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Project Title: *Translational Evaluation of Combination Hypomethylation with Immune Checkpoint Blockade in Advanced Pancreatic Cancer*

ABSTRACT

While new combinations of cytotoxic chemotherapy significantly improve survival for patients with locally advanced and metastatic pancreatic adenocarcinoma (PDA), the majority will progress on first-line therapy after a median of 5-7 months. There is no standard second-line treatment with clear overall survival benefit. Pre-clinical data in the KPC mouse model of pancreatic cancer shows that treatment with decitabine inhibits tumor growth, upregulates interferon-related genes, and polarizes the immune response towards a favorable macrophage phenotype and infiltrating CD8 T-cell population. By combining decitabine with a checkpoint inhibitor, there is marked decrease in tumor progression, prolonged tumor doubling time, and increased overall survival. This data suggests that hypomethylation may be an important anti-tumor mechanism in PDA and may be combined with checkpoint inhibition to potentiate tumor control. The goal of this project is to determine the efficacy of combination azacitidine and pembrolizumab in patients with advanced PDA after disease progression on first-line therapy.

For Aim 1, we will assess the efficacy of combined hypomethylation and PD-1 inhibition in a single-arm phase II study of azacitidine induction followed by pembrolizumab in patients with advanced PDA with disease progression on first-line cytotoxic therapy, using a primary endpoint of progression-free survival (PFS). We hypothesize that treatment with the combination will improve PFS compared to what has been historically achieved with second-line chemotherapy. For Aim 2, we will characterize the effects of hypomethylation and PD-1 inhibition on a) global DNA methylation by evaluating baseline and post-treatment (after 8 weeks of therapy) tumor biopsies and bimonthly peripheral blood samples and 2) the tumor immune microenvironment by analyzing baseline and post-treatment tumor biopsies for tumor infiltrating lymphocytes, macrophage infiltration, and PD-L1 expression. We hypothesize that the combination will alter gene signature pathways and shift the immune milieu to enhance immune activation, thereby delaying progression of pancreatic cancer. This trial will evaluate the novel combination of a hypomethylating agent with anti-PD1-therapy, as well as further characterize the effects of epigenetic modification and sensitization to immunotherapy in PDA. Results of this trial may ultimately lead to a more effective second-line treatment option for advanced PDA patients.