



## Team Progress Updates

### SU2C–Prostate Cancer Foundation Prostate Dream Team: “Precision Therapy of Advanced Prostate Cancer”



The Team hypothesizes that the molecular qualities of a patient's CRPC can guide the doctor in choosing a “personalized” treatment. Their study includes patients with metastatic prostate cancer who participated in one of 4 clinical trials for novel drugs for mCRPC, at five leading clinical centers. To accomplish their objectives, they 1) implemented a multicenter study that systematically evaluated patients enrolling in 4 clinical trials for CRPC, 2) identified predictors of response, and 3) identified predictors of resistance.

Armed with information about the genetic makeup of 500 patients, the Dream Team aimed to be able to direct patients toward the treatment most likely to have an effect on their specific tumor. The hope has been that this personalized or precision approach will lead to more effective and lasting treatments, and potentially spare patients from unnecessary therapies that are expensive, highly toxic, and all too often provide little or no benefit.

For patients with cancers that do not respond to a given therapy, the Team assessed if individual genetic changes might suggest other potential therapeutic approaches. In parallel, the Team also performed laboratory studies of CRPC treatments to test the predictors of response and/or resistance. These laboratory studies helped the Dream Team to identify and prioritize the best drug targets. The team reported the following progress:

#### December 2016

- In the final progress report period of the Dream Team grant, the Team continued to accrue patients to their 10 open clinical trials (two additional trials were closed due to lack of company support).
- The Team continued to analyze sequencing data from previously collected patient samples. Thus far, sequencing data of 399 samples have been uploaded to cBioPortal, developed by this Team, which integrates genomic and clinical data.
- This Team has generated the largest collection of genomic data on clinical metastatic castration-resistant prostate cancer patients to date. These data encompass alterations in genes that may inform treatment strategies. Further, the results from the Team's TOPARP clinical trial (treatment with Olaparib), indicating that 12% of men with metastatic CRPC have inherited mutations in genes that take part in DNA repair pathways, influence treatment decisions.
- These data support routine DNA screening in both patients with metastatic prostate cancer and their families to elucidate whether mutations in DNA repair pathways are actual cancer predisposition changes.





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- The Team is actively working to change screening and treatment guidelines based on these findings.

### June 2016

- All clinical trials steadily accrued patients.
- The Team compared the methods and technology applied across all the SU2C clinical trial sites that are performing gene sequencing. This confirms and validates the successful collaborative nature of the SU2C-Prostate Cancer Foundation Dream Team model.
- Preclinical studies using mouse models and tumor organoids are continuing to progress.
- A large study was published showing that approximately 10-15% of mCRPC patients carry a mutation specific to DNA repair that is an inherited genetic mutation. Not only do these mutation carriers have a worse prognosis from localized prostate cancer and develop faster resistance, but these results suggest that genetic screening may be strongly encouraged in mCRPC patients as treatment options may differ depending on whether or not they carry the DNA repair mutation(s).

### December 2015

- A total of 559 patients have been enrolled on the study across all five sites and 301 patients have been successfully sequenced. This was the largest collection of genomic data on mCRPC patients to date.
- The Team reported that prostate cancer patients with specific mutations in genes involved in a process called DNA repair respond well to a drug called Olaparib (currently FDA approved to treat ovarian cancer).
- The team continued focused efforts on patients that have failed or progressed on therapies to find out how resistance occurs and what biomarkers doctors can be used to identify resistant tumors.
- The genomic data from 150 metastatic prostate cancer samples was shared to the public via a web-based platform called cBioPortal ([cbioportal.org](http://cbioportal.org)).
- Bone metastases analyses in patients enrolled in drug studies were performed, with 70-80% of bone biopsies containing tumor cells. These tumor cells were used for genomic analyses.

### June 2015

- Continued patient enrollment in clinical trials and the analysis of samples.
- Conducted an initial analysis of the first 150 patients' tumor samples. The Team has found the following:



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- Several, diverse genetic changes in advanced CRPC tumor samples, some of which are plausibly responsible for tumor progression.
- 89% of patients with CRPC had tumor cell changes that may be good targets for treatment.
- This work was published in a high impact journal, *Cell*.
- The Team's efforts thus far have resulted in the largest collection of genomic data on mCRPC patients to date, that will lead to improved understanding of the biological basis as well as clinical management of CRPC.

### December 2014

- Enrolled over 348 patients in clinical trials, from which 234 patients' tumors have been successfully characterized.
- Conducted an initial analysis of the first 150 patients' samples.
  - Identified a diversity of molecular alterations in advanced castration-resistant prostate cancer, a number of which are plausibly responsible for tumor progression.
- Generated the largest collection of genomic data on metastatic castration-resistant prostate cancer patients to date.

### June 2014

- Of the 189 patients enrolled in clinical trials, 126 patient samples' tumors have been sequenced.
- Results from these sequencing efforts revealed that two genes (called TP53 and FLT4) are frequently mutated, and confirmed the known status of Androgen Receptor gene amplifications.
- Continued development of mouse models for CRPC and testing treatment agents using these models.
- Continued improvements to the process for collecting patient's samples.
- Discovered new changes in cellular pathways that may have immediate implications for patients who harbor specific mutations.

### December 2013

During the first year, the Dream Team laid the foundation for executing their proposed studies.

- All 5 clinical sites continued to enroll patients, and collect and process patient tumor samples.



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- Preliminary data from sequencing patients' tumors suggested that there may be common genetic changes in castration resistant prostate cancer.
- Clinical data indicated that PARP inhibitors may be beneficial to treat CRPC patients with BRCA mutations.
- Olaparib works well against sporadic advanced prostate cancer. Efforts were made to define the tumor characteristics of responding patients.
- Response to ABT-888/Abiraterone was observed. Further analyses needed to be done to determine if response is related to specific genetic changes (TMPRSS2/ERG rearrangements).

### February 2013

- All 5 clinical sites secured regulatory approval and enrolled patients;
- A unified and efficient pipeline for collecting and processing patient tumor samples has been established;
- On the basis of certain mutations identified in patient tumor samples, seven patients were directed to participate in a specific Phase II clinical trial -- one comparing treatment with abiraterone together with the investigational drug ABT888 (also known as veliparib) or abiraterone alone; and
- The Dream Team also conducted preclinical studies in mice to elucidate the mechanisms of resistance to treatment with either abiraterone or enzalutamide (Xtandi).