Evidence of T reg depletion and Corresponding Early Efficacy after Tumor Necrosis Factor Receptor 2 (TNFR2) Blockade by BI-1808 in Cutaneous T Cell Lymphoma (CTCL) Patients

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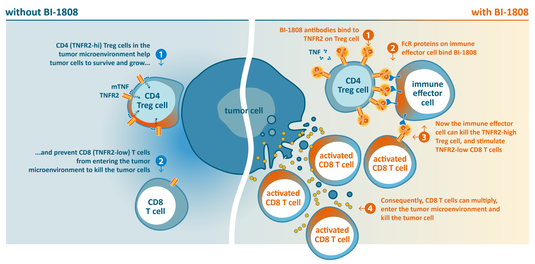
Conclusions

Early data show evidence of strong efficacy of BI-1808 in advanced CTCL combined with a good safety profile.

Background

- BI-1808 is a monoclonal antibody targeting TNFR2, and has demonstrated single agent antitumor activity across a variety of solid cancer forms during early clinical development.
- Tumor necrosis factor receptor-2 (TNFR2) influences tumor development and metastasis through multiple mechanisms. TNFR2 facilitates tumor immune evasion by stimulating various immune suppressive cell types, such as regulatory T-cells (Tregs) and myeloid-derived suppressor cells (MDSCs), and can function as an oncogene. Conversely, TNFR2 also exhibits antitumor properties by costimulating cytotoxic T-cells.
- TNFR2 overexpression on malignant $CD4^+CD26$- T-cells points to its possible implication in the pathogenesis of CTCL. BI-1808 inhibits the interaction between TNFR2 and its ligand TNF-α, resulting in the depletion of regulatory T cells (Tregs) through FcγR mechanisms and promoting the expansion of intratumoral $CD8^+$ T cells. This novel approach reveals a potential new treatment for CTCL.



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 malignancies or T-cell lymphomas, including CTCL.
- The study consists of a completed Phase 1 dose escalation of single agent BI-1808 and combination of BI-1808 with pembrolizuma. Ongoing Phase 2a consists of dose expansion as single agent and in combination therapy in separate cohorts for Ovarian Cancer, All tumor types, TCL/CTCL and Melanoma.
- This poster presents the single agent cohort enrolling patients with T-cell lymphomas, including CTCL. Advanced mycosis fungoides (MF) and Sézary syndrome (SS) who have previously failed or progressed on systemic therapy are enrolled.

Cancer history

Patient ID, cancer type	Sex, Age (yrs.)	Stage at diagnosis	Dose (mg) BI-1808, Q3W	Prior treatments, #) = regimen line
0602-0002, MF	F, 28	IIB	1000	1) Bexarotene, 2) Radiotherapy, 3) Methotrexate/Valchlor gel, 4) Durvalumab
0601-0001, SS	M, 66	IV	1000	1) Radiotherapy, 2) Mogamulizumab, 3) Peginterferon α-2A, 4) Romidepsin
0601-0002, SS	M, 64	IV	1000	1) Radiotherapy, 2) Romidepsin, 3) Brentuximab, 4) Acitretin/Photopheresis, 5) Cyclophosphamide/ Doxorubicin/Romidepsin/Vincristine, 6) Gemcitabine, 7) Vorinostat/Photopheresis, 8) Mogamulizumab, 9) Pembrolizumab, 10) Pralatrexate
0602-0004, MF	M, 68	IIB	1000	1) Radiotherapy, 2) Methotrexate, 3) TTI-621, 4) BNZ-131-1-40, 5) Durvalumab/Lenalidomide, 6) Methotrexate/Imiquimod cream, 7) Mogamulizumab

BI-1808 shows single agent activity in patients with tumor types where immune checkpoint inhibitors have shown limited efficacy.

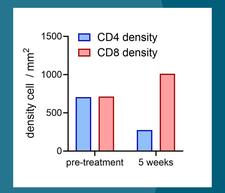
Targeting TNFR2 is a new and exciting potential treatment opportunity for CTCL.

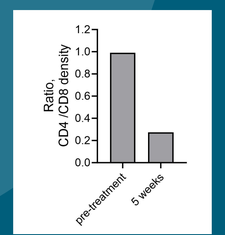
Patient case 0601-0001

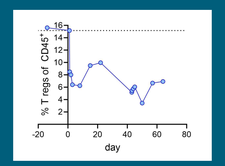
66 year old male patient presented with stage IV Sézary Syndrome at diagnosis. Previously treated with radiotherapy, mogamulizumab, peginterferon α-2A and romidepsin with stable disease as previous best response. After treatment with single agent BI-1808 1000 mg Q3W, the patient showed clinical improvement, and was classified as partial responder at first scheduled assessment at week 9. The patient has exhibited continued improvement and tolerating the treatment well, currently still on treatment.

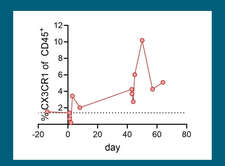
Biopsy staining show a clear reduction in $CD4^+$ cells and an increase in $CD8^+$ cells in tumor already at five weeks into treatment.

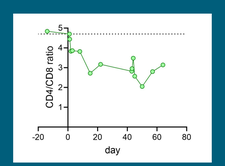
Flow cytometry show a clear and immediate reduction in $CD4^+$ T reg, despite very high baseline levels. The patient also exhibited a marked increase in $CX3CR1^+CD8^+$T cells after 3rd injection, and a substantial decrease in CD4/CD8 ratio indicative of a beneficial immune response.



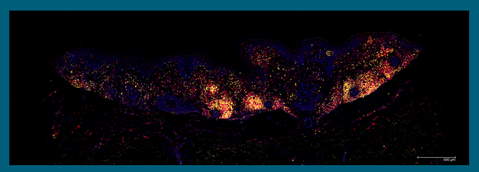






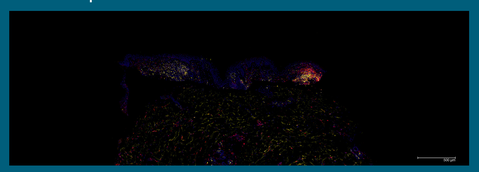


Baseline



Immunofluorescence staining of CTCL skin biopsy before treatment. $CD8^+$ cells yellow, $CD4^+$ cells red and nuclei blue. Scale bar 500 um

5 week post 1st treatment



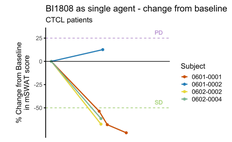
Immunofluorescence staining of CTCL skin biopsy 5 weeks after first treatment. $CD8^+$ cells yellow, $CD4^+$ cells red, and nuclei blue. Scale bar 500 um.

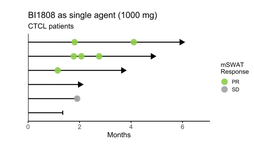
Results

- As of Oct 15, 2024, 8 subjects with CTCL received BI-1808 as single-agent Q3W. All treatment related adverse events were classified as a mild or moderate with no related grade ≥ 3 AE reported.
- Of 4 evaluable patients at cut-off, 3 exhibited Partial Response (1 MF, 2 SS) and 1 patient showed Stable Disease by mSWAT (modified severity-weighted assessment tool). All patients were heavily pretreated.
- Immunofluorescence multiplex staining of skin biopsies revealed extensive $CD8^+$ T cell infiltration and elevated granzyme B levels at five weeks post-treatment initiation.

Response assessments through mSWAT

- 4 patients are evaluable post treatment, out of 7 patients treated with BI-1808 single agent
- 3 exhibited partial response (50-99% decrease from baseline), with 1 patient showing stable disease.





Safety and tolerability

BI-1808 Monotherapy	PHASE II A
Administration route	IV
Dose	1000mg
Number of subjects	8 (100%)
Subjects with any grade TEAEs related to BI-1808	3 (38%)
Subjects with ≥Grade 3 TEAEs related to BI-1808	0
Subjects with serious TEAEs related to BI-1808	1 (13%)
Subjects with treatment related AE:s that led to discontinuation	0

Additional disease assessments

	Timepoint	Target lesions	Non-target lesions	Sezary cells
0602-0002, MF	W1	No	No	- (B0, 27.1)
	W9	NA	NA	SD (B0, 41.1)
0601-0001, SS	W1	No	Present, pathological	- (B0, 0)
	W9	NA	Present, pathological	SD (B0, 0)
	W10	NA	NA	NA
	W13	NA	NA	NA
0601-0002, SS	W1	Present	Present	- (B2, 1133)
	W9	(21% reduction)	Present	SD (B1, 817)
0602-0004, MF	W1	No	No	- (B0, 32.12)
	W9	NA	NA	SD (B0, 48.6)

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Study identifier:
EudraCT Number: 2020-002090-10