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Phase 1/2a Clinical Trial of BI 1808, a Monoclonal Antibody to Tumor Necrosis Factor Receptor 2 (TNFR2) as Single Agent and in Combination with Pembrolizumab

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BI-1808

BI-1808 is a first-in-class human IgG1 monoclonal antibody (mAb) targeting TNFR2. It blocks the interaction of TNFR2 with its ligand TNF-α. In immunocompetent mouse tumor models, it confers FcγR-dependent depletion of intratumoral Tregs and expansion of intratumoral CD8+ T cells (Figure 1). Upon co-administration of BI-1808 and anti-PD-1 surrogate antibodies to immunocompetent tumor-bearing mice with moderate sensitivity to checkpoint blockade, complete cures were observed in all treated mice, indicating a potentially synergistic activity of the combination treatment.

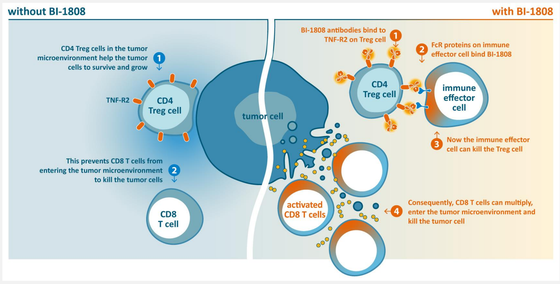

Figure 1. Schematic representation of the mechanism of action for BI-1808

Patient case: GIST

The best response after treatment with BI-1808 as single-agent to date was observed in a 55-year-old male patient with GIST. GIST is a gastrointestinal tumor of mesenchymal origin where immune checkpoints inhibitors have previously shown very limited activity. In a phase II study published in 2022 there was no objective response (OR) observed in 19 Nivolumab treated GIST patients, and only 1 of 16 Nivolumab + Ipilimumab combination treated patients showed OR [1].

The patient in this study presented with clinically progressive disease for more than 6 months, with multiple metastatic lesions. The patient had received 12 prior lines of treatment but was checkpoint inhibitor naïve. Eight full doses of BI-1808 1000 mg Q3W have been administered to date, and treatment has been well tolerated. The patient was initially considered to have progressive disease based on radiology but showed signals of clinical benefit. In a confirmatory scan, all target lesions showed a reduction. In the most recent scan, only 2 out of 4 target lesions were still present, and the sum of diameters is 48% of baseline (Figure 3). BI-1808 therapy is still ongoing.

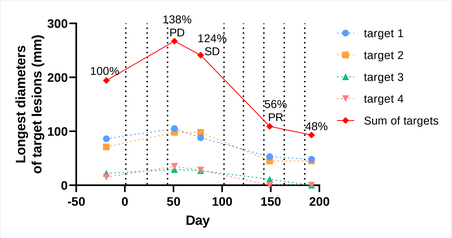

Figure 3. Tumor dynamics of GIST patient after administration of BI-1808 as single agent therapy

Study design

The safety and tolerability profile of BI-1808 as a single agent and in combination with pembrolizumab is being investigated in the Phase 1/2a clinical trial 19-BI-1808-01. The study population includes patients with advanced malignancies or T-cell lymphoma (TCL). Study 19-BI-1808-01 consists of Phase 1 Parts A and B (dose escalation as single agent and in combination with pembrolizumab, respectively), and Phase 2a Parts A and B (dose expansion cohorts with treatment as single agent and in combination, respectively) (Figure 2). Dose escalation is based on the modified toxicity probability interval-2 protocol (mTPI-2), investigating ascending dose levels of 25-1000 mg once every three weeks (Q3W). In the combination part, BI-1808 was initiated at 225 mg. The study design is intended to enable identification of single agent sRP2D as well as combination cRP2D of BI-1808.

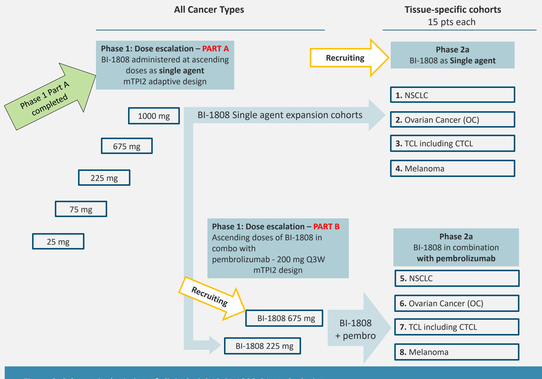

Figure 2. Schematic depiction of clinical trial 19-BI-1808-01 study design

Pharmacokinetics and pharmacodynamics

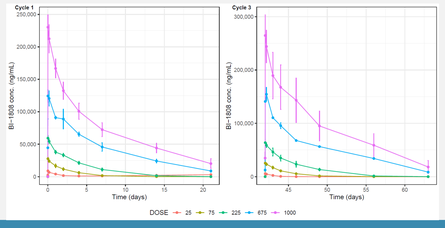

Figure 4. BI-1808 serum concentration vs time after single or repeat dosing Q3W across doses of 25 through 1000 mg.

BI-1808 appears to exhibit evidence of non-linear pharmacokinetics caused by target mediated drug disposition in line with the expectation for a mAb with affinity to a human target (Figure 4). The terminal t½ at the higher dose levels administered is approximately 8 days. The apparent volume of distribution suggests limited distribution to peripheral tissue. Preliminary data suggests similar pharmacokinetics of BI-1808 as monotherapy compared to after coadministration with pembrolizumab. At doses of ≥ 675 mg Q3W, $t_{½}$ was approximately 8 days, resulting in accumulation of drug, with serum concentrations exceeding preclinical IC_{50} throughout the dose interval.

Receptor occupancy of TNFR2 in peripheral blood was analyzed in 14 subjects (Figure 5). All subjects reached >95% receptor saturation within 4 hours post-infusion. Subjects receiving 675 mg or 1000 mg BI-1808 maintained near full receptor saturation throughout the dose interval.

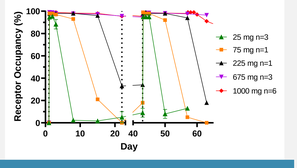

Figure 5. TNFR2 receptor occupancy vs time after single or repeat dosing Q3W across doses of 25 through 1000 mg.

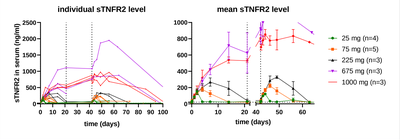

Figure 6. sTNFR2 serum concentration vs time after single or repeat dosing Q3W across doses of 25 through 1000 mg.

Administration of BI-1808 increases the levels of soluble TNFR2 (sTNFR2) in peripheral blood of treated subjects (Figure 6). BI-1808 treatment resulted in increased levels of sTNFR2 in all subjects treated, and the levels were sustained in a dose-dependent manner. The levels of sTNFR2 in blood appeared to correlate with receptor saturation. sTNFR2 levels increased or were maintained if receptor saturation was near full.

Study results to date

As of October 4th, 2023, 24 subjects have received doses of up to 1000 mg BI-1808 as single-agent, and 9 subjects have received 225 mg doses of BI-1808 in combination with pembrolizumab. All patients in the monotherapy arm to this date were diagnosed with various advanced solid malignancies. To confirm the tolerability of the top dose of 1000 mg Q3W, an additional cohort consisting of 6 patients was enrolled at this dose level.

In the completed monotherapy arm dose escalation across 25-1000 mg dose range, no Gr3/4 AEs related to BI-1808 were observed, no DLTs were declared and no MTD was reached. The number of potentially related AEs of Gr1/2 have been evenly distributed across the dose range, with no target system organ class of special notice identified.

The best clinical responses recorded have been 1 partial response (PR), and 7 stable disease (SD) in 21 evaluable patients in the monotherapy arm. As seen in the adjacent table, this patient population is heavily pre-treated, and a large majority of patients has tumor types known to have limited response to immune checkpoint inhibitors. Disease control in the stable disease patients lasted between 1.5 – 4.3 months. The patient with partial response is still ongoing.

Dose escalation of BI-1808 in combination with pembrolizumab is ongoing but is not completed. Phase 2a Part A is now open for enrollment.

Dose	Disease	Sex	Age	Prior Treatments	Prior PD-1(L) therapy	Best response to BI-1808	Duration of clinical benefit (SD/PR)
25 mg	OCULAR MELANOMA	M	72	3	Y	SD	>19 weeks
25 mg	NON-SMALL CELL LUNG CANCER	M	73	4	N	PD	
25 mg	MESOTHELIOMA	M	67	4	N	PD	
25 mg	OVARIAN CANCER	F	66	4 + Surgery	N	PD	
75 mg	CERVICAL CANCER	F	65	6	Y	PD	
75 mg	BLADDER CANCER	M	69	3	Y	PD	
75 mg	LEIOMYOSARCOMA	F	75	1	N	SD	>11 weeks
75 mg	PERITONEUM EPITHELIAL MESOTHELIOMA	F	42	4	N	SD	n/a
75 mg	NON-SMALL CELL LUNG CANCER	M	65	0	N	SD	>7 weeks
225 mg	SQUAMOUS THYMUS CARCINOMA	F	62	6	Y	SD	10 weeks
225 mg	ENDOMETRIAL CANCER	F	70	6	N	PD	
225 mg	SYNOVIAL SARCOMA	M	22	6	N	PD	
675 mg	OCULAR MELANOMA	F	41	4	Y	PD	
675 mg	COLORECTAL CANCER	M	78	3	N	PD	
675 mg	METASTATIC SQUAMOUS CELL LUNG CANCER	M	63	3	Y	PD	
1000 mg	PANCREATIC CANCER	F	60	3	N	PD	
1000 mg	COLORECTAL CANCER	M	70	5 + Surgery	N	PD	
1000 mg	CHOLANGIO CARCENOMA	F	56	5	N	SD	12 weeks
1000 mg	PANCREATIC CANCER	M	57	3	Y	PD	
1000 mg	GASTROINTESTINAL STROMAL TUMOR (GIST)	M	55	12	N	PR (ongoing)	>17 weeks
1000 mg	PANCREATIC CANCER	F	39	4	Y	PD	
1000 mg	COLORECTAL CANCER	M	51	3	N	SD	>7 weeks
1000 mg	PROSTATE CANCER	M	79	6	N	PD	
1000 mg	MAXILLARY SINUS CANCER	M	67	2	N	PD	

Table 1. Overview of patients enrolled and treated with BI-1808 as single agent in the dose escalation phase

Conclusions

- Preliminary data from the BI-1808 monotherapy arm from the clinical trial 19-BI-1808-01 Phase 1 Part A show encouraging results for future development. BI-1808 exhibit a favorable safety profile, with no DLT observed in the monotherapy arm, and was well tolerated in across all dose levels studied.
- In a heavily pretreated patient population, the use of BI-1808 monotherapy currently shows a robust partial response in one GIST patient (still on treatment), and additional 7 SD out of 21 evaluable patients. The PK/PD data enabled identification of a wide dose range where complete target coverage can be achieved with a favorable safety profile.

References:

1) Singh A. *et al.* Clin Cancer Res 2022 **28**(1) "A Randomized Phase II Study of Nivolumab Monotherapy or Nivolumab Combined with Ipilimumab in Patients with Advanced Gastrointestinal Stromal Tumors "

Additional study inforamtion:

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USAS
Study 19-BI-1808-01 is also known as KEYNOTE-D20
EudraCT Number: 2020-002090-10 ClinicalTrials.gov ID NCT04752826

Contact information:

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