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**PD-1/PD-L1 blockade antibodies coordinate with vaccine therapy to overcome multiple immunosuppressive pathways and improve effector T cell infiltration in pancreatic adenocarcinoma**

**Research Synopsis:**

Pancreatic cancer (PDA) is highly resistant to standard treatment regimens and new therapies are sorely needed. Our phase I/II human clinical trials utilizing a GM-CSF secreting allogeneic pancreas tumor vaccine (GVAX) have been shown to be safe and tumor antigen specific responses have correlated with prolonged survival. However, pancreatic tumors consist of a strong immunosuppressive network, enabling tumor immune evasion and blunting vaccine-induced responses. Programmed cell death 1 (PD-1) and its ligand programmed cell death ligand 1 (PD-L1) constitute a major tolerance mechanism. Clinical trials of  $\alpha$ PD-1 and  $\alpha$ PD-L1 antibodies have proven effective in solid tumors, although objective responses were not seen in a small subset of PDA patients. GVAX treated patients have demonstrated infiltration of PD-1<sup>+</sup> T cells, which is a major immunosuppressive mechanism in the tumor microenvironment. We aimed to manipulate the PDA tumor microenvironment through the blockade of PD-1 or PD-L1 in combination with GVAX. We hypothesized that the use of PD-1 or PD-L1 blocking antibody and GVAX will improve vaccine therapy and pancreatic cancer survival.

Immunohistochemistry analysis of human PDA resected from patients two weeks after GVAX therapy revealed significant upregulation of PD-L1 membranous staining compared to unvaccinated patients. Similarly, in a preclinical metastatic model of murine PDA, GVAX therapy significantly upregulated PD-L1 expression on neoplastic cells. We subsequently demonstrated that combinatorial therapy of GVAX with PD-1 blockade significantly improves survival and cure rates compared to vaccine and checkpoint monotherapy in a highly stringent pancreatic cancer murine model. Combinatorial therapy significantly increased effector T cell trafficking to the tumor microenvironment and overcame additional immune checkpoint mechanisms. Taken together, our findings support the combination of GVAX vaccine therapy with  $\alpha$ PD-1 or  $\alpha$ PD-L1 blockade in pancreatic cancer patients.