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

#983P

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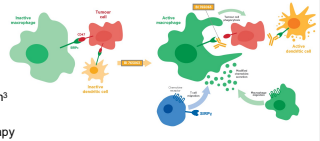
Introduction

- BI 765063 is a first-in-class, humanised IgG4 monoclonal antibody (mAb) antagonist of signal-regulatory protein α (SIRPα) that blocks the "don't eat me" signal of the SIRPα/CD47 axis, enhancing tumour cell phagocytosis and increasing antigen presentation to drive anti-tumour responses[1,2]
- BI 765063 strongly binds to the V1 SIRPα allele but lacks SIRPγ binding, thereby preserving T-cell activation[3]
- 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 year[3]
- Here we report an update from the trial on dose escalation results of the combination of BI 765063 + ezabenlimab (BI 754091[4]; a programmed death protein-1 [PD-1 inhibitor]) in patients with advanced solid tumours

Figure 1. BI 765063 (anti-SIRPα) 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 ezabenlimab in adult patients with advanced solid tumours

Methods

- This is a two-step, open-label, multicentre Phase I trial in patients genetically SIRPα V1/V1 homozygous or V1/V2 heterozygous with advanced solid tumours who had failed or were ineligible for standard therapy
- **Step 1 (completed)**: dose escalation monotherapy[3] or in combination with ezabenlimab (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 ezabenlimab (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 ezabenlimab (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 SIRPα 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-(L)1 therapy, n (%)	8 (44.4)

Key findings and conclusions

- The first-in-class, selective SIRPα inhibitor BI 765063 in combination with the PD-1 inhibitor ezabenlimab 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

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Efficacy

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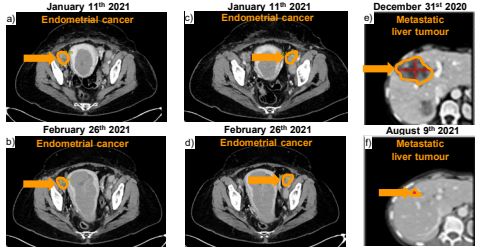


Figure 4. CT scans of: a V1/V2 heterozygous 72-year-old female patient with endometrial cancer; right iliac before (a) and after (b) and left iliac before (c) and after (d) treatment with BI 765063 and ezabenlimab; a V1/V1 homozygous 44-year-old female patient with MSS CRC; liver segment before (e) and after (f) treatment with BI 765063 and ezabenlimab

- Figure 4 shows CT scans of two patients with a confirmed (i)PR: one with MSS 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 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 (in ≥3 patients)

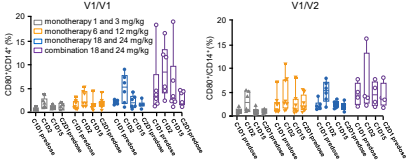
Patients (N=18) with:	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)
Total with TRAEs*	12 (66.7)	2 (11.1)	8 (44.4)	1 (5.6)
Infusion-related reaction	5 (27.8)	2 (11.1)	3 (16.7)	0
Fatigue	5 (27.8)	3 (16.7)	2 (11.1)	0
Arthralgia*	4 (22.2)	2 (11.1)	1 (5.6)	0
Rash maculo-papular	4 (22.2)	3 (16.7)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

*Includes one patient with arthralgia of unknown grade

Efficacy and biomarker results

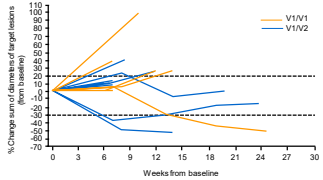
- BI 765063 showed dose-proportional systemic exposure and full receptor occupancy (RO) saturation in Cycle 1 at the 18 and 24 mg/kg dose levels

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 ezabenlimab, 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
- 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)

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



References and abbreviations

1. Delord J-P, et al. Blood 2019;134(Suppl1):1040; 2. Gauttier V, et al. J Clin Invest 2020;130:6109–23; 3. Champiat S, et al. J Clin Oncol 2021;39(Suppl15): 2623; 4. Johnson, M, et al. Ann Oncol 2018;29(Suppl7):vii60. 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.

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