

# 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

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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<sup>1,2</sup>

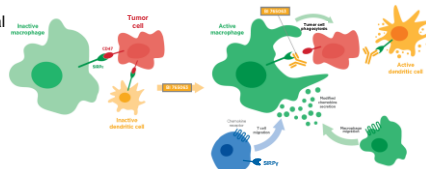


Figure 1. BI 765063 (anti-SIRPα) mechanism of action

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

- 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

## 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

## Methods

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

### 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<sup>+</sup> 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 ezabenzimab (anti-PD-1 antibody) is ongoing

## Efficacy Please scan the QR code for additional efficacy results

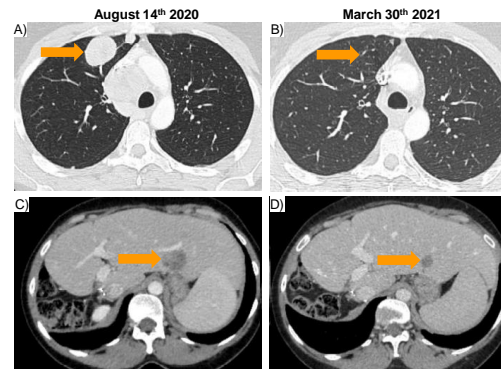


Figure 4. CT scans of a patient with HCC; A and B: lung before and after treatment with BI 765063, respectively; C and D: liver before and after treatment with BI 765063, respectively; BI 765063 monotherapy at 24 mg/kg (39 weeks of treatment, ongoing)

- 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\*

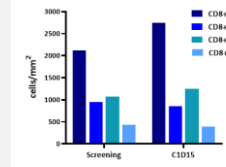
Patients with:	All grades n (%)	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
<b>Total with TRAEs (in ≥4 patients)</b>	41 (82.0)	17 (34.0)	23 (46.0)	1 (2.0)	0	0
IRR	24 (48.0)	10 (20.0)	13 (26.0)	1 (2.0)	0	0
Fatigue	7 (14.0)	6 (12.0)	1 (2.0)	0	0	0
Headache	5 (10.0)	5 (10.0)	0	0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

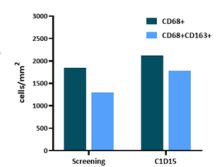
\*Highest grade shown. AE, adverse event; IRR, infusion-related reaction; TRAE, treatment-related AE

## Clinical efficacy and biomarker case study

### CD8<sup>+</sup> TIL densities in the tumor area and PD-L1 expression\*



### CD68<sup>+</sup>/CD163<sup>+</sup> macrophages in the tumor biopsy\*

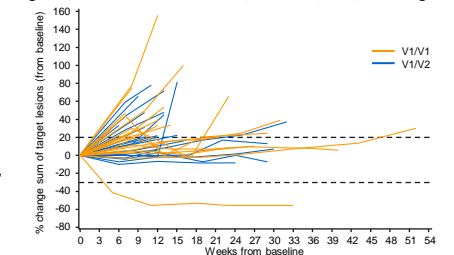


- The patient's tumor biopsy showed high CD8<sup>+</sup> T-cell and macrophage infiltration at baseline
- Increased CD8<sup>+</sup> T-cell infiltration (+30%) was observed at 2 weeks after administration of the first dose
- PD-L1 scoring by CPS showed increased on-treatment expression

	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



\*CD69: activated T cells; K167: 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

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

## References

- Delord J-P, et al. Blood 2019;134 (suppl\_1):1040.
- Gauttier V, et al. J Clin Invest 2020;130(11):6109–6123.