proportional systemic exposure and full receptor occupancy (RO) saturation in Cycle 1 at the 18 and 24 mg/kg dose levels

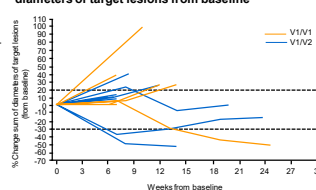
Figure 2. Preliminary analysis of peripheral blood CD80⁺ monocytes



- Treatment with BI 765063 at 18 and 24 mg/kg, as monotherapy or in combination with ezabenzimab, lead to an apparent transient increase in the percentage of activated CD80⁺/CD14⁺ monocytes in V1/V1 and V1/V2 patients at Cycle 1 Day 2, in line with the expected mechanism of action

- Figure 3 shows preliminary results of the percentage change in the sum of target lesions compared with baseline in all patients

Figure 3. Spider plot of percentage change in sum of diameters of target lesions from baseline



- Three patients had a confirmed (i)PR: two patients with endometrial cancer (MSS, PD-L1 CPS: 46%, three prior systemic lines; microsatellite and PD-L1 CPS unknown, two prior systemic lines) and one patient with MSS CRC (PD-L1 CPS: 6.3%, five prior systemic lines) with maximum target lesion shrinkages of 37%, 53%, and 50%, respectively
- Another patient with hepatocellular carcinoma (HCC) had (i)stable disease (SD; maximum target lesion shrinkage: 7%) with normalised levels of alpha fetoprotein (AFP)

References and abbreviations

- Delord J-P, et al. Blood 2019;134(Suppl1):1040.
- Gautier V, et al. J Clin Invest 2020;130:6109–23.
- Champiat S, et al. J Clin Oncol 2021;39(Suppl1):2623.
- Johnson M, et al. Ann Oncol 2018;29(Suppl7):v60.
- CD47, cluster of differentiation 47; CPS, combined positive score; ECOG PS, Eastern Cooperative Oncology Group performance status; IgG4, immunoglobulin G4; (i) immune; iRECIST, immune Response Evaluation Criteria in Solid Tumors; IV, intravenously; q3w, every three weeks.