Scientific Abstract

SU2C-Lustgarten Foundation For Pancreatic Research Interception Research Team:

"Developing Novel Approaches to Treat and Evaluate Early Pancreatic Cancer"

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

Pancreatic ductal adenocarcinoma will soon be the second leading cause of cancer death in the U.S. Unfortunately, the standard-of-care is woefully inadequate and few patients are cured. To intercept pancreatic cancer at its earliest stages when it can be more successfully treated, the Team is undertaking a comprehensive approach with two major aims. These include:

- Test novel and intensive preoperative treatments allowing more patients to have successful and effective surgery and eradicate micrometastatic disease;
- Use organoids to identify robust biomarkers of response to standard and immunotherapies.

Over the past several years, team members have developed a clinical trial platform that enables the efficient translation of preclinical hypotheses into patients, and fuels the science to drive the next generation of therapeutic hypotheses. The early results have demonstrated striking outcomes by integrating intensive therapies in the preoperative setting. Indeed, borderline resectable patients receiving FOLFIRINOX followed by chemoradiation and surgery demonstrated a 56 percent R0 resection rate (surgery with complete removal of visible and microscopic tumor) with a 2 year overall survival of 59 percent (81% for resected patients).

A similar approach was taken in unresectable patients with the addition of Losartan based on preclinical data showing that it leads to a profound remodeling of the tumor microenvironment, including a marked increase in CD8 T-cells infiltrating the tumor. This study in patients judged at presentation to be categorically unresectable resulted in a remarkable 56 percent R0 resection rate. We now seek to improve this paradigm by adding inhibitors of immune checkpoints.

During this randomized phase II study, we will prospectively validate the predictive potential of pancreatic organoids obtained from patients prior to starting therapy. We will use biopsies to establish tumor-derived organoids and attempt to identify an individual's likelihood to respond to therapy with FOLFIRINOX. Moreover, we will assess sensitivities of organoids to additional therapies and whether any predictors of survival can be gleaned. Additional tumor and blood will be collected for future analysis to be supported by investigators by leveraging other grants and philanthropy.