A Single Arm, Open Label Phase II trial of Bipolar Androgen Therapy in Men with Metastatic Castration Resistant Prostate Cancer (mCRPC): A Comparison of Post-Abiraterone vs. Post-Enzalutamide Patients. (RESTORE TRIAL)

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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 castration resistant prostate cancer 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 previously reported the efficacy of BAT in mCRPC patients that were progressing on enzalutamide. In this study, we compared the effect of BAT in mCRPC patients whose last therapy was abiraterone vs. enzalutamide. In addition, we examined the benefit of abiraterone or enzalutamide rechallenge after progression on BAT.

Methods/Results: Fifty-seven (57) mCRPC patients (n=28 post abiraterone; n=29 post enzalutamide) were enrolled and received at lease one dose of BAT monotherapy, 400mg intramuscularly every 28 days. The co-primary endpoints were a 50% decline in PSA from baseline (PSA50) for BAT and for enzalutamide/abiraterone rechallenge. 5/28 (17.9%) of post-abiraterone patients compared to 9/29 (31%) in the post enzalutamide group achieved a PSA50 response (P=0.35). Post BAT rechallenge with abiraterone (n=19) or enzalutamide (n=22) resulted in a PSA50 response rate of 15.8% (n=3/19) and 68.2% (n=15/22), respectively (P=0.001). The total duration of benefit (i.e. PFS on BAT + PFS on rechallenge = "PFS2") was significantly longer in the post enzalutamide vs. post-abiraterone patients – 12.75 months vs. 8.125 months; P=0.04.

Conclusions: BAT may be an effective treatment strategy for men with mCRPC. We observed a non-significant increase in PSA50 response to BAT in patients progressing on enzalutamide compared to abiraterone. Interestingly, rechallenge with enzalutamide following BAT induced a significantly higher PSA50 response rate compared to abiraterone rechallenge. Our data suggest that BAT may be more effective at resensitizing mCRPC to direct AR antagonists compared to abiraterone. Further clinical study is warranted.

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