Abstract #2641

19-BI-1808-01, a Phase 1/2a Clinical Trial of BI-1808, a Tumor Necrosis Factor Receptor 2 (TNFR2) Blocker/Depleter with or without Pembrolizumab

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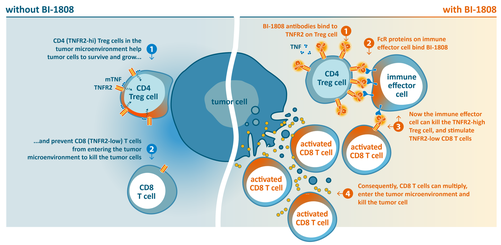
Conclusions

Early data from dose escalation phase show strong evidence of single agent antitumor activity of BI-1808 across various indications. BI-1808 induces significant regulatory T-cell depletion, as well as clear signs of CD8+ T cell activation in responding patients.

BI-1808 has a favorable safety profile with no notable safety findings as monotherapy, and is also well tolerated combined with pembrolizumab.

Background

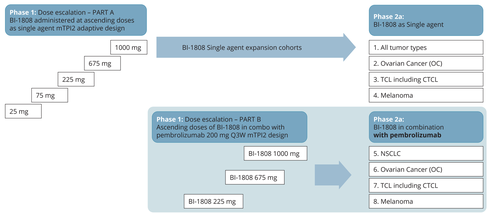
BI-1808 is a fully human IgG1 mAb that targets TNFR2 by blocking interaction of TNFR2 with ligand TNF-α, confers FcγR-dependent depletion of Treg and mediates expansion of intratumoral CD8+ T cells. In preclinical studies, murine surrogate antibody confers impressive antitumor activity in several immune competent tumor models, and upon co-administration with anti-PD-1 in models with low/partial sensitivity to checkpoint blockade, complete cures were observed in all treated mice. Thus, targeting TNFR2 using this approach offers a promising and novel treatment of cancer paradigm for patients.



Methods

Safety and tolerability profile of BI-1808 as a single agent and in combination with pembrolizumab is currently being investigated in the Phase 1/2a clinical trial 19-BI-1808-01, enrolling patients with advanced solid malignancies or T-cell lymphomas, including CTCL. The study consists of Phase 1 dose escalation of single agent and combination with pembrolizumab. Phase 2a consists of dose expansion as single agent and in combination therapy in separate cohorts for OC, NSCLC, TCL/CTCL and Melanoma. Response is assessed according to RECIST and iRECIST.

Baseline Demographics	All patients (n=35)		
Number of patients	65	**Prior Lines of Therapy**	
Age		Median (range)	3.5 (0-7)
Median (range)	60 Y (20-79)	0	2
Sex		1	13
Female	38	2	5
Male	27	3	12
ECOG PS		4	14
0	43	≥5	17
1	22	**Prior checkpoint inhibitor**	20



Single agent activity demonstrated across various tumor types by BI-1808, a first-in-class ligand-blocking TNFR2 targeting antibody

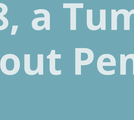
Targeting TNFR2 with a ligand blocking and FcγR engaging antibody is a new and exciting potential treatment opportunity, and may add further antitumor activity when combined with anti-PD1 treatment.

Case study PR: 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.

Current case is a 55-year-old male patient with GIST, who presented with clinically progressive disease for more than 6 months, with multiple metastatic lesions.

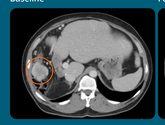
The patient received totally 12 previous courses with imatinib, sunitinib, remurafenib, pazopanib, regorafenib, ripretinib, sorafenib, and in two instances regorafenib and imatinib were administered in combination with everolimus. The patient was initially considered to have progressive disease based on radiology but showed signals of clinical benefit. In a confirmatory scan, all target lesions showed a reduction with 2/4 target lesions eventually being not detectable. In the most recent scan total tumor burden is reduced by 61% of baseline, with BI-1808 therapy 13 months and ongoing.



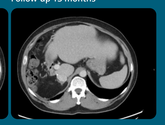
Individual lesion sizes and total tumor burden vs time

Regulatory T cell dynamics vs time

Baseline

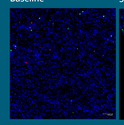


Follow-up 13 months

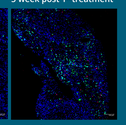


IF data from NSCLC showing T-cell infiltration in tumor *(green = CD8+, red = granzyme B).*

Baseline



5 week post 1st treatment



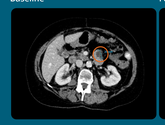
Case study CR: Ovarian Cancer

63-year-old patient with ovarian cancer, Stage IIIA at diagnosis, entered the study with progressive disease after last prior line of treament (bevacizumab+topotecan). First line of therapy was paclitaxel+ carboplatin, followed by one line of carboplatin+doxorubicin, and third line olaparib. As immune checkpoint inhibitors (ICI) are considered to have modest activity in ovarian cancer, the patient was ICI naïve prior to BI-1808 treatment. At screening, patient presented one target lesion of 25 mm and two larger non-target cystic lesions. At first post-treatment scan 9 weeks post treatment start, no quantifiable tumor mass could be measured.

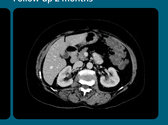
Individual lesion sizes and total tumor burden vs time

Regulatory T cell dynamics vs time

Baseline



Follow-up 2 months

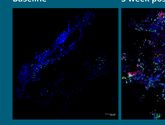


Case study SD: NSCLC

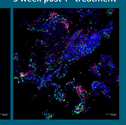
65-year-old male with Stage IV lung cancer. Patient had received no previous immunotherapy, and declined chemotherapy. Prior to treatment patient had one lesion in the lung, and two lesions of the liver. At second scan patient exhibited a 21% decrease in tumor burden.

IF data showed an apparent immune activation in tumor with CD8+ T-cell infiltration and granzyme B expression. The patient was however diagnosed with an unrelated prostate cancer and was taken off trial.

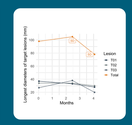
Baseline



5 week post 1st treatment



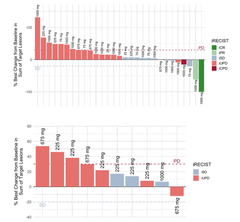
IF data from NSCLC showing clear immune activation in tumor *(green = CD8, red = granzyme B)*

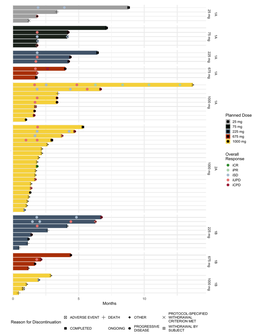


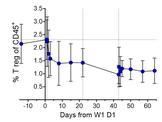
Individual lesion sizes and total tumor burden vs time

Results

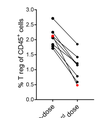
- As of April 19, 2024, 44 subjects received doses of 25 mg up to 1000 mg BI-1808 as single-agent Q3W and 18 subjects received BI-1808 at doses from 225 mg up to 1000 mg in combination with pembrolizumab 200 mg Q3W.
- At doses of ≥ 675 mg Q3W, BI-1808 $t_{1/2}$ was approximately one week leading to accumulation of drug, leading to complete receptor occupancy throughout the dosing interval, a substantial increase in sTNFR2 and a significant reduction of regulatory T-cells.
- Across the completed monotherapy arm dose escalation covering 25 to 1000 mg dose, no Gr3/4 AEs related to BI-1808 monotherapy were observed. Number of potentially related AEs of Gr1/2 have been evenly distributed across the dose range, with no target organ class of notice identified. No severe infusion related reactions have been observed.
- Out of 26 evaluable subject receiving BI-1808 as monotherapy, one unconfirmed complete response (uCR) at first scan was observed in ovarian cancer. A GIST patient exhibit partial response (PR) and still ongoing after 1 year, and 9 subjects showed stable disease (SD) as best clinical response. One NSCLC patient with SD showed an emerging tumor reduction but developed an unrelated secondary cancer before response was confirmed.
- In responding patients, a substantial CD8+ T cell activation could be observed preceeding the tumor reduction seen on radiology scans. In addition, an increase in the intratumoral ratio of CD8+ T cells / T regs were seen in these patients as early as 5 weeks post treatment.
- In the combination cohort with pembrolizumab, 3/8 evaluable subjects showed SD, with the longest duration of 4 months and ongoing. 1 DLT (colitis) was observed in the 225 mg BI-1808 + pembrolizumab cohort, and 1 DLT (fatigue) in the 1000 mg BI-1808 + pembrolizumab cohort out of 19 subjects treated.



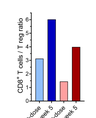




Data from 1000 mg monotherapy cohort show substantial T-reg depletion compared to baseline.
(Dashed horisontal line = baseline. Dashed vertical lines = BI-1808 dosing occasions)



Pre and post treatment T-reg data from monotherapy patients in 1000 mg cohorts.
(Red colour is GIST patient)



Tumor biopsies collected pre and 5 weeks post treatment were stained for Foxp3+ CD4+ T reg cells and CD8+ T cells using immunofluorescence. Percentages of stained area were quantified and a pre and post treatment CD8+/T reg ratio were calculated. As seen in the figure, BI-1808 increase the intratumoral CD8+/T reg ratio in these patients.

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Study identifier: EudraCT Number: 2020-002090-10
ClinicalTrials.gov ID: NCT04752826

This study is in collaboration with Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA