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

Heather H. Cheng, MD, PhD[1,2], **Roman Gulati, MS**[2], **Arun Azad, PhD, MBBS**[3], **Rosa Nadal, MD**[4], **Przemyslaw Twardowski, MD**[5], **Ulka N. Vaishampayan, MD**[6], **Neeraj Agarwal, MD**[7], **Elisabeth I. Heath, MD**[6], **Sumanta K. Pal, MD**[5], **Hibba-tul Rehman, MD**[4], **Amanda Leiter, BA**[8], **Julia A. Batten, APRN**[7], **R. Bruce Montgomery, MD**[1,2], **Matthew D. Galsky, MD**[8], **Emmanuel S. Antonarakis, MD**[4], **Kim N. Chi, MD**[3], and **Evan Y. Yu, MD**[1,2]

[1]University of Washington, Seattle, U.S.A.

[2]Fred Hutchinson Cancer Research Center, Seattle, U.S.A.

[3]British Columbia Cancer Agency, Vancouver, Canada

[4]Sidney Kimmel Cancer Center/Johns Hopkins University, Baltimore, U.S.A.

[5]City of Hope Cancer Center, Duarte, U.S.A.

[6]Karmanos Cancer Institute/Wayne State University, Detroit, U.S.A.

[7]Huntsman Cancer Institute/University of Utah, Salt Lake City, U.S.A.

[8]Tisch Cancer Institute/Icahn School of Medicine at Mount Sinai, New York, U.S.A.

Abstract

BACKGROUND—Enzalutamide and abiraterone are new androgen-axis disrupting treatments for metastatic castration resistant prostate cancer (mCRPC). We examined 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 baseline

CORRESPONDING AUTHOR: Dr. Evan Y. Yu, Division of Medical Oncology, Department of Medicine, University of Washington, Seattle Cancer Care Alliance, 825 Eastlake Ave. E., Seattle, WA 98109, USA, Telephone: (206) 288-7595, Facsimile: (206) 288-2042, evanyu@uw.edu.

CONFLICT OF INTEREST:

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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 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.

Keywords

(6) enzalutamide; abiraterone; chemotherapy; docetaxel; sequencing; prostate cancer; mCRPC

INTRODUCTION

Treatment of men with metastatic castration resistant prostate cancer (mCRPC) has recently undergone unprecedented advances with the Food and Drug Administration approval of 6 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, Inc., Horsham, U.S.A) is an inhibitor of CYP-17 lyase, a critical enzyme in synthesis of AR ligands(1). Enzalutamide (Medivation, Inc., San Francisco, U.S.A.) 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 abiraterone(5–9) 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.

PATIENTS and METHODS

Patients

The study was performed in accordance with the declaration of Helsinki Declaration 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 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).

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(13), 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 ANOVA for continuous variables and χ^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, in complete 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”). 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 less prior treatment (Abi +Doce-Naïve) (Table 1)(14–16). In addition, 59% (182/310) *were not* taking steroids at start of enzalutamide and 39% (120/310) of patients *were* taking steroids at the start of enzalutamide (Table 1).

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 due to progression of disease with 27 (14%) due to symptomatic progression only, 25 (13%) due to PSA progression only, and the remaining 143 (72%) due to more than one measure of progression. No patients were reported as discontinuing enzalutamide for radiographic progression only. Eight patients discontinued enzalutamide due to toxicity only and 1 for financial reasons.

PSA decline resulting from enzalutamide treatment

In the Abi+Doce-Naive group (N=36), 24 (67%) achieved ≥30% PSA decline (PSA_{30}) and 21 (58%) achieved a ≥50% PSA decline (PSA_{50}) (Figure 1a). In the Prior-Abi group (N =79), 22 (28%) achieved PSA_{30} and 14 (18%) achieved PSA_{50}(Figure 1b). In the Prior-Doce group (N =30), 13 (43%) achieved PSA_{30} and 9 (30%) achieved PSA_{50} (Figure 1c). In the Prior-Abi+Doce group (N =165), 40 (24%) achieved PSA_{30} and 28 (17%) achieved PSA_{50} (Figure 1d).

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 7 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 endpoints 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, 19 (27%) achieved PSA_{30}, and 14 (20%) achieved PSA_{50}. This suggests that even among patients who have primary resistance to abiraterone, a subset will be sensitive to subsequent enzalutamide.

Conversely, of 109 patients who achieved PSA_{50} on 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. Of 70 patients who achieved no detectable PSA decline on prior abiraterone, 35 (50%) also failed to achieve any 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 to 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)(5–8, 17). 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 (Supplemental 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 PSA_{30} with subsequent enzalutamide, indicating that prior treatment does not preclude a PSA response to enzalutamide. However, in this context, median duration of enzalutamide was less than 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 non-uniform schedules of PSA and radiographic evaluation, and to non-uniform triggers for changing therapy across sites. Thus, our study was largely limited to PSA response and PSA-PFS and OS as endpoints, and it was not feasible to analyze radiographic progression-free survival as an endpoint. 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) (14–16, 18). Hence, *our results should not be interpreted as a measure of treatment 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 AR_{F876L} (21–24). 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, e.g., 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 (28), (29). 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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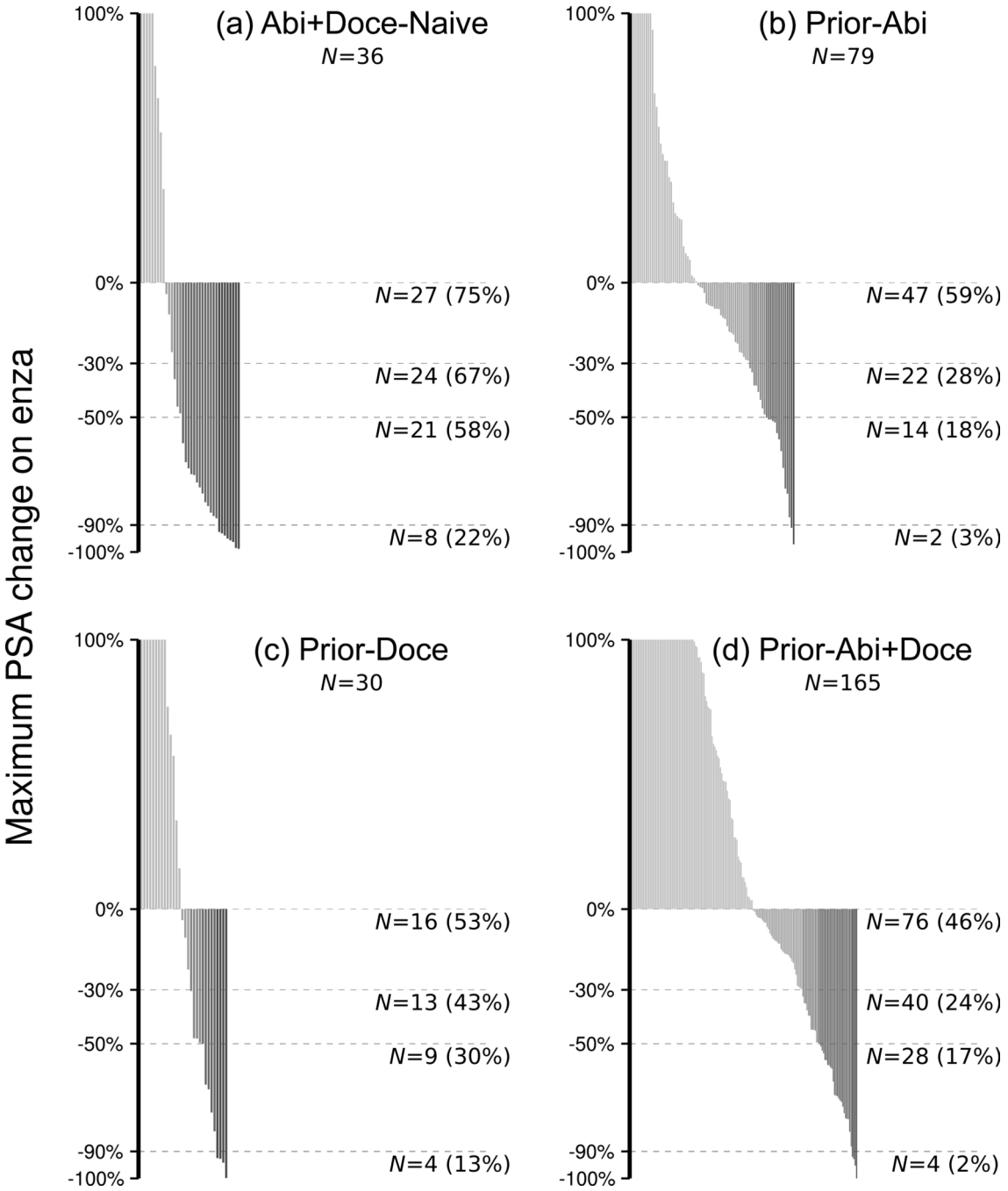

Figure 1.

PSA waterfall plots showing the maximal percent PSA change from baseline in patients who received (a) enzalutamide (Abi+Doce-Naive); (b) enzalutamide after prior abiraterone (Prior-Abi); (c) enzalutamide after prior docetaxel (Prior-Doce); (d) enzalutamide after prior abiraterone and docetaxel (Prior-Abi+Doce).

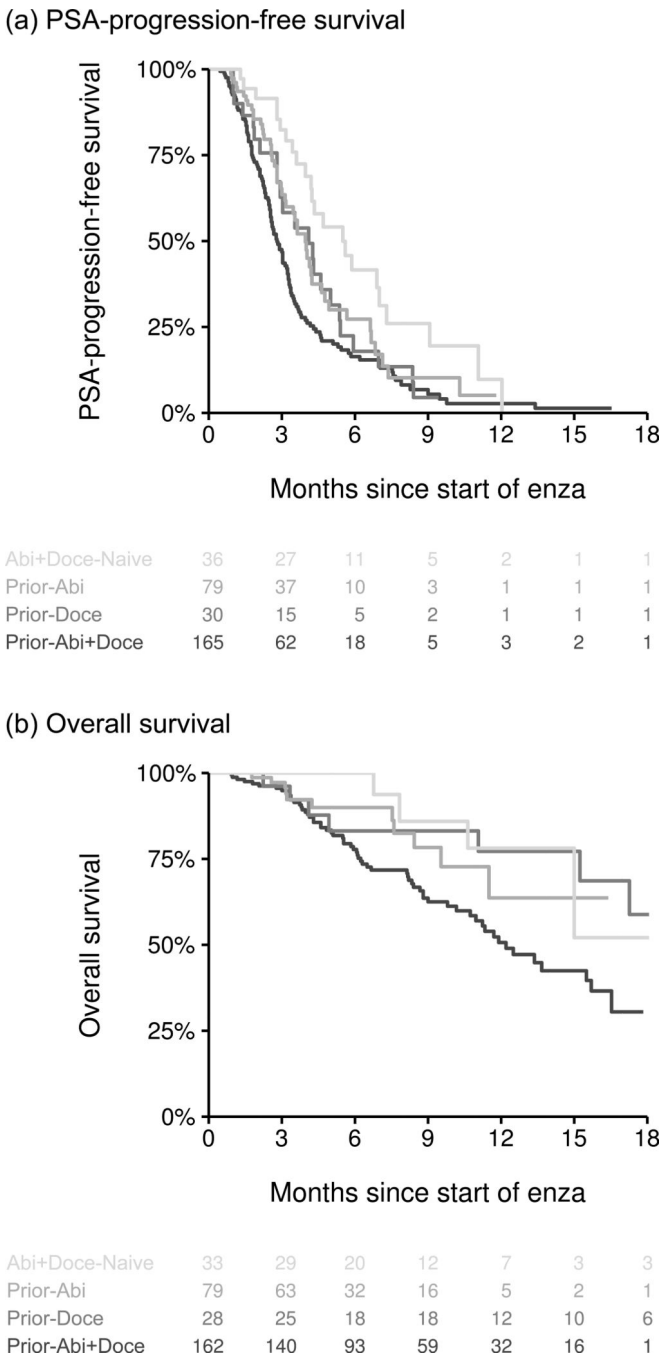

Figure 2.

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).

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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***	
		mean	***min-max***	***mean***	***min-max***	***mean***	***min-max***	***mean***	***min-max***	***mean***	***min-max***
PSA at diagnosis		266	0.2–20400	67	1.2–706	196	0.2–5800	892	2.5–20400	242	1.3–7500
Age at start of enza		64	40–90	64	47–79	66	47–90	61	40–75	62	43–87
Years since diagnosis at start of enza		8.4	0.6–27	7.9	0.8–20	9	0.6–27	8.4	0.9–23	8	1.2–23
Labs at start of enza	PSA	246	0.3–3600	76	0.3–393	208	1.8–3600	219	4.7–2109	306	0.8–2560
	albumin	3.8	1.8–4.9	4.1	3.3–4.8	3.9	2.5–4.6	3.7	2.7–4.9	3.7	1.8–4.6
	alkaline phosphatase	227	10–7420	167	35–1701	213	10–1233	181	45–875	256	37–7420
	hemoglobin	11.8	7.2–15.6	12.4	9.9–15.4	11.9	7.2–14.8	11.9	8.2–15.6	11.5	7.4–15.5
	LDH	295	79–1929	355	142–520	273	95–717	334	157–1294	290	79–1929
		count	*%*	*count*	*%*	*count*	*%*	*count*	*%*	*count*	*%*
Gleason at diagnosis	<7	24	8%	2	6%	1	13%	2	7%	10	6%
	7	81	26%	12	33%	21	27%	9	30%	39	24%
	>7	173	56%	22	61%	42	53%	15	50%	94	57%
	unknown	32	10%	0	0%	6	8%	4	13%	22	13%
ECOG at start of enza	0	77	25%	12	33%	24	30%	5	17%	36	22%
	1	128	41%	20	56%	28	35%	10	33%	70	42%
	2	55	18%	2	6%	12	15%	10	33%	31	19%
	3	14	5%	2	6%	6	8%	1	3%	7	4%
	unknown	36	12%	0	0%	9	11%	4	13%	21	13%
Sites of metastases at start of enza											
	bone only	144	46%	18	50%	43	54%	14	47%	69	42%
	bone and lymph node	91	29%	11	31%	20	25%	8	27%	52	32%
	lymph node only	17	6%	3	8%	8	10%	3	10%	3	2%
	any liver	3	1%	0	0%	0	0%	0	0%	3	2%
	any lung	23	7%	1	27%	5	6%	2	7%	15	9%

		All *N=310*		Abi+Doce-Naïve *N=36*		Prior-Abi *N=79*		Prior-Doce *N=30*		Prior- Abi+Doce *N=165*	
		mean	***min-max***	***mean***	***min-max***	***mean***	***min-max***	***mean***	***min-max***	***mean***	***min-max***
	other	16	5%	3	8%	3	4%	3	10%	9	5%
Prior abiraterone	yes	244	79%	0	0%	79	100%	0	0%	165	100%
	no	66	21%	36	100%	0	0%	30	100%	0	0%
Prior docetaxel*	yes	195*	63%	0	0%	0	0%	30*	100%	165*	100%
	no	115	37%	36	100%	36	100%	0	0%	0	0%
Steroids at start of enza	yes	120	39%	1	3%	43	54%	9	30%	65	39%
	no	182	59%	23	64%	33	42%	21	70%	95	58%
	unknown	8	3%	12	33%	3	4%	0	0%	5	3%

* 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

Table 2

Graded PSA Responses to Abiraterone and Enzalutamide

	BEST PSA RESPONSE TO SUBSEQUENT ENZALUTAMIDE					
BEST PSA RESPONSE TO PRIOR ABIRATERONE	*Total* N=236*	*no decline N=117*	*any decline N=119*	*≥30% PSA decline*	*≥50% PSA decline*	*≥90% PSA decline*
	no decline N=70	35/70 (50%)	35/70 (50%)	19	14	3
	any decline N=166	82/166 (49%)	84/166 (51%)	40	26	2
	≥30% PSA decline N=129	67	62	36	24	2
	≥50% PSA decline N=109	56	53	30	20	2
	≥90% PSA declineN=36	20	16	9	5	0

* Of 244 patients that received abiraterone prior to enzalutamide, 236 had sufficient data to evaluate PSA response to abiraterone.

Table 3

PSA Response Following Treatment with Enzalutamide

Context	*N* =	≥30% PSA response	≥50% PSA response	≥90% PSA response	Reference
Abi+Doce-Naive	*854*		78%	47%	(4; PREVAIL)
	36	67%	58%	22%	*
Prior-Abi	*47*		26%		(9)
	79	28%	18%	3%	*
Prior-Doce	*731*		54%	25%	(2; AFFIRM)
	30	43%	30%	13%	*
Prior-Abi+Doce	*39*	41%	13%	3%	(5)
	35	37%	29%		(17)
	61		21%		(6)
	23		39%	4%	(7)
	68		22%		(9)
	165	24%	17%	2%	*

* current study highlighted in gray