Biomarker analyses from the Phase I clinical trial of the first-in-class SIRPα immune checkpoint inhibitor BI 765063 in patients with advanced solid tumors

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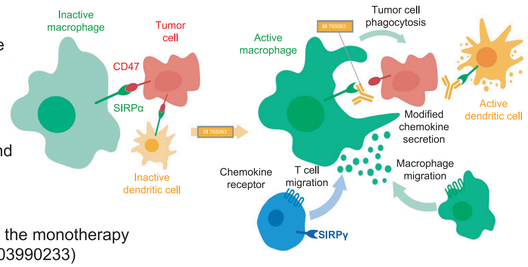
Introduction

- BI 765063 is a first-in-class, humanized IgG4 monoclonal antibody that binds selectively to the V1 allele of signal regulatory protein α (SIRPα) blocking the SIRPα/CD47 "don't eat me" pathway (Figure 1)[1,2]
- Preclinical studies showed that SIRPα blockade led to macrophage and T-cell recruitment into the tumor xenografts, and induced upregulation of chemokines, cytokines and adaptive immune function genes in human tumor explants[2]
- Here we report biomarker analyses from the monotherapy cohort of the ongoing Phase I trial (NCT03990233)

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



Objective and Methods

Please scan the QR code for additional details on methods

Objective of the biomarker analysis

To characterize the impact of BI 765063 on peripheral blood immune cells (PBMCs), as well as on the tumor microenvironment

Methods

- This is an open-label, multicenter Phase I trial in patients genetically SIRPα V1/V1 homozygous or V1/V2 heterozygous with advanced solid tumors who had failed or were ineligible for standard therapy
- Paired tumor biopsies were collected before treatment and two weeks after first BI 765063 infusion

Patient demographics and disease characteristics

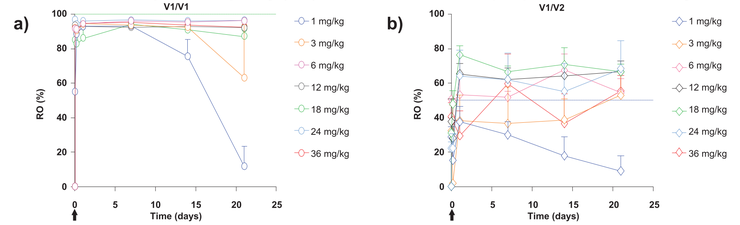
- A total of 50 patients (V1/V1: 26; V1/V2: 24) received BI 765063 IV from 0.02 mg/kg to 36 mg/kg, q3w (Table 1)
- The most frequent tumor types were:
  - Ovarian (n=9)
  - Colorectal (n=8)
  - NSCLC (n=4)
  - Breast (n=4)
  - Melanoma (n=3)
  - Kidney (n=3)

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)
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)

Results

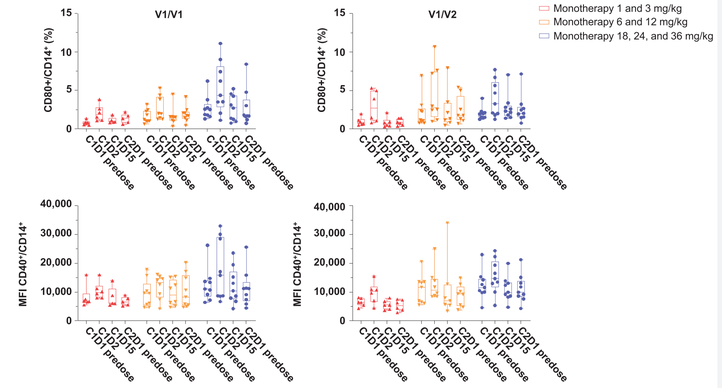
Figure 2. BI 765063 receptor occupancy (RO) on V1 SIRPα allele in peripheral CD14⁺ monocytes



- a) BI 765063 full RO was achieved at trough levels (Cycle 2 Day 1, pre-dose) in V1/V1 patients treated with doses of 6 mg/kg and higher; b) RO was more heterogenous in V1/V2 patients, ranging from 40% to 80% and reaching an apparent saturation at 12 mg/kg and higher

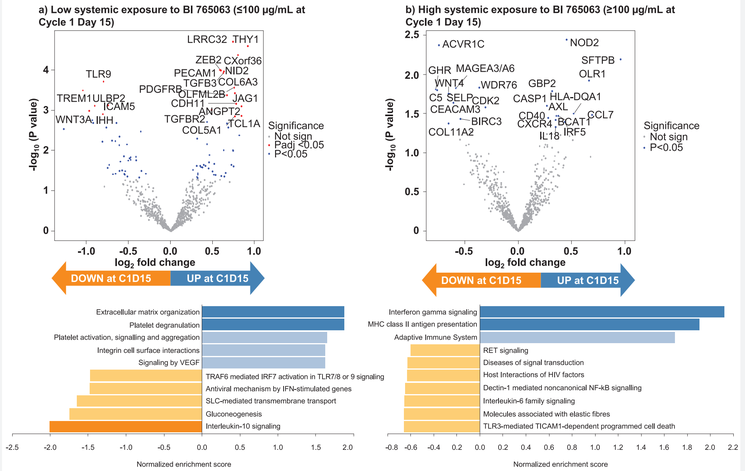
Results

Figure 3. Immunophenotyping of peripheral monocytes from patients treated with BI 765063



- Treatment with BI 765063 monotherapy at 18–36 mg/kg led to an apparent transient increase in the percentage of activated CD80⁺/CD14⁺ and CD40⁺/CD14⁺ monocytes in V1/V1 and V1/V2 patients at Cycle 1 Day 2

Figure 4. NanoString tumor expression profiling



- a) In paired tumor biopsies (n=26), IFNγ, MHC class II antigen presentation gene pathways, and CCL7 transcripts appeared to be upregulated at Cycle 1 Day 15 in patients with high systemic exposure (≥100 µg/mL); b) in contrast, metastasis pathways are upregulated at Cycle 1 Day 15 in patients with low systemic exposure (≤100 µg/mL)

Results

Figure 5. CT scans of a patient with HCC show a partial response maintained for >18 months, with treatment still ongoing; a) and b): lung before and after treatment with BI 765063 monotherapy, respectively; c) and d): liver before and after treatment with BI 765063 monotherapy, respectively

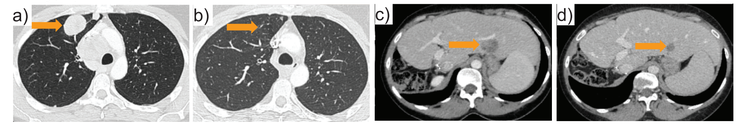
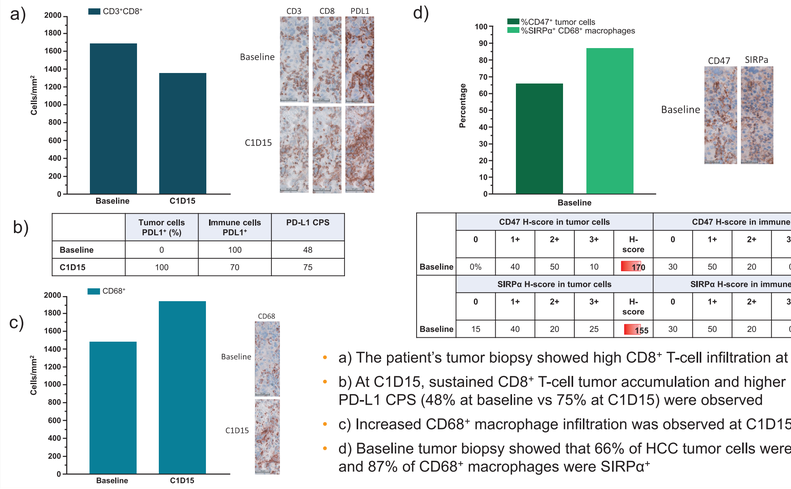


Figure 6. Tumor microenvironment analysis of the patient with HCC showing a partial response



b)

	Tumor cells PDL1+ (%)	Immune cells PDL1+	PD-L1 CPS
Baseline	0	100	48
C1D15	100	70	75

	CD47 H-score in tumor cells					CD47 H-score in immune cells				
	0	1+	2+	3+	H-score	0	1+	2+	3+	H-score
Baseline	0%	40	50	10	170	30	50	20	0	90
	SIRPα H-score in tumor cells					SIRPα H-score in immune cells				
	0	1+	2+	3+	H-score	0	1+	2+	3+	H-score
Baseline	15	40	20	25	155	30	50	20	0	90

- a) The patient's tumor biopsy showed high CD8⁺ T-cell infiltration at baseline
- b) At C1D15, sustained CD8⁺ T-cell tumor accumulation and higher PD-L1 CPS (48% at baseline vs 75% at C1D15) were observed
- c) Increased CD68⁺ macrophage infiltration was observed at C1D15
- d) Baseline tumor biopsy showed that 66% of HCC tumor cells were CD47⁺, and 87% of CD68⁺ macrophages were SIRPα⁺

Key findings and conclusions

- These data strongly suggest that the first-in-class SIRPα inhibitor BI 765063 acts as an immunomodulator of the tumor microenvironment, leading to upregulation of IFNγ signaling and MHC class II antigen presentation pathways in both V1/V1 and V1/V2 patients; this is consistent with preclinical findings, and in-line with its mechanism of action
- Increases in CD80⁺ and CD40⁺ monocyte expression in the blood suggest a rapid engagement of the innate immune system. The on-treatment biopsy of the responder showed an increase in CD68⁺ macrophages and sustained CD8⁺ T-cell infiltration, accompanied by higher PD-L1 expression on tumor cells
- These early signals will be further evaluated in similar samples from the ongoing expansion cohorts in more homogeneous patient populations

Scan this QR code or visit the URL for an electronic copy of the poster, supplementary content, and a list of abbreviations†

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