



## Scientific Abstract

### SU2C–Lustgarten Foundation Pancreatic Cancer Dream Team: “Transforming Pancreatic Cancer to Treatable Disease”



*[This abstract was provided by the scientists when their application was accepted.]*

**BACKGROUND:** Pancreatic ductal adenocarcinoma (PDA) remains a major clinical problem. PDA has a unique tumor microenvironment (TME) composed of stromal tissue supporting suppressive immune cells that provide a hostile environment for inducing antitumor immunity.

**HYPOTHESIS:** The immunosuppressive PDA milieu can be reprogrammed into an immuno-stimulatory one to enable tumor rejection, converting PDA into a treatable disease.

#### **AIMS:**

- 1) Conduct combination clinical trials and establish biomarkers of TME reprogramming – each trial focusing on a novel immune suppressive pathway within the TME. As part of these trials, establish a centralized program of biomarker assessment that will help to predict response and understand mechanism, including next generation sequencing of patient tumors to reveal tumor mutations that drive tumor-specific T cell responses in patients after treatment.
- 2) Conduct phase 1A and 1B clinical trials evaluating an antagonist antibody targeting CD47 expressed on tumor cells to avoid phagocytosis by monocytes, for safety and antitumor activity.
- 3) Conduct a dose seeking study of AMD3100, an inhibitor of the chemokine CXCR4, for the ability to enhance T cell infiltration into the TME.
- 4) Conduct pre-clinical studies in PDA mouse models to identify optimal combinatorial approaches and that will drive the next generation of clinical trials.

**DESIGN:** We are targeting multiple immune-suppressive pathways – PD-1/PD-L1, suppressive monocytes (via CD40), pro-tumoral B cells, CXCL12 expressed by tumor stroma, and the antiphagocytosis signal, CD47. We are evaluating enhanced T cell infiltration into the TME by two methods: a prime/boost vaccine (GVAX/*Listeria*) and combination chemotherapy. These trials include:

- GVAX plus recombinant *Listeria* with or without anti-PD-1 monoclonal antibody in second line metastatic disease. This trial has reached its endpoint and the database has been closed for analyses. IHC and TCR sequencing on these same specimens were recently completed.
- Agonist CD40 antibody in combination with chemotherapy in the neoadjuvant and adjuvant setting for patients with resectable disease. Sixty percent of the target patient accrual has been met.





- BTK inhibitor ibrutinib with chemotherapy for the first line treatment of metastatic disease. The study has already completed enrollment.
- Phase 1A and 1B clinical trials evaluating an antagonist antibody targeting CD47 (a molecule expressed on tumor cells to avoid phagocytosis by monocytes), for safety and antitumor activity. This study is complete and has been taken over by a biotechnology company to further develop the agent.
- A pilot clinical trial testing AMD3100, an inhibitor of the chemokine CXCR4, for the ability to enhance T cell infiltration into the TME. This study opened a second site and enrolled 3 patients in the past 6 months. RNAseq of tumor is showing interesting correlates.

Biomarker assays have been established and a set of standard operating procedures for the procurement, processing, and analysis of biosamples, have been implemented across all trials. Likewise, an extensive series of standard operating procedures for mouse studies have been set up. The mouse studies where combinations of different potential therapeutic agents were tested, have been completed. The results of these studies provided the rationale for 2 additional clinical trials that are now FDA approved and IRB approved. We have also developed the databases needed to collect the immune data from both the clinical and preclinical studies and these are being populated.

**DELIVERABLES:**

- Clinically tested approaches for inducing and facilitating T cells
- Combination immunotherapies tested in the clinic
- Biomarkers of TME reprogramming
- Annotated tissue bank and database