ORIGINAL ARTICLE

Activity of enzalutamide in men with metastatic castration-resistant prostate cancer is affected by prior treatment with abiraterone and/or docetaxel

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BACKGROUND: Enzalutamide and abiraterone are new androgen-axis disrupting treatments for metastatic castration-resistant prostate cancer (mCRPC). We examined the response and outcomes of enzalutamide-treated mCRPC patients in the real-world context of prior treatments of abiraterone and/or docetaxel.

METHODS: We conducted a seven-institution retrospective study of mCRPC patients treated with enzalutamide between January 2009 and February 2014. We compared the baseline characteristics, PSA declines, PSA progression-free survival (PSA-PFS), duration on enzalutamide and overall survival (OS) across subgroups defined by prior abiraterone and/or docetaxel.

RESULTS: Of 310 patients who received enzalutamide, 36 (12%) received neither prior abiraterone nor prior docetaxel, 79 (25%) received prior abiraterone, 30 (10%) received prior docetaxel and 165 (53%) received both prior abiraterone and prior docetaxel. Within these groups, respectively, >30% PSA decline was achieved among 67, 28, 43 and 24% of patients; PSA-PFS was 5.5 (95% CI 4.2–9.1), 4.0 (3.2–4.8), 4.1 (2.9–5.4) and 2.8 (2.5–3.2) months; median duration of enzalutamide was 9.1 (7.3–not reached), 4.7 (3.7–7.7), 5.4 (3.8–8.4) and 3.9 (3.0–4.6) months. Median OS was reached only for the patients who received both prior abiraterone and docetaxel and was 12.2 months (95% CI 10.7–16.5). 12-month OS was 78% (59–100%), 64% (45–90%), 77% (61–97%) and 51% (41–62%). Of 70 patients who failed to achieve any PSA decline on prior abiraterone, 19 (27%) achieved >30% PSA decline with subsequent enzalutamide.

CONCLUSIONS: The activity of enzalutamide is blunted after abiraterone, after docetaxel, and still more after both, suggesting subsets of overlapping and distinct mechanisms of resistance.

INTRODUCTION

Treatment of men with metastatic castration-resistant prostate cancer (mCRPC) has recently undergone unprecedented advances with the Food and Drug Administration approval of six new agents, including abiraterone acetate and enzalutamide. Both are oral agents whose mechanism of action is through interference of the androgen receptor (AR) signaling pathway, an important driver of prostate cancer even in the castration-resistant state. Abiraterone (Janssen Biotech, Horsham, PA, USA) is an inhibitor of CYP-17 lyase, a critical enzyme in synthesis of AR ligands.1 Enzalutamide (Medivation, San Francisco, CA, USA) is an irreversible AR antagonist that also interferes with intracellular AR trafficking and signaling.2 Both have been demonstrated in Phase III trials to provide clinical benefit before and after the initiation of docetaxel chemotherapy.1–4 Given the similarities and differences in mechanisms of action between the two, a key question is what the effect of prior AR-targeted therapy is on the efficacy of subsequent AR-targeted therapy. Several smaller retrospective studies have reported results of enzalutamide treatment after abiraterone5–9 and of abiraterone treatment after enzalutamide.10–12 Together, they suggest reduced response rates of a second AR-targeted agent following a first, which could reflect similar and/or overlapping mechanisms of resistance to these agents.

To more comprehensively understand the activity of enzalutamide, we report the collective therapeutic experience of 310 patients treated with enzalutamide at 7 academic institutions. The primary objective of our study was to describe the effect of prior therapies (specifically abiraterone and docetaxel) on enzalutamide treatment outcomes in real-world clinical practice.

MATERIALS AND METHODS

Patients

The study was performed in accordance with the Declaration of Helsinki of 1975 (as revised in 1983). Following IRB approval at our respective institutions, de-identified clinical data were collected on 310 patients with mCRPC treated with enzalutamide.

We collected the clinical data including: baseline patient and tumor characteristics, clinical and laboratory measurements at start of enzalutamide, prior systemic therapies and duration and response to therapy and reasons for enzalutamide discontinuation (Table 1).

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Endpoints
PSA decline on enzalutamide was defined as the maximum change in PSA relative to the baseline measurement before starting enzalutamide. PSA progression-free survival (PSA-PFS) was time from starting enzalutamide to PSA progression, as defined by Prostate Cancer Working Group 2 (PCWG2) criteria, with other events (including death) censored. Overall survival was time from starting enzalutamide to death from any cause. Patients still on enzalutamide on February 5, 2014, were censored.

Statistics
Baseline characteristics were compared between patients using one-way analysis of variance for continuous variables and \( \chi^2 \)-tests for categorical variables. \( P \)-values < 0.05 were considered statistically significant. Patients achieving >0%, >30%, >50% and >90% PSA declines were compared across subgroups defined by prior treatments and visualized with waterfall plots. PSA-PFS and OS were evaluated using Kaplan–Meier estimation stratified by prior treatments, which were compared using log-rank tests, incomplete case analyses.

RESULTS
Patient characteristics
We collected data from 310 men with mCRPC treated with enzalutamide between January 2009 and February 2014. Patient characteristics at diagnosis and at initiation of enzalutamide are shown in Table 1. 36 (12%) received neither prior abiraterone nor prior docetaxel ('Abi+Doce-Naive'), 79 (25%) received prior abiraterone ('Prior-Abi'), 30 (10%) received prior docetaxel ('Prior-Doce') and 165 (53%) received prior abiraterone and prior docetaxel ('Prior-Abi+Doce').

Table 1. Patient demographics

|                      | All N=310 | Abi+Doce-Naïve N=36 | Prior-Abi N=79 | Prior-Doce N=30 | Prior-Abi+Doce N=165 |
|----------------------|-----------|---------------------|---------------|----------------|---------------------|
| **PSA at diagnosis** | Mean 266  | Min-max 0.2–20400 | Mean 67 1.2–706 | Mean 196 0.2–5800 | Mean 892 2.5–20400 | Mean 242 1.3–7500 |
| **Age at start of enza** | Mean 64   | Min-max 40–90 | Mean 64 47–79 | Mean 66 47–90 | Mean 61 40–75 | Mean 62 43–87 |
| **Years since diagnosis at start of enza** | Mean 8.4  | Min-max 0.6–27 | Mean 7.9 0.8–20 | Mean 9 0.6–27 | Mean 8.4 0.9–23 | Mean 8 1.2–23 |
| **Labs at start of enza** | Mean 246 | Min-max 0.3–3600 | Mean 76 0.3–393 | Mean 208 1.8–3600 | Mean 219 4.7–2109 | Mean 306 0.8–2560 |
| PSA                   | Mean 3.8  | Min-max 1.8–4.9 | Mean 4.1 3.3–4.8 | Mean 3.9 2.5–4.6 | Mean 3.7 2.7–4.9 | Mean 3.7 1.8–4.6 |
| Albumin               | Mean 227  | Min-max 10–7420 | Mean 167 35–1701 | Mean 213 10–1233 | Mean 181 45–875 | Mean 256 37–7420 |
| Alkaline phosphatase  | Mean 11.8  | Min-max 7.2–15.6 | Mean 12.4 9.9–15.4 | Mean 11.9 7.2–14.8 | Mean 11.9 8.2–15.6 | Mean 11.5 7.4–15.5 |
| Hemoglobin            | Mean 295  | Min-max 79–1929 | Mean 355 142–520 | Mean 273 95–717 | Mean 334 157–1294 | Mean 290 79–1929 |
| **Gleason at diagnosis** | Count 24  | % 8% | Count 2 6% | Count 1 13% | Count 2 7% | Count 10 6% |
| <7                   | Count 81 | % 26% | Count 12 33% | Count 21 27% | Count 9 30% | Count 39 24% |
| >7                   | Count 173  | % 56% | Count 22 61% | Count 42 53% | Count 15 50% | Count 94 57% |
| Unknown               | Count 32  | % 10% | Count 0 0% | Count 6 8% | Count 8 6% | Count 22 13% |
| **ECOG performance status at start of enzalutamide** | Count 77  | % 25% | Count 12 33% | Count 24 30% | Count 5 17% | Count 36 22% |
| 0                    | Count 128  | % 41% | Count 20 56% | Count 28 35% | Count 10 33% | Count 70 42% |
| 1                    | Count 55  | % 18% | Count 2 6% | Count 12 15% | Count 10 33% | Count 31 19% |
| 2                    | Count 14  | % 5% | Count 2 6% | Count 6 8% | Count 1 3% | Count 7 4% |
| Unknown               | Count 36  | % 12% | Count 0 0% | Count 9 11% | Count 4 3% | Count 21 13% |
| **Sites of metastases at start of enza** | Count 144 | % 46% | Count 18 50% | Count 43 54% | Count 14 47% | Count 69 42% |
| Bone only | Count 91 | % 29% | Count 11 31% | Count 20 25% | Count 8 27% | Count 52 32% |
| Lymph node only       | Count 17 | % 6% | Count 3 8% | Count 8 10% | Count 3 10% | Count 3 2% |
| Any liver             | Count 3 | % 1% | Count 0 0% | Count 0 0% | Count 0 0% | Count 3 2% |
| Any lung              | Count 23 | % 7% | Count 1 27% | Count 5 6% | Count 2 7% | Count 15 9% |
| Other                 | Count 16 | % 5% | Count 3 8% | Count 3 4% | Count 3 10% | Count 9 5% |
| **Prior abiraterone** | Count 244 | % 79% | Count 0 0% | Count 79 100% | Count 0 0% | Count 165 100% |
| No                   | Count 66  | % 21% | Count 36 100% | Count 0 0% | Count 30 100% | Count 0 0% |
| **Prior docetaxel**   | Count 195 | % 63% | Count 0 0% | Count 0 0% | Count 30 100% | Count 165 100% |
| No                   | Count 115 | % 37% | Count 36 100% | Count 36 100% | Count 0 0% | Count 0 0% |
| **Steroids at start of enza** | Count 120 | % 39% | Count 1 3% | Count 43 54% | Count 9 30% | Count 65 39% |
| No                   | Count 182 | % 59% | Count 23 64% | Count 33 42% | Count 21 70% | Count 95 58% |
| Unknown               | Count 8  | % 3% | Count 3 33% | Count 3 4% | Count 0 0% | Count 5 3% |

Abbreviation: ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase. *46/310 (15%) patients had received second line or second course of chemotherapy, 6 in the Prior-Doce group and 40 in the Prior-Abi-Doce group.
docetaxel (‘Prior-Abi+Doce’). The breakdown of patients comprising each group per site are shown in Supplementary Figure 1.

Fifteen percent (46/310) of patients had received a second line/course of chemotherapy prior to enzalutamide (38 cabazitaxel, 8 second course of docetaxel) with 6 in the Prior-Doce group and 40 in the Prior-Abi+Doce group. Patients who received two lines of prior chemotherapy were similar in our analyses to patients who received one line of prior docetaxel (data not shown), so they were combined into the same group for simplicity.

At the time of starting enzalutamide, the patients who had received more lines of prior treatment (Prior-Abi+Doce, Prior-Doce, Prior-Abi) generally had clinical characteristics associated with worse outcomes compared with patients who had fewer lines of prior treatment (Abi+Doce-Naive) (Table 1).14–16 In addition, 59% (182/310) were not taking steroids at start of enzalutamide (data not shown), so they were combined into the same group for simplicity.

Enzalutamide treatment delivered
At data lock, 101 (33%) of the 310 patients were still receiving enzalutamide and 209 (67%) had stopped. Median duration of therapy in the Abi+Doce-Naive group was 9.1 months (95% CI 7.3–not reached), in the Prior-Abi group was 4.7 months (3.7–7.7), in the Prior-Doce group was 5.4 months (3.8–8.4), and in the Prior-Abi+Doce group was 3.9 months (3.0–4.6). Of the 209 patients who stopped enzalutamide, 200 (96%) stopped because of progression of the disease with 27 (14%) because of symptomatic progression only, 25 (13%) because of PSA progression only and the remaining 143 (72%) because of more than one measure of progression. No patients were reported to have discontinued enzalutamide due to radiographic progression only. Eight patients discontinued enzalutamide due to toxicity only and one due to financial reasons.

PSA decline resulting from enzalutamide treatment
In the Abi+Doce-Naive group (N = 36), 24 (67%) achieved ≥30% PSA decline (PSA30) and 21 (58%) achieved ≥50% PSA decline (PSA50) (Figure 1a). In the Prior-Abi group (N = 79), 22 (28%) achieved PSA30 and 14 (18%) achieved PSA50 (Figure 1b). In the Prior-Doce group (N = 30), 13 (43%) achieved PSA30 and 9 (30%) achieved PSA50 (Figure 1c). In the Prior-Abi+Doce group (N = 165), 40 (24%) achieved PSA30 and 28 (17%) achieved PSA50 (Figure 1d).
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PSA progression-free survival and overall survival
We evaluated PSA-PFS for all 310 patients and OS for 302 patients with complete vital status information. Although there was no mandated interval of PSA monitoring, the average time between measurements at the seven sites ranged 3.0–4.9 weeks. Mean PSA-PFS in the Abi+Doce-Naive group was 5.5 months (95% CI 4.2–9.1), in the Prior-Abi group was 4.0 months (3.2–4.8), in the Prior-Doce group was 4.1 months (2.9–5.4) and in the Prior-Abi+Doce group was 2.8 months (2.5–3.2), (Figure 2a, \(P=0.0004\)).

Median OS was reached only for patients in the Prior-Abi+Doce group and was 12.2 months (95% CI 10.7–16.5) (Figure 2b, \(P=0.008\), log-rank test). Because OS end points had not been met in all groups, we also evaluated 12-month OS, which was 78% (59–100%), 64% (45–90%), 77% (61–97%), and 51% (41–62%) for the groups, respectively.

Graded PSA responses to prior abiraterone and subsequent enzalutamide
To explore the relationship between PSA declines on abiraterone and subsequent enzalutamide, we tabulated patients who received both treatments and for whom complete PSA response data to both was available (Table 2). Of 70 patients who failed to achieve any PSA decline on prior abiraterone, 35 (50%) achieved any PSA decline on subsequent enzalutamide. Of 109 patients who achieved no detectable PSA response to prior abiraterone, 56 (51%) achieved no PSA decline on subsequent enzalutamide, indicating that response to prior abiraterone does not necessarily associate with response to subsequent enzalutamide. Conversely, of 109 patients who achieved PSA50 on prior abiraterone, 56 (51%) achieved no PSA decline on subsequent enzalutamide, suggesting these patients had primary resistance to both agents (as defined by failure to achieve any PSA decline).

DISCUSSION
Our study represents a large, multicenter retrospective study that likely captures greater heterogeneity in patient characteristics and physician practice patterns than previous reports, and thus arguably serves as a more robust examination of the activity of enzalutamide in the ‘real world’.

These results are notable when compared with the Phase III AFFIRM and PREVAIL trials and clearly demonstrate that the activity of enzalutamide is attenuated by prior abiraterone and, to a lesser extent, docetaxel chemotherapy (Table 3).\(^3\) In addition, the observed response rates in our study were less than in the comparable patient populations of AFFIRM (post-docetaxel, abiraterone-naïve) and PREVAIL (pre-docetaxel, abiraterone-naïve), perhaps in part due to more advanced disease in our population (Supplementary Table 1). This may follow the observation that real life results in clinical practice are often not as pronounced as in prospective clinical trials.

Our results also suggest that, compared to the abiraterone- and docetaxel-naïve context, the effect of prior docetaxel attenuates PSA response to enzalutamide, and the effect of prior abiraterone attenuates PSA response still further. However, the effect of prior docetaxel and prior abiraterone is comparable to the effect of prior abiraterone alone on enzalutamide activity. This implies more overlap in resistance between abiraterone and enzalutamide than between docetaxel and enzalutamide. These mechanisms of resistance are being actively studied, and are discussed in further detail below.

Even among patients in the Prior-Abi+Doce group, nearly a quarter achieved PSA50 with subsequent enzalutamide, indicating that prior treatment does not preclude a PSA response to enzalutamide. However, in this context, median duration of enzalutamide was <4 months, emphasizing the need for additional treatment options.

Our study is limited by its retrospective nature and is therefore subject to patient selection bias, and to nonuniform schedules of PSA and radiographic evaluation, and to nonuniform triggers for changing therapy across sites. Thus, our study was largely limited to PSA response and PSA-PFS and OS as end points, and it was not feasible to analyze radiographic PFS as an end point. The differences we observed in overall survival between the four groups, although ostensibly statistically significant, are likely a result of differences in lines of prior therapy as suggested by differences in baseline prognostic characteristics (Table 1).\(^14\) Hence, our results should not be interpreted as a measure of treatment

![Kaplan–Meier survival curves of (a) PSA-progression-free survival (\(P=0.0004\)) and (b) overall survival (\(P=0.008\)) for patients who received enzalutamide (Abi+Doce-Naive), enzalutamide after prior abiraterone (Prior-Abi), enzalutamide after prior docetaxel (Prior-Doce) and enzalutamide after prior abiraterone and docetaxel (Prior-Abi+Doce).](image-url)
effectiveness or recommendation for a particular treatment sequence. A more rigorous evaluation of optimal sequencing would involve comparing the combined duration of therapy of two or three agents in a randomized, prospective fashion.

The mechanisms of resistance to AR-targeted therapy are actively being studied and include: intracellular androgen synthesis by tumor cells,19 signaling via alternative steroid receptors such as the glucocorticoid receptor,20 and amplification of AR and development of AR splice variants such as AR-V7 and AR mutants such as ARF876L.18,19 Evidence also suggests taxanes may act through inhibition of AR signaling such that resistance to taxanes confers cross-resistance to enzalutamide.25,26 Moreover, feedback with other pathways, for example, PI3K, may be important for tumor survival.27 Non-invasive, blood-based assays to detect resistance mechanisms are also being investigated as potential predictive biomarkers.18,28 If these strategies are validated, patients could be monitored for pre-existing and/or development of early resistance, thus paving the way for more refined AR-targeted treatment approaches for men with mCRPC.

In summary, our data serve to illustrate the substantial but incomplete cross-resistance between enzalutamide and abiraterone and, to a lesser extent, between enzalutamide and docetaxel chemotherapy. Our study substantively adds to the growing evidence that tumors of individual patients with mCRPC may have overlapping or distinct mechanisms of resistance to enzalutamide and abiraterone.

**CONFLICT OF INTEREST**

The coauthors declare the following conflicts of interest: AA declares research support from Janssen, Janssen Biotech, Medivation/Astellas and Sanoﬁ-Aventis. BD declares research support and honoraria from Medivation/Astellas. HH declares research support from Medivation/Astellas. KNC is a consultant/advisor to Astellas and is a consultant/advisor for Dendreon, BioMotiv and has equity in Dual Therapeutics. ESA is a consultant/advisor to Medivation/Astellas, Janssen Biotech and Sanofi US. KHC is a consultant/advisor to Janssen Biotech. EYY declares research funding from Bristol-Myers Squibb, Dendreon, GTx, Imclone/Jilly, Janssen and OncoGeneX and honoraria from Bayer, Dendreon, Janssen Biotech, Medivation/Astellas and Sanofi US. All remaining authors have declared no conflicts of interest.

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Supplementary Information accompanies the paper on the Prostate Cancer and Prostatic Diseases website (http://www.nature.com/pcan)