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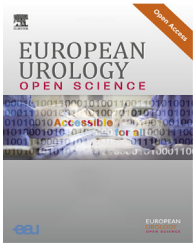

European Association of Urology

Brief Correspondence

Clinical Efficacy of Bipolar Androgen Therapy in Men with Metastatic Castration-Resistant Prostate Cancer and Combined Tumor-Suppressor Loss

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Abstract

Bipolar androgen therapy (BAT) relies on oscillating levels of serum testosterone as a way to treat patients with metastatic castration-resistant prostate cancer (mCRPC). Aggressive-variant prostate cancers typically require combination chemotherapy and are frequently associated with loss-of-function mutations in tumor suppressor genes. Here we report clinical outcomes after BAT among patients with mCRPC harboring pathogenic alterations in at least two of three genes: *TP53*, *PTEN*, and *RB1*. In this setting, BAT induced a meaningful PSA_{50} response rate, progression-free survival and overall survival, particularly in patients without prior chemotherapy.

Patient summary: Bipolar androgen therapy, in which drugs are used to raise testosterone levels and then allow them to decrease again in a cycle, may be a safe and effective treatment for prostate cancer that is resistant to testosterone suppression and has mutations in tumor suppressor genes. A randomized study comparing this approach to chemotherapy is needed to confirm the findings.

Bipolar androgen therapy (BAT) is an emerging treatment strategy for patients with metastatic castration-resistant prostate cancer (mCRPC). During BAT, serum testosterone is cycled from supraphysiologic down to near-castrate levels every month [1]. Multiple clinical trials have demonstrated the benefit of BAT as a single-agent strategy and its ability to resensitize patients to prior novel androgen receptor (AR)-targeted therapies [2,3].

Treatment resistance to AR-targeted therapies occurs through a variety of mechanisms, including lineage plasticity, a process by which the prostate cancer undergoes a series of molecular events resulting in less reliance on AR signaling [4]. Loss-of-function mutations in tumor suppressor genes have been associated with lineage plasticity and the emergence of neuroendocrine prostate cancers or other AR-indifferent cancers. Thus, the presence of at least two mutations in *TP53*, *RB1*, and/or *PTEN* has been proposed as a prognostic biomarker associated with aggressive prostate cancer variants [5]. These aggressive-variant prostate cancers are largely resistant to AR-targeted therapies, but

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may respond favorably to taxane and platinum doublet chemotherapy [6,7].

Even though prostate-specific antigen (PSA) production is directly stimulated by testosterone, we have shown that BAT can induce deep PSA responses in some patients with mCRPC harboring inactivating *TP53* or DNA-repair gene mutations [8]. Given the efficacy of BAT in *TP53*-mutated mCRPC, we hypothesized that BAT may yield a clinical benefit in prostate cancers with an AR-indifferent phenotype, which would address an unmet medical need.

We identified 22 patients with aggressive-variant mCRPC, defined as inactivating mutations or genomic loss in at least two of three specific genes (*TP53*, *RB1*, and/or *PTEN*), identified via clinical-grade next-generation DNA sequencing or immunohistochemistry (IHC) of either a primary or metastatic tumor. These patients were treated with testosterone cypionate 400 mg intramuscularly every 28 d in one of three prospective clinical trials (NCT02090114, NCT03554317, and NCT02286921). All patients were also maintained on luteinizing hormone–releasing hormone agonist/antagonist therapy if not surgically castrated. Treatment status for mCRPC ranged from treatment-naïve to heavily pretreated patients with multiple novel AR-targeted therapies in addition to taxane chemotherapy. Here we report the clinical efficacy of BAT in terms of the PSA_{50} response rate (≥50% decline from baseline) and composite progression-free survival (PFS, defined as the first of either radiographic or clinical progression), and overall survival (OS). A full description of clinical and pathologic characteristics is provided in the supplement.

The PSA_{50} response rate in the cohort was 45.5% (n = 10/22; 95% confidence interval [CI] 24.4–67.8%; Fig. 1). An additional two patients experienced a decline in PSA from baseline that did not reach the PSA_{50} threshold (PSA_{any} = 54.5%; n = 12/22). All patients who experienced PSA reductions on BAT had a pathogenic *TP53* mutation (while no PSA reductions were observed in patients with combined *PTEN*/*RB1* inactivation). No patients in this cohort had mutations in all three genes of interest. Interestingly, two patients who were previously resistant to enzalutamide were rechallenged following BAT. Both patients experienced a PSA_{50} response to enzalutamide retreatment. To better understand the duration of benefit, we estimated the median PFS on BAT, which was 4.8 mo (95% CI 2.8–8.5; Fig. 2A). Since this was a heterogeneous population with respect to prior therapies, we also assessed the effect of prior chemotherapy on PFS. Patients who received prior taxane chemotherapy had a shorter median PFS in comparison to chemotherapy-naïve patients (8.4 vs 3.6 mo; log-rank p = 0.04; Fig. 2B). The median OS estimate for the whole cohort was 34 mo (95% CI 15–not reached; Fig. 2C). Similarly, patients without prior chemotherapy had a longer median OS in comparison to taxane-treated patients (38 vs 15.1 mo; log-rank p = 0.04; Fig. 2D).

In a randomized trial, Corn et al [7] compared carboplatin in combination with cabazitaxel versus cabazitaxel alone in men with mCRPC. A post hoc analysis revealed that patients with alterations in at least two of *TP53, PTEN*, and *RB1*, determined via circulating tumor DNA or IHC analysis, had an estimated PFS of 2.2 mo with cabazitaxel alone versus 6.0 mo with carboplatin-cabazitaxel (p = 0.0003). OS (17.4 vs 9.9 mo; p = 0.002) favored the carboplatin-cabazitaxel arm in this cohort with combined tumor-suppressor losses. In a separate study, an OS of ∼14 mo was observed for patients with $TP53^{-}/RB1^{-}$ mCRPC at the start of novel AR-targeted therapy [9]. The median OS approached 3 yr following treatment with BAT in our analysis, suggesting potential long-term benefits in comparison to these prior studies. Similar to the study by Corn et al [7], our patient population was heavily pretreated, with chemotherapy-naïve patients experiencing the most favorable outcomes. Although chemotherapy remains the mainstay of treatment for this aggressive subtype of prostate cancer, grade ≥3 adverse events, including fatigue (20%) and neutropenia (16%), were observed with combination chemotherapy. In the largest randomized clinical trial using BAT, the majority of adverse events were of low grade (grade <2) [2]. Our data suggest that BAT may induce clinically meaningful responses in aggressive-variant prostate cancers with a more favorable safety profile in comparison to a taxane/platinum doublet. Although anecdotal, the observation that two patients achieved PSA responses to enzalutamide rechallenge suggests that BAT has potential for resensitization to novel AR-targeted therapies.

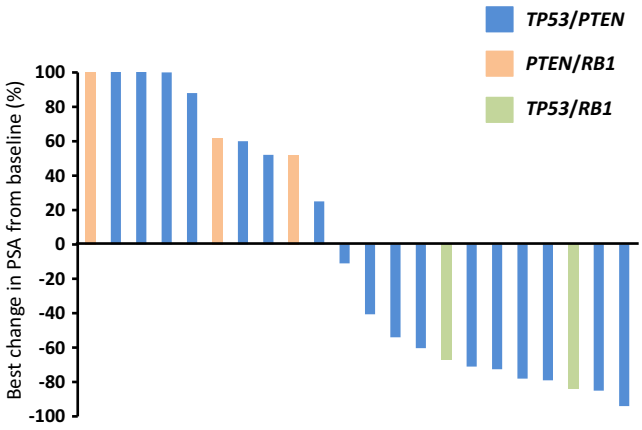

Fig. 1 – Waterfall plot of prostate-specific antigen (PSA) response in patients with androgen receptor–indifferent metastatic castration-resistant prostate cancer treated with bipolar androgen therapy. The best change in PSA from baseline is shown for each patient stratified by molecular profile. The PSA_{50} response rate was estimated at 45.5%.

Several limitations of this analysis should be addressed. (1) The number of patients is small. The confidence intervals for the PFS and OS estimates are wide and broad conclusions are not prudent. (2) There was random sampling of patients. The data come from a small number of patients across different clinical trials for whom clinical-grade molecular analyses were available. It is likely that other patients in these studies may have had the requisite molecular profile. This approach may have led to unintended bias in the study. (3) We did not identify any patients with neuroendocrine features on pathology. Pathology review was conducted on archived tissue and may not have detected neuroendocrine transformation in late-stage disease. (4) The study includes patient with a molecular profile detected via IHC or next-generation sequencing. It is possible that

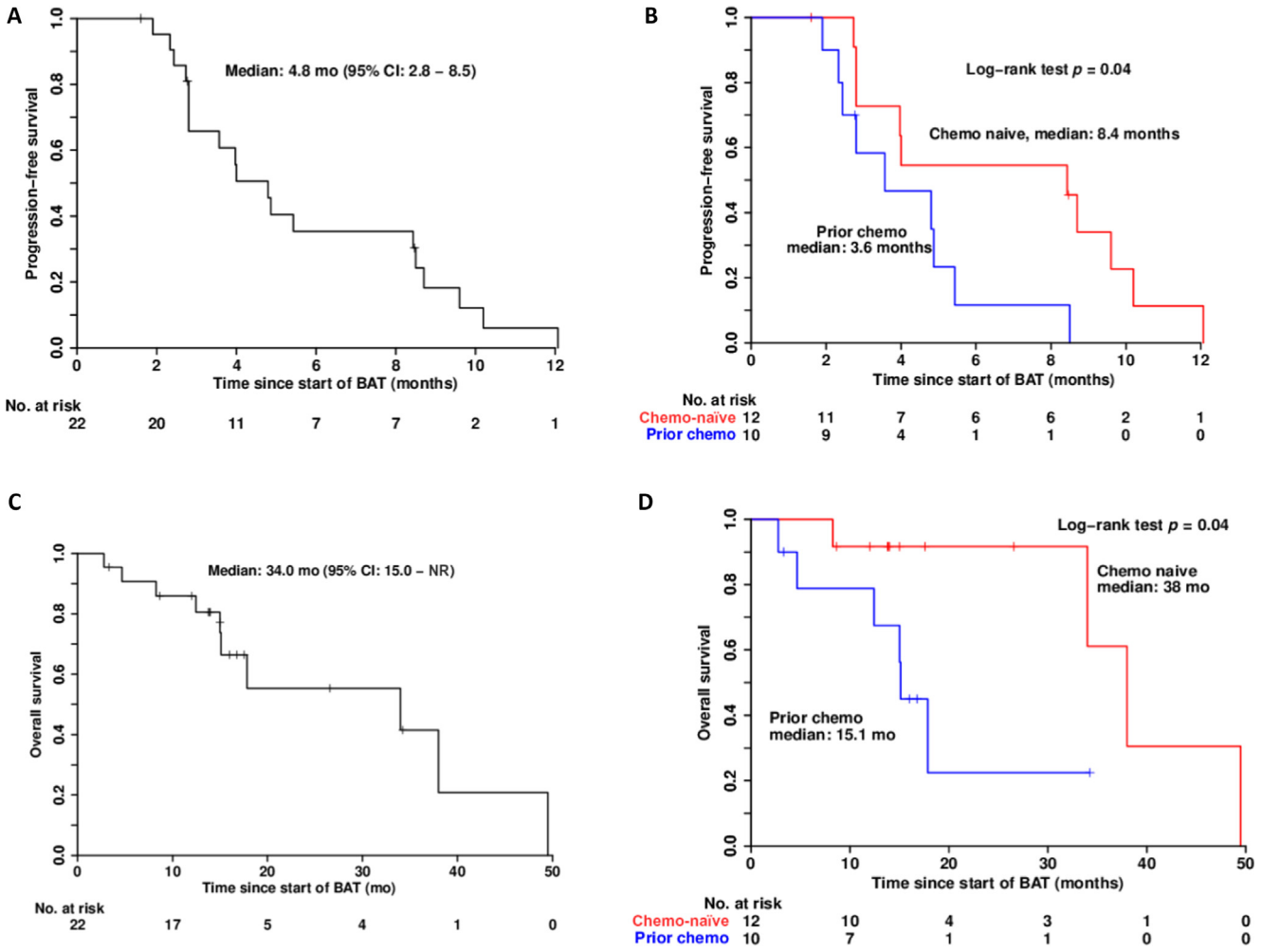

Fig. 2 – Progression-free survival (PFS) and overall survival (OS) on bipolar androgen therapy. Kaplan-Meier estimates of (A) composite PFS in the entire cohort and (B) PFS stratified by prior chemotherapy exposure. PFS was longer for chemotherapy-naïve patients (red) than for patients treated with prior taxane-based chemotherapy (blue): 8.4 mo (95% CI 2.8–NR) versus 3.6 mo (95% CI 1.9–NR); log-rank *p* = 0.04. Kaplan-Meier estimates of (C) OS in the entire cohort and (D) OS stratified by prior chemotherapy exposure. OS was longer for chemotherapy-naïve patients (red) than for patients treated with prior taxane-based chemotherapy (blue): 38 mo (95% CI 34–NR) versus 15.1 mo (2.8–NR); log-rank *p* = 0.04. chemo = chemotherapy; CI = confidence interval; NR = not reached.

clinical benefit may have been differentially affected by the technique used for eligibility. (5) The study is not randomized. Corn et al. [7] reported significant PFS and OS differences across different treatment paradigms using the carboplatin-cabazitaxel combination. Although our PSA response rates and PFS and OS estimates suggest preliminary efficacy, a randomized study with BAT is necessary to derive further conclusions.

Our findings suggest that BAT may have a role in treatment of an aggressive molecular phenotype of mCRPC characterized by combined tumor-suppressor losses. Given the tolerability of BAT in comparison to combination chemotherapy, more patients may be eligible for this unique treatment paradigm. Further study of BAT in this clinical setting is warranted.

Author contributions: Mark C. Markowski had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Markowski, Wang, De Marzo, Schweizer, Antonarakis, Denmeade.
Acquisition of data: Markowski, Schweizer, Denmeade.
Analysis and interpretation of data: Markowski, Wang, De Marzo, Schweizer, Antonarakis, Denmeade.
Drafting of the manuscript: Markowski, Antonarakis.
Critical revision of the manuscript for important intellectual content: Markowski, Wang, De Marzo, Schweizer, Antonarakis, Denmeade.
Statistical analysis: Wang.
Obtaining funding: Markowski, Denmeade, Antonarakis.
Administrative, technical, or material support: Markowski.
Supervision: Antonarakis, Denmeade.
Other: None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.euros.2022.05.006.

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