A Multi-Center Phase 2a Trial of the CXCR4 inhibitor Motixafortide (BL-8040) in Combination with Pembrolizumab and Chemotherapy, in Patients with Metastatic Pancreatic Adenocarcinoma
The COMBAT Study

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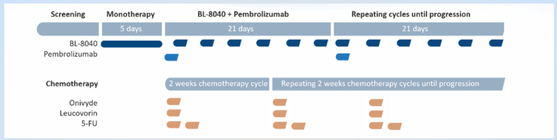
Background

- **Improving outcomes of PDAC with checkpoint inhibitors (CPIs) have been ineffective, underscoring the need to co-target alternative pathways.**
- **Preclinical data showed that CXCR4-SDF1 axis modulates the tumor microenvironment (TME) in PDAC and that CXCR4 inhibition enhances T cell access to the TME, increasing tumor sensitivity to CPIs[1].**
- **This was confirmed in the COMBAT Cohort 1 study showing that the dual combination of BL-8040 and Pembrolizumab increases activated CD8+ T cells and decreases myeloid derived suppressor cells (MDSCs) within the TME[2].**
- **Moreover, pre-clinical studies showed that adding Chemotherapy to the dual combination resulted in improved efficacy vs Chemotherapy alone[3].**
- **BL-8040 (Motixafortide) is a novel CXCR4 antagonist being developed for multiple oncology indications**
- **The COMBAT Cohort 2, aims to test the safety and efficacy of the combination (BL-8040/Pembrolizumab/Chemotherapy) in 2L mPDAC diagnosed at stage 4.**

Methods

<u>Study design</u>: Open label, multinational, multicenter Phase 2a



<u>Study regimen (Cohort 2)</u>: Subjects received 5 days priming with BL-8040, followed by BL-8040 BIW + Pembrolizumab Q3W + Chemotherapy (Onivyde/5-FU/ Leucovorin (LV)) Q2W

Main inclusion criteria	Endpoints
• Stage 4 PDAC at diagnosis • Progressed after 1L gemcitabine-based Rx	• Overall response rate (ORR) according to RECIST v1.1 Disease control rate (DCR) • Confirmed ORR (cORR) • Duration of response • PFS and OS • Safety and tolerability

cORR (Confirmed ORR) according to RECISTv1.1

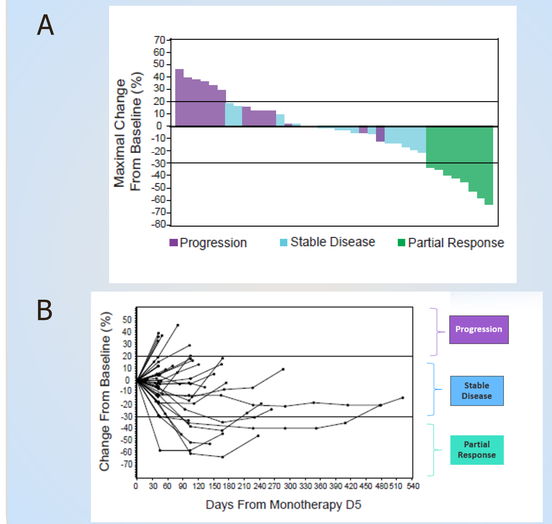
Baseline Characteristics, >70% of Patients Have Liver Metastasis

Table 1. Baseline characteristics of subjects enrolled in the Cohort 2 of the COMBAT trial with triple combination therapy

Demographic Characteristics	N (%)
ITT	43
mITT (evaluable population)	38
Male (%)	24 (55.8%)
Female (%)	19 (44.2%)
Mean Age (range)	68 years (40 to 85)
Patients by Country	
• USA	17
• Israel	7
• Spain	19
Number of Prior Lines of Treatment	
• 1	43 (100%)
ECOG Performance-Status	
• 0	14 (31.3 %)
• 1	29 (68.7%)
Disease Stage at Diagnosis	
• Stage IV	42 (97.6%)
Number of MSI-H (tested in 39 subjects)	0
Baseline median CA19-9 (range)	934 (1.2 to 123,112)
Site of Metastasis	
• Liver	32 (74.5%)
• Lung	11 (25.6%)
• Lymph node	11 (25.6%)
• Other	12 (27.9%)

Legend: MSI-H, Microsatellite instability high.

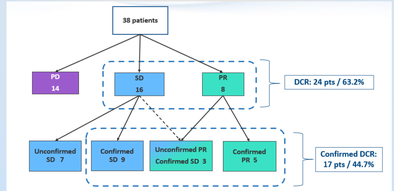
Efficacy: Waterfall and Spider Plot



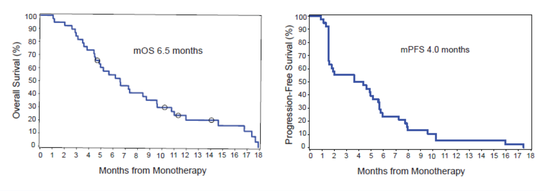
Analysis of evaluable population (mITT; N=38) **A** Waterfall plot analysis showing max. % change in the sum of longest diameters measured of target lesions vs. baseline **B** Spider plot analysis showing the sum of longest diameters (mm) of target lesions by best response according to RECISTv1.1

Efficacy: Response and Disease Control Rate

COMBAT Cohort 2		mITT (N=38)		
		No. of Subjects	% of Subjects	95% CI
Best response	ORR (PR)	8	21.1%	8.1-34.0
	cORR	5	13.2%	2.4-23.9
	SD	16	42.1%	26.4-57.8
	DCR	24	63.2%	47.8-78.5
	PD	14	36.8%	21.5-52.2



Efficacy: Overall Survival and Progression Free Survival



Analysis of evaluable population (mITT; N=38) **Left panel**, K-M estimates of OS measured in months from monotherapy Day 1 to death. Circles displayed identify censoring. **Right panel**, K-M estimates of PFS measured in months from monotherapy Day 1 to death.

Efficacy of Treatment Combination According to Liver MTS status

Analysis Set	Liver Metastasis (N=30)	No Liver Metastasis (N=8)
mOS (months, mITT N=38)	**5.9**	**8.4**
95% CI (months)	4.4 - 9.6	3.5 - 10.8
mPFS (months, mITT N=38)	**1.9**	**5.4**
95% CI (months)	1.5 - 5.7	1.5 - 8.0
ORR (mITT N=38)	**16.7%**	**37.5%**
95% CI	3.3% - 30.0%	4.0% - 71.0%
DCR (mITT N=38)	**56.7%**	**87.5%**
95% CI	38.9% - 74.4%	64.6% - 100.0%

Safety: Treatment Related AEs of Combination

Treatment Related Adverse Events	All	Grade≥ 3
Nausea and vomiting	74.4%	18.60%
Asthenia	67.4%	16.30%
Injection site reactions	55.8%	4.70%
Diarrhea	53.5%	14%
Appetite disorders	41.9%	9.30%
Pruritus	39.5%	--
Anemia	37.2%	11.60%
Neutropenia	14.0%	7%
Febrile Neutropenia	2.3%	2.3%
Rashes, eruptions and exanthems	30.2%	--
Gastrointestinal and abdominal pain	30.2%	--
Musculoskeletal and connective tissue pain and discomfort	30.2%	4.60%
Dermal and epidermal conditions	25.6%	--
Edema	23.3%	4.70%
Weight decrease	20.9%	2.30%
Hyperpigmentation disorders	20.9%	--
Gastrointestinal atonic and hypomotility disorders	20.9%	--

Adverse events reported in >20% of patients

Treatment was well tolerated, and the rates of severe neutropenia and infections were substantially lower than expected. These data suggest that BL-8040 mechanism of action may add benefits to chemotherapy and support the development of motixafortide in the treatment of pancreatic cancer.

Summary & Conclusions

- **The combination of BL-8040, Pembrolizumab and Chemotherapy is tolerable and shows encouraging results with cORR 13.2%, mPFS 4.0 months and mOS 6.5 months (compared to 7.7%, ~3 months and 4.7 months, respectively, on a historical basis for Chemotherapy alone in the stage 4 diagnosis subpopulation)[4]**
- **SD of 42.1% and DCR of 63.2% were also higher than historical data on SoC chemotherapy used in 2L patients**
- **The incidence of severe neutropenia and infections is lower than the historical data on Chemotherapy**
- **The results from the Cohort 2 of the COMBAT Study suggest that BL-8040 + Pembrolizumab may expand the efficacy and safety benefit of Chemotherapy (Onivyde/5-FU/LV) in mPDAC, and warrants further investigation in a randomized study**

References

[1]Feig, C. et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc. Natl Acad. Sci. USA 110, 20212–20217 (2013).*[2] Bockorny et al, BL-8040, a CXCR4 antagonist, in combination with pembrolizumab and chemotherapy for pancreatic cancer: the COMBAT trial. *Nature Medicine 26, 878–885(2020)* [3]Abraham, M., et al. Effect of BL-8040, high-affinity CXCR4 antagonist, on T-cell infiltration, tumor growth, and synergy with immunomodulatory agents. *Journal of Clinical Oncology* 35, no. 15_suppl. (2017)[4] Macarulla T. et al, Liposomal Irinotecan + 5-FU/LV in Metastatic Pancreatic Cancer: Subgroup Analyses of Patient, Tumor, and Previous Treatment Characteristics in the Pivotal NAPOLI-1 Trial. Pancreas. 49 (1):62–75 (2020).