Team Progress Updates

SU2C–Prostate Cancer Foundation Prostate Dream Team:
"Targeting Adaptive Pathways in Metastatic Castration-Resistant Prostate Cancer"

Prostate cancer, the most commonly diagnosed cancer among men in North America, is generally treated with hormonal therapy. If the cancer spreads to other sites in the body and no longer responds to hormonal therapy, it is called metastatic castration-resistant prostate cancer (mCRPC). It is treated with drugs such as abiraterone acetate and enzalutamide, which target androgen function, and docetaxel and cabazitaxel, which target microtubule dynamics.

Unfortunately, nearly all patients with mCRPC develop resistance to these treatments, resulting in significant pain, suffering, and death. The goal of this Dream Team is to improve the outcomes for men with mCRPC who are no longer responsive to treatment by understanding the causes of resistance, and developing treatments to overcome them.

Led by Eric Small, MD, and Owen Witte, MD, the team has explored the idea that resistance is a result of the prostate cancer cells using common cellular responses, called adaptive pathways, to escape current therapies. Team members believe that by identifying these pathways and inhibiting them, they will be able to overcome treatment resistance and profoundly improve survival and quality of life for patients.

The team reported the following progress:
Over 48 months of funding, through 5 clinical sites, the Team enrolled 245 patients, and procured 300 distinct metastatic biopsies either at the time of enrollment or after the patient has progressed on subsequent therapies.

The Team studied samples from patients who were treated with enzalutamide. By doing so, they found that blocking a protein called CREB1 can slow down the growth of resistant cells.

The Team characterized resistance to treatment as a phenomenon linked to preexisting stem-like cells in prostate cancer patients. This characterization is key to devising strategies to inhibit the growth of these stem-like cells.

The team also developed a potential method of detecting the onset of resistance through blood samples. They observed that the DNA in patients who became resistant to enzalutamide, olaparib, and talazoparib contained mutations or changes, especially in genes that are involved in repairing the DNA. Not only did the Team isolate the DNA from the blood of the patients, but they also obtained circulating tumor cells (CTCs), which are tumor cells present in the circulatory system. They found that studying the androgen receptor gene in these CTCs is like studying the androgen receptor gene in biopsies. An increase in the number of copies of the androgen receptor gene in these CTCs signals that the patients are not responding to therapy. The possibility that blood samples from

patients can be used to more easily identify whether a patient is becoming resistant to therapy means that patients would not have to have more invasive biopsies. Because blood samples are easier to obtain, it would be easier to monitor a patient's response to therapy than having to undergo surgery to obtain biopsies.

Another important goal of the Dream Team was to conduct molecularly guided clinical trials that are based on the understanding of the mechanisms behind development of drug resistance. One of these mechanisms is autophagy, in which the cell gets rid of certain components to refresh itself and improve its ability to survive. Given that cells may undergo autophagy to protect themselves from being killed by enzalutamide, the Team conducted a clinical trial where patients were treated with a drug that inhibits the autophagy process, plus enzalutamide.

The Team also observed that the ERK protein is hyperactivated in samples of metastatic prostate cancer. They have initiated a Phase II clinical trial where patients who have become resistant to enzalutamide or abiraterone would be treated with a drug inhibiting a related pathway.