Safety, pharmacokinetics, efficacy, and preliminary biomarker data of first-in-class BI 765063, a selective SIRPα inhibitor: results of monotherapy dose escalation in Phase 1 study in patients with advanced solid tumors

#2623

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Introduction

- BI 765063 is a first-in-class humanized IgG4 monoclonal antibody antagonist of SIRPα (expressed on myeloid cells) that blocks the "don't eat me" signal of the SIRPα/CD47 axis, a vital innate immune checkpoint, enhancing tumor cell phagocytosis and increasing antigen presentation to drive anti-tumor responses[1,2]
  - BI 765063 binds to the V1 SIRPα allele with high affinity and to the V2 SIRPα allele with low affinity
  - BI 765063 lacks SIRPγ binding, thereby preserving T-cell activation
- We report results of the BI 765063 monotherapy dose escalation in patients with advanced solid tumors

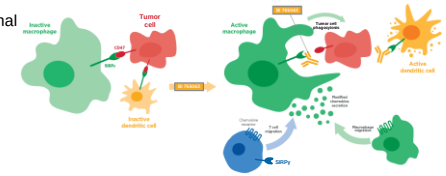

Figure 1. BI 765063 (anti-SIRPα) mechanism of action

CD, cluster of differentiation; IgG4, immunoglobulin G4; SIRP, signal-regulatory protein

Objectives

- The escalating phase aimed to determine DLTs, MTD, and RP2D of BI 765063 monotherapy in V1/V1 homozygous and V1/V2 heterozygous patients with advanced solid tumors

DLTs, dose-limiting toxicities; MTD, maximum tolerated dose; RP2D, recommended phase 2 dose

Methods

Study design and treatment

- This is a two-step, open-label, multicenter Phase 1 study in patients with advanced solid tumors
- Step 1: dose escalation monotherapy, (results presented here) and in combination with anti-PD-1;
  Step 2: dose confirmation/expansion
- Nine dose levels of BI 765063 were evaluated in the absence of DLTs: 0.02, 0.2, 1, 3, 6, 12, 18, 24, and 36 mg/kg, given IV every 3 weeks
- Dose-escalation was guided by a BLRM approach with overdose control

Patient population

- Adult patients (≥18 years) with advanced solid tumors who progressed on or were not eligible for standard therapy, with an ECOG PS of 0–1 and ≥1 SIRPα V1 allele, are to be enrolled
- Patients with symptomatic brain metastases are excluded

Primary endpoints

DLTs and MTD

Secondary and further endpoints

Safety, PK, RO in peripheral CD14⁺ monocytes, and efficacy (RECIST 1.1)

BLRM, Bayesian Logistic Regression Model; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenously; PD-1, programmed cell death protein-1; PK, pharmacokinetics; RECIST, Response Evaluation Criteria in Solid Tumors; RO, receptor occupancy

Patient demographics and disease characteristics

- A total of 50 patients received at least one dose of BI 765063 monotherapy: 26 V1/V1 patients dosed from 0.02 to 36 mg/kg; 24 V1/V2 patients dosed from 1 to 36 mg/kg
- The most frequent tumors were: ovarian (n=9), colorectal (n=8), NSCLC (n=4), breast (n=4), melanoma (n=3), kidney (n=3)

Table 1. Patient demographics and disease characteristics

	All patients (N=50)
Median age, years (range)	60 (37–76)
Female, n (%)	28 (56.0)
White, n (%)	49 (98.0)
Metastatic disease at screening, n (%)	50 (100.0)
V1/V1 SIRPα polymorphism, n (%)	26 (52.0)
ECOG PS at baseline, n (%)	
0	26 (52.0)
1	24 (48.0)
Median number of prior lines of systemic therapies, n (range)	5 (1–10)

Conclusions

- The first-in-class SIRPα inhibitor BI 765063 showed preliminary anti-tumor activity, with 1 patient with HCC experiencing a durable PR (>9 months, ongoing)
- BI 765063 was well tolerated with no reported DLTs; no hemotoxic AEs, frequently associated with CD47-targeting therapies, were observed as BI 765063 targets SIRPα on myeloid cells, preserving red blood cells and platelets
  - BI 765063 showed dose-proportional systemic exposure and full RO saturation
  - BI 765063 dose escalation in combination with ezabenlimab (anti-PD-1 antibody) is ongoing

Efficacy

Please scan the QR code for additional efficacy results

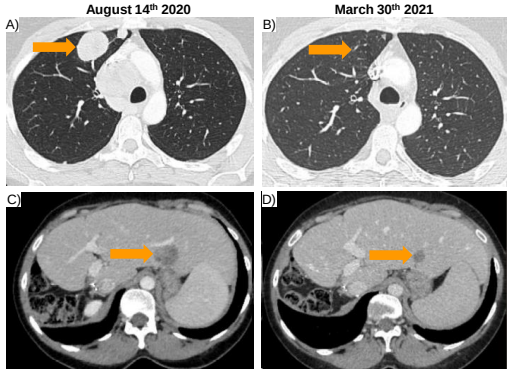

Figure 4. CT scans of a patient with HCC; A and B: lung before and after treatment with BI 765063, respectively; C and D: liver before and after treatment with BI 765063, respectively; BI 765063 monotherapy at 24 mg/kg (39 weeks of treatment, ongoing)

- Figure 4 shows CT scans of a patient with HCC with a durable PR, demonstrating a maintained tumor shrinkage of 55% after 9 months

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Safety, PK, and RO

- No DLTs were reported; the MTD was not reached. No treatment-related anemia/thrombocytopenia was observed
- One patient had a treatment-related serious AE (two instances of IRR)
- Most treatment-related IRRs were low-grade and experienced during the first cycle, and all were reversible after transient interruption, prolonged infusion and/or antihistamines ± paracetamol

Table 2. Summary of AEs*

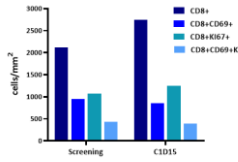
Patients with:	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Total with TRAEs (in ≥4 patients)	41 (82.0)	17 (34.0)	23 (46.0)	1 (2.0)	0	0
IRR	24 (48.0)	10 (20.0)	13 (26.0)	1 (2.0)	0	0
Fatigue	7 (14.0)	6 (12.0)	1 (2.0)	0	0	0
Headache	5 (10.0)	5 (10.0)	0	0	0	0
Diarrhea	4 (8.0)	3 (6.0)	1 (2.0)	0	0	0
Arthralgia	4 (8.0)	3 (6.0)	1 (2.0)	0	0	0
TRAEs leading to treatment discontinuation	1 (2.0)	0	0	1 (2.0)	0	0

- BI 765063 showed dose-proportional systemic exposure and full RO saturation in Cycle 1 from the 6 mg/kg dose

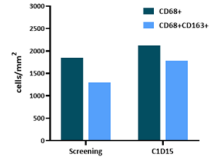
*Highest grade shown. AE, adverse event; IRR, infusion-related reaction; TRAE, treatment-related AE

Clinical efficacy and biomarker case study

CD8⁺ TIL densities in the tumor area and PD-L1 expression*



CD68⁺/CD163⁺ macrophages in the tumor biopsy*



- The patient's tumor biopsy showed high CD8⁺ T-cell and macrophage infiltration at baseline
- Increased CD8⁺ T-cell infiltration (+30%) was observed at 2 weeks after administration of the first dose
- PD-L1 scoring by CPS showed increased on-treatment expression

	Tumor cells PD-L1⁺	Immune cells PD-L1⁺	PD-L1 CPS
Screening	0%	100%	48
C1D15	100%	70%	75

Figure 2. Tumor IHC analysis from a patient with HCC showing a PR; at baseline: TP53 mutation, PTEN loss, MSS, PD-L1 neg

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

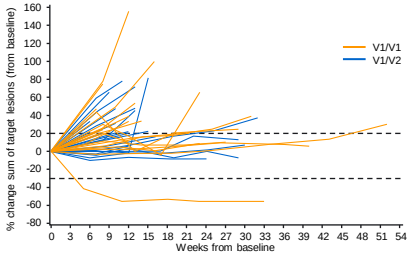


Figure 3. Spider plot of percentage change in sum of target lesions from baseline

*CD69: activated T cells; Ki67: proliferating T cells; CD68: pan macrophages; CD163: M2-like macrophages.
CPS, combined positive score; CT, computerized tomography; IHC, immunohistochemistry; HCC, hepatocellular carcinoma; PD-L1, programmed death ligand-1; PR, partial response; PTEN, phosphatase and tensin homolog; MSS, microsatellite stable; TIL, tumor-infiltrating lymphocyte; TP53, tumor protein P53

References

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