



## Team Progress Updates

### SU2C PI3K Dream Team:

#### “Targeting the PI3K Pathway in Women’s Cancers”



The PI3K pathway is a complex signaling cascade that, in concert with other signaling networks, regulates cell survival and growth. This pathway is mutated in more cancer patients than any other pathway, making it an attractive target for agents that inhibit these genetic aberrations at the molecular level.

The scientists involved in this Dream Team focus on breast, ovarian, and endometrial cancers, all of which frequently have mutations in a set of genes that regulate the PI3K pathway. Many drugs to inhibit this pathway have been developed and currently are in clinical trials. However, as with other “targeted” therapies, only a fraction of patients who enroll in these trials benefit.

The goal of this Dream Team is to discover approaches that predict which patients will respond positively to PI3K inhibitors. This project aims to allow clinicians to use biomarkers and imaging techniques to predict which patients will benefit from PI3K pathway inhibitors, leading to the development of therapeutic combinations that will hit multiple targets in the complex pathways that contribute to cancer cell growth.

The team reported the following progress:

#### December 2013

- The Dream Team has continued to enroll patients in the “Discovery Trials” that are still open. One study was closed due to insufficient evidence of clinical benefit, while four other Discovery Trials remain active. Two of the three “Demonstration Trials” are open and continues to accrue well. The last Demonstration Trials should open in the second quarter of 2014.
- The Dream Team has also continued to conduct retrospective analyses of patient tissues in order to identify biomarkers of response to therapy. In addition, the Dream Team is using a recently validated CLIA-compliant assay to prospectively test the genetic composition of the tumors of all patients enrolled in their trials.

#### June 2013

- All of the year one, year two, and year three milestones have been completed. The Dream Team has completed all of their “Exploratory Trials” and some of their “Discovery Trials”, and expects that all these will be completed at the end of this fourth and last year of funding. One of the three “Demonstration Trials” is open and continues to accrue well.





## Team Progress Updates

- The other two Demonstration Trials should open in the next several months; one by the end of summer 2013, and the other in the second quarter of 2014. A total of 854 patients have now been enrolled in all types of SU2C clinical studies.
- The Dream Team continued to conduct retrospective analyses of patient tissues in order to identify biomarkers of response to therapy. To date, they have obtained 8398 samples from 226 patients. In parallel, the Dream Team is using cell lines and mouse models to study the same drug combinations used in their clinical trials in order to identify response biomarkers as well as biomarkers of innate and acquired resistance.

### December 2012

- At the three-year mark, a total of 762 patients have been enrolled in all types of SU2C clinical studies. A major challenge in the implementation of the "Demonstration Trials", which are the highest priority for the Dream Team, has been the excessive toxicity observed when combining PI3K pathway-targeted drugs with other drugs. Most of the Dream Team's efforts in the first 30 months were devoted to developing dosing schedules that circumvented these toxicities without reducing efficacy.
- At the end of this period, the Dream Team reported the completion of all the phase I work for two of the demonstration trials. All exploratory trials were now closed; these studies have allowed the Team to develop biomarkers for their Demonstration Trials. These exploratory trials have also been instrumental in assessing toxicities of PI3K-pathway inhibitors in patients.
- The Dream Team continued to conduct retrospective analysis samples collected from patients in clinical trials.

### June 2012

- All of the year one and two milestones have been completed. Ongoing clinical trials continue to enroll and three additional drug combination trials will begin enrollment within the next few months. One last clinical trial, a phase II study testing a broad-range PI3K inhibitor called BKM120 in patients with metastatic triple-negative breast cancer was planned and, pending IRB approval, will soon begin enrollment.
- The Dream Team continued to conduct retrospective analysis on patient tissues. In a BRCA-mutant breast cancer mouse model, the Dream Team has seen promising results using a PI3K inhibitor and PARP inhibitor in combination; tumors disappeared and have not reappeared by 5 months after withdrawing the drugs.
- Over twenty PI3K pathway-targeted drugs and seven drugs targeting interacting pathways have been tested in 57 breast cancer cells lines, 54 ovarian cancer cell lines, and 37 endometrial cancer cell lines to identify potentially novel biomarkers.



## Team Progress Updates

### December 2011

- The Dream Team continued to meet their milestones. During this period, the Dream Team completed additional drug combination testing in cell lines. They also made progress in their clinical trials; approximately 500 patients were enrolled by the 24-month mark.
- The Dream Team developed several innovative screening approaches to find drug combinations that inhibit the PI3K pathway, and identify the patients whose types of tumors will respond to these drugs. Using techniques developed during the first 18 months of the project, the biomarker working group within the Dream Team analyzed samples collected from patients participating in clinical trials.

### June 2011

- During this period, the Dream Team continued their biomarker studies and made some important observations. They found that a PI3K inhibitor combined with a PARP inhibitor was effective in several models of breast cancer, including those with a BRCA1 mutation. Other studies showed that MYC and MET proteins may contribute to resistance to PI3K inhibitor treatment in mice that have a mutation in the PIK3CA gene. The Dream Team also identified three ways to measure tumor response to treatment in vitro.
- Additional cell lines were collected to continue testing combination drug therapies and nine out of 14 planned clinical trials opened for patient enrollment during this period.

### December 2010

- During this period, the Dream Team continued characterizing the breast, ovarian, and endometrial cancer cell lines. Additionally, they analyzed the following patient tumor samples to determine the specific mutation (or mutations) present in PI3K: 1000 breast, 500 ovarian, and 400 endometrial cancers.
- Cell-based screens for combination therapies were developed. Drug combinations were tested in three-dimensional cell cultures, mouse models, and patient-derived xenografts in mice. The Team also developed new models of PI3K-specific breast cancer to study mechanisms of drug resistance.
- In the first 12 months of the project, a total of 13 clinical trials to identify biomarkers and test responses to PI3K inhibitors were enrolling or set to begin: two phase I combination trials for patients with endometrial or advanced breast cancers, two phase I/II combination trials for breast cancer, and nine phase II trials testing single-agent and combination therapy in endometrial, ovarian, and breast cancers.



## Team Progress Updates

June 2010

- In the first 6 months of the project, the Dream Team established a website ([www.pi3k.org](http://www.pi3k.org)) to share information within their team and with the public. A mouse model for PI3K-specific breast cancer was developed and the Dream Team started examining characteristics of drug resistance in the tumor. A mouse model of BRCA1 breast cancer also showed promising responses to PI3K inhibitor treatment and provided data to develop co-clinical trials later in the project.
- The Dream Team proposed taking a personalized medicine approach. With this in mind, they successfully developed biomarker assays to identify five common PI3K mutations and began using these assays to match patients with PI3K mutations to potential treatments.
- Ten phase II clinical trials, spanning breast, ovarian, and endometrial cancers, were designed and two started enrolling.
- Testing of PI3K inhibitors in combination with other standard treatments was started in over 100 breast, ovarian, and endometrial cell lines. Promising combinations were tested in mouse models.
- The Dream Team also successfully implanted patients' tumor cells into mice to generate mouse models referred to as patient-derived xenografts. This technique allows several treatments to be tested against a patient's tumor before treatment is given to that patient.