



Team Progress Updates

SU2C Pancreatic Dream Team:

“Cutting Off the Fuel Supply: A New Approach in the Treatment of Pancreatic Cancer”



Cancer of the pancreas is one of the deadliest forms of cancer, with a five-year survival rate of only 8.5%. More than 44,000 people die from pancreatic cancer each year in the United States. New approaches are urgently needed.

The SU2C Pancreatic Dream Team is studying ways to cut off the “fuel supply” that pancreatic tumors need to grow, trying to determine whether pancreatic cancers depend on glutamine and/or glucose for survival, as other cells do. If so, the information can be used to help devise new therapeutic strategies.

The team is also investigating whether agents that hinder the ability of cells to effectively use glucose and/or glutamine hold promise for pancreatic cancer patients. The team is conducting clinical trials on drugs that impair the breakdown of glutamine, such as aminooxyacetate, phenformin, and LDH-A inhibitors.

The breakdown of glucose and glutamine can generate a large amount of metabolic waste and change the stroma, the dense cells surrounding the tumor. Unfortunately, these changes can protect cancer cells from the effects of chemotherapy. Thus, the team is also testing whether chemotherapy (nab-paclitaxel) directed against the stroma cells can be used to improve the treatment of pancreatic cancer patients.

The team reported the following progress:

June 2015

In their final 6 months of SU2C funding the Dream Team continued to analyze recently completed studies, and reported continued progress and new findings as follows:

- The Dream Team has had success in developing a new imaging method to scan patients for tumors. The new imaging approach, which measures glutamine in the tumors instead of the standard measurement of glucose, works well in a number of different cancer types, including pancreatic cancer and is better than glucose imaging in brain cancer.
- Dream Team members tested if glutamine imaging can help identify tumors that will be most sensitive to particular drugs, which will help doctors to select the best treatment for some patients.
- The Dream Team has performed genetic analysis of pancreatic cancers and found:





Team Progress Updates

- Genetic mutations in four genes that may predict better survival after surgical removal of pancreatic tumors;
- A number of genetic mutations that are “clinically actionable”, meaning that there are existing drugs that could be used to treat the cancer. They found that 38 percent of pancreatic tumors had clinically actionable mutations.
- The Dream Team showed that early detection of pancreatic cancer was possible by testing blood samples for tumor DNA, a “liquid biopsy”. They found that the blood test was a much more sensitive way to find out if disease had recurred - compared to standard-of-care imaging approaches; the return of the disease was identified 6.5 months earlier using liquid biopsy testing, compared with using imaging techniques.

December 2014

- In laboratory studies, this Dream Team has found that a vitamin D-like compound can reprogram the tumor microenvironment - the cells and structures that surround and support pancreatic cancer cells in tumors – so that anti-cancer drugs work better. They are now testing the addition of a vitamin D-like drug to chemotherapy in clinical trials.
- The Dream Team developed and tested a new imaging method to scan patients for pancreatic tumors and metastases. The results are promising that this approach is safe and effective, and may be superior to current techniques for some cancers, including pancreatic cancer.
- The Dream Team continued to enroll patients in their ongoing trials that test addition of Vismodegib (a basal cell carcinoma/medulloblastoma treatment) or hydrochloroquine (an anti-malarial agent) to the frontline therapy for pancreatic cancer, nab-paclitaxel/gemcitabine.

June 2014

- The Dream Team started a new pilot trial to test whether a vitamin D-like compound can be used to reprogram the cells and structures that surround and support cancer cells in pancreatic tumors.
- A trial was started that explored whether “maintenance” therapy can be used successfully in patients after they have completed chemotherapy. An anti-growth drug called metformin was tested with or without another anti-growth drug called rapamycin.



Team Progress Updates

December 2013

- The combination of nab-paclitaxel (Abraxane) plus gemcitabine, reported by this Dream Team to significantly improve overall survival in advanced pancreatic cancer by almost 2 months, is now FDA approved as a first-line treatment of patients with metastatic adenocarcinoma of the pancreas.
- Tumor samples from patients before and after treatment with nab-paclitaxel plus gemcitabine have been collected to determine the mechanism for the combination's beneficial effects.
- This Dream Team has developed a better dye (^{18}F fluoroglutamine) for imaging pancreatic tumors by positron emission tomography (PET). Compared to the standard technique (^{18}F fluoro-D-glucose PET), the new dye appears better for identifying pancreatic tumors that have spread to the brain and liver.
- The gene mutations and metabolic changes in patient tumor samples were analyzed to help in the discovery of new drugs and to personalize treatments so that patients receive the best course of therapy for their disease.

June 2013

- The phase III study of ABI-007 (nab-paclitaxel) plus gemcitabine versus gemcitabine in advanced adenocarcinoma of the pancreas met its primary endpoint of significantly improving overall survival. The median overall survival was 8.5 months for patients receiving nab-paclitaxel and gemcitabine versus 6.7 months for patients receiving gemcitabine alone. The results were reported at ASCO 2013 Gastrointestinal Cancer Symposium in late January 2013.
- Upon re-evaluation of the stop criteria, following results of the phase III trial of nab-paclitaxel plus gemcitabine, the phase II study of gemcitabine and nab-paclitaxel in combination with GDC-0449 (the Hedgehog pathway inhibitor) has been re-opened with an additional three patients enrolled.
- A maximal dose of hydroxychloroquine was determined for the phase II study of hydroxychloroquine in combination with gemcitabine and nab-paclitaxel to inhibit autophagy in pancreatic cancer. The phase II part of the study has been opened.
- The proper form of calcipotriol has been identified in the calcipotriol proof-of-concept trial in patients undergoing surgery for pancreatic ductal adenocarcinoma. The Dream Team is working with the pharmaceutical company to obtain access to the drug. High-throughput assays are being developed to evaluate cell signaling in tumor samples obtained from the trial.
- The Dream Team has enrolled six patients in the phase 0 trial to test glutamine tracers in patients with localized and resectable PDAC with a goal of 20 patients. Early results indicate



Team Progress Updates

that glutamine imaging agents may be superior to glucose agents in visualizing brain metastases.

- A protocol has been written and is waiting for institutional review board (IRB) approval for the trial involving biopsy before and after nab-paclitaxel and gemcitabine treatment followed by extensive metabolic/lipidomics and micropinocytosis studies. In addition, an assay to determine expression levels of micropinocytosis-associated genes has been developed by the Dream Team.
- A protocol was proposed to Celgene who agreed to supply the TORC 1/2 inhibitor CC-223 for a trial of metformin plus rapamycin plus TORC1/2 in patients in which best response to previous treatment was achieved. Assays to evaluate the mTOR pathway have been developed.

December 2013

- The phase III study of ABI-007 (nab-paclitaxel) plus gemcitabine versus gemcitabine in advanced adenocarcinoma of the pancreas met its accrual target. Patients who received the combination therapy demonstrated a significant improvement in overall survival compared to patients receiving gemcitabine alone.
- The phase II study of therapy selected by molecular profiling in patients with previously treated advanced pancreatic cancer met its accrual target and its primary endpoint of one-year overall survival for 20 percent of patients.
- The phase I/II trial of gemcitabine + nab-paclitaxel + GDC-0449 (the Hedgehog pathway inhibitor) has been closed to enrollment based on interim analysis that it did not meet its primary objective.
- The trial to investigate tumor and normal tissue for biologic endpoints in pancreatic cancer has nearly met its accrual target.

June 2012

- The Dream Team has fully enrolled the 842 patients for its double-blind phase III clinical trial and data analysis has begun. The phase II clinical trial of a three-drug combination therapy for patients with advanced pancreatic cancer has continued and, after 6 months follow up, the Dream Team observed a partial response in 33 percent of the patients and stable disease in another 48 percent of the patients.
- The Team continued enrollment for their 75-person metabolomics (the chemical fingerprints of all the cellular processes that take place in a cell) profiling study. The results from the first 25 samples led to the hypothesis that these tumors acquire their nutrients through ingestion of the fluid and proteins surrounding the cells by a process called macropinocytosis.
- The Dream Team continued efforts to move the new glutamine tracers into a clinical trial at Memorial Sloan Kettering Cancer Center (MSKCC) and the University of Pennsylvania (UPenn).



Team Progress Updates

PET imaging studies for evaluation of metabolic mechanisms of these new tracers were performed in other rodent models.

December 2011

- By the 24-month mark, the Dream Team had enrolled 719 of the targeted 842 patients in its double-blind phase III clinical trial to test a combination of nab-paclitaxel and gemcitabine in patients with advanced pancreatic cancer. In addition, they were treating 43 patients in their phase II clinical trial of a three-drug combination therapy for patients with advanced pancreatic cancer.

June 2011

- The Dream Team completed profiling analyses and comparisons of pancreatic stellate cells and normal pancreatic epithelial cells. The goal is to use this information to identify potential druggable targets, including androgen, glucocorticoid, and estrogen receptors. Drugs used to treat other types of cancer are already available for these targets.
- The Dream Team started studying potential glutamine imaging agents that may be used during the PET scans performed on cancer patients to monitor tumor growth. After regulatory approval is obtained, the first human studies will begin.
- The Dream Team completed preclinical evaluation of four different targeted therapies: AOA, FX11, phenformin, and hydroxychloroquine. AOA is a glutamine metabolism inhibitor; FX11 is a glucose-metabolism inhibitor; phenformin modulates glucose and lipid metabolism; hydroxychloroquine is an autophagy (controlled breakdown of damaged organelles in a cell) inhibitor.
- These findings led the Dream Team to modify its phase I/II trial and use hydroxychloroquine instead of phenformin.

December 2010

- The Dream Team launched a phase I/II clinical trial of a three-drug combination therapy for patients with advanced pancreatic cancer. This trial will combine the paired chemotherapy agents being studied in the phase III trial (nab-paclitaxel and gemcitabine) with a third drug that works by inhibiting a pathway called Hedgehog, which is known to play a critical role in cancer growth.
- The Dream Team completed nuclear-receptor profiling on two pancreatic stellate (support cells in the pancreas) cell lines. The leading candidate for a therapeutic target is the vitamin D receptor.



Team Progress Updates

- The Dream Team initiated a preclinical study investigating the efficacy of three agents that affect glucose and glutamine metabolizing enzymes. Tumors from 15 patients were implanted in mice, and treated with the investigational agents. Preliminary results indicate that Phenformin, which regulates glucose and lipid metabolism, is promising for pancreatic cancer therapy.

June 2010

- The Dream Team initiated a multi-center, randomized phase III trial testing a two-drug combination (nab-paclitaxel and gemcitabine) in patients with pancreatic cancer. Previously, a phase I/II trial showed that a combination of these two therapies decreased a molecular marker of pancreatic cancer and increased survival for patients with advanced pancreatic cancer.
- Team members at Princeton University and Johns Hopkins Medical Institutions created standard procedures for collecting, shipping, storing, and analyzing samples. These tests have been used for animal and xenograft tissues and are ready for use with human samples.
- Pancreatic cancers feed on glutamine, and understanding how they take in the nutrient and use it will open new avenues to combat the tumor. During this six month period, significant progress was made in synthesizing forms of glutamine that can be tracked using advanced imaging techniques. One form was tested and efficiently taken up by the tumor in mouse models. Synthesis of another form of glutamine was optimized and ready for testing in mice. This form is tracked using magnetic resonance imaging instead of a PET/CT scan, allowing patients to avoid radiation exposure.