Abstract #2593

Phase 1/2a Clinical Trial of BI-1206, an Anti-CD32b (FcγRIIB) Antibody, in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors Previously Treated with Anti-PD-1/L1

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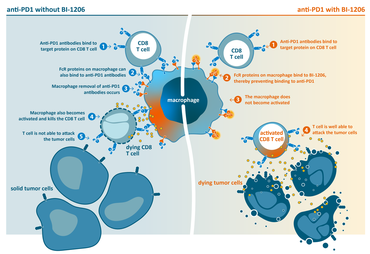
Conclusions

Coadministration of BI-1206 with pembrolizumab was well tolerated in a heavily pretreated population, with promising responses to treatment observed in melanoma, including uveal melanoma, who previously failed anti-PD1 therapy.

Background

PD-1 blockade has demonstrated positive anti-tumor activity across multiple tumor types. While the anti-tumoral response can be substantial and even curative, response rates remain low in many cancer types. Long-lasting responses are only observed in a minority of patients, and additional immunotherapeutic alternatives are needed.

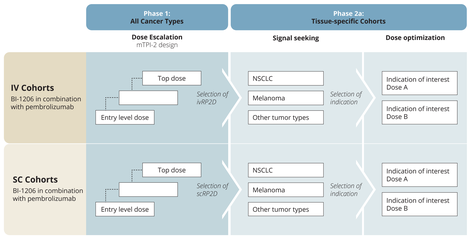
Combining anti-PD-1 with other immunotherapies may improve the durability and depth of anti-tumoral immune responses. Non-clinical data suggest anti-PD-1 interactions with macrophage Fc gamma receptors (FcγRs) compromise therapeutic activity by several mechanisms including the rapid removal of anti-PD-1 from its target on CD8+ T-cells and phagocytosis of anti-PD-1 coated CD8+ T cells. Accordingly, we and others have shown that blockade of Fc/FcγR interactions with immunocompetent antibodies overcomes these resistance mechanisms and enhances anti-PD-1 efficacy in vitro and in vivo. BI-1206 is a fully human IgG1 targeting CD32b (FcγRIIB), the inhibitory FcγRIIB, a receptor highly upregulated in the tumor microenvironment.



Methods

This is a Ph1/2a trial in patients with advanced solid tumors who received prior treatment to evaluate safety, tolerability and PK/PD of BI-1206 at ascending IV and SC doses after coadministration with pembrolizumab 200 mg Q3W using a mTPI-2 design.

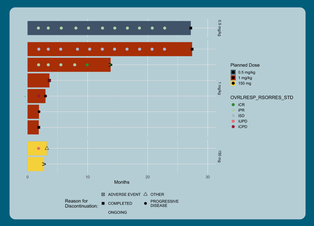
Phase 2 a will explore the efficacy of BI-1206 and pembrolizumab in tissue-specific cohorts at RP2D, followed by a dose optimization phase for safety/efficacy in indications with positive signals.



CD32b blockade by BI-1206 in combination with pembrolizumab lead to responses in melanoma patients who previously failed on anti-PD1 therapy

IV administration of BI-1206 lead to sustained blockade of CD32b for 5-7 days. This may be important to maximize anti-PD-1 efficacy, sparing FcγR-dependent CD8+ T cell phagocytosis and minimizing PD-1/L1 immune-suppressive signaling. Subcutaneous administration shows great promise to provide a further extended duration of receptor occupancy with increased tolerability.

Waterfall plot depicting best response to treatment of melanoma patients in Study 18-BI-1206-03

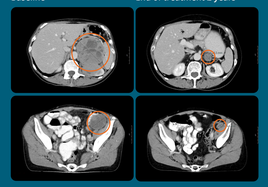


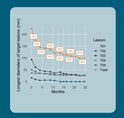
Swimmer plot depicting time on treatment and response assesment of melanoma patients in Study 18-BI-1206-03

Case study 1: PR

69 YO female, uveal melanoma.
No response to prior immunotherapy or chemotherapy. Multiples lines of ICIs and Chemo. Progressing when entering study. Showed early partial response at first scan on BI-1206 + pembrolizumab, continued PR deepening during whole study duration (2years) with tumor burden reduced by 56% at end of trial.

Baseline | End of treatment 2 years





Tumor assesment vs time on study

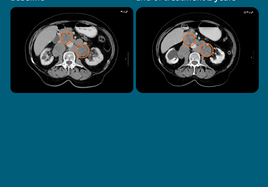
Prior treatments

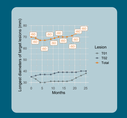
Regimen	Agents	Treatment Setting	Best response	Reason for stop
1	Pembrolizumab Entinostat	Palliative	SD	PD
2	Temozolomide	Palliative	PD	PD
3	Paclitaxel	Palliative	PD	PD
4	ATOR-1017 (a4-1BB)	Palliative	SD	PD

Case study 2: SD

78 YO female, with stage IV M1a melanoma.
6 lines of prior treatment. Three of these prior lines contained ICI therapy (aPD-1; aPD-1 + aCTLA-4 and a4-1BB) without observed response. On study exhibited Stable Disease, ongoing SD 2.5 years after trial initiation and six months after treatment.

Baseline | End of treatment 2 years





Tumor assesment vs time on study

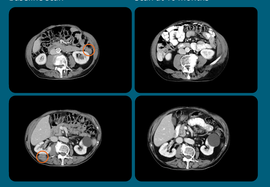
Prior treatments

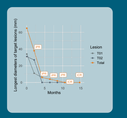
Regimen	Agents	Treatment Setting	Best response	Reason for stop
1	Nivolumab	Palliative	SD	PD
2	Ipilimumab Nivolumab	Palliative	SD	PD
3	Dabrafenib Trametinib	Palliative	PR	PD
4	Temozolomid	Palliative	PD	PD
5	ATOR-1017 (a4-1BB)	Palliative	SD	PD
6	Mektovi Braftovi	Palliative	SD	AE

Case study 3: CR

77 YO male melanoma patient, stage IV.
Deep Partial Response at first scan at 2 months, evolving to CR at 10 months, still ongoing at 16 months.

Baseline scan | Scan at 16 months





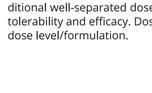
Tumor assesment vs time on study

Prior treatments

Regimen	Agents	Treatment Setting	Best response	Reason for stop
1	Nivolumab	Adjuvant	NE	Completed
2	Ipilimumab Nivolumab	Palliative	PR	AE
3	Nivolumab	Palliative	SD	AE

Results

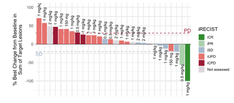
- Dose escalation with BI-1206 intravenously (IV) has been completed with no formal MTD defined in the range of 0.5 mg/kg through 2.0 mg/kg. The most frequent related adverse events were infusion-related reactions (IRR). Adequate premedication with corticosteroids or split dose administration reduced the risk and/or intensity of these events. Thrombocytopenia and elevated transaminases were also reported. None of these required intervention.
- Subcutaneous (SC) administration of BI-1206 was well tolerated with no significant local reactions. In addition to mitigating IRR, SC administration also led to extended target coverage, as demonstrated through prolonged receptor occupancy of CD32b. SC dose escalation is still ongoing.



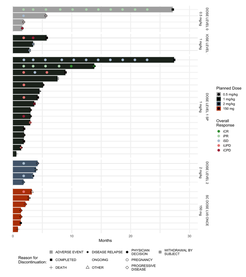
Intravenous administration of BI-1206 lead to high receptor occupancy of CD32b on B-cells, which is sustained for 5-7 days. Subcutaneous administration show great promise to provide a further extended duration of receptor occupancy with increased tolerability. SC dose escalation is still ongoing.

Receptor occupancy after 1 mg/kg IV (green n=6) and 150 mg SC (blue n=7).

- Subjects were heavily pretreated, with a median of 4 lines of therapy, and most patients had received previous immune checkpoint inhibitors. Out of 23 evaluable patients, 22 patients had received prior aPD-(L)1 therapy. 19 of which had progressed while on therapy.
- After receiving BI-1206+pembrolizumab, 7 patients showed SD, including one lasting >24 months in a heavily treated metastatic melanoma patient. Furthermore, long-lasting PR (>24 months) was observed in a uveal melanoma patient, and confirmed CR was observed in a metastatic melanoma patient who previously received three prior anti-PD-1 containing treatments (one including anti-CTLA4).



Waterfall plot depicting best response to treatment in all patients of Study 18-BI-1206-03.



Swimmer plot depicting time on treatment and response assesment in Study 18-BI-1206-03.

Baseline Demographics	All patients (n=35)
Age	
Median (range)	60 years (20-79)
Sex	
Female	21 (60%)
Male	14 (40%)
ECOG PS	
0	11
1	24
Prior Lines of Therapy	
Median (range)	4 (1-10)
1	8 (23%)
2	4 (11%)
3	3 (9%)
4	7 (20%)
≥5	12 (34%)
Prior checkpoint inhibitor	
	32 (91%)

Safety findings	BI-1206 + Pembrolizumab					
TEAEs	**IV**				**SC**	**Total**
Dose (SD= split dose)	0.5 mg/kg	1 mg/kg	1mg/kg SD	2 mg/kg	150 mg	N=35
Number of subjects	N=4	N=4	N=16	N=4	N=7	
Subjects with at least 1 TEAE any grade	4 (100%)	4 (100%)	16 (100%)	4(100%)	7 (100%)	35 (100%)
Subjects with ≥Grade 3 TEAEs	2 (50%)	2 (50%)	8 (50%)	4 (100%)	6 (86%)	22 (63%)
Subjects with TEAEs related to study treatment	4 (100%)	4 (100%)	16 (100%)	4 (100%)	5 (71%)	33 (94%)
Subjects with ≥Grade 3 TEAEs related to study treatment	2 (50%)	2 (50%)	6 (38%)	4 (100%)	0	14 (40%)
Subjects with serious TEAEs related to study treatment	1 (25%)	2 (50%)	1 (6%)	1 (25%)	0	5 (14%)
Subjects with treatment related AEs that led to discontinuation	0	1 (25%)	2 (13%)	0	0	3 (9%)
TEAEs of interest related to BI-1206 in combination with pembrolizumab						
Subjects with any grade Infusion related reaction (IRR)	2 (50%)	3 (75%)	9 (56%)	3 (75%)	0	17 (49%)
Subjects with ≥Grade 3 Infusion related reaction (IRR)	0	1 (25%)	2 (13%)	0	0	3 (9%)
Subjects with any grade Thrombocytopenia	1 (25%)	1 (25%)	2 (13%)	3 (75%)	0	7 (20%)
Subjects with ≥Grade 3 Thrombocytopenia	0	1 (25%)	1 (6%)	2 (50%)	0	3 (9%)
Subjects with any grade Increased ALT/AST	2 (50%)	1 (25%)	5 (31%)	2 (50%)	0	10 (29%)
Subjects with ≥Grade 3 Increased ALT/AST	1 (25%)	0	0	1 (25%)	0	2 (6%)

Future plans

IV dose level has been selected for signal seeking in Ph2a (RP2D), while appropriate dose for use of SC in Ph2a will be determined after completion of dose escalation. The Ph2a consists of 3 expansion cohorts at the RP2D, each comprising a specific subset of subjects with advanced solid tumors (e.g., NSCLC, melanoma, and other tumors responsive to PD-1/PD-L1 inhibition). If a positive efficacy signal is confirmed, an additional well-separated dose level will be introduced for dose optimization for safety, tolerability and efficacy. Dose optimization may be performed against more than one dose level/formulation.

Contact information: 18-BI-1206-03@bioinvent.com
Study identifier: EUCT number: 2023-509846-36-0
ClinicalTrials.gov ID: NCT04219254

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