343 MULTIOMIC BIOMARKER SIGNATURES IDENTIFY SUBSETS OF PATIENTS WHO MAY BENEFIT FROM EITHER NIVOLUMAB OR SOTIGALIMAB IN COMBINATION WITH CHEMOTHERAPY IN METASTATIC PANCREATIC CANCER

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Background Gemcitabine/nab-Paclitaxel (GnP) is a standard of care regimen for first-line metastatic pancreatic ductal adenocarcinoma (PDAC) and has a 1-year overall survival (OS) rate of approximately 35%. There is an urgent need for novel therapeutics and precision medicine approaches in PDAC. PRINCE, a randomized phase 2 trial, reported an increased 1-year OS relative to historical data, for patients treated with nivolumab (nivo)/GnP (57.3%, p = 0.007, n=34) and sotigalimab (sotiga) (APX005M; CD40 agonist)/GnP (48.1%, p = 0.062, n= 36).

Methods To investigate immune modulatory and pharmacodynamic (PD) effects of nivo or sotiga in combination with GnP we used several orthogonal minimally invasive, blood-based biomarker technologies. Immune population profiles were evaluated by CyTOF and features of T cell phenotype and function by multicolor flow cytometry. Soluble proteins were evaluated with predefined panels using the Olink platform (Immuno-oncology (IO) and Immune Response) along with an unbiased mass spectrometry proteomic approach (Biognosys) that identified circulating soluble proteins of significance.

Results Relative to baseline, patients who received nivo/GnP had numerically increased frequencies of proliferating, activated CD8+ and CD4+ effector memory T cells in circulation across multiple timepoints. These patients also had significantly increased levels of soluble proteins associated with type II interferon responses and immune cell migration and T cell activation, as well as significantly decreased levels of immunomodulatory proteins.Patients who received sotiga/GnP had increased expression of the co-stimulatory molecule CD86 on conventional dendritic cells. These patients also had significantly increased concentrations of soluble proteins associated with mature antigen presenting cells, and the activation of helper CD4+ T cells, B cells, and monocytes. Significant increases in soluble proteins associated with type-1 cell-mediated effector immunity and decreases in immunosuppressive factors were observed in both arms. Significant proteins were defined as $p \leq 0.05$, log2 expression fold change ≥ 0.5 (Olink) and Sparse PLS discriminant analysis was used with zero as a threshold (Biognosys).

Conclusions This study is a first to use multiomic minimally invasive biomarker approaches in PDAC to demonstrate PD effects and immune modulation with immunotherapy/chemotherapy combinations. Orthogonal assays demonstrate that nivo/GnP and sotiga/GnP elicit unique immune responses and the observed effects are consistent with their distinct mechanisms of action. These data suggest that multiomic biomarker signatures may identify subsets of patients who may benefit from an immunotherapy/chemo approach in PDAC. Moreover, results from these analyses will support early phase clinical study development decisions.

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Ethics Approval This study was approved by University of Pennsylvania Institutional Review Board; Federalwide assurance #00004028.

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