

Brief Correspondence

Clinical Outcomes from Androgen Signaling–directed Therapy after Treatment with Abiraterone Acetate and Prednisone in Patients with Metastatic Castration-resistant Prostate Cancer: Post Hoc Analysis of COU-AA-302

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Abstract

In the COU-AA-302 trial, abiraterone acetate plus prednisone significantly increased overall survival for patients with chemotherapy-naïve metastatic castration-resistant prostate cancer (mCRPC). Limited information exists regarding response to subsequent androgen signaling–directed therapies following abiraterone acetate plus prednisone in patients with mCRPC. We investigated clinical outcomes associated with subsequent abiraterone acetate plus prednisone (55 patients) and enzalutamide (33 patients) in a post hoc analysis of COU-AA-302. Prostate-specific antigen (PSA) response was assessed. Median time to PSA progression was estimated using the Kaplan–Meier method. The PSA response rate ($\geq 50\%$ PSA decline, unconfirmed) was 44% and 67%, respectively. The median time to PSA progression was 3.9 mo (range 2.6–not estimable) for subsequent abiraterone acetate plus prednisone and 2.8 mo (range 1.8–not estimable) for subsequent enzalutamide. The majority of patients (68%) received intervening chemotherapy before subsequent abiraterone acetate plus prednisone or enzalutamide. While acknowledging the limitations of post hoc analyses and high censoring ($>75\%$) in both treatment groups, these results suggest that subsequent therapy with abiraterone acetate plus prednisone or enzalutamide for patients who progressed on abiraterone acetate is associated with limited clinical benefit.

Patient summary: This analysis showed limited clinical benefit for subsequent abiraterone acetate plus prednisone or enzalutamide in patients with metastatic castration-resistant prostate cancer following initial treatment with abiraterone acetate plus prednisone. This analysis does not support prioritization of subsequent abiraterone acetate plus prednisone or enzalutamide following initial therapy with abiraterone acetate plus prednisone.

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The clinical benefit of abiraterone acetate plus prednisone (hereafter referred to as AA) has been demonstrated in patients with metastatic castration-resistant prostate cancer (mCRPC) [1,2], although acquired resistance to AA treatment remains a clinical challenge, be it primary resistance to AA noted at study initiation [3] or secondary drug resistance via upregulation of CYP-17A1, androgen receptor (AR) overexpression, AR splice variants, or other mechanisms [4]. Limited information exists regarding response to subsequent androgen signaling-directed therapies following AA treatment. Androgen signaling-directed therapies such as AA and enzalutamide (ENZ), which inhibit the biosynthesis of androgens [5] and the AR [6], respectively, initially extend survival in chemotherapy-naïve patients with mCRPC [2,7], but may be subject to cross-resistance because of the shared targeted signaling pathway. Although acquired resistance to either AA or ENZ treatment does not preclude a response to the other agent, previous small studies suggest that sequential administration of androgen signaling-directed therapy is associated with limited response rates and brief duration of response for mCRPC patients [8,9]. Thus, we conducted a post hoc analysis of data on subsequent AA or ENZ therapy in AA-treated patients from the COU-AA-302 trial.

COU-AA-302 (NCT00887198) was a phase 3, multinational, randomized, double-blind, placebo-controlled study of AA versus prednisone alone in chemotherapy-naïve patients with mCRPC. Data were collected retrospectively after the third interim analysis of COU-AA-302, source-verified, and entered into the database. Complete prostate-specific antigen (PSA) data were available for 88 patients before and at the time of disease progression on subsequent androgen signaling-directed therapies. The PSA response ($\geq 50\%$ PSA decline) was assessed. The median time to PSA progression with 95% confidence interval was estimated using the Kaplan-Meier method. Further details on the study design and statistical methods are provided in the Supplementary material.

After on-study AA treatment, 55 patients received subsequent AA (AA-then-AA) and 33 patients received subsequent ENZ (AA-then-ENZ) as the first subsequent androgen signaling-directed therapy (Supplementary Table 1). Ten patients (18%) in the AA-then-AA group went on to receive ENZ as a second subsequent androgen signaling-directed therapy; no patients were administered AA after subsequent ENZ. A total of 69% (38/55) of patients in the AA-then-AA group and 67% (22/33) in the AA-then-ENZ group received intervening chemotherapy with docetaxel or cabazitaxel.

Baseline patient characteristics were generally similar between the AA-then-AA and AA-then-ENZ groups (Supplementary Table 2). The median time from initial diagnosis to first dose was longer in patients receiving subsequent ENZ (6 yr) than in those receiving subsequent AA (4 yr).

In COU-AA-302, AA treatment and outcomes were generally similar between the subsequent therapy subgroups, with some differences noted in treatment responses (Supplementary Table 3). The median treatment duration for on-study AA was 11 mo (interquartile range [IQR] 6–14) for the AA-then-AA group and 19 mo (IQR 12–28) for the AA-then-ENZ group. Rates of treatment discontinuation for on-study AA because of adverse events were low in both groups (7% and 3%, respectively). The post-treatment $\geq 50\%$ PSA decline was calculated and observed in 46% (25/55) of patients in the AA-then-AA group and 76% (25/33) of the AA-then-ENZ group.

Responses to subsequent AA or ENZ were associated with modest clinical outcomes (Table 1). The median time to PSA progression on subsequent therapy was 3.9 mo (range 2.6–not estimable [NE]) for the AA-then-AA group and 2.8 mo (range 1.8–NE) mo for the AA-then-ENZ group (Table 1, Fig. 1). Post-treatment $\geq 50\%$ PSA decline, as assessed by the investigator, was the most commonly reported clinical outcome during subsequent therapy (24/55, 44% in the AA-then-AA group and 22/33, 67% in the AA-then-ENZ group).

Table 1 – Outcomes for subsequent AA or ENZ therapy

	AA then AA (n = 55)	AA then ENZ (n = 33)
Exposure to subsequent AA or ENZ therapy		
Median treatment duration, mo (IQR)	4 (2–9)	5 (3–8)
Median time to PSA progression on subsequent therapy ^a , mo	3.9 (2.6–NE)	2.8 (1.8–NE)
Outcomes during subsequent therapy, n (%)	27 (49)	22 (67)
Clinical symptom improvement	10 (18)	4 (12)
Radiographic improvement ^b	1 (2)	1 (3)
$\geq 50\%$ PSA decline	24 (44)	22 (67)
Other	0	1 (3)
Reasons for treatment discontinuation during subsequent therapy ^c , n (%)		
Radiographic progression	10 (18)	5 (15)
Clinical progression	17 (31)	9 (27)
PSA progression only	28 (51)	13 (39)
Adverse event	3 (5)	0
Therapy ongoing	6 (11)	11 (33)
Other	14 (25)	6 (18)

AA = abiraterone acetate plus prednisone; ENZ = enzalutamide; IQR = interquartile range; NE = not estimable; PSA = prostate-specific antigen.

^a Based on Prostate Cancer Working Group 2 criteria.

^b Refers to improvement as assessed by computed tomography, magnetic resonance imaging, or bone scans.

^c Patients could be counted in more than one outcome or reason for discontinuation.

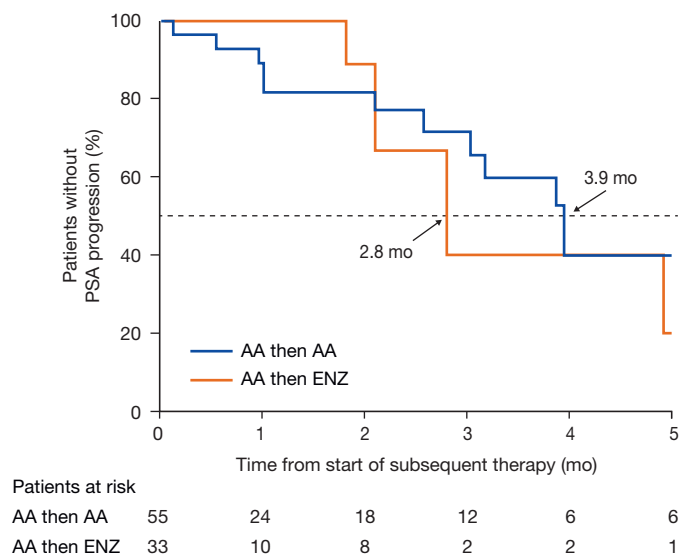


Fig. 1 – Time to PSA progression on subsequent therapy for the AA-then-AA and AA-then-ENZ subgroups. PSA = prostate-specific antigen; AA = abiraterone acetate + prednisone; ENZ = enzalutamide.

In this post hoc analysis of subsequent androgen signaling-directed therapy after AA treatment in patients with chemotherapy-naïve mCRPC, retreatment with AA or subsequent treatment with ENZ was associated with limited clinical benefit as assessed by PSA response and time to PSA progression. The limited clinical benefit observed for ENZ after AA is consistent with a published analysis of this sequence in patients with mCRPC who received prior docetaxel, in which 16 of 35 patients (46%) achieved a >50% decline in PSA and 14 (40%) had a rising PSA as the best response [10]. The response rate in this study by Schrader et al and in the present study suggests partial cross-resistance between AA and ENZ when sequenced.

AA was administered more frequently as the first subsequent androgen signaling-directed therapy when compared to ENZ (63% vs 38% of patients). AA was also more frequently administered than ENZ (63% vs 49% of patients). As the majority of patients (68%) received intervening chemotherapy, the limited clinical benefit observed from subsequent AA and ENZ suggests that chemotherapy did not sensitize the disease to androgen signaling-directed therapy.

The strengths of this analysis include the evaluation of patient data from a global, multicenter, prospective trial, making it the largest reported experience to date regarding subsequent AR-directed therapy after AA treatment. The limitations include the relatively small size of the patient population, high censoring (>75%) in both treatment groups, investigator bias with regard to choice of subsequent therapy, and the retrospective nature of the analysis, which may have been hindered by selection bias, incomplete data reporting, inconsistent use of the response criteria by study investigators, premature discontinuation of subsequent therapy, use of PSA alone to estimate tumor response, as this may overestimate antitumor activity of endocrine agents, and other unknown variables.

In summary, after treatment with AA for mCRPC, retreatment with AA or subsequent treatment with ENZ is associated with limited clinical benefit. These observations support the development of novel approaches to overcoming acquired resistance. Predicting effective strategies that would benefit patients after AA treatment and determining which patients would likely have a therapeutic response remain a challenge.

Author contributions: Matthew R. Smith 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: de Bono, Kheoh, Li, Ryan, Small, Smith, Todd, Saad, De Porre, Yu.

Acquisition of data: de Bono, Fizazi, Li, Saad, De Porre, Rathkopf, Yu.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2017.03.007>.

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