2022 ACG-IRG Pilot Grant

Immunotherapy Mechanisms and Targeting of SWI/SNF Complex Mutations in Pancreatic Cancer

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Abstract:

Immune checkpoint inhibitors (ICIs), which have transformed the care of multiple malignancies, fail to demonstrate efficacy in pancreatic cancer. Recently, genomic biomarkers have been associated with response to ICIs: microsatellite instability high (MSI-H) and tumor mutation burden (TMB) >10 mutations/Mb, however, these are also rare in pancreatic cancer (PC). Our preliminary data discovered that alterations in Switch/ Sucrose Non-Fermentable (SWI/SNF) chromatin remodeling genes (ARID1A, ARID1B, PBRM1, SMARCA4 and SMARCB1, etc.) predispose metastatic PC patients to improved outcomes with immunotherapy after multiple lines of chemotherapy. Eight of 9 patients (89%) achieved an objective response, including a complete remission, with the two longest responses ongoing at 33+ and 36+ months. Median progression-free (mPFS) and overall survival (mOS) in SWI/SNF mutant patients on ICI was 9 and 15 months, versus those SWI/SNF mutant patients not on ICI (4 and 10 months, respectively). Responses occurred even in the presence of MSI- H, low TMB and/or low PD-L1 expression. Therefore, a small subset of patients with PC have genomic alterations in SWI/SNF chromatin remodeling components and these patients appear to be responsive to ICIs.

This proposal develops an expanded prospective trial combined with patient tumor immune profiling to uncover the mechanism of ICI response in SWI/SNF mutant pancreatic cancer (PC) patients**. Aim 1** will complete an investigator initiated, open label, single center trial of Cemiplimab and Gemcitabine (CemGem) in patients with unresectable, metastatic pancreatic cancer harboring a SWI/SNF mutation who have failed or are intolerable to FOLFIRINOX or Gemcitabine/nab-paclitaxel chemotherapy (2nd line or greater). A total of 40 SWI/SNF altered PC patients will be on the experimental arm at the opening of trial. They will be compared against 40 matched patients on investigator chosen 2nd line therapy from opening of trial. At diagnosis and prior to enrollment in trial, all metastatic PC patients will receive next generation sequencing (NGS) of their tumor per UCSD standard of care. Patients with SWI/SNF mutations will be considered for the experimental arm. An initial 20 patients will be enrolled, treated with combination therapy, and assessed as a futility analysis. If a primary endpoint signal exists: (1) mOS > 15 months (2) mPFS > 9 months, (3) Overall Response Rate (ORR) > 40%, (4) total time on treatment with CemGem > 6 months, and (5) low treatment-related adverse events, an expansion cohort of an additional 20 more patients will be enrolled (40 total patients in experimental arm). **Aim 2** will determine the mechanism of SWI/SNF mutant PC patient response to ICI through tumor immune microenvironment (TIME) characterization. This aim will implement Nanostring technology to profile the immune cell and tumor microenvironment of patient PC and blood samples before and after administration of CemGem therapy (through a post-treatment biopsy as able). The Nanostring PanCancer IO 360 platform will evaluate each patient's tumor and the TIME in over 770 genes of interest within: (1) the PI3K-Akt pathway, (2) immune cell adhesion and migration, (3) costimulatory signaling, (4) lymphoid compartment, and (5) metabolic stress compartments. The 'immune profiling' results of patients within our SWI/SNF mutated clinical trial will provide the basis for future laboratory research to inhibit SWI/SNF proteins in unmutated pancreatic cancer patients and incite a response to immunotherapy in otherwise immune-refractory tumors. Overall, a small subset of patients with pancreatic cancer have genomic alterations in the SWI/SNF chromatin

remodeling components and these patients appear to be responsive to ICIs, suggesting the need for prospective trials and mechanism determination.