Background BXCL701 (talabostat), an oral innate immune activator, is currently in a Phase 2a/b trial in combination with pembrolizumab in patients with metastatic castration-resistant prostate cancer (mCRPC) of small cell neuroendocrine (SCNC) phenotype. Preclinical data suggest that BXCL701 inhibition of DPP8/9 and DPP4 is a pharmacologic strategy that can increase immune cell content and function in the tumor microenvironment (TME) to enhance the efficacy of immunotherapy. Here, we report an exploratory biomarker analysis of samples from the Phase 2a study.

Methods To characterize the cellular and molecular landscape of the TME, the Neogenomics MultiOmyx immunofluorescence platform was applied to pre-treatment FFPE tissues of 4 responders (Rs) and 8 non-responders (NRs). Similarly, mutational profiling of circulating tumor DNA was assessed to determine the predictive value of mutation burden or specific gene mutations. Additional mechanism-based pharmacodynamic endpoints were evaluated by comparing pre-treatment and post-treatment immune activation by serum cytokine analysis using the MSD platform.

Results In this exploratory analyses, baseline DPP9 expression was higher in tumors of Rs, with median number of positive cells per mm$^2$ of 23.8 (range 0–341) in the stroma and 7.2 (range 0–419) in the tumor bed vs. 0.0 (range 0–812) and 0.0 (range 0–162) (p= 0.003272 and 0.01301 respectively) in NRs. Programmed-death ligand-1 (PD-L1) expression and immune cell infiltration were low with innate immune cells as the predominant cell type. CD16-positive cells, CD68-positive macrophages, and T cells but not PD-L1 expression in the TME predicted the responder population. This phenotype along with a low mutation burden and low microsatellite instability (MSI) in these tumors suggest a pharmacologic mechanism where BXCL701 modulates an otherwise cold ICI-refractory TME into a permissive phenotype that enhances responsiveness to PD-1 blockade. Analysis of cytokine levels demonstrated general increases with a notable 15.1- vs. 7.4-fold induction of IFN-gamma in the Rs vs. NRs respectively although this did not reach statistical significance in this small sample set. Increased production of the inflammasome-dependend cytokines IL-1 beta and IL-18 was also observed, rising maximally to 42-fold. Other effector cytokines including IP-10 (range 0.6–14.0-fold), CXCL9 (range 1.3–55.6-fold) and TNF-alpha (range 1.3–4.3-fold) were also remarkably induced post-dose.

Conclusions DPP9 overexpression has provisionally been identified as a response-predictive biomarker in BXCL701 and pembrolizumab combination treatment in mCRPC patients with SCNC phenotype. Additional biomarker analyses are ongoing to build on this finding. It will also be validated in the randomized Phase 2b SCNC trial planned to initiate in 2H 2023.

Trial Registration ClinicalTrials.gov Identifier: NCT03910660

REFERENCES