COncurrent adMinistration of Bipolar Androgen Therapy and nivolumab in men with metastatic Castration-Resistant Prostate Cancer [COMBAT-CRPC]

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Background: Androgen deprivation therapy (ADT) is the backbone of treatment for metastatic prostate cancer, and while ADT is initially highly effective, prostate cancers invariably adapt to a low-testosterone environment, leading to castration resistance. However, a paradoxical inhibition of cell growth has been observed in both androgen-sensitive and CRPC cell lines following the addition of high-dose testosterone. We have conducted several clinical trials investigating a mode of supraphysiologic testosterone therapy termed Bipolar Androgen Therapy (BAT), in which testosterone levels are rapidly driven to the supraphysiologic range followed by a return to near-castrate levels over 28-day treatment cycles with favorable results. We have observed intriguing tumor responses in 2 mCRPC patients with intact DNA repair processes (*i.e.* no repair gene mutations) that were treated sequentially (on two different trials) with BAT followed by PD-1 inhibition, and achieved dramatic PSA/RECIST responses to PD-1 blockade. Based on these preliminary data, we believe that further study of BAT with PD-1 inhibition is warranted.

Methods/Results: Forty-four (44) CRPC patients will receive 12-weeks of BAT monotherapy followed by combination treatment with BAT plus Nivolumab. This BAT lead-in will result in DNA damage and genomic instability, leading to neoantigen formation, and increased sensitivity to PD-1 blockade. Both tumor tissue and circulating cell-free tumor DNA (ctDNA) will be prospectively collected and molecularly characterized from patients. We expect that bi-allelic loss of DNA repair genes will associate with high mutational burden and increased responses to BAT plus Nivolumab.

Conclusions: We are conducting a biomarker-rich Phase II clinical trial investigating BAT in combination with immune checkpoint inhibition. If successful, we will better understand the mechanism of action of BAT alone as well as determining the role of BAT in priming the response to nivolumab.

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